Research of Inducing Apoptosis and Ferroptosis in Ovarian Cancer and Its Synergistic Anticancer Significance

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Abstract: Ovarian cancer (OC), as a highly malignant tumor of female reproductive system, has the highest mortality. At present, in the clinical treatment of OC, although the action mechanism of some chemical drugs is clear and the curative effect is remarkable, they are easy to result in drug resistance, which seriously hinders the anticancer effect of chemotherapeutic drugs. In this brief article, we summarized the two cell death modes of apoptosis and ferroptosis, discussed the correlation between apoptosis, ferroptosis and OC, and emphasized the synergistic effect of combined application of drugs that can induce cell apoptosis and ferroptosis to deal with the drug resistance of OC. The latest progress of this subject will help to deal with the drug resistance of OC and expand more ideas for clinical treatment.

1 INTRODUCTION

Ovarian cancer (OC) is a malignant tumor of the reproductive system, its mortality rate ranked the top among North American women in cancer death. (Henley, 2020) In the clinical treatment, surgery, radiotherapy and adjuvant chemotherapy are commonly used, and chemotherapy is widely appeared in tumor treatment. However, drug resistance is one of the severe problems face by cancer patients in the process of chemotherapy treatment. (Emmings, 2019)

Apoptosis escape is considered one of the result of cancer development, which promote the resistance of tumor cells to radiotherapy and chemotherapy. (Skarkova, 2019) One mechanism for drug resistance is alterations in apoptotic molecules that ultimately help the cell's ability to evade death. Therefore, it is essential to restore apoptosis of OC cells. Besides, ferroptosis, as a new form of regulated cell death (RCD), can enhance the therapeutic effect of chemotherapeutic drugs on tumors. (Scott, 2012) Therefore, ferroptosis associated with lipid reactive oxygen species has received clinical attention and considered as a underlying therapeutic strategy for OC. (Bebber, 2020)

This article focuses on two types of cell death process known as apoptosis and ferroptosis. We discuss recent cases of OC treatment by inducing apoptosis and ferroptosis of OC cells and their synergistic antitumor significance. Therefore, it is a new strategy to cause tumor cells to cooperate with ferroptosis and apoptosis to conquer OC. The main pathways of apoptosis and ferroptosis together with the relationship between ferroptosis, apoptosis and OC are discussed to find a breakthrough for OC therapy.

2 APOPTOSIS

Apoptosis is a biochemical process of cell decomposition through the interaction of specific proteins and the programmed transmission of death-inducing signals. (Simon, 2019) It was reported that some molecules contained similar B-cell lymphoma 2 (Bcl-2) homology domains (BH domains) in protein structure, and these molecules are all classified as Bcl-2 family molecules. (Maji, 2018) Bcl-2 family proteins as indicator of chemotherapy response and prognosis in patients with advanced OC, suggesting that Bcl-2 family proteins are closely related to the mechanism of apoptosis escape in OC cells. Therefore, Bcl-2 family proteins become promising targets for OC because apoptosis of OC cells could be regulated by Bcl-2 family, which provided ideas for OC treatment. (Ridder, 2021) The Bcl-2 family proteins were classified into three

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subcategories: anti-apoptotic Bcl-2 family proteins, pro-apoptotic Bcl-2 family proteins and BH3-only proteins. (Basu, 2021) (Fig.1) Many researchers have targeted anti-apoptotic proteins to reverse the apoptotic escape of OC cells and thus reverse drug resistance. The anti-apoptotic family proteins include Bcl-2, Bcl-extra long (Bcl-xL) and Myeloid leukemia 1 (Mcl-1).

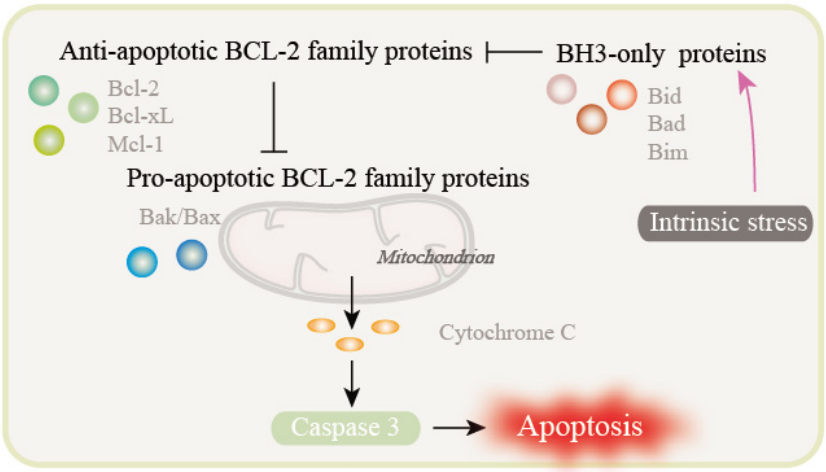

Figure 1: Processes of apoptosis induced by Bcl-2 family proteins.

2.1 Regulation of BCL-2 and BCL-xL in Ovarian Cancer

Combinations of two or more synthetic anticancer drugs have been reported as possible alternatives for improving efficacy and reducing the expected toxicity and side effects of drugs. (Xu, 2011) Takuhei Yokoyama et al. evaluated the possible synergistic cytotoxicity of combination therapy with two drugs in high-grade serous OC cells. The results showed that two drugs could induce more apoptosis and produce synergistic cytotoxic effect on HGSOC cells through inhibition of Bcl-2/Bcl-xL. (Yokoyama, 2017) The inhibiton of Bcl-2/Bcl-xL caused the release of Bcl-2 associated X protein (Bax) and Bcl-2 homologous antagonist/killer protein (Bak). Then the oligomerization of effectors Bax and Bak caused the release of cytochrome c (cyto c), which lead to the activation of caspases and the induction of apoptosis. In addition, nano-targeting systems for OC were being developed, and Farideh Rezaie Amale et al. considered that gold nanoparticles was a promising and appropriate targeting system for enhancing anti-tumor activity against OC cells. (Amale, 2021)

2.2 Regulation of Mcl-1 in Ovarian Cancer

At present, UMI-77 is considered to be an effective inhibitor to reduce the activity of Mcl-1 protein, and there are also many studies targeting Mcl-1 through other small molecules. Qi et al. revealed the intervention effect of apigenin on OC. (Qi, 2020) They investigated the effect of apigenin and determined its mechanism in the regulation of chemotherapy resistance. The results showed that apigenin increased the Bax/Bcl-2 ratio and by down-regulating Mcl-1 on OC. Enhanced permeability lead to the release of various apoptotic stimulators into the cytoplasm, thus promoting caspases to trigger cell apoptosis. Apigenin triggered cell death in OC cells by enhancing mitochondria-regulated cell death and eliminated cisplatin (DDP)-induced resistance.

3 FERROPTOSIS

Ferroptosis is a novel non-apoptotic programmed cell death process. With the development of research, the general pathogenesis of ferroptosis has been partially elucidated. The general process of ferroptosis is the direct or indirect activation of different signaling pathways through the induction of small molecules, thereby decreasing the activity of glutathione peroxidase 4 (GPX4) and inhibiting the intracellular antioxidant energy. This leads to excessive accumulation of reactive oxygen species (ROS), which ultimately leads to cell death. (Xie, 2016) The occurrence of ferroptosis can be regulated by a variety of pathways. (Fig. 2) (1) System xc- is a cystine-glutamate reverse transporter system that

binds to a twelve-channel transmembrane transporter protein SLC7A11 (xCT). Cystine and glutamate enter cells through system xc- on the cell membrane. The following step is the synthesis of glutathione (GSH), the substrate of GPX4. (Imai, 2017) (2) Iron is closely related to ROS accumulation and ferroptosis. Almost all lipid peroxides can be diminished by iron chelators, which closely connects the process of iron metabolism with the occurrence of ferroptosis. (Minotti, 1987) During iron ion oxidation, it is oxidized to lipid ROS by Fenton reaction. (3) The survival of all cells requires the maintenance of membrane fluidity, and polyunsaturated fatty acids (PUFAs) on lipid membranes are one of the factors that maintain this fluidity. Doll et al. reported that the acyl-CoA synthase long chain family member 4 (ACSL4) that synthesized during PUFAs oxidation drives ferroptosis through the accumulation of membrane phospholipids. (Doll, 2017) (4) Mevalonate pathway (MVA) is a metabolic pathway that synthesizes the precursor of steroid and terpenoid biomolecular synthesis using acetyl coenzyme A as raw material. (Shimada) Coenzyme Q10 (CoQ10) can be produced through this pathway. As an endogenous antioxidant, it inhibits ferroptosis by blocking lipid peroxidation process.

3.1 The Regulation of System xc- / GPX4 / GSH

Hong Ting et al. suggested that the cell death and tumor suppression induced by olaparib in OC is ferroptosis, and suggested that olaparib partially promotes ferroptosis by inhibiting SLC7A11-mediated GSH biosynthesis. (Hong, 2021) In addition, Cheng Qi et.al suggested that erastin in combination with DDP synergistically inhibits OC cell growth and maximizes the efficacy of OC treatment. (Cheng, 2021) When erastin was used in combination with DDP, cell survival and the activity of GPX4 were significantly reduced, while ROS levels were elevated and ferroptosis occurred. Direct targeting of GPX4 may be more effective, and Li et al. confirmed that inhibition of GPX4 inhibited the growth of OC cells, induced ferroptosis, reduced Fe3+ accumulation, and inhibited lipid peroxidation reduction ability. (Li, 2021)

3.2 The Regulation of ACSL4

ACSL4 is upregulated in a variety of cancers, including OC, which promotes resistance to conventional therapy through lipid metabolism disorder. (Cui, 2018) Targeting ACSL4 could be a key therapeutic approach for OC treatment. Ma et al. found that ACSL4 was over-expressed in OC and ferroptosis could be regulated in OC through targeting ACSL4. (Ma, 2020) They demonstrated that knockdown or over-expression of Tumor suppressor sensitized and inhibited erastin and RSL3 induced ferroptosis in OC cells, respectively.

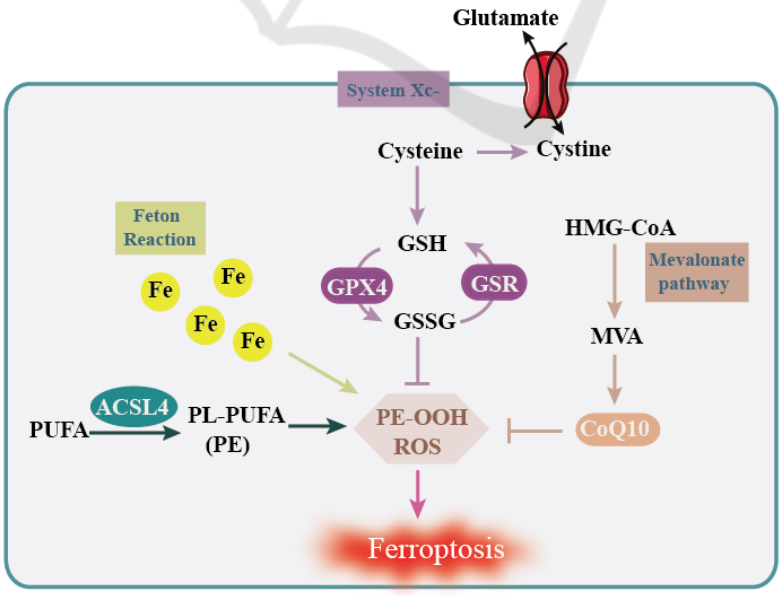

Figure 2: Processes of ferroptosis.

4 CONCLUSIONS

This article focuses on the treatment of OC by inducing apoptosis and ferroptosis in recent years. (Table 1) Unfortunately, there are few studies on the synergistic treatment of OC by apoptosis and ferroptosis. The significance of this article lies in that it is of great significance to select the lowest effective dose of multiple drugs for OC treatment, not only to reduce the toxic and side effects of drugs, but also to achieve the synergistic effect of ferroptosis and apoptosis against cancer. Such treatment combinations may lead to novel treatment strategies that reduce the recurrence or drug resistance in order to increase the sensitivity of OC to drugs.

Table 1: Summary of targets that promote cell death in ovarian cancer.

Mode of cell death	Targets	Cell lines	Rf.
Apoptosis	Bcl-2/Bcl-xL	OVCAR3; OVCAR8; OV90	11
Apoptosis	Bcl-2	A2780; HEK-293	12
Apoptosis	Mcl-1	SKOV3; SKOV3/DPP	13
Ferroptosis	SLC7A11	HEY; A2780	19
Ferroptosis	GPX4	A2780; SKOV3; OVCA433; OVCAR5; OVCAR8; HEY; HOSEpiC	21
Ferroptosis	ACSL4	HO8910; SKOV3	23

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