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Publication Date

2021-02-01

DOI

10.1016/j.pharmthera.2020.107670

Peer reviewed



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Carcinogenesis: Failure of resolution of inflammation?

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ARTICLE INFO

Available online 3 September 2020

Keywords:

Eicosanoid
Carcinogen
Inflammation
Resolution
Resolvin
Soluble epoxide hydrolase

ABSTRACT

Inflammation in the tumor microenvironment is a hallmark of cancer and is recognized as a key characteristic of carcinogens. However, the failure of resolution of inflammation in cancer is only recently being understood. Products of arachidonic acid and related fatty acid metabolism called eicosanoids, including prostaglandins, leukotrienes, lipoxins, and epoxyeicosanoids, critically regulate inflammation, as well as its resolution. The resolution of inflammation is now appreciated to be an active biochemical process regulated by endogenous specialized pro-resolving lipid autacoid mediators which combat infections and stimulate tissue repair/regeneration. Environmental and chemical human carcinogens, including aflatoxins, asbestos, nitrosamines, alcohol, and tobacco, induce tumor-promoting inflammation and can disrupt the resolution of inflammation contributing to a devastating global cancer burden. While mechanisms of carcinogenesis have focused on genotoxic activity to induce mutations, nongenotoxic mechanisms such as inflammation and oxidative stress promote genotoxicity, proliferation, and mutations. Moreover, carcinogens initiate oxidative stress to synergize with inflammation and DNA damage to fuel a vicious feedback loop of cell death, tissue damage, and carcinogenesis. In contrast, stimulation of resolution of inflammation may prevent carcinogenesis by clearance of cellular debris via macrophage phagocytosis and inhibition of an eicosanoid/cytokine storm of pro-inflammatory mediators. Controlling the host inflammatory response and its resolution in carcinogen-induced cancers will be critical to reducing carcinogen-induced morbidity and mortality. Here we review the recent evidence that stimulation of resolution of inflammation, including pro-resolution lipid mediators and soluble epoxide hydrolase inhibitors, may be a new chemopreventive approach to prevent carcinogen-induced cancer that should be evaluated in humans.

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Abbreviations: 12-O-tetradecanoylphorbol-13-acetate, TPA; 4-nitroquinoline 1-oxide, 4-NQO; 7,12-dimethylbenz[a]anthracene, DMBA; Aflatoxin B₁, AFB₁; Azoxymethane, AOM; benzo[a]pyrene, BaP; Dextran sodium sulfate, DSS; Diethylstilbestrol, DES; Hepatocellular carcinoma, HCC; Inducible nitric oxide synthase, iNOS; Lipopolysaccharide, LPS; Liquid chromatography-tandem mass spectrometry, LC-MS/MS; N-butyl-N-(4-hydroxybutyl)-nitrosamine, BBN; N-nitrosobis(2-oxopropyl)amine, BoP; N-nitrosodiethylamine, NDEA / Diethylnitrosamine DEN; N-nitrosodimethylamine, NDMA / Dimethylnitrosamine DMN; N-nitrosomethylbenzylamine, NMBA; Nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, NNK; Nuclear factor erythroid-2 related factor 2, Nrf2; Perfluorinated carboxylic acids, PCFAs; Perfluorooctanoic acid, PFOA/C8; Phorbol 12-myristate 13-acetate, PMA; Polycyclic aromatic hydrocarbons, PAHs; Soluble epoxide hydrolase, sEH; Specialized pro-resolving mediators, SPMs.

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1. Introduction

Carcinogens induce inflammation, an established hallmark of cancer (Greten & Grivennikov, 2019; Hanahan & Weinberg, 2011; Mantovani, Allavena, Sica, & Balkwill, 2008). With potential exposure to greater than 15 million environmental chemicals worldwide, controlling inflammation and its resolution will be a critical component of the successful prevention and treatment of cancer (Gilligan et al., 2019; Panigrahy et al., 2019; Sulciner et al., 2018). Uncontrolled local and systemic hyperinflammation is an underlying driving force of diseases including cardiovascular disease (e.g. atherosclerosis and myocardial infarction), abdominal aortic aneurysm, heart arrhythmias, arthritis, central nervous system disorders, periodontal disease, inflammatory bowel disease, gallstones, sepsis, infection, stroke/epilepsy, infection, acute respiratory distress syndrome (ARDS), fibrosis (e.g. liver, kidney and lung), portal hypertension, fatty liver, neurodegenerative diseases (e.g. Alzheimer's disease), traumatic brain injury, asthma, obesity, diabetes, pain, severe coronavirus disease (e.g. COVID-19), and autoimmune diseases (Chelko et al., 2019; Chiang et al., 2012; Espinoza et al., 2016; Imig & Hammock, 2009; Libby, 2002; Mehta et al., 2020; Serhan, 2014; Spite et al., 2009). Over the past century, the study of anti-inflammatory mechanisms has focused on the suppression of pro-inflammatory mediators, such as cytokines, eicosanoids, and enzymes (Wang & Dubois, 2010). In recent years, a new direction has emerged to "turn off" inflammation with the discovery of a new superfamily of endogenous specialized pro-resolving lipid-autacoid mediators (SPMs), such as resolvins, which have potent novel inflammation clearing ('pro-resolution') activity without being immunosuppressive (Serhan, 2014; Serhan et al., 2002; Serhan et al., 2009). Unlike the majority of anti-inflammatory agents including the nonsteroidal anti-inflammatory drugs (NSAIDs) such as celecoxib and ibuprofen that work by directly suppressing cyclooxygenase (COX-2) enzyme activity, SPMs are endogenous inhibitors of inflammation, which function as "brake signals" to turn off inflammation (Serhan, 2014). These pro-resolution lipid autacoids act through clearance of cellular debris by immune cells such as macrophages resulting in reduced localized pro-inflammatory cytokines in a process termed "resolution" (Serhan, 2014). Failure of resolution via reduced SPMs (e.g. resolvins) is a key biological mechanism of pathogenesis and a unifying component of many underlying chronic inflammatory human diseases such as obesity, infection, asthma, wound healing, Alzheimer's Disease, Parkinson's disease, aging, sepsis, *Pseudomonas aeruginosa* infections, periodontitis, cardiovascular diseases, obesity, inflammatory bowel disease, neuroinflammation, respiratory diseases, multiple sclerosis, arthritis, cystic fibrosis, scleroderma, ocular disorders (e.g. age-related macular degeneration), atherosclerosis, rheumatic diseases, leukemia, sickle cell anemia, and chronic liver disease (e.g. cirrhosis) (Arita et al., 2005; Arnardottir et al., 2016; Chiang et al., 2012; Claria et al., 1998; Flitter et al., 2017; Fredman et al., 2016; Haworth, Cernadas, Yang, Serhan, & Levy, 2008; Karp et al., 2004; Kasuga et al., 2008; Kowal-Bielecki, Kowal, Distler, & Gay, 2007; Levy et al., 2005; Li et al., 2020; Lukiw et al., 2005; Matte et al., 2019; Merched, Ko, Gotlinger, Serhan, & Chan, 2008; Neuhof et al., 2013; Planaguma et al., 2008; Serhan, 2014; Serhan & Levy, 2018; Stenke, Edenius, Samuelsson, & Lindgren, 1991; Yacoubian & Serhan, 2007).

Inflammation was first described according to the four cardinal signs: calor (heat), pallor/dolor (pain), rubor (redness), and tumor (swelling), which reflect the pro-tumorigenic activity of cytokines, immune cells, and blood vessels (e.g. angiogenesis) in the tumor

microenvironment (Serhan, 2017; Sulciner et al., 2018). In healthy individuals, the acute inflammatory response(s) is self-limited and can be classically divided into initiation and resolution phases (Serhan, 2014). Neutrophils (polymorphonuclear leukocytes) are one of the first immune cell types to enter the wounded area and remove microbes as well as cellular debris (Serhan & Levy, 2018). Cancer is viewed as a wound that does not heal, thus attracting similar cell types and mechanisms as wound healing and tissue regeneration (Dvorak, 1986). A paradigm shift is emerging in our understanding of the pathogenesis of pathological inflammation which not only results from the persistent activation of inflammatory signals, but also the failure of engaging pro-resolving mechanisms including clearance of cell death "debris" and counter-regulation of pro-inflammatory cytokines (Serhan, 2014; Serhan & Levy, 2018). Experimental and human studies suggest that cancer progression results from the "failure to clear debris" after chemotherapy, radiation, or surgery (Chaurio et al., 2013; da Silva-Jr, Chammas, Lepique, & Jancar, 2017; Ford et al., 2015; Gartung et al., 2019; Gilligan et al., 2019; Gunjal et al., 2015; Huang et al., 2011; Panigrahy et al., 2019; Revesz, 1956; Sulciner et al., 2018; Ye et al., 2018). Thus, failure to engage resolution of inflammation mechanisms including clearance of debris may lead to carcinogenesis. Differentiating between suppression and resolution of inflammation is critical to mechanistic studies in inflammation-driven diseases including cancer (Fishbein et al., 2020; Gilligan et al., 2019; Kuang, Hua, Zhou, & Yang, 2016; Panigrahy et al., 2019; Serhan, 2014; Shan et al., 2020; Sulciner et al., 2018; Ye et al., 2018).

A key concept in resolution of inflammation is that the immune system can be beneficial in fighting cancer, in accordance with the increasing interest in immune-mediated approaches in targeting cancer (Serhan, 2011; Sharma & Allison, 2015). In 1790 the Scottish surgeon John Hunter remarked "Inflammation in itself is not to be considered as a disease" (Turk, 1994). In 1893 William Coley successfully treated sarcomas with bacterial mixtures, leading to tumor regression (Coley, 1910). It has been known from the 11th Century "The Canon of Medicine," an historical encyclopedia of medical books, that inflammation is not entirely bad and can be good – "pus bonum ert laudabile" (good and laudable pus) (Serhan, 2011). "Laudable pus" was believed to be a sign of a healthy, healing wound (Freiberg, 2017), and the Serhan laboratory discovered pro-resolution lipid mediators that are biosynthesized in the resolving inflammatory exudates to identify the "stop" signals which turn inflammation off (Serhan, 2014; Serhan et al., 2002; Serhan et al., 2009; Serhan, Hamberg, & Samuelsson, 1984). In Taber's Cyclopedic Medical Dictionary "resolution" is defined as "cessation of inflammation without suppuration; the return to normal" (Serhan, 2011). Although it was previously believed that the resolution of inflammation was a passive process, it is now widely appreciated to be an active reprogramming of the immune environment regulated by pro-resolution lipid mediators (Serhan, 2014; Serhan et al., 2002; Serhan et al., 2009; Serhan & Levy, 2018). While blocking inflammation can be beneficial in cancer (Coussens, Zitvogel, & Palucka, 2013; Greten & Grivennikov, 2019; Mantovani, 2009), stimulating the resolution of inflammation via pro-resolution mediators is an entirely distinct and unique approach from neutralizing pro-inflammatory factors via the clearance of pro-tumorigenic cellular debris (Serhan, 2014; Serhan & Levy, 2018). Pro-resolution mechanisms are multi-pronged including counter-regulating a series of pro-inflammatory mediators such as cytokines, chemokines, and eicosanoids ("eicosanoid and cytokine storm") by stimulating the clearance of cellular debris (Sulciner et al., 2018).

2. Inflammation and Cancer

The relationship between inflammation and cancer harkens back over 150 years ago to 1863 when Rudolf Virchow suggested that chronic inflammation from tissue injury stimulates the proliferation of cells leading to cancer (Balkwill & Mantovani, 2001). Virchow's hypothesis that cancer is initiated at sites of "lymphoreticular infiltrate" is highly relevant to many cancer patients as pancreatitis, hepatitis, colitis, esophagitis, cholangitis, *Helicobacter pylori* and other chronic inflammatory diseases are established risk factors for cancer in these tissues (Beasley, 1988; Greene, Huang, Serhan, & Panigrahy, 2011; Guerra et al., 2007; Guerra et al., 2011; Rutter et al., 2004). Virchow studied the four signs of inflammation (redness, swelling, heat and pain) and hypothesized a link between microinflammation and subsequent tumor progression (Heidland, Klassen, Rutkowski, & Bahner, 2006). Experimental studies have indeed confirmed that inflammation can stimulate or induce tumor initiation, growth, and metastasis (Bogen, 2019; Chang et al., 2019; Coussens & Werb, 2002; Fishbein et al., 2020; Gartung et al., 2019; Gilligan et al., 2019; Guerra et al., 2007; Mantovani et al., 2008; Panigrahy et al., 2019; Sulciner et al., 2018; Wang & Dubois, 2010). Cancers arise frequently at sites of chronic inflammation and injury as the observation that secondary tumors occur at the points of injury (e.g. tumor growth next to surgical placement of glass rods) was noted in 1914 (Jones & Rous, 1914). The wound inflammatory response stimulates the growth of pre-neoplastic cells and cancer progression (Antonio et al., 2015). Experimental evidence demonstrates that cancer therapies including chemotherapy, radiation, and surgery can stimulate tumor growth via a pro-tumorigenic host response including a eicosanoid/cytokine storm of pro-inflammatory and pro-angiogenic mediators (Camphausen et al., 2001; Chang et al., 2019; Filippou & Karagiannis, 2020; Fishbein et al., 2020; Gartung et al., 2019; Karagiannis et al., 2017; Shaked, 2019; Sulciner et al., 2018; Volk-Draper et al., 2014). Wounding including surgery or biopsy can stimulate cancer growth via inflammation and angiogenesis (Alieva et al., 2017; Forget, Simonet, & De Kock, 2013; Hobson et al., 2013; Krall et al., 2018; Lee et al., 2009; Panigrahy et al., 2019).

Chronic inflammation and infection contributes to about 25% of all human cancers, including various tumor types such as hepatocellular, bladder and prostate cancer (De Marzo et al., 2007; Greene et al., 2011; Sulciner, Gartung, Gilligan, Serhan, & Panigrahy, 2018). For example, inflammation initiates cancer growth within 5 to 8 months in a genetically engineered model of pancreatic cancer (Guerra et al., 2007). The importance of inflammation in cancer was further demonstrated in a randomized double-blind trial in patients with atherosclerosis. Patients who received canakinumab, an IL-1 β inhibitor used to treat systemic inflammatory diseases, developed significantly reduced incidence of lung cancer and cancer-related mortality (Ridker et al., 2017). Chronic inflammation also increases the risk of various malignancies such as those of the gastrointestinal tract including colorectal (CRC), gastric, gallbladder, and esophageal cancers (Aggarwal, Shishodia, Sandur, Pandey, & Sethi, 2006; Espinoza et al., 2016; Wang & Dubois, 2010). Increased infiltration of innate immune cells to the tumor, such as macrophages and neutrophils, correlates with increased angiogenesis and poor prognosis (Pollard, 2004). In contrast, lymphocytic/monocytic inflammatory infiltrates can be associated with tumor inhibition and a beneficial prognosis (Zhang et al., 2003). The inflammatory cells in the tumor may be genetically stable, and thus less susceptible to development of drug resistance making them an ideal target for new cancer therapies.

The traditional view that cancer is a cell-autonomous disease driven by genetic changes with selection for fast-growing and increasingly malignant cell clones has been supplanted with the understanding that cancer requires support from the host tissue microenvironment, including immune cells such monocytes/macrophages, neutrophils, and lymphocytes as well as endothelial cells, pericytes, fibroblasts and cancer stem cells (Folkman, 2007; Joyce, 2005). An early event in tumor

progression is the recruitment of monocytes to the tumor site, where they differentiate into macrophages (Balkwill & Mantovani, 2001). Tumor infiltrating immune cells such as macrophages play a key role in tumor growth, angiogenesis, and inflammation (Pollard, 2004) and exhibit critical crosstalk in tumor cell-stromal cell communication via pro-inflammatory and pro-resolution mediators (Gilligan et al., 2019; Panigrahy et al., 2019; Sulciner et al., 2018).

Cancer therapies either directly (e.g. chemotherapy and radiation) or indirectly (e.g. targeted therapies such as immunotherapy and anti-angiogenic therapy) result in apoptotic tumor cell death ("tumor cell debris"). However, apoptotic cell death ("debris") is a double-edged sword and can paradoxically stimulate tumor growth and metastasis via pro-inflammatory mechanisms including a macrophage-secreted "cytokine and eicosanoid storm" of pro-angiogenic mediators (Chang et al., 2019; Fishbein et al., 2020; Gartung et al., 2019; Revesz, 1956; Sulciner et al., 2018). Therapy-induced inflammation and immune infiltration in cancer from chemotherapy, radiation, and immunotherapies can be beneficial by triggering anti-tumor immunity or detrimental by stimulating tumor growth via immunosuppression (Greten & Grivennikov, 2019). Over the past century anti-inflammatory therapies in cancer have focused on suppressing pro-inflammatory "go" signals such as cytokines, angiogenic factors and eicosanoids (Gilroy, Lawrence, Perretti, & Rossi, 2004; Serhan, 2014). Targeting inflammation and angiogenesis allows for the development of intervention strategies that can complement the traditional cell-autonomous cancer approaches which target the mutational capacity of tumors. Traditional anti-inflammatory agents such as steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), coxibs, and selective cytokine blockade exhibit potent anti-tumor activity in various pre-cancer models (Wang & Dubois, 2010). Cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome (CYP) P450 enzymes and their inhibitors are widely used to treat inflammation and cancer. The prostaglandin receptors (e.g. EP1, EP2, EP3, and EP4) are overexpressed in cancers and are a target to treat various types of cancer, e.g. breast and colorectal cancer (Majumder, Nandi, Omar, Ugwuagbo, & Lala, 2018; Wang & Dubois, 2010). Moreover, anti-inflammatories such as aspirin have exhibited potent chemopreventive activity in patients (Gilligan et al., 2019). However, in clinical trials anti-inflammatory agents have resulted only in transient anti-tumor activity, multiple toxicities, and immunosuppression severely limiting their use in cancer patients and individuals with inflammatory disorders at risk for cancer (e.g. inflammatory bowel disease) (Milagre et al., 2015; Panigrahy et al., 2019; Sandhu et al., 2013; Serhan, 2014). Side effects and toxicities from their immunosuppressive activity include impaired wound healing, fungal infections, osteoporosis, stomach bleeding, increased thrombosis, cardiovascular (e.g. heart attacks) and kidney toxicity (Serhan, 2014; Wang & Dubois, 2010). Moreover, anti-cytokine biologics designed to block pro-inflammatory factors may abrogate host defense against infections and increase risk of other cancers. In dramatic contrast, pro-resolution lipid mediators such as resolvins, lipoxins, protectins, and maresins are non-immunosuppressive, anti-thrombotic, anti-angiogenic, anti-fibrotic, stimulate the clearance of debris, stimulate tissue repair/regeneration, enhance post-ischemic revascularization, promote wound healing and exhibit potent biological activity at nanogram concentrations without overt toxicity reported to date (Cherpokova et al., 2019; de la Rosa et al., 2018; Gilligan et al., 2019; Hellmann et al., 2018; Jin et al., 2009; Norling et al., 2011; Panigrahy et al., 2019; Qu et al., 2012; Serhan & Levy, 2018; Sulciner et al., 2018; Zhang et al., 2016).

3. Carcinogens and inflammation

A carcinogen is defined as a chemical substance, or a mixture of chemical substances, after inhalation, ingestion, dermal application or injection which induces cancer, increases its incidence, or shortens the time to tumor occurrence (i.e. latency) at any dosage level by any route in any species of animals as compared to controls (Luch, 2005).

Examples include tobacco, natural and synthetic chemicals, and environmental toxins (National Toxicology P, 2011). Although it is challenging to estimate the number of cancer deaths caused by carcinogen exposure, an astonishing 70–95% of cancer cases can be traced to identified risk factors including diet (30–35%), tobacco (25–30%), infections (15–20%), obesity (10–20%), alcohol (4–6%), and others, including pollutants and radiation (10–15%) (Anand et al., 2008; Madia, Worth, Whelan, & Corvi, 2019). Substances that induce tumors in animals are considered as presumed or suspected human carcinogens until convincing evidence to the contrary is presented (Maronpot, Flake, & Huff, 2004). To establish a chemical as a human carcinogen requires experimental animal studies, human epidemiological cancer studies, clinical studies, and/or samples from human tissues exposed to the carcinogen to demonstrate a causal relationship (Suarez-Torres, Alzate, & Orjuela-Ramirez, 2020). Many substances which have limited evidence from human studies but have sufficient evidence from animal carcinogenicity studies may also be carcinogens.

Since the 1970s the International Agency for Research for Cancer (IARC) has screened over 1000 agents which exhibited a cancer risk to humans (Krewski et al., 2019). Over 100 carcinogenic agents can be divided into six general categories: (I) pharmaceuticals; (II) biological agents; (III) arsenic, metals, fibers and dusts; (IV) radiation; (V) personal habits and indoor combustions; and (VI) chemical agents and related occupations (Krewski, Rice, et al., 2019). Carcinogens including nitrosamines and aflatoxins can initiate or stimulate tumor growth and metastasis via multiple mechanisms including inflammation (Shi, Godschalk, & van Schooten, 2017; Smith et al., 2016). Inflammation is a driving force for genotoxicity including impaired particle clearance leading to macrophage activation and persistent inflammation (Borm, Tran, & Donaldson, 2011). Human carcinogens recently were categorized by 10 key characteristics of carcinogens including: (1) to be electrophilic or metabolically activated, (2) genotoxic, (3) alter DNA repair, (4) lead to epigenetic alterations or genomic instability, (5) generate oxidative stress, (6) chronic inflammation, (7) immunosuppression, (8) activate receptor mediated signaling, (9) cause cell immortalization and (10) alter cell proliferation, cell death, and angiogenesis (Fig. 1) (Smith et al., 2016; Smith et al., 2020). These key characteristics of carcinogens provide a mechanistic basis to evaluate the activity of carcinogens (Guyton et al., 2018; Smith et al., 2016). Many carcinogens exhibit several of the 10 key characteristics, with an average of four characteristics per agent (Krewski et al., 2019). These characteristics of carcinogens help to create the necessary tumor micro-environment for tumor initiation and progression via mechanisms distinct from the hallmarks of cancer (Guyton, Rieswijk, Wang, Chiu, & Smith, 2018; Smith et al., 2016; Smith et al., 2020). These key characteristics may also lead to the development of human-based assays and biomarkers for assessing cancer risk (Fielden et al., 2018). At low concentrations, a chemical mixture has synergistic pro-tumorigenic activity on benign and malignant cells at a significantly lower concentration than as single chemicals (Dairkee, Luciani-Torres, Moore, Jaffee, & Goodson 3rd., 2018). Carcinogens may not directly be genotoxic but cause DNA damage by stimulating inflammation. Chronic inflammation triggers oxidative stress via the release of pro-inflammatory cytokines and stimulation of cell proliferation, leading to DNA damage (Krewski, Bird, et al., 2019). Heavy metals such as arsenic, aluminum, nickel, cadmium, chromium, cobalt, palladium, and titanium induce severe damage triggering pro-inflammatory cytokines and oxidative stress (Jomova & Valko, 2011; Magrone, Russo, & Jirillo, 2019). Carcinogens such as *per*- and polyfluoroalkyl substances (PFAS) cause cancer in animals and increase risk of cancer in humans via several key characteristics including oxidative stress, immunosuppression, and receptor-mediated activity (Temkin, Hocevar, Andrews, Naidenko, & Kamendulis, 2020). Primary genotoxicity can result from carcinogen-induced particles (e.g. from polycyclic aromatic hydrocarbons) while oxidative stress-induced DNA damage can induce secondary genotoxicity (Schins & Knaapen, 2007).

This important classification of key characteristics focused on the mechanisms of action of the cancer-causing activity of carcinogens provides a robust platform for novel chemopreventive treatment approaches to carcinogen-induced cancers. The carcinogenic potential of a compound is its ability to induce neoplasia via genotoxicity, cytotoxicity, proliferation, and inflammation depending on dose and duration of exposure (Doe et al., 2019). Importantly, inflammation can induce genetic changes which can cause cancer (Kay, Thadhani, Samson, & Engelward, 2019; Kiraly, Gong, Olipitz, Muthupalani, & Engelward, 2015). Cancer may be initiated with a mutation post-exposure to a DNA-damaging carcinogen, followed by pro-tumorigenic mechanisms such as inflammation which fuel the fire (Aggarwal et al., 2006; Cooks, Harris, & Oren, 2014). Oxidative stress including reactive oxygen and nitrogen species (RONS) critically mediate cancer progression by carcinogens and pathogens (Kay et al., 2019; Meira et al., 2008). While oxidative stress can induce DNA damage and inflammation, repair of DNA lesions formed by RONS during chronic inflammation can protect from carcinogen-induced cancers (Meira et al., 2008). DNA damage also indirectly promotes inflammation through cytotoxicity (Kay et al., 2019). Excessive DNA damage during proliferation may not be cleared by DNA repair pathways, resulting in cell death including apoptosis, necroptosis, necrosis, or senescence. Thus, DNA damage is considered essential to carcinogenesis.

Initiators of carcinogenesis include radiation, certain chemotherapeutics and chemicals such as aflatoxin, urethane, tryptophan metabolites, and nitrosamines, can cause an irreversible genetic modification in a normal cell leading to cancer (Chung & Gadupudi, 2011; Molho-Pessach & Lotem, 2007; Xie et al., 2012). Initiators can bind to and alter the DNA to generate adducts. The initiation stage is an event in which carcinogens usually induce mutations or other modifications in critical genes, which can produce cancer stem cells (He, Liu, & Lubman, 2012; Tirino et al., 2013). A compound that acts as both an initiator and a promoter is referred to as a 'complete carcinogen' because tumor development can occur without the application of another compound (Rastogi, Dogra, Khanna, & Das, 2006). In studies of mouse skin carcinogenesis, a linear relationship has been observed between the dose of initiator and the quantity of tumors that can be produced (Gills et al., 2006). Thus, the more exposure to the carcinogen, the higher the risk of developing tumors (Kang et al., 2018). Cancer risk and slope factor are calculated in a linear dose-response (Kang et al., 2018). All known human carcinogens that have been studied for carcinogenesis in experimental animals have generated positive results in one or more animal species (Tomatis, Aitio, Wilbourn, & Shuker, 1989; Wilbourn et al., 1986). For several carcinogens, such as aflatoxins and vinyl chloride, carcinogenesis in experimental models of cancer was established before epidemiological studies confirmed their carcinogenesis in humans (Vainio et al., 1995).

The mechanism of action of carcinogens traditionally has been simplified as genotoxic and/or nongenotoxic. A genotoxic carcinogen is defined as a chemical that causes cancer by directly altering the genetic material of target cells, while non-genotoxic carcinogens are chemicals that can induce cancer by mechanisms not related to direct genetic damage. Many genotoxic carcinogens cause cancer in carcinogenic bioassays in animals (Lee et al., 2014). Concerning cancer risk assessment, genotoxic carcinogens exert carcinogenic potential regardless of the animal species. Thus, chemicals that are carcinogenic via genotoxicity to rodents are also presumed to be carcinogenic to humans unless proven otherwise. Because genotoxic carcinogens are mutagenic and may act through interaction with DNA to produce irreversible genetic changes in target organ cells, they may exhibit no dose threshold for their carcinogenic potential (Preussmann, 1980; Tomatis et al., 1997). A genotoxic chemical can induce mutations (e.g. induction of DNA modifications). Carcinogens may induce a specific gene mutation frequently observed in a particular cancer increasing the risk of cancer (Moore et al., 2008). While carcinogen-induced DNA damage can cause cancer, some studies suggest that DNA adducts alone or mutations alone may not be

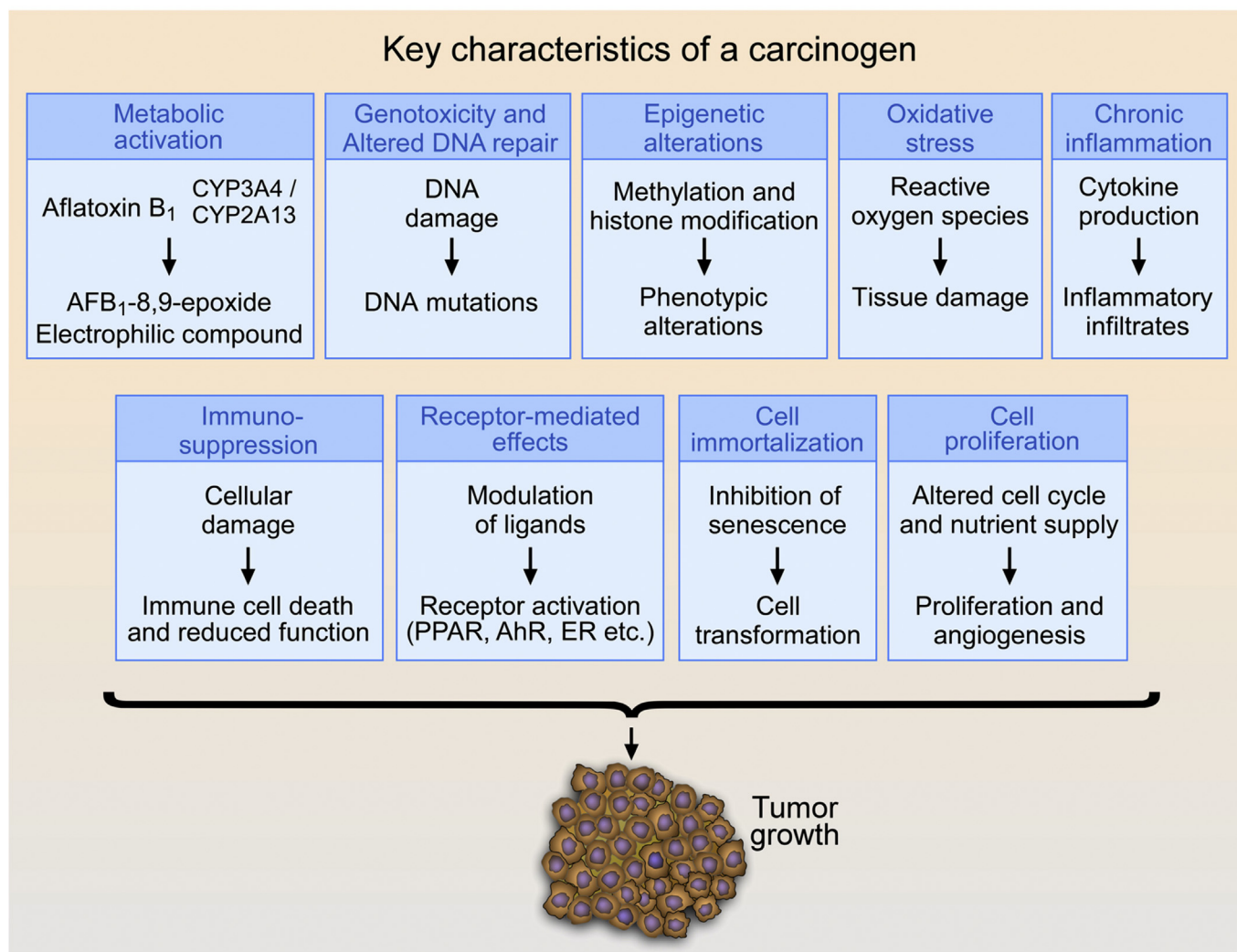


Fig. 1. Key characteristics of carcinogens.

Represents the 10 key characteristics of carcinogens adapted from Table 1 in (M. T. Smith et al., 2016). 1. Metabolic activation 2. Is genotoxic 3. Alters DNA repair 4. Leads to epigenetic alterations 5. Generates oxidative stress, 6. Chronic inflammation, and 7. Immunosuppression 8. Activates receptor mediated signaling 9. Causes cell immortalization and 10. Increases cell proliferation. Adapted from Smith et al. *Environmental Health Perspectives* 124:62016.

sufficient to cause cancer (Bogen, 2019; Johnson et al., 2014). Non cell-autonomous mechanisms such as inflammation and angiogenesis may also be critical to tumor initiation and progression (Folkman, 2007). Importantly, proliferation of cells alone does not cause cancer as tumors can also develop in tissues subjected to infection, wounding, and inflammation (Coussens & Werb, 2002; Krall et al., 2018; Panigrahy et al., 2019).

Carcinogens (e.g. aflatoxins, nitrosamines, asbestos, dioxins, tobacco, and alcohol) can initiate and stimulate cancer progression through various mechanism including inflammation, oxidative stress, DNA damage, cytotoxicity, acute or chronic injury, and subsequent regenerative proliferation via cell death (e.g. apoptosis) (Bogen, 2019; Klaunig, Hocevar, & Kamendulis, 2012; Yao & Zhong, 2005). Environmental and occupational exposure to carcinogenic metals (e.g. arsenic, chromium, and vanadium) causes cancer via cell apoptosis, inflammation, DNA damage, and lipid peroxidation (Chen, Vallyathan, Castranova, & Shi, 2001). There are over 8000 compounds identified as carcinogens to date. Carcinogens can stimulate cancer via the production of critical pro-inflammatory, pro-angiogenic and pro-tumorigenic cytokines/transcription factors, including TNF- α , IL-6, and NF- κ B, as well as proto-oncogenes (e.g., c-Myc) (Chen, Yan, & Ye, 1998; George, Tsuchishima, & Tsutsumi, 2019). Moreover, carcinogens may impair the host protective immune response via immunotoxicity, including increased

apoptosis of leukocytes and reactive oxygen species (Iwaniuk, Jablonska, Jablonski, Ratajczak-Wrona, & Garley, 2015; Jablonski, Jablonska, & Chojnowski, 2001; Jablonski, Jablonska, & Leonik, 2011; Nowak, Ratajczak-Wrona, Garley, & Jablonska, 2018; Ratajczak-Wrona et al., 2014). Impaired resolution of inflammation can lead to many human diseases including cancer (Gartung et al., 2019; Panigrahy et al., 2019; Serhan & Levy, 2018; Sulciner et al., 2018). Carcinogens can disrupt inflammation resolution by impairing host-protective immune cells (e.g. neutrophil and macrophage) phagocytosis of debris (Fishbein et al., 2020; Mehrzad et al., 2011; Moon, Rhee, & Pyo, 1999). Impaired clearance of debris fuels a pro-tumorigenic feedback loop between inflammation, DNA damage and carcinogenesis which can be aggravated by the tumor cell debris generated by cytotoxic cancer therapy including chemotherapy and radiation (Chang et al., 2019; Gartung et al., 2019; Huang et al., 2011; Sulciner et al., 2018). Cross-talk between the cellular responses to DNA damage, RNA processing, and the extracellular vesicles mediate metastasis (Meng, Yang, & Camp, 2019). Thus, differentiating between genotoxic and non-genotoxic mechanisms emphasizing the critical role of the tumor microenvironment including cancer stem cells (or tumor initiating cells), circulating tumor cells, inflammation and angiogenesis are critical for tumor initiation, tumor promotion, tumor dormancy escape and tumor progression (Alitalo et al., 2013; Balkwill, Charles, & Mantovani, 2005; Fujiki,

Sueoka, & Suganuma, 2013; Hanahan & Coussens, 2012; Hanahan & Folkman, 1996; Hanahan & Weinberg, 2000, 2011; Trosko, 2001).

4. Human carcinogens

More than 1,400 chemicals and chemical groups are known or likely carcinogens. Human carcinogens include a wide range of substances from alcohol, nitrosamines, aflatoxins, physical stressors (e.g. UV and ionizing radiations), and infections include viruses-, bacteria- and parasites-induced infections (e.g. HIV, hepatitis, HPV and *H. pylori*). Infections, tobacco smoking, carcinogens (e.g. aflatoxins, nitrosamines, polycyclic aromatics), alcohol, obesity, inflammatory bowel disease and other diseases with a chronic inflammatory component have been associated with various cancers (Mantovani, Marchesi, Malesci, Laghi, & Allavena, 2017). Infectious agents including *Helicobacter pylori*, hepatitis B virus (HBV), hepatitis C virus (HCV), and human papillomavirus have been classified as carcinogenic agents in humans by International Agency for Research on Cancer (IARC). For example, almost half the world's population is infected by the pathogen *Helicobacter pylori*, categorized as a group I carcinogen, which is responsible for the highest rate of cancer deaths through the world (Chmiela, Karwowska, Gonciarz, Allushi, & Staczek, 2017). Carcinogens are grouped into aminoazo dyes, aromatic amines and amides, aromatic hydrocarbons, metals, natural compounds, olefins, and paraffines/ethers (Luch, 2005). Environmental exposures to soot, wood dust, vinyl chloride, sulfuric acid, coal emissions, nitrosamines, and other carcinogens may occur via occupations such as carpentry, plastic production, automobile manufacturing, mining and other industries (Hidajat et al., 2019; Rogers, Vaughan, Davis, & Thomas, 1995; Song, Wu, & Guan, 2015). People can be exposed to chemical carcinogens such as trichloroethylene in daily routines in house cleaning compounds, benzidine which used to be used often for color dyes, or asbestos found in housing insulation (Kumagai-Takei et al., 2018).

While exposure to certain carcinogens has declined with preventative education, other carcinogens cannot be completely avoided as they occur naturally or in the diet. Aflatoxins are mycotoxins produced by fungi which may contaminate a large portion of the world's food supply leading to cancer progression including hepatocellular carcinoma (HCC) (Marchese et al., 2018; Xue et al., 2019; Zhang et al., 2019). Other natural carcinogens include minerals like cadmium, nickel or erionite, thorium, crystalline silica, ultraviolet light, or radon gases. Arsenic can be found in contaminated ground water. Polycyclic aromatic hydrocarbons (PAH), such as benzo[*a*]pyrene (BaP) or dibenz[*a,h*]anthracene (DBA), can also be ingested in the diet or result in exposure in work environments (Luch, 2005; Poirier, 2016).

Two of the most common human carcinogens are alcohol and tobacco, which is the leading risk factor for lung cancer with up to 80% of lung cancer deaths resulting from smoking inducing inflammation mechanisms such as increased macrophage recruitment, delayed clearance of neutrophils, and stimulation of reactive oxygen species (Walser et al., 2008). While ethanol is not genotoxic nor mutagenic, its metabolite acetaldehyde is a potent local carcinogen (Salaspuro, 2017). Tobacco smoke is also associated with many other carcinogens such as benzene, naphthalene, cadmium, and nickel compounds. Environmental risk factors for bladder cancer, for example, include tobacco smoking, occupational exposure to aromatic amines, exposure to arsenic, chronic infection with *Schistosoma* species, radiation therapy to nearby organs, and the use of alkylating agents (Freedman, Silverman, Hollenbeck, Schatzkin, & Abnet, 2011; Grosse et al., 2013; Johansson & Cohen, 1997), and smokers are more than twice as likely to get bladder cancer than non-smokers. Moreover, the increased risk from smoking, although progressively decreasing after cessation, remains elevated by 62% and 50% even after 25 and 32 years, respectively (Brennan et al., 2000). The carcinogen alcohol can lead to 4–6% of cancers (Madia et al., 2019). Chronic consumption of alcohol stimulates inflammation

due to leakage of bacteria and bacterial products, predominantly lipopolysaccharide (LPS), from the gut into the bloodstream and the liver.

Aflatoxins are a group of mycotoxins produced by *Aspergillus* fungi which are natural carcinogens and contaminate a large portion of the world's food supply including grains and other food sources in tropical and subtropical climates, wetlands, and high temperatures. Up to 5 billion people exposed to aflatoxins are at increased risk for developing hepatocellular carcinoma (HCC) as the carcinogen causes up to 28% of HCC cases globally (Liu & Wu, 2010; Strosnider et al., 2006; Yang et al., 2019). Although aflatoxins have been primarily characterized as hepatocarcinogens, they are also carcinogenic in other tissues including mammary and lung (Eldridge, Gould, & Butterworth, 1992; Yang et al., 2012; Yi et al., 2017). Aflatoxins have been linked to high levels of gallbladder cancers in Bolivia and Peru, as well as esophageal squamous cell carcinomas in China (Asai et al., 2012; Xue et al., 2019). Aflatoxins require bioactivation to reactive epoxides for genotoxic activity. The carcinogenicity of aflatoxins can result from metabolic activation of AFB₁ to a genotoxic epoxide, with a high prevalence of point mutations in the p53 gene (Chappell, Pogribny, Guyton, & Rusyn, 2016; Tam, Foley, Devereux, Maronpot, & Massey, 1999). AFB₁ exposure can induce genotoxicity as reflected by sister chromatid exchange, micronuclei, chromosomal alterations, and DNA and protein adducts (Humans, 2012). Aflatoxin precursors and metabolites can generate cytotoxic and immunosuppressive nongenotoxic activity (Bianco et al., 2012). AFB₁ exhibits the highest hepatotoxic potential and has synergistic carcinogenic effects with fumonisin B₁, another hepatocarcinogen, as well as with lipopolysaccharide (LPS), hepatitis C, and alcohol (Abbes, Ben Salah-Abbes, Jebali, Younes, & Oueslati, 2016; Barton, Ganey, & Roth, 2000; Chu et al., 2018). Aflatoxins have demonstrated genotoxic as well as nongenotoxic mechanisms of carcinogenesis including significant numbers of DNA-adducts from AFB₁ from HCC analysis (Chen, Zhang, Lu, & Santella, 1992; Wang, Xu, Yu, & Xu, 2017).

Triclosan (TCS) is a chemical that is commonly used in toothpaste, cosmetics, cooking materials, and other products as an antimicrobial but has recently been identified as a possible carcinogen. Up to 75% of people in the United States have likely been exposed to the chemical (Weatherly & Gosse, 2017). Importantly, this carcinogen exposure induces an inflammatory response even at very low doses by activating TLR4 signaling and altering gut microbiota predisposing to colon carcinogenesis (Yang et al., 2018). TCS has been found in fluids and tissues of people of all ages and has demonstrated a wide range of effects including endocrine disruption, induction of inflammation and oxidative stress, epigenetic alterations, and carcinogenicity (Yueh & Tukey, 2016).

The perfluorinated carboxylic acids (PFCAs) are a family of synthetic perfluorinated compounds that include perfluorooctanoic acid (PFOA, also known as C8), perfluorooctane sulfonate (PFOS), and perfluorononanoic acid (PFNA). PFOA has been used in the manufacture of items such as Teflon non-stick coating, Gore-Tex water-repellent gear, microwave popcorn bags, carpet, and fire-fighting foam (Nicole, 2013). Most carcinogens such as PFOA frequently exhibit several modes of action in causing cancer in animals. For example, PFOA can initiate and cause cancer through promoting oxidative stress and DNA damage (Klaunig et al., 2012; Yao & Zhong, 2005). PFOA can also stimulate breast and colon cancer cell invasion via matrix metalloproteinases (MMPs) (Miao et al., 2015; Zhang et al., 2014).

Nitrosamines including *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA) play a critical role in the initiation stage of carcinogenesis (Hong et al., 1991; Ratajczak-Wrona, Jablonska, Garley, Jablonski, & Radziwon, 2013). IARC has classified NDMA and NDEA as probable carcinogens to humans (Group 2A) (Wang, Yu, An, & Yang, 2016). NDMA induces cancer via a dose-response (Peto, Gray, Brantom, & Grasso, 1984). NDMA has demonstrated highly carcinogenic, mutagenic, and teratogenic activity (Dennehy & Loepky, 2005; Fitzgerald & Robinson, 2007; Zhang et al., 2016). Nitrosamines have been associated with an increased risk of many cancers including gastric, esophageal, nasopharyngeal, and bladder cancers (Bartsch,

Ohshima, Shuker, Pignatelli, & Calmels, 1990; Mirvish, 1995). N-nitroso compounds are used as a prototype carcinogens to induce various types of cancer in animal models, including liver, lung, bile duct and pancreatic (Sharma & Singh, 2014). In a large matched case-control study of pancreatic cancer, a significant positive association was found for NDEA, NDMA and pancreatic cancer (Zheng et al., 2018). Moreover, extensive studies have demonstrated the cytotoxicity, genotoxicity, carcinogenicity, mutagenicity, as well as reproductive and developmental toxicity of nitrosamines (Chen & Young, 2009; Yin et al., 2019; Zhao et al., 2008; Zhou, Boyd, Qin, Hrudey, & Li, 2009). Tumors in multiple organs have been induced by nitrosamine compounds in 39 species including higher primates (Bogovski & Bogovski, 1981). NDMA causes cancer both as a single dose and with long-term exposure to lower quantities (Pottegard et al., 2018). Other carcinogens such as dibenzo [*a,l*]pyrene (DBP) can potently transform cells, even in the absence of detected DNA adducts (Nesnow et al., 1997).

5. Carcinogenesis is a multi-stage, multi-mechanism process

Although epidemiology and studies with human tissues or cells are relevant to carcinogen exposure in humans, the mechanistic of action studies underlying carcinogenesis are focused in animal models for obvious ethical considerations. Laboratory animals are routinely utilized to mimic cancer in humans because there are more genetic, physiologic, biochemical, and metabolic similarities than differences to humans, large sample size, reproducibility, and feasibility to generate various cancers as well as study the mechanism of action of carcinogens (Maronpot et al., 2004). For example, NDMA is a powerful carcinogen which induces 100% incidence of transitional cell carcinoma of the urinary bladder in the rat and the Syrian golden hamster (Lijinsky & Taylor, 1975; Reznik-Schuller, 1981). An example of an initiation-promotion model is a DMBA-induced, phorbol 12-myristate 13-acetate (PMA) promoted or 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-promoted squamous cell carcinoma (Monga et al., 2014; Muller-Decker et al., 2002). A frequent model of colon carcinogenesis is induced by azoxymethane (AOM) and promoted with dextran sodium sulfate (DSS) (Hattori et al., 2019; Yamaguchi, Takai, Hosono, & Seki, 2014; Yang et al., 2018). *N*-nitrosomethylbenzylamine (NMBA)-induced tumorigenesis in esophagus is a model of human esophageal squamous cell carcinoma used for investigations of chemical carcinogenesis (Carlton et al., 2002; Yan et al., 2015). Nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung cancer is commonly used to study mechanisms of lung and smoking-induced carcinogenesis (Rioux & Castonguay, 1998; Zheng & Takano, 2011). 4-nitroquinoline 1-oxide (4-NQO) is utilized to induce tongue and oral cancers (Yanai et al., 2002). *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine (BBN) is used to create a mouse model of human muscle invasive bladder cancer to study histological, physiological, molecular, and mutational mechanisms of carcinogenesis (Fantini et al., 2018). Various chemically induced cancer models reflect various routes of exposure as tools to study mechanisms of carcinogens (Fig. 2).

Carcinogenesis, the process of initiating and stimulating cancer, is viewed as a multi-hit/multi-step process from the transition of normal cells into cancer cells via multiple mechanisms of action. In experimental cancer models, carcinogenesis is a multi-stage, multi-mechanism process, consisting of the "initiation," "promotion," and "progression" (Weinstein et al., 1984). The well-established mouse skin model is an important tool to study the mechanisms of multistage carcinogenesis (Marks, Furstenberger, Neufang, & Muller-Decker, 2003; Perez-Losada & Balmain, 2003; Slaga, Budunova, Gimenez-Conti, & Aldaz, 1996; Zoumpourlis, Solakidi, Papatoma, & Papaevangelou, 2003). Initiation can be induced by the topical application of the carcinogen 7,12-dimethylbenz[*a*]anthracene (DMBA), which is potently immunosuppressive. Here, mutations are not sufficient to induce malignant transformation. In the mouse skin model the first stage involves a tumor initiator with the genetic material of stem cells leading to changes in

growth control and/or differentiation. The major activity of tumor promoters is the specific expansion of the initiated stem cells in the skin (Perez-Losada & Balmain, 2003; Slaga et al., 1996). This can occur by both direct and indirect mechanisms that involve the direct growth stimulation of the initiated cells or cytotoxicity (Perez-Losada & Balmain, 2003). Promotion of tumorigenesis is generated by the topical application of phorbol esters such as TPA to the skin, leading to epithelial cell proliferation with increased expression of the ligand EGF as well as cyclin D1, c-Jun, c-Fos, and c-Myc (DiGiovanni, Rho, Xian, & Beltran, 1994). TPA-treated mice form multiple benign papillomas and conversion to malignant squamous carcinomas within 10–20 weeks. An initiated cell can be amplified to a premalignant lesion, such as a papilloma in the skin, a nodule in the breast, or a polyp in the colon eventually invading and metastasizing to distal sites (the "progression" phase) (Trosko & Carruba, 2017).

Notably, bacterial and viral infections can also be carcinogenic. *Helicobacter pylori*, hepatitis B or C, Epstein-Barr virus, and other infections are associated with increased cancer risk and carcinogenesis (Moss & Blaser, 2005). In a mouse model benzo(*a*)pyrene (BaP) and lipopolysaccharide (LPS) promote lung tumorigenesis (Huang et al., 2019). Multiple liver infections including liver fluke and *Clonorchis sinensis* administered with NDMA cause experimental cholangiocarcinoma (Kim, Bae, Choi, & Hong, 2019; Laothong et al., 2013). Hepatitis C virus is synergistic with AFB₁ in hepatocarcinogenesis including an enhanced inflammatory response and lipid peroxidation (Jeannot et al., 2012; London et al., 1995). While viral or bacterial infections can induce DNA methylation indirectly via chronic inflammation, certain viruses have direct activity on the epigenetics of host cells (Hattori & Ushijima, 2016).

Anti-bacterial agents can improve outcome by reducing associated inflammation and manipulating the microbiome in colon carcinogenicity models (Hattori et al., 2019). Parasite infection results in immune responses to generate nitrosamines (NDMA) in humans (Satarug et al., 1998). Additionally, carcinogens such as aflatoxin B₁ may promote influenza viral replication demonstrating synergy between environmental toxins and infections in causing cancer (Sun et al., 2018). The immune response to bacterial infection including stimulated eicosanoid production (e.g. prostaglandin E₂ (PGE₂)) and cytokines (e.g. IL-8) shows the tight association between carcinogenesis and the immune response, particularly an inflammatory response (Biarc et al., 2004).

6. Detection of carcinogens

An important strategy to prevent carcinogen-induced cancers is the detection of environmental carcinogens. Biomonitoring is critical to evaluating exposure to chemical carcinogens and involves the measurement of chemicals or their metabolites in various human samples including blood, urine, breast milk, and hair. Carcinogens can originate from various sources such as heavy metals, pesticides, industrial chemicals, commercial products and solvents. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis is a powerful analytical technique utilized to detect genotoxic and non-genotoxic chemicals (e.g. in the environment and food) at very low concentrations (Escriva, Font, Manyes, & Berrada, 2017). One-step competitive enzyme immunoassays have been developed for monitoring carcinogen (e.g. fumonisin B1 and ochratoxin A) contamination in food such as cereals (Liu et al., 2015; Shu et al., 2016). Many genotoxic carcinogens may also be detected via DNA binding assays with a new biosensor assay detecting carcinogens in contaminated food samples with a 24-base guanine rich DNA segment at ranges as low as 0.0001 ppm (Sani, Heng, Marugan, & Rajab, 2018). DNA adducts formed from genotoxic carcinogens can be identified in exposed people. Environmental carcinogens can be detected in serum, blood, and urine samples allowing for the measurement of chemicals such as tobacco and lead (Pirkle, Osterloh, Needham, & Sampson, 2005). Detection methods including electrochemical detection, mass spectrometry, fluorescence, and

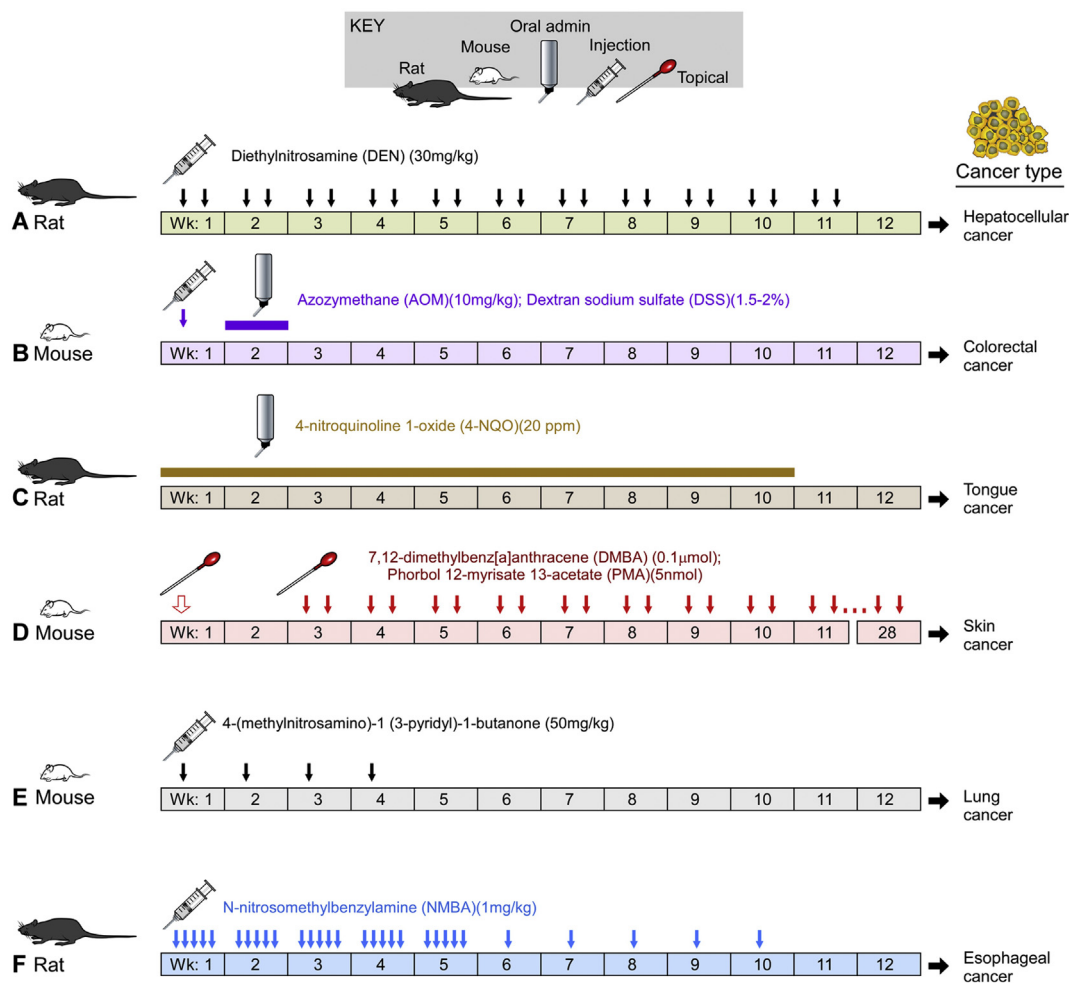


Fig. 2. Experimental models of carcinogen-induced cancers.

A) Intraperitoneal injection of male Sprague-Dawley rats with 30 mg/kg Diethylnitrosamine (DEN) twice a week for 11 weeks led to hepatocellular carcinoma B) Male C57BL/6J mice or BALB/c mice injected intraperitoneally week one with 10 mg/kg azoxymethane (AOM) and one week later given 1.5% or 2% dextran sodium sulfate (DSS) in the drinking water for one week leading to colon carcinomas. C) Male F344 rats given 20 p.p.m. 4-nitroquinoline 1-oxide (4-NQO) in drinking water for 10 weeks led to tongue squamous cell carcinoma or papilloma. D) NMRI mice exposed to single epicutaneous application of 0.1 μ mol 7,12-dimethylbenz[a]anthracene (DMBA) in acetone and two weeks later exposed twice a week to 5 nmol phorbol 12-myristate 13-acetate (PMA) for 28 weeks leading to skin papilloma and carcinoma. E) Male A/J mice were injected intraperitoneally with 50 mg/kg 4-(methylnitrosamino)-1 (3-pyridyl)-1-butanone (nicotine-derived nitrosamine ketone (NNK)) for 4 weeks led to lung adenocarcinoma. F) Male F344 rats injected subcutaneously with 1 mg/kg N-nitrosomethylbenzylamine (NMBA) 5 times a week for 5 weeks and then once a week for 5 more weeks led to esophageal papilloma and carcinomas.

immunohistochemistry, have advanced to accelerator mass spectrometry, which can detect about 1 in 10^{12} nucleotides if labeled with a heavy isotope. Importantly, this mass spectrometry technique can be used to identify DNA as well as protein adduct formation to more accurately determine chemical carcinogen exposure in human populations (Poirier, Santella, & Weston, 2000). A metabolomics approach can predict the activity of non-genotoxic carcinogens via alterations in the levels of eicosanoids and reactive oxygen species (Ament et al., 2013).

7. Mechanisms of pro-tumorigenic activity by carcinogens

7.1. Genotoxicity and mutations

Genotoxicity is measured via a series of in vitro and in vivo assays such as gene mutations in bacteria and mammalian cells; chromosomal aberrations, micronuclei formation, unscheduled DNA synthesis or DNA damage in mammalian cells and in rodents. Environmental mutagens such as ultraviolet light or cigarette smoke can lead to a high mutation rate in certain cancer types (e.g., skin and lung) (Srivastava, Reid, Ghosh, & Kramer, 2016). Carcinogens can act as environmental stress factors and induce cancer-promoting genotoxicity by binding and mutating DNA via adduct formation. Carcinogens are metabolized by the

human body to generate DNA-reactive species. Further, carcinogens can induce epigenetic changes which can lead to cellular transformation. DNA repair is critical for cancer prevention as DNA repair prevents the genetic mutations in normal cells (Kay et al., 2019). Examples of genotoxic carcinogens include NDMA or 4,4'-methylenedianiline (MDA) which bind directly to DNA generating adducts, DNA damage, and mutations (Kossler et al., 2015). Cancer risk is determined beyond only DNA mutations. Aflatoxin B₁ (AFB₁) exposure generates genetic mutations via DNA adducts and is associated with a specific mutational pattern, including a mutational signature of TP53, in humans with aflatoxin-induced HCC (Besaratina, Kim, Hainaut, & Pfeifer, 2009; Chawanthayatham et al., 2017). Nitrosamines, including NDMA, are mutagenic, genotoxic, and carcinogenic, even at low doses (Wagner, Hsu, Lagunas, Mitch, & Plewa, 2012; Wang, Qin, Dong, Lv, & Wang, 2017). Genotoxic carcinogens, such as NDMA, can induce DNA double-strand breaks in the comet assay and induce transformation of non-tumorigenic cells, such as NIH3T3 fibroblasts, to cancer causing cells (Le Hegarat et al., 2010; Liviach, Creus, & Marcos, 2011; Wang, Xu, et al., 2017; Winter et al., 2008). Genotoxicity induced by NDMA is further demonstrated in extrahepatic tissues of rats by the persistence of DNA damage in the lung, liver, kidney and nasal cavity (Brendler, Tompa, Hutter, Preussmann, & Pool-Zobel, 1992; Pool, Brendler,

Liegibel, Tompa, & Schmezer, 1990; Pool-Zobel et al., 1992). Also, N-nitroso compounds such as NDMA activate *ras* oncogenes, which play a pro-tumorigenic role in the development of various cancers (e.g., colon) (Tricker & Preussmann, 1991). DNA damage induced by NDEA increases micronuclei due to DNA breakage that could not be repaired, leading to an increase in chromosomal aberrations, and apoptotic cell death which can lead to cancer (Aiub et al., 2011; Fishbein et al., 2020). Thus, carcinogens can initiate tumor growth via genotoxic mechanisms in synergy with nongenotoxic processes including cell death, inflammation, oxidative stress, angiogenesis and tissue injury.

7.2. Nongenotoxic mechanisms

Non-cell-autonomous contribution to tumorigenesis from the non-transformed “host-tissue”, epitomized by tumor vasculature and inflammation, are crucial for tumor expansion and progression (Bhowmick, Neilson, & Moses, 2004; Folkman, 2007; Greten & Grivennikov, 2019). The tumor stroma is comprised of a variety of cells essential for tumor growth, including “tumor associated” fibroblasts, inflammatory cells (e.g. macrophages), and the pericytes surrounding the tumor endothelium (Hanahan & Coussens, 2012). Nongenotoxic carcinogens such as 1,4-dichlorobenzene (DCB), phenobarbital sodium (PB), benzene, asbestos, arsenic or piperonyl butoxide (PBO) do not interact directly with DNA but promote carcinogenesis via other key characteristics of carcinogens (Smith et al., 2016; Smith et al., 2020). Many carcinogens can exhibit both genotoxic and nongenotoxic activities. In a study of mRNA biomarkers following carcinogen exposure signatures of nongenotoxic carcinogens involved cell injury and necrosis leading to regenerative proliferation, as well as immunosuppression (Kossler et al., 2015). However, many chemicals considered to be nongenotoxic carcinogens actually possess certain genotoxic activities (Melnick, Kohn, & Portier, 1996). Importantly, chronic inflammation can lead to genetic instability and DNA damage without direct DNA adduct mechanisms of genotoxic carcinogens, which along with the ability to dysregulate DNA repair pathways potentially promotes carcinogenesis (Mantovani, 2009). Interestingly, both genotoxic, and non-genotoxic carcinogens generate oxidative stress as an underlying cause for carcinogenesis (Deferme, Wolters, Claessen, Briede, & Kleinjans, 2015). A new highly innovative model of carcinogenesis has been proposed as the Inflammation Somatic Model (ISM) based off the 2-stage somatic mutation model suggesting genotoxic effects are not sufficient to promote carcinogenesis and that inflammation as well as oxidative stress can prime tissues for cancer growth (Bogen, 2019). Importantly, AFB₁-induced hepatocarcinogenesis was prevented in rats with systemic administration of an anti-inflammatory and antioxidant CDDO-Im despite significant DNA adduct burden suggesting a protective effect and a DNA damage threshold (Eaton & Schaupp, 2014; Johnson et al., 2014). Thus, carcinogens can generate a feedforward cycle of tissue damage, inflammation, oxidative stress, mutagenesis, cell death, and subsequent regeneration and carcinogenesis (Fig. 3).

7.3. Inflammation and DNA damage

Inflammation generated from carcinogens, such as crystalline silica, can be a critical underlying mechanism promoting genotoxicity (Borm et al., 2011). Inflammation-induced cell proliferation potentially stimulates carcinogen-induced mutations (Kiraly et al., 2015). These elegant studies demonstrate a key mechanism by which inflammation can act synergistically with DNA damage to induce mutations that drive cancer progression and cancer recurrence (Kiraly et al., 2015). Inflammation enhances the production of reactive chemical species that damage DNA which may stimulate mutations (Kay et al., 2019). Inflammation and cholangiocarcinoma (bile duct tumors) can be induced by NDMA combined with infections (Wongsena et al., 2018; Yothaisong et al., 2014). Infection and NDMA-induced tumor tissue exhibit significantly

higher numbers of inflammatory cells (especially eosinophils), bile duct proliferation, and IL-17+ cell infiltration compared to normal livers (Wongsena et al., 2018). NDMA activates the PI3K-Akt/PKB pathway in human neutrophils which activates pro-inflammatory transcription factors NF- κ B, c-Jun, and FosB involved in nitric oxide (NO) production (through modulation of inducible nitric oxide synthase (iNOS) expression) (Ratajczak-Wrona et al., 2014). Thus, nitrosamines including NDMA stimulate inflammation via oxidative stress and an immune response (Hebels, Jennen, Kleinjans, & de Kok, 2009). The association between N-nitroso precursors and esophageal cancer may be modified by inflammation (Rogers et al., 1995). NDEA stimulates inflammatory cell infiltration (e.g. lymphocytes, neutrophils, eosinophils, and Kupffer cells), pro-inflammatory cytokines, including the IL-1 and IL-6 signaling pathway, as well as oxidative stress and proliferation in the liver, stomach and colon including cyclooxygenase (COX-2) expression in hepatic tissues (Ding, Wu, Wei, Shu, & Peng, 2017; Duan et al., 2014; Hebels et al., 2009; Mansour et al., 2019). Thus, inflammation plays a critical role in carcinogen-induced cancers.

Carcinogens such as NDMA also induce fibrosis leading to inflammation accompanied by the infiltration of lymphocytes, monocytes, granulocytes, and macrophages into the space of Disse (Koyama & Brenner, 2017). Activation of transcription factors including NF- κ B, c-Jun, and FosB in inflammatory cells underlie NDMA-induced NO synthesis/release (Ratajczak-Wrona et al., 2013). N-nitrosamines are activated by inflammatory cells, such as macrophages (Sheweita, El-Shahat, Bazeed, Abu El-Maati, & O'Connor, 2004). NDMA increases the proliferation of macrophages and expression of Raf in tumor-bearing lungs. Thus, the increase of both Raf and PCNA in the lung parenchyma surrounding NDMA-induced lung tumors suggesting an important lung tumor-macrophage interaction (Ramakrishna et al., 2002). IL-1 β is also able to contribute to fibrosis while TNF- α increases anti-apoptotic signals to avoid cell death (Amicone & Marchetti, 2018). Importantly, while carcinogens can induce inflammation, chronic inflammation can also increase carcinogen exposure and uptake within the body by weakening barrier functions (Greten & Grivennikov, 2019).

7.4. Pro-inflammatory signaling

Nuclear factor kappa B (NF- κ B) is a transcription factor that plays a critical role in inflammation, cancer invasion, regulation of apoptosis, oxidative stress, tumor progression, and metastasis (Karin, 2009; Karin & Greten, 2005; Shi et al., 2017). NF- κ B is activated by Toll-like receptors (TLR) signaling microbes, tissue damage, or primary cytokines and can trigger production of multiple pro-inflammatory cytokines, prostaglandin synthesis enzymes (including COX), nitric oxide (NO) synthase, angiogenic molecules, and other pro-tumorigenic mediators. STAT3/NF- κ B signaling is important in cancer-related inflammation associated with IL-6-induced chronic inflammation (Colotta, Allavena, Sica, Garlanda, & Mantovani, 2009). In addition to inflammation and oxidative stress, NF- κ B plays a larger role in avoidance of apoptosis, which permits tumor cells to evade death while also allowing non-tumor cells to accumulate damaged cells, mutations, and increased compensatory proliferation (Yang, Kim, & Seki, 2019). In a MYC transgenic model of hepatocellular carcinoma, deletion of NF- κ B essential modulator (NEMO) from hepatocytes led to accelerated tumorigenesis but also switched the tumor phenotype from HCC to combined hepatocellular cholangiocarcinoma as NF- κ B plays a modulatory role (He et al., 2019). PFOA can regulate MMPs (e.g. MMP2 and MMP9) release by regulating NF- κ B phosphorylation levels (Corsini et al., 2011; Miao et al., 2015). PFOA also induces the expression of the pro-tumorigenic molecules MMP2 and MMP9 via NF- κ B in breast cancer cells (Zhang et al., 2014). In a model of NDMA-induced esophageal carcinoma lyophilized black raspberries demonstrated anti-tumorigenic activity via the downregulation of NF- κ B signaling leading to reduced oxidative stress markers and upregulation of antioxidant enzymes GPx and SOD (Shi, Godschalk, & van Schooten,

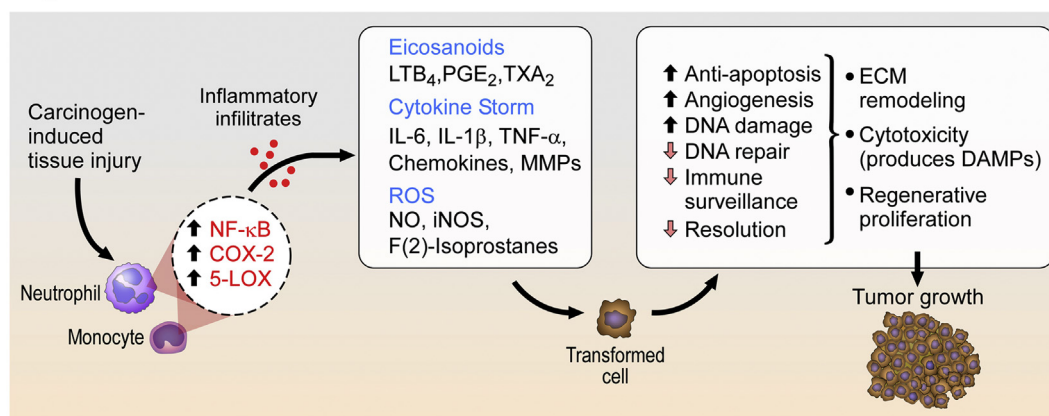


Fig. 3. Nongenotoxic mechanisms of carcinogenesis.

Following carcinogen exposure inflammation is induced leading to inflammatory infiltrates at the location of exposure. With the upregulation of NF-κB, COX-2, and 5-LOX inflammatory cells are triggered to release a storm of pro-inflammatory and tissue regenerative eicosanoids, cytokines, and reactive oxygen species. The factors generate DNA mutations, cell damage, and epigenetic alterations leading to cellular transformation. In addition, the inflammation and oxidative stress leads to upregulated anti-apoptotic mechanisms, angiogenesis, and DNA damage but downregulated DNA repair, immune surveillance, and resolution. Together, these processes driven by carcinogen induced inflammation alter the microenvironment allowing for extracellular matrix remodeling, cytotoxicity and damage-associated molecular pattern (DAMP) signaling, and regenerative proliferation resulting in tumor growth.

2017). Chemopreventive activity of natural compounds, including flavonoids, in nitrosamine-induced hepatocarcinogenesis can lead to anti-inflammatory and antioxidant activity with reduction of MMP and VEGF angiogenic signals via NF-κB inhibition (Bishayee et al., 2013; Liao et al., 2019; Sadeeshkumar et al., 2017; Sivaramakrishnan & Niranjali Devaraj, 2009; Subramanian & Arul, 2013). In a NDEA-induced hepatocarcinogenesis model, deletion of IκB kinase Beta (IKKβ) activates NF-κB from hepatocytes demonstrating increased tumorigenesis via ROS production, JNK activation, and hepatocyte death. However, hepatocarcinogenesis was decreased with IKKβ deletion from hepatocytes and Kupffer cells via reduced compensatory proliferation of hepatocytes demonstrating not only the importance of NF-κB signaling and its reduction in tumor associated immune cells, but the importance of cellular crosstalk in carcinogen-induced cancers (Maeda, Kamata, Luo, Leffert, & Karin, 2005). Thus, NF-κB activation can mediate carcinogen-induced inflammatory cancers.

7.5. Pro-inflammatory cytokines

Downstream signaling of NF-κB leads to chronic inflammation via upregulation of a series of pro-inflammatory cytokines and chemokines which promote carcinogenesis. Importantly, “cytokine storms” which are well established in infection (e.g. severe coronavirus (COVID-19) (Hammock, Wang, Gilligan, & Panigrahy, 2020; Panigrahy et al., 2020), are becoming appreciated in the setting of cancer therapy as immunotherapy and chemotherapy create an inflammatory tumor microenvironment via the release of a series of cytokines by immune cells (Filippou & Karagiannis, 2020; Gartung et al., 2019). In a model of NMBA-induced esophageal tumorigenesis, deficiency of riboflavin increases pro-inflammatory cytokines, elevating levels of peripheral neutrophils and monocytes, as well as the oxidative stress marker 8-OHdG (Pan et al., 2019). In addition, NDMA increases gut permeability, which accelerates the entry of LPS into the blood stream. Activated Kupffer cells then produce several cytokines and growth factors such as TNF-α, TGF-β1, PDGF, and IL-1β (George, Tsuchishima, & Tsutsumi, 2019). These signaling molecules drive chronic inflammation with continued carcinogen exposure as the pro-inflammatory cytokines such as IL-1β, IL-6, IL-22, IFN-γ, and TNF-α further activate NF-κB and TGF-β generating a feedforward pro-tumorigenic inflammatory cycle (George, Tsuchishima, & Tsutsumi, 2019). Further, co-exposure to AFB₁ and FB₁ increase carcinogenicity via upregulation of IL-10, IL-4,

lipid peroxidation (LP), and caspase 3 (Abbes et al., 2016). Anticarcinogenic compounds, such as cordycepin, a component of a rare caterpillar fungus, demonstrated protective effects in NDEA-induced HCC via downregulation of pro-inflammatory cytokines IL-6, IL-1β, IL-2, TNF-α and modulation of the PI3K-Akt-mTOR pathway (Keshari et al., 2017; Zeng et al., 2017). In an AOM/DSS model of colon carcinogenesis, an anti-cancer compound celastrol, reduces COX-2, TNF-α, IL-6, IL-1β and iNOS (Barker et al., 2018). Another natural product, flaxseed, was able to reduce lung tumorigenesis in an NNK carcinogen-induced model affected Akt/JNK/MAPK signaling pathways to reduce the carcinogen-induced pro-inflammatory IL-6, IL-8 and increase the anti-inflammatory IL-12α (Chikara et al., 2018). Demonstrating the importance of the pro-inflammatory cytokine TNF-α, TNF-α inhibition or deletion inhibits tumorigenesis in a NDEA-induced HCC model while reducing proliferation preventing activation of progenitor cells (Jing et al., 2018).

Other carcinogens such as asbestos have extensive changes on immune cells including expression of MMP7, CXCR5, CXCL13, and CD44 on exposed T cells and increased IL-6 initiating crosstalk between B and T cells with mesothelial and epithelial cells (Kumagai-Takei et al., 2018). Additionally, PFOA stimulates the production of critical pro-tumorigenic cytokines in multiple tissues including TNF-α, IL-1β and IL-6 in the liver or spleen, and increases proto-oncogenes (e.g. c-Myc activity in the spleen and thymus), which may be another important mechanism by which carcinogens cause cancer (Son et al., 2009; Yang, 2010). PFOA may therefore impair the host-protective immune response. Carcinogen-induced immunotoxicity also occurs in other animals such as harbor porpoises living in oceans contaminated by persistent organic pollutants, polychlorinated biphenyls, and polybrominated diphenyl ether, resulting in impaired cellular responses from atrophy of the thymus and splenic depletion (Beineke, Siebert, Stott, Muller, & Baumgartner, 2007).

7.6. Eicosanoids

Products of arachidonic acid metabolism called eicosanoids, including prostaglandins, leukotrienes, lipoxins, and other cyclooxygenase or lipoxygenase products are potent regulators of inflammation, angiogenesis, and tissue homeostasis (Greene et al., 2011; Imig & Hammock, 2009; Wang & Dubois, 2010). Arachidonic acid is cleaved from the cell membrane by phospholipase 2 (PLA₂) and other enzymes and when in the cytosol can be metabolized by 3 main branches: cyclooxygenase

(COX), lipoxygenase (LOX), and cytochrome P450 (CYP) enzymes. Studies on the arachidonic acid pathway initially focused on its role in inflammatory and cardiovascular diseases (Imig & Hammock, 2009; Zeldin, 2001). Most recently, arachidonic acid-derived eicosanoids have attracted increasing attention due to the increasing evidence of their role in cancer biology (Hyde & Missailidis, 2009; Sulciner et al., 2018). Besides epoxyeicosatrienoic acids (EETs), CYP also generate hydroxyeicosatrienoic acids (HETEs) (Zeldin, 2001) whose role in cancer biology is not as extensively characterized as the COX and LOX-derived eicosanoids (Guo et al., 2008; Moreno, 2009).

Eicosanoid dysregulation can lead to chronic inflammation and oxidative stress or prevent pro-apoptotic signals generating the accumulation of damaged cells. The ratios of eicosanoids with opposing effects can be used to predict pathology following carcinogen exposure (Jelinska, Bialek, Gielecinska, Mojska, & Tokarz, 2017). Interestingly, NNK can interact with beta-adrenergic receptors to directly stimulate the release of arachidonic acid, which could lead to aberrant eicosanoid production (Schuller, Tithof, Williams, & Plummer 3rd, 1999). In addition to their roles in inflammation, the eicosanoid pathways also play a role in metabolism and bioactivation of carcinogens. CYP450 enzymes are also the main activators of many environmental carcinogens as they play a large role in drug and toxin metabolism. Interestingly, COX isoenzymes generate ROS and also may be responsible for bioactivation of multiple carcinogens via metabolism of aromatic and heterocyclic amines or polycyclic hydrocarbons which may account for the carcinogen specific activity of cyclooxygenases (Wiese, Thompson, & Kadlubar, 2001). Additionally, LOX is a peroxidase also generating ROS and free radicals may play an important role in the bioactivation of NNK via oxidation as the CYP450 enzymes were found to be only partially responsible for its activation (Smith, Stoner, & Yang, 1995).

The COX pathway leads to pro-tumorigenic and pro-inflammatory activity in multiple models, including carcinogen-induced cancers. COX-2 activation can sensitive tissues to genotoxic carcinogens (Muller-Decker et al., 2002). A tobacco carcinogen upregulates COX-1 expression correlated with NF- κ B activation (Rioux & Castonguay, 2000). Carcinogenesis of the skin upregulates COX-2 and prostanoid signaling but suppression of COX-2 and PGE₂ synthase may have anti-tumorigenic effects (DeCicco-Skinner et al., 2013; Enoki et al., 2012). COX-2 was also demonstrated to stimulate tumorigenesis in a breast cancer model as COX-2 deletion reduced inflammation-associated carcinogenesis (Markosyan et al., 2011). NF- κ B activation also increases colon carcinogenesis via upregulation of COX-2 leading to aberrant eicosanoid production (Li et al., 2019). Interestingly, a flavonoid with anti-cancer properties regulates NDEA-induced carcinogenesis by downregulating COX-2/PGE₂, as well as increasing antioxidants (Siddiqi, Saidullah, & Sultana, 2018). However, the role of COX-2 may be context-dependent as COX-2 overexpression and upregulated prostaglandins can suppress tumorigenesis in skin (Bol et al., 2002). Moreover, COX-2 can also be host-protective by generating anti-inflammatory and pro-resolution lipid mediators from arachidonic acid including lipoxins and pro-resolution prostaglandins (Gilroy & Colville-Nash, 2000; Levy, Clish, Schmidt, Gronert, & Serhan, 2001).

The lipoxygenase (LOX) pathways also play important roles in carcinogen-induced cancers via inflammation. Interestingly, ethanol stimulates carcinogenesis in a 4-NQO oral carcinogenesis model via induction of the 5-LOX pathway (Guo, Wang, Zhang, Sun, & Chen, 2011). Similarly, use of a 5-LOX inhibitor (garcinol) or herbal extracts (zyflamend) block LTB₄ to exhibit chemopreventive activity in a DMBA-induced oral carcinogenesis model (Chen et al., 2012; Yang et al., 2008). Interestingly, cumin, a common spice used in curries, contained curcumin which inhibited TPA-induced skin inflammation by inhibiting the LOX metabolites 5-HETE and 8-HETE, as well as multiple prostaglandins (Huang et al., 1991). In an AOM/DSS model of colon inflammation-associated carcinogenesis, cysteinyl leukotriene receptor 1 (CysLT1R) deletion reduced pro-inflammatory cytokines leading to decreased leukocyte and macrophage infiltration via eicosanoid

regulation (Osman et al., 2017). However, 15-lipoxygenase-1 (ALOX15) generates other lipid mediators which terminate inflammation, and downregulates NF- κ B signaling, IL-6, IL-1 β , and TNF- α in AOM/DSS-induced colorectal cancer-associated inflammation (Tian et al., 2017). Zileuton, a 5-LOX inhibitor, is more potent in inhibiting DMBA oral carcinogenesis than celecoxib, a selective COX-2 inhibitor, via suppression of eicosanoids. A leukotriene A₄ hydrolase (LTA₄H) inhibitor suppresses carcinogenesis via eicosanoid regulation (Sun et al., 2006). However, as each of these eicosanoid pathways play key roles in carcinogen-associated inflammation, dual eicosanoid inhibition (e.g. dual COX-2/sEH inhibition) may exhibit more potent anti-tumor activity than targeting a single eicosanoid pathway (Fishbein et al., 2020; Gartung et al., 2019; Zhang, Panigrahy, et al., 2014). Supplementation of vitamin E or selenium in NMBA-exposed esophagus inhibited carcinogenesis via downregulation of both COX and LOX pathways inhibiting proliferation and angiogenesis (Yang et al., 2011).

In the context of arachidonic acid metabolism CYP450 enzymes generate monohydroxyeicosatrienoic acids (HETEs) and epoxyeicosatrienoic acids (EETs) (Panigrahy, Greene, Pozzi, Wang, & Zeldin, 2011; Zeldin, 2001). CYP450-derived eicosanoids including EETs and epoxydocosapentaenoic acids (EDPs) play a key role in angiogenesis, tumor growth, and metastasis (Imig & Hammock, 2009; Panigrahy et al., 2012; Zhang et al., 2013). Epoxygenated fatty acids (EpFA), eicosanoid metabolites generated by CYP450, were increased in the plasma and colon of azoxymethane (AOM)/dextran sodium sulfate (DSS)-induced colon carcinogenesis (Wang et al., 2019). Generally, EETs, which are further metabolized into pro-inflammatory dihydroxyeicosatrienoic acids (DHETs) by soluble epoxide hydrolase (sEH), exhibit anti-inflammatory and pro-angiogenic activity (Gartung et al., 2019; Panigrahy et al., 2012; Zhang et al., 2014). Analysis of patients with HCC demonstrated favorable survival prognostics with increased CYP4F2, CYP4F12, and CYP4V2 expression (Eun, Cho, Lee, Seong, & Kim, 2018). Pharmacologic inhibition or genetic ablation of CYP monooxygenases, which generate epoxygenated fatty acids including EpOME, suppressed AOM/DSS-induced colon tumorigenesis (Wang et al., 2019). 2,3,7,8-tetrachlorodibenzop-dioxin, an environmental carcinogen, activates the aryl hydrocarbon receptor (AHR) transcription factor for CYP enzymes leading to dysregulated eicosanoid production (Diani-Moore, Ma, Gross, & Rifkind, 2014). Importantly, following dioxin exposure these arachidonic acid metabolites were found in the heart of a chick embryo even though the heart lacks enzymes to metabolize arachidonic acid, suggesting systemic movement of eicosanoids may generate profound and chronic effects (Diani-Moore et al., 2014).

7.7. Oxidative stress

Oxidative stress results from an imbalance between production of free radicals and reactive oxygen or nitrogen species (RONS) and their elimination by through protective mechanisms, including antioxidants (Tu, Wang, Li, Liu, & Sha, 2019). Inflammation can stimulate tumor-promoting and tumor-initiating reactive chemical species, which can damage DNA leading to genetic instability, a hallmark of cancer, and oxidative stress. Oxidative and endoplasmic reticulum stress is often intertwined in inflammatory processes and is also induced by environmental carcinogens to promote tumor growth (Fishbein et al., 2020; Nowsheen, Aziz, Kryston, Ferguson, & Georgakilas, 2012). The importance of oxidative stress is demonstrated via nongenotoxic carcinogens, such as dicyclanil hepatocarcinogenesis and arsenic, and their ability to induce DNA damage indirectly via increased ROS production, mitochondrial damage, upregulation of stress genes, and biomarkers such as 8-hydroxy-deoxyguanosine (8-OHdG) (Liu et al., 2005; Moto et al., 2006). Inflammation, including upregulation of COX-2, recruits leukocytes including neutrophils which can trigger oxidative damage, thus anti-inflammation can also prevent oxidative insult during tumorigenesis (Murakami et al., 2000). Interestingly, neutrophils can also generate further production of N-nitroso carcinogens during intestinal

inflammation promoting colon carcinogenesis (Vermeer et al., 2004). NDMA increases iNOS in neutrophils associated with carcinogenesis (Ratajczak-Wrona et al., 2014). Red meat, known to contain multiple carcinogenic compounds including nitrosamines, polycyclic aromatic hydrocarbons (PAHs), and heterocyclic aromatic amines (HAAs), increases the risk of human cancers via lipid peroxidation, inflammation, and generation of reactive oxygen species (Turesky, 2018). N-nitroso compounds and their metabolism stimulate pro-inflammatory reactive oxygen species causing cellular injury (Aiub, Pinto, & Felzenszwalb, 2003, 2004; Akshatha, Raval, Arpitha, Raval, & Ghodasara, 2018; Bansal, Bansal, Soni, & Bhatnagar, 2005b). Oxidative stress-induced cell injury plays a crucial role in NDEA-induced carcinogenesis as a single necrogenic dose of NDEA enhances levels of hepatic lipid peroxidation (LPO) and conjugated dienes as markers of oxidative stress (Bansal, Bansal, Soni, & Bhatnagar, 2005a).

The genotoxic activity of nitrosamine compounds such as NDMA can stimulate pathways of oxidative stress and inflammation leading to carcinogenesis (Hebels et al., 2009). NDMA stimulates reactive oxygen species and induces toxicity including a dramatic change in the body weight of animals (Sharma & Singh, 2014). The NDMA-induced genotoxic activity and DNA damage in cancer cells can be measured by DNA strand breaks and oxidative DNA damage induced by intracellular reactive oxygen species (ROS). ROS are an important mechanism for tumor promotion and oxidative stress. As a consequence of NDEA-induced oxidative and nitrosative DNA damage (Klaunig & Kamendulis, 2004; Unsal & Belge-Kurutas, 2017), inflammatory markers such as IL-1 β and TNF- α are significantly elevated in liver, stomach and colon (Mansour et al., 2019). The NDMA-mediated increase in NO production may also contribute to oxidative stress, a factor in the pathophysiology of numerous immune disorders. NO is a versatile regulator of numerous bodily processes and a major signaling molecule (Ratajczak-Wrona et al., 2013), while iNOS is found in various cells, including neutrophils (Beck et al., 1999; Mantovani, Cassatella, Costantini, & Jaillon, 2011). Thus, carcinogens could regulate immune cells and inflammation, in part, by affecting NO formation which may lead to modulated immune function.

Other carcinogen-induced processes, such as fibrosis, contribute to the vicious cycle of inflammation and oxidative stress during carcinogenesis (Ahmad & Ahmad, 2018; George, Tsuchishima, & Tsutsumi, 2019). These processes lead to cellular injury and initiate inflammatory responses by releasing a variety of pro-inflammatory cytokines and growth factors that trigger activation and transformation of resting hepatic stellate cells into myofibroblast-like cells, which initiate increased synthesis of connective tissue proteins, especially collagens (George, Tsuchishima, & Tsutsumi, 2019). NDMA-induced liver fibrosis results in the enhanced oxidative stress leading to the generation of oxyradicals which can bind to proteins and cellular constituents (Ahmad & Ahmad, 2018). Further, oxidative stress and ROS can lead to fibrosis and abnormal healing following injury which can lead to cellular transformation and carcinogenesis (George, Tsuchishima, & Tsutsumi, 2019; George, Tsutsumi, & Tsuchishima, 2019).

Many antioxidants exhibit anti-carcinogenic activity in experimental models. Antioxidants may be used for the prevention of arsenic-induced carcinogenesis, NDMA-induced hepatocellular carcinogenesis, and NDEA-induced esophageal carcinogenesis (Hei & Filipic, 2004; Shetty, Kumar, & Bharati, 2019; Shi, Godschalk, & van Schooten, 2017). Tocopherols, a form of vitamin E, have been suggested to have antioxidant properties, including ability to physically trap nitrogen species leading to protection in an AOM/DSS model of colon carcinogenesis (Bansal et al., 2005b; Ju et al., 2009; Lambert et al., 2009; Lee, Ju, et al., 2009). A flavonoid antioxidant, silymarin, inhibits a 4-NQO-induced tongue carcinogenesis model leading to increased apoptosis and decreased proliferation (Yanai et al., 2002). Citral suppressed NDEA-induced HCC via inhibiting the suppression of antioxidants triggered by carcinogen exposure (Krishnan et al., 2020).

Nuclear factor erythroid 2-related factor 2 (Nrf2) is an important regulatory molecule of oxidative stress and a potential therapeutic agent in carcinogen-induced cancer. Inhibition of Nrf2 stimulates oxidative stress, inflammation, circulating cytokines, and proliferation leading to intestinal carcinogenesis (Cheung et al., 2014). NDEA stimulates inflammatory and oxidative stress markers via COX-2 upregulation, yet ginger extract demonstrated protective effects via Nrf2 activation to suppress oxidation and inflammation (Mansour et al., 2019). AFB₁ upregulates Nrf2 signaling in response to oxidative stress, although expression of the SOD antioxidant is downregulated (Wang et al., 2017). In liver carcinogenesis Nrf2 activation as a result of AHR and CYP1B1 downregulation led to restoration of liver tissue and reduced oxidative damage (Bose et al., 2020). A novel compound, CDDO-Im, with anti-inflammatory properties also activates Nrf2 to potentially inhibit AFB₁-induced carcinogenesis in 100% of animals (Eaton & Schaupp, 2014; Johnson et al., 2014). A structurally similar compound in the family of synthetic pentacyclic oleanane triterpenoids, CDDO-Me is in clinical development. Further, a family of compounds with the same activity but simpler synthesis, tricyclic-bis-enone (TBE) compounds, is also potent in reducing oxidative stress to inhibit AFB₁-induced carcinogenesis (Liby et al., 2008). Thus, inhibition of oxidative stress is a potent therapeutic approach to carcinogen-induced cancers.

Clinic inflammatory scores, including neutrophil to lymphocyte ratio or platelet to leukocyte ratio, can also predict cancer patient outcome (Diaz-Beveridge et al., 2018; He & Lin, 2017; Liu et al., 2017; Peng et al., 2017). Pro-inflammatory cytokines such as IL-6 and IL-8 may be used to predict patient outcome for example in HCC patients undergoing transarterial chemoembolization (Loosen et al., 2018). In an animal model of NDEA-induced HCC, the hepatic inflammation-fibrosis-cancer axis (IFC), including upregulation of TNF- α , IL-6, TGF- β 1 and JAK2/STAT3 signaling, may predict carcinogen exposure after week 14–22 (Ding et al., 2017). The neutrophil/lymphocyte ratio (NLR) could be a prognostic predictor for urologic tumors, including kidney tumors. Interleukin-1 β (IL-1 β) and interleukin (IL-18) are products of activated inflammasomes that play central roles in innate immunity and inflammation. C-reactive protein (CRP), a prototypical pro-inflammatory cytokine and marker, may also be reflective of tumor progression through inflammation. An elevated serum level of CRP as an inflammation biomarker may portend a poor prognosis of cancer patients, including kidney and bladder cancer (Dai et al., 2014; Michigan, Johnson, & Master, 2011).

7.8. Cell death (“debris”)-generated inflammation

Cancer therapy-generated tumor cell debris can stimulate tumor growth via a storm of pro-inflammatory cytokines and eicosanoids (Chang et al., 2019; Gartung et al., 2019; Sulciner, Serhan, et al., 2018). Cellular debris (apoptotic cells) and inflammation-induced cellular damage can induce cellular proliferation to activate a “Phoenix Rising” Pathway) to promote wound healing and tissue regeneration of the damaged tissue (Li et al., 2010). Cytotoxicity-induced pro-inflammatory activity of carcinogens and tissue damage/injury may lead to inflammation as a cancer co-initiator and predict low or negligible risk at noninflammatory carcinogen doses (Bogen, 2019). Inflammation activated-stem cells involved in tissue repair in damaged tissue and may lead to cancer if the normal termination of inflammation is suppressed by mutations (Bogen, 2019). Non-mutagenic cytotoxic agents such as alcohol, chloroform, and ultraviolet light induce cell death triggering cytokines which stimulate hyperplasia and tumor growth (Chang et al., 2019; Gartung et al., 2019; Sulciner, Serhan, et al., 2018; Trosko, 2001). While carcinogen-induced inflammation and oxidative stress can lead to cellular damage, cell death can play a complex role in carcinogenesis by either stimulating or inhibiting tumor growth (Bonavita, Pelly, & Zelenay, 2018; Sulciner, Serhan, et al., 2018). While cell death is beneficial to prevent accumulation of cells with accumulated DNA damage, it also generates stress signals leading to more

inflammation and regenerative proliferation which can stimulate tumor growth. Carcinogens in tobacco smoke, including nicotine-derived nitrosamine ketone (NNK), trigger the IKK β /JNK1 mediated apoptotic pathway leading to a subsequent proliferation response, while other carcinogens including aflatoxins trigger cell death via ROS production (Sakurai et al., 2008; Takahashi, Ogata, Nishigaki, Broide, & Karin, 2010; Zhang et al., 2015). Oxidative stress induced by carcinogens as nitric oxide induces cell death associated with COX-2 and PPAR γ signaling (Lim, Jang, & Surh, 2003). In a naphthalene-induced nasal tumor model a dual mode of action links genotoxic and cytotoxic effects (Bogen, 2019). Interestingly, in a NDEA-induced model of HCC, prevention of hepatocyte apoptotic pathways and inflammatory pathways inhibited carcinogenesis (Wree et al., 2015). Persistent apoptosis is a determinant for hepatocellular carcinoma, and lower rates of apoptosis via lower caspase 8 are associated with less aggressive disease (Boege et al., 2017).

As damage associated molecular patterns (DAMPs) released by dead cells generate inflammation, tissue injury and signal through NF- κ B, the accumulation of these dead cells may promote carcinogenesis ((He et al., 2019); Hernandez et al., 2018). Chemotherapy-generated apoptotic tumor cells ("tumor cell debris") stimulate macrophages to release a cytokine and eicosanoid storm promoting the chronic inflammatory environment during tumor growth (Chang et al., 2019; Gartung et al., 2019; Sulciner, Serhan, et al., 2018). Tumor cells killed from chemotherapy or radiation, release soluble factors and extracellular vesicles, which can induce an immunosuppressive tumor microenvironment to trigger regenerative processes leading to increased proliferation of remaining tumor cells (Jiang, Gu, Dai, Huang, & Tian, 2020; Keklikoglou et al., 2019). Interestingly, NDEA-induced hepatocellular carcinoma was stimulated by NADPH oxidase 1 (NOX1) induction of pro-inflammatory cytokines including TNF- α and IL-6 via DAMPs released by dying hepatocytes demonstrating the importance of immune and non-immune cell crosstalk in carcinogenesis (Liang et al., 2019). In a study of three nongenotoxic carcinogens, cadmium chloride, methyl carbamate, and lithocholic acid, genome wide methylation analysis demonstrated changes in cancer and surveillance pathways, but also in autophagy pathways a mechanism by which the body clears damaged cells (Hwang, Yeom, Eom, Lee, & Lee, 2019). Another nongenotoxic carcinogen, fumonisin B1, induces carcinogenesis via induction of apoptosis and necrosis leading to regenerative proliferation (Dragan et al., 2001). NDMA-induced cytotoxic activity and apoptosis in various organs (e.g., large bowel) can lead to inflammation (Potten, Li, O'Connor, & Winton, 1992). In a liver model, NDMA-induced DNA adducts and cell necrosis were concentrated mainly in hepatocytes, suggesting the release of mitogenic stimuli to stimulate the proliferation of the cells (Lee, Cameron, & Archer, 1993).

Natural compounds, including rice bran, with anti-carcinogenic effects induce apoptosis and thus reduce the accumulation of mutated cells, but simultaneously inhibit inflammation and regenerative proliferation (Badr El-Din, Ali, Othman, French, & Ghoneum, 2020). Many environmental carcinogens dysregulate the cycles of cell death and proliferation by regulating pro- and anti-apoptotic proteins such as Bax, Bcl-2, caspases and other signaling cascades. Thiamethoxam-induced hepatocarcinogenesis not only stimulated oxidative stress and inflammation in rabbits, but upregulated anti-apoptotic proteins leading to transformed cell survival (El Okle, El Euony, Khafaga, & Lebda, 2018). An initiating hepatocarcinogenic dose of NDEA stimulated the apoptotic index via increased caspase-3 and Bax expression (Kang, Wanibuchi, Morimura, Gonzalez, & Fukushima, 2007).

7.9. Dormancy escape

Dormancy is a stage in cancer progression where the cancer cells are not dividing but survive in a quiescent state. Dormant tumors have been identified at autopsy in normal adults who died of trauma and without prior history or clinical evidence of cancer (Folkman, 2001; Harach,

Franssila, & Wasenius, 1985). The reported incidence of these dormant tumor cells has been as high as 39% for in situ breast carcinoma, 46% for in situ prostate cancer, and 36% for thyroid carcinoma (Black & Welch, 1993). Thus, it is highly likely that many humans exposed to carcinogens already exhibit dormant tumors. These dormant tumors can act as a tumor initiator and promotion of tumor dormancy escape occurs when exposed to carcinogens. The trigger of dormancy escape, as numerous animal studies have shown, is typically of non-genetic nature and can include: wounding at a site near or distant from the site of the occult tumor, surgery, chemotherapy, radiation, biopsy, sustained inflammation, stimulated angiogenesis or the presence of non-mutagenic factors that perturb the metabolism of cells (Panigrahy et al., 2012; Panigrahy et al., 2019). Cell death can paradoxically trigger dormancy escape by the stimulation of pro-inflammatory and pro-angiogenic cytokines which suggests that cell death generated by carcinogens can stimulate tumor growth (Fishbein et al., 2020; Gartung et al., 2019; Sulciner, Gartung, et al., 2018). In experimental models, tumor dormancy escape can occur by 90 days post-tumor cell injection of dormant tumor cells by the stimulation of angiogenesis (Panigrahy et al., 2012).

7.10. Carcinogen-induced immunosuppression

A dysregulated immune system following carcinogen exposure can lead to chronic inflammation, but also immunosuppressive activity may further damage the host response to protect from cancer. Chronic inflammation, including signaling molecules such as PGE₂, can lead to immunosuppression in the tumor microenvironment (Wang & DuBois, 2016, 2018). For example, pro-tumorigenic activity of NNK on alveolar macrophages modulated by PGE₂ included immunosuppression (Therriault, Proulx, Castonguay, & Bissonnette, 2003). In a DMBA model of skin carcinogenesis, in xeroderma pigmentosa mice which are more susceptible, the carcinogen-induced not only pro-inflammatory mediators but also increased systemic immunosuppression (Miyachi-Hashimoto, Kuwamoto, Urade, Tanaka, & Horio, 2001). In an AOM/DSS model of colon carcinogenesis myeloid derived suppressor cells and their chemotaxis via CXCR2 promoted tumorigenesis via inhibition of CD8+ activity (Kato et al., 2013). Importantly, chronic exposure to carcinogens such as NDMA induce marked and persistent immunosuppression of cellular and humoral responses (Desjardins, Fournier, Denizeau, & Krzystyniak, 1992).

Carcinogens, including aflatoxins and tamoxifen, disrupt inflammation resolution and the innate immune system by impairing host-protective neutrophil and macrophage phagocytosis of debris (Lukac, Kusic, Kordic, Koncar, & Bolanca, 1994; Mannerstrom, Maenpaa, Toimela, Salminen, & Tahti, 2001; Mehrzad et al., 2011; Moon et al., 1999). In addition, NDMA can negatively impact neutrophil phagocytic activity, oxygen metabolism, and functions associated with production and release of immunologically-active molecules (Jablonski, Jablonska, & Moniuszko-Jakoniuk, 2007), thus impairing inflammation resolution. NDMA is immunotoxic to immune cells, cell-mediated immunity and inflammation (e.g., mononuclear cells and neutrophils (PMN)) (Holsapple, Bick, & Duke, 1985; Jablonski et al., 2011). Reduced host resistance to infectious agents (reduced response to streptococci and influenza challenge) following NDMA administration also indicate systemic toxicity on humoral immunity (Thomas et al., 1985). NDMA also impairs the cellular immune response by altering the production and/or maturation/differentiation of bone marrow stem cells into functional macrophages (Myers, Dickens, & Schook, 1987; Myers, Pullen, & Schook, 1986; Myers, Schook, & Bick, 1987).

Cytotoxic carcinogens can trigger cell death of lymphocytes leading to an immunosuppression without the ability to control the accumulating transformed cells (Badr, El-Reda, El-Gamal, & Farid, 2020; Chen et al., 2016). NDMA may impair the host immune response and exhibit immunotoxicity, including increased apoptosis (death) of leukocytes and production of pro-tumorigenic reactive oxygen species (Iwaniuk

et al., 2015; Jablonski et al., 2001; Jablonski et al., 2011; Nowak et al., 2018; Ratajczak-Wrona et al., 2014). PFOA also exhibits immunotoxic potential in mice (Son et al., 2009). The toxic activity of NDMA greatly influences the biological activity and lifespan of immune cells (Iwaniuk et al., 2015), including neutrophils, by inducing a respiratory burst and subsequent release of ROS responsible for the apoptosis of these cells (Jablonski et al., 2001). NDMA can also modulate the apoptosis of human neutrophils by regulating the expression of death receptor DR5 as well as through the release of its soluble form (sDR5) (Jablonski et al., 2007). In a prospective clinical study the hepatocellular carcinoma tumor microenvironment exhibited pro-angiogenic and pro-inflammatory activity, but also a distinctly immunosuppressed environment including upregulation of PD-1, PD-L1 and FoxP3 regulatory immune cells in patients (Critelli et al., 2017; O'Rourke, Sagar, Shah, & Shetty, 2018).

Carcinogens generate further immune suppressed environments through inhibition of the adaptive immune system. One of the primary cell targets of NDMA is the B-lymphocyte, thus likely reducing the overall reactivity of both T- and B-lymphocytes as exposure suppresses the IgM antibody-forming cell response to sheep red blood cells in a dose-dependent manner (Holsapple, Mc Nerney, Barnes, & White Jr., 1984; Holsapple, Tucker, Mc Nerney, & White Jr., 1984; White Jr. & Holsapple, 1984). NDMA depressed T-lymphocyte function as measured by T-cell proliferation in response to T-cell mitogens (Holsapple et al., 1985). NDMA suppresses T-cell-dependent antibody response (Jeong & Lee, 1998). PFOA causes splenic and thymic atrophy with suppressed thymocyte proliferation (Yang, Xie, Eriksson, Nelson, & DePierre, 2001). PFOA also inhibited CD4⁺CD8⁺ populations, demonstrating impaired splenocyte and thymocyte maturation from CD4⁻CD8⁻ to CD4⁺CD8⁺ cells (Son et al., 2009). Normally, immune cells, such as T lymphocytes, secrete soluble factors (cytokines) that activate phagocytes to destroy the pathogens they have internalized (Yang, Xie, Alexson, Nelson, & DePierre, 2002). Furthermore, phagocytes utilize antibodies generated by B lymphocytes to allow them to recognize and destroy pathogens (Hansson, 1997; Stemme et al., 1995). Carcinogens such as aflatoxins generate tumor cell death ("debris") that can trigger tumor dormancy escape via an eicosanoid and cytokine storm of pro-inflammatory as well as pro-angiogenic mediators (Fishbein et al., 2020). Thus, carcinogen exposure may disrupt host-protective anti-tumor host immune responses and impair the resolution of inflammation.

8. Therapeutic approaches

8.1. Resolution and anti-inflammation are not equivalent

Epidemiologic evidence suggests that the nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin reduces the risk and incidence of cancer (Gilligan et al., 2019; Wang & Dubois, 2010). However, severe toxicity including bleeding has precluded the routine application of anti-inflammatory agents in the chemoprevention and treatment of cancer. Moreover, selective cytokine or eicosanoid blockade may not be sufficient to prevent carcinogen-induced cancers (Fishbein et al., 2020; Gartung et al., 2019). Inflammatory transcription factors such as Nrf2 can reduce the DNA damage by neutralizing reactive chemicals with antioxidants and upregulating DNA repair pathways (Kay et al., 2019). The triterpenoid oleanane, a highly potent anti-inflammatory agent, prevents hepatocellular carcinoma (HCC) in an experimental rat model while only partially reducing AFB₁-DNA adducts (Johnson et al., 2014). Other anti-inflammatory mechanisms designed to reduce cancer risk include a healthy diet, exercise, antioxidants, and spices (e.g. curcumin).

A new potentially-paradigm shifting direction of inflammation research has emerged with the discovery of the autacoid superfamily of specialized pro-resolving lipid autacoid mediators (SPMs), including resolvins, maresins, protectins, and lipoxins, as key mediators in the resolution of inflammation, possessing potent inflammation clearing

activity without being immunosuppressive (Mukherjee, Marcheselli, Serhan, & Bazan, 2004; Serhan et al., 1984; Serhan et al., 2002; Serhan et al., 2009). The resolution of inflammation is now appreciated to be an active process regulated by SPMs, which are endogenously produced in multiple tissues throughout the human body (Serhan & Levy, 2018). Pro-resolution mediators resolvins may have a dual function in cancer associated-inflammation: inhibiting the pro-inflammation activities of pro-inflammatory cytokines while activating macrophages to phagocytize tumor-promoting cellular debris, thereby preventing chronic inflammation that stimulates tumor growth. Targeting endogenous lipid autacoid mediators such as lipoxins and resolvins offers an entirely new approach to cancer therapy via cell autonomous and non-cell autonomous mechanisms in the tumor microenvironment (Bai et al., 2019; Gilligan et al., 2019; Kuang et al., 2016; Lu, Xu, Yin, Xu, & Jiang, 2018; Panigrahy et al., 2019; Shan et al., 2020; Sulciner, Serhan, et al., 2018; Sun et al., 2019; Ye et al., 2018; Zhong, Lee, & Surh, 2018).

8.2. Cyclooxygenase (COX) inhibition

Selective COX-2 inhibitors (coxibs) and nonselective NSAIDs can reduce the incidence of cancers in humans and in experimental models (Wang & Dubois, 2010). The risk for colorectal cancer is increased in patients with inflammatory bowel disease. COX-2 and PGD₂ have been identified as potential therapeutic targets for the chemoprevention of colon cancer (Wang & Dubois, 2010). However, COX-2 is also a pivotal enzyme necessary to stimulate the resolution of inflammation and production of specialized pro-resolving mediators (SPMs) such as lipoxins (Wallace, 2006). Given the important roles of COX-2 (in part through biosynthesis of PGD₂) in the resolution of inflammation, inhibition of COX-2 may be "resolution toxic" (Gilroy et al., 1999; Panigrahy et al., 2019; Serhan & Levy, 2018). Inflammation (e.g. paw swelling) in COX-2 KO mice failed to resolve and exhibited significant leukocyte infiltration. COX-2 is an important source of PGD₂ (15-deoxy-Δ¹²⁻¹⁴PGJ₂) and is also essential for driving resolution of the inflammatory response in the lung (Gilroy et al., 1999). Human fibroblasts generate pro-resolving peroxisome proliferator-activated receptor-γ ligands in a COX-2-dependent manner via pro-resolving prostaglandins (Lacy et al., 2016). Thus, inhibition of COX-2 impairs resolution of inflammation because prostaglandins such as PGE₂ initiate a lipid mediator class switching to SPMs such as lipoxins to accelerate the resolution of inflammation (Levy et al., 2001).

8.3. Nonsteroidal anti-inflammatory drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for inflammatory diseases, pain, fever and include aspirin, celecoxib, ibuprofen, sulindac, diclofenac, and ketorolac (Wang & Dubois, 2010). NSAIDs that block the enzymatic activity of COX and subsequent production of prostaglandins, are widely used to treat inflammation and pain (Marnett, 2009) and exhibit anti-cancer activity (Arber & DuBois, 1999; Gilligan et al., 2019; Hudis, Subbaramaiah, Morris, & Dannenberg, 2012). However, the adverse side effects of NSAIDs such as bleeding prevent their chronic use at high doses (Wang & Dubois, 2010). Certain NSAIDs are selective COX-1 and/or COX-2 inhibitors. Aspirin exhibits anti-cancer activity by inhibiting inflammation and triggering the resolution of inflammation (Gilligan et al., 2019; Shiff & Rigas, 1999; Wang & Dubois, 2010). NSAIDs inhibit angiogenesis, including suppressing carcinogen-induced angiogenic signaling of cytokines, NF-κB, MMP-2 and MMP-9 in colon cancer progression (Vaish, Piplani, Rana, & Sanyal, 2013).

The NSAID sulindac can prevent carcinogen-induced intrahepatic cholangiocarcinoma in experimental models (Wentz et al., 2009). The loss of 15-hydroxyprostaglandin dehydrogenase, a prostaglandin-degrading enzyme that inhibits COX-2, stimulate tumor growth. However, sulindac, but not aspirin or celecoxib, overcomes the low 15-PGDH expression to reduce AOM-induced colon carcinogenesis

demonstrating a difference in anti-tumor activity with various NSAIDs (Fink et al., 2015). Sulindac partially inhibits NDEA-induced HCC, although statins exhibit more potent anti-inflammatory and anti-cancer activity (Bakiri et al., 2017). AFB₁ upregulates COX-2 which activates the inflammasome leading to tumor-promoting inflammation. In contrast, celecoxib reduced this inflammation demonstrating the regulation of inflammation by eicosanoids and inflammatory mediators (Zhang et al., 2019). Additionally, etodolac, a COX-2 inhibitor, suppresses N-nitrosobis(2-oxopropyl)amine (BoP)-induced experimental biliary carcinogenesis (Tsuneoka et al., 2005).

While initial studies have focused on colorectal cancers, low-dose aspirin exhibits anti-tumor activity in other tumor-types, including lung, breast, prostate, and metastatic cancers (Wang & Dubois, 2010). Aspirin can stimulate resolution by triggering the biosynthesis of resolvins, lipoxins and protectins (Gilligan et al., 2019; Serhan, 2014). Compelling evidence of aspirin's anti-cancer activity stems from patients receiving low-dose aspirin for cardioprevention, in which a substantial fraction (20–30%) benefits from a decrease in cancer incidence. Importantly, the use of low-dose aspirin in cancer patients is limited by adverse side effects, such as gastrointestinal bleeding and hemorrhagic stroke, that necessitate hospitalization (Gilligan et al., 2019). Aspirin-triggered resolvins and lipoxins may account for aspirin's anti-tumor activity at least in part without the toxicity of aspirin (Claria & Serhan, 1995; Gilligan et al., 2019). Because SPMs are not triggered by other NSAIDs besides aspirin, this may explain why aspirin's beneficial anti-tumor activity has not been fully recapitulated with other NSAIDs (Gilligan et al., 2019).

However, NSAIDs can down-regulate pro-tumorigenic cytokines but also generate toxic side effects and may be immunosuppressive resulting in increased risk for infections. Pre-treatment of the NSAID carprofen impaired initiation of inflammatory- and overlapping resolution response and promoted cardiorenal syndrome and heart failure (Krishnan et al., 2019). The classic cyclooxygenase inhibitors, celecoxib and indomethacin, that block thromboxanes and prostanoids do not inhibit production of the clot-driven SPM cluster (Norris & Serhan, 2018). Additionally, NSAIDs have been associated with gastrointestinal (GI) injury for a century (Wang & Dubois, 2010). It was the discovery by Vane in 1971 that these drugs suppress the biosynthesis of prostaglandins (PGs) that first suggested that autacoids may play a role in the maintenance of GI mucosal injury (Vane, 1971). Coadministration of a selective COX-2 inhibitor with aspirin inhibits pro-resolution lipoxin synthesis in the stomach increasing gastric mucosal damage (Fiorucci et al., 2002). Administration of synthetic LXA₄ prior to aspirin resulted in a dose-dependent reduction in the extent of gastric damage. Thus, aspirin-triggered lipoxins reduce injury to the gastric mucosa (Wallace & Fiorucci, 2003).

Standard anti-inflammatories such as steroids, NSAIDs, COX-2 inhibitors, and cytokine antagonists do not clear debris and may be "resolution toxic" (Gilroy et al., 1999; Panigrahy et al., 2019; Serhan, 2014). For example, in a model of CCL4-induced liver fibrosis and inflammation the use of celecoxib reduced PGE₂ levels which was not sufficient to inhibit the liver injury and inflammation (Harris et al., 2018). Acetaminophen and indomethacin also generate 18-HEPE production, whereas selective cyclooxygenase-2 (COX-2) inhibitors block 18-HEPE production (Serhan & Levy, 2018). Both 18-HEPE and RvE1 are anti-inflammatory, stopping leukocyte migration and stimulating resolution of inflammation. NSAIDs and COX-2-inhibitors impair inflammation resolution, efferocytosis, and neutralize PGE₂ and PGD₂-induced class switching to SPMs. Other "resolution toxic" drugs including lipoxygenase (LOX) inhibitors as 5-LOX plays a critical role in the biosynthesis of two classes of SPMs, lipoxins and resolvins. Lidocaine impairs resolution by inhibiting efferocytosis (Serhan & Levy, 2018). In contrast, frequently used drugs such as aspirin promote resolution through acetylation of COX-2, and triggering production of R-epimer lipoxins, resolvins, and protectins. Statins also boost SPMs and the resolution of inflammation (Serhan, 2014). Glucocorticoids can have mixed

activity regarding resolution of inflammation by increasing the pro-resolving annexin A and efferocytosis but are immunosuppressive (Schif-Zuck et al., 2011). Dexamethasone can stimulate SPM production to stimulate resolution of airway inflammation as well as macrophage phagocytosis of apoptotic cells (Maderna, Yona, Perretti, & Godson, 2005; Pyriou, Chairakaki, Tamvakopoulos, & Andreacos, 2018).

While PGE₂ and LTB₄ initiate inflammation following tissue injury, PGD₂ is a pro-resolution prostaglandin that triggers the switch from initiation of inflammation to resolution by inducing 15-LOX and SPM production which is upregulated in colitis patients who undergo long term remission (Serhan, 2014; Vong, Ferraz, Panaccione, Beck, & Wallace, 2010). Thus, pro-resolution prostaglandins inhibit IKK β to suppress NF- κ B induced chronic inflammation, may be a therapeutic approach to carcinogen-induced inflammation (Rossi et al., 2000). Alternatively, more specific inhibition of microsomal PGE synthase (mPGES-1) suppressed carcinogen-induced colon cancer without broadly blocking prostaglandin signaling as a potential mechanism to reduce NSAID-associated toxicity (Nakanishi et al., 2011). Thus, inhibition of eicosanoid enzyme pathways may disrupt inflammation resolution in carcinogen-induced cancers which can be restored via supplementation of pro-resolution lipid mediators.

8.4. Specialized Pro-resolving Mediators (SPMs)

A paradigm shift is emerging in our understanding of the resolution of inflammation as an active biochemical process with the discovery of novel endogenous specialized pro-resolving lipid autacoid mediators (SPMs), such as resolvins, lipoxins, protectins and maresins (Serhan, 2014). Resolvins and other pro-resolution lipid mediators stimulate macrophage-mediated clearance of cellular debris and counter pro-inflammatory cytokine production, a process called inflammation resolution. Resolution indices utilized temporal lipidomics, proteomics, and flow cytometry to establish relationships between cell trafficking, eicosanoids, pro-resolving lipid mediators and chemokines/cytokines (Bannenberg et al., 2005; Schwab, Chiang, Arita, & Serhan, 2007). Tumor-associated macrophages (TAM) family members (TYRO3, AXL and MerTK) play important roles in the resolution of inflammation in many diseases including infections and cancer via efferocytosis (Duan et al., 2019). MerTK signaling also has an important role in the resolution of inflammation by stimulating production of SPMs, including lipoxin A₄ (LXA₄) and RvD1 (Cai et al., 2018). MerTK-deficient mice exhibit impaired phagocytosis of apoptotic cells contributing to development of allergic inflammation (Felton et al., 2018), atherosclerosis (Thorp, Cui, Schrijvers, Kuriakose, & Tabas, 2008), or autoimmune diseases (Rothlin, Carrera-Silva, Bosurgi, & Ghosh, 2015).

SPMs (e.g. resolvins, protectins, and maresins) are biosynthesized from omega-3 fatty acids EPA and DHA and consist of families including resolvins (D and E series), maresins and their conjugates in tissue repair, protectins, and arachidonic acid-derived eicosanoid lipoxins (Serhan & Levy, 2018). SPMs function via G protein coupled receptors including GPR32, GPR18, ChemR23, GPR37, and LGR6 have been identified for RvD1, RvD2, RvE1, PD1, and Mar 1, respectively (Bang et al., 2018; Chiang, Dallii, Colas, & Serhan, 2015; Chiang, Liberos, Norris, de la Rosa, & Serhan, 2019; Krishnamoorthy et al., 2010; Ohira et al., 2010). In a metabololipidomics LC-MS/MS analysis screening included products of the DHA-derived bioactive metabolome (resolvins of the D series, maresins, protectins), EPA-derived bioactive metabolome (lipoxins, resolvins of the E series), and AA-derived mediators (lipoxins, leukotrienes, prostanoids) all of which regulate specific inflammatory disease processes. SPMs function potently in other inflammatory diseases including reducing thrombosis (Cherpokova et al., 2019). SPMs inhibit the recruitment of neutrophils that produce DNA damaging oxygen radicals, which may inhibit the carcinogen-induced inflammation promoting oxidative damage and mutagenesis. Limiting neutrophil tissue damage may also inhibit regenerative proliferation triggered as an injury response. SPMs, including protectins such as protectin DX,

can reduce the production of reactive oxygen species and downregulate the activity of COX-2 in neutrophils (Liu et al., 2014). Notably, electrical stimulation of the vagus nerve is an alternate approach to stimulate the local production of SPMs while reducing prostaglandins and leukotrienes (Serhan et al., 2018).

Lipoxins are the first SPMs discovered although it took a long time to uncover their role in resolution of inflammation as potent, active stop signals for immune cell (e.g. neutrophil) infiltration and are biosynthesized from arachidonic acid (Serhan et al., 1984). Lipoxins (LX) are trihydroxytetraene-containing eicosanoids typically generated through transcellular biosynthetic pathways involving either 5- and 15-lipoxygenases (LOX) or 5- and 12-LOX. Lipoxins are produced relatively early during resolution of self-limited acute inflammatory responses (Serhan, 2014). Lipoxins are biosynthesized by immune cells such as neutrophils and macrophages in response to stresses such as inflammatory stimuli, injury, or infection. Endogenous lipoxins are the only arachidonic acid-derived SPM, and act as antagonists of pro-inflammatory and pro-tumorigenic leukotrienes. The Serhan laboratory utilized lipid mediator metabololipidomics, proteomics (liquid chromatography–tandem mass spectrometry [LC-MS/MS]), and cell trafficking in self-limited exudates to identify three more new families of pro-resolving mediators, termed the “resolvins” (short for resolution phase interaction products), “protectins,” and “maresins” (short for macrophage mediators in resolving inflammation) (Mukherjee et al., 2004; Serhan et al., 2002; Serhan et al., 2009). Each family is structurally distinct and biosynthesized from essential fatty acid precursors eicosapentaenoic acid (EPA), docosapentaenoic acid (n-3DPA), or docosahexaenoic acid (DHA).

Aspirin stimulates the biosynthesis aspirin-triggered specialized pro-resolving mediators (AT-SPMs) from omega-3 polyunsaturated fatty acid substrates, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) by acetylation of COX-2 (Serhan et al., 2002). AT-SPMs include endogenous production of aspirin-triggered lipoxins, aspirin-triggered resolvins and aspirin-triggered neuroprotectins (Claria, Lee, & Serhan, 1996; Claria & Serhan, 1995; Petasis et al., 2012; Serhan, 2014; Serhan, Dalli, Colas, Winkler, & Chiang, 2015; Takano, Clish, Gronert, Petasis, & Serhan, 1998). Stable analogues of lipoxin A₄, lipoxin B₄, and aspirin-triggered lipoxin A₄ inhibit neutrophil infiltration more potently than aspirin and rescue resolution deficits in various inflamed tissue injury models (Clish et al., 1999; Schwab et al., 2007; Serhan, 2005; Takano et al., 1997). Aspirin-triggered resolvin D3 are potent immunoresolvents, including blocking neutrophil transmigration as well as stimulating macrophage phagocytosis and efferocytosis (Dalli et al., 2013). Aspirin-triggered resolvins can mediate the anti-proliferative and anti-tumor activity of aspirin (Claria et al., 1996; Gilligan et al., 2019). Aspirin-triggered resolvins can mediate the anti-tumor activity of aspirin at >10,000 fold lower doses than aspirin without toxicity in experimental cancer models via resolution of inflammation (Gilligan et al., 2019). Preoperative administration of the NSAID ketorolac and/or resolvins (RvD2, RvD3, and RvD4) activate endogenous resolution programs before surgery to eliminate micrometastases and reduce tumor recurrence (Panigrahy et al., 2019).

Importantly, as NF-κB is central to inducing tissue injury and inflammation in carcinogenesis, SPMs have been shown to downregulate this signaling via activation of NF-κB regulators, including 15-epi-lipoxin A₄ induction of A20 and SIGIRR via its ALX/FPR2 receptor signaling following LPS-induced inflammation (Sham et al., 2018). Resolvin D1 protects from LPS-induced inflammation in a lung injury model via inhibition of damaging oxidative stress (Wang et al., 2014). Upregulation of the ALOX-15/LXA4 pathway in a PMA-induced skin inflammation model can promote the resolution of inflammation via inhibition of IFN-γ (Zhang et al., 2013). Resolvin D1 in colitis-associated cancer inhibits c-Myc and TNF-α in colon cancer cells (Zhong et al., 2018). In an inflammatory intestinal model, protectin D1_{n-3DPA} and resolvin D5_{n-3DPA} protected against colitis and intestinal injury, both of which are risk factors for intestinal carcinogenesis (Gobbetti et al., 2017).

An important function of pro-resolution mediators or signaling pathways is the induction of macrophage phagocytosis and efferocytosis. Clearance of microbes as well as apoptotic cells is important in multiple inflammatory diseases, including carcinogen-induced cancers as dead cells or increased microbe uptake can stimulate chronic inflammatory cycles. Peroxisome proliferator-activated receptors (PPARs) stimulate macrophage phagocytosis to promote clearance of infection and inhibit pro-inflammatory mediators in macrophages, which may be key to “resolve” inflammation-driven cancers (DuBois et al., 1998; Penas et al., 2015). As targeting specific macrophage phenotypes is crucial to the resolution of inflammation in carcinogen-induced cancers, a MerTK macrophage phenotype has been demonstrated to induce phagocytosis and prevent liver damage (Triantafyllou et al., 2018). Additionally, LTB₄, a potentially pro-inflammatory mediator, can be detected via PPAR-α binding which signals for its metabolism and clearance in the liver to control pro-inflammatory signaling (Devchand et al., 1996). Thus, exploring multiple targets involved in the resolution of inflammation may elucidate novel therapeutics in carcinogen-induced inflammation and cancer.

SPMs also induce a macrophage phenotype switch from a generally M1 to M2 phenotype which promotes efferocytosis and phagocytosis functions (Werz et al., 2018). Hypoxia activates resolution metabolomes (SPM-biosynthetic circuits) which stimulate resolution including resolvins in M2-like human macrophages via interactions with erythrocytes which store omega-3 fatty acids to increase phagocytosis and efferocytosis (Norris, Libreros, & Serhan, 2019). This clearance of dead and damaged cells would inhibit the increased inflammatory response to DAMPs and reduce the debris-induced macrophage-derived cytokine storm. SPMs, including resolvins, have functioned to clear therapy-generated dead cells to prevent their generation of tumor promoting inflammation, as well as prevent micrometastases to prolong survival in surgery-stimulated tumor dormancy escape models (Panigrahy et al., 2019; Sulciner, Serhan, et al., 2018). In addition, phagocytosis of inflammatory microbes which may have increased in the tissue via carcinogen exposure and failed barrier function may prevent synergistic tumorigenic inflammation. Macrophage phenotype is of utmost importance in the tumor microenvironment, as M1-like macrophages produce prostaglandins and leukotrienes generating an inflammatory and pro-tumorigenic microenvironment, while M2-like macrophages translocate 5-LOX and 15-LOX-1 to produce resolvins and maresins in response to inflammatory bacteria stimuli (Werz et al., 2018).

A critical difference between pro-resolution mediators (“resolving” inflammation) compared to anti-inflammation (“blocking” inflammation) is that while most anti-inflammatory agents can lead eventually to immunosuppression, the resolution of inflammation in an active endogenous reprogramming of the immune response to turn off inflammation without being immunosuppressive. In surgery-stimulated and chemotherapy-stimulated cancer models preoperative stimulation of inflammation resolution via resolvins (RvD2, RvD3, and RvD4) inhibited metastases and induced T cell responses (Panigrahy et al., 2019). SPMs also promote the differentiation of B cells to be antibody-producing thus endogenously enhancing the adaptive immune system (Ramon, Gao, Serhan, & Phipps, 2012). SPMs not only inhibit macrophage-derived pro-inflammatory cytokines but prevent activated CD8+ and CD4+ cells from releasing inflammatory cytokines without inhibiting T regulatory cells (Aoki et al., 2008; Aoki et al., 2010). Thus, the resolution of inflammation via SPMs may be a novel approach to preventing carcinogen-induced cancers via downregulation of pro-inflammatory cytokines, suppression of neutrophil infiltration, reduced oxidative damage, and clearance of carcinogen-generated debris (Fig. 4).

8.5. Lipoxins

The most extensively studied SPMs in cancer biology at this time are the lipoxins (e.g. LXA₄). Lipoxins suppress cancer cell proliferation in

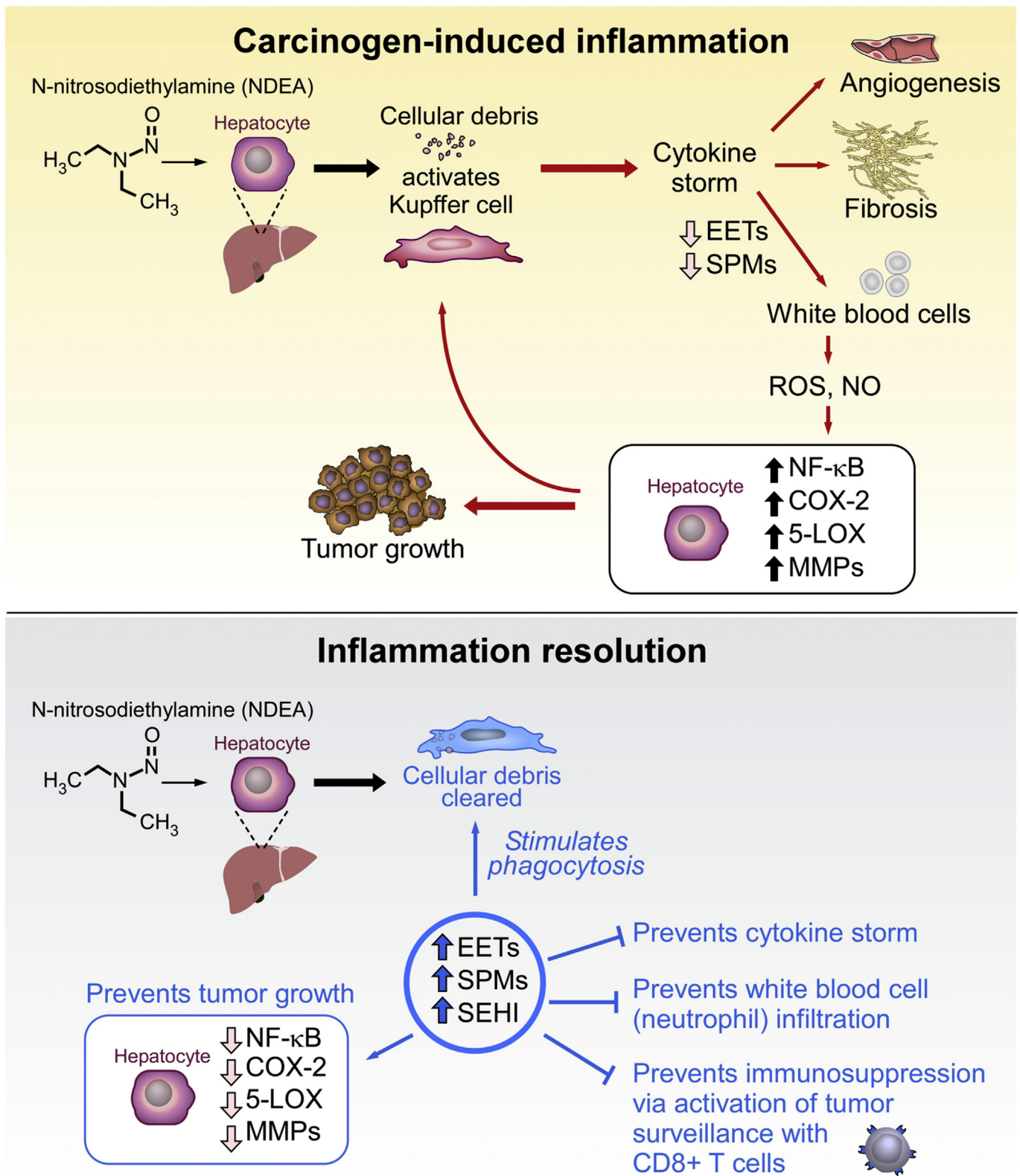


Fig. 4. Inflammation resolution in carcinogen-induced cancer. Carcinogen (NDEA) induced inflammation causes tissue damage and cell death of normal cells (hepatocytes) generating cellular debris. These dead cells activate local macrophages (Kupffer cells) to a pro-inflammatory phenotype generating a cytokine storm. This chronic inflammation reduces pro-resolving mediators including SPMs and EETs and signals for angiogenesis, fibrosis, and inflammatory cell infiltration. Infiltrating white blood cells add to the tissue injury by producing reactive oxygen and nitrogen species triggering the upregulation of NF-κB, COX-2, 5-LOX, and MMPs in surrounding hepatocytes generating a vicious cycle leading to tumor growth. However, resolution of inflammation via SPMs or sEH inhibition may break this pro-tumorigenic cycle. Resolution promotes macrophage phagocytosis of cellular debris, inhibits the cytokine storm, suppresses inflammatory infiltration, and is not immunosuppressive leading to the downregulation of NF-κB, COX-2, 5-LOX, and MMPs and inhibition of carcinogenesis.

culture and in animal xenograft models inhibit tumor cell invasion (Chen et al., 2010; Claria et al., 1996; Schottelius et al., 2002; Zhou et al., 2009). Lipoxins exhibit anti-inflammatory actions by inhibiting NF- κ B signaling pathway (Gewirtz et al., 2002). Lipoxins inhibit pro-inflammatory cytokines (IL-8) and adhesion molecule (i.e., ICAM-1) expression in human astrocytoma brain tumor cells (Decker, McBean, & Godson, 2009). LXA₄ potently inhibits the leukocyte trafficking to the inflammatory site and stimulates the phagocytosis of apoptotic cells by tissue macrophages (Ariel, Chiang, Arita, Petasis, & Serhan, 2003; Chen et al., 2010). ATL-1, a synthetic analogue of 15-epi-lipoxin A₄, inhibited melanoma tumor progression via switching tumor associated macrophages (TAM) from an M2- to an M1-cytotoxic like profile, promoting inhibitory activity on tumor cell proliferation and survival, and triggering tumor cell apoptosis (Simoes et al., 2017). LXA₄ can inhibit MAPK signaling to suppress aberrant COX-2 expression induced by IL-1 β signaling in endometriosis, an inflammatory risk factor for endometrial cancer (Dai et al., 2019). However, ATL-1 had no direct effect on cancer cell proliferation (Simoes et al., 2017). Additionally, LXA₄ did not exert any direct anti-proliferative effect on liver cancer (H22 cells) (Chen et al., 2010).

Cancer progression including leukemia and colorectal cancer is associated with down-regulation of lipoxins (Liu et al., 2019; Stenke et al., 1991). Downregulation of lipoxin A₄ (LXA₄) plays a role in Kaposi's sarcoma (KS)-associated herpesvirus (KSHV) infection pathogenesis and KS-related cancer (Chandrasekharan, Huang, Hwang, & Sharma-Walia, 2016). Serum LXA₄ levels were decreased in colorectal cancer patients and specifically in the tumor tissue, while cancer patients expressed higher serum levels of LTB₄, IL-1 β , IL-6, CXCL8, TNF- α , and CCL2. LXA₄ suppresses the colorectal tumor levels of pro-inflammatory mediators IL-1 β , IL-6, TNF- α and LTB₄ while up-regulating anti-inflammatory IL-10 expression (Liu et al., 2019). LXA₄ also inhibited the infiltration of CD45+ leukocytes and CD68+ macrophages in the colorectal tumor tissue. LXA₄ suppresses the expressions of p-ERK, p-P38 and NF- κ B in the xenograft, inhibit the proliferation and migration of colorectal cancer cells stimulated by activated macrophage-conditioned media (Liu et al., 2019). Kaposi's sarcoma (KS) occurs is frequently identified in HIV infected patients (Chandrasekharan et al., 2016). The lipoxin receptor ALX/FPRL1 was expressed on human KS tissue sections (Chandrasekharan et al., 2016). Treating KS-IMM cells with lipoxins (LXA₄ or 15-epi-LXA₄) reduced the levels of pro-inflammatory cytokines IL-6 and IL-8, enzymes COX-2, 5-LO, and their metabolites (Marginean & Sharma-Walia, 2015).

Lipoxins and their analogues are potent inhibit tumor growth including hepatocellular carcinoma, melanoma, and Kaposi's sarcoma by suppressing angiogenesis such as endothelial cell proliferation, endothelial cell migration, VEGFA-induced angiogenesis, VEGF-induced permeability, VEGF-stimulated VEGFR2 (KDR/FLK-1) phosphorylation, COX-2, 5-LO, PGE₂ and LTB₄ (Baker, O'Meara, Scannell, Maderna, & Godson, 2009; Cezar-de-Mello et al., 2008; Chen et al., 2010; Fierro, Kutok, & Serhan, 2002; Hao et al., 2011; Jin et al., 2009; Marginean & Sharma-Walia, 2015; Simoes et al., 2017; Vieira et al., 2014). LXA₄ inhibits VEGF and HIF-1 α production by H22 hepatocellular carcinoma tumor cells in a dose-dependent manner (Chen et al., 2010). The lipoxin analogue BML-111 inhibited serum VEGF production in vivo in H-22 tumor bearing mice (Chen et al., 2010). In murine hepatocarcinoma, melanoma and CRC xenograft models, LXA₄ suppressed tumor growth by targeting regulatory B cells (Bregs) through the inhibition of important signaling pathways (Wang et al., 2015). Bregs inhibit functions of CD8⁺ cytotoxic T cell in the tumor microenvironment. Thus, LXA₄ may induce sustained anti-tumor immunity favoring the CD8⁺ T cell response. Lipoxin metabolically stable analogs may protect from tumor extravasation by inhibiting VEGF-induced endothelial permeability (Vieira et al., 2014).

SPMs also exhibit cell-autonomous activity on cancer cells, independent of their anti-inflammatory action. In a murine model of liver cancer, LXA₄ inhibits hepatocarcinoma tumor growth by regulating

the induction of MDSCs in response to T-reg depletion and inhibiting tumor angiogenesis (Chen et al., 2010; Zhang et al., 2010). LXA₄ also suppresses acute myeloid leukemia cell migration and stimulates the phagocytic clearance of apoptotic cells by all-trans retinoic acid (ATRA)-treated alveolar macrophages (Tsai et al., 2012). Interestingly, LXA₄ shares structural similarities with estrogen 17-estradiol and possesses anti-estrogenic activity by competing for estrogen receptors, suggesting a potential effect in estrogen-associated diseases, such as endometrial cancer (Canny & Lessey, 2013).

Lipoxin A₄ as an endogenous lipid mediator can reprogram the tumor stroma to target pancreatic and liver cancer. LXA₄ inhibited pancreatic cancer cell invasion by inhibiting the reactive oxygen species as well as MMP9 and MMP2 (Zong et al., 2016). In patients with pancreatic cancer, a low Lipoxin effect score (LES) has been observed. Specifically, a low LES tended to correlate with lymph node and distant metastasis. The "Lipoxin effect score" (LES) was the product of the immunohistochemistry scores of both 15-LOX and FPRL1. LES was correlated with aggressive metastatic potential in pancreatic tissue from pancreatic cancer patients (Zong et al., 2017). In PDAC, human pancreatic stellate cells (hPSCs), the main precursors of pancreatic cancer associated fibroblasts (CAFs), become activated and induce fibrosis by secreting extracellular matrix, which presents a barrier to anti-cancer drugs (Schnittert, Heinrich, Kuinty, Storm, & Prakash, 2018). Lipoxin A₄ can disrupt the pro-tumoral paracrine signaling of human (hPSCs) (Schnittert et al., 2018). LXA₄ inhibited the activation of hPSCs into CAF-like myofibroblasts in vitro and inhibited hPSC-induced tumor-promoting activity (Schnittert et al., 2018). LXA₄ can also inhibit renal and lung fibrosis (Mitchell et al., 2004; Roach, Feghali-Bostwick, Amrani, & Bradding, 2015). Lipoxin A₄ also inhibited pancreatic tumor growth via anti-fibrotic mechanisms such as reduced collagen I expression and thus may increase the efficacy of chemotherapy and radiation in pancreatic cancer (Schnittert et al., 2018). LXA₄ also reduced tumor angiogenesis as determined by a reduction in the endothelial marker CD31 (Schnittert et al., 2018). In a liver metastasis model in nude mice, the LXA₄ analogue mimetic BML-111, could inhibit the metastasis of pancreatic cancer cells (Zong et al., 2017). Lipoxin reverses mesenchymal phenotypes to attenuate invasion and metastasis via inhibition of autocrine TGF- β 1 signaling in pancreatic cancer (Zong et al., 2017). EMT is a metastasis-promoting process in which cancer cells lose epithelial phenotypes such as E-cadherin expression and acquire mesenchymal characteristics including elevated expression of N-cadherin and vimentin expression (Zong et al., 2017).

Aspirin-triggered-lipoxin, 15-epi-LXA₄ analog, is a potent inhibitor of endothelial cell responses and angiogenesis in vitro and in vivo. Lipoxin and AT-LXA₄ treatment of a cancer-induced bone pain model results in suppression of spinal pro-inflammatory cytokines including IL-1 and TNF- α (Hu et al., 2012). LXA₄ administration also promoted the regression of DMBA/TPA- induced papillomas and reduced several pro-inflammatory cytokines including IFN- γ in papilloma tissue (Wang et al., 2013). IFN- γ maintains inflammation and papilloma growth by repressing LXA₄, demonstrating a dynamic balance between pro-inflammatory factors and pro-resolution lipid mediators (Wang et al., 2013). Lipoxins promote resolution of inflammation increasing papilloma regression independent of upregulating IFN- γ by enhancing anti-tumor immunity. Thus, lipoxins are a potential treatment for papillomas and other cancer types.

8.6. Resolvins

SPMs such as resolvins are entirely unique from traditional anti-inflammatory agents in that they actively promote resolution of inflammation via activation of macrophages to clear inflammatory cell debris and killing/clearing microbes, counter-regulate pro-inflammatory cytokines, and halt leukocyte infiltration to reduce the propagation of inflammation at pico-nanogram concentrations (Serhan, 2014). Reduced resolvins have already proven to be critically involved in a number of

autoimmune diseases characterized by uncontrolled inflammation (Serhan, 2014; Serhan & Levy, 2018). Resolvins are highly effective in treating diseases driven by excessive inflammation at picogram levels in vivo (logs lower than aspirin or dexamethasone) in a wide variety of experimental pre-clinical models of inflammatory diseases (Aoki et al., 2008; Arita et al., 2005; Bannenberg, 2009; Bento, Claudino, Dutra, Marcon, & Calixto, 2011; Connor et al., 2007; Duffield et al., 2006; Gonzalez-Periz et al., 2009; Hansson, Robertson, & Soderberg-Naucler, 2006; Hassan & Gronert, 2009; Hasturk et al., 2007; Haworth et al., 2008; Hong, Gronert, Devchand, Moussignac, & Serhan, 2003; Jin et al., 2009; Kasuga et al., 2008; Merched et al., 2008; Serhan et al., 2002; Spite et al., 2009; Tian, Lu, Sherwood, Hongqian, & Hong, 2009; Van Dyke & Serhan, 2003). Clinical trials show increasing resolvins activity in inflammatory diseases such as dry eye inflammation and periodontal diseases can reduce local inflammation (Serhan & Levy, 2018).

Demonstrating the importance of resolvins in cancer, the neutralization of resolvins D1 receptor GPR32-mimics FPR1-silencing which increases angiogenesis and tumorigenesis of gastric cancer cells (Prevette et al., 2017). Formyl peptide receptors (FPR1, 2, and 3) are pattern recognition receptors of the G-protein-coupled (GPCR) family that recognize both exogenous and endogenous “danger” signals, and can trigger inflammation while FPR2/ALX activates resolution (Ye et al., 2009). Genetic deletion of FPR1 in gastric cancer cells promoted angiogenesis and enhanced the response to pro-inflammatory cytokines and impairing inflammation resolution (Prevette et al., 2015). The resolvins receptors (GPR32 for RvD1 and GPR 18 for RvD2) are down regulated during cancer progression in oral cancer cells (Ye et al., 2018). While both RvD1 and RvD2 inhibited oral tumor cell proliferation in vitro, RvD2 suppressed tumor growth in an oral squamous cell carcinoma xenograft models via macrophage efferocytosis and reduced tumor-derived cytokines/chemokines (TNF- α , IL-6, CXCL10, and MCP-1), CD11b^bLy6G myeloid cell infiltration, nociception, reduction of tumor necrosis, and decreased neutrophil infiltration (Ye et al., 2018). Tissue resolvins of the D series was identified as potential biomarker in endometrial cancer patients and correlated with improved patient survival (Eritja et al., 2017). Resolvin D1 (RvD1) also increases miR-138-5p expression by over 60-fold compared to control directly targeted FOXC1 to reduce cancer cell growth and invasion in NSCLC in vitro (Bai et al., 2019). RvD1 decreased cell viability and cell invasion in A549, H1299 and LLC cells in a dose-dependent manner and affected Akt and Erk1/2 phosphorylation (Bai et al., 2019). Specifically, in lung cancer, FOXC1 plays a critical role in tumor microenvironment to promoted cancer progression (Cao et al., 2018; Lin et al., 2017). RvD1 regulates the expression of several miRNAs. These studies establish the mechanistic linkage between miR-138-5p and inflammation resolution (Bai et al., 2019). RvD1 also inhibits skin inflammation via reducing cytokine levels including IL-1 β , IL-6, IL-33, TNF- α , and oxidative stress induced by ultraviolet irradiation (Saito et al., 2018).

Epithelial mesenchymal transition (EMT) is a biological process that plays a critical role in cancer progression (Lee, 2018). Resolvins (RvD1 and RvD2) inhibit TGF- β 1-induced epithelial mesenchymal transition (EMT) in lung cancer cells via their receptors ALX/FPR2 and GPR32 receptors, resulting in inhibition of ZEB1 expression (Lee, Park, Lee, & Lee, 2013). TGF- β 1, one of the featured mediators in the resolution of inflammation and key components comprising the tumor microenvironment, can induce EMT of lung cancer cells. AT-RvD1 suppresses the TGF- β 1-induced EMT by mTOR pathway inhibition reducing the expression of PKM2, which affects cellular energy metabolism and oxidative stress (Liu, Yuan, Li, Cao, & Shu, 2016). Blocking the process of EMT can be an essential strategy in the development of anti-cancer drugs. EMT involves down-regulation of epithelial proteins such as E-cadherin and keratins and the acquisition of mesenchymal marker proteins, including vimentin and EMT-related transcription factors such as Snail1 and zinc-finger E-box binding 1 (ZEB1) (Lee, 2018). Snail, Twist, and ZEB transcription factors are well-known transcription factors involved in the EMT process. A cancer stem cell (CSC) is a cancer cell

that undergoes a self-renewal and differentiation. Activation of EMT in cancer cells is closely related to the entry of cancer cells into CSC state (Chaffer, San Juan, Lim, & Weinberg, 2016). Resolvins (e.g. RvD1) impaired paracrine activity of carcinoma-associated fibroblasts (CAFs)-derived COMP by targeting FPR2/ROS/FOXO1 signaling to inhibit EMT and cancer stemness in HCC in a receptor-dependent manner (Sun et al., 2019). Thus, RvD1 may be a potential agent to inhibit many cancers dependent on cancer stem cells such as hepatocellular carcinoma (Sun et al., 2019). CAFs-derived COMP induced EMT and cancer stem cell-like properties to promote invasion and metastasis of HCC (Sun et al., 2019), which was in accordance with previous findings that IL-6 secreted by CAFs confers stem-like properties in HCC via the upregulation of stemness-correlated transcription factors including Sox2, Oct4 and Nanog (Li, Wang, Xiong, et al., 2019).

Resolvins (e.g. RvE1) also inhibit the oncoprotein c-Myc expression which is overexpressed in a large variety of human cancers such as colon cancer (Zhong et al., 2018). The suppression of TNF- α -induced upregulation of c-Myc in normal cells was mediated through attenuation of NF- κ B signaling (Zhong et al., 2018). RvD1 stimulated c-Myc degradation through direct interaction with the ALX/FPR2 receptor (Zhong et al., 2018). RvD1 induces cytotoxic activity and elevated caspase-3 activity in natural killer (NK) cells in pancreatic ductal adenocarcinoma cells (PDAC) cells (Halder et al., 2015). RvD1 and RvD2 also exhibited anti-inflammatory activity by inhibiting LPS-interferon (IFN)- γ -induced M1 polarization as well as promoting interleukin-4 (IL-4)-mediated M2a polarization. These differential polarization processes were mediated, at least in part, by protein kinase A. Thus, regulation of macrophage polarization using RvDs may be a potential therapeutic approach in the management of prostate cancer (Shan et al., 2020). The communication between human monocyte-derived M2-like macrophages (MDM) and cancer cells in co-incubations can strikingly modulate the biosynthetic capacities to produce bioactive LM including lipoxin A₄, resolvins D2 and D5 were elevated after coculture with human A549 epithelial lung carcinoma cells (Werner et al., 2020).

Current therapy for HCC and hepatoblastoma includes resection, transplantation, radiofrequency ablation, chemoembolization and sorafenib (Villanueva, Hernandez-Gea, & Llovet, 2013). Resolvin D1 and E1 prevent liver injury and progression from hepatitis to liver cancer in murine models (Kuang et al., 2016). Resolvins protect from acute liver injury (e.g. carbon tetrachloride) (Chen et al., 2016). Resolvin D1 and E1 prevent concanavalin A (Con A)-induced liver injury and the changes of hepatitis to liver cancer in mice by inhibition of inflammatory cytokine secretion and NF- κ B/AP-1 activity (Kuang et al., 2016). RvD1 and RvE1 inhibit Con A-induced liver injury, the production of TNF- α , IFN- γ , IL-2, IL-1 β and IL-6, NF- κ B and AP-1 signaling, TLR4, I κ B α , IKK β , MyD88, JNK, ERK and p38, and necrosis in mice (Kuang et al., 2016). Resolvins (e.g. 17(R)-Resolvin D1) can regulate Toll-like receptor 4-mediated inflammatory responses of human macrophages to LPS and *E. coli* (Palmer et al., 2011). Resolvins (e.g. RvD1) also inhibits the proliferation of LPS-treated liver cancer cells and reduces the expression and release of TNF- α , IL-1 β and IL-6 at the protein and mRNA levels in LPS-treated liver cancer cells (Lu et al., 2018). In addition, RvD1 decreases p-ERK, p-JNK and p-p38 levels in LPS-treated liver cancer cells (Lu et al., 2018).

Resolvins may have the potential to resolve damaging inflammation generated by tobacco smoke, one of the most widespread worldwide carcinogens. Chronic secondhand exposure to tobacco smoke stimulated the levels of pro-inflammatory cytokines IL-17A, IL-6, IL-1 β , and TNF- α in the lungs and impairs bacterial clearance from the lungs (Bhat et al., 2018). Pro-resolution mediators such as resolvins suppressed macrophage production of smoke-induced pro-inflammatory cytokines, enzymes, and lipid mediators (Croasdell et al., 2015). Resolvins also increased anti-inflammatory cytokines, promoted an M2 macrophage phenotype, and restored cigarette smoke-induced defects in phagocytosis (Croasdell et al., 2015). Resolvin D1 (RvD1) suppressed production of pro-inflammatory mediators by primary human

cells in a dose-dependent manner. RvD1 administered with cigarette smoke exposure reduced neutrophilic lung inflammation and production of pro-inflammatory cytokines, while upregulating the anti-inflammatory cytokine IL-10 in mice (Hsiao et al., 2013).

Alarmins such as high-mobility group box 1 (HMGB1) can disrupt the resolution of inflammation by inhibiting macrophage efferocytosis induced by SPMs (Kang et al., 2015). HMGB1 plays an important role in maintaining inflammation and can be actively released from various immune cells such as macrophages, monocytes, NK cells, dendritic cells, and endothelial cells, as well as from dead (e.g. necrotic) cells (Scaffidi, Misteli, & Bianchi, 2002). HMGB1 enhances inflammatory reactions by potentiating the activity of pro-inflammatory mediators such as LPS and cytokines, and by suppressing the phagocytosis of apoptotic neutrophils (Banerjee et al., 2011; Liu et al., 2008). HMGB1 suppresses resolvin D1-induced phagocytosis via induction of resolvin D1-inactivating enzyme, 15-hydroxyprostaglandin dehydrogenase (Kang et al., 2015). HMGB1 suppressed RvD1-enhanced phagocytosis of MDA-MB-231 cancer cells and gene silencing of HMGB1 restored the phagocytic capability of MDA-MB-231 cells (Kang et al., 2015). Hepatocellular carcinoma ensues in the presence of excessive hepatic apoptosis and necroptosis in the tumor microenvironment which directs lineage commitment to either hepatocellular carcinoma or intrahepatic cholangiocarcinoma (Seehawer et al., 2018). The clearance of necroptotic cells are inefficiently taken up by macrophages in diseases characterized by impaired inflammation resolution (Gerlach et al., 2020). Necroptotic cells are inefficiently taken up by macrophages because they have increased surface expression of CD47, a “don't eat me” signal (Gerlach et al., 2020). Resolvin D1 enhanced the clearance of necroptotic cells in advanced murine plaques by the release of the “eat me signal” calreticulin from macrophages in a CDC42 dependent manner (Gerlach et al., 2020).

8.7. SPMs in humans

Evidence in humans demonstrates the importance of pro-resolving lipid mediators in the cancer patients. The pro-inflammatory response in response to hepatobiliary surgery is associated with low circulating concentrations of lipoxin A₄ and resolvins of the D series which were the opposite of IL-6 and cortisol which were elevated after surgery for liver tumors (Cata et al., 2017). The systemic inflammatory markers in the plasma C-reactive protein (CRP) and interleukin-6 were decreased in lung cancer patients administered EPA and DHA supplementation undergoing chemotherapy in a double-blind placebo-controlled study (Finocchiaro et al., 2012). In another study, compared with healthy volunteers, the levels of serum pro-inflammatory cytokines in colon cancer patients increase while the level of RvD1 decreased significantly associated with higher TNM stage of colon cancer (Zhuang, Meng, Xi, & Wu, 2018). Concentrations of IL-6, IL-1 β , IL-10 and TNF- α gradually increased with the advancement of TNM staging (Zhuang et al., 2018). In stage III, concentrations of IL-6, IL-1 β , and IL-10 were the highest, TNF- α concentration was the highest in stage IV. RvD1 concentration gradually decreased with the advancement of TNM staging (Zhuang et al., 2018).

Resolvin E1 (RvE1) plays a key role in the resolution of acute inflammation when immunonutrition is supplemented with EPA in patients undergoing a severely stressful operation (Uno et al., 2016). Pre-operative immunonutrition reduced pro-inflammatory responses and protected against the aggravation of post-operative complications in patients undergoing major hepatobiliary resection (Uno et al., 2016). In clinical randomized trials focused on dietary interventions that can boost SPMs, omega-3 fatty acids increased resolvins (e.g. RvE1) in patients undergoing hepatobiliary surgery for liver cancer, resulting in lower rates of infections, complications, and disease progression (Uno et al., 2016). The omega-3 fatty acid Lovaza stimulates SPM production in coronary artery disease patients (Elajami et al., 2016). SPMs were also boosted in military personnel and in traumatic brain injury patients administered with substrate supplementation

(Bisicchia et al., 2018). Peripheral blood markers of inflammation as well as inflammation resolution markers (e.g. resolvins) have been identified in cancer patients. ω -3 PUFAs exhibit anti-tumor activity in a variety of cancers such as breast cancer. SPMs may account for the anti-inflammatory and anti-cancer activity of ω -3 PUFA at least in part.

Maresins (e.g. MaR1) can also inhibit EMT of mouse type II alveolar epithelial cells and improve bleomycin-induced lung fibrosis (Wang, Li, et al., 2015). Protectin DX (PDX), a PD1 isomer that is a double lipoxygenation product, reverses bleomycin-induced lung fibrosis by reversing EMT and alleviates acute kidney injury (Duffield et al., 2006; Li et al., 2017). Docosahexaenoic acid (DHA) with A549 lung cancer cells can generate maresins (e.g. MaR1) and protectins (e.g. PD1/NPD1). The role of maresins and protectins in cancer remain of interest in the years ahead now that they are widely available. Thus, SPMs may be a novel approach to resolve multiple pro-tumorigenic processes Table 1.

8.8. Annexin A1 and Gaseous mediators

In addition to SPMs, inflammation resolution is also controlled by a variety of endogenous mediators including protein/peptide mediators, such as annexin A1 and annexin A1-derived peptides which stimulate inflammation resolution (Perretti et al., 2002). Interestingly, estrogen can stimulate resolution of inflammation in macrophages (Villa, Rizzi, Vegeto, Ciana, & Maggi, 2015). Other pro-resolution mediators are IL-10, gases (e.g. carbon monoxide and hydrogen sulfide), TGF- β , formyl-Peptide Receptors, Selenoproteins, Galectin-1, and nucleotides (e.g. adenosine and inosine) (Arbiser, Bonner, Ward, Elsej, & Rao, 2018; Nelson et al., 2016; Wallace, Ianaro, Flannigan, & Cirino, 2015). Drugs that stimulate resolution include aspirin, statins, omega-3 fatty acids, annexin A1 and annexin A1-derived peptides, statins, glucocorticoids, diclofenac, α -melanocyte stimulating hormone, erythropoietin, kinase inhibitors, galectins, chemerin, adrenocorticotropic hormone, gaseous mediators (e.g. hydrogen sulfide and carbon monoxide), purine (adenosine) as well as neuromediators and pioglitazone (Serhan & Levy, 2018). Drugs that may be resolution toxic include NSAIDs, COX-2 inhibitors, and lidocaine which impair efferocytosis (Serhan & Levy, 2018).

8.9. Diet, exercise and supplementation

Both omega-3 fatty acids and aspirin, which are known to reduce cancer risk, trigger the body's production of resolvins (Sun et al., 2007). Although resolvins inhibit primary tumor growth at doses over 10,000 fold less than omega-3 fatty acids, due to their rapid metabolism in vivo, an alternative approach for clinical application of SPMs in cancer is to increase their endogenous synthesis through dietary and pharmacologic intervention (Serhan, 2014). Omega-3 polyunsaturated fatty acids are precursors for many SPMs; for example, DHA is the substrate that aspirin-acetylated COX-2 converts to aspirin-triggered resolvins (e.g. AT-RvD1). In human subjects, dietary intake of DHA and EPA with aspirin treatment effectively increased plasma resolvin levels (Serhan, 2014). Similarly, mice fed a high omega-3 diet exhibited high levels of resolvins and omega-3 fatty acids in their tissues, serum, and plasma.

Thus, dietary interventions have been suggested as an approach to carcinogen associated inflammation. For example, in a DMBA-induced mammary carcinogenesis model low dose EPA and DHA demonstrated chemopreventive activity (Noguchi et al., 1997). A diet high in omega-3 fatty acids opposes the western diet, high in omega-6 fatty acids, which promotes inflammatory macrophage- and colitis-associated colon carcinogenesis (Kim et al., 2010). Importantly, DHA supplementation may increase the efficacy of HCC patients receiving sorafenib via increased anti-angiogenic and anti-tumorigenic lipids such as 19,20-epoxydocosapentaenoic acid (EDP) (Leineweber et al., 2020; Zhang, Panigrahy, et al., 2013). Additionally, diets, based off elite crop varieties containing anticancer effects have been demonstrated to reduce

Table 1
SPM cancer-related mechanisms.

Tumorigenic process	Specialized Pro-Resolving Mediators	Mechanisms	References
Anti-tumor activity	AT-RvD1, AT-RvD3, AT-LXA4	Aspirin-triggered SPMs suppress tumor growth	Gilligan et al.
	RvD2, RvD3, RvD4	Pre-operative supplementation eliminates micrometastases	Panigrahy et al.
	Resolvin receptor FPR1	Regulation of inflammation, angiogenesis, and gastric tumorigenesis	Prevete et al. Bai et al.
	RvD1	Inhibition of lung cancer growth and metastasis (miR138-5p/FOXO1)	Zhong et al.
	RvD1	Inhibits c-MYC in colon cancer cells	Claria et al.
Cancer associated loss of SPMs	15-epi-LXs	Produced by lung adenocarcinoma cell-leukocyte interactions inhibit proliferation	
	RvD1, LXA ₄	Loss during human colon cancer progression	Zhuang et al., Liu et al.
	Resolvin receptors GPR18, GPR32	Resolvin receptors downregulated in oral cancer cells	Ye et al.
	LXA ₄	Downregulated via IFN- γ signaling during inflammatory papilloma persistence	Wang et al.
Angiogenesis	Lipoxins (LXA ₄)	Lipoxin deficiency in leukemia, lymphoma and kaposi's sarcoma	Stenke et al., Chandrasekharan et al.
	LXA ₄ , BML-111	Inhibits VEGF and HIF-1 α to suppress hepatocarcinoma growth	Chen et al.
	LXA ₄ , 15-epi- LXA ₄	Anti-angiogenic and anti-inflammatory in Kaposi's sarcoma tumor cells	Marginean et al.
Inflammation	ATL-1 (15-epi- LXA ₄)		Vieira et al.
	PD1 _{n-3DPA} , RvD5 _{n-3DPA} , LXA ₄	Inhibit VEGF-induced permeability and tumor cell migration Protect inflammatory colitis induced injury	Gobbetti et al., Gewirtz et al.
	RvD1, RvD2	Inhibition of oral cancer derived cytokines and inflammatory cells	Ye et al.
	RvD1, RvE1	NF- κ B suppression prevention of liver hepatitis transition to cancer	Kuang et al.
	RvD1		Lu et al.
	RvD2, RvD3, RvD4, RvE1, AT-RvD1, AT-RvD3, AT-LXA4	LPS induced cancer cell proliferation inhibited via MAPK pathway targeting	Sulciner et al., Gilligan et al., Panigrahy et al.
	LXA ₄	Resolution and phagocytosis of inflammatory tumor-cell debris	Decker et al.
EPITHELIAL-MESENCHYMAL TRANSITION		Inhibits IL-8 and ICAM-1 in brain tumor cells	
	RvD1, AT-RvD1	Inhibition of TGF- β 1 for suppression of ZEB1, mTOR signaling	Lee et al., Liu et al.
	RvD1, AT-RVD1	Inhibition of carcinoma associated fibroblast signaling to inhibit EMT	Sun et al.
Fibrosis and invasion	Mar1, PDX		Wang et al., Li et al.
	LXA ₄	Inhibition of bleomycin induced fibrosis and EMT Inhibits pancreatic cell invasion via ROS/MMP and TGF- β 1	Zong et al.
	LXA ₄	Inhibits pancreatic cancer fibroblast activation	Schnittert et al.
	LXA ₄	Inhibits hepatocyte growth factor induced invasion	Zhou et al.
Immunosuppression	LXA ₄	Inhibit leukemia cell migration and induces phagocytosis of apoptotic cells	Tsai et al.
	RvD2, RvD3, RvD4	Induction of anti-tumor T-cell response	Panigrahy et al.
	RvD1	Induction of NK cell cytotoxicity to pancreatic cancer cells	Halder et al.
	RvD2, RvD5, LXA ₄	SPMs produced by cancer cell interaction with macrophages	Werner et al.
	ATL-1, LXA ₄	Induction of tumor cell apoptosis by TAMs to inhibit melanoma	Simoes et al.
LXA ₄	Target Breg cells to allow for CD8+ immunosurveillance and regulate MDSCs	Wang et al., Zhang et al.	

hepatocarcinogenesis from NDEA by downregulating TNF- α /IL-6, increasing antioxidants, and increasing apoptosis without stimulating regenerative proliferation (Zheng et al., 2019). Additionally, EPA suppressed IL-6-induced chronic inflammation in high fat diet and carcinogen-induced HCC (Inoue-Yamauchi, Itagaki, & Oda, 2018). In a colon cancer model EPA also reduced MMP9 cytokine production via NOTCH1 signaling to exhibit protective effects (Fazio et al., 2016). Alternatively, caloric restriction has been suggested as a mechanism to alter metabolic pathways in NDEA-induced HCC rather than diet leading to altered inflammation, oxidative stress, cell migration, injury and oncogenesis (Ploeger, Manivel, Boatner, & Mashek, 2017). Human plasma and serum found to consist of eicosanoids and SPMs, additional omega-3 or acetylsalicylic acid supplementation also increased plasma SPM levels inducing increased phagocytosis (Colas, Shinohara, Dalli, Chiang, & Serhan, 2014). In a randomized double blinded placebo controlled study marine oil supplements containing fatty acid precursors increased SPM levels in blood samples and reprogrammed blood cells to a pro-resolution phenotype (Souza et al., 2020). An additional clinical trial demonstrated efficacy of fish oil to benefit patients undergoing gastrointestinal surgery via regulation of TNF- α and NF- κ B (Wang, Yu, Kang, & Ma, 2012). Stretching of connective tissue stimulates murine production of SPMs including resolvins, suggesting the potential for beneficial cancer protective activity of exercise (Berrueta et al., 2016).

However, benefits of dietary intervention and fatty acid supplements results are not always validated. In one study dietary fish oil enhanced azaserine-induced pancreatic carcinogenesis in rats (Appel & Woutersen, 1996). Fish oil supplementation may require additional regulation of what lipids specifically are in the product as it is not one specific compound. In a model of carcinogen-induced inflammatory colon cancer the EPA:AA lipid ratio helped predict PGE₂ levels in the tumor tissue of mice fed with a fish oil diet or western fat diet. Thus, the beneficial activity of diets on lipid production may depend on the pre-existing tumor lipid microenvironment (Djuric et al., 2017). While fish oils have been suggested as an important source of antioxidants one group found environmental pollutants to outweigh the benefits of antioxidants in fish oil without proper regulation of persistent organic pollutants (Hong et al., 2017). In a study of women diagnosed with breast cancer omega-3 fatty acid intake did not affect overall breast cancer risk, although it did marginally reduce the risk of estrogen and progesterone receptor positive breast cancers, which was increased with omega-6 fatty acid intake (Kiyabu et al., 2015).

8.10. Epoxyeicosanoids and sEH inhibition

Epoxyeicosatrienoic acid (EETs) are lipid signaling molecules which act as autocrine and paracrine mediators of proliferation, migration, and inflammation in several tissues (Spector & Norris, 2007). EETs are fatty acid epoxides (EpFA) produced via the epoxidation of arachidonic acid catalyzed by cytochrome P450 (CYP) enzymes. Most CYP enzymes are general oxidases showing varying degrees of selectivity for the substrate and the product formed. In normal animals CYP2C8 or CYP2J2 appear largely responsible for production of EpFA and are metabolized by soluble epoxide hydrolase (sEH) to the corresponding 1, 2-diols. Members of the CYP4A, CYP2C, and CYP2J families of epoxygenases are among the most extensively studied (Fleming, 2007), however, in animals with induced cytochrome P450s other families may dominant production of EpFA. While CYP4A enzymes produce the vasoconstrictor 20-hydroxyeicosatrienoic acid (20-HETE), the CYP2C and CYP2J enzymes convert arachidonic acid to the bioactive epoxyeicosatrienoic acids (EETs), including 5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET. EETs are metabolized by soluble epoxide hydrolase (sEH) to less active dihydroxyeicosanoic acids (DHETs). EETs, which function primarily as autocrine and paracrine mediators of arachidonic acid-induced relaxation in the cardiovascular and renal systems, are short-lived and quickly metabolized in most tissues (Campbell & Falck, 2007; Fleming, 2008). EETs secreted mainly by endothelial cells have critical roles in cellular

proliferation, migration and inflammation; their major target cells are blood vessels (Spector & Norris, 2007). The EET producing enzymes of the CYP2C and CYP2J subfamilies have been found in endothelial cells (ECs) in vitro and in vivo (Fleming, 2007; Pozzi et al., 2005). Indeed, CYP2C enzymes are induced by hypoxia, and endothelial cells are a major source of EETs during inflammation and angiogenesis. Targeted inhibition of the EET-inactivating enzyme sEH raises the levels of the cardioprotective EETs. Thus, soluble epoxide hydrolase (sEH) inhibitors are in clinical development being evaluated in phase II clinical trials for hypertension. The role of EETs and soluble epoxide hydrolase inhibitors as classical mediators of inflammation offer targets for drugs directed towards the tumor stroma for cancer therapy.

sEH inhibition and epoxy fatty acids are dual functioning to inhibit inflammation-induced carcinogenesis and enhance NSAID-induced ulcer healing at the site of inflammation via suppressing reactive oxygen species, improved mitochondrial function (Jones et al., 2019). sEH is overexpressed in ulcerative colitis (UC)-associated dysplasia and adenocarcinoma (Zhang et al., 2013). EETs are anti-inflammatory and inhibit cytokine-mediated endothelial cell adhesion preventing leukocyte infiltration via NF- κ B (Node et al., 1999). sEH inhibition inhibits inflammatory bowel disease (IBD) and IBD-tumor development including dextran sulfate sodium (DSS)-induced carcinogenesis via suppressed cytokines/chemokines including MCP-1, iNOS, VCAM-1, IL-1 β and TNF- α (Zhang et al., 2012; Zhang et al., 2013; Zhang, Li, et al., 2013).

Inhibition of sEH inhibits chronic pancreatitis and the progression of pancreatic intraepithelial neoplasms (PanIN) via dual inhibition of sEH and RAF1 proto-oncogene serine/threonine kinase (c-RAF)(Liao et al., 2016). Omega-3 epoxy fatty acids combined with a sEH inhibitor inhibited pancreatic carcinoma via anti-inflammatory, anti-proliferation, reduced mutant Kras-activated signals, and anti-angiogenic activity (Xia et al., 2019). Soluble epoxide hydrolase (sEH) inhibitors stabilize arachidonic acid-derived epoxyeicosatrienoic acids (EETs), which also stimulate inflammation resolution by promoting the production of pro-resolution mediators (e.g. lipoxins), activating anti-inflammatory processes, and preventing the cytokine storm. sEH inhibition can inhibit vascular permeability to prevent diabetic retinopathy (Hu et al., 2017).

Poly-unsaturated fatty acids also generate EETs which are metabolites of the omega-6 fatty acid arachidonic acid (Lopez-Vicario et al., 2015; Zhang, Panigrahy, et al., 2013). EETs may potentially downregulate endoplasmic reticulum (ER) stress responses as demonstrated in response to cigarette smoke damage (Yu et al., 2015). Thus, inhibition of sEH may allow for their stability and prolonged effects and has demonstrated pro-resolution activity such as stimulation of SPMs and activating anti-cytokine programs in multiple inflammatory diseases, including those which are risk factors for cancer induction (Schmelzer et al., 2005; Wang et al., 2018; Yao et al., 2019; Yu et al., 2015). Importantly, the sEH eicosanoid pathway has been suggested to be involved in the progression of colorectal cancer, including obesity-associated cancer (Zhang, Sanidad, & Zhang, 2019). Inflammatory mediators, including angiotensin, TNF- α and NF- κ B can upregulate sEH expression in immune cells (Bastan et al., 2018). sEH inhibitors (sEHI) downregulate NF- κ B and other inflammatory markers leading to decreased pro-inflammatory cytokines and nitric oxide metabolites and upregulates lipoxins to generate resolution (Schmelzer et al., 2005). In addition to downregulating a series of pro-inflammatory cytokines, EETs promote macrophage phagocytosis (Bystrom et al., 2013), which may have implications for the clearance of carcinogen-generated dead cells. Importantly, inhibition of sEH also promotes the generation of SPMs such as lipoxin generation (Ono et al., 2014). A metabolomics approach identified a critical role for cytochrome P450 (CYP)-generated epoxygenerated fatty acids and sEH-mediated eicosanoids were elevated in the plasma and colon of azoxymethane (AOM)/dextran sodium sulfate (DSS)-induced colon cancer (Wang et al., 2019).

However, the role of EETs in cancer is complex as these epoxyeicosanoids may stimulate pro-angiogenic and pro-tumorigenic

mechanisms (Imig & Hammock, 2009; Panigrahy et al., 2012). The CYP3A4 produced EETs play a role in breast cancer progression, including in tamoxifen-resistant subsets via proliferation, angiogenesis, and migration (Thuy Phuong et al., 2017). While EETs can be mildly pro-angiogenic, inhibition of sEH prevents angiogenic diseases such as diabetic retinopathy (Hu et al., 2017). Interestingly, EET-induced angiogenesis is suppressed by simultaneous inhibition of COX-2 by preventing COX mediated metabolism to pro-angiogenic lipids (Rand et al., 2019). Importantly, sEHs may also reduce the toxicities of NSAIDs and COX-2 inhibitors via anti-inflammation and inhibition of oxidative injury as well as barrier breakdown (Jones et al., 2019). To minimize the pro-angiogenic activity of sEH inhibitor and the GI toxicity of COX-2 inhibitors, a novel COX-2/sEH inhibitor (PTUPB) was synthesized which potently inhibits inflammation (Hwang et al., 2011). Cancer progression is stimulated by inflammation, fibrosis, and oxidative stress. Dual COX-2/sEH inhibition via PTUPB inhibits allergic airway inflammation, pulmonary fibrosis, kidney injury and sepsis via anti-oxidative stress (Dileepan et al., 2019; Hye Khan et al., 2016; Zhang et al., 2020; Zhang et al., 2019). Dual COX-2/sEH inhibition inhibits primary tumor growth including glioblastoma growth, metastasis and potentiates the antitumor efficacy of chemotherapeutic agents such as cisplatin (Li et al., 2017; Wang et al., 2018; Zhang, Panigrahy, et al., 2014). A novel dual COX-2/sEH inhibitor (PTUPB) inhibits debris-stimulated ovarian tumor growth by preventing an eicosanoid and cytokine surge of pro-inflammatory and pro-angiogenic mediators (Gartung et al., 2019). PTUPB inhibits high-fat diet-induced non-alcoholic fatty liver disease via inhibition of fibrosis, collagen deposition and pro-inflammatory cytokines (Sun et al., 2020). sEH is a therapeutic target as it is upregulated in obesity-induced colonic inflammation and sEH inhibition reduces obesity-induced activation of Wnt signaling in mice (Wang et al., 2018). Notably, carcinogen-induced cell death dose-dependently promotes tumor dormancy escape and progression by triggering oxidative stress as well as an eicosanoid/cytokine storm of pro-inflammatory mediators (Fishbein et al., 2020). In contrast, dual COX-2/sEH inhibition prevents inflammation-initiated tumor growth by preventing the eicosanoid/cytokine storm and reducing oxidative stress, as well as by promoting macrophage-mediated efferocytosis of tumor debris (Fishbein et al., 2020). Thus, inhibition of sEH may synergize with COX-2 inhibition while reducing the toxicity of COX-2 inhibition.

Thus, EETs may additionally be a novel approach to resolving carcinogen-induced inflammation via anti-inflammatory signaling and stimulation of macrophage phagocytosis. Importantly, in bronchiolar cells in which oxidative stress reduced lipoxin production, sEHs stimulated pro-resolution mechanisms by stimulating the levels of lipoxins (Ono et al., 2014). Stimulation of resolution of inflammation, via SPMs or EETs, may be a novel chemopreventive approach to carcinogen-induced cycles of inflammation, cell death, oxidative stress, and carcinogenesis (Fig. 4).

9. Outlook

Cancer accounts for over 8 million deaths annually worldwide and presents one of the largest disease morbidity and mortality (Cortes et al., 2020). The prognosis for patients with cancer remains poor. Despite many exciting advances in research, many cancers remain deadly unless diagnosed early before advanced metastatic disease. The most effective treatment for patients is prevention and early detection. While carcinogens induce inflammation, a hallmark of cancer and a key characteristic of their pro-tumorigenic activity (Hanahan & Weinberg, 2011; Mantovani et al., 2008; Smith et al., 2016), they also disrupt the resolution of inflammation. Thus, the loss of inflammation resolution is an emerging mechanism of cancer pathogenesis (Gilligan et al., 2019; Liu et al., 2019; Panigrahy et al., 2019; Serhan & Levy, 2018; Sulciner, Gartung, et al., 2018; Sulciner, Serhan, et al., 2018; Ye et al., 2018). Carcinogens continue to play a large role in the disease and social burdens of cancer globally. However, genotoxic mechanisms alone may

not be sufficient for carcinogenesis and increased tumor risk (Bogen, 2019; Johnson et al., 2014), and more studies are required to further characterize nongenotoxic mechanisms including "failed" inflammation resolution. There is a malignant pro-tumorigenic feedback loop between apoptosis, inflammation, DNA damage, and carcinogenesis. Chronic inflammation and oxidative stress are largely intertwined processes which contribute via feedback loops to a microenvironment of stress, injury, and regeneration (Newsheen et al., 2012). Initial carcinogen exposure induces inflammatory pathways and signaling through NF- κ B leads to cytokine production, inflammatory infiltrates, and reactive oxygen species in a pro-tumorigenic environment. Controlling the local and systemic inflammatory response will be essential to prevent carcinogen-induced cancers. Stimulation of resolution via supplementation of specifically pro-resolution lipid mediators may be a potent and less toxic non-immunosuppressive approach to reduce and prevent carcinogenesis at an early stage (Gilligan et al., 2019). Importantly, SPMs, including resolvins, lipoxins, and protectins, as well as sEH inhibitors are currently in clinical trials for other inflammatory diseases and could be rapidly translated for the management of carcinogen-induced cancers. Pro-resolution therapies can complement current anti-carcinogen strategies via debris clearance and inflammatory cytokine suppression. Further studies including human cancer trials are needed to evaluate the stimulation of resolution of inflammation to prevent and treat carcinogen-induced cancers.

Acknowledgments

The authors are supported by NIH grants including R01GM038765 (to CNS); National Institute of Environmental Health Science Superfund Research Program grant P42 ES004699, and National Institute of Environmental Health Science (River Award R35ES030443) (to BDH); and the Credit Unions Kids at Heart Team (to DP); the C.J. Buckley Pediatric Brain Tumor Fund (DP); and the Joe Andruzzi Foundation (to DP). This manuscript has not been published elsewhere.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

References

- Abbes, S., Ben Salah-Abbes, J., Jebali, R., Younes, R. B., & Oueslati, R. (2016). Interaction of aflatoxin B1 and fumonisin B1 in mice causes immunotoxicity and oxidative stress: Possible protective role using lactic acid bacteria. *Journal of Immunotoxicology* 13(1), 46–54. <https://doi.org/10.3109/1547691X.2014.997905>.
- Aggarwal, B. B., Shishodia, S., Sandur, S. K., Pandey, M. K., & Sethi, G. (2006). Inflammation and cancer: How hot is the link? *Biochemical Pharmacology* 72(11), 1605–1621 doi: S0006-2952(06)00389-3 [pii] <https://doi.org/10.1016/j.bcp.2006.06.029>.
- Ahmad, A., & Ahmad, R. (2018). Proteomic approach to identify molecular signatures during experimental hepatic fibrosis and resveratrol supplementation. *International Journal of Biological Macromolecules* 119, 1218–1227. <https://doi.org/10.1016/j.ijbiomac.2018.08.062>.
- Aiub, C. A., Gadermaier, G., Silva, I. O., Felzenszwalb, I., Pinto, L. F., Ferreira, F., & Eckl, P. (2011). N-nitrosodiethylamine genotoxicity evaluation: A cytochrome P450 induction study in rat hepatocytes. *Genetics and Molecular Research* 10(4), 2340–2348. <https://doi.org/10.4238/2011.October.5.4>.
- Aiub, C. A., Pinto, L. F., & Felzenszwalb, I. (2003). N-Nitrosodiethylamine mutagenicity at low concentrations. *Toxicology Letters* 145(1), 36–45. [https://doi.org/10.1016/s0378-4274\(03\)00263-7](https://doi.org/10.1016/s0378-4274(03)00263-7).
- Aiub, C. A., Pinto, L. F., & Felzenszwalb, I. (2004). Standardization of conditions for the metabolic activation of N-nitrosodiethylamine in mutagenicity tests. *Genetics and Molecular Research* 3(2), 264–272.
- Akshatha, G. M., Raval, S. K., Arpitha, G. M., Raval, S. H., & Ghodasara, D. J. (2018). Immunohistochemical, histopathological study and chemoprotective effect of Solanum nigrum in N-nitrosodiethylamine-induced hepatocellular carcinoma in Wistar rats. *Vet World* 11(4), 402–409. <https://doi.org/10.14202/vetworld.2018.402-409>.
- Alieva, M., Margarido, A. S., Wiele, T., Abels, E. R., Colak, B., Boquetale, C., ... van Rhee, J. (2017). Preventing inflammation inhibits biopsy-mediated changes in tumor cell behavior. *Scientific Reports* 7(1), 7529. <https://doi.org/10.1038/s41598-017-07660-4>.
- Alitalo, A. K., Proulx, S. T., Karaman, S., Aebischer, D., Martino, S., Jost, M., ... Detmar, M. (2013). VEGF-C and VEGF-D Blockade inhibits inflammatory Skin carcinogenesis.

- Cancer Research* 73(14), 4212–4221. <https://doi.org/10.1158/0008-5472.CAN-12-4539>.
- Ament, Z., Waterman, C. L., West, J. A., Waterfield, C., Currie, R. A., Wright, J., & Griffin, J. L. (2013). A metabolomics investigation of non-genotoxic carcinogenicity in the rat. *Journal of Proteome Research* 12(12), 5775–5790. <https://doi.org/10.1021/pr4007766>.
- Amicone, L., & Marchetti, A. (2018). Microenvironment and tumor cells: two targets for new molecular therapies of hepatocellular carcinoma. *Translational Gastroenterology Hepatology* 3, 24. <https://doi.org/10.21037/tgh.2018.04.05>.
- Anand, P., Kunnumakkara, A. B., Sundaram, C., Harikumar, K. B., Tharakan, S. T., Lai, O. S., ... Aggarwal, B. B. (2008). Cancer is a preventable disease that requires major lifestyle changes. *Pharmaceutical Research* 25(9), 2097–2116. <https://doi.org/10.1007/s11095-008-9661-9>.
- Antonio, N., Bonnelykke-Behrndtz, M. L., Ward, L. C., Collin, J., Christensen, I. J., Steiniche, T., ... Martin, P. (2015). The wound inflammatory response exacerbates growth of pre-neoplastic cells and progression to cancer. *The EMBO Journal* 34(17), 2219–2236. <https://doi.org/10.15252/emboj.201490147>.
- Aoki, H., Hisada, T., Ishizuka, T., Utsugi, M., Kawata, T., Shimizu, Y., ... Mori, M. (2008). Resolvin E1 dampens airway inflammation and hyperresponsiveness in a murine model of asthma. *Biochemical and Biophysical Research Communications* 367(2), 509–515. <https://doi.org/10.1016/j.bbrc.2008.01.012>.
- Aoki, H., Hisada, T., Ishizuka, T., Utsugi, M., Ono, A., Koga, Y., ... Mori, M. (2010). Protective effect of resolvin E1 on the development of asthmatic airway inflammation. *Biochemical and Biophysical Research Communications* 400(1), 128–133. <https://doi.org/10.1016/j.bbrc.2010.08.025>.
- Appel, M. J., & Woutersen, R. A. (1996). Dietary fish oil (MaxEPA) enhances pancreatic carcinogenesis in azaserine-treated rats. *British Journal of Cancer* 73(1), 36–43. <https://doi.org/10.1038/bjc.1996.7>.
- Arber, N., & DuBois, R. N. (1999). Nonsteroidal anti-inflammatory drugs and prevention of colorectal cancer. *Current Gastroenterology Reports* 1(5), 441–448.
- Arbiser, J. L., Bonner, M. Y., Ward, N., Eley, J., & Rao, S. (2018). Selenium unmasks protective iron armor: A possible defense against cutaneous inflammation and cancer. *Biochimica et Biophysica Acta - General Subjects*. <https://doi.org/10.1016/j.bbagen.2018.05.018>.
- Ariel, A., Chiang, N., Arita, M., Petasis, N. A., & Serhan, C. N. (2003). Aspirin-triggered lipoxin A4 and B4 analogs block extracellular signal-regulated kinase-dependent TNF- α secretion from human T cells. *Journal of Immunology* 170(12), 6266–6272.
- Arita, M., Yoshida, M., Hong, S., Tjonahen, E., Glickman, J. N., Petasis, N. A., ... Serhan, C. N. (2005). Resolvin E1, an endogenous lipid mediator derived from omega-3 eicosapentaenoic acid, protects against 2,4,6-trinitrobenzene sulfonic acid-induced colitis. *Proceedings of the National Academy of Sciences of the United States of America* 102(21), 7671–7676. doi: 0409271102 [pii] <https://doi.org/10.1073/pnas.0409271102>.
- Arnardottir, H. H., Dalli, J., Norling, L. V., Colas, R. A., Perretti, M., & Serhan, C. N. (2016). Resolvin D3 Is Dysregulated in Arthritis and Reduces Arthritic Inflammation. *Journal of Immunology* 197(6), 2362–2368. <https://doi.org/10.4049/jimmunol.1502268>.
- Asai, T., Tsuchiya, Y., Okano, K., Piscoya, A., Nishi, C. Y., Ikoma, T., & Yamamoto, M. (2012). Aflatoxin contamination of red chili pepper from Bolivia and Peru, countries with high gallbladder cancer incidence rates. *Asian Pacific Journal of Cancer Prevention* 13(10), 5167–5170. <https://doi.org/10.7314/apjcp.2012.13.10.5167>.
- Badr El-Din, N. K., Ali, D. A., Othman, R., French, S. W., & Ghoneim, M. (2020). Chemopreventive role of arabinoside rice bran, MGN-3/Biobran, on liver carcinogenesis in rats. *Biomedicine & Pharmacotherapy* 126. <https://doi.org/10.1016/j.biopha.2020.110064>.
- Badr, G., El-Reda, G. A., El-Gamal, H., & Farid, M. E. (2020). Exposure to radioactive rocks from the Egyptian eastern desert attenuates the efficiency of the immune organs and induces apoptosis of blood lymphocytes in rat model. *Environmental Science and Pollution Research International* 27(8), 8684–8695. <https://doi.org/10.1007/s11356-019-07572-y>.
- Bai, X., Shao, J., Zhou, S., Zhao, Z., Li, F., Xiang, R., ... Pan, J. (2019). Inhibition of lung cancer growth and metastasis by DHA and its metabolite, rVd1, through miR-138-5p/FOXO1 pathway. *Journal of Experimental & Clinical Cancer Research* 38(1), 479. <https://doi.org/10.1186/s13046-019-1478-3>.
- Baker, N., O'Meara, S. J., Scannell, M., Maderna, P., & Godson, C. (2009). Lipoxin A4: anti-inflammatory and anti-angiogenic impact on endothelial cells. *Journal of Immunology* 182(6), 3819–3826. <https://doi.org/10.4049/jimmunol.0803175>.
- Bakiri, L., Hamacher, R., Grana, O., Guio-Carrion, A., Campos-Olivas, R., Martinez, L., ... Wagner, E. F. (2017). Liver carcinogenesis by FOS-dependent inflammation and cholesterol dysregulation. *The Journal of Experimental Medicine* 214(5), 1387–1409. <https://doi.org/10.1084/jem.20160935>.
- Balkwill, F., Charles, K. A., & Mantovani, A. (2005). Smoldering and polarized inflammation in the initiation and promotion of malignant disease. *Cancer Cell* 7(3), 211–217. doi: S1535-6108(05)00066-8 [pii] <https://doi.org/10.1016/j.ccr.2005.02.013>.
- Balkwill, F., & Mantovani, A. (2001). Inflammation and cancer: back to Virchow? *Lancet* 357(9255), 539–545. [https://doi.org/10.1016/S0140-6736\(00\)04046-0](https://doi.org/10.1016/S0140-6736(00)04046-0).
- Banerjee, S., de Freitas, A., Friggeri, A., Zmijewski, J. W., Liu, G., & Abraham, E. (2011). Intracellular HMGB1 negatively regulates efferocytosis. *Journal of Immunology* 187(9), 4686–4694. <https://doi.org/10.4049/jimmunol.1101500>.
- Bang, S., Xie, Y. K., Zhang, Z. J., Wang, Z., Xu, Z. Z., & Ji, R. R. (2018). GPR37 regulates macrophage phagocytosis and resolution of inflammatory pain. *The Journal of Clinical Investigation* 128(8), 3568–3582. <https://doi.org/10.1172/JCI99888>.
- Bannenberg, G. L. (2009). Resolvins: Current understanding and future potential in the control of inflammation. *Current Opinion in Drug Discovery & Development* 12(5), 644–658.
- Bannenberg, G. L., Chiang, N., Ariel, A., Arita, M., Tjonahen, E., Gotlinger, K. H., ... Serhan, C. N. (2005). Molecular circuits of resolution: formation and actions of resolvins and protectins. *Journal of Immunology* 174(7), 4345–4355 (doi: 174/7/4345 [pii]).
- Bansal, A. K., Bansal, M., Soni, G., & Bhatnagar, D. (2005a). Modulation of N-nitrosodiethylamine (NDEA) induced oxidative stress by vitamin E in rat erythrocytes. *Human & Experimental Toxicology* 24(6), 297–302. <https://doi.org/10.1191/0960327105ht5330a>.
- Bansal, A. K., Bansal, M., Soni, G., & Bhatnagar, D. (2005b). Protective role of Vitamin E pre-treatment on N-nitrosodiethylamine induced oxidative stress in rat liver. *Chemico-Biological Interactions* 156(2–3), 101–111. <https://doi.org/10.1016/j.cbi.2005.08.001>.
- Barker, E. C., Kim, B. G., Yoon, J. H., Tochtrop, G. P., Letterio, J. J., & Choi, S. H. (2018). Potent suppression of both spontaneous and carcinogen-induced colitis-associated colorectal cancer in mice by dietary celastrol supplementation. *Carcinogenesis* 39(1), 36–46. <https://doi.org/10.1093/carcin/bgx115>.
- Barton, C. C., Ganey, P. E., & Roth, R. A. (2000). Lipopolysaccharide augments aflatoxin B (1)-induced liver injury through neutrophil-dependent and -independent mechanisms. *Toxicological Sciences* 58(1), 208–215. <https://doi.org/10.1093/toxsci/58.1.208>.
- Bartsch, H., Ohshima, H., Shuker, D. E., Pignatelli, B., & Calmels, S. (1990). Exposure of humans to endogenous N-nitroso compounds: implications in cancer etiology. *Mutation Research* 238(3), 255–267.
- Bastan, I., Ge, X. N., Dileepan, M., Greenberg, Y. G., Guedes, A. G., Hwang, S. H., ... Sriramarao, P. (2018). Inhibition of soluble epoxide hydrolase attenuates eosinophil recruitment and food allergen-induced gastrointestinal inflammation. *Journal of Leukocyte Biology* 104(1), 109–122. <https://doi.org/10.1002/JLB.3MA1017-423R>.
- Beasley, R. P. (1988). Hepatitis B virus. The major etiology of hepatocellular carcinoma. *Cancer* 61(10), 1942–1956. [https://doi.org/10.1002/1097-0142\(19880515\)61:10<1942::aid-cnrc2820611003>3.0.co;2-j](https://doi.org/10.1002/1097-0142(19880515)61:10<1942::aid-cnrc2820611003>3.0.co;2-j).
- Beck, K. F., Eberhardt, W., Frank, S., Huwiler, A., Messmer, U. K., Muhl, H., & Pfeilschifter, J. (1999). Inducible NO synthase: role in cellular signalling. *The Journal of Experimental Biology* 202, 645–653 Pt 6.
- Beineke, A., Siebert, U., Stott, J., Muller, G., & Baumgartner, W. (2007). Phenotypical characterization of changes in thymus and spleen associated with lymphoid depletion in free-ranging harbor porpoises (*Phocoena phocoena*). *Veterinary Immunology and Immunopathology* 117(3–4), 254–265. <https://doi.org/10.1016/j.vetimm.2007.03.009>.
- Bento, A. F., Claudino, R. F., Dutra, R. C., Marcon, R., & Calixto, J. B. (2011). Omega-3 fatty acid-derived mediators 17(R)-hydroxy docosahexaenoic acid, aspirin-triggered resolvin D1 and resolvin D2 prevent experimental colitis in mice. *Journal of Immunology* 187(4), 1957–1969. doi: jimmunol.1101305 [pii] <https://doi.org/10.4049/jimmunol.1101305>.
- Berrueta, L., Muskaj, I., Olenich, S., Butler, T., Badger, G. J., Colas, R. A., ... Langevin, H. M. (2016). Stretching impacts inflammation resolution in connective tissue. *Journal of Cellular Physiology* 231(7), 1621–1627. <https://doi.org/10.1002/jcp.25263>.
- Besaratinia, A., Kim, S. I., Hainaut, P., & Pfeifer, G. P. (2009). In vitro recapitulation of TP53 mutagenesis in hepatocellular carcinoma associated with dietary aflatoxin B1 exposure. *Gastroenterology* 137(3), 1127–1137. doi: 1127-1137 e1121-1125 <https://doi.org/10.1053/j.gastro.2009.06.002>.
- Bhat, T. A., Kalathil, S. G., Bogner, P. N., Miller, A., Lehmann, P. V., Thatcher, T. H., ... Thanavala, Y. (2018). Secondhand smoke induces inflammation and impairs immunity to respiratory infections. *Journal of Immunology* 200(8), 2927–2940. <https://doi.org/10.4049/jimmunol.1701417>.
- Bhowmick, N. A., Neilson, E. G., & Moses, H. L. (2004). Stromal fibroblasts in cancer initiation and progression. *Nature* 432(7015), 332–337.
- Bianco, G., Russo, R., Marzocco, S., Velotto, S., Autore, G., & Severino, L. (2012). Modulation of macrophage activity by aflatoxins B1 and B2 and their metabolites aflatoxins M1 and M2. *Toxicol* 59(6), 644–650. <https://doi.org/10.1016/j.toxicol.2012.02.010>.
- Biarç, J., Nguyen, I. S., Pini, A., Gosse, F., Richert, S., Thiers, D., & Scholler-Guinard, M. (2004). Carcinogenic properties of proteins with pro-inflammatory activity from *Streptococcus infantarius* (formerly *S. bovis*). *Carcinogenesis* 25(8), 1477–1484. <https://doi.org/10.1093/carcin/bgh091>.
- Bishayee, A., Thoppil, R. J., Mandal, A., Darvesh, A. S., Ohanyan, V., Meszaros, J. G., ... Bhatia, D. (2013). Black currant phytoconstituents exert chemoprevention of diethylnitrosamine-initiated hepatocarcinogenesis by suppression of the inflammatory response. *Molecular Carcinogenesis* 52(4), 304–317. <https://doi.org/10.1002/mc.21860>.
- Bisicchia, E., Sasso, V., Catanzaro, G., Leuti, A., Besharat, Z. M., Chiacchiarini, M., ... Chirchich, V. (2018). Resolvin D1 halts remote neuroinflammation and improves functional recovery after focal brain damage Via ALX/FP2 receptor-regulated MicroRNAs. *Molecular Neurobiology* 55(8), 6894–6905. <https://doi.org/10.1007/s12035-018-0889-z>.
- Black, W. C., & Welch, H. G. (1993). Advances in diagnostic imaging and overestimations of disease prevalence and the benefits of therapy. *The New England Journal of Medicine* 328(17), 1237–1243. <https://doi.org/10.1056/NEJM199304293281706>.
- Boege, Y., Malehmir, M., Healy, M. E., Bettermann, K., Lorentzen, A., Vucur, M., ... Weber, A. (2017). A dual role of caspase-8 in triggering and sensing proliferation-associated DNA damage, a key determinant of liver cancer development. *Cancer Cell* 32(3), 342–359 e310. <https://doi.org/10.1016/j.ccell.2017.08.010>.
- Bogen, K. T. (2019). Inflammation as a cancer co-initiator: New mechanistic model predicts low/negligible risk at noninflammatory carcinogen doses. *Dose Response* 17(2). <https://doi.org/10.1177/1559325819847834> 1559325819847834.
- Bogovski, P., & Bogovski, S. (1981). Animal species in which N-nitroso compounds induce cancer. *International Journal of Cancer* 27(4), 471–474.
- Bol, D. K., Rowley, R. B., Ho, C. P., Pilz, B., Dell, J., Swerdel, M., ... Fischer, S. M. (2002). Cyclooxygenase-2 overexpression in the skin of transgenic mice results in suppression of tumor development. *Cancer Research* 62(9), 2516–2521.
- Bonavita, E., Pelly, V. S., & Zelenay, S. (2018). Resolving the dark side of therapy-driven cancer cell death. *The Journal of Experimental Medicine* 215(1), 9–11. <https://doi.org/10.1084/jem.20172044>.
- Borm, P. J., Tran, L., & Donaldson, K. (2011). The carcinogenic action of crystalline silica: a review of the evidence supporting secondary inflammation-driven genotoxicity as a

- principal mechanism. *Critical Reviews in Toxicology* 41(9), 756–770. <https://doi.org/10.3109/10408444.2011.576008>.
- Bose, P., Siddique, M. U. M., Acharya, R., Jayaprakash, V., Sinha, B. N., Lapenna, A., & Pattanayak, S. P. (2020). Quinazolinone derivative BNUA-3 ameliorated [NDEA+2-AAF]-induced liver carcinogenesis in SD rats by modulating AhR-CYP1B1-Nrf2-Keap1 pathway. *Clinical and Experimental Pharmacology & Physiology* 47(1), 143–157. <https://doi.org/10.1111/1440-1681.13184>.
- Brendler, S. Y., Tompa, A., Hutter, K. F., Preussmann, R., & Pool-Zobel, B. L. (1992). In vivo and in vitro genotoxicity of several N-nitrosamines in extrahepatic tissues of the rat. *Carcinogenesis* 13(12), 2435–2441.
- Brennan, P., Bogillot, O., Cordier, S., Greiser, E., Schill, W., Vineis, P., et al., & Boffetta, P. (2000). Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies. *International Journal of Cancer* 86(2), 289–294.
- Bystrom, J., Thomson, S. J., Johansson, J., Edin, M. L., Zeldin, D. C., Gilroy, D. W., Bishop-Bailey, D., et al. (2013). Inducible CYP2J2 and its product 11,12-EET promotes bacterial phagocytosis: a role for CYP2J2 deficiency in the pathogenesis of Crohn's disease? *PLoS One* 8(9), e75107. <https://doi.org/10.1371/journal.pone.0075107>.
- Cai, B., Kasikara, C., Doran, A. C., Ramakrishnan, R., Birge, R. B., & Tabas, I. (2018). MerTK signaling in macrophages promotes the synthesis of inflammation resolution mediators by suppressing CaMKII activity. *Science Signaling* 11(549). <https://doi.org/10.1126/scisignal.aar3721>.
- Campbell, W. B., & Falck, J. R. (2007). Arachidonic acid metabolites as endothelium-derived hyperpolarizing factors. *Hypertension* 49(3), 590–596 doi: 01.HYP.0000255173.50317.fc [pii] <https://doi.org/10.1161/01.HYP.0000255173.50317.fc>.
- Camphausen, K., Moses, M. A., Beecken, W. D., Khan, M. K., Folkman, J., & O'Reilly, M. S. (2001). Radiation therapy to a primary tumor accelerates metastatic growth in mice. *Cancer Research* 61(5), 2207–2211.
- Canny, G. O., & Lessey, B. A. (2013). The role of lipoxin A4 in endometrial biology and endometriosis. *Mucosal Immunology* 6(3), 439–450. <https://doi.org/10.1038/mi.2013.9>.
- Cao, S., Wang, Z., Gao, X., He, W., Cai, Y., Chen, H., & Xu, R. (2018). FOXCl induces cancer stem cell-like properties through upregulation of beta-catenin in NSCLC. *Journal of Experimental & Clinical Cancer Research* 37(1), 220. <https://doi.org/10.1186/s13046-018-0894-0>.
- Carlton, P. S., Gopalakrishnan, R., Gupta, A., Liston, B. W., Habib, S., Morse, M. A., & Stoner, G. D. (2002). Pirosixam is an ineffective inhibitor of N-nitrosomethylbenzylamine-induced tumorigenesis in the rat esophagus. *Cancer Research* 62(15), 4376–4382.
- Cata, J. P., Velasquez, J. F., Ramirez, M. F., Vauthey, J. N., Gottumukkala, V., Conrad, C., ... Aloia, T. (2017). Inflammation and pro-resolution inflammation after hepatobiliary surgery. *World Journal of Surgical Oncology* 15(1), 152. <https://doi.org/10.1186/s12957-017-1220-6>.
- Cezar-de-Mello, P. F., Vieira, A. M., Nascimento-Silva, V., Villela, C. G., Barja-Fidalgo, C., & Fierro, I. M. (2008). ATL-1, an analogue of aspirin-triggered lipoxin A4, is a potent inhibitor of several steps in angiogenesis induced by vascular endothelial growth factor. *British Journal of Pharmacology* 153(5), 956–965. <https://doi.org/10.1038/sj.bjpp.0707650>.
- Chaffer, C. L., San Juan, B. P., Lim, E., & Weinberg, R. A. (2016). EMT, cell plasticity and metastasis. *Cancer Metastasis Reviews* 35(4), 645–654. <https://doi.org/10.1007/s10555-016-9648-7>.
- Chandrasekharan, J. A., Huang, X. M., Hwang, A. C., & Sharma-Walia, N. (2016). Altering the anti-inflammatory lipoxin microenvironment: a New insight into Kaposi's Sarcoma-associated herpesvirus pathogenesis. *Journal of Virology* 90(24), 11020–11031. <https://doi.org/10.1128/JVI.01491-16>.
- Chang, J., Bhasin, S. S., Bielenberg, D. R., Sukhatme, V. P., Bhasin, M., Huang, S., ... Panigrahy, D. (2019). Chemotherapy-generated cell debris stimulates colon carcinoma tumor growth via osteopontin. *The FASEB Journal* 33(1), 114–125. <https://doi.org/10.1096/fj.201800019RR>.
- Chappell, G., Pogribny, I. P., Guyton, K. Z., & Rusyn, I. (2016). Epigenetic alterations induced by genotoxic occupational and environmental human chemical carcinogens: A systematic literature review. *Mutation Research, Reviews in Mutation Research* 768, 27–45. <https://doi.org/10.1016/j.mrrev.2016.03.004>.
- Chaurio, R., Janko, C., Schorn, C., Maueroeder, C., Bilyy, R., Gaip, U., ... Munoz, L. E. (2013). UVB-irradiated apoptotic cells induce accelerated growth of co-implanted viable tumor cells in immune competent mice. *Autoimmunity* 46(5), 317–322. <https://doi.org/10.3109/08916934.2012.754433>.
- Chawanthayatham, S., Valentine, C. C., 3rd, Fedele, B. I., Fox, E. J., Loeb, L. A., Levine, S. S., ... Essigmann, J. M. (2017). Mutational spectra of aflatoxin B1 in vivo establish biomarkers of exposure for human hepatocellular carcinoma. *Proceedings of the National Academy of Sciences of the United States of America* 114(15), E3101–E3109. <https://doi.org/10.1073/pnas.1700759114>.
- Chelko, S. P., Asimaki, A., Lowenthal, J., Bueno-Beti, C., Bedja, D., Scalco, A., ... Saffitz, J. E. (2019). Therapeutic modulation of the immune response in arrhythmogenic cardiomyopathy. *Circulation* 140(18), 1491–1505. <https://doi.org/10.1161/CIRCULATIONAHA.119.040676>.
- Chen, C. J., Zhang, Y. J., Lu, S. N., & Santella, R. M. (1992). Aflatoxin B1 DNA adducts in smeared tumor tissue from patients with hepatocellular carcinoma. *Hepatology* 16(5), 1150–1155.
- Chen, D., Yan, R., & Ye, Y. (1998). Influence of compensatory hepatocyte proliferation on the carcinogenesis of N-nitrosodimethylamine. *Zhonghua Bing Li Xue Za Zhi* 27(2), 105–108.
- Chen, F., Vallyathan, V., Castranova, V., & Shi, X. (2001). Cell apoptosis induced by carcinogenic metals. *Molecular and Cellular Biochemistry* 222(1–2), 183–188.
- Chen, J., Chen, K., Yuan, S., Peng, X., Fang, J., Wang, F., ... Geng, Y. (2016). Effects of aflatoxin B1 on oxidative stress markers and apoptosis of spleens in broilers. *Toxicology and Industrial Health* 32(2), 278–284. <https://doi.org/10.1177/0748233713500819>.
- Chen, W. H., & Young, T. M. (2009). Influence of nitrogen source on NDMA formation during chlorination of diuron. *Water Research* 43(12), 3047–3056. <https://doi.org/10.1016/j.watres.2009.04.020>.
- Chen, X., Gong, X., Jiang, R., Wang, B., Kuang, G., Li, K., & Wan, J. (2016). Resolvin D1 attenuates CCl4-induced acute liver injury involving up-regulation of HO-1 in mice. *Immunopharmacology and Immunotoxicology* 38(2), 61–67. <https://doi.org/10.3109/08923973.2015.115517>.
- Chen, X., Zhang, X., Lu, Y., Shim, J. Y., Sang, S., Sun, Z., & Chen, X. (2012). Chemoprevention of 7,12-dimethylbenz[a]anthracene (DMBA)-induced hamster cheek pouch carcinogenesis by a 5-lipoxygenase inhibitor, garcinol. *Nutrition and Cancer* 64(8), 1211–1218. <https://doi.org/10.1080/01635581.2012.718032>.
- Chen, Y., Hao, H., He, S., Cai, L., Li, Y., Hu, S., ... Chen, X. (2010). Lipoxin A4 and its analogue suppress the tumor growth of transplanted H22 in mice: the role of antiangiogenesis. *Molecular Cancer Therapeutics* 9(8), 2164–2174 doi: 1535-7163.MCT-10-0173 [pii] <https://doi.org/10.1158/1535-7163.MCT-10-0173>.
- Cherpokova, D., Jouvene, C. C., Libreros, S., DeRo, E. P., Chu, L., de la Rosa, X., ... Serhan, C. N. (2019). Resolvin D4 attenuates the severity of pathological thrombosis in mice. *Blood* 134(17), 1458–1468. <https://doi.org/10.1182/blood.2018886317>.
- Cheung, K. L., Lee, J. H., Khor, T. O., Wu, T. Y., Li, G. X., Chan, J., ... Kong, A. N. (2014). Nrf2 knockout enhances intestinal tumorigenesis in Apc(min/+) mice due to attenuation of anti-oxidative stress pathway while potentiates inflammation. *Molecular Carcinogenesis* 53(1), 77–84. <https://doi.org/10.1002/mc.21950>.
- Chiang, N., Dalli, J., Colas, R. A., & Serhan, C. N. (2015). Identification of resolvin D2 receptor mediating resolution of infections and organ protection. *The Journal of Experimental Medicine* 212(8), 1203–1217. <https://doi.org/10.1084/jem.20150225>.
- Chiang, N., Fredman, G., Backhed, F., Oh, S. F., Vickery, T., Schmidt, B. A., & Serhan, C. N. (2012). Infection regulates pro-resolving mediators that lower antibiotic requirements. *Nature* 484(7395), 524–528. <https://doi.org/10.1038/nature11042>.
- Chiang, N., Libreros, S., Norris, P. C., de la Rosa, X., & Serhan, C. N. (2019). Maresin 1 activates LGR6 receptor promoting phagocyte immunoresolvent functions. *The Journal of Clinical Investigation* 129(12), 5294–5311. <https://doi.org/10.1172/JCI129448>.
- Chikara, S., Mamidi, S., Sreedasyam, A., Chittem, K., Pietrofesa, R., Zuppa, A., ... Reindl, K. M. (2018). Flaxseed consumption inhibits chemically induced lung tumorigenesis and modulates expression of phase II enzymes and inflammatory cytokines in A/J mice. *Cancer Prevention Research (Philadelphia, Pa.)* 11(1), 27–37. <https://doi.org/10.1158/1940-6207.CAPR-17-0119>.
- Chmiela, M., Karwowska, Z., Gonciarz, W., Allushi, B., & Staczk, P. (2017). Host pathogen interactions in *Helicobacter pylori* related gastric cancer. *World Journal of Gastroenterology* 23(9), 1521–1540. <https://doi.org/10.3748/wjg.v23i9.1521>.
- Chu, Y. J., Yang, H. I., Wu, H. C., Lee, M. H., Liu, J., Wang, L. Y., ... Chen, C. J. (2018). Aflatoxin B1 exposure increases the risk of hepatocellular carcinoma associated with hepatitis C virus infection or alcohol consumption. *European Journal of Cancer* 94, 37–46. <https://doi.org/10.1016/j.ejca.2018.02.010>.
- Chung, K. T., & Gadupudi, G. S. (2011). Possible roles of excess tryptophan metabolites in cancer. *Environmental and Molecular Mutagenesis* 52(2), 81–104. <https://doi.org/10.1002/em.20588>.
- Claria, J., Lee, M. H., & Serhan, C. N. (1996). Aspirin-triggered lipoxins (15-epi-LX) are generated by the human lung adenocarcinoma cell line (A549)-neutrophil interactions and are potent inhibitors of cell proliferation. *Molecular Medicine* 2(5), 583–596.
- Claria, J., & Serhan, C. N. (1995). Aspirin triggers previously undescribed bioactive eicosanoids by human endothelial cell-leukocyte interactions. *Proceedings of the National Academy of Sciences of the United States of America* 92(21), 9475–9479.
- Claria, J., Titos, E., Jimenez, W., Ros, J., Gines, P., Arroyo, V., ... Rodes, J. (1998). Altered biosynthesis of leukotrienes and lipoxins and host defense disorders in patients with cirrhosis and ascites. *Gastroenterology* 115(1), 147–156. [https://doi.org/10.1016/s0016-5085\(98\)70376-2](https://doi.org/10.1016/s0016-5085(98)70376-2).
- Clish, C. B., O'Brien, J. A., Gronert, K., Stahl, G. L., Petasis, N. A., & Serhan, C. N. (1999). Local and systemic delivery of a stable aspirin-triggered lipoxin prevents neutrophil recruitment in vivo. *Proceedings of the National Academy of Sciences of the United States of America* 96(14), 8247–8252. <https://doi.org/10.1073/pnas.96.14.8247>.
- Colas, R. A., Shinohara, M., Dalli, J., Chiang, N., & Serhan, C. N. (2014). Identification and signature profiles for pro-resolving and inflammatory lipid mediators in human tissue. *American Journal of Physiology. Cell Physiology* 307(1), C39–C54. <https://doi.org/10.1152/ajpcell.00024.2014>.
- Coley, W. B. (1910). The Treatment of Inoperable Sarcoma by Bacterial Toxins (the Mixed Toxins of the *Streptococcus erysipelas* and the *Bacillus prodigiosus*). *Proceedings of the Royal Society of Medicine* 3(Surg Sect), 1–48.
- Colotta, F., Allavena, P., Sica, A., Garlanda, C., & Mantovani, A. (2009). Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* 30(7), 1073–1081. <https://doi.org/10.1093/carcin/bgp127>.
- Connor, K. M., SanGiovanni, J. P., Lofqvist, C., Aderman, C. M., Chen, J., Higuchi, A., ... Smith, L. E. (2007). Increased dietary intake of omega-3 polyunsaturated fatty acids reduces pathological retinal angiogenesis. *Nature Medicine* 13(7), 868–873 doi: nm1591 [pii] <https://doi.org/10.1038/nm1591>.
- Cooks, T., Harris, C. C., & Oren, M. (2014). Caught in the cross fire: p53 in inflammation. *Carcinogenesis* 35(8), 1680–1690. <https://doi.org/10.1093/carcin/bgu134>.
- Corsini, E., Avogadro, A., Galbiati, V., dell'Agli, M., Marinovich, M., Galli, C. L., & Germolec, D. R. (2011). In vitro evaluation of the immunotoxic potential of perfluorinated compounds (PFCS). *Toxicology and Applied Pharmacology* 250(2), 108–116. <https://doi.org/10.1016/j.taap.2010.11.004>.
- Cortes, J., Perez-Garcia, J. M., Llombart-Cussac, A., Curigliano, G., El Saghir, N. S., Cardoso, F., ... Arribas, J. (2020). Enhancing global access to cancer medicines. *CA: a Cancer Journal for Clinicians* 70(2), 105–124. <https://doi.org/10.3322/caac.21597>.
- Coussens, L. M., & Werb, Z. (2002). Inflammation and cancer. *Nature* 420(6917), 860–867.

- Coussens, L. M., Zitvogel, L., & Palucka, A. K. (2013). Neutralizing tumor-promoting chronic inflammation: A magic bullet? *Science* 339(6117), 286–291. <https://doi.org/10.1126/science.1232227>.
- Critelli, R., Milosa, F., Faillaci, F., Condello, R., Turola, E., Marzi, L., ... Villa, E. (2017). Micro-environment inflammatory infiltrate drives growth speed and outcome of hepatocellular carcinoma: a prospective clinical study. *Cell Death & Disease* 8(8), e3017. <https://doi.org/10.1038/cddis.2017.395>.
- Crosdell, A., Thatcher, T. H., Kottmann, R. M., Colas, R. A., Dalli, J., Serhan, C. N., ... Phipps, R. P. (2015). Resolvins attenuate inflammation and promote resolution in cigarette smoke-exposed human macrophages. *American Journal of Physiology. Lung Cellular and Molecular Physiology* 309(8), L888–L901. <https://doi.org/10.1152/ajplung.00125.2015>.
- Dai, J., Tang, K., Xiao, W., Yu, G., Zeng, J., Li, W., ... Ye, Z. Q. (2014). Prognostic significance of C-reactive protein in urological cancers: a systematic review and meta-analysis. *Asian Pacific Journal of Cancer Prevention* 15(8), 3369–3375.
- Dai, S., Zhu, M., Wu, R., Lin, D., Huang, Z., Ren, L., ... Chen, Q. (2019). Lipoxin A4 Suppresses IL-1beta-Induced Cyclooxygenase-2 Expression Through Inhibition of p38 MAPK Activation in Endometriosis. *Reproductive Sciences* 26(12), 1640–1649. <https://doi.org/10.1177/1933719119828115>.
- Dairkee, S. H., Luciani-Torres, G., Moore, D. H., Jaffee, I. M., & Goodson, W. H., 3rd. (2018). A ternary mixture of common chemicals perturbs benign human breast epithelial cells more than the same chemicals do individually. *Toxicological Sciences* 165(1), 131–144. <https://doi.org/10.1093/toxsci/kfy126>.
- Dalli, J., Winkler, J. W., Colas, R. A., Armarodotti, H., Cheng, C. Y., Chiang, N., ... Serhan, C. N. (2013). Resolvin D3 and aspirin-triggered resolvin D3 are potent immunoregulators. *Chemistry & Biology* 20(2), 188–201. <https://doi.org/10.1016/j.chembiol.2012.11.010>.
- De Marzo, A. M., Platz, E. A., Sutcliffe, S., Xu, J., Gronberg, H., Drake, C. G., ... Nelson, W. G. (2007). Inflammation in prostate carcinogenesis. *Nature Reviews. Cancer* 7(4), 256–269. <https://doi.org/10.1038/nrc2090>.
- DeCicco-Skinner, K. L., Nolan, S. J., Deshpande, M. M., Trovato, E. L., Dempsey, T. A., & Wiest, J. S. (2013). Altered prostanoid signaling contributes to increased skin tumorigenesis in Tpl2 knockout mice. *PLoS One* 8(2), e56212. <https://doi.org/10.1371/journal.pone.0056212>.
- Decker, Y., McBean, G., & Godson, C. (2009). Lipoxin A4 inhibits IL-1beta-induced IL-8 and ICAM-1 expression in 1321N1 human astrocytoma cells. *American Journal of Physiology. Cell Physiology* 296(6), C1420–C1427 doi: 00380.2008 [pii] <https://doi.org/10.1152/ajpcell.00380.2008>.
- Deferme, L., Wolters, J., Claessen, S., Briede, J., & Kleinjans, J. (2015). Oxidative stress mechanisms do not discriminate between genotoxic and nongenotoxic liver carcinogens. *Chemical Research in Toxicology* 28(8), 1636–1646. <https://doi.org/10.1021/acs.chemrestox.5b00222>.
- Dennehy, M. K., & Loeppky, R. N. (2005). Mass spectrometric methodology for the determination of glyoxaldehyde deoxyguanosine and O6-hydroxyethyldeoxyguanosine DNA adducts produced by nitrosamine bident carcinogens. *Chemical Research in Toxicology* 18(3), 556–565. <https://doi.org/10.1021/tx049802o>.
- Desjardins, R., Fournier, M., Denizeau, F., & Krzymysiak, K. (1992). Immunosuppression by chronic exposure to N-nitrosodimethylamine (NDMA) in mice. *Journal of Toxicology and Environmental Health* 37(3), 351–361. <https://doi.org/10.1080/15287399209531676>.
- Devchand, P. R., Keller, H., Peters, J. M., Vazquez, M., Gonzalez, F. J., & Wahli, W. (1996). The PPARalpha-leukotriene B4 pathway to inflammation control. *Nature* 384(6604), 39–43.
- Diani-Moore, S., Ma, Y., Gross, S. S., & Rifkind, A. B. (2014). Increases in levels of epoxyeicosatrienoic and dihydroxyeicosatrienoic acids (EETs and DHETs) in liver and heart in vivo by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and in hepatic EET:DHET ratios by cotreatment with TCDD and the soluble epoxide hydrolase inhibitor AUDA. *Drug Metabolism and Disposition* 42(2), 294–300. <https://doi.org/10.1124/dmd.113.055368>.
- Diaz-Beveridge, R., Bruixola, G., Lorente, D., Caballero, J., Rodrigo, E., Segura, A., ... Aparicio, J. (2018). An internally validated new clinical and inflammation-based prognostic score for patients with advanced hepatocellular carcinoma treated with sorafenib. *Clinical & Translational Oncology* 20(3), 322–329. <https://doi.org/10.1007/s12094-017-1720-4>.
- DiGiovanni, J., Rho, O., Xian, W., & Beltran, L. (1994). Role of the epidermal growth factor receptor and transforming growth factor alpha in mouse skin carcinogenesis. *Progress in Clinical and Biological Research* 387, 113–138.
- Dileepan, M., Rastle-Simpson, S., Greenberg, Y., Wijesinghe, D. S., Kumar, N. G., Yang, J., ... Rao, S. P. (2019). Effect of dual sEH/COX-2 inhibition on allergen-induced airway inflammation. *Frontiers in Pharmacology* 10, 1118. <https://doi.org/10.3389/fphar.2019.01118>.
- Ding, Y. F., Wu, Z. H., Wei, Y. J., Shu, L., & Peng, Y. R. (2017). Hepatic inflammation-fibrosis-cancer axis in the rat hepatocellular carcinoma induced by diethylnitrosamine. *Journal of Cancer Research and Clinical Oncology* 143(5), 821–834. <https://doi.org/10.1007/s00432-017-2364-z>.
- Djurić, Z., Aslam, M. N., Simon, B. R., Sen, A., Jiang, Y., Ren, J., ... Brenner, D. E. (2017). Fatty acid and lipidomic data in normal and tumor colon tissues of rats fed diets with and without fish oil. *Data in Brief* 13, 661–666. <https://doi.org/10.1016/j.dib.2017.06.032>.
- Doe, J. E., Boobis, A. R., Dellarco, V., Fenner-Crisp, P. A., Moretto, A., Pastoor, T. P., ... Wolf, D. C. (2019). Chemical carcinogenicity revisited 2: Current knowledge of carcinogenesis shows that categorization as a carcinogen or non-carcinogen is not scientifically credible. *Regulatory Toxicology and Pharmacology* 103, 124–129. <https://doi.org/10.1016/j.yrtph.2019.01.024>.
- Dragan, Y. P., Bidlack, W. R., Cohen, S. M., Goldsworthy, T. L., Hard, G. C., Howard, P. C., ... Voss, K. A. (2001). Implications of apoptosis for toxicity, carcinogenicity, and risk assessment: fumonisin B(1) as an example. *Toxicological Sciences* 61(1), 6–17. <https://doi.org/10.1093/toxsci/61.1.6>.
- Duan, X. Y., Pan, Q., Yan, S. Y., Ding, W. J., Fan, J. G., & Qiao, L. (2014). High-saturate-fat diet delays initiation of diethylnitrosamine-induced hepatocellular carcinoma. *BMC Gastroenterology* 14, 195. <https://doi.org/10.1186/s12876-014-0195-9>.
- Duan, Y., Luo, L., Qiao, C., Li, X., Wang, J., Liu, H., ... Feng, J. (2019). A novel human anti-AXL monoclonal antibody attenuates tumour cell migration. *Scandinavian Journal of Immunology* 90(2). <https://doi.org/10.1111/sji.12777>.
- DuBois, R. N., Gupta, R., Brockman, J., Reddy, B. S., Krakow, S. L., & Lazar, M. A. (1998). The nuclear eicosanoid receptor, PPARgamma, is aberrantly expressed in colonic cancers. *Carcinogenesis* 19(1), 49–53.
- Duffield, J. S., Hong, S., Vaidya, V. S., Lu, Y., Fredman, G., Serhan, C. N., & Bonventre, J. V. (2006). Resolvin D series and protectin D1 mitigate acute kidney injury. *Journal of Immunology* 177(9), 5902–5911. <https://doi.org/10.4049/jimmunol.177.9.5902>.
- Dvorak, H. F. (1986). Tumors: Wounds that do not heal. Similarities between tumor stroma generation and wound healing. *The New England Journal of Medicine* 315(26), 1650–1659. <https://doi.org/10.1056/NEJM198612253152606>.
- Eaton, D. L., & Schaub, C. M. (2014). Of mice, rats, and men: Could Nrf2 activation protect against aflatoxin hepatocarcinogenesis in humans? *Cancer Prevention Research (Philadelphia, Pa.)* 7(7), 653–657. <https://doi.org/10.1158/1940-6207.CAPR-14-0119>.
- El Okle, O. S., El Euony, O. I., Khafaga, A. F., & Lebda, M. A. (2018). Thiamethoxam induced hepatotoxicity and pro-carcinogenicity in rabbits via motivation of oxidative stress, inflammation, and anti-apoptotic pathway. *Environmental Science and Pollution Research International* 25(5), 4678–4689. <https://doi.org/10.1007/s11356-017-0850-0>.
- Elajami, T. K., Colas, R. A., Dalli, J., Chiang, N., Serhan, C. N., & Welty, F. K. (2016). Specialized proresolving lipid mediators in patients with coronary artery disease and their potential for clot remodeling. *The FASEB Journal* 30(8), 2792–2801. <https://doi.org/10.1096/fj.201500155R>.
- Eldridge, S. R., Gould, M. N., & Butterworth, B. E. (1992). Genotoxicity of environmental agents in human mammary epithelial cells. *Cancer Research* 52(20), 5617–5621.
- Enoki, T., Tominaga, T., Takashima, F., Ohnogi, H., Sagawa, H., & Kato, I. (2012). Anti-tumor-promoting activities of agaro-oligosaccharides on two-stage mouse skin carcinogenesis. *Biological & Pharmaceutical Bulletin* 35(7), 1145–1149. <https://doi.org/10.1248/bpb.b12-00188>.
- Eritja, N., Jove, M., Fasmer, K. E., Gatiús, S., Portero-Otin, M., Trovik, J., ... Matias-Guiu, X. (2017). Tumour-microenvironmental blood flow determines a metabolomic signature identifying lysophospholipids and resolvin D as biomarkers in endometrial cancer patients. *Oncotarget* 8(65), 109018–109026. <https://doi.org/10.18632/oncotarget.22558>.
- Escriva, L., Font, G., Manyes, L., & Berrada, H. (2017). Studies on the presence of mycotoxins in biological samples: An overview. *Toxins (Basel)* 9(8). <https://doi.org/10.3390/toxins9080251>.
- Espinoza, J. A., Bizama, C., Garcia, P., Ferreccio, C., Javle, M., Miquel, J. F., ... Roa, J. C. (2016). The inflammatory inception of gallbladder cancer. *Biochimica et Biophysica Acta* 1865(2), 245–254. <https://doi.org/10.1016/j.bbcan.2016.03.004>.
- Eun, H. S., Cho, S. Y., Lee, B. S., Seong, I. O., & Kim, K. H. (2018). Profiling cytochrome P450 family 4 gene expression in human hepatocellular carcinoma. *Molecular Medicine Reports* 18(6), 4865–4876. <https://doi.org/10.3892/mmr.2018.9526>.
- Fantini, D., Glaser, A. P., Rimar, K. J., Wang, Y., Schipma, M., Varghese, N., ... Meeks, J. J. (2018). A Carcinogen-induced mouse model recapitulates the molecular alterations of human muscle invasive bladder cancer. *Oncogene* 37(14), 1911–1925. <https://doi.org/10.1038/s41388-017-0099-6>.
- Fazio, C., Piazzi, G., Vitaglione, P., Fogliano, V., Munarini, A., Prossomariti, A., ... Ricciardiello, L. (2016). Inflammation increases NOTCH1 activity via MMP9 and is counteracted by Eicosapentaenoic Acid-free fatty acid in colon cancer cells. *Scientific Reports* 6. <https://doi.org/10.1038/srep20670>.
- Felton, J. M., Lucas, C. D., Dorward, D. A., Duffin, R., Kipari, T., Vermeren, S., ... Rossi, A. G. (2018). Mer-mediated eosinophil efferocytosis regulates resolution of allergic airway inflammation. *The Journal of Allergy and Clinical Immunology* 142(6), 1884–1893 e1886. <https://doi.org/10.1016/j.jaci.2018.01.029>.
- Fielden, M. R., Ward, L. D., Minocherhomji, S., Nioi, P., Lebec, H., & Jacobson-Kram, D. (2018). Modernizing human cancer risk assessment of therapeutics. *Trends in Pharmaceutical Sciences* 39(3), 232–247. <https://doi.org/10.1016/j.tips.2017.11.005>.
- Fierro, I. M., Kutok, J. L., & Serhan, C. N. (2002). Novel lipid mediator regulators of endothelial cell proliferation and migration: aspirin-triggered-15R-lipoxin A(4) and lipoxin A(4). *The Journal of Pharmacology and Experimental Therapeutics* 300(2), 385–392. <https://doi.org/10.1124/jpet.300.2.385>.
- Filippou, P. S., & Karagiannis, G. S. (2020). Cytokine storm during chemotherapy: a new companion diagnostic emerges? *Oncotarget* 11(3), 213–215. <https://doi.org/10.18632/oncotarget.27442>.
- Fink, S. P., Dawson, D. M., Zhang, Y., Kresak, A., Lawrence, E. G., Yang, P., ... Markowitz, S. D. (2015). Sulindac reversal of 15-PGDH-mediated resistance to colon tumor chemoprevention with NSAIDs. *Carcinogenesis* 36(2), 291–298. <https://doi.org/10.1093/carcin/bgu241>.
- Finocchiaro, C., Segre, O., Fadda, M., Monge, T., Scigliano, M., Schena, M., ... Canuto, R. A. (2012). Effect of n-3 fatty acids on patients with advanced lung cancer: a double-blind, placebo-controlled study. *The British Journal of Nutrition* 108(2), 327–333. <https://doi.org/10.1017/S0007114511005551>.
- Fiorucci, S., de Lima, O. M., Jr., Mencarelli, A., Palazzetti, B., Distrutti, E., McKnight, W., ... Wallace, J. L. (2002). Cyclooxygenase-2-derived lipoxin A4 increases gastric resistance to aspirin-induced damage. *Gastroenterology* 123(5), 1598–1606. <https://doi.org/10.1053/gast.2002.36558>.
- Fishbein, A., Wang, W., Yang, H., Yang, J., Hallisey, V. M., Deng, J., ... Panigrahy, D. (2020). Resolution of eicosanoid/cytokine storm prevents carcinogen and inflammation-initiated hepatocellular cancer progression. *Proceedings of the National Academy of Sciences of the United States of America*. <https://doi.org/10.1073/pnas.2007412117>.

- Fitzgerald, D. J., & Robinson, N. I. (2007). Development of a tolerable daily intake for N-nitrosodimethylamine using a modified benchmark dose methodology. *Journal of Toxicology and Environmental Health. Part A* 70(19), 1670–1678. <https://doi.org/10.1080/15287390701434844>.
- Fleming, I. (2007). Epoxyeicosatrienoic acids, cell signaling and angiogenesis. *Prostaglandins & Other Lipid Mediators* 82(1–4), 60–67 doi: S1098-8823(06)00052-9 [pii] <https://doi.org/10.1016/j.prostaglandins.2006.05.003>.
- Fleming, I. (2008). Vascular cytochrome p450 enzymes: physiology and pathophysiology. *Trends in Cardiovascular Medicine* 18(1), 20–25 doi: S1050-1738(07)00243-5 [pii] <https://doi.org/10.1016/j.tcm.2007.11.002>.
- Flitter, B. A., Hvorecny, K. L., Ono, E., Eddens, T., Yang, J., Kwak, D. H., ... Bomberger, J. M. (2017). Pseudomonas aeruginosa sabotages the generation of host proresolving lipid mediators. *Proceedings of the National Academy of Sciences of the United States of America* 114(1), 136–141. <https://doi.org/10.1073/pnas.1610242114>.
- Folkman, J. (2001). Angiogenesis. In E. Braunwald, A. S. Fauci, D. L. Kasper, S. L. Hauser, D. L. Longo, & J. L. Jameson (Eds.), *Harrison's Textbook of Internal Medicine* (pp. 517–530). McGraw-Hill.
- Folkman, J. (2007). Angiogenesis: an organizing principle for drug discovery? *Nature Reviews. Drug Discovery* 6(4), 273–286 doi: nrd2115 [pii] <https://doi.org/10.1038/nrd2115>.
- Ford, C. A., Petrova, S., Pound, J. D., Voss, J. J., Melville, L., Paterson, M., ... Gregory, C. D. (2015). Oncogenic properties of apoptotic tumor cells in aggressive B cell lymphoma. *Current Biology* 25(5), 577–588. <https://doi.org/10.1016/j.cub.2014.12.059>.
- Forget, P., Simonet, O., & De Kock, M. (2013). Cancer surgery induces inflammation, immunosuppression and neo-angiogenesis, but is it influenced by analgesics? *F1000Res* 2, 102. <https://doi.org/10.12688/f1000research.2-102.v1>.
- Fredman, G., Hellmann, J., Proto, J. D., Kuriakose, G., Colas, R. A., Dorweiler, B., ... Tabas, I. (2016). An imbalance between specialized pro-resolving lipid mediators and pro-inflammatory leukotrienes promotes instability of atherosclerotic plaques. *Nature Communications* 7, 12859. <https://doi.org/10.1038/ncomms12859>.
- Freedman, N. D., Silverman, D. T., Hollenbeck, A. R., Schatzkin, A., & Abnet, C. C. (2011). Association between smoking and risk of bladder cancer among men and women. *JAMA* 306(7), 737–745. <https://doi.org/10.1001/jama.2011.1142>.
- Freiberg, J. A. (2017). The myths of laudable pus along with an explanation for its origin. *Journal of Community Hospital Internal Medicine Perspectives* 7(3), 196–198. <https://doi.org/10.1080/20009666.2017.1343077>.
- Fujiki, H., Sueoka, E., & Suganuma, M. (2013). Tumor promoters: from chemicals to inflammatory proteins. *Journal of Cancer Research and Clinical Oncology*. <https://doi.org/10.1007/s00432-013-1455-8>.
- Gartung, A., Yang, J., Sukhatme, V. P., Bielenberg, D. R., Fernandes, D., Chang, J., ... Panigrahy, D. (2019). Suppression of chemotherapy-induced cytokine/lipid mediator surge and ovarian cancer by a dual COX-2/sEH inhibitor. *Proceedings of the National Academy of Sciences of the United States of America* 116(5), 1698–1703. <https://doi.org/10.1073/pnas.1803999116>.
- George, J., Tsuchishima, M., & Tsutsumi, M. (2019). Molecular mechanisms in the pathogenesis of N-nitrosodimethylamine induced hepatic fibrosis. *Cell Death & Disease* 10(1), 18. <https://doi.org/10.1038/s41419-018-1272-8>.
- George, J., Tsutsumi, M., & Tsuchishima, M. (2019). Alteration of trace elements during pathogenesis of N-Nitrosodimethylamine Induced Hepatic Fibrosis. *Scientific Reports* 9(1), 708. <https://doi.org/10.1038/s41598-018-37516-4>.
- Gerlach, B. D., Marinello, M., Heinz, J., Rymut, N., Sansbury, B. E., Riley, C. O., ... Fredman, G. (2020). Resolvin D1 promotes the targeting and clearance of necroptotic cells. *Cell Death and Differentiation* 27(2), 525–539. <https://doi.org/10.1038/s41418-019-0370-1>.
- Gewirtz, A. T., Collier-Hyams, L. S., Young, A. N., Kucharzik, T., Guilford, W. J., Parkinson, J. F., ... Madara, J. L. (2002). Lipoxin A4 analogs attenuate induction of intestinal epithelial proinflammatory gene expression and reduce the severity of dextran sodium sulfate-induced colitis. *Journal of Immunology* 168(10), 5260–5267. <https://doi.org/10.4049/jimmunol.168.10.5260>.
- Gilligan, M. M., Gartung, A., Sulciner, M. L., Norris, P. C., Sukhatme, V. P., Bielenberg, D. R., ... Panigrahy, D. (2019). Aspirin-triggered proresolving mediators stimulate resolution in cancer. *Proceedings of the National Academy of Sciences of the United States of America* 116(13), 6292–6297. <https://doi.org/10.1073/pnas.1804000116>.
- Gills, J. J., Jeffery, E. H., Matusheski, N. V., Moon, R. C., Lantvit, D. D., & Pezzuto, J. M. (2006). Sulforaphane prevents mouse skin tumorigenesis during the stage of promotion. *Cancer Letters* 236(1), 72–79. <https://doi.org/10.1016/j.canlet.2005.05.007>.
- Gilroy, D. W., & Colville-Nash, P. R. (2000). New insights into the role of COX 2 in inflammation. *Journal of Molecular Medicine (Berlin, Germany)* 78(3), 121–129.
- Gilroy, D. W., Colville-Nash, P. R., Willis, D., Chivers, J., Paul-Clark, M. J., & Willoughby, D. A. (1999). Inducible cyclooxygenase may have anti-inflammatory properties. *Nature Medicine* 5(6), 698–701. <https://doi.org/10.1038/9550>.
- Gilroy, D. W., Lawrence, T., Perretti, M., & Rossi, A. G. (2004). Inflammatory resolution: new opportunities for drug discovery. *Nature Reviews. Drug Discovery* 3(5), 401–416. <https://doi.org/10.1038/nrd1383>.
- Gobbetti, T., Dalli, J., Colas, R. A., Federici Canova, D., Aursnes, M., Bonnet, D., ... Perretti, M. (2017). Protectin D1n-3 DPA and resolvin D5n-3 DPA are effectors of intestinal protection. *Proceedings of the National Academy of Sciences of the United States of America* 114(15), 3963–3968. <https://doi.org/10.1073/pnas.1617290114>.
- Gonzalez-Periz, A., Horrillo, R., Ferre, N., Gronert, K., Dong, B., Moran-Salvador, E., ... Claria, J. (2009). Obesity-induced insulin resistance and hepatic steatosis are alleviated by omega-3 fatty acids: a role for resolvins and protectins. *The FASEB Journal* 23(6), 1946–1957 doi: fj.08-125674 [pii] <https://doi.org/10.1096/fj.08-125674>.
- Greene, E. R., Huang, S., Serhan, C. N., & Panigrahy, D. (2011). Regulation of inflammation in cancer by eicosanoids. *Prostaglandins & Other Lipid Mediators* 96(1–4), 27–36. <https://doi.org/10.1016/j.prostaglandins.2011.08.004>.
- Greten, F. R., & Grivennikov, S. I. (2019). Inflammation and cancer: Triggers, mechanisms, and consequences. *Immunity* 51(1), 27–41. <https://doi.org/10.1016/j.immuni.2019.06.025>.
- Grosse, Y., Loomis, D., Lauby-Secretan, B., El Ghissassi, F., Bouvard, V., Benbrahim-Tallaa, L., ... International Agency for Research on Cancer Monograph Working, G (2013). Carcinogenicity of some drugs and herbal products. *The Lancet Oncology* 14(9), 807–808.
- Guerra, C., Collado, M., Navas, C., Schuhmacher, A. J., Hernandez-Porrás, I., Canamero, M., ... Barbacid, M. (2011). Pancreatitis-induced inflammation contributes to pancreatic cancer by inhibiting oncogene-induced senescence. *Cancer Cell* 19(6), 728–739. <https://doi.org/10.1016/j.ccr.2011.05.011>.
- Guerra, C., Schuhmacher, A. J., Canamero, M., Grippo, P. J., Verdaguier, L., Perez-Gallego, L., ... Barbacid, M. (2007). Chronic pancreatitis is essential for induction of pancreatic ductal adenocarcinoma by K-Ras oncogenes in adult mice. *Cancer Cell* 11(3), 291–302. <https://doi.org/10.1016/j.ccr.2007.01.012>.
- Gunjal, P. M., Schneider, G., Ismail, A. A., Kakar, S. S., Kucia, M., & Ratajczak, M. Z. (2015). Evidence for induction of a tumor metastasis-receptive microenvironment for ovarian cancer cells in bone marrow and other organs as an unwanted and underestimated side effect of chemotherapy/radiotherapy. *Journal of Ovarian Research* 8, 20. <https://doi.org/10.1186/s13048-015-0141-7>.
- Guo, A. M., Sheng, J., Scicli, G. M., Arbab, A. S., Lehman, N. L., Edwards, P. A., ... Scicli, A. G. (2008). Expression of CYP4A1 in U251 human glioma cell induces hyperproliferative phenotype in vitro and rapidly growing tumors in vivo. *The Journal of Pharmacology and Experimental Therapeutics* 327(1), 10–19. <https://doi.org/10.1124/jpet.108.140889jpet.108.140889> [pii].
- Guo, Y., Wang, X., Zhang, X., Sun, Z., & Chen, X. (2011). Ethanol promotes chemically induced oral cancer in mice through activation of the 5-lipoxygenase pathway of arachidonic acid metabolism. *Cancer Prevention Research (Philadelphia, Pa.)* 4(11), 1863–1872. <https://doi.org/10.1158/1940-6207.CAPR-11-0206>.
- Guyton, K. Z., Rieswijk, L., Wang, A., Chiu, W. A., & Smith, M. T. (2018). Key Characteristics Approach to Carcinogenic Hazard Identification. *Chemical Research in Toxicology* 31(12), 1290–1292. <https://doi.org/10.1021/acs.chemrestox.8b00321>.
- Guyton, K. Z., Rusyn, I., Chiu, W. A., Corpet, D. E., van den Berg, M., Ross, M. K., ... Smith, M. T. (2018). Application of the key characteristics of carcinogens in cancer hazard identification. *Carcinogenesis* 39(4), 614–622. <https://doi.org/10.1093/carcin/bgy031>.
- Halder, R. C., Almasi, A., Sagong, B., Leung, J., Jewett, A., & Fiala, M. (2015). Curcuminoids and omega-3 fatty acids with anti-oxidants potentiate cytotoxicity of natural killer cells against pancreatic ductal adenocarcinoma cells and inhibit interferon gamma production. *Frontiers in Physiology* 6, 129. <https://doi.org/10.3389/fphys.2015.01029>.
- Hammock, B. D., Wang, W., Gilligan, M. M., & Panigrahy, D. (2020). Eicosanoids: the Overlooked Storm in COVID-19? *The American Journal of Pathology*. <https://doi.org/10.1016/j.ajpath.2020.06.010>.
- Hanahan, D., & Coussens, L. M. (2012). Accessories to the crime: functions of cells recruited to the tumor microenvironment. *Cancer Cell* 21(3), 309–322. <https://doi.org/10.1016/j.ccr.2012.02.022>.
- Hanahan, D., & Folkman, J. (1996). Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell* 86(3), 353–364.
- Hanahan, D., & Weinberg, R. A. (2000). The hallmarks of cancer. *Cell* 100(1), 57–70.
- Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: the next generation. *Cell* 144(5), 646–674 doi: S0092-8674(11)00127-9 [pii] <https://doi.org/10.1016/j.cell.2011.02.013>.
- Hansson, G. K. (1997). Cell-mediated immunity in atherosclerosis. *Current Opinion in Lipidology* 8(5), 301–311.
- Hansson, G. K., Robertson, A. K., & Soderberg-Naucler, C. (2006). Inflammation and atherosclerosis. *Annual Review of Pathology* 1, 297–329. <https://doi.org/10.1146/annurev.pathol.1.110304.100100>.
- Hao, H., Liu, M., Wu, P., Cai, L., Tang, K., Yi, P., ... Ye, D. (2011). Lipoxin A4 and its analog suppress hepatocellular carcinoma via remodeling tumor microenvironment. *Cancer Letters* 309(1), 85–94. <https://doi.org/10.1016/j.canlet.2011.05.020>.
- Harach, H. R., Franssila, K. O., & Wasenius, V. M. (1985). Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. *Cancer* 56(3), 531–538.
- Harris, T. R., Kodani, S., Rand, A. A., Yang, J., Imai, D. M., Hwang, S. H., & Hammock, B. D. (2018). Celecoxib Does Not Protect against Fibrosis and Inflammation in a Carbon Tetrachloride-Induced Model of Liver Injury. *Molecular Pharmacology* 94(2), 834–841. <https://doi.org/10.1124/mol.118.11831>.
- Hassan, I. R., & Gronert, K. (2009). Acute changes in dietary omega-3 and omega-6 polyunsaturated fatty acids have a pronounced impact on survival following ischemic renal injury and formation of renoprotective docosahexaenoic acid-derived protectin D1. *Journal of Immunology* 182(5), 3223–3232 doi: 182/5/3223 [pii] <https://doi.org/10.4049/jimmunol.0802064>.
- Hasturk, H., Kantarci, A., Goguet-Surmenian, E., Blackwood, A., Andry, C., Serhan, C. N., & Van Dyke, T. E. (2007). Resolvin E1 regulates inflammation at the cellular and tissue level and restores tissue homeostasis in vivo. *Journal of Immunology* 179(10), 7021–7029 doi: 179/10/7021 [pii].
- Hattori, N., Niwa, T., Ishida, T., Kobayashi, K., Imai, T., Mori, A., ... Ushijima, T. (2019). Antibiotics suppress colon tumorigenesis through inhibition of aberrant DNA methylation in an azoxymethane and dextran sulfate sodium colitis model. *Cancer Science* 110(1), 147–156. <https://doi.org/10.1111/cas.13880>.
- Hattori, N., & Ushijima, T. (2016). Epigenetic impact of infection on carcinogenesis: mechanisms and applications. *Genome Medicine* 8(1), 10. <https://doi.org/10.1186/s13073-016-0267-2>.
- Haworth, O., Cernadas, M., Yang, R., Serhan, C. N., & Levy, B. D. (2008). Resolvin E1 regulates interleukin 23, interferon-gamma and lipoxin A4 to promote the resolution of allergic airway inflammation. *Nature Immunology* 9(8), 873–879 doi: ni.1627 [pii] <https://doi.org/10.1038/ni.1627>.

- He, C. B., & Lin, X. J. (2017). Inflammation scores predict the survival of patients with hepatocellular carcinoma who were treated with transarterial chemoembolization and recombinant human type-5 adenovirus H101. *PLoS One* 12(3). <https://doi.org/10.1371/journal.pone.0174769>.
- He, J., Gerstenlauer, M., Chan, L. K., Leithauser, F., Yeh, M. M., Wirth, T., & Maier, H. J. (2019). Block of NF- κ B signaling accelerates MYC-driven hepatocellular carcinogenesis and modifies the tumor phenotype towards combined hepatocellular cholangiocarcinoma. *Cancer Letters* 458, 113–122. <https://doi.org/10.1016/j.canlet.2019.05.023>.
- He, J., Liu, Y., & Lubman, D. M. (2012). Targeting glioblastoma stem cells: Cell surface markers. *Current Medicinal Chemistry* 19(35), 6050–6055.
- He, Y., Li, S., Tang, D., Peng, Y., Meng, J., Peng, S., ... Yang, H. (2019). Circulating Peroxiredoxin-1 is a novel damage-associated molecular pattern and aggravates acute liver injury via promoting inflammation. *Free Radical Biology & Medicine* 137, 24–36. <https://doi.org/10.1016/j.freeradbiomed.2019.04.012>.
- Hebels, D. G., Jennen, D. G., Kleinjans, J. C., & de Kok, T. M. (2009). Molecular signatures of N-nitroso compounds in Caco-2 cells: implications for colon carcinogenesis. *Toxicological Sciences* 108(2), 290–300. <https://doi.org/10.1093/toxsci/kfp035>.
- Hei, T. K., & Filipic, M. (2004). Role of oxidative damage in the genotoxicity of arsenic. *Free Radical Biology & Medicine* 37(5), 574–581. <https://doi.org/10.1016/j.freeradbiomed.2004.02.003>.
- Heidland, A., Klassen, A., Rutkowski, P., & Bahner, U. (2006). The contribution of Rudolf Virchow to the concept of inflammation: what is still of importance? *Journal of Nephrology* 19(Suppl. 10), S102–S109.
- Hellmann, J., Sansbury, B. E., Wong, B., Li, X., Singh, M., Nuutila, K., ... Spite, M. (2018). Biosynthesis of D-Series resolvins in skin provides insights into their role in tissue repair. *The Journal of Investigative Dermatology* 138(9), 2051–2060. <https://doi.org/10.1016/j.jid.2018.03.1498>.
- Hernandez, C., Huebener, P., Pradere, J. P., Antoine, D. J., Friedman, R. A., & Schwabe, R. F. (2018). HMGB1 links chronic liver injury to progenitor responses and hepatocarcinogenesis. *The Journal of Clinical Investigation* 128(6), 2436–2451. <https://doi.org/10.1172/JCI91786>.
- Hidajat, M., McElvenny, D. M., Ritchie, P., Darnton, A., Mueller, W., van Tongeren, M., & Vocht, F. (2019). Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow-up. *Occupational and Environmental Medicine* 76(4), 250–258. <https://doi.org/10.1136/oemed-2018-105181>.
- Hobson, J., Gummadijala, P., Silverstrim, B., Grier, D., Bunn, J., James, T., & Rincon, M. (2013). Acute inflammation induced by the biopsy of mouse mammary tumors promotes the development of metastasis. *Breast Cancer Research and Treatment* 139(2), 391–401. <https://doi.org/10.1007/s10549-013-2575-1>.
- Holsapple, M. P., Bick, P. H., & Duke, S. S. (1985). Effects of N-nitrosodimethylamine on cell-mediated immunity. *Journal of Leukocyte Biology* 37(4), 367–381.
- Holsapple, M. P., Mc Nerney, P. J., Barnes, D. W., & White, K. L., Jr. (1984). Suppression of humoral antibody production by exposure to 1,2,3,6,7,8-hexachlorodibenzo-p-dioxin. *The Journal of Pharmacology and Experimental Therapeutics* 231(3), 518–526.
- Holsapple, M. P., Tucker, A. N., Mc Nerney, P. J., & White, K. L., Jr. (1984). Effects of N-nitrosodimethylamine on humoral immunity. *The Journal of Pharmacology and Experimental Therapeutics* 229(2), 493–500.
- Hong, J. Y., Smith, T., Lee, M. J., Li, W. S., Ma, B. L., Ning, S. M., ... Yang, C. S. (1991). Metabolism of carcinogenic nitrosamines by rat nasal mucosa and the effect of diallyl sulfide. *Cancer Research* 51(5), 1509–1514.
- Hong, M. Y., Hoh, E., Kang, B., DeHamer, R., Kim, J. Y., & Lumibao, J. (2017). Fish oil contaminated with persistent organic pollutants induces colonic aberrant crypt foci formation and reduces antioxidant enzyme gene expression in rats. *The Journal of Nutrition* 147(8), 1524–1530. <https://doi.org/10.3945/jn.117.251082>.
- Hong, S., Gronert, K., Devchand, P. R., Moussignac, R. L., & Serhan, C. N. (2003). Novel docosatrienes and 17S-resolvins generated from docosahexaenoic acid in murine brain, human blood, and glial cells. Autacoids in anti-inflammation. *The Journal of Biological Chemistry* 278(17), 14677–14687. <https://doi.org/10.1074/jbc.M300218200> [pii].
- Hsiao, H. M., Sapinoro, R. E., Thatcher, T. H., Croasdel, A., Levy, E. P., Fulton, R. A., ... Sime, P. J. (2013). A novel anti-inflammatory and pro-resolving role for resolvins D1 in acute cigarette smoke-induced lung inflammation. *PLoS One* 8(3), e58258. <https://doi.org/10.1371/journal.pone.0058258>.
- Hu, J., Dziumbala, S., Lin, J., Bibli, S. I., Zukunft, S., de Mos, J., ... Fleming, I. (2017). Inhibition of soluble epoxide hydrolase prevents diabetic retinopathy. *Nature* 552(7684), 248–252. <https://doi.org/10.1038/nature25013>.
- Hu, S., Mao-Ying, Q. L., Wang, J., Wang, Z. F., Mi, W. L., Wang, X. W., ... Wang, Y. Q. (2012). Lipoxins and aspirin-triggered lipoxin alleviate bone cancer pain in association with suppressing expression of spinal proinflammatory cytokines. *Journal of Neuroinflammation* 9, 278. <https://doi.org/10.1186/1742-2094-9-278>.
- Huang, L., Duan, S., Shao, H., Zhang, A., Chen, S., Zhang, P., ... Feng, F. (2019). NLRP3 deletion inhibits inflammation-driven mouse lung tumorigenesis induced by benzo(a) pyrene and lipopolysaccharide. *Respiratory Research* 20(1), 20. <https://doi.org/10.1186/s12931-019-0983-4>.
- Huang, M. T., Lysz, T., Ferraro, T., Abidi, T. F., Laskin, J. D., & Conney, A. H. (1991). Inhibitory effects of curcumin in vitro lipooxygenase and cyclooxygenase activities in mouse epidermis. *Cancer Research* 51(3), 813–819.
- Huang, Q., Li, F., Liu, X., Li, W., Shi, W., Liu, F. F., ... Li, C. Y. (2011). Caspase 3-mediated stimulation of tumor cell repopulation during cancer radiotherapy. *Nature Medicine* 17(7), 860–866. <https://doi.org/10.1038/nm.2385>.
- Hudis, C. A., Subramaniam, K., Morris, P. G., & Dannenberg, A. J. (2012). Breast cancer risk reduction: no pain, no gain? *Journal of Clinical Oncology* 30(28), 3436–3438. <https://doi.org/10.1200/JCO.2012.44.8597>.
- Humans (2012). I.W.G.O.T.E.O.C.R.T. Chemical agents and related occupations. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* 100, 9–562 Pt F.
- Hwang, S. H., Wagner, K. M., Morisseau, C., Liu, J. Y., Dong, H., Weckler, A. T., & Hammock, B. D. (2011). Synthesis and structure-activity relationship studies of urea-containing pyrazoles as dual inhibitors of cyclooxygenase-2 and soluble epoxide hydrolase. *Journal of Medicinal Chemistry* 54(8), 3037–3050. <https://doi.org/10.1021/jm2001376>.
- Hwang, S. H., Yeom, H., Eom, S. Y., Lee, Y. M., & Lee, M. (2019). Genome-wide DNA methylation changes in transformed foci induced by nongenotoxic carcinogens. *Environmental and Molecular Mutagenesis* 60(7), 576–587. <https://doi.org/10.1002/em.22285>.
- Hyde, C. A., & Missailidis, S. (2009). Inhibition of arachidonic acid metabolism and its implication on cell proliferation and tumour-angiogenesis. *International Immunopharmacology* 9(6), 701–715 doi: S1567-5769(09)00062-9 [pii] <https://doi.org/10.1016/j.intimp.2009.02.003>.
- Hye Khan, M. A., Hwang, S. H., Sharma, A., Corbett, J. A., Hammock, B. D., & Imig, J. D. (2016). A dual COX-2/sEH inhibitor improves the metabolic profile and reduces kidney injury in Zucker diabetic fatty rat. *Prostaglandins & Other Lipid Mediators* 125, 40–47. <https://doi.org/10.1016/j.prostaglandins.2016.07.003>.
- Imig, J. D., & Hammock, B. D. (2009). Soluble epoxide hydrolase as a therapeutic target for cardiovascular diseases. *Nature Reviews. Drug Discovery* 8(10), 794–805 doi: nrd2875 [pii] <https://doi.org/10.1038/nrd2875>.
- Inoue-Yamauchi, A., Itagaki, H., & Oda, H. (2018). Eicosapentaenoic acid attenuates obesity-related hepatocellular carcinogenesis. *Carcinogenesis* 39(1), 28–35. <https://doi.org/10.1093/carcin/bgx112>.
- Iwaniuk, A., Jablonska, E., Jablonski, J., Ratajczak-Wrona, W., & Garley, M. (2015). Expression of selected proteins of the extrinsic and intrinsic pathways of apoptosis in human leukocytes exposed to N-nitrosodimethylamine. *Human & Experimental Toxicology* 34(6), 591–600. <https://doi.org/10.1177/0960327114551391>.
- Jablonski, J., Jablonska, E., & Chojnowski, M. (2001). The influence of very low doses of N-nitrosodimethylamine (NDMA) on the apoptosis of rat neutrophils in vivo. The role of reactive oxygen species. *Toxicology* 165(1), 65–74.
- Jablonski, J., Jablonska, E., & Leonik, A. (2011). The effect of N-nitrosodimethylamine (NDMA) on Bax and Mcl-1 expression in human neutrophils. *Bulletin of Environmental Contamination and Toxicology* 87(6), 638–642. <https://doi.org/10.1007/s00128-011-0400-2>.
- Jablonski, J., Jablonska, E., & Moniuszko-Jakoniuk, J. (2007). The effect of N-nitrosodimethylamine on TRAIL and DR5 expression in human neutrophils—preliminary study. *Immunopharmacology and Immunotoxicology* 29(2), 287–296. <https://doi.org/10.1080/08923970701513021>.
- Jeannot, E., Boorman, G. A., Kosyk, O., Bradford, B. U., Shymoniak, S., Tumorbaatar, B., ... Rysun, I. (2012). Increased incidence of aflatoxin B1-induced liver tumors in hepatitis virus C transgenic mice. *International Journal of Cancer* 130(6), 1347–1356. <https://doi.org/10.1002/ijc.26140>.
- Jelinska, M., Bialek, A., Gielecinska, I., Mojska, H., & Tokarz, A. (2017). Impact of conjugated linoleic acid administered to rats prior and after carcinogenic agent on arachidonic and linoleic acid metabolites in serum and tumors. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 126, 1–8. <https://doi.org/10.1016/j.plefa.2017.08.013>.
- Jeong, H. G., & Lee, Y. W. (1998). Protective effects of diallyl sulfide on N-nitrosodimethylamine-induced immunosuppression in mice. *Cancer Letters* 134(1), 73–79. [https://doi.org/10.1016/s0304-3835\(98\)00246-8](https://doi.org/10.1016/s0304-3835(98)00246-8).
- Jiang, M. J., Gu, D. N., Dai, J. J., Huang, Q., & Tian, L. (2020). Dark side of cytotoxic therapy: Chemoradiation-induced cell death and tumor repopulation. *Trends Cancer* 6(5), 419–431. <https://doi.org/10.1016/j.trecan.2020.01.018>.
- Jin, Y., Arita, M., Zhang, Q., Saban, D. R., Chauhan, S. K., Chiang, N., ... Dana, R. (2009). Anti-angiogenesis effect of the novel anti-inflammatory and pro-resolving lipid mediators. *Investigative Ophthalmology & Visual Science* 50(10), 4743–4752 doi: iovs.08-2462 [pii] <https://doi.org/10.1167/iov.08-2462>.
- Jing, Y., Sun, K., Liu, W., Sheng, D., Zhao, S., Gao, L., & Wei, L. (2018). Tumor necrosis factor- α promotes hepatocellular carcinogenesis through the activation of hepatic progenitor cells. *Cancer Letters* 434, 22–32. <https://doi.org/10.1016/j.canlet.2018.07.001>.
- Johansson, S. L., & Cohen, S. M. (1997). Epidemiology and etiology of bladder cancer. *Seminars in Surgical Oncology* 13(5), 291–298.
- Johnson, N. M., Egnor, P. A., Baxter, V. K., Sporn, M. B., Wible, R. S., Sutter, T. R., ... Roebuck, B. D. (2014). Complete protection against aflatoxin B(1)-induced liver cancer with a triterpenoid: DNA adduct dosimetry, molecular signature, and genotoxicity threshold. *Cancer Prevention Research (Philadelphia, Pa.)* 7(7), 658–665. <https://doi.org/10.1158/1940-6207.CAPR-13-0430>.
- Jomova, K., & Valko, M. (2011). Advances in metal-induced oxidative stress and human disease. *Toxicology* 283(2–3), 65–87. <https://doi.org/10.1016/j.tox.2011.03.001>.
- Jones, F. S., & Rous, P. (1914). On the cause of the localization of secondary tumors at points of injury. *The Journal of Experimental Medicine* 20(4), 404–412. <https://doi.org/10.1084/jem.20.4.404>.
- Jones, R. D., Liao, J., Tong, X., Xu, D., Sun, L., Li, H., & Yang, G. Y. (2019). Epoxy-Oxylipins and soluble epoxide hydrolase metabolic pathway as targets for NSAID-induced gastroenteropathy and inflammation-associated carcinogenesis. *Frontiers in Pharmacology* 10, 731. <https://doi.org/10.3389/fphar.2019.00731>.
- Joyce, J. A. (2005). Therapeutic targeting of the tumor microenvironment. *Cancer Cell* 7(6), 513–520. <https://doi.org/10.1016/j.ccr.2005.05.024>.
- Ju, J., Hao, X., Lee, M. J., Lambert, J. D., Lu, G., Xiao, H., ... Yang, C. S. (2009). A gamma-tocopherol-rich mixture of tocopherols inhibits colon inflammation and carcinogenesis in azoxymethane and dextran sulfate sodium-treated mice. *Cancer Prevention Research (Philadelphia, Pa.)* 2(2), 143–152. <https://doi.org/10.1158/1940-6207.CAPR-08-0099>.
- Kang, D. S., Yang, J. H., Kim, H. S., Koo, B. K., Lee, C. M., Ahn, Y. S., ... Seo, Y. R. (2018). Application of the adverse outcome pathway framework to risk assessment for predicting carcinogenicity of chemicals. *Journal of Cancer Prevention* 23(3), 126–133. <https://doi.org/10.15430/JCP.2018.23.3.126>.

- Kang, G. J., Lee, H. J., Kang, Y. P., Kim, E. J., Kim, H. J., Byun, H. J., ... Lee, C. H. (2015). High-mobility group box 1 suppresses resolvin D1-induced phagocytosis via induction of resolvin D1-inactivating enzyme, 15-hydroxyprostaglandin dehydrogenase. *Biochimica et Biophysica Acta* 1852(9), 1981–1988. <https://doi.org/10.1016/j.bbdis.2015.07.005>.
- Kang, J. S., Wanibuchi, H., Morimura, K., Gonzalez, F. J., & Fukushima, S. (2007). Role of CYP2E1 in diethylnitrosamine-induced hepatocarcinogenesis in vivo. *Cancer Research* 67(23), 11141–11146. <https://doi.org/10.1158/0008-5472.CAN-07-1369>.
- Karagiannis, G. S., Pastoriza, J. M., Wang, Y., Harney, A. S., Entenberg, D., Pignatelli, J., ... Oktay, M. H. (2017). Neoadjuvant chemotherapy induces breast cancer metastasis through a TMEM-mediated mechanism. *Science Translational Medicine* 9(397). <https://doi.org/10.1126/scitranslmed.aan0026>.
- Karin, M. (2009). NF-kappaB as a critical link between inflammation and cancer. *Cold Spring Harbor Perspectives in Biology* 1(5). <https://doi.org/10.1101/cshperspect.a000141>.
- Karin, M., & Greten, F. R. (2005). NF-kappaB: linking inflammation and immunity to cancer development and progression. *Nature Reviews. Immunology* 5(10), 749–759. <https://doi.org/10.1038/nri1703>.
- Karp, C. L., Flick, L. M., Park, K. W., Softic, S., Greer, T. M., Keledjian, R., ... Patisis, N. A. (2004). Defective lipoxin-mediated anti-inflammatory activity in the cystic fibrosis airway. *Nature Immunology* 5(4), 388–392. <https://doi.org/10.1038/ni1056> [pii].
- Kasuga, K., Yang, R., Porter, T. F., Agrawal, N., Patisis, N. A., Irimia, D., ... Serhan, C. N. (2008). Rapid appearance of resolvin precursors in inflammatory exudates: novel mechanisms in resolution. *Journal of Immunology* 181(12), 8677–8687 (doi: 181/12/8677 [pii]).
- Katoh, H., Wang, D., Daikoku, T., Sun, H., Dey, S. K., & Dubois, R. N. (2013). CXCR2-expressing myeloid-derived suppressor cells are essential to promote colitis-associated tumorigenesis. *Cancer Cell* 24(5), 631–644. <https://doi.org/10.1016/j.ccr.2013.10.009>.
- Kay, J., Thadhani, E., Samson, L., & Engelward, B. (2019). Inflammation-induced DNA damage, mutations and cancer. *DNA Repair (Amst)* 83. <https://doi.org/10.1016/j.dnarep.2019.102673>.
- Keklikoglou, I., Cianciaruso, C., Guc, E., Squadrito, M. L., Spring, L. M., Tazyman, S., ... De Palma, M. (2019). Chemotherapy elicits pro-metastatic extracellular vesicles in breast cancer models. *Nature Cell Biology* 21(2), 190–202. <https://doi.org/10.1038/s41556-018-0256-3>.
- Keshari, A. K., Singh, A. K., Kumar, U., Raj, V., Rai, A., Kumar, P., ... Saha, S. (2017). 5H-benzo [h]thiazolo[2,3-b]quinazolines ameliorate NDEA-induced hepatocellular carcinogenesis in rats through IL-6 downregulation along with oxidative and metabolic stress reduction. *Drug Design, Development and Therapy* 11, 2981–2995. <https://doi.org/10.2147/DDDT.S143075>.
- Kim, E. M., Bae, Y. M., Choi, M. H., & Hong, S. T. (2019). Connexin 43 plays an important role in the transformation of cholangiocytosis with Clonochis sinensis excretory-secretory protein and N-nitrosodimethylamine. *PLoS Neglected Tropical Diseases* 13(4). <https://doi.org/10.1371/journal.pntd.0006843>.
- Kim, I. W., Myung, S. J., Do, M. Y., Ryu, Y. M., Kim, M. J., Do, E. J., ... Kim, J. H. (2010). Western-style diets induce macrophage infiltration and contribute to colitis-associated carcinogenesis. *Journal of Gastroenterology and Hepatology* 25(11), 1785–1794. <https://doi.org/10.1111/j.1440-1746.2010.06332.x>.
- Kiraly, O., Gong, G., Olipitz, W., Muthupalani, S., & Engelward, B. P. (2015). Inflammation-induced cell proliferation potentiates DNA damage-induced mutations in vivo. *PLoS Genetics* 11(2). <https://doi.org/10.1371/journal.pgen.1004901>.
- Kiyabu, G. Y., Inoue, M., Saito, E., Abe, S. K., Sawada, N., Ishihara, J., ... Group, J. S (2015). Fish n - 3 polyunsaturated fatty acids and n - 6 polyunsaturated fatty acids intake and breast cancer risk: The Japan Public Health Center-based prospective study. *International Journal of Cancer* 137(12), 2915–2926. <https://doi.org/10.1002/ijc.29672>.
- Klaunig, J. E., Hocevar, B. A., & Kamendulis, L. M. (2012). Mode of Action analysis of perfluorooctanoic acid (PFOA) tumorigenicity and Human Relevance. *Reproductive Toxicology* 33(4), 410–418. <https://doi.org/10.1016/j.reprotox.2011.10.014>.
- Klaunig, J. E., & Kamendulis, L. M. (2004). The role of oxidative stress in carcinogenesis. *Annual Review of Pharmacology and Toxicology* 44, 239–267. <https://doi.org/10.1146/annurev.pharmtox.44.101802.121851>.
- Kossler, N., Matheis, K. A., Ostfeldt, N., Bach Toft, D., Dhalluin, S., Deschl, U., & Kalkuhl, A. (2015). Identification of specific mRNA signatures as fingerprints for carcinogenesis in mice induced by genotoxic and nongenotoxic hepatocarcinogens. *Toxicological Sciences* 143(2), 277–295. <https://doi.org/10.1093/toxsci/kfu248>.
- Kowal-Bielecka, O., Kowal, K., Distler, O., & Gay, S. (2007). Mechanisms of disease: Leukotrienes and lipoxins in scleroderma lung disease—insights and potential therapeutic implications. *Nature Clinical Practice. Rheumatology* 3(1), 43–51. <https://doi.org/10.1038/ncprheum0375>.
- Koyama, Y., & Brenner, D. A. (2017). Liver inflammation and fibrosis. *The Journal of Clinical Investigation* 127(1), 55–64. <https://doi.org/10.1172/JCI88881>.
- Krall, J. A., Reinhardt, F., Mercury, O. A., Pattabiraman, D. R., Brooks, M. W., Dougan, M., ... Weinberg, R. A. (2018). The systemic response to surgery triggers the outgrowth of distant immune-controlled tumors in mouse models of dormancy. *Science Translational Medicine* 10(436). <https://doi.org/10.1126/scitranslmed.aan3464>.
- Krewski, D., Bird, M., Al-Zoughool, M., Birkett, N., Billard, M., Milton, B., ... Zielinski, J. M. (2019). Key characteristics of 86 agents known to cause cancer in humans. *Journal of Toxicology and Environmental Health. Part B, Critical Reviews* 22(7–8), 244–263. <https://doi.org/10.1080/10937404.2019.1643536>.
- Krewski, D., Rice, J. M., Bird, M., Milton, B., Collins, B., Lajoie, P., ... Zielinski, J. M. (2019). Concordance between sites of tumor development in humans and in experimental animals for 111 agents that are carcinogenic to humans. *Journal of Toxicology and Environmental Health. Part B, Critical Reviews* 22(7–8), 203–236. <https://doi.org/10.1080/10937404.2019.1642586>.
- Krishnamoorthy, S., Recchiuti, A., Chiang, N., Yacoubian, S., Lee, C. H., Yang, R., ... Serhan, C. N. (2010). Resolvin D1 binds human phagocytes with evidence for proresolving receptors. *Proceedings of the National Academy of Sciences of the United States of America* 107(4), 1660–1665 doi: 0907342107 [pii] <https://doi.org/10.1073/pnas.0907342107>.
- Krishnan, P., Sundaram, J., Salam, S., Subramaniam, N., Mari, A., Balaraman, G., & Thiruvengadam, D. (2020). Citral inhibits N-nitrosodimethylamine-induced hepatocellular carcinoma via modulation of antioxidants and xenobiotic-metabolizing enzymes. *Environmental Toxicology*. <https://doi.org/10.1002/tox.22933>.
- Krishnan, V., Booker, D., Cunningham, G., Jadapalli, J. K., Kain, V., Pullen, A. B., & Halade, G. V. (2019). Pretreatment of carprofen impaired initiation of inflammatory- and overlapping resolution response and promoted cardiorenal syndrome in heart failure. *Life Sciences* 218, 224–232. <https://doi.org/10.1016/j.lfs.2018.12.048>.
- Kuang, H., Hua, X., Zhou, J., & Yang, R. (2016). Resolvin D1 and E1 alleviate the progress of hepatitis toward liver cancer in long-term concanavalin A-induced mice through inhibition of NF-kappaB activity. *Oncology Reports* 35(1), 307–317. <https://doi.org/10.3892/or.2015.4389>.
- Kumagai-Takei, N., Yamamoto, S., Lee, S., Maeda, M., Masuzzaki, H., Sada, N., ... Otsuki, T. (2018). Inflammatory alteration of human T cells exposed continuously to asbestos. *International Journal of Molecular Sciences* 19(2). <https://doi.org/10.3390/ijms19020504>.
- Lacy, S. H., Woeller, C. F., Thatcher, T. H., Maddipati, K. R., Honn, K. V., Sime, P. J., & Phipps, R. P. (2016). Human lung fibroblasts produce proresolving peroxisome proliferator-activated receptor-gamma ligands in a cyclooxygenase-2-dependent manner. *American Journal of Physiology. Lung Cellular and Molecular Physiology* 311(5), L855–L867. <https://doi.org/10.1152/ajplung.00272.2016>.
- Lambert, J. D., Lu, G., Lee, M. J., Hu, J., Ju, J., & Yang, C. S. (2009). Inhibition of lung cancer growth in mice by dietary mixed tocopherols. *Molecular Nutrition & Food Research* 53(8), 1030–1035. <https://doi.org/10.1002/mnfr.200800438>.
- Laothong, U., Pinlaor, P., Boonsiri, P., Pairojkul, C., Priprem, A., Johns, N. P., ... Pinlaor, S. (2013). Melatonin inhibits cholangiocarcinoma and reduces liver injury in Opisthorchis viverrini-infected and N-nitrosodimethylamine-treated hamsters. *Journal of Pineal Research* 55(3), 257–266. <https://doi.org/10.1111/jpi.12068>.
- Le Hegarat, L., Dumont, J., Josse, R., Huet, S., Lancelleur, R., Mourou, A., ... Fessard, V. (2010). Assessment of the genotoxic potential of indirect chemical mutagens in HepaRG cells by the comet and the cytokinesis-block micronucleus assays. *Mutagenesis* 25(6), 555–560. <https://doi.org/10.1093/mutage/geq039>.
- Lee, C. H. (2018). Epithelial-mesenchymal transition: Initiation by cues from chronic inflammatory tumor microenvironment and termination by anti-inflammatory compounds and specialized pro-resolving lipids. *Biochemical Pharmacology* 158, 261–273. <https://doi.org/10.1016/j.bcp.2018.10.031>.
- Lee, H. J., Ju, J., Paul, S., So, J. Y., DeCastro, A., Smolarek, A., ... Suh, N. (2009). Mixed tocopherols prevent mammary tumorigenesis by inhibiting estrogen action and activating PPAR-gamma. *Clinical Cancer Research* 15(12), 4242–4249. <https://doi.org/10.1158/1078-0432.CCR-08-3028>.
- Lee, H. J., Park, M. K., Lee, E. J., & Lee, C. H. (2013). Resolvin D1 inhibits TGF-beta1-induced epithelial mesenchymal transition of A549 lung cancer cells via lipoxin A4 receptor/formyl peptide receptor 2 and GPR32. *The International Journal of Biochemistry & Cell Biology* 45(12), 2801–2807. <https://doi.org/10.1016/j.bjocel.2013.09.018>.
- Lee, J. W., Shahzad, M. M., Lin, Y. G., Armaiz-Pena, G., Mangala, L. S., Han, H. D., ... Sood, A. K. (2009). Surgical stress promotes tumor growth in ovarian carcinoma. *Clinical Cancer Research* 15(8), 2695–2702. <https://doi.org/10.1158/1078-0432.CCR-08-2966>.
- Lee, V. M., Cameron, R. G., & Archer, M. C. (1993). The role of hepatocyte heterogeneity in the initiation of hepatocarcinogenesis. *Carcinogenesis* 14(7), 1403–1408.
- Lee, W. J., Kim, S. C., Lee, S. J., Lee, J., Park, J. H., Yu, K. S., ... Kwon, S. W. (2014). Investigating the different mechanisms of genotoxic and non-genotoxic carcinogens by a gene set analysis. *PLoS One* 9(1), e86700. <https://doi.org/10.1371/journal.pone.0086700>.
- Leineweber, C. G., Pietzner, A., Zhang, I. W., Blessin, U. B., Rothe, M., Schott, E., & Weylandt, K. H. (2020). Assessment of the Effect of Sorafenib on Omega-6 and Omega-3 Epoxyicosanoid Formation in Patients with Hepatocellular Carcinoma. *International Journal of Molecular Sciences* 21(5). <https://doi.org/10.3390/ijms21051875>.
- Levy, B. D., Bonnans, C., Silverman, E. S., Palmer, L. J., Marigowda, G., Israel, E., ... Blood, I. (2005). Diminished lipoxin biosynthesis in severe asthma. *American Journal of Respiratory and Critical Care Medicine* 172(7), 824–830. <https://doi.org/10.1164/rccm.200410-1413OC>.
- Levy, B. D., Clish, C. B., Schmidt, B., Gronert, K., & Serhan, C. N. (2001). Lipid mediator class switching during acute inflammation: Signals in resolution. *Nature Immunology* 2(7), 612–619. <https://doi.org/10.1038/89759>.
- Li, B., Wang, Y., Yin, L., Huang, G., Xu, Y., Su, J., ... Lu, J. (2019). Glucocorticoids promote the development of azoxymethane and dextran sulfate sodium-induced colorectal carcinoma in mice. *BMC Cancer* 19(1), 94. <https://doi.org/10.1186/s12885-019-5299-8>.
- Li, C., Wu, X., Liu, S., Shen, D., Zhu, J., & Liu, K. (2020). Role of resolvins in the inflammatory resolution of neurological diseases. *Frontiers in Pharmacology* 11, 612. <https://doi.org/10.3389/fphar.2020.00612>.
- Li, F., Huang, Q., Chen, J., Peng, Y., Roop, D. R., Bedford, J. S., & Li, C. Y. (2010). Apoptotic cells activate the “phoenix rising” pathway to promote wound healing and tissue regeneration. *Science Signaling* 3(110), ra13. <https://doi.org/10.1126/scisignal.2000634>.
- Li, H., Hao, Y., Zhang, H., Ying, W., Li, D., Ge, Y., ... Jin, S. (2017). Posttreatment with Protetin DX ameliorates bleomycin-induced pulmonary fibrosis and lung dysfunction in mice. *Scientific Reports* 7, 46754. <https://doi.org/10.1038/srep46754>.
- Li, J., Zhou, Y., Wang, H., Gao, Y., Li, L., Hwang, S. H., ... Hammock, B. D. (2017). COX-2/SEH dual inhibitor PTUPB suppresses glioblastoma growth by targeting epidermal growth factor receptor and hyaluronan mediated motility receptor. *Oncotarget* 8(50), 87353–87363. <https://doi.org/10.18632/oncotarget.20928>.

- Li, Y., Wang, R., Xiong, S., Wang, X., Zhao, Z., Bai, S., ... Cheng, B. (2019). Cancer-associated fibroblasts promote the stemness of CD24(+) liver cells via paracrine signaling. *Journal of Molecular Medicine (Berlin, Germany)* 97(2), 243–255. <https://doi.org/10.1007/s00109-018-1731-9>.
- Liang, S., Ma, H. Y., Zhong, Z., Dhar, D., Liu, X., Xu, J., ... Brenner, D. A. (2019). NADPH Oxidase 1 in Liver Macrophages Promotes Inflammation and Tumor Development in Mice. *Gastroenterology* 156(4), 1156–1172 e1156. <https://doi.org/10.1053/j.gastro.2018.11.019>.
- Liao, J., Hwang, S. H., Li, H., Liu, J. Y., Hammock, B. D., & Yang, G. Y. (2016). Inhibition of chronic pancreatitis and murine pancreatic intraepithelial neoplasia by a dual inhibitor of c-RAF and soluble epoxide hydrolase in LSL-KrasG(1)(2)D/Pdx-1-Cre Mice. *Anticancer Research* 36(1), 27–37.
- Liao, S., Lin, J., Liu, J., Chen, T., Xu, M., & Zheng, J. (2019). Chemoprevention of elite tea variety CFT-1 rich in EGCG against chemically induced liver cancer in rats. *Food Science & Nutrition* 7(8), 2647–2665. <https://doi.org/10.1002/fsn3.1121>.
- Libby, P. (2002). Inflammation in atherosclerosis. *Nature* 420(6917), 868–874. <https://doi.org/10.1038/nature01323> [pii].
- Liby, K., Yore, M. M., Roebuck, B. D., Baumgartner, K. J., Honda, T., Sundararajan, C., ... Sporn, M. B. (2008). A novel acetylenic tricyclic bis-(cyano enone) potentially induces phase 2 cytoprotective pathways and blocks liver carcinogenesis induced by aflatoxin. *Cancer Research* 68(16), 6727–6733. <https://doi.org/10.1158/0008-5472.CAN-08-1123>.
- Lijinsky, W., & Taylor, H. W. (1975). Induction of urinary bladder tumors in rats by administration nitrosomethyl-dodecylamine. *Cancer Research* 35(4), 958–961.
- Lim, S. Y., Jang, J. H., & Surh, Y. J. (2003). Induction of cyclooxygenase-2 and peroxisome proliferator-activated receptor-gamma during nitric oxide-induced apoptotic PC12 cell death. *Annals of the New York Academy of Sciences* 1010, 648–658. <https://doi.org/10.1196/annals.1299.119>.
- Lin, Y. J., Shyu, W. C., Chang, C. W., Wang, C. C., Wu, C. P., Lee, H. T., ... Hsieh, C. H. (2017). Tumor Hypoxia regulates forkhead box C1 to promote lung cancer progression. *Theranostics* 7(5), 1177–1191. <https://doi.org/10.7150/tno.17895>.
- Liu, C., Li, L., Lu, W. S., Du, H., Yan, L. N., Yang, J. Y., & Yang, J. (2017). Neutrophil-lymphocyte Ratio Plus prognostic nutritional index predicts the outcomes of patients with unresectable hepatocellular carcinoma after transarterial chemoembolization. *Scientific Reports* 7(1), 13873. <https://doi.org/10.1038/s41598-017-13239-w>.
- Liu, G., Wang, J., Park, Y. J., Tsuruta, Y., Lorne, E. F., Zhao, X., & Abraham, E. (2008). High mobility group protein-1 inhibits phagocytosis of apoptotic neutrophils through binding to phosphatidylserine. *Journal of Immunology* 181(6), 4240–4246. <https://doi.org/10.4049/jimmunol.181.6.4240>.
- Liu, H., Zeng, J., Huang, W., Xu, Q., Ye, D., Sun, R., & Zhang, D. (2019). Colorectal cancer is associated with a deficiency of Lipoxin A4, an endogenous anti-inflammatory mediator. *Journal of Cancer* 10(19), 4719–4730. <https://doi.org/10.7150/jca.32456>.
- Liu, M., Boussetta, T., Makni-Maalej, K., Fay, M., Driss, F., El-Benna, J., ... Guichardant, M. (2014). Protectin DX, a double lipoxigenase product of DHA, inhibits both ROS production in human neutrophils and cyclooxygenase activities. *Lipids* 49(1), 49–57. <https://doi.org/10.1007/s11745-013-3863-6>.
- Liu, S. X., Davidson, M. M., Tang, X., Walker, W. F., Athar, M., Ivanov, V., & Hei, T. K. (2005). Mitochondrial damage mediates genotoxicity of arsenic in mammalian cells. *Cancer Research* 65(8), 3236–3242. <https://doi.org/10.1158/0008-5472.CAN-05-0424>.
- Liu, X., Xu, Y., Wan, D. B., Xiong, Y. H., He, Z. Y., Wang, X. X., ... Hammock, B. D. (2015). Development of a nanobody-alkaline phosphatase fusion protein and its application in a highly sensitive direct competitive fluorescence enzyme immunoassay for detection of ochratoxin A in cereal. *Analytical Chemistry* 87(2), 1387–1394. <https://doi.org/10.1021/ac504305z>.
- Liu, Y., & Wu, F. (2010). Global burden of aflatoxin-induced hepatocellular carcinoma: a risk assessment. *Environmental Health Perspectives* 118(6), 818–824. <https://doi.org/10.1289/ehp.0901388>.
- Liu, Y., Yuan, X., Li, W., Cao, Q., & Shu, Y. (2016). Aspirin-triggered resolvin D1 inhibits TGF-beta1-induced EMT through the inhibition of the mTOR pathway by reducing the expression of PKM2 and is closely linked to oxidative stress. *International Journal of Molecular Medicine* 38(4), 1235–1242. <https://doi.org/10.3892/ijmm.2016.2721>.
- Liviác, D., Creus, A., & Marcos, R. (2011). Genotoxic evaluation of the non-halogenated disinfection by-products nitrosodimethylamine and nitrosodiethylamine. *Journal of Hazardous Materials* 185(2–3), 613–618. <https://doi.org/10.1016/j.jhazmat.2010.09.062>.
- London, W. T., Evans, A. A., McGlynn, K., Buetow, K., An, P., Gao, L., ... Shen, F. (1995). Viral, host and environmental risk factors for hepatocellular carcinoma: a prospective study in Haimen City, China. *Intervirology* 38(3–4), 155–161. <https://doi.org/10.1159/000150426>.
- Loosen, S. H., Schulze-Hagen, M., Leyh, C., Benz, F., Vucur, M., Kuhl, C., ... Luedde, T. (2018). IL-6 and IL-8 Serum Levels Predict Tumor Response and Overall Survival after TACE for Primary and Secondary Hepatic Malignancies. *International Journal of Molecular Sciences* 19(6). <https://doi.org/10.3390/ijms19061766>.
- Lopez-Vicario, C., Alcaraz-Quiles, J., Garcia-Alonso, V., Rius, B., Hwang, S. H., Titos, E., ... Claria, J. (2015). Inhibition of soluble epoxide hydrolase modulates inflammation and autophagy in obese adipose tissue and liver: role for omega-3 epoxides. *Proceedings of the National Academy of Sciences of the United States of America* 112(2), 536–541. <https://doi.org/10.1073/pnas.1422590112>.
- Lu, Y., Xu, Q., Yin, G., Xu, W., & Jiang, H. (2018). Resolvin D1 inhibits the proliferation of lipopolysaccharide-treated HepG2 hepatoblastoma and PLC/PRF/5 hepatocellular carcinoma cells by targeting the MAPK pathway. *Experimental and Therapeutic Medicine* 16(4), 3603–3610. <https://doi.org/10.3892/etm.2018.6651>.
- Luch, A. (2005). Nature and nurture – Lessons from chemical carcinogenesis. *Nature Reviews. Cancer* 5(2), 113–125. <https://doi.org/10.1038/nrc1546>.
- Lukac, J., Kusic, Z., Kordic, D., Koncar, M., & Bolanca, A. (1994). Natural killer cell activity, phagocytosis, and number of peripheral blood cells in breast cancer patients treated with tamoxifen. *Breast Cancer Research and Treatment* 29(3), 279–285. <https://doi.org/10.1007/BF00666482>.
- Lukiw, W. J., Cui, J. G., Marcheselli, V. L., Bodker, M., Botkjaer, A., Gotlinger, K., ... Bazan, N. G. (2005). A role for docosahexaenoic acid-derived neuroprotectin D1 in neural cell survival and Alzheimer disease. *The Journal of Clinical Investigation* 115(10), 2774–2783. <https://doi.org/10.1172/JCI25420>.
- Maderna, P., Yona, S., Perretti, M., & Godson, C. (2005). Modulation of phagocytosis of apoptotic neutrophils by supernatant from dexamethasone-treated macrophages and annexin-derived peptide Ac(2–26). *Journal of Immunology* 174(6), 3727–3733.
- Madia, F., Worth, A., Whelan, M., & Corvi, R. (2019). Carcinogenicity assessment: Addressing the challenges of cancer and chemicals in the environment. *Environment International* 128, 417–429. <https://doi.org/10.1016/j.envint.2019.04.067>.
- Maeda, S., Kamata, H., Luo, J. L., Leffert, H., & Karin, M. (2005). IKKbeta couples hepatocyte death to cytokine-driven compensatory proliferation that promotes chemical hepatocarcinogenesis. *Cell* 121(7), 977–990. <https://doi.org/10.1016/j.cell.2005.04.014>.
- Magrone, T., Russo, M. A., & Jirillo, E. (2019). Impact of heavy metals on host cells: special focus on nickel-mediated pathologies and novel interventional approaches. *Endocrine, Metabolic & Immune Disorders Drug Targets*. <https://doi.org/10.2174/1871530319666191129120253>.
- Majumder, M., Nandi, P., Omar, A., Ugwuagbo, K. C., & Lala, P. K. (2018). EP4 as a therapeutic target for aggressive human breast cancer. *International Journal of Molecular Sciences* 19(4). <https://doi.org/10.3390/ijms19041019>.
- Mannerstrom, M., Maenpaa, H., Toimela, T., Salminen, L., & Tahti, H. (2001). The phagocytosis of rod outer segments is inhibited by selected drugs in retinal pigment epithelial cell cultures. *Pharmacology & Toxicology* 88(1), 27–33. <https://doi.org/10.1034/j.1600-0773.2001.088001027.x>.
- Mansour, D. F., Abdallah, H. M. I., Ibrahim, B. M. M., Hegazy, R. R., Esmail, R. S. E., & Abdel-Salam, L. O. (2019). The carcinogenic agent diethylnitrosamine induces early oxidative stress, inflammation and proliferation in rat liver, stomach and colon: protective effect of ginger extract. *Asian Pacific Journal of Cancer Prevention* 20(8), 2551–2561. <https://doi.org/10.31557/APJCP.2019.20.8.2551>.
- Mantovani, A. (2009). Cancer: Inflaming metastasis. *Nature* 457(7225), 36–37 doi: 457036b [pii] <https://doi.org/10.1038/457036b>.
- Mantovani, A., Allavena, P., Sica, A., & Balkwill, F. (2008). Cancer-related inflammation. *Nature* 454(7203), 436–444. <https://doi.org/10.1038/nature07205>.
- Mantovani, A., Cassatella, M. A., Costantini, C., & Jaillon, S. (2011). Neutrophils in the activation and regulation of innate and adaptive immunity. *Nature Reviews. Immunology* 11(8), 519–531. <https://doi.org/10.1038/nri3024>.
- Mantovani, A., Marchesi, F., Malesci, A., Laghi, L., & Allavena, P. (2017). Tumour-associated macrophages as treatment targets in oncology. *Nature Reviews. Clinical Oncology* 14(7), 399–416. <https://doi.org/10.1038/nrclinonc.2016.217>.
- Marchese, S., Polo, A., Ariano, A., Velotto, S., Costantini, S., & Severino, L. (2018). Aflatoxin B1 and M1: Biological properties and their involvement in cancer development. *Toxins (Basel)* 10(6). <https://doi.org/10.3390/toxins10060214>.
- Marginean, A., & Sharma-Walia, N. (2015). Lipoxins exert antiangiogenic and anti-inflammatory effects on Kaposi's sarcoma cells. *Translational Research* 166(2), 111–133. <https://doi.org/10.1016/j.trsl.2015.02.009>.
- Markosyan, N., Chen, E. P., Ndong, V. N., Yao, Y., Sterner, C. J., Chodosh, L. A., & Smyth, E. M. (2011). Deletion of cyclooxygenase 2 in mouse mammary epithelial cells delays breast cancer onset through augmentation of type 1 immune responses in tumors. *Carcinogenesis* 32(10), 1441–1449. <https://doi.org/10.1093/carcin/bgr134>.
- Marks, F., Furstemberger, G., Neufang, G., & Muller-Decker, K. (2003). Mouse skin as a model for cancer chemoprevention by nonsteroidal anti-inflammatory drugs. *Recent Results in Cancer Research* 163, 46–57 (discussion 264–266).
- Marnett, L. J. (2009). The COXIB experience: a look in the rearview mirror. *Annual Review of Pharmacology and Toxicology* 49, 265–290. <https://doi.org/10.1146/annurev.pharmtox.011008.145638>.
- Maronpot, R. R., Flake, G., & Huff, J. (2004). Relevance of animal carcinogenesis findings to human cancer predictions and prevention. *Toxicologic Pathology* 32(Suppl. 1), 40–48.
- Matte, A., Recchiuti, A., Federti, E., Koehl, B., Mintz, T., El Nemer, W., ... De Franceschi, L. (2019). Resolution of sickle cell disease-associated inflammation and tissue damage with 17R-resolvin D1. *Blood* 133(3), 252–265. <https://doi.org/10.1182/blood-2018-07-865378>.
- Mehrzad, J., Klein, G., Kamphues, J., Wolf, P., Grabowski, N., & Schubert, H. J. (2011). In vitro effects of very low levels of aflatoxin B(1) on free radicals production and bactericidal activity of bovine blood neutrophils. *Veterinary Immunology and Immunopathology* 141(1–2), 16–25. <https://doi.org/10.1016/j.vetimm.2011.01.010>.
- Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., & Manson, J. J. H. Across Speciality Collaboration, U. K. (2020). COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 395(10229), 1033–1034. [https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0).
- Meira, L. B., Bugni, J. M., Green, S. L., Lee, C. W., Pang, B., Borenshtein, D., ... Samson, L. D. (2008). DNA damage induced by chronic inflammation contributes to colon carcinogenesis in mice. *The Journal of Clinical Investigation* 118(7), 2516–2525. <https://doi.org/10.1172/JCI35073>.
- Melnick, R. L., Kohn, M. C., & Portier, C. J. (1996). Implications for risk assessment of suggested nongenotoxic mechanisms of chemical carcinogenesis. *Environmental Health Perspectives* 104(Suppl. 1), 123–134. <https://doi.org/10.1289/ehp.96104s1123>.
- Meng, X., Yang, S., & Camp, V. J. A. (2019). The interplay between the DNA damage response, RNA processing and extracellular vesicles. *Frontiers in Oncology* 9, 1538. <https://doi.org/10.3389/fonc.2019.01538>.
- Merched, A. J., Ko, K., Gotlinger, K. H., Serhan, C. N., & Chan, L. (2008). Atherosclerosis: Evidence for impairment of resolution of vascular inflammation governed by specific

- lipid mediators. *The FASEB Journal* 22(10), 3595–3606 doi: fj.08-112201 [pii] <https://doi.org/10.1096/fj.08-112201>.
- Miao, C., Ma, J., Zhang, Y., Chu, Y., Li, J., Kuai, R., ... Peng, H. (2015). Perfluorooctanoic acid enhances colorectal cancer DLD-1 cells invasiveness through activating NF-kappaB mediated matrix metalloproteinase-2/-9 expression. *International Journal of Clinical and Experimental Pathology* 8(9), 10512–10522.
- Michigan, A., Johnson, T. V., & Master, V. A. (2011). Preoperative C-reactive protein level adjusted for comorbidities and lifestyle factors predicts overall mortality in localized renal cell carcinoma. *Molecular Diagnosis & Therapy* 15(4), 229–234. <https://doi.org/10.2165/11534900-000000000-00000>.
- Milagre, C. S., Gopinathan, G., Everitt, G., Thompson, R. G., Kulbe, H., Zhong, H., ... Balkwill, F. R. (2015). Adaptive upregulation of EGFR limits attenuation of tumor growth by neutralizing IL6 antibodies, with implications for combined therapy in ovarian cancer. *Cancer Research* 75(7), 1255–1264. <https://doi.org/10.1158/0008-5472.CAN-14-1801>.
- Mirvish, S. S. (1995). Role of N-nitroso compounds (NOC) and N-nitrosation in etiology of gastric, esophageal, nasopharyngeal and bladder cancer and contribution to cancer of known exposures to NOC. *Cancer Letters* 93(1), 17–48. [https://doi.org/10.1016/0304-3835\(95\)03786-V](https://doi.org/10.1016/0304-3835(95)03786-V).
- Mitchell, D., Rodgers, K., Hanly, J., McMahon, B., Brady, H. R., Martin, F., & Godson, C. (2004). Lipoxins inhibit Akt/PKB activation and cell cycle progression in human mesangial cells. *The American Journal of Pathology* 164(3), 937–946. [https://doi.org/10.1016/S0002-9440\(10\)63181-1](https://doi.org/10.1016/S0002-9440(10)63181-1).
- Miyachi-Hashimoto, H., Kuwamoto, K., Urade, Y., Tanaka, K., & Horio, T. (2001). Carcinogen-induced inflammation and immunosuppression are enhanced in xeroderma pigmentosum group A model mice associated with hyperproduction of prostaglandin E2. *Journal of Immunology* 166(9), 5782–5791. <https://doi.org/10.4049/jimmunol.166.9.5782>.
- Molho-Pessach, V., & Lotem, M. (2007). Ultraviolet radiation and cutaneous carcinogenesis. *Current Problems in Dermatology* 35, 14–27. <https://doi.org/10.1159/000106407>.
- Monga, J., Aggarwal, V., Suthar, S. K., Monika, Nongalleima, K., & Sharma, M. (2014). Topical (+)-catechin emulsified gel prevents DMBA/TPA-induced squamous cell carcinoma of the skin by modulating antioxidants and inflammatory biomarkers in BALB/c mice. *Food Funct* 5(12), 3197–3207. <https://doi.org/10.1039/c4fo00531g>.
- Moon, E. Y., Rhee, D. K., & Pyo, S. (1999). Inhibition of various functions in murine peritoneal macrophages by aflatoxin B1 exposure in vivo. *International Journal of Immunopharmacology* 21(1), 47–58. [https://doi.org/10.1016/S0192-0561\(98\)00069-1](https://doi.org/10.1016/S0192-0561(98)00069-1).
- Moore, M. M., Heflich, R. H., Haber, L. T., Allen, B. C., Shipp, A. M., & Kodell, R. L. (2008). Analysis of in vivo mutation data can inform cancer risk assessment. *Regulatory Toxicology and Pharmacology* 51(2), 151–161. <https://doi.org/10.1016/j.yrtph.2008.01.015>.
- Moreno, J. J. (2009). New aspects of the role of hydroxyicosatetraenoic acids in cell growth and cancer development. *Biochemical Pharmacology* 77, 1), 1–10 doi: S0006-2952(08)00521-2 [pii] <https://doi.org/10.1016/j.bcp.2008.07.033>.
- Moss, S. F., & Blaser, M. J. (2005). Mechanisms of disease: Inflammation and the origins of cancer. *Nature Clinical Practice Oncology* 2(2), 90–97 quiz 91 p following 113 <https://doi.org/10.1038/ncponc0081>.
- Moto, M., Okamura, M., Mugeruma, M., Ito, T., Jin, M., Kashida, Y., & Mitsumori, K. (2006). Gene expression analysis on the dicyclanil-induced hepatocellular tumors in mice. *Toxicologic Pathology* 34(6), 744–751. <https://doi.org/10.1080/01926230600932471>.
- Mukherjee, P. K., Marcheselli, V. L., Serhan, C. N., & Bazan, N. G. (2004). Neuroprotectin D1: A docosahexaenoic acid-derived docosatriene protects human retinal pigment epithelial cells from oxidative stress. *Proceedings of the National Academy of Sciences of the United States of America* 101(22), 8491–8496. <https://doi.org/10.1073/pnas.0402531101>.
- Muller-Decker, K., Neufang, G., Berger, I., Neumann, M., Marks, F., & Furstenberger, G. (2002). Transgenic cyclooxygenase-2 overexpression sensitizes mouse skin for carcinogenesis. *Proceedings of the National Academy of Sciences of the United States of America* 99(19), 12483–12488. <https://doi.org/10.1073/pnas.192323799>.
- Murakami, A., Nakamura, Y., Torikai, K., Tanaka, T., Koshiba, T., Koshimizu, K., ... Ohgashi, H. (2000). Inhibitory effect of citrus nobilinetin on phorbol ester-induced skin inflammation, oxidative stress, and tumor promotion in mice. *Cancer Research* 60(18), 5059–5066.
- Myers, M. J., Dickens, C. S., & Schook, L. B. (1987). Alteration of macrophage anti-tumor activity and transferrin receptor expression by exposure to dimethylnitrosamine in vivo. *Immunopharmacology* 13(3), 195–205. [https://doi.org/10.1016/0162-3109\(87\)90058-0](https://doi.org/10.1016/0162-3109(87)90058-0).
- Myers, M. J., Pullen, J. K., & Schook, L. B. (1986). Alteration of macrophage differentiation into accessory and effector cells from exposure to dimethylnitrosamine (DMN) in vivo. *Immunopharmacology* 12(2), 105–115. [https://doi.org/10.1016/0162-3109\(86\)90036-6](https://doi.org/10.1016/0162-3109(86)90036-6).
- Myers, M. J., Schook, L. B., & Bick, P. H. (1987). Mechanisms of benzo(a)pyrene-induced modulation of antigen presentation. *The Journal of Pharmacology and Experimental Therapeutics* 242(2), 399–404.
- Nakanishi, M., Menoret, A., Tanaka, T., Miyamoto, S., Montrose, D. C., Vella, A. T., & Rosenberg, D. W. (2011). Selective PGE(2) suppression inhibits colon carcinogenesis and modifies local mucosal immunity. *Cancer Prevention Research (Philadelphia, Pa.)* 4(8), 1198–1208. <https://doi.org/10.1158/1940-6207.CAPR-11-0188>.
- National Toxicology, P (2011). NTP 12th Report on Carcinogens. *Report on Carcinogens* 12, iii–499.
- Nelson, S. M., Shay, A. E., James, J. L., Carlson, B. A., Urban, J. F., Jr., & Prabhu, K. S. (2016). Selenoprotein expression in macrophages is critical for optimal clearance of parasitic helminth nipponstrongylus brasiliensis. *The Journal of Biological Chemistry* 291(6), 2787–2798. <https://doi.org/10.1074/jbc.M115.684738>.
- Nesnow, S., Davis, C., Nelson, G., Ross, J. A., Allison, J., Adams, L., & King, L. C. (1997). Comparison of the morphological transforming activities of dibenzo[a,l]pyrene and benzo[a]pyrene in C3H10T1/2CL8 cells and characterization of the dibenzo[a,l]pyrene-DNA adducts. *Carcinogenesis* 18(10), 1973–1978. <https://doi.org/10.1093/carcin/18.10.1973>.
- Neuhofer, A., Zeyda, M., Mascher, D., Itariu, B. K., Murano, I., Leitner, L., ... Stulnig, T. M. (2013). Impaired local production of proresolving lipid mediators in obesity and 17-HDHA as a potential treatment for obesity-associated inflammation. *Diabetes* 62(6), 1945–1956. <https://doi.org/10.2337/db12-0828>.
- Nicole, W. (2013). PFOA and cancer in a highly exposed community: new findings from the C8 science panel. *Environmental Health Perspectives* 121(11–12), A340. <https://doi.org/10.1289/ehp.121-A340>.
- Node, K., Huo, Y., Ruan, X., Yang, B., Spiecker, M., Ley, K., ... Liao, J. K. (1999). Anti-inflammatory properties of cytochrome P450 epoxygenase-derived eicosanoids. *Science* 285(5431), 1276–1279 (doi: 7768 [pii]).
- Noguchi, M., Minami, M., Yagasaki, R., Kinoshita, K., Earashi, M., Kitagawa, H., ... Miyazaki, I. (1997). Chemoprevention of DMBA-induced mammary carcinogenesis in rats by low-dose EPA and DHA. *British Journal of Cancer* 75(3), 348–353. <https://doi.org/10.1038/bjc.1997.57>.
- Norling, L. V., Spite, M., Yang, R., Flower, R. J., Perretti, M., & Serhan, C. N. (2011). Cutting edge: humanized nano-proresolving medicines mimic inflammation-resolution and enhance wound healing. *Journal of Immunology* 186(10), 5543–5547 doi: jimmunol.1003865 [pii] <https://doi.org/10.4049/jimmunol.1003865>.
- Norris, P. C., Libereros, S., & Serhan, C. N. (2019). Resolution metabolomes activated by hypoxic environment. *Science Advances* 5(10), eaax4895. <https://doi.org/10.1126/sciadv.aax4895>.
- Norris, P. C., & Serhan, C. N. (2018). Metabololipidomic profiling of functional immunoresolvent clusters and eicosanoids in mammalian tissues. *Biochemical and Biophysical Research Communications* 504(3), 553–561. <https://doi.org/10.1016/j.bbrc.2018.03.037>.
- Nowak, K., Ratajczak-Wrona, W., Garley, M., & Jablonska, E. (2018). The effect of ethanol and N-nitrosodimethylamine on the iNOS-dependent NO production in human neutrophils. Role of NF-kappaB. *Xenobiotica* 48(5), 498–505. <https://doi.org/10.1080/00498254.2017.1342150>.
- Nowshen, S., Aziz, K., Kryston, T. B., Ferguson, N. F., & Georgakilas, A. (2012). The interplay between inflammation and oxidative stress in carcinogenesis. *Current Molecular Medicine* 12(6), 672–680. <https://doi.org/10.2174/156652412800792642>.
- Ohira, T., Arita, M., Omori, K., Recchiuti, A., Van Dyke, T. E., & Serhan, C. N. (2010). Resolvin E1 receptor activation signals phosphorylation and phagocytosis. *The Journal of Biological Chemistry* 285(5), 3451–3461 doi: M109.044131 [pii] <https://doi.org/10.1074/jbc.M109.044131>.
- Ono, E., Dutilleul, S., Kazani, S., Wechsler, M. E., Yang, J., Hammock, B. D., ... Blood Institute's Asthma Clinical Research, N (2014). Lipoxin generation is related to soluble epoxide hydrolase activity in severe asthma. *American Journal of Respiratory and Critical Care Medicine* 190(8), 886–897. <https://doi.org/10.1164/rccm.201403-0544OC>.
- O'Rourke, J. M., Sagar, V. M., Shah, T., & Shetty, S. (2018). Carcinogenesis on the background of liver fibrosis: Implications for the management of hepatocellular cancer. *World Journal of Gastroenterology* 24(39), 4436–4447. <https://doi.org/10.3748/wjg.v24.i39.4436>.
- Osman, J., Savari, S., Chandrashekar, N. K., Bellamkonda, K., Douglas, D., & Sjolander, A. (2017). Cysteinyl leukotriene receptor 1 facilitates tumorigenesis in a mouse model of colitis-associated colorectal cancer. *Oncotarget* 8(21), 34773–34786. <https://doi.org/10.18632/oncotarget.16718>.
- Palmer, C. D., Mancuso, C. J., Weiss, J. P., Serhan, C. N., Guinan, E. C., & Levy, O. (2011). 17 (R)-Resolvin D1 differentially regulates TLR4-mediated responses of primary human macrophages to purified LPS and live E. coli. *Journal of Leukocyte Biology* 90(3), 459–470. <https://doi.org/10.1189/jlb.0311145>.
- Pan, F., Chen, Y., He, J. Z., Long, L., Chen, Y., Luo, H. J., ... Xu, L. Y. (2019). Dietary riboflavin deficiency promotes N-nitrosomethylbenzylamine-induced esophageal tumorigenesis in rats by inducing chronic inflammation. *American Journal of Cancer Research* 9(11), 2469–2481.
- Panigrahy, D., Edin, M. L., Lee, C. R., Huang, S., Bielenberg, D. R., Butterfield, C. E., ... Zeldin, D. C. (2012). Epoxyeicosanoids stimulate multiorgan metastasis and tumor dormancy escape in mice. *The Journal of Clinical Investigation* 122(1), 178–191. <https://doi.org/10.1172/JCI58128.58128> [pii].
- Panigrahy, D., Gartung, A., Yang, J., Yang, H., Gilligan, M. M., Sulciner, M. L., ... Sukhatme, V. P. (2019). Preoperative stimulation of resolution and inflammation blockade eradicates micrometastases. *The Journal of Clinical Investigation* 129(7), 2964–2979. <https://doi.org/10.1172/JCI127282>.
- Panigrahy, D., Gilligan, M. M., Huang, S., Gartung, A., Cortes-Puch, I., Sime, P. J., ... Hammock, B. D. (2020). Inflammation resolution: a dual-pronged approach to averting cytokine storms in COVID-19? *Cancer Metastasis Reviews*. <https://doi.org/10.1007/s10555-020-09889-4>.
- Panigrahy, D., Greene, E. R., Pozzi, A., Wang, D. W., & Zeldin, D. C. (2011). EET signaling in cancer. *Cancer Metastasis Reviews* 30(3–4), 525–540. <https://doi.org/10.1007/s10555-011-9315-y>.
- Penas, F., Mirkin, G. A., Vera, M., Cevay, A., Gonzalez, C. D., Gomez, M. I., ... Goren, N. B. (2015). Treatment in vitro with PPARalpha and PPARgamma ligands drives M1-to-M2 polarization of macrophages from T. cruzi-infected mice. *Biochimica et Biophysica Acta* 1852(5), 893–904. <https://doi.org/10.1016/j.bbadis.2014.12.019>.
- Peng, J., Li, H., Ou, Q., Lin, J., Wu, X., Lu, Z., ... Pan, Z. (2017). Preoperative lymphocyte-to-monocyte ratio represents a superior predictor compared with neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios for colorectal liver-only metastases survival. *Oncotargets and Therapy* 10, 3789–3799. <https://doi.org/10.2147/OTT.S140872>.
- Perez-Losada, J., & Balmain, A. (2003). Stem-cell hierarchy in skin cancer. *Nature Reviews. Cancer* 3(6), 434–443. <https://doi.org/10.1038/nrc1095>.

- Perretti, M., Chiang, N., La, M., Fierro, I. M., Marullo, S., Getting, S. J., ... Serhan, C. N. (2002). Endogenous lipid- and peptide-derived anti-inflammatory pathways generated with glucocorticoid and aspirin treatment activate the lipoxin A4 receptor. *Nature Medicine* 8(11), 1296–1302. <https://doi.org/10.1038/nm786> [pii].
- Petasis, N. A., Yang, R., Winkler, J. W., Zhu, M., Uddin, J., Bazan, N. G., & Serhan, C. N. (2012). Stereocontrolled total synthesis of neuroprotectin D1/protectin D1 and its aspirin-triggered stereoisomer. *Tetrahedron Letters* 53(14), 1695–1698. <https://doi.org/10.1016/j.tetlet.2012.01.032>.
- Peto, R., Gray, R., Brantom, P., & Grasso, P. (1984). Nitrosamine carcinogenesis in 5120 rodents: chronic administration of sixteen different concentrations of NDEA, NDMA, NPYR and NPIP in the water of 4440 inbred rats, with parallel studies on NDEA alone of the effect of age of starting (3, 6 or 20 weeks) and of species (rats, mice or hamsters). *IARC Scientific Publications*(57), 627–665.
- Pirkle, J. L., Osterloh, J., Needham, L. L., & Sampson, E. J. (2005). National exposure measurements for decisions to protect public health from environmental exposures. *International Journal of Hygiene and Environmental Health* 208(1–2), 1–5. <https://doi.org/10.1016/j.ijheh.2005.01.001>.
- Planaguma, A., Kazani, S., Marijowda, G., Haworth, O., Mariani, T. J., Israel, E., ... Levy, B. D. (2008). Airway lipoxin A4 generation and lipoxin A4 receptor expression are decreased in severe asthma. *American Journal of Respiratory and Critical Care Medicine* 178(6), 574–582. <https://doi.org/10.1164/rccm.200801-0610C>.
- Ploeger, J. M., Manivel, J. C., Boatner, L. N., & Mashek, D. G. (2017). Caloric restriction prevents carcinogen-initiated liver tumorigenesis in mice. *Cancer Prevention Research (Philadelphia, Pa.)* 10(11), 660–670. <https://doi.org/10.1158/1940-6207.CAPR-17-0174>.
- Poirier, M. C. (2016). Linking DNA adduct formation and human cancer risk in chemical carcinogenesis. *Environmental and Molecular Mutagenesis* 57(7), 499–507. <https://doi.org/10.1002/em.22030>.
- Poirier, M. C., Santella, R. M., & Weston, A. (2000). Carcinogen macromolecular adducts and their measurement. *Carcinogenesis* 21(3), 353–359. <https://doi.org/10.1093/carcin/21.3.353>.
- Pollard, J. W. (2004). Tumour-educated macrophages promote tumour progression and metastasis. *Nature Reviews. Cancer* 4(1), 71–78. <https://doi.org/10.1038/nrc1256>.
- Pool, B. L., Brendler, S. Y., Liegibel, U. M., Tompa, A., & Schmezer, P. (1990). Employment of adult mammalian primary cells in toxicology: in vivo and in vitro genotoxic effects of environmentally significant N-nitrosodialkylamines in cells of the liver, lung, and kidney. *Environmental and Molecular Mutagenesis* 15(1), 24–35.
- Pool-Zobel, B. L., Klein, R. G., Liegibel, U. M., Kuchenmeister, F., Weber, S., & Schmezer, P. (1992). Systemic genotoxic effects of tobacco-related nitrosamines following oral and inhalational administration to Sprague-Dawley rats. *The Clinical Investigator* 70(3–4), 299–306.
- Pottegard, A., Kristensen, K. B., Ernst, M. T., Johansen, N. B., Quartarolo, P., & Hallas, J. (2018). Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study. *BMJ* 362, k3851. <https://doi.org/10.1136/bmj.k3851>.
- Potten, C. S., Li, Y. Q., O'Connor, P. J., & Winton, D. J. (1992). A possible explanation for the differential cancer incidence in the intestine, based on distribution of the cytotoxic effects of carcinogens in the murine large bowel. *Carcinogenesis* 13(12), 2305–2312.
- Pozzi, A., Macias-Perez, I., Abair, T., Wei, S., Su, Y., Zent, R., ... Capdevila, J. H. (2005). Characterization of 5,6- and 8,9-epoxyeicosatrienoic acids (5,6- and 8,9-EET) as potent in vivo angiogenic lipids. *The Journal of Biological Chemistry* 280(29), 27138–27146.
- Preussmann, R. (1980). The problem of thresholds in chemical carcinogenesis some views on theoretical and practical aspects. *Journal of Cancer Research and Clinical Oncology* 97(1), 1–14.
- Prevete, N., Liotti, F., Illiano, A., Amoresano, A., Pucci, P., de Paulis, A., & Melillo, R. M. (2017). Formyl peptide receptor 1 suppresses gastric cancer angiogenesis and growth by exploiting inflammation resolution pathways. *Oncoimmunology* 6(4), e1293213. <https://doi.org/10.1080/2162402X.2017.1293213>.
- Prevete, N., Liotti, F., Visciano, C., Marone, G., Melillo, R. M., & de Paulis, A. (2015). The formyl peptide receptor 1 exerts a tumor suppressor function in human gastric cancer by inhibiting angiogenesis. *Oncogene* 34(29), 3826–3838. <https://doi.org/10.1038/onc.2014.309>.
- Pyrillou, K., Chairakaki, A. D., Tamvakopoulos, C., & Andreakos, E. (2018). Dexamethasone induces omega3-derived immunoresolvents driving resolution of allergic airway inflammation. *The Journal of Allergy and Clinical Immunology* 142(2), 691–695 e694. <https://doi.org/10.1016/j.jaci.2018.04.004>.
- Qu, X., Zhang, X., Yao, J., Song, J., Nikolic-Paterson, D. J., & Li, J. (2012). Resolvins E1 and D1 inhibit interstitial fibrosis in the obstructed kidney via inhibition of local fibroblast proliferation. *The Journal of Pathology* 228(4), 506–519. <https://doi.org/10.1002/path.4050>.
- Ramakrishna, G., Perella, C., Birely, L., Diwan, B. A., Fornwald, L. W., & Anderson, L. M. (2002). Decrease in K-ras p21 and increase in Raf1 and activated Erk 1 and 2 in murine lung tumors initiated by N-nitrosodimethylamine and promoted by 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Toxicology and Applied Pharmacology* 179(1), 21–34. <https://doi.org/10.1006/taap.2001.9344>.
- Ramon, S., Gao, F., Serhan, C. N., & Phipps, R. P. (2012). Specialized proresolving mediators enhance human B cell differentiation to antibody-secreting cells. *Journal of Immunology* 189(2), 1036–1042. <https://doi.org/10.4049/jimmunol.1103483>.
- Rand, A. A., Rajamani, A., Kodani, S. D., Harris, T. R., Schlatt, L., Barnych, B., ... Hammock, B. D. (2019). Epoxyeicosatrienoic acid (EET)-stimulated angiogenesis is mediated by epoxy hydroxyeicosatrienoic acids (EHETs) formed from COX-2. *Journal of Lipid Research* 60(12), 1996–2005. <https://doi.org/10.1194/jlr.M094219>.
- Rastogi, S., Dogra, R. K., Khanna, S. K., & Das, M. (2006). Skin tumorigenic potential of aflatoxin B1 in mice. *Food and Chemical Toxicology* 44(5), 670–677. <https://doi.org/10.1016/j.fct.2005.09.008>.
- Ratajczak-Wrona, W., Jablonska, E., Garley, M., Jablonski, J., & Radziwon, P. (2013). Role of ERK1/2 kinase in the expression of iNOS by NDMA in human neutrophils. *Indian Journal of Experimental Biology* 51(1), 73–80.
- Ratajczak-Wrona, W., Jablonska, E., Garley, M., Jablonski, J., Radziwon, P., Iwaniuk, A., & Grubczak, K. (2014). PI3K-Akt/PKB signaling pathway in neutrophils and mononuclear cells exposed to N-nitrosodimethylamine. *Journal of Immunotoxicology* 11(3), 231–237. <https://doi.org/10.3109/1547691X.2013.826307>.
- Revesz, L. (1956). Effect of tumour cells killed by x-rays upon the growth of admixed viable cells. *Nature* 178(4547), 1391–1392.
- Reznik-Schuller, H. M. (1981). Ultrastructure of tumors induced in the rat urinary bladder by nitrosomethyldecylamine. *Virchows Archiv. A, Pathological Anatomy and Histology* 392(1), 63–71.
- Ridker, P. M., MacFadyen, J. G., Thuren, T., Everett, B. M., Libby, P., Glynn, R. J., & Group, C. T. (2017). Effect of interleukin-1beta inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. *Lancet* 390(10105), 1833–1842. [https://doi.org/10.1016/S0140-6736\(17\)32247-X](https://doi.org/10.1016/S0140-6736(17)32247-X).
- Rioux, N., & Castonguay, A. (1998). Prevention of N-nitrosodimethylamine tumorigenesis in A/J mice by acetylsalicylic acid and NS-398. *Cancer Research* 58(23), 5354–5360.
- Rioux, N., & Castonguay, A. (2000). The induction of cyclooxygenase-1 by a tobacco carcinogen in U937 human macrophages is correlated to the activation of NF-kappaB. *Carcinogenesis* 21(9), 1745–1751. <https://doi.org/10.1093/carcin/21.9.1745>.
- Roach, K. M., Feghall-Bostwick, C. A., Amrani, Y., & Bradding, P. (2015). Lipoxin A4 attenuates constitutive and TGF-beta1-dependent profibrotic activity in human lung myofibroblasts. *Journal of Immunology* 195(6), 2852–2860. <https://doi.org/10.4049/jimmunol.1500936>.
- Rogers, M. A., Vaughan, T. L., Davis, S., & Thomas, D. B. (1995). Consumption of nitrate, nitrite, and nitrosodimethylamine and the risk of upper aerodigestive tract cancer. *Cancer Epidemiology, Biomarkers & Prevention* 4(1), 29–36.
- de la Rosa, X., Norris, P. C., Chiang, N., Rodriguez, A. R., Spur, B. W., & Serhan, C. N. (2018). Identification and Complete Stereochemical Assignments of the New Resolving Conjugates in Tissue Regeneration in Human Tissues that Stimulate Proresolving Phagocyte Functions and Tissue Regeneration. *The American Journal of Pathology* 188(4), 950–966. <https://doi.org/10.1016/j.ajpath.2018.01.004>.
- Rossi, A., Kapahi, P., Natoli, G., Takahashi, T., Chen, Y., Karin, M., & Santoro, M. G. (2000). Anti-inflammatory cyclopentenone prostaglandins are direct inhibitors of Ikb kinase. *Nature* 403, 103–108.
- Rothlin, C. V., Carrera-Silva, E. A., Bosurgi, L., & Ghosh, S. (2015). TAM receptor signaling in immune homeostasis. *Annual Review of Immunology* 33, 355–391. <https://doi.org/10.1146/annurev-immunol-032414-112103>.
- Rutter, M., Saunders, B., Wilkinson, K., Rumbles, S., Schofield, G., Kamm, M., & Forbes, A. (2004). Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 126(2), 451–459. <https://doi.org/10.1053/j.gastro.2003.11.010>.
- Sadeeshkumar, V., Duraikannu, A., Ravichandran, S., Kodisundaram, P., Fredrick, W. S., & Gopalakrishnan, R. (2017). Modulatory efficacy of dieckol on xenobiotic-metabolizing enzymes, cell proliferation, apoptosis, invasion and angiogenesis during NDEA-induced rat hepatocarcinogenesis. *Molecular and Cellular Biochemistry* 433(1–2), 195–204. <https://doi.org/10.1007/s11010-017-3027-8>.
- Saito, P., Melo, C. P. B., Martinez, R. M., Fattori, V., Cezar, T. L. C., Pinto, I. C., ... Casagrande, R. (2018). The Lipid Mediator Resolvin D1 Reduces the Skin Inflammation and Oxidative Stress Induced by UV Irradiation in Hairless Mice. *Frontiers in Pharmacology* 9, 1242. <https://doi.org/10.3389/fphar.2018.01242>.
- Sakurai, T., He, G., Matsuzawa, A., Yu, G. Y., Maeda, S., Hardiman, G., & Karin, M. (2008). Hepatocyte necrosis induced by oxidative stress and IL-1 alpha release mediate carcinogen-induced compensatory proliferation and liver tumorigenesis. *Cancer Cell* 14(2), 156–165. <https://doi.org/10.1016/j.ccr.2008.06.016>.
- Salaspuu, M. (2017). Key role of local acetaldehyde in upper GI tract carcinogenesis. *Best Practice & Research. Clinical Gastroenterology* 31(4), 491–499. <https://doi.org/10.1016/j.bpg.2017.09.016>.
- Sandhu, S. K., Papadopoulos, K., Fong, P. C., Patnaik, A., Messiou, C., Olmos, D., ... Tolcher, A. W. (2013). A first-in-human, first-in-class, phase I study of carlumab (CNTO 888), a human monoclonal antibody against CC-chemokine ligand 2 in patients with solid tumors. *Cancer Chemotherapy and Pharmacology* 71(4), 1041–1050. <https://doi.org/10.1007/s00280-013-2099-8>.
- Sani, N. D. M., Heng, L. Y., Marugan, R., & Rajab, N. F. (2018). Electrochemical DNA biosensor for potential carcinogen detection in food sample. *Food Chemistry* 269, 503–510. <https://doi.org/10.1016/j.foodchem.2018.07.035>.
- Satarug, S., Haswell-Elkins, M. R., Sithithaworn, P., Bartsch, H., Ohshima, H., Tsuda, M., ... Elkins, D. B. (1998). Relationships between the synthesis of N-nitrosodimethylamine and immune responses to chronic infection with the carcinogenic parasite, *Opisthorchis viverrini*, in men. *Carcinogenesis* 19(3), 485–491. <https://doi.org/10.1093/carcin/19.3.485>.
- Scaffidi, P., Misteli, T., & Bianchi, M. E. (2002). Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. *Nature* 418(6894), 191–195. <https://doi.org/10.1038/nature00858>.
- Schif-Zuck, S., Gross, N., Assi, S., Rostoker, R., Serhan, C. N., & Ariel, A. (2011). Saturated-efferocytosis generates pro-resolving CD11b low macrophages: modulation by resolvins and glucocorticoids. *European Journal of Immunology* 41(2), 366–379. <https://doi.org/10.1002/eji.201040801>.
- Schins, R. P., & Knaepen, A. M. (2007). Genotoxicity of poorly soluble particles. *Inhalation Toxicology* 19(Suppl. 1), 189–198. <https://doi.org/10.1080/08958370701496202>.
- Schmelzer, K. R., Kubala, L., Newman, J. W., Kim, I. H., Eiserich, J. P., & Hammock, B. D. (2005). Soluble epoxide hydrolase is a therapeutic target for acute inflammation. *Proceedings of the National Academy of Sciences of the United States of America* 102(28), 9772–9777 doi: 0503279102 [pii] <https://doi.org/10.1073/pnas.0503279102>.

- Schnittert, J., Heinrich, M. A., Kuninty, P. R., Storm, G., & Prakash, J. (2018). Reprogramming tumor stroma using an endogenous lipid lipoxin A4 to treat pancreatic cancer. *Cancer Letters* 420, 247–258. <https://doi.org/10.1016/j.canlet.2018.01.072>.
- Schottelius, A. J., Giesen, C., Asadullah, K., Fierro, I. M., Colgan, S. P., Bauman, J., ... Parkinson, J. F. (2002). An aspirin-triggered lipoxin A4 stable analog displays a unique topical anti-inflammatory profile. *Journal of Immunology* 169(12), 7063–7070.
- Schuller, H. M., Tithof, P. K., Williams, M., & Plummer, H., 3rd. (1999). The tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone is a beta-adrenergic agonist and stimulates DNA synthesis in lung adenocarcinoma via beta-adrenergic receptor-mediated release of arachidonic acid. *Cancer Research* 59(18), 4510–4515.
- Schwab, J. M., Chiang, N., Arita, M., & Serhan, C. N. (2007). Resolvin E1 and protectin D1 activate inflammation-resolution programmes. *Nature* 447(7146), 869–874 doi: nature05877 [pii] <https://doi.org/10.1038/nature05877>.
- Seehawer, M., Heinzmann, F., D'Artista, L., Harbig, J., Roux, P. F., Hoenicke, L., & Zender, L. (2018). Necroptosis microenvironment directs lineage commitment in liver cancer. *Nature* 562(7725), 69–75. <https://doi.org/10.1038/s41586-018-0519-y>.
- Serhan, C. N. (2005). Lipoxins and aspirin-triggered 15-epi-lipoxins are the first lipid mediators of endogenous anti-inflammation and resolution. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 73(3–4), 141–162. <https://doi.org/10.1016/j.plefa.2005.05.002>.
- Serhan, C. N. (2011). The resolution of inflammation: the devil in the flask and in the details. *The FASEB Journal* 25(5), 1441–1448 (doi: 25/5/1441 [pii] 10.1096/fj.11-0502ufm).
- Serhan, C. N. (2014). Pro-resolving lipid mediators are leads for resolution physiology. *Nature* 510(7503), 92–101. <https://doi.org/10.1038/nature13479>.
- Serhan, C. N. (2017). Treating inflammation and infection in the 21st century: new hints from decoding resolution mediators and mechanisms. *The FASEB Journal* 31(4), 1273–1288. <https://doi.org/10.1096/fj.2016101222R>.
- Serhan, C. N., Dalli, J., Colas, R. A., Winkler, J. W., & Chiang, N. (2015). Protectins and maresins: New pro-resolving families of mediators in acute inflammation and resolution bioactive metabolome. *Biochimica et Biophysica Acta* 1851(4), 397–413. <https://doi.org/10.1016/j.bbali.2014.08.006>.
- Serhan, C. N., de la Rosa, X., & Jouvencé, C. C. (2018). Cutting Edge: Human Vagus Produces specialized proresolving mediators of inflammation with electrical stimulation reducing proinflammatory eicosanoids. *Journal of Immunology* 201(11), 3161–3165. <https://doi.org/10.4049/jimmunol.1800806>.
- Serhan, C. N., Hamberg, M., & Samuelsson, B. (1984). Lipoxins: novel series of biologically active compounds formed from arachidonic acid in human leukocytes. *Proceedings of the National Academy of Sciences of the United States of America* 81(17), 5335–5339.
- Serhan, C. N., Hong, S., Gronert, K., Colgan, S. P., Devchand, P. R., Mirick, G., & Moussignac, R. L. (2002). Resolvins: A family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. *The Journal of Experimental Medicine* 196(8), 1025–1037.
- Serhan, C. N., & Levy, B. D. (2018). Resolvins in inflammation: Emergence of the pro-resolving superfamily of mediators. *The Journal of Clinical Investigation* 128(7), 2657–2669. <https://doi.org/10.1172/JCI97943>.
- Serhan, C. N., Yang, R., Martinod, K., Kasuga, K., Pillai, P. S., Porter, T. F., ... Spite, M. (2009). Maresins: novel macrophage mediators with potent antiinflammatory and proresolving actions. *The Journal of Experimental Medicine* 206(1), 15–23 (doi: jem.20081880 [pii] 10.1084/jem.20081880).
- Shaked, Y. (2019). The pro-tumorigenic host response to cancer therapies. *Nature Reviews. Cancer* 19(12), 667–685. <https://doi.org/10.1038/s41568-019-0209-6>.
- Sham, H. P., Walker, K. H., Abdunour, R. E., Krishnamoorthy, N., Douda, D. N., Norris, P. C., ... Levy, B. D. (2018). 15-epi-Lipoxin A4, Resolvin D2, and Resolvin D3 Induce NF-kappaB regulators in bacterial pneumonia. *Journal of Immunology* 200(8), 2757–2766. <https://doi.org/10.4049/jimmunol.1602090>.
- Shan, K., Feng, N., Cui, J., Wang, S., Qu, H., Fu, G., ... Chen, Y. Q. (2020). Resolvin D1 and D2 inhibit tumour growth and inflammation via modulating macrophage polarization. *Journal of Cellular and Molecular Medicine*. <https://doi.org/10.1111/jcmm.15436>.
- Sharma, P., & Allison, J. P. (2015). The future of immune checkpoint therapy. *Science* 348(6230), 56–61. <https://doi.org/10.1126/science.aaa8172>.
- Sharma, V., & Singh, M. (2014). Ameliorative effects of operculina turpethum and its isolated stigma-5,22dien-3- α -beta-D-glucopyranoside on the hematological parameters of male mice exposed to N-Nitrosodimethylamine, a Potent Carcinogen. *Toxicology International* 21(1), 29–36. <https://doi.org/10.4103/0971-6580.128789>.
- Shetty, S., Kumar, R., & Bharati, S. (2019). Mito-TEMPO, a mitochondria-targeted antioxidant, prevents N-nitrosodiethylamine-induced hepatocarcinogenesis in mice. *Free Radical Biology & Medicine* 136, 76–86. <https://doi.org/10.1016/j.freeradbiomed.2019.03.037>.
- Sheweita, S. A., El-Shahat, F. G., Bazeed, M. A., Abu El-Maati, M. R., & O'Connor, P. J. (2004). Effects of Schistosoma haematobium infection on drug-metabolizing enzymes in human bladder cancer tissues. *Cancer Letters* 205(1), 15–21. <https://doi.org/10.1016/j.canlet.2003.09.023>.
- Shi, N., Chen, F., Zhang, X., Clinton, S. K., Tang, X., Sun, Z., & Chen, T. (2017). Suppression of oxidative stress and NF-kappaB/MAPK signaling by lyophilized black raspberries for esophageal cancer prevention in rats. *Nutrients* 9(4). <https://doi.org/10.3390/nu9040413>.
- Shi, Q., Godschalk, R. W. L., & van Schooten, F. J. (2017). Inflammation and the chemical carcinogen benzo[a]pyrene: Partners in crime. *Mutation Research* 774, 12–24. <https://doi.org/10.1016/j.mrrev.2017.08.003>.
- Shiff, S. J., & Rigas, B. (1999). The role of cyclooxygenase inhibition in the antineoplastic effects of nonsteroidal antiinflammatory drugs (NSAIDs). *The Journal of Experimental Medicine* 190(4), 445–450. <https://doi.org/10.1084/jem.190.4.445>.
- Shu, M., Xu, Y., Liu, X., Li, Y., He, Q., Tu, Z., ... Hammock, B. D. (2016). Anti-idiotypic nanobody-alkaline phosphatase fusion proteins: Development of a one-step competitive enzyme immunoassay for fumonisin B1 detection in cereal. *Analytica Chimica Acta* 924, 53–59. <https://doi.org/10.1016/j.aca.2016.03.053>.
- Siddiqi, A., Saidullah, B., & Sultana, S. (2018). Anti-carcinogenic effect of hesperidin against renal cell carcinoma by targeting COX-2/PGE2 pathway in Wistar rats. *Environmental Toxicology* 33(10), 1069–1077. <https://doi.org/10.1002/tox.22626>.
- da Silva-Jr, I. A., Chammas, R., Lepique, A. P., & Jancar, S. (2017). Platelet-activating factor (PAF) receptor as a promising target for cancer cell repopulation after radiotherapy. *Oncogenesis* 6(1), e296. <https://doi.org/10.1038/oncsis.2016.90>.
- Simoes, R. L., De-Brito, N. M., Cunha-Costa, H., Morandi, V., Fierro, I. M., Roitt, I. M., & Barja-Fidalgo, C. (2017). Lipoxin A4 selectively programs the profile of M2 tumor-associated macrophages which favour control of tumor progression. *International Journal of Cancer* 140(2), 346–357. <https://doi.org/10.1002/ijc.30424>.
- Sivaramakrishnan, V., & Niranjali Devaraj, S. (2009). Morin regulates the expression of NF-kappaB-p65, COX-2 and matrix metalloproteinases in diethylnitrosamine induced rat hepatocellular carcinoma. *Chemico-Biological Interactions* 180(3), 353–359. <https://doi.org/10.1016/j.cbi.2009.02.004>.
- Slaga, T. J., Budunova, I. V., Gimenez-Conti, I. B., & Aldaz, C. M. (1996). The mouse skin carcinogenesis model. *The Journal of Investigative Dermatology. Symposium Proceedings* 1(2), 151–156.
- Smith, M. T., Guyton, K. Z., Gibbons, C. F., Fritz, J. M., Portier, C. J., Rusyn, I., ... Straif, K. (2016). Key Characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environmental Health Perspectives* 124(6), 713–721. <https://doi.org/10.1289/ehp.1509912>.
- Smith, M. T., Guyton, K. Z., Kleinstreuer, N., Borrel, A., Cardenas, A., Chiu, W. A., ... Fielden, M. (2020). The Key characteristics of carcinogens: Relationship to the hallmarks of cancer, relevant biomarkers, and assays to measure them. *Cancer Epidemiology, Biomarkers & Prevention*. <https://doi.org/10.1158/1055-9965.EPI-19-1346>.
- Smith, T. J., Stoner, G. D., & Yang, C. S. (1995). Activation of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in human lung microsomes by cytochromes P450, lipoygenase, and hydroperoxidase. *Cancer Research* 55(23), 5566–5573.
- Son, H. Y., Lee, S., Tak, E. N., Cho, H. S., Shin, H. I., Kim, S. H., & Yang, J. H. (2009). Perfluorooctanoic acid alters T lymphocyte phenotypes and cytokine expression in mice. *Environmental Toxicology* 24(6), 580–588. <https://doi.org/10.1002/tox.20459>.
- Song, P., Wu, L., & Guan, W. (2015). Dietary nitrates, nitrites, and nitrosamines intake and the risk of gastric cancer: A meta-analysis. *Nutrients* 7(12), 9872–9895. <https://doi.org/10.3390/nu7125505>.
- Souza, P. R., Marques, R. M., Gomez, E. A., Colas, R. A., De Matteis, R., Zak, A., ... Dalli, J. (2020). Enriched marine oil supplements increase peripheral blood specialized pro-resolving mediators concentrations and reprogram host immune responses: A randomized double-blind placebo-controlled study. *Circulation Research* 126(1), 75–90. <https://doi.org/10.1161/CIRCRESAHA.119.315506>.
- Spector, A. A., & Norris, A. W. (2007). Action of epoxyeicosatrienoic acids on cellular function. *American Journal of Physiology. Cell Physiology* 292(3), C996–1012 doi: 00402.2006 [pii] <https://doi.org/10.1152/ajpcell.00402.2006>.
- Spite, M., Norling, L. V., Summers, L., Yang, R., Cooper, D., Petasis, N. A., & Serhan, C. N. (2009). Resolvin D2 is a potent regulator of leukocytes and controls microbial sepsis. *Nature* 461(7268), 1287–1291. <https://doi.org/10.1038/nature08541>.
- Srivastava, S., Reid, B. J., Ghosh, S., & Kramer, B. S. (2016). Research needs for understanding the biology of overdiagnosis in cancer screening. *Journal of Cellular Physiology* 231(9), 1870–1875. <https://doi.org/10.1002/jcp.25227>.
- Stemme, S., Faber, B., Holm, J., Wiklund, O., Witztum, J. L., & Hansson, G. K. (1995). T lymphocytes from human atherosclerotic plaques recognize oxidized low density lipoprotein. *Proceedings of the National Academy of Sciences of the United States of America* 92(9), 3893–3897.
- Stenke, L., Edenius, C., Samuelsson, J., & Lindgren, J. A. (1991). Deficient lipoxin synthesis: a novel platelet dysfunction in myeloproliferative disorders with special reference to blastic crisis of chronic myelogenous leukemia. *Blood* 78(11), 2989–2995.
- Strosnider, H., Azziz-Baumgartner, E., Banziger, M., Bhat, R. V., Breiman, R., Brune, M. N., ... Wilson, D. (2006). Workgroup report: public health strategies for reducing aflatoxin exposure in developing countries. *Environmental Health Perspectives* 114(12), 1898–1903. <https://doi.org/10.1289/ehp.9302>.
- Suarez-Torres, J. D., Alzate, J. P., & Orjuela-Ramirez, M. E. (2020). The NTP report on carcinogens: A valuable resource for public health, a challenge for regulatory science. *Journal of Applied Toxicology* 40(1), 169–175. <https://doi.org/10.1002/jat.3894>.
- Subramanian, P., & Arul, D. (2013). Attenuation of NDEA-induced hepatocarcinogenesis by naringenin in rats. *Cell Biochemistry and Function* 31(6), 511–517. <https://doi.org/10.1002/cbf.2929>.
- Sulciner, M. L., Gartung, A., Gilligan, M. M., Serhan, C. N., & Panigrahy, D. (2018). Targeting lipid mediators in cancer biology. *Cancer Metastasis Reviews* 37(2–3), 557–572. <https://doi.org/10.1007/s10555-018-9754-9>.
- Sulciner, M. L., Serhan, C. N., Gilligan, M. M., Mudge, D. K., Chang, J., Gartung, A., ... Panigrahy, D. (2018). Resolvins suppress tumor growth and enhance cancer therapy. *The Journal of Experimental Medicine* 215(1), 115–140. <https://doi.org/10.1084/jem.20170681>.
- Sun, C. C., Zhang, C. Y., Duan, J. X., Guan, X. X., Yang, H. H., Jiang, H. L., ... Zhang, J. (2020). PTUPB ameliorates high-fat diet-induced non-alcoholic fatty liver disease via inhibiting NLRP3 inflammasome activation in mice. *Biochemical and Biophysical Research Communications* 523(4), 1020–1026. <https://doi.org/10.1016/j.bbrc.2019.12.131>.
- Sun, L., Wang, Y., Wang, L., Yao, B., Chen, T., Li, Q., ... Tu, K. (2019). Resolvin D1 prevents epithelial-mesenchymal transition and reduces the stemness features of hepatocellular carcinoma by inhibiting paracrine of cancer-associated fibroblast-derived COMP. *Journal of Experimental & Clinical Cancer Research* 38(1), 170. <https://doi.org/10.1186/s13046-019-1163-6>.
- Sun, Y., Su, J., Liu, Z., Liu, D., Gan, F., Chen, X., & Huang, K. (2018). Aflatoxin B1 Promotes Influenza Replication and Increases Virus Related Lung Damage via Activation of

- TLR4 Signaling. *Frontiers in Immunology* 9, 2297. <https://doi.org/10.3389/fimmu.2018.02297>.
- Sun, Y. P., Oh, S. F., Uddin, J., Yang, R., Gotlinger, K., Campbell, E., ... Serhan, C. N. (2007). Resolvin D1 and its aspirin-triggered 17R epimer. Stereochemical assignments, anti-inflammatory properties, and enzymatic inactivation. *The Journal of Biological Chemistry* 282(13), 9323–9334 (doi: M609212200 [pii] 10.1074/jbc.M609212200).
- Sun, Z., Sood, S., Li, N., Ramji, D., Yang, P., Newman, R. A., ... Chen, X. (2006). Involvement of the 5-lipoxygenase/leukotriene A4 hydrolase pathway in 7,12-dimethylbenz[a]anthracene (DMBA)-induced oral carcinogenesis in hamster cheek pouch, and inhibition of carcinogenesis by its inhibitors. *Carcinogenesis* 27(9), 1902–1908. <https://doi.org/10.1093/carcin/bgl039>.
- Takahashi, H., Ogata, H., Nishigaki, R., Broide, D. H., & Karin, M. (2010). Tobacco smoke promotes lung tumorigenesis by triggering IKK β - and JNK1-dependent inflammation. *Cancer Cell* 17(1), 89–97. <https://doi.org/10.1016/j.ccr.2009.12.008>.
- Takano, T., Clish, C. B., Gronert, K., Petasis, N., & Serhan, C. N. (1998). Neutrophil-mediated changes in vascular permeability are inhibited by topical application of aspirin-triggered 15-epi-lipoxin A4 and novel lipoxin B4 stable analogues. *The Journal of Clinical Investigation* 101(4), 819–826. <https://doi.org/10.1172/JCI1578>.
- Takano, T., Fiore, S., Maddox, J. F., Brady, H. R., Petasis, N. A., & Serhan, C. N. (1997). Aspirin-triggered 15-epi-lipoxin A4 (LXA4) and LXA4 stable analogues are potent inhibitors of acute inflammation: evidence for anti-inflammatory receptors. *The Journal of Experimental Medicine* 185(9), 1693–1704. <https://doi.org/10.1084/jem.185.9.1693>.
- Tam, A. S., Foley, J. F., Devereux, T. R., Maronpot, R. R., & Massey, T. E. (1999). High frequency and heterogeneous distribution of p53 mutations in aflatoxin B1-induced mouse lung tumors. *Cancer Research* 59(15), 3634–3640.
- Temkin, A. M., Hocevar, B. A., Andrews, D. Q., Naidenko, O. V., & Kamendulis, L. M. (2020). Application of the key characteristics of carcinogens to per and polyfluoroalkyl substances. *International Journal of Environmental Research and Public Health* 17(5). <https://doi.org/10.3390/ijerph17051668>.
- Therriault, M. J., Proulx, L. I., Castonguay, A., & Bissonnette, E. Y. (2003). Immunomodulatory effects of the tobacco-specific carcinogen, NNK, on alveolar macrophages. *Clinical and Experimental Immunology* 132(2), 232–238. <https://doi.org/10.1046/j.1365-2249.2003.02142.x>.
- Thomas, P., Fugmann, R., Aranyi, C., Barbera, P., Gibbons, R., & Fenters, J. (1985). The effect of dimethylnitrosamine on host resistance and immunity. *Toxicology and Applied Pharmacology* 77(2), 219–229. [https://doi.org/10.1016/0041-008x\(85\)90321-7](https://doi.org/10.1016/0041-008x(85)90321-7).
- Thorp, E., Cui, D., Schrijvers, D. M., Kurikose, G., & Tabas, I. (2008). MerTK receptor mutation reduces efferocytosis efficiency and promotes apoptotic cell accumulation and plaque necrosis in atherosclerotic lesions of apoE $^{-/-}$ mice. *Arteriosclerosis, Thrombosis, and Vascular Biology* 28(8), 1421–1428. <https://doi.org/10.1161/ATVBAHA.108.167197>.
- Thuy Phuong, N. T., Kim, J. W., Kim, J. A., Jeon, J. S., Lee, J. Y., Xu, W. J., ... Kang, K. W. (2017). Role of the CYP3A4-mediated 11,12-epoxyicosatrienoic acid pathway in the development of tamoxifen-resistant breast cancer. *Oncotarget* 8(41), 71054–71069. <https://doi.org/10.18632/oncotarget.20329>.
- Tian, H., Lu, Y., Sherwood, A. M., Hongqian, D., & Hong, S. (2009). Resolvins E1 and D1 in choroid-retinal endothelial cells and leukocytes: biosynthesis and mechanisms of anti-inflammatory actions. *Investigative Ophthalmology & Visual Science* 50(8), 3613–3620 doi: iovs.08-3146 [pii] <https://doi.org/10.1167/iov.08-3146>.
- Tian, R., Zuo, X., Jaoude, J., Mao, F., Colby, J., & Shureiqi, I. (2017). ALOX15 as a suppressor of inflammation and cancer: Lost in the link. *Prostaglandins & Other Lipid Mediators* 132, 77–83. <https://doi.org/10.1016/j.prostaglandins.2017.01.002>.
- Tirino, V., Desiderio, V., Paino, F., De Rosa, A., Papaccio, F., La Noce, M., & Papaccio, G. (2013). Cancer stem cells in solid tumors: an overview and new approaches for their isolation and characterization. *The FASEB Journal* 27(1), 13–24. <https://doi.org/10.1096/fj.12-218222>.
- Tomatis, L., Aitio, A., Wilbourn, J., & Shuker, L. (1989). Human carcinogens so far identified. *Japanese Journal of Cancer Research* 80(9), 795–807.
- Tomatis, L., Huff, J., Hertz-Picciotto, I., Sandler, D. P., Bucher, J., Boffetta, P., ... Barrett, J. C. (1997). Avoided and avoidable risks of cancer. *Carcinogenesis* 18(1), 97–105.
- Triantafyllou, E., Pop, O. T., Possamai, L. A., Wilhelm, A., Liaskou, E., Singanayagam, A., ... Antoniadis, C. G. (2018). MerTK expressing hepatic macrophages promote the resolution of inflammation in acute liver failure. *Gut* 67(2), 333–347. <https://doi.org/10.1136/gutjnl-2016-313615>.
- Tricker, A. R., & Preussmann, R. (1991). Carcinogenic N-nitrosamines in the diet: occurrence, formation, mechanisms and carcinogenic potential. *Mutation Research* 259(3–4), 277–289.
- Trosko, J. E. (2001). Commentary: is the concept of “tumor promotion” a useful paradigm? *Molecular Carcinogenesis* 30(3), 131–137.
- Trosko, J. E., & Carruba, G. (2017). “Bad Luck Mutations”: DNA mutations are not the whole answer to understanding cancer risk. *Dose Response* 15(2), 1559325817716585. <https://doi.org/10.1177/1559325817716585>.
- Tsai, W. H., Shih, C. H., Wu, H. Y., Chien, H. Y., Chiang, Y. C., Lai, S. L., ... Hsu, H. C. (2012). Role of lipoxin A4 in the cell-to-cell interaction between all-trans retinoic acid-treated acute promyelocytic leukemic cells and alveolar macrophages. *Journal of Cellular Physiology* 227(3), 1123–1129. <https://doi.org/10.1002/jcp.22832>.
- Tsuneoka, N., Tajima, Y., Kitazato, A., Fukuda, K., Kitajima, T., Kuroki, T., ... Kanematsu, T. (2005). Chemopreventive effect of a cyclooxygenase-2-specific inhibitor (etodolac) on chemically induced biliary carcinogenesis in hamsters. *Carcinogenesis* 26(2), 465–469. <https://doi.org/10.1093/carcin/bgh311>.
- Tu, W., Wang, H., Li, S., Liu, Q., & Sha, H. (2019). The anti-inflammatory and anti-oxidant mechanisms of the Keap1/Nrf2/ARE signaling pathway in chronic diseases. *Aging and Disease* 10(3), 637–651. <https://doi.org/10.14336/AD.2018.0513>.
- Turesky, R. J. (2018). Mechanistic evidence for red meat and processed meat intake and cancer risk: A follow-up on the International Agency for Research on Cancer Evaluation of 2015. *Chimia (Aarau)* 72(10), 718–724. <https://doi.org/10.2533/chimia.2018.718>.
- Turk, J. L. (1994). Inflammation: John Hunter’s “A treatise on the blood, inflammation and gun-shot wounds”. *International Journal of Experimental Pathology* 75(6), 385–395.
- Uno, H., Furukawa, K., Suzuki, D., Shimizu, H., Ohtsuka, M., Kato, A., ... Miyazaki, M. (2016). Immunonutrition suppresses acute inflammatory responses through modulation of resolvin E1 in patients undergoing major hepatobiliary resection. *Surgery* 160(1), 228–236. <https://doi.org/10.1016/j.surg.2016.01.019>.
- Unsal, V., & Belge-Kurutas, E. (2017). Experimental hepatic carcinogenesis: oxidative stress and natural antioxidants. *Open Access Macedonian Journal of Medical Sciences* 5(5), 686–691. <https://doi.org/10.3889/oamjms.2017.101>.
- Vainio, H., Wilbourn, J. D., Sasco, A. J., Partensky, C., Gaudin, N., Heseltine, E., & Eragne, I. (1995). Identification of human carcinogenic risks in IARC monographs. *Bulletin du Cancer* 82(5), 339–348.
- Vaish, V., Piplani, H., Rana, C., & Sanyal, S. N. (2013). Angiostatic properties of sulindac and celecoxib in the experimentally induced inflammatory colorectal cancer. *Cell Biochemistry and Biophysics* 66(2), 205–227. <https://doi.org/10.1007/s12013-012-9469-4>.
- Van Dyke, T. E., & Serhan, C. N. (2003). Resolution of inflammation: a new paradigm for the pathogenesis of periodontal diseases. *Journal of Dental Research* 82(2), 82–90.
- Vane, J. R. (1971). Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature: New Biology* 231(25), 232–235.
- Vermeer, I. T., Henderson, L. Y., Moonen, E. J., Engels, L. G., Dallinga, J. W., van Maanen, J. M., & Kleinjans, J. C. (2004). Neutrophil-mediated formation of carcinogenic N-nitroso compounds in an in vitro model for intestinal inflammation. *Toxicology Letters* 154(3), 175–182. <https://doi.org/10.1016/j.toxlet.2004.07.013>.
- Vieira, A. M., Neto, E. H., Figueiredo, C. C., Barja Fidalgo, C., Fierro, I. M., & Morandi, V. (2014). ATL-1, a synthetic analog of lipoxin, modulates endothelial permeability and interaction with tumor cells through a VEGF-dependent mechanism. *Biochemical Pharmacology* 90(4), 388–396. <https://doi.org/10.1016/j.bcp.2014.05.019>.
- Villa, A., Rizzi, N., Vegeto, E., Ciana, P., & Maggi, A. (2015). Estrogen accelerates the resolution of inflammation in macrophage cells. *Scientific Reports* 5, 15224. <https://doi.org/10.1038/srep15224>.
- Villanueva, A., Hernandez-Gea, V., & Llovet, J. M. (2013). Medical therapies for hepatocellular carcinoma: a critical view of the evidence. *Nature Reviews. Gastroenterology & Hepatology* 10(1), 34–42. <https://doi.org/10.1038/nrgastro.2012.199>.
- Volk-Draper, L., Hall, K., Griggs, C., Rajput, S., Kohio, P., DeNardo, D., & Ran, S. (2014). Paclitaxel therapy promotes breast cancer metastasis in a TLR4-dependent manner. *Cancer Research* 74(19), 5421–5434. <https://doi.org/10.1158/0008-5472.CAN-14-0067>.
- Vong, L., Ferraz, J. G., Panaccione, R., Beck, P. L., & Wallace, J. L. (2010). A pro-resolution mediator, prostaglandin D(2), is specifically up-regulated in individuals in long-term remission from ulcerative colitis. *Proceedings of the National Academy of Sciences of the United States of America* 107(26), 12023–12027 doi: 1004982107 [pii] <https://doi.org/10.1073/pnas.1004982107>.
- Wagner, E. D., Hsu, K. M., Lagunas, A., Mitch, W. A., & Plewa, M. J. (2012). Comparative genotoxicity of nitrosamine drinking water disinfection byproducts in Salmonella and mammalian cells. *Mutation Research* 741(1–2), 109–115. <https://doi.org/10.1016/j.mrgentox.2011.11.006>.
- Wallace, J. L. (2006). COX-2: a pivotal enzyme in mucosal protection and resolution of inflammation. *ScientificWorldJournal* 6, 577–588. <https://doi.org/10.1100/tsw.2006.122>.
- Wallace, J. L., & Fiorucci, S. (2003). A magic bullet for mucosal protection and aspirin is the trigger! *Trends in Pharmacological Sciences* 24(7), 323–326. [https://doi.org/10.1016/S0165-6147\(03\)00166-4](https://doi.org/10.1016/S0165-6147(03)00166-4).
- Wallace, J. L., Ianaro, A., Flannigan, K. L., & Cirino, G. (2015). Gaseous mediators in resolution of inflammation. *Seminars in Immunology* 27(3), 227–233. <https://doi.org/10.1016/j.smim.2015.05.004>.
- Walser, T., Cui, X., Yanagawa, J., Lee, J. M., Heinrich, E., Lee, G., ... Dubinett, S. M. (2008). Smoking and lung cancer: the role of inflammation. *Proceedings of the American Thoracic Society* 5(8), 811–815. <https://doi.org/10.1513/pats.200809-100TH>.
- Wang, C., Xiao, M., Liu, X., Ni, C., Liu, J., Erben, U., & Qin, Z. (2013). IFN-gamma-mediated downregulation of LXA4 is necessary for the maintenance of nonresolving inflammation and papilloma persistence. *Cancer Research* 73(6), 1742–1751. <https://doi.org/10.1158/0008-5472.CAN-12-2801>.
- Wang, D., & Dubois, R. N. (2010). Eicosanoids and cancer. *Nature Reviews. Cancer* 10(3), 181–193 doi: nrc2809 [pii] <https://doi.org/10.1038/nrc2809>.
- Wang, D., & DuBois, R. N. (2016). The Role of Prostaglandin E(2) in Tumor-Associated Immunosuppression. *Trends in Molecular Medicine* 22, 1, 1–3. <https://doi.org/10.1016/j.molmed.2015.11.003>.
- Wang, D., & DuBois, R. N. (2018). Role of prostanoids in gastrointestinal cancer. *The Journal of Clinical Investigation* 128(7), 2732–2742. <https://doi.org/10.1172/JCI97953>.
- Wang, F., Zhang, H., Ma, A. H., Yu, W., Zimmermann, M., Yang, J., ... Pan, C. X. (2018). COX-2/sEH Dual Inhibitor PTUPB Potentiates the Antitumor Efficacy of Cisplatin. *Molecular Cancer Therapeutics* 17(2), 474–483. <https://doi.org/10.1158/1535-7163.MCT-16-0818>.
- Wang, H. Y., Qin, M., Dong, L., Lv, J. Y., & Wang, X. (2017). Genotoxicity of a Low-Dose Nitrosamine Mixture as Drinking Water Disinfection Byproducts in NIH3T3 Cells. *International Journal of Medical Sciences* 14(10), 961–969. <https://doi.org/10.7150/ijms.20121>.
- Wang, J., Yu, J. C., Kang, W. M., & Ma, Z. Q. (2012). Superiority of a fish oil-enriched emulsion to medium-chain triacylglycerols/long-chain triacylglycerols in gastrointestinal surgery patients: a randomized clinical trial. *Nutrition* 28(6), 623–629. <https://doi.org/10.1016/j.nut.2011.08.004>.
- Wang, L., Yuan, R., Yao, C., Wu, Q., Christelle, M., Xie, W., ... Yao, S. (2014). Effects of resolvin D1 on inflammatory responses and oxidative stress of lipopolysaccharide-induced acute lung injury in mice. *Chinese Medical Journal* 127(5), 803–809.

- Wang, W., Yang, J., Edin, M. L., Wang, Y., Luo, Y., Wan, D., ... Zhang, G. (2019). Targeted Metabolomics Identifies the Cytochrome P450 Monooxygenase Eicosanoid Pathway as a Novel Therapeutic Target of Colon Tumorigenesis. *Cancer Research* 79(8), 1822–1830. <https://doi.org/10.1158/0008-5472.CAN-18-3221>.
- Wang, W., Yang, J., Zhang, J., Wang, Y., Hwang, S. H., Qi, W., ... Zhang, G. (2018). Lipidomic profiling reveals soluble epoxide hydrolase as a therapeutic target of obesity-induced colonic inflammation. *Proceedings of the National Academy of Sciences of the United States of America* 115(20), 5283–5288. <https://doi.org/10.1073/pnas.1721711115>.
- Wang, W., Yu, J., An, W., & Yang, M. (2016). Occurrence and profiling of multiple nitrosamines in source water and drinking water of China. *Science Total Environment* 551–552, 489–495. <https://doi.org/10.1016/j.scitotenv.2016.01.175>.
- Wang, W. J., Xu, Z. L., Yu, C., & Xu, X. H. (2017). Effects of aflatoxin B1 on mitochondrial respiration, ROS generation and apoptosis in broiler cardiomyocytes. *Animal Science Journal* 88(10), 1561–1568. <https://doi.org/10.1111/asj.12796>.
- Wang, Y., Li, R., Chen, L., Tan, W., Sun, Z., Xia, H., ... Shang, Y. (2015). Maresin 1 Inhibits epithelial-to-mesenchymal transition in vitro and attenuates bleomycin induced lung fibrosis in vivo. *Shock* 44(5), 496–502. <https://doi.org/10.1097/SHK.0000000000000446>.
- Wang, Z., Cheng, Q., Tang, K., Sun, Y., Zhang, K., Zhang, Y., ... Huang, B. (2015). Lipid mediator lipoxin A4 inhibits tumor growth by targeting IL-10-producing regulatory B (Breg) cells. *Cancer Letters* 364(2), 118–124. <https://doi.org/10.1016/j.canlet.2015.04.030>.
- Weatherly, L. M., & Gosse, J. A. (2017). Triclosan exposure, transformation, and human health effects. *Journal of Toxicology and Environmental Health. Part B, Critical Reviews* 20(8), 447–469. <https://doi.org/10.1080/10937404.2017.1399306>.
- Weinstein, I. B., Gattoni-Celli, S., Kirschmeier, P., Lambert, M., Hsiao, W., Backer, J., & Jeffrey, A. (1984). Multistage carcinogenesis involves multiple genes and multiple mechanisms. *Journal of Cellular Physiology. Supplement* 3, 127–137. <https://doi.org/10.1002/jcp.1041210416>.
- Wentz, S. C., Yip-Schneider, M. T., Gage, E. A., Saxena, R., Badve, S., & Schmidt, C. M. (2009). Sulindac prevents carcinogen-induced intrahepatic cholangiocarcinoma formation in vivo. *The Journal of Surgical Research* 157(1), e87–e95. <https://doi.org/10.1016/j.jss.2008.10.006>.
- Werner, M., Pace, S., Czapska, A., Jordan, P. M., Gerstmeier, J., Koeberle, A., & Werz, O. (2020). Communication between human macrophages and epithelial cancer cell lines dictates lipid mediator biosynthesis. *Cellular and Molecular Life Sciences*. <https://doi.org/10.1007/s00181-019-03413-w>.
- Werz, O., Gerstmeier, J., Librero, S., De la Rosa, X., Werner, M., Norris, P. C., ... Serhan, C. N. (2018). Human macrophages differentially produce specific resolvins or leukotriene signals that depend on bacterial pathogenicity. *Nature Communications* 9(1), 59. <https://doi.org/10.1038/s41467-017-02538-5>.
- White, K. L., Jr., & Holsapple, M. P. (1984). Direct suppression of in vitro antibody production by mouse spleen cells by the carcinogen benzo(a)pyrene but not by the noncarcinogenic congener benzo(e)pyrene. *Cancer Research* 44(8), 3388–3393.
- Wiese, F. W., Thompson, P. A., & Kadlubar, F. F. (2001). Carcinogen substrate specificity of human COX-1 and COX-2. *Carcinogenesis* 22(1), 5–10. <https://doi.org/10.1093/carcin/22.1.5>.
- Wilbourn, J., Haroun, L., Heseltine, E., Kaldor, J., Partensky, C., & Vainio, H. (1986). Response of experimental animals to human carcinogens: an analysis based upon the IARC Monographs programme. *Carcinogenesis* 7(11), 1853–1863.
- Winter, H. K., Ehrlich, V. A., Grusch, M., Lackner, A., Schulte-Hermann, R., Grasl-Kraupp, B., ... Knasmüller, S. (2008). Use of four new human-derived liver-cell lines for the detection of genotoxic compounds in the single-cell gel electrophoresis (SCGE) assay. *Mutation Research* 657(2), 133–139. <https://doi.org/10.1016/j.mrgentox.2008.08.012>.
- Wongsena, W., Charoensuk, L., Dangtakot, R., Pinalor, P., Intuyod, K., & Pinalor, S. (2018). Melatonin suppresses eosinophils and Th17 cells in hamsters treated with a combination of human liver fluke infection and a chemical carcinogen. *Pharmacological Reports* 70(1), 98–105. <https://doi.org/10.1016/j.pharep.2017.07.017>.
- Wree, A., Johnson, C. D., Font-Burgada, J., Eguchi, A., Povero, D., Karin, M., & Feldstein, A. E. (2015). Hepatocyte-specific Bid depletion reduces tumor development by suppressing inflammation-related compensatory proliferation. *Cell Death and Differentiation* 22(12), 1985–1994. <https://doi.org/10.1038/cdd.2015.46>.
- Xia, R., Sun, L., Liao, J., Li, H., You, X., Xu, D., ... Yang, G. Y. (2019). Inhibition of pancreatic carcinoma growth through enhancing omega-3 Epoxy polyunsaturated fatty acid profile by inhibition of soluble epoxide hydrolase. *Anticancer Research* 39(7), 3651–3660. <https://doi.org/10.21873/anticancer.13513>.
- Xie, X. L., Wei, M., Yunoki, T., Kakehashi, A., Yamano, S., Kato, M., & Wanibuchi, H. (2012). Long-term treatment with L-isoleucine or L-leucine in AIN-93G diet has promoting effects on rat bladder carcinogenesis. *Food and Chemical Toxicology* 50(11), 3934–3940. <https://doi.org/10.1016/j.fct.2012.07.063>.
- Xue, K. S., Tang, L., Sun, G., Wang, S., Hu, X., & Wang, J. S. (2019). Mycotoxin exposure is associated with increased risk of esophageal squamous cell carcinoma in Huaian area, China. *BMC Cancer* 19(1), 1218. <https://doi.org/10.1186/s12885-019-6439-x>.
- Yacoubian, S., & Serhan, C. N. (2007). New endogenous anti-inflammatory and proresolving lipid mediators: implications for rheumatic diseases. *Nature Clinical Practice Rheumatology* 3(10), 570–579 quiz 571 p following 589. <https://doi.org/10.1038/nprheum0616>.
- Yamaguchi, M., Takai, S., Hosono, A., & Seki, T. (2014). Bovine milk-derived alpha-lactalbumin inhibits colon inflammation and carcinogenesis in azoxymethane and dextran sodium sulfate-treated mice. *Bioscience, Biotechnology, and Biochemistry* 78(4), 672–679. <https://doi.org/10.1080/09168451.2014.890034>.
- Yan, S., Tian, S., Kang, Q., Xia, Y., Li, C., Chen, Q., ... Li, Z. (2015). Rhizoma paridis saponins suppresses tumor growth in a rat model of N-Nitrosomethylbenzylamine-induced esophageal cancer by inhibiting cyclooxygenases-2 Pathway. *PLoS One* 10(7), e0131560. <https://doi.org/10.1371/journal.pone.0131560>.
- Yanida, Y., Kohno, H., Yoshida, K., Hirose, Y., Yamada, Y., Mori, H., & Tanaka, T. (2002). Dietary silymarin suppresses 4-nitroquinoline 1-oxide-induced tongue carcinogenesis in male F344 rats. *Carcinogenesis* 23(5), 787–794. <https://doi.org/10.1093/carcin/23.5.787>.
- Yang, H., Fang, J., Jia, X., Han, C., Chen, X., Yang, C. S., & Li, N. (2011). Chemopreventive effects of early-stage and late-stage supplementation of vitamin E and selenium on esophageal carcinogenesis in rats maintained on a low vitamin E/selenium diet. *Carcinogenesis* 32(3), 381–388. <https://doi.org/10.1093/carcin/bgq279>.
- Yang, H., Wang, W., Romano, K. A., Gu, M., Sanidad, K. Z., Kim, D., ... Zhang, G. (2018). A common antimicrobial additive increases colonic inflammation and colitis-associated colon tumorigenesis in mice. *Science Translational Medicine* 10(443). <https://doi.org/10.1126/scitranslmed.aan4116>.
- Yang, J. D., Hainaut, P., Gores, G. J., Amadou, A., Plymoth, A., & Roberts, L. R. (2019). A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nature Reviews. Gastroenterology & Hepatology* 16(10), 589–604. <https://doi.org/10.1038/s41575-019-0186-y>.
- Yang, J. H. (2010). Perfluorooctanoic acid induces peroxisomal fatty acid oxidation and cytokine expression in the liver of male Japanese medaka (*Oryzias latipes*). *Chemosphere* 81(4), 548–552. <https://doi.org/10.1016/j.chemosphere.2010.06.028>.
- Yang, P., Sun, Z., Chan, D., Cartwright, C. A., Vijjeswarapu, M., Ding, J., ... Newman, R. A. (2008). Zylflamend reduces LTB4 formation and prevents oral carcinogenesis in a 7,12-dimethylbenz[alpha]anthracene (DMBA)-induced hamster cheek pouch model. *Carcinogenesis* 29(11), 2182–2189. <https://doi.org/10.1093/carcin/bgn181>.
- Yang, Q., Xie, Y., Alexson, S. E., Nelson, B. D., & DePierre, J. W. (2002). Involvement of the peroxisome proliferator-activated receptor alpha in the immunomodulation caused by peroxisome proliferators in mice. *Biochemical Pharmacology* 63(10), 1893–1900.
- Yang, Q., Xie, Y., Eriksson, A. M., Nelson, B. D., & DePierre, J. W. (2001). Further evidence for the involvement of inhibition of cell proliferation and development in thymic and splenic atrophy induced by the peroxisome proliferator perfluorooctanoic acid in mice. *Biochemical Pharmacology* 62(8), 1133–1140.
- Yang, X. J., Lu, H. Y., Li, Z. Y., Bian, Q., Qiu, L. L., Li, Z., ... Wang, S. L. (2012). Cytochrome P450 2A13 mediates aflatoxin B1-induced cytotoxicity and apoptosis in human bronchial epithelial cells. *Toxicology* 300(3), 138–148. <https://doi.org/10.1016/j.tox.2012.06.010>.
- Yang, Y. M., Kim, S. Y., & Seki, E. (2019). Inflammation and liver cancer: Molecular mechanisms and therapeutic targets. *Seminars in Liver Disease* 39(1), 26–42. <https://doi.org/10.1055/s-0038-1676806>.
- Yao, L., Cao, B., Cheng, Q., Cai, W., Ye, C., Liang, J., ... Zhu, Y. (2019). Inhibition of soluble epoxide hydrolase ameliorates hyperhomocysteinemia-induced hepatic steatosis by enhancing beta-oxidation of fatty acid in mice. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 316(4), G527–G538. <https://doi.org/10.1152/ajpgi.00148.2018>.
- Yao, X., & Zhong, L. (2005). Genotoxic risk and oxidative DNA damage in HepG2 cells exposed to perfluorooctanoic acid. *Mutation Research* 587(1–2), 38–44. <https://doi.org/10.1016/j.mrgentox.2005.07.010>.
- Ye, R. D., Boulay, F., Wang, J. M., Dahlgren, C., Gerard, C., Parmentier, M., ... Murphy, P. M. (2009). International union of basic and clinical pharmacology. LXXIII. Nomenclature for the formyl peptide receptor (FPR) family. *Pharmacological Reviews* 61(2), 119–161. <https://doi.org/10.1124/pr.109.001578>.
- Ye, Y., Scheff, N. N., Bernabe, D., Salvo, E., Ono, K., Liu, C., ... Schmidt, B. L. (2018). Anti-cancer and analgesic effects of resolvins D2 in oral squamous cell carcinoma. *Neuropharmacology* 139, 182–193. <https://doi.org/10.1016/j.neuropharm.2018.07.016>.
- Yi, L., Shen, H., Zhao, M., Shao, P., Liu, C., Cui, J., ... Zhang, X. (2017). Inflammation-mediated SOD-2 upregulation contributes to epithelial-mesenchymal transition and migration of tumor cells in aflatoxin G1-induced lung adenocarcinoma. *Scientific Reports* 7(1), 7953. <https://doi.org/10.1038/s41598-017-08537-2>.
- Yin, Y., Li, T., Kuang, D., Lu, Y., Shen, Y., Xu, J., ... Wang, X. (2019). Probabilistic health risk assessment of nitrosamines in drinking water of Shaoxing, Zhejiang, China. *Environmental Science and Pollution Research International*. <https://doi.org/10.1007/s11356-018-4026-3>.
- Yothaisong, S., Thane, M., Namwat, N., Yongvanit, P., Boonmars, T., Puapairoj, A., & Loilome, W. (2014). *Opisthorchis viverrini* infection activates the PI3K/ AKT/PTEN and Wnt/beta-catenin signaling pathways in a Cholangiocarcinogenesis model. *Asian Pacific Journal of Cancer Prevention* 15(23), 10463–10468.
- Yu, G., Zeng, X., Wang, H., Hou, Q., Tan, C., Xu, Q., & Wang, H. (2015). 14,15-epoxyeicosatrienoic Acid suppresses cigarette smoke extract-induced apoptosis in lung epithelial cells by inhibiting endoplasmic reticulum stress. *Cellular Physiology and Biochemistry* 36(2), 474–486. <https://doi.org/10.1159/000430113>.
- Yueh, M. F., & Tukey, R. H. (2016). Triclosan: A widespread environmental toxicant with many biological effects. *Annual Review of Pharmacology and Toxicology* 56, 251–272. <https://doi.org/10.1146/annurev-pharmtox-010715-103417>.
- Zeldin, D. C. (2001). Epoxygenase pathways of arachidonic acid metabolism. *The Journal of Biological Chemistry* 276(39), 36059–36062. <https://doi.org/10.1074/jbc.R100030200> [pii].
- Zeng, Y., Lian, S., Li, D., Lin, X., Chen, B., Wei, H., & Yang, T. (2017). Anti-hepatocarcinoma effect of cordycepin against NDEA-induced hepatocellular carcinomas via the PI3K/Akt/mTOR and Nrf2/HO-1/NF-kappaB pathway in mice. *Biomedicine & Pharmacotherapy* 95, 1868–1875. <https://doi.org/10.1016/j.biopha.2017.09.069>.
- Zhang, B., Jia, H., Liu, J., Yang, Z., Jiang, T., Tang, K., ... Huang, B. (2010). Depletion of regulatory T cells facilitates growth of established tumors: a mechanism involving the regulation of myeloid-derived suppressor cells by lipoxin A4. *Journal of Immunology* 185(12), 7199–7206 doi: jimmunol.1001876 [pii] <https://doi.org/10.4049/jimmunol.1001876>.

- Zhang, C. Y., Duan, J. X., Yang, H. H., Sun, C. C., Zhong, W. J., Tao, J. H., ... Guan, C. X. (2019). COX-2/sEH dual inhibitor PTUPB alleviates bleomycin-induced pulmonary fibrosis in mice via inhibiting senescence. *The FEBS Journal*. <https://doi.org/10.1111/febs.15105>.
- Zhang, G., Liu, X., Wang, C., Qu, L., Deng, J., Wang, H., & Qin, Z. (2013). Resolution of PMA-induced skin inflammation involves interaction of IFN-gamma and ALOX15. *Mediators of Inflammation* 2013, 930124. <https://doi.org/10.1155/2013/930124>.
- Zhang, G., Panigrahy, D., Hwang, S. H., Yang, J., Mahakian, L. M., Wettersten, H. I., ... Hammock, B. D. (2014). Dual inhibition of cyclooxygenase-2 and soluble epoxide hydrolase synergistically suppresses primary tumor growth and metastasis. *Proceedings of the National Academy of Sciences of the United States of America* 111(30), 11127–11132. <https://doi.org/10.1073/pnas.1410432111>.
- Zhang, G., Panigrahy, D., Mahakian, L. M., Yang, J., Liu, J. Y., Stephen Lee, K. S., ... Hammock, B. D. (2013). Epoxy metabolites of docosahexaenoic acid (DHA) inhibit angiogenesis, tumor growth, and metastasis. *Proceedings of the National Academy of Sciences of the United States of America* 110(16), 6530–6535. <https://doi.org/10.1073/pnas.1304321110>.
- Zhang, J., Orang'o, O., Tonui, P., Tong, Y., Maina, T., Kiptoo, S., ... Brown, D. R. (2019). Detection and concentration of plasma aflatoxin is associated with detection of oncogenic human papillomavirus in Kenyan women. *Open Forum Infectious Diseases* 6(9). <https://doi.org/10.1093/ofid/ofz354>.
- Zhang, J., Sanidad, K. Z., & Zhang, G. (2019). Cytochrome P450 monooxygenase/soluble epoxide hydrolase-mediated eicosanoid pathway in colorectal cancer and obesity-associated colorectal cancer. *Oncoscience* 6(9–10), 371–375. <https://doi.org/10.18632/oncoscience.488>.
- Zhang, J., Zheng, N., Liu, J., Li, F. D., Li, S. L., & Wang, J. Q. (2015). Aflatoxin B1 and aflatoxin M1 induced cytotoxicity and DNA damage in differentiated and undifferentiated Caco-2 cells. *Food and Chemical Toxicology* 83, 54–60. <https://doi.org/10.1016/j.fct.2015.05.020>.
- Zhang, L., Conejo-García, J. R., Katsaros, D., Gimotty, P. A., Massobrio, M., Regnani, G., ... Coukos, G. (2003). Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. *The New England Journal of Medicine* 348(3), 203–213.
- Zhang, L. Y., Zhan, D. L., Chen, Y. Y., Wang, W. H., He, C. Y., Lin, Y., ... Lin, Z. N. (2019). Aflatoxin B1 enhances pyroptosis of hepatocytes and activation of Kupffer cells to promote liver inflammatory injury via dephosphorylation of cyclooxygenase-2: an in vitro, ex vivo and in vivo study. *Archives of Toxicology* 93(11), 3305–3320. <https://doi.org/10.1007/s00204-019-02572-w>.
- Zhang, M. J., Sansbury, B. E., Hellmann, J., Baker, J. F., Guo, L., Parmer, C. M., ... Spite, M. (2016). Resolvin D2 Enhances Postischemic Revascularization While Resolving Inflammation. *Circulation* 134(9), 666–680. <https://doi.org/10.1161/CIRCULATIONAHA.116.021894>.
- Zhang, O., Zou, X., Li, Q. H., Sun, Z., Liu, Y. D., & Zhong, R. G. (2016). Experimental and theoretical investigation of effects of ethanol and acetic acid on carcinogenic NDMA Formation in simulated gastric fluid. *The Journal of Physical Chemistry. A* 120(26), 4505–4513. <https://doi.org/10.1021/acs.jpca.6b02582>.
- Zhang, W., Li, H., Dong, H., Liao, J., Hammock, B. D., & Yang, G. Y. (2013). Soluble epoxide hydrolase deficiency inhibits dextran sulfate sodium-induced colitis and carcinogenesis in mice. *Anticancer Research* 33(12), 5261–5271.
- Zhang, W., Liao, J., Li, H., Dong, H., Bai, H., Yang, A., ... Yang, G. Y. (2012). Reduction of inflammatory bowel disease-induced tumor development in IL-10 knockout mice with soluble epoxide hydrolase gene deficiency. *Molecular Carcinogenesis*. <https://doi.org/10.1002/mc.21918>.
- Zhang, W., Liao, J., Li, H., Dong, H., Bai, H., Yang, A., ... Yang, G. Y. (2013). Reduction of inflammatory bowel disease-induced tumor development in IL-10 knockout mice with soluble epoxide hydrolase gene deficiency. *Molecular Carcinogenesis* 52(9), 726–738. <https://doi.org/10.1002/mc.21918>.
- Zhang, W., Wang, F., Xu, P., Miao, C., Zeng, X., Cui, X., ... Fu, Z. (2014). Perfluorooctanoic acid stimulates breast cancer cells invasion and up-regulates matrix metalloproteinase-2/-9 expression mediated by activating NF-kappaB. *Toxicology Letters* 229(1), 118–125. <https://doi.org/10.1016/j.toxlet.2014.06.004>.
- Zhang, Y. F., Sun, C. C., Duan, J. X., Yang, H. H., Zhang, C. Y., Xiong, J. B., ... Guan, C. X. (2020). A COX-2/sEH dual inhibitor PTUPB ameliorates cecal ligation and puncture-induced sepsis in mice via anti-inflammation and anti-oxidative stress. *Biomedicine & Pharmacotherapy* 126, 109907. <https://doi.org/10.1016/j.biopha.2020.109907>.
- Zhao, Y. Y., Boyd, J. M., Woodbeck, M., Andrews, R. C., Qin, F., Hrudey, S. E., & Li, X. F. (2008). Formation of N-nitrosamines from eleven disinfection treatments of seven different surface waters. *Environmental Science & Technology* 42(13), 4857–4862.
- Zheng, H. C., & Takano, Y. (2011). NNK-induced lung tumors: A Review of animal model. *Journal of Oncology* 2011, 635379. <https://doi.org/10.1155/2011/635379>.
- Zheng, J., He, J., Liao, S., Cheng, Z., Lin, J., Huang, K., ... Yang, Z. (2019). Preventive effects of combinative natural foods produced by elite crop varieties rich in anticancer effects on N-nitrosodiethylamine-induced hepatocellular carcinoma in rats. *Food Science & Nutrition* 7(1), 339–355. <https://doi.org/10.1002/fsn3.896>.
- Zheng, J., Stuff, J., Tang, H., Hassan, M., Daniel, C. R., & Li, D. (2018). Dietary N-nitroso compounds and risk of pancreatic cancer: results from a large case-control study. *Carcinogenesis*. <https://doi.org/10.1093/carcin/bgy169>.
- Zhong, X., Lee, H. N., & Surh, Y. J. (2018). RvD1 inhibits TNFalpha-induced c-Myc expression in normal intestinal epithelial cells and destabilizes hyper-expressed c-Myc in colon cancer cells. *Biochemical and Biophysical Research Communications* 496(2), 316–323. <https://doi.org/10.1016/j.bbrc.2017.12.171>.
- Zhou, W. J., Boyd, J. M., Qin, F., Hrudey, S. E., & Li, X. F. (2009). Formation of N-nitrosodiphenylamine and two new N-containing disinfection byproducts from chloramination of water containing diphenylamine. *Environmental Science & Technology* 43(21), 8443–8448. <https://doi.org/10.1021/es901935v>.
- Zhou, X. Y., Li, Y. S., Wu, P., Wang, H. M., Cai, Z. Y., Xu, F. Y., & Ye, D. Y. (2009). Lipoxin A (4) inhibited hepatocyte growth factor-induced invasion of human hepatoma cells. *Hepatology Research* 39(9), 921–930. <https://doi.org/10.1111/j.1872-034X.2009.00520.x>.
- Zhuang, Q., Meng, Q., Xi, Q., & Wu, G. (2018). Association of serum inflammatory cytokines and Resolvin D1 concentration with pathological stage of colon cancer. *Zhonghua Wei Chang Wai Ke Za Zhi* 21(11), 1285–1290.
- Zong, L., Chen, K., Jiang, Z., Chen, X., Sun, L., Ma, J., ... Wang, Z. (2017). Lipoxin A4 reverses mesenchymal phenotypes to attenuate invasion and metastasis via the inhibition of autocrine TGF-beta1 signaling in pancreatic cancer. *Journal of Experimental & Clinical Cancer Research* 36(1), 181. <https://doi.org/10.1186/s13046-017-0655-5>.
- Zong, L., Li, J., Chen, X., Chen, K., Li, W., Li, X., ... Sun, H. (2016). Lipoxin A4 attenuates cell invasion by inhibiting ROS/ERK/MMP pathway in pancreatic cancer. *Oxidative Medicine and Cellular Longevity* 2016, 6815727. <https://doi.org/10.1155/2016/6815727>.
- Zoumpourlis, V., Solakidi, S., Papatoma, A., & Papaevangelou, D. (2003). Alterations in signal transduction pathways implicated in tumour progression during multistage mouse skin carcinogenesis. *Carcinogenesis* 24(7), 1159–1165. <https://doi.org/10.1093/carcin/bgg067>.