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Review Article

Ferroptosis, a new form of cell death: mechanisms, biology and role in gynecological malignant tumor

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Abstract: Ferroptosis, a term coined by Dixon et al. in 2012, refers to an iron-dependent form of regulated cell death driven by an overload of lipid peroxides on cellular membranes. It is morphologically and mechanistically distinct from apoptosis and other types of regulated cell death. Many studies have confirmed that ferroptosis is involved in the occurrence and development of many diseases, such as neurodegenerative diseases, chronic cardiovascular diseases, respiratory diseases and even tumors. While in the systemic diseases of obstetrics and gynecology, the related researches are still limited. In this article, we retrieved PubMed and WEB OF SCI databases for articles and reviews published before May 6, 2022, using "ferroptosis, ferroptosis regulator, gynecological tumors" as keywords, and comprehensively reviewed on their basis. Here, we systematically summarize the studies on the mechanism and characteristics of ferroptosis, investigate the role of ferroptosis in clinical systemic diseases of obstetrics and gynecology, evaluate the research status, unsolved problems and further research directions of ferroptosis, so as to let people learn more about ferroptosis and establish a research foundation for the exploration of the treatment strategies for ferroptosis-mediated diseases.

Keywords: Ferroptosis, gynecological tumors, mechanisms, biology

Introduction

In 2003, Dolma et al. [1] discovered that the compound erastin can induce the death of tumor cells with RAS oncogene mutation. Cellular ferroptosis has three characteristics, including the loss of lipid peroxide repair ability, the peroxidation of phospholipids containing polyunsaturated fatty acids, and the dependence on redox iron. In 2012, Dixon et al. [1] officially named Erastin-induced cell death with unique morphological, biochemical and genetic characteristics as ferroptosis. The morphology of cells with ferroptosis was manifested as obvious mitochondrial atrophy, dissolution or absence of mitochondrial cristae, fracture of mitochondrial outer membrane, exhaustion of intracellular glutathione, decrease of glutathione peroxidase 4 activity, NADPH-dependent lipid peroxidation, and iron-dependent generation reactive oxygen [2]. The important products of ferroptosis process are reactive oxygen species (ROS) and lipid peroxides. Studies have shown that high levels of ROS in tumor cells can induce various modes of cell death such as ferroptosis [3]. Lipid peroxidation can increase the permeability of the membrane, as well as modulate the shape and curvature of the membrane, making it easier for oxidants to enter and eventually inducing cell death [4, 5]. Studies have proved that ferroptosis is associated with various pathologies, such as ischemia-reperfusion injury, degenerative disease, cancer, etc. Moreover, ferroptosis has been found generally occurred in a variety of malignant tumor cells, including lung cancer,

breast cancer and ovarian cancer [6-12]. Therefore, induction of ferroptosis may be a promising therapy strategy for malignant tumors.

To date, significant progress has been made in the specific mechanisms of ferroptosis and its potential influences on different courses of gynecological tumors, especially concerning cancer prevention and treatment, with the aim to elucidate its underlying pathogenesis and drug resistance mechanism and to search for effective biomarkers and intervention targets. Herein, this paper reviews the research progress and mechanism of ferroptosis, thereby providing new ideas for the diagnosis and treatment of gynecological malignant tumors.

Ferroptosis and its metabolic characteristics

The consequence of iron accumulation

Iron is one of the essential nutrients for living organisms. In general, iron balance in cells is a balance between iron absorption, output, utilization, and storage. Excess iron can cause tissue damage and increase the risk of cancer. The most important mechanism of iron biotoxicity is that excessive Fe^{2+} in cells, known as Fenton reaction, may result in ROS accumulation and a large amount of hydroxyl free radicals, which could lead to the damage of cellular proteins, lipids and DNA [13]. The intervention of iron absorption and metabolism has become a method to treat cancer and other diseases. Tumor cells can increase intracellular iron content by regulating iron metabolism pathway, thus making cancer tissues more sensitive to the way of ferroptosis. The application of iron-based nanoparticles can induce ferroptosis in tumor cells, thus inhibiting tumor growth [2]. Studies have shown that intracellular iron overload could be prevented by knockout of transferrin receptor (TFRC) on the cell surface, while iron storage in the inert pool could be increased by upregulation of cytoplasmic ferritin to inhibit the occurrence of ferroptosis [14]. Similarly, inhibition of the transcription factor iron responsive element binding protein 2 (IREB2), which regulates iron metabolism, could suppress ferroptosis [15]. Instead, knocking out solute carrier family 40 member A1 (SLC40A1) to block intracellular iron output was proved to accelerate Erastin-induced ferroptosis in neuroblastoma cells [16]. In summary, iron metabolic pathways and ferritin phagocytosis are key points to the regulation of ferroptosis.

Lipid peroxidation

Lipid peroxidation refers to the loss of hydrogen atoms of lipid under the action of free radicals or lipid peroxidase, leading to oxidative break of lipid carbon chain and the production of lipid free radicals, lipid hydroperoxides and active aldehydes (malondialdehyde, 4-hydroxynonenal) as well as other cytotoxic substances. Eventually, the oxidative degradation of lipids causes cell damage [17]. The harm of lipid peroxidation in ferroptosis is mainly reflected in the oxidative degradation of important biofilm components, including polyunsaturated fatty acid (PUFA) and phosphatidylethanolamine (PE). PUFA is the main component of phospholipids in cell and organelle membranes, and also an important substrate for the synthesis of PE, the main component in the inner layer of phospholipid bilayer. Phospholipid bilayer, as the structural basis for maintaining cell membrane fluidity, plays an important role in maintaining cell growth, proliferation, differentiation, senescence, death and immunity. Lipid peroxidation can change the molecular configuration of PUFA, destroy the fluidity and stability of cell membrane structure, increase the permeability of cell membrane, thus the cells are prone to rupture and death. PUFA has a high affinity with free radicals and the hydrogen atoms between its double bonds are easily oxidized by free radicals. The lipid peroxidation of PUFA can be divided into two stages. Firstly, Lipid free radical Lipid ROS (L) is generated from active oxygen species such as hydroxyl radical and hydrogen peroxide by obtaining hydrogen atoms in PUFA. Then, the Lipid radical acts with oxygen molecules to create a Lipid peroxyl radicals (LOO-). Lipid hydroperoxide robs the hydrogens from other PUFA to form a lipid free radical and lipid hydroperoxide (LOOH). The lipid peroxidation free radical can continuously participate in the oxidation process of PUFAs, resulting in a cascade reaction characteristic of PUFAs lipid peroxidation. PE refers to glycerophospholipid in biofilms, accounting for about 40% of the total phospholipids in mitochondrial inner membrane and about 15%-25% of the total phospholipids in other organelles biofilms [18].

PE has a variety of cellular functions, including being a precursor of phosphatidylcholine and an important substrate for post-translational modification, affecting membrane topology, promoting cell and organelles membrane fusion, oxidative phosphorylation, mitochondrial biogenesis and autophagy, etc. [19]. The affinity between PE and free radicals is not high, and the oxidation sites need to be formed under the action of two enzymes before lipid peroxidation occurs [20, 21]. Apoptosis inducing factor mitochondria-associated 2 (AIFM2) could synergize with Coenzyme Q10 (CoQ10), a lipid peroxidation radical scavenger, to inhibit ferroptosis in cells and therefore was renamed to ferroptosis inhibitor 1.

Ferroptosis and three major antioxidant pathways

To prevent damage caused by iron overload and lipid peroxide accumulation, cells establish three major antioxidant mechanisms to resist Ferroptosis. As an important intracellular antioxidant substance, glutathione peroxidase 4 (GPX4) was firstly discovered, which hydrolyzes phospholipid peroxides depending on the cofactor glutathione (GSH). The synthesis of GSH requires cysteine, which were synthesized from extracellular cystine transported by cystine/glutamate reverse transporters (Xc-system), as a raw material. The Xc-system consists of the SLC7A11 and SLC3A2 subunits. Erastin and sulfasalazine (SAS) can inhibit the Xc-system, reduce intracellular GSH, cause cellular redox imbalance and promote cellular ferroptosis. Studies have found that interferon γ secreted by CD8+ T cells can down-regulate the Xc-system and affect the synthesis of GSH, thereby promoting phospholipid peroxidation and ferroptosis in tumor cells [22]. Ferroptosis inhibitor protein 1 (FSP1) is a newly discovered ferroptosis inhibitor protein that can inhibit ferroptosis caused by GPX4 deficiency. The N-terminus of FSP1 protein, recruited to the plasma membrane by myristoylation, mediates NADH-dependent reduction of CoQ10 and acts as a free radical trapping antioxidant, thereby preventing lipid peroxidation. Thus NADH-FSP1-CoQ10 inhibits phospholipid peroxidation and ferroptosis independently and synergistically with GPX4/GSH [19, 23]. In addition, Kraft *et al.* [24] found that overexpression of GTP cyclohydrolase 1 (GCH1) had a protective effect on cells treated with ferroptosis inducer RSL3, erastin or GPX4 gene knockout, but could not protect cells from apoptosis inducers. It can be seen that GCH1 has ferroptosis resistance, and its mechanism is to catalyze GTP to generate tetrahydrobiopterin (BH4) with redox activity. Furthermore, activation of GCH1/BH4 in cysteinease-treated cells synergistically produces CoQ10. These results indicated that the NADH-FSP1-CoQ10 and GCH1/BH4 pathways act as endogenous antioxidant pathways independently and could cooperate with the GPX4/GSH system to inhibit ferroptosis. In summary, abnormalities in iron metabolism, lipid metabolism and antioxidant system-specific proteins are associated with the sensitivity to ferroptosis. The studies of ferroptosis inducers also target the above specific proteins, so the application of ferroptosis inducers in the treatment of tumors could be a new strategy worth exploring.

Ferroptosis regulators

One of the major challenges in cancer research is how to effectively kill tumor cells while leaving normal cells undamaged. The use of ferroptosis inducer or inhibitor to reasonably regulate ferroptosis is a new direction to improve the effectiveness and pertinence of tumor treatment [25].

Inducers of ferroptosis

Dixon *et al.* [26] have found four ways to initiate ferroptosis. Thus, ferroptosis inducers can mainly be divided into four classes. The first class of ferroptosis inducers are mainly Xc-system inhibitors, including Erastin and Erastin analogues. Whether these drugs can be used *in vivo* is still under investigation. Some tumor cells cannot induce ferroptosis by inhibiting the Xc-system, which may be related to the activation of the glutathione-independent thioredoxin antioxidant system pathway [27]. The inducers of ferroptosis are shown in **Table 1**.

Targeting system Xc-1 class

Erastin can selectively kill RAS-mutant tumor cells by directly inhibiting the activity of System Xc-, inducing cystine depletion and then ferroptosis. Erastin also causes mitochondrial dysfunction by binding to mitochondrial voltage-

Table 1. Ferroptosis inducers

Chemical compound	Mechanism of action
Cyst(e)inase [27]	Cystine depletion
Piperazine Erastin [28]	System Xc-inhibitor
Imidazole ketone Erastin [29]	System Xc-inhibitor
Sorafenib [30]	System Xc-inhibitor
Altretamine [31]	Inhibition of GPX4 activity
Withaferin A [32]	Inhibition of GPX4 activity
FIN56 [33]	Activate squalene synthase
Statins [34]	Reduce the synthesis of coenzyme Q10
Erastin [58]	System Xc-inhibitor
(1S, 3R)-RSL3 [62]	Co-order binding of GPX4 at the sun-substituted cysteine site

dependent anion channels (VDAC2 and VDAC3), resulting in the accumulation of lipid ROS, which in turn activates ferroptosis. However, Erastin's poor water solubility and unstable metabolism limit its use *in vivo*. Piperazine Erastin, a derivative of Erastin, has better water solubility and metabolic stability than Erastin. It has been reported to exhibit antitumor activity in xenograft models of human fibrosarcoma cells by inducing ferroptosis [28].

In addition, imidazole ketone Erastin, another derivative of Erastin, induced ferroptosis and inhibited tumor growth in mouse tumor xenotransplantation models [29]. Sorafenib is an FDA-approved multikinase inhibitor that induces ferroptosis in hepatocellular carcinoma cells by inhibiting System Xc-, thereby achieving antitumor activity. In addition to the anti-inflammatory activity, sulfasalazine can also inhibit System Xc- and induce ferroptosis in non-Hodgkin's lymphoma cells, thus inhibit the growth of lymphoma cells [30].

Targeting GPX4 class

Altretamine is an alkylated anti-tumor drug approved by FDA and mainly used in the clinical treatment of ovarian cancer [31]. It has also been shown to inhibit ferroptosis induced by GPX4 and the growth of diffuse large B-cell lymphoma cells, thereby playing an anti-tumor role *in vitro* [30]. Withaferin A, a steroidal lipid substance isolated from South African Dioxylum, can directly inhibit GPX4 and lead to ferroptosis in neuroblastoma, which provides a new strategy for the treatment of high-risk neuroblastoma [32].

Targeting squalene synthase-mevalerate pathway

FIN56 directly binds and activates squalene synthase downstream of mevalonate pathway, reduces the synthesis of coenzyme Q10 and indirectly depletes or inactivates GPX4, thereby inducing ferroptosis [33]. Statins (such as silvastatin and simvastatin) can induce ferroptosis in human fibrosarcoma cell lines by blocking the mevalonate pathway to reduce coenzyme Q10 synthesis [34].

Targeting Fe^{2+} class

Heme oxygen-ase-1 (HO-1) catalyzes the reduction of heme to carbon monoxide, biliverdin and free iron, thereby increasing the level of lipid ROS and inducing ferroptosis [35]. By directly oxidizing Fe^{2+} and indirectly inactivating GPX4, FINO2 leads to the accumulation of lipid compounds and depletion of cystine, then induces ferroptosis [36].

Ferroptosis inhibitors

Among ferroptosis inhibitors, ferroptosis inhibitor 1 (Fer-1) inhibits ferroptosis by slowing the accumulation of lipid peroxides, which may result from their free radical trapping antioxidant activity rather than their potency as lipoxysynthase inhibitors [37]. The removal of ferroptosis inducers is not enough to revive ferroptosis cells, and the aid of ferroptosis suppressors is needed. Some studies [38] found that when Fer-1 was added after the ferroptosis inducer was removed, the cells undergoing ferroptosis could recover. Other ferroptosis inhibitors, such as desferramine and the antioxidant vitamin C,

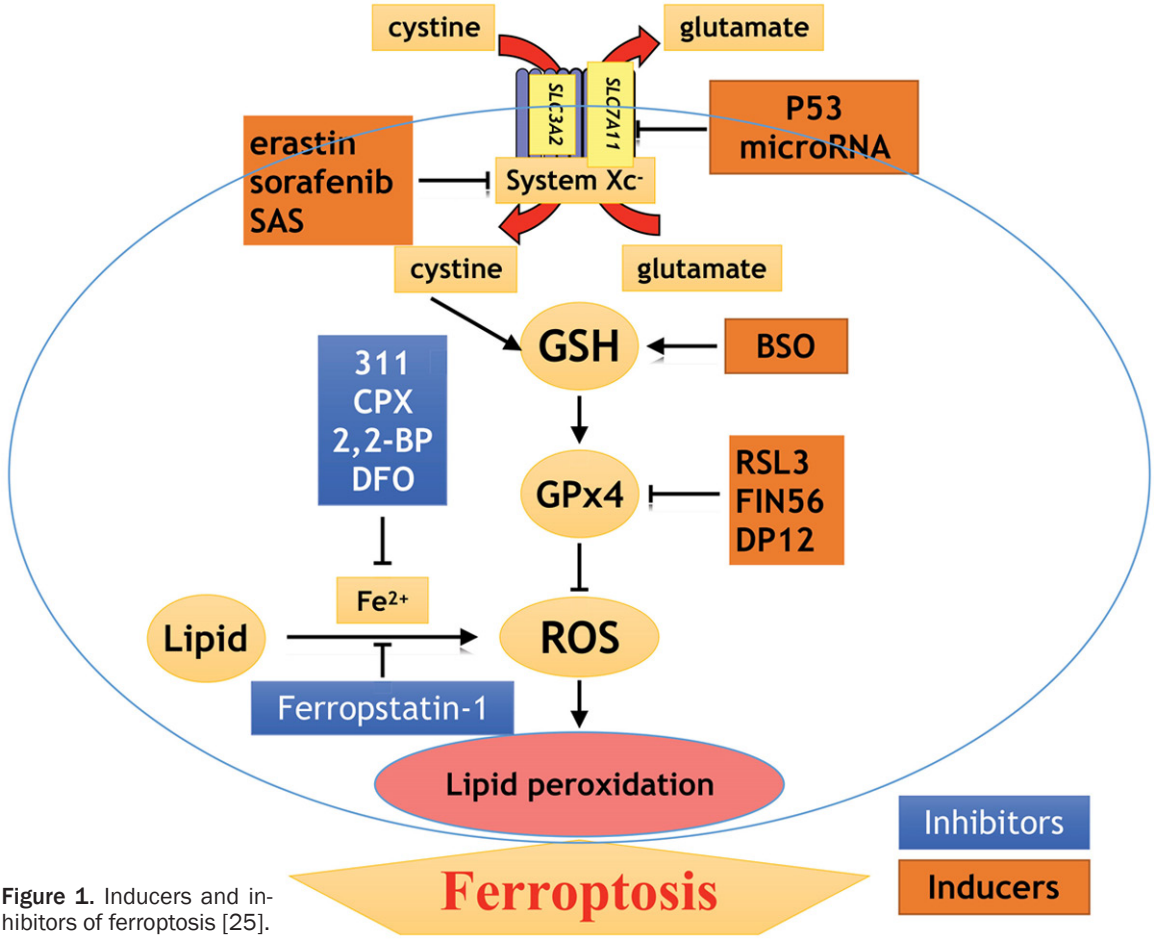

Figure 1. Inducers and inhibitors of ferroptosis [25].

are unable to revive cells with the addition of ferroptosis inducers because they act on the upstream pathway that initiates ferroptosis rather than the downstream pathway that performs it. The inducers and inhibitors of ferroptosis are shown in **Figure 1**.

Research progress of ferroptosis in gynecological tumors

Correlation between ferroptosis and breast cancer

Breast cancer is the most common cancer among women, with 1.7 million people diagnosed worldwide and approximately half a million people dead from this disease each year [39]. Although surgical resection, radiotherapy, chemotherapy, endocrine therapy and targeted therapy have been applied for treatment, the prognosis of patients with breast cancer is still not satisfactory [40]. Therefore, there is an urgent need to develop novel therapeutic management for these patients who require more precise interventions. In recent years, studies have found that ferroptosis plays a crucial role in the evolution of breast cancer. It is known that cystine is an important material resource for the synthesis of GSH, so the reduction of cystine, GSH and GPX4 can lead to ferroptosis of breast cancer cells and further inhibit tumor growth [41, 42]. GPX4 expression is usually upregulated in breast cancer, which is closely associated with increased expression of SLC7A11 and SLC3A2, two subunits of the cystine-glutamate reverse transporter (xCT). Meanwhile, xCT can also interact with MUC1-C and CD44 variant (CD44v) in TNBC to up-regulate GSH level and inhibit the occurrence of ferroptosis, resulting in the high proliferation and invasion activity of tumor cells [43, 44]. In addition, a variety of genes/proteins, non-coding RNAs (ncRNAs) and signaling pathways are involved in the regulatory process of ferroptosis in breast cancer. For example, by targeting SLC7A11/xCT, miR-5096 increases the accu-

mulation levels of ROS, OH-, lipid ROS and iron in milk adenocarcinoma cells, while reduces GSH level and mitochondrial membrane potential, thereby causing mitochondrial contraction and partial crest loss, that is, inducing ferroptosis in breast cancer cells, which further inhibits the proliferation, migration and invasion of breast cancer cells [45]. miR-324-3p and miR-382-5p induce ferroptosis and inhibit the progression of breast cancer through binding to the 3'-UTR of GPX4 and SLC7A11 [37, 46]. However, circRNA RHOT1 can inhibit the occurrence of ferroptosis through the miR-106a-5p/STAT3 axis, thus promoting the progression of breast cancer [47]. Glycogen synthase kinase-3β (GSK-3β) can up-regulate nuclear factor erythroid 2-related factor 2 (NF-E2), and the expression of NF-E2 and GPX4 inhibit the ferroptosis of tumor cells and promote the evolution of tumor [48]. Stearoyl-coa desaturase-1 (SCD1) is a fatty acid binding protein-4 (FABP4) in the tumor microenvironment and serves as a protective agent, which can rescue the cancer cells from ferroptosis induced by oxidative stress [49]. Overactivation of PI3K-AKT-mTOR signaling pathway is also mediated by sterol regulatory element binding protein 1 (SREBP1)/SCD1 mediated lipid synthesis to suppress the occurrence of death [50] iron in recurrent breast cancer epithelial mesenchymal transformation (EMT) regulators TWIST and SNAIL significantly induce Ferroptosis in tumor cells in a DDR2-dependent manner [51]. In addition, ACSL4 and KLF4 are also key molecules in the ferroptosis signaling pathway, which can inhibit the ferroptosis of milk adenocarcinoma cells and maintain their malignant biological characteristics [52]. The role of tumor suppressor p53 in ferroptosis is also of concern; the related research has found that its inhibition or promotion effect on ferroptosis in tumors mainly depends on the surrounding cell environment [53]. The results of current researches report that p53 mainly promotes ferroptosis in breast cancer, but its specific molecular mechanism remains to be further explored. Another central event that causes ferroptosis in tumor cells is intracellular iron accumulation. Studies have found that high-saturation iron saturated Lactoferrin/Holo-Lactoferrin (Holo-Lf) can significantly increase the iron content in breast cancer cells (MDA-MB-231) and promote ROS generation, thus leading to ferroptosis in cells; however, low saturation lactoferrin can up-regulate the expression of SLC7A11 and increase the production of GSH, thereby inhibiting the ferroptosis of MDA-MB-231 cells [54]. Disruption of the function of CISD2 in human breast cancer cells results in the immediate destruction of mitochondrial labile iron and the enhancement of mitochondrial ROS level, leading to the activation of ferroptosis [55]. Iron autophagy is also one of the main ways to regulate ferritin level and iron content in the body, while ferritin deposition is the key to induce ferroptosis. Iron transport is also one of the main reasons for the increase of iron contents in cells. Ferro-portin 1 (FPN1) is an iron-carrying protein, and knockout of this gene can lead to intracellular iron overload and ferroptosis [56, 57]. Therefore, ferroptosis plays an important role in the evolution of breast cancer and inducing ferroptosis of tumor cells can effectively prevent its malignant progression, so as to improve the survival and prognosis of patients.

The treatment of breast cancer that mainly focus on regulating ferroptosis

Breast cancer has become the most common malignant tumor in Chinese women, with the treatment strategies including surgery, chemotherapy, endocrine therapy, radiation therapy and targeted therapy. However, the probability of breast cancer recurrence and metastasis caused by drug resistance is still high. Sun *et al.* [47] found that lidocaine inhibited the growth and metastasis of breast cancer and ovarian cancer cells. The underlying mechanism is the induction of ferroptosis mediated by up-regulating miR-382-5p, thereby inhibiting the level of SLC7A11. Based on RNA sequence analysis, Li *et al.* [48] and Song *et al.* [49] found that curcumin can promote iron overload in breast cancer cells through the HO-1 pathway, as well as down-regulate GPX4 expression to trigger ferroptosis in breast cancer cells. Moreover, inhibition of GPX4 can enhance the sensitivity of TNBC cells to gefitinib. Wu *et al.* [50] demonstrated that regulating the balance between GSK-3β/Nrf2 can enhance the sensitivity of breast cancer to ferroptosis caused by Erastin, which is a promising treatment intervention. Zhang *et al.* [58] showed that circRNA RHOT1 promoted breast cancer progression and inhibited iron ptosis through the miR-106a-5p/STAT3 axis. The study shows the significant role of ferroptosis in the treatment of breast cancer,

especially for the drug-resistant cancer. This may partly explain the poor response of AR receptor inhibitors to LAR type breast cancer in clinical trials [59].

The correlation between ferroptosis and ovarian cancer

Ovarian cancer (OVCA) is one of the most lethal malignancies with a five-year relative survival below 50% by virtue of its high recurrence rate and inadequate early detection methods. For OVCA patients, modern treatment approaches include debulking surgery, chemotherapy, angiogenesis inhibitors, poly ADP-ribose polymerase (PARP) inhibitors, and immunotherapy depending on the histological type and staging of the tumor. However, in most cases, simple standard treatment may not satisfactory; thus, more effective strategies of treatment are urgently needed [59]. In recent years, studies have shown that ferroptosis plays an important role in the development of ovarian cancer. Compared with normal ovarian tissues, iron metabolism in malignant ovarian tissues is seriously disturbed. The shift to an "iron-seeking" phenotype appears to be an early event in the development of malignant ovarian cancer, and similar changes observed in the precursor lesions further support this idea. However, the increased dependence on iron, known as "iron addiction", promotes the growth and invasion of tumor cells. And the presence of high iron levels in tumor cells also provide an opportunity for targeted intervention through ferroptosis. According to relevant studies, Zhang *et al.* [73] treated ovarian cancer cells with superparamagnetic iron oxide incubated with human serum, which further increased the contents of iron and superoxygenated lipids and eventually induced ferroptosis during the initiation of P53 in ovarian cancer cells. Ma *et al.* [60] have found that miR-424-5p inhibits ACSL4 by directly targeting the 3'-UTR of ACSL4 in ovarian cancer cells, which subsequently reduces erastin and RSL3-induced ferroptosis. Chan *et al.* [61] found that MAP30, the main active ingredient of momordica momordica, increased the production of ROS in ovarian cancer cells in a dose-dependent manner, while decreased the ratio of GSH/GSSG and the expression of Gpx4 protein, thus inducing the occurrence of ferroptosis in ovarian cells. The combination of MAP30 and cisplatin has a synergistic effect on cisplatin cisplatin-induced cytotoxicity of ovarian cancer cells, and the combined intraperitoneal injection of low-dose cisplatin and MAP30 can significantly inhibit the tumor spread and growth of mice with ovarian cancer mice.

The treatment of ovarian cancer that mainly focus on regulating ferroptosis

At present, platinum drug resistance is one of the major problems remained to be solved in the treatment of gynecological malignant tumors. It was reported that overexpression of transcriptional coactivator with PDZ-binding motif (TAZ), a sensor of cell density, sensitizes OVCA cells to ferroptosis. Meanwhile, in chemoresistant recurrent OVCA cells, lower level of TAZ decreases OVCA cells' sensitivity to ferroptosis [62]. In platinum-tolerant OVCA cells, one study inspected that expression of Wnt receptor Frizzled-7 (FZD7) positively alters glutathione metabolism pathways including GPX4. Posterior to exposure to GPX4 inhibitors, FZD7+ platinum-tolerant OVCA cells are more likely to experience ferroptosis, opening new avenues for platinum-tolerant OVCA treatment. In addition, Qi *et al.* [63] confirmed that erastin can act as a cofactor to enhance the toxicity of ovarian cancer cells by promoting the production of ROS and inducing ferroptosis in conjunction with cisplatin. Drug inhibition of PARP is a promising therapeutic strategy for advanced ovarian cancer (BRCA1/2 germline mutation) lacking homologous recombination pathways. Hong *et al.* [64] have found that P53-dependent downregulation of SLC7A11 is one of the main pharmacological mechanisms. In addition, ferroptosis inducers (FINS) can reverse PARP inhibitor resistance in BRCA1/2 ovarian cancer cells and xenografts. Futhermore, Yang *et al.* [65] have reported that the susceptibility of ovarian cancer cells to ferroptosis was negatively correlated with the degree of cell integration, and the knockdown of the density-related receptor protein TAZ could enhance the resistance of ovarian cancer cells to ferroptosis.

Ferroptosis is concerned with cervical cancer and endometrial cancer

Wu *et al.* [66] found that circEPSTI1 expression was significantly up-regulated in cervical cancer tissues and promoted the proliferation of

cervical cancer cells through miR375/409-3P/515-5P-SLC7A11 axis. It is suggested that circEPSTI1 may be a therapeutic target or candidate prognostic marker for cervical cancer. Qi *et al.* [63] found that the gene profiles of elevated-expressed TFRC, ACACA and SQLE as well as low-expressed PHKG2 were highly correlated with the poor prognosis of patients with cervical cancer through a comprehensive analysis the genetic data of 60 cervical cancer cases. Among them, TFR1 encoded by *TFRC* is an indispensable transporter for cellular iron absorption. At present, studies concerning ferroptosis in other gynecological are limited. Yin *et al.* [67] identified a new prognostic feature of 8 FRG (MDM2, GPX4, PRKAA2, PRNP, SLC11A2, ATP5MC3, PHKG2 and ACO1), which can potentially predict the prognosis of endometrial cancer. In addition, Wang *et al.* [68] found that the silencing of PTPN18, a member of the protein tyrosine phosphatase family associated with the occurrence and development of multiple human cancers, may induce ferroptosis in endometrial cancer by targeting the p38/Gpx4/XCT axis.

The treatment of endometrial cancer that mainly focus on regulating ferroptosis

In the studies related to lipid metabolism in endometrial cancer, visceral fat-specific adipokine, an adipokine secreted by visceral fat, stimulates apoptosis of endometrial cancer cell by activating the JAK signaling pathway and the upregulation of P53, which induces ferroptosis in cells by inhibiting the expression of SLC7A11. According to the lipidomics analysis, peroxisomes provide substrates for ferroptosis through synthesizing polyunsaturated ether phospholipids [69]. Relevant research suggests that inhibitors targeting endometrial cancer cells, such as GPX4 and FSP1, can down-regulate the sensitivity of ferroptosis [70]. Previous studies have shown that ferroptosis is associated with tumor metastasis and recurrence, and endometrial cancer is no exception. FANCD2, an inhibitor of ferroptosis, is a nuclear protein involved in DNA damage repair that inhibits iron accumulation and lipid peroxidation in erastin-induced ferroptosis [71]. FANCD2 overexpression is often associated with lymphatic vascular invasion and advanced tumor development in type I endometrial carcinoma, and is prone to recurrent in type II endometrial carcinoma, with the 5-year survival rate lower than that of other patients. Accumulating evidence suggests that induction of ferroptosis may be an effective approach to combat tumor drug resistance. Wang *et al.* [68] found that PTEN silencing affected the proliferation of human endometrial cancer KLE cells by targeting p-p38/GPX4/xCT pathway to induce ferroptosis. Moreover, studies have found that the natural compound juglone can induce cellular oxidative stress in endometrial cancer cells, thus resulting in ferroptosis [72, 73]. Sulfasalazine, an inhibitor of the glutamine transporter, is more toxic in paclitaxel-resistant cells and induces cell death via ferroptosis in endometrial serous carcinoma [74]. In conclusion, ferroptosis plays an important role in proliferation, invasion, metastasis and drug resistance of endometrial cancer, and its underlying mechanism remains to be explored in the future.

Outlook on the treatment of gynecological malignancies

In order to maintain the high demand for cell proliferation, cancer cells must engage in metabolic pathways that regulate amino acid synthesis, glycolysis, oxidative phosphorylation, the tricarboxylic acid cycle, and the pentose phosphate pathway. Line coordination reprogramming makes cancer cells heavily dependent on intracellular antioxidant mechanisms and exhibit increased iron requirements. This could lead to a targetable susceptibility to iron death and provide new ideas for the discovery of new cancer therapeutic targets. Current studies on iron death in gynecological malignancies mainly focus on the antioxidant pathway SLC7A11/GSH/GPX4. Iron homeostasis, lipid metabolism and mechanisms related to FSP1 and DHODH remain to be further explored and studied. In addition, The unique advantage of inducing ferroptosis in cancer treatment is that it can not only improve the sensitivity of chemoradiotherapy and targeted therapy, but also synergistically activate immune cells, creating opportunities for ferroptosis inducers to become suitable enhancers of immune checkpoint inhibitors [75]. New ferroptosis inducers are under constant development. The US FDA has used attriamine, sorafenib and silica nanoparticles as ferroptosis inducers to treat tumors, among which sorafenib has been approved for the treatment of hepatocellular

carcinoma [76]. However, its efficacy in the treatment of gynecological malignant tumors remains to be further studied and explored. Ferroptosis inducer is expected to be a new generation of adjuvant anticancer drugs to improve the prognosis of cancer patients.

Disclosure of conflict of interest

None.

Abbreviations

GSH, glutathione; ROS, reactive oxygen; TFRC, Transferrin receptor; PUFA, Polyunsaturated fatty acid; PE, phosphatidylethanolamine; FSP1, Ferroptosis-suppressor-protein 1; FPN1, Ferro-portin 1; NcRNAs, non-coding RNAs; IREB2, Iron responsive element binding protein 2; GSK-3β, glycogen synthase kinase-3β; SCD1, Stearoyl-Coa Desaturase-1; LPCAT3, Lyso phosphatidylcholine Acyltransferase 3; AIFM2, Apoptosis inducing factor mitochondria-associated 2; SREBP1, sterol regulatory element binding protein 1; PTB, preterm birth; EVCT, extra villouscytotrophoblast; PE, preeclampsia.

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