Metabolism, Metastasis and Drug Resistance in Cancer

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Abstract: Cancer is a heterogeneous disease caused by abnormal cell mutation, which has the characteristics of continuous growth, invasion and metastasis. Despite research advances in cell biology, physiology and pharmacology over the past decades, the mortality of cancer remains a healthcare issue. Current treatments are not very effective in treating advanced tumors. Tumor microenvironment (TME) is a complex environment referring to the surrounding tumor cells, including surrounding blood vessels, immune cells, fibroblasts, bone marrow-derived inflammatory cells, various signal molecules and extracellular matrix (ECM). A large number of studies have proved the key role of tumor microenvironment in the development of cancer. Cancer associated fibroblasts (CAFs) interact with cancer cells to produce growth factors, inflammatory factors and other factors, inhibit the immune system and promote tumor proliferation and invasion. Tumor cells provide good conditions for cancer development by remodeling ECM and glycolysis. This paper has aims and objectives to outline the effects of the interaction between TME and tumor cells on tumor metabolism, metastasis and drug resistance. The molecular mechanism of TME change promoting tumor development is discussed and the current therapeutic strategies for targeting tumor drug resistance are mentioned. Future research with the help of artificial intelligence using large data sets as well as genome sequencing from cancer patients is required to identify novel targets with fewer side effects in different individuals for personalized medicine.

1 INTRODUCTION

Cancer is the second leading cause of death in the world. While medical advancements over the past few decades have increased the survival rate of cancer, still cancers mortality rate remains. The World Health Organization International Agency for research on cancer (IARC) estimated that there were 19.29 million new cancer cases in 2020, including 10.06 million males and 9.23 million females, causing 9.96 million cancer deaths worldwide, including 5.53 million males and 4.43 million females. Although research advances have tackled some diseases such as infections successfully, cancer still has a high mortality. While both tumor and normal tissues are composed of various cell types, the physiological functions of tumor and normal organs are different (Egeblad, Nakasone et al. 2010).

One of the most common phenotypes of cancer cells is uncontrolled cell proliferation. Despite understanding the mechanism of the cell cycle, many treatments are not specific and have severe side effects with negative consequences on healthy and rapidly dividing cell. The rapid growth of cancer cells is mainly due to mutations conferring the ability to use a wide range of nutrients to adapt to changing environmental conditions. Current genome engineering methods such as CRISPR/Cas gene editing is not specific and validated for use in cancer (Hanahan, Weinberg 2011). For example, tumor cells are mainly powered by aerobic glycolysis rather than glucose oxidative phosphorylation in their microenvironment, and an increased expression of fatty acid synthase (FASN) causes elevated fatty acid synthesis during tumorigenesis of breast and prostate cancers to support tumor metabolism, maintenance and growth, or competitively damage anti-tumor immunity (Lyssiotis, Kimmelman 2017).

While there are plenty of information about metabolism, metastasis and drug resistance in cancer, still significant unknown areas are present in our knowledge. This paper aims to provide a brief

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overview of the existing information, point out to gaps in our knowledge and propose some ideas for future research, hoping to provide a summary for clinicians and researchers working on cancer as well as opening new avenues for research and discussion.

2 METHODS AND MATERIALS

2.1 Aims and Objectives

This paper aims to investigate existing published and peer-reviewed literature on metabolism, metastasis and drug resistance in cancer to identify gaps in our knowledge about the topic.

2.2 Designed Approach for the Literature Search

A search strategy was designed and followed to identify appropriate peer-reviewed articles written in English from 2005-2020 from the publicly available database PubMed.

The following terminology was used to identify papers: cancer AND metastasis AND metabolism AND drug resistance in the search engine.

2.3 Inclusion and Exclusion Criteria

Papers published in languages other than English and beyond the date bracket of 2005-2020 were excluded from the final search result.

3 DISCUSSION

Studying metabolic changes of cancer cells, including epigenetic processes that may lead to tumorigenesis, malignancy and cancer stem cell generation can help us to find more effective treatments. While surgical resection can treat some tumors during the early stages of tumorigenesis, metastasis can lead to tumor recurrence and even death (Steeg 2016). Therefore, controlling the metastasis of cancer cells is one of the crucial means to reduce mortality among cancer patients. The stability of the normal epithelium structure acts as the internal barrier against the invasion of cancer cells. Epithelial mesenchymal transition (EMT) is the key to metastasis and invasion that is usually defined by the loss of epithelial marker E-cadherin and the increase of mesenchymal marker vimentin (Liu, Liu et al. 2018). The initial metastatic cells usually undergo EMT (Thiery, Acloque et al. 2009), change their shape, transform their metabolism, enter lymphatic vessels or vascular lumens， attach to other cells as well as the extracellular matrix to invade and transfer to other parts of the body through venous and arterial circulation (Pantel, Brakenhoff et al. 2008) (Figure 1).

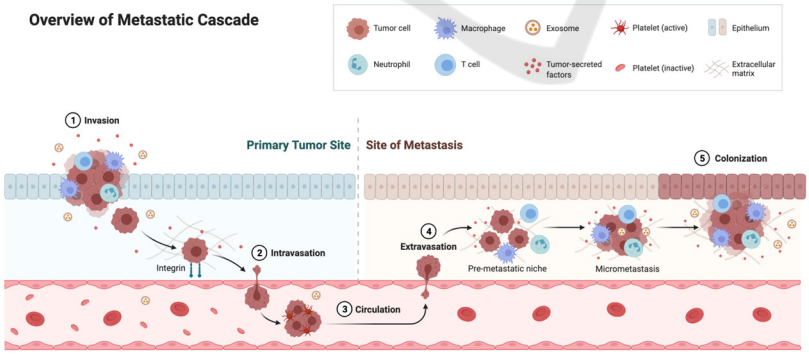

Figure 1：An overview of different stages of cancer metastasis cascade from invasion to colonization. The figure was generated using Biorender.

Besides surgery, radiotherapy, immunotherapy, endocrine therapy and gene therapy have been used in the treatment of various cancers. Chemotherapy is still a common method in the treatment of cancer (Figure 2) due to many factors, such as its potential to destroy cancer cells and ease of administration in the treatment of inoperable cancer.

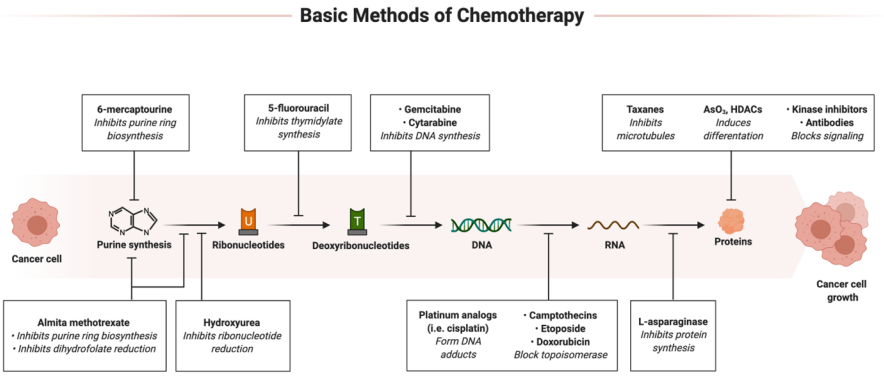

Figure 2: Basic methods of chemotherapy, including different drugs and chemicals used on different components of cancer cells and their function. The figure was generated using Biorender.

Beyond issues such as side effects to damage healthy cells, drug resistance can hinder chemotherapy. Drug resistance can emerge because of tumor heterogeneity, tumor growth kinetics, undruggable genomic drivers, selective therapeutic pressure such as the abnormal expression of drug transporters as efflux transporters increased and uptake transporters decreased, immune system and tumor microenvironment, as well as the presence of gene mutation (loss of tumor suppressor genes, abnormal expression of proto-oncogenes) (Luqmani 2005) (Figure 3).

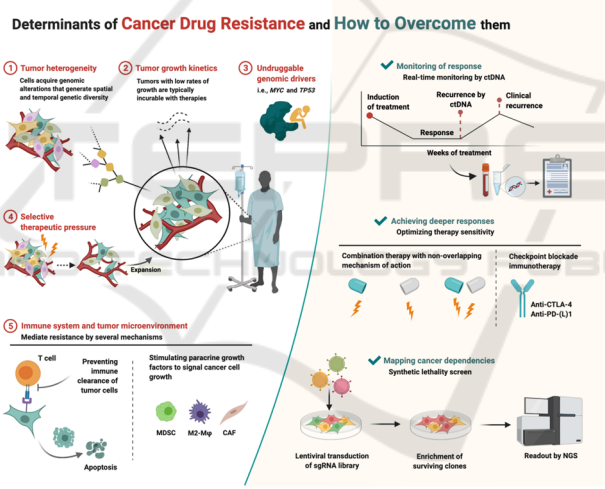

Figure 3. The determinants of cancer drug resistance and several ways to overcome drug resistance. The figure was generated using Biorender.

3.1 Tumor Microenvironment, Tumor Growth, and Metastasis

The environment within the tissue strongly affects the survival and proliferation of tumor cells. Tumor cells transform their environment to form tumor microenvironment (TME) to maintain their survival and proliferation (Reina-Campos, Moscat et al. 2017). Understanding the effect of cellular and non-cellular components in TME on the metabolism of cancer cells can provide a new way for the diagnosis and treatment of cancer. Under normal circumstances, the main function of activated fibroblasts is tissue regeneration (Du, Che 2014). During carcinogenesis, cancer cells produce a loose microenvironment which is conducive to the further development and invasion of tumor. The microenvironment changes its own morphological characteristics, which not only leads to an increase of the number of immune and inflammatory cells such as macrophages, but more importantly, mediates recruitment of cancer related fibroblasts (CAFs) into the tumor matrix by the growth factors secreted by tumor cells. CAF supports the growth, movement and

invasion of cancer cells, leading to tumor progression, metastasis and chemoresistance(Du, Che 2014).

CAF acts similar to pro-inflammatory factors in the early stage of cancer development. Inflammatory immune cells accumulate in the inflammation sites to provide soluble growth and survival factors, matrix remolding enzymes, reactive oxygen species and other bioactive molecules(Kuzet and Gaggioli 2016). These components have different effects on the proliferation, angiogenesis, invasion and metastasis of cancer cells.

The immune system can prevent the occurrence of primary tumor (through immune surveillance) and metastasis by recognizing tumor specific antigen (Bai, Meng et al. 2019). However, tumor can induce anti-tumor immune response and immune suppression mechanism to avoid the attack of immune system. Macrophages are two phenotypes: M1 like macrophages and M2 like macrophages. The development of cancer is closely related to the transformation of macrophages (Bai, Meng et al. 2019). The differentiation, growth and chemotaxis of macrophages are regulated by a variety of growth factors. colony-stimulating factor-1 (CSF-1) induces macrophages to transform into highly plastic non polarized (M0) macrophages. NF-κB in TME and p50 form dimer to inhibit NF-κB signal promotes macrophages to transform from M1 inflammatory phenotype to M2 trophic phenotype (Bai, Meng et al. 2019). This change will promote the development of malignant tumors (Figure 4).

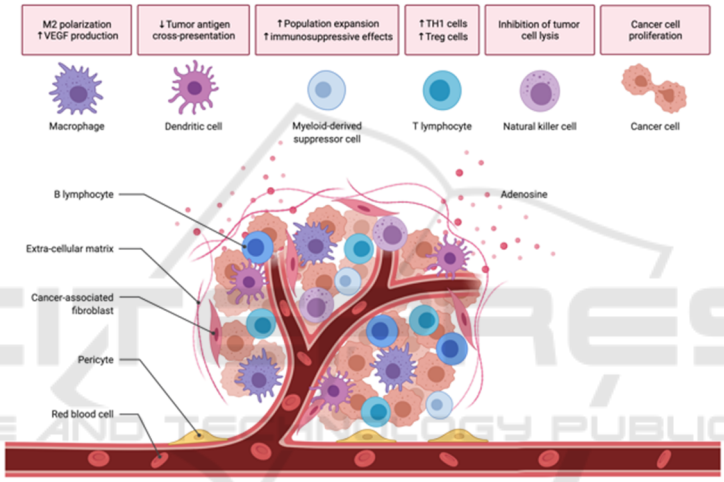

Figure 4: The role of different immune cells in the proliferation of tumor cells. The figure was generated using Biorender.

4 CONCLUSION AND OUTLOOK

Complex TME supports the growth, metastasis and drug resistance of primary tumors. Studying the mechanism of TME affecting tumor development may facilitate cancer diagnosis and provides more effective treatments. Determining the development stage of tumor by identifying tumor markers can improve the prognosis of patients. However, the detection of a single biomarker often cannot accurately explain the problem. Therefore, the current research direction is to detect multiple biomarkers to more accurately judge the development process of cancer and predict the prognosis of patients. The detection of some biomarkers for TME mentioned in this paper provides new approaches for cancer diagnosis, monitoring and treatment development. At the same time, it provides guidance for doctors to formulate appropriate treatment methods. The study of the mechanism of tumor reprogramming microenvironment and the development of drugs for TME has created a new era of cancer medicine. At present, some targeted therapies have been developed. Compared with traditional chemotherapy and radiotherapy, it has better therapeutic effects and fewer side effects, which brings hope to develop new treatment methods for cancer that are difficult to treat by conventional means. Future research with the help of artificial intelligence utilizing big data sets is required to establish a robust map of key molecules in tumor microenvironment for each cancer. Furthermore, potential molecules identified from such 'connectome' of tumor microenvironment can be tested for drug responsiveness to design more effective medication targets with fewer side effects. In addition, with the availability of genome testing,

tumors genome in different individuals can be genetically sequenced to identify specific mutations and provide them with specific treatment for personalized medicine.

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