Crosstalk between ferroptosis and endoplasmic reticulum stress: A potential target for ovarian cancer therapy (Review)

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Abstract. Ferroptosis is a unique mode of cell death driven by iron-dependent phospholipid peroxidation, and its mechanism primarily involves disturbances in iron metabolism, imbalances in the lipid antioxidant system and accumulation of lipid peroxides. Protein processing, modification and folding in the endoplasmic reticulum (ER) are closely related regulatory processes that determine cell function, fate and survival. The uncontrolled proliferative capacity of malignant cells generates an unfavorable microenvironment characterized by high metabolic demand, hypoxia, nutrient deprivation and acidosis, which promotes the accumulation of misfolded or unfolded proteins in the ER, leading to ER stress (ERS). Ferroptosis and ERS share common pathways in several diseases, and the two interact to affect cell survival and death. Additionally, cell death pathways are not linear signaling cascades, and different pathways of cell death may be interrelated at multiple levels. Ferroptosis and ERS in ovarian cancer (OC) have attracted increasing research interest; however, both are discussed separately regarding OC. The present review aims to summarize the associations and potential links between ferroptosis and ERS, aiming to provide research references for the development of therapeutic approaches for the management of OC.

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Abbreviations: OC, ovarian cancer; ER, endoplasmic reticulum; ERS, endoplasmic reticulum stress; UPR, unfolded protein response; TF, transferrin; TFR, transferrin receptor; ROS, reactive oxygen species; HGSOC, high-grade serous ovarian cancer; HIF, hypoxia-inducible factor; SLC40A1, solute carrier family 40 member 1; PUFA, polyunsaturated fatty acid; PLOOH, phospholipid hydroperoxide; PLOH, phospholipid hydroxide; OH·, hydroxyl radical; LPO, lipid peroxide; GSH, glutathione; GPX4, glutathione peroxidase 4; FSP1, ferroptosis suppressor protein 1; CoQ10, coenzyme Q10; CoQ10H2, ubiquinol-10; GCH1, guanosine triphosphate cyclohydrolase 1; BH4, tetrahydrobiopterin; BH2, dihydrobiopterin; DHFR, dihydrofolate reductase; DHODH, dihydroorotate dehydrogenase; PAX8, paired box 8; SLC7A11, solute carrier family 7 member 11; IRE1α, inositol-requiring protein 1α; PERK, protein kinase RNA-like ER kinase; ATF6, activating transcription factor 6; BiP, binding immunoglobulin protein; RNase, ribonuclease; XBP1, homeostasis transcription factor X-box protein 1; CHOP, C/EBP homologous protein; ATF4, activating transcription factor 4; miRs, microRNAs; CARM1, coactivator associated arginine methyltransferase 1; eIF2α, eukaryotic translation initiation factor 2α; GADD34, growth arrest DNA-damage 34; Nrf2, nuclear factor erythroid 2-related factor 2; S2P, metalloprotease site 2; DHA, dihydroartemisinin; HO-1, heme oxygenase-1; SIRT1, sirtuin 1

Key words: OC, ferroptosis, ERS, lipid peroxidation, UPR

Contents

1. Introduction

Ovarian cancer (OC) ranks third among all gynecologic malignancies, is one of the three most diagnosed malignancies in the female reproductive system and has the highest mortality rate among gynecologic tumors (1). Due to the insidious nature of its onset during the early stages, the majority of patients are diagnosed with advanced-stage OC in the first instance, and at this stage, the primary treatment methods, such as surgery, radiotherapy, chemotherapy and immunotherapy, have well-established side effects, including recurrence, metastasis and chemotherapy resistance, and thus, OC is characterized by a high mortality rate (2). As the incidence of OC is increasing annually, with an increasing number of younger individuals developing OC (3,4), the need for methods and biomarkers to allow earlier detection and more effective treatment options after diagnosis is becoming ever more pertinent (5-8).

Ferroptosis, distinct from apoptosis, necrosis and autophagy, is an iron-dependent form of programmed cell death triggered by lipid peroxide (LPO) accumulation (9). While conventional

cancer therapies usually eliminate tumor cells by inducing cell death to generate drug resistance, ferroptosis has become an increasingly researched topic in cancer therapy given its role in regulating cell death (10-12). Several studies have shown that ferroptosis is associated with resistance to cancer treatment, potentially allowing for the reversal of cancer treatment resistance (13-15). Current research has shown that neurological disorders, kidney damage, breast cancer, pancreatic cancer and several other diseases are associated with ferroptosis (16-19). Among these, ferroptosis is most closely related to malignant tumors, and tumor cells may be notably sensitive to ferroptosis (20). Ferroptosis can regulate the development of OC through different mechanisms or factors, thereby increasing the sensitivity of OC cells to ferroptosis-targeting therapeutics, and thus, combatting resistance to chemotherapy (21,22) and improving the efficacy of chemotherapeutic drugs in the management of OC (23). Additionally, a related study has demonstrated the pattern of immune infiltration and associated genetic features of ferroptosis, which can hopefully be applied to predict the prognosis of patients with OC (24). The combination of ferroptosis with chemotherapy, nanotechnology, X-ray therapy and photodynamic therapy has been demonstrated to improve therapeutic efficacy (25), providing potential targets and novel therapeutic directions for ferroptosis in the treatment of OC.

The endoplasmic reticulum (ER) is involved in lipid metabolism, Ca^{2+} regulation, and protein processing, folding and transport, and is an important organelle in eukaryotic cells (26). ER stress (ERS) is induced in cells by hypoxic conditions, genetic mutations, nutrient deficiencies and oxidative stress, which leads to the accumulation of misfolded and unfolded proteins in the lumen of the ER and the activation of the unfolded protein response (UPR) to counteract the unfavorable external environments (27). However, sustained high-intensity ERS, which results in cell death when the tolerance threshold of the UPR is exceeded (28), can lead to a range of diseases such as cancer, atherosclerosis, diabetic retinopathy and ischemic nephropathy (29,30). The adverse microenvironment in tumor cells due to high metabolic demands and oxidative stress, among others, interferes with ER homeostasis in immune cells, which can have an impact on protective anticancer immunity (31). A study has shown that targeting the relevant pathways in ERS can inhibit the proliferation of OC cells and reduce their resistance to chemotherapy (32). Thus, ERS serves a key role in the development of OC, as well as in its treatment.

Several studies have found that ferroptosis and ERS share a common regulatory pathway and that the two can alter the development of several diseases by interacting with each other (33-36). However, to the best of our knowledge, the link between them has not been investigated in detail in studies on the pathogenesis of OC or related therapies. Therefore, the present review discusses the mechanisms of ferroptosis and ERS in OC and the potential relevance of both to highlight novel strategies and potential targets for the treatment of OC.

2. Ferroptosis in OC

Ferroptosis is a mode of programmed cell death characterized by excessive accumulation of iron, lipid antioxidation and lipid peroxidation (37). Patients with OC frequently exhibit resistance to chemotherapy, and a study has shown that this is closely related to ferroptosis (38).

Iron metabolism in OC. Iron is one of the essential trace elements in the human body and serves an important role in human growth and development, energy metabolism, and immune system functions (39). Abnormalities in iron metabolism affect redox reactions, gene regulation, enzymatic reactions and DNA synthesis or repair (40). In the human body, iron has a complex and elaborate circulatory mechanism to ensure its proper distribution, utilization and storage to maintain appropriate and non-toxic cellular iron levels (41). Iron in the body exists in two forms, Fe^{2+} and Fe^{3+}, and there are transport carriers and modes for the different forms of iron. Daily intake of dietary iron includes heme iron and non-heme iron (42). They arrive in the intestinal lumen as Fe^{3+} and are reduced to Fe^{2+} by duodenal cytochrome B to be absorbed; non-heme iron in the intestine is absorbed via divalent metal transporter protein 1 (43). Heme iron is then transported into the duodenal epithelium via heme carrier protein 1 and is absorbed, internalized, and broken down into Fe^{2+} and heme oxygenase-1 (HO-1) (44). Thereafter, iron can remain in the enterocytes or enter the bloodstream from the basolateral membrane of intestinal epithelial cells via membrane iron transport protein 1, while being oxidized by ferrous oxidase or ceruloplasmin to produce Fe^{3+} (45). Upon entering the bloodstream, plasma transferrin (TF) spreads the captured Fe^{3+} throughout the cells of the body and is used by various organs to synthesize specific iron-containing components through TF receptor (TFR)-mediated holo-TF endocytosis (46). For example, the liver synthesizes hemosiderin, muscle tissue produces myoglobin and the bone marrow produces red blood cells containing hemoglobin. Cells promote iron uptake primarily through the TF and TFR systems, and Fe^{3+} is reduced to Fe^{2+} by ferric oxide reductase, most of which binds to ferritin to form storage iron, and a small portion enters the cytoplasm to collectively form the labile iron pool (47). Due to the instability and high oxidizability of Fe^{2+}, excess iron ions catalyze the production of reactive oxygen species (ROS), which promotes lipid peroxidation through the Fenton reaction (48), thereby causing oxidative damage to lipid membranes, proteins and DNA, and ultimately leading to cell death (49). Among the three main mechanisms of ferroptosis, excessive accumulation of Fe^{2+} in the labile iron pool increases the sensitivity of cells to ferroptosis and is the initial component responsible for ferroptosis (47).

To the best of our knowledge, the initial signal for ferroptosis has not yet been identified, but ferroptosis is closely related to the levels of intracellular free iron content (50). Iron metabolism serves a key role in the pathophysiology of OC, and the degree of intracellular iron accumulation serves a decisive role in the course of OC (51). Concurrently, abnormalities in iron metabolism, especially the acquisition and retention of excess iron, contribute to tumorigenesis and tumor growth (52,53). Iron accumulation increases the risk of diseases such as cancer and damage to tissues (54). Therefore, maintaining homeostasis of intracellular iron ions is critical. According to Basuli *et al* (55), OC-initiating cells show high iron dependence. Increased iron efflux also decreases the proliferation and invasion of OC-initiating cells, and conversely increased

iron uptake increases OC cell proliferation and invasion. High-grade serous OC (HGSOC) typically originates from the fallopian tube and is diagnosed at a later stage, and it has been observed that the iron content of HGSOC is higher than that of normal ovarian tissues and low-grade serous OC, suggesting that there is a strong association between HGSOC and iron metabolism (56). In addition, the malignant transformation and metastasis of cancer cells are closely associated with changes in cellular redox status (57). The molecular damage caused by the excessive and harmful ROS catalyzed by free iron is often referred to as 'oxidative damage', and Bauckman *et al* (58) reported that ROS can transform normal ovarian tissue into cancerous tissue by promoting the MAPK pathway. In addition, ROS can hydroxylate DNA residues to generate the highly mutagenic 8-hydroxy-2'-deoxyguanosine, elevated levels of which have been found to be associated with a poor prognosis in patients with HGSOC (59,60). Iron polyporphyrin heme binds to p53, interfering with p53-DNA interactions, leading to nuclear export and cellular degradation of p53, and increased susceptibility to HGSOC (61,62). Basuli *et al* (55) demonstrated that excess iron simultaneously affects tumor cell proliferation, metabolism and metastasis. Increasing the expression of ferroportin on cell membranes (63), decreasing iron intake (64), or decreasing the concentration of TF (65) and TFR *in vivo* (66) can inhibit tumor growth. In addition, iron metabolism can contribute to the development of OC by regulating hypoxia-inducible factor (HIF). HIF-1α induces OC progression by inhibiting p53 function, promoting IL-6 expression or being regulated by long non-coding RNAs (67,68). Iron metabolism is also closely related to resistance to chemotherapy, and solute carrier family 40 member 1 (SLC40A1), an iron metabolism-related gene, which is the only known iron-exporting gene (69), serves a crucial role in transporting iron from the intracellular environment to the extracellular environment, and thus, the physiological expression of SLC40A serves a vital role in the regulation of iron homeostasis. SLC40A1-induced iron overload leads to cisplatin resistance in OC (70). Upregulation of SLC40A1 reduces cisplatin resistance by exporting iron, decreasing the intracellular iron concentration and oxidative stress. By contrast, an increase in the intracellular iron concentration and enhanced oxidative stress induced by the downregulation of SLC40A1 increase cisplatin resistance (70). Thus, modulating iron levels to influence the redox system may be a potential strategy to reverse drug resistance in OC therapy.

The iron-dependent nature of OC tumor-initiating cells also makes them sensitive to drugs that induce ferroptosis, as well as to iron chelators, providing a potential therapeutic approach for the management of OC (71). Desferrioxamine (72), a natural iron chelator used in the treatment of iron overload, has shown promising results in the treatment of OC. Wang *et al* (72) assessed the effects of desferrioxamine on OC cell lines and found that it not only inhibited OC stem cells but also enhanced cisplatin efficacy, improved resistance to chemotherapy and increased the length of survival. There are also drugs that regulate iron metabolism in several ways and may have effects on other biological processes. For example, artemisinin is known for its anti-malarial, anti-inflammatory and antitumor effects, and its compounds (artesunate) can reduce cell proliferation and induce ROS production in OC cells (73). In addition, artesunate can activate the function of lysosomes, promote the degradation of ferritin and lead to the release of iron in lysosomes, and thereby mediate cell death (74). Regulators, including iron uptake-related regulators (75), iron storage-related regulators (76) and iron transport-related regulators (77), influence the pathological process of OC through the regulation of iron metabolism levels.

Lipid peroxidation in OC. Ferroptosis is an iron-dependent non-apoptotic cell death mechanism caused by iron-dependent membrane lipid peroxidation and massive accumulation of cellular ROS (78). Membrane lipids serve an important role in the regulation of cell fate and lipid metabolism, which is fundamental in determining the fate of ferroptosis (79), and is similarly critical for ferroptosis execution.

Among various lipids, polyunsaturated fatty acids (PUFAs) associated with several phospholipids such as phosphatidylethanolamine and phosphatidylcholine are responsible for inducing lipid peroxidation in ferroptosis. Phospholipids containing PUFAs are susceptible to oxidation, but less oxidizable saturated/monounsaturated fatty acids protect cells from ferroptosis (80). Thus, the enzymes and pathways that regulate the metabolism of PUFAs and monounsaturated fatty acids, as well as the balance of PUFAs and monounsaturated fatty acids in membrane phospholipids, can influence cellular sensitivity to ferroptosis (81). The findings of the aforementioned study provide a novel strategy for lipid peroxidation treatment of OC ferroptosis. Since the membrane phospholipids of PUFAs that drive ROS production catalyzed by iron ions interacting with PUFAs are responsible for triggering lipid peroxidation leading to cellular ferroptosis, and not free PUFA itself, the enzymes that bind free PUFA to phospholipids serve a crucial role in ferroptosis (81). Acyl-CoA synthetase long-chain family member 4 is an essential component of ferroptosis execution as shown by microarray analysis of ferroptosis-resistant cell lines and using a genome-wide CRISPR-based genetic screening system (82). Under the catalytic action of Acyl-CoA synthetase long-chain family member 4, free long-chain fatty acids are converted to acyl-CoA by linking with CoA. Acyl-CoA inserts into membrane phospholipids and binds to phosphatidylethanolamine to form PUFA phospholipids catalyzed by lysophosphatidylcholine acyltransferase 3 (83). Lipid peroxidation, via two primary mechanisms, non-enzymatic spontaneous oxidation and enzyme-mediated lipid peroxidation (84), results in the production of phospholipid hydroperoxides (PLOOHs), and if antioxidants do not convert PLOOH to phospholipid hydroxides (PLOHs) in a timely manner, the resulting accumulation of PLOOH leads to extensive lipid peroxidation and activation of the antioxidant system, directly inducing damage to cell membranes and ultimately leading to cell dysfunction and ferroptosis (85). Non-enzymatic lipid peroxidation (also known as lipid autoxidation) is a free radical-driven chain reaction. Hydroxyl radicals (OH·) are generated through the reaction of H_2O_2 with Fe^{2+}, which reacts with PUFAs in the plasma membrane in a Fenton reaction to generate LPO, leading to ferroptosis (86,87). Enhanced accumulation of LPO is therefore necessary to increase the efficiency of ferroptosis (88), and OH· is the most active ROS (89), and thus, it also serves as an emerging cancer treatment target for the management of OC via chemodynamic

therapy. H_2O_2 nano-enzymes developed by Sun *et al* (90) using CoNi alloys encapsulated with nitrogen-doped carbon nanotubes exhibited glucose oxidase and lactate oxidase activities to effectively disrupt the antioxidant defense system by catalyzing the formation of OH·, increasing ROS content in the tumor microenvironment and damaging the tumor cells, while depleting glutathione (GSH) to induce ferroptosis of the cells. Liang *et al* (91) demonstrated that polydopamine-mediated Michael addition combined with Fe^{2+} depletion of GSH enhanced OH· accumulation and ultimately resulted in the intracellular release of the chemotherapeutic drug doxorubicin, thus inducing ferroptosis. In addition, lipid peroxidation is tightly regulated by various metabolic and signaling pathways, such as the cytochrome P450 oxidoreductase pathway, and iron-containing enzymes, including lipoxygenase, also contribute to the process of lipid peroxidation (92). Enzymatic lipid peroxidation, conversely, is a process of direct oxidation of free PUFAs into various types of lipid hydroperoxides catalyzed by lipoxygenase (93,94). Among them, the arachidonic acid lipoxygenase family regulates lipid peroxidation. It has been shown that the binding of 5-lipoxygenase to microsomal GSH S-transferase 1 led to a decrease in lipid peroxidation and mediated ferroptosis in cancer cells (95). 12-lipoxygenase, conversely, has been identified as a key factor in p53-mediated ferroptosis under conditions of ROS-induced stress (96), while the expression levels of 15-lipoxygenase are associated with the spermine/spermine N1-acetyltransferase 1 gene, a transcriptional target of p53 (97). Zhang *et al* (98) demonstrated that chemotherapeutic drugs for OC induced excessive lipid peroxidation through ROS and initiated ovarian cell ferroptosis, thus leading to ovarian cell death. A study (99) has demonstrated that p53 serves an important role in the ferroptosis process. p53 exhibits a bidirectional regulatory effect based on specific environmental conditions. When lipid peroxidation levels are low, p53 inhibits the occurrence of ferroptosis, promoting cell survival. However, when excess lipid peroxidation persists, ferroptosis is induced (99).

In summary, further studies on the effects of various lipid metabolic pathways on lipid peroxidation and ferroptosis from the perspective of chemotherapy-induced oxidative stress and ferroptosis may help control ovarian damage and improve the quality of life of patients with OC. All of them will provide a deeper understanding of ferroptosis and therapeutic strategies for OC.

Lipid antioxidation in OC. Oxidative damage occurs due to an imbalance between the cellular antioxidant system with the production of free radicals and/or the neutralization or elimination of their deleterious effects. ROS-mediated lipid peroxidation is a key step to drive cellular ferroptosis, and inactivation of the antioxidant system is the primary cause of ferroptosis (100). At present, it has been shown that the primary antioxidant systems regulating ferroptosis include the System Xc^--GSH-GSH peroxidase 4 (GPX4) pathway, the ferroptosis suppressor protein 1 (FSP1)-coenzyme Q10 (CoQ10) pathway, the guanosine triphosphate cyclohydrolase 1 (GCH1)-tetrahydrobiopterin (BH4) pathway and the dihydroorotate dehydrogenase (DHODH)-$CoQ10H_2$ pathway. Among these, the System Xc^--GSH-GPX4 pathway is the most fundamental antioxidant system, which serves a key role in protecting cells from ferroptosis (101). An overview of the primary antioxidant systems regulating ferroptosis is shown in Fig. 1.

System Xc^--GSH-GPX4 pathway. The System Xc^--GSH-GPX4 pathway serves a key role in the antioxidant defense mechanism of ferroptosis. System Xc^- is a cystine-glutamate reverse transporter protein composed of solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2 (102). System Xc^- oxidizes intracellular cystine to cysteine, which is further converted to GSH (103). By contrast, GPX4 protects cells against ferroptosis by reducing reactive PLOOH to nontoxic PLOH, which involves GSH (the reducing cofactor of GPX4) (104). Inhibition of GPX4 induces lipid ROS accumulation and induces the onset of ferroptosis, thereby inhibiting tumor cell proliferation (105).

Studies have shown that erastin (38), sorafenib (106), sulfasalazine (107) and p53 (108) could cause GSH production and induce ferroptosis by inhibiting System Xc^-. Metallothionein-1G is a key factor and potential therapeutic target for regulating sorafenib resistance in human hepatocellular carcinoma. Downregulating metallothionein-1G increases lipid peroxidation and GSH depletion, leading to ferroptosis in hepatocellular carcinoma (106). Yuan *et al* (109) used an innovative approach, employing a combination of chemotherapy and chemokinetic therapy, which inhibited malignant cell proliferation by inactivating GPX4 by inducing GSH depletion, and this approach showed a high degree of biosafety. Luo *et al* (110) found that paired box 8 (PAX8) (a GPX4-dependent OC susceptibility gene) depletion sensitized OC cells to GPX4 inhibitors. The combination of PAX8 inhibitor and RSL3 inhibited proliferation and induced ferroptosis in OC cells (110). In addition, the System Xc^--GSH-GPX4 pathway is a key antioxidant system that prevents lipid peroxidation-mediated ferroptosis, and blocking this pathway promotes the onset of ferroptosis in tumor cells and prevents chemotherapeutic resistance (111). Okuno *et al* (112) reported that the System Xc^- transporter, which is involved in the transport of cystine and glutamate, had a regulatory effect on intracellular GSH levels and cisplatin resistance in OC cell lines. The results revealed that cisplatin-resistant variant OC cells had an ~4.5-fold higher rate of cystine uptake and higher intracellular GSH levels than OC cell lines due to the acquisition of cystine transporter activity mediated by the System Xc^-; however, the GSH levels were decreased following glutamate overdose. Cystine uptake was also inhibited. It is therefore suggested that System Xc^- serves an important role in maintaining higher levels of GSH and can confer cisplatin resistance in OC cell lines. In addition, a study has shown that the release of GSH and cysteine in OC fibroblasts contributes to the reduction of nuclear accumulation of platinum (112). Additionally, $CD8^+$ T cells can inhibit this resistance by regulating GSH and cysteine metabolism in fibroblasts (113).

In summary, inhibition of System Xc^-, depletion of GSH and reduction of GPX4 activity all mediate metabolic processes involving amino acids that increase sensitivity to ferroptosis-inducing agents, and targeting this system may reverse chemotherapeutic resistance and reduce the rate of OC progression.

FSP1-CoQ10-NADPH pathway. Bersuker *et al* (114) identified FSP1 as a potent resistance factor to ferroptosis, arguing

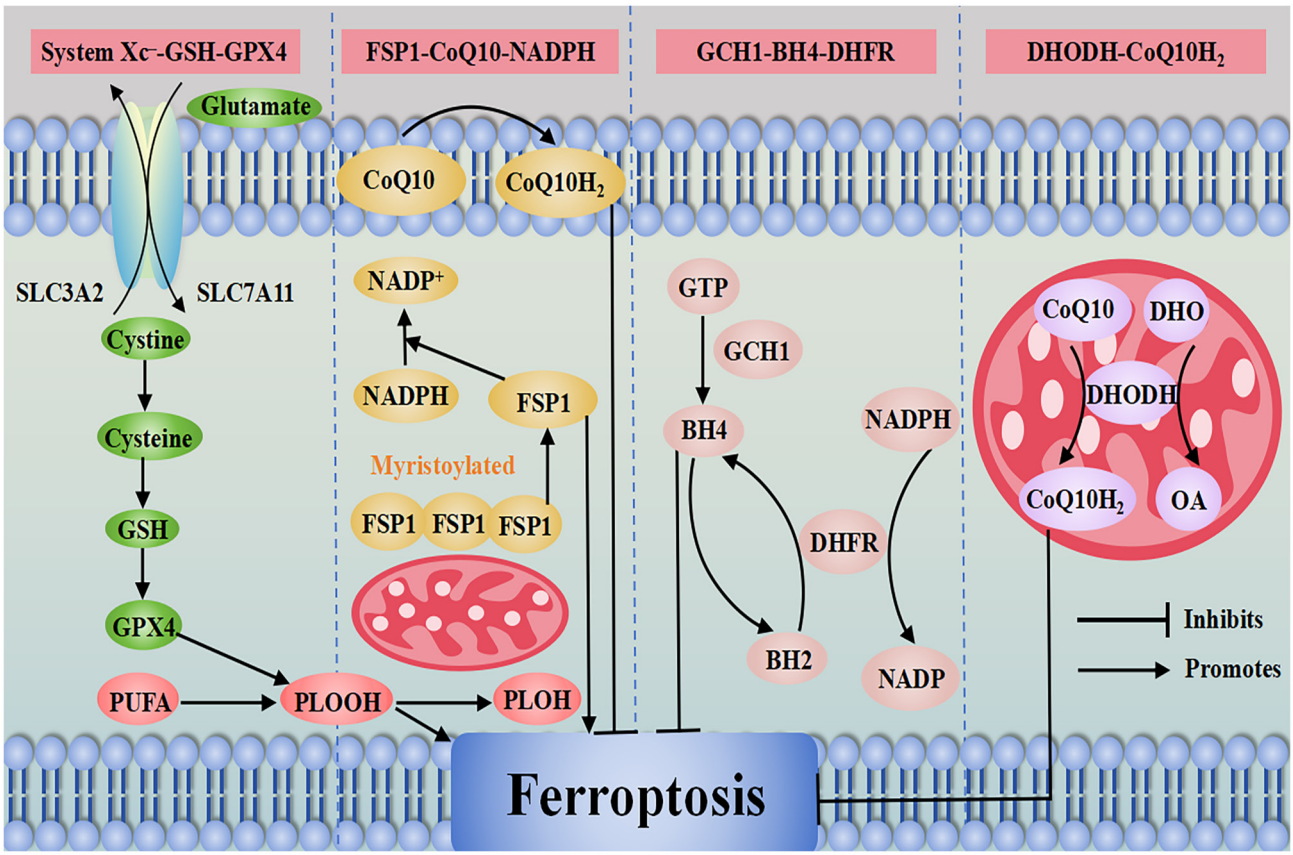

Figure 1. Primary antioxidant systems regulating ferroptosis. System Xc⁻-GSH-GPX4: Cystine is oxidized to cysteine through the System Xc-, which leads to the synthesis of GSH, and GPX4 reduces PLOOH to PLOH with the participation of GSH, which induces the onset of ferroptosis when GPX4 is inhibited. FSP1-CoQ10-NADPH: FSP1 promotes the transfer of CoQ10 from mitochondria to the cell membrane by myristoylation of the N-terminus with the participation of CoQ10 and its reduction to $CoQ10H_2$ catalyzed by NADPH, which prevents cellular ferroptosis by trapping free radicals. GCH1-BH4-DHFR: GCH1 is the rate-limiting enzyme for the biosynthesis of BH4. BH4 acts as a free radical-trapping antioxidant, inhibiting ferroptosis. It is recycled by DHFR and subjected to redox cycling. DHODH-$CoQ10H_2$: DHODH is located on the outer surface of the inner mitochondrial membrane and inhibits cellular ferroptosis by reducing lipid reactive oxygen species in mitochondria by reducing CoQ10 to $CoQ10H_2$. Supplementation with DHODH substrates or products (DHO or OA) regulates cellular ferroptosis. BH2, dihydrobiopterin; BH4, tetrahydrobiopterin; CoQ10, CoQ10, coenzyme Q10; $CoQ10H_2$, ubiquinol-10; DHFR, dihydrofolate reductase; DHO, dihydroorotate; DHODH, dihydroorotate dehydrogenase; FSP1, ferroptosis suppressor protein 1; GCH1, guanosine triphosphate cyclohydrolase 1; GSH, glutathione; GPX4, glutathione peroxidase 4; OA, orotate; PLOH, phospholipid hydroxide; PLOOH, phospholipid hydroperoxide; PUFA, polyunsaturated fatty acid; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11.

that the FSP1-CoQ10-NADPH pathway is independent of the classical System Xc⁻-GSH-GPX4 pathway, highlighting another pathway involved in the antioxidant regulation of ferroptosis and suggesting that its pharmacological inhibition may render cancer cells sensitive to ferroptosis-inducing chemotherapeutic agents. FSP1 is a key protein that prevents cells from undergoing ferroptosis, and knockdown of FSP1 increases the sensitivity of cell lines to ferroptosis-inducing agents, as well as being a positive regulator of mitochondrial apoptosis. FSP1 is recruited to the plasma membrane via myristoylation, thereby inhibiting ferroptosis (114,115). FSP1 is primarily associated with the outer mitochondrial membrane and undergoes myristoylation at the N-terminus to promote the transfer of CoQ10 from mitochondria to the cell membrane. The NADPH-catalyzed reduction of CoQ10 to ubiquinol-10 ($CoQ10H_2$) traps free radicals mediating lipid peroxidation, and thus prevents ferroptosis of cells (114). In addition, it has been shown that downregulation of stearoyl-CoA desaturase-1 was followed by a reduction in the lipophilic antioxidant CoQ10, which induced the potential for ferroptosis by inhibiting intracellular synthesis of protective lipids. Inhibition of stearoyl-CoA desaturase-1 enhanced the antitumor effects of ferroptosis inducers in OC cell lines. Combining stearoyl-CoA desaturase-1 inhibitors with ferroptosis inducers may offer a novel treatment option for the management of OC (116). The small molecule compound FIN56 inhibits CoQ10 synthesis in the mevalonate pathway by binding to and activating squalene synthase, resulting in a decrease in CoQ10 levels, and thus, increasing sensitivity to ferroptosis (117).

Nanogels developed by Yang *et al* (118) enhanced cellular lipid peroxidation through inhibition of the FSP1-CoQ10-NADPH pathway, leading to ferroptosis of immunogenic cells, and resulting in effective tumor ablation and immune responses in a mouse breast cancer model. Furthermore, downregulation of FSP1 in hepatocellular carcinoma cells promoted sorafenib-induced ferroptosis (119).

Therefore, the FSP1-CoQ10-NADPH pathway may complement and work with the System Xc⁻-GSH-GPX4 pathway to inhibit lipid peroxidation in ferroptosis, providing a potential therapeutic strategy for the treatment of OC.

GCH1-BH4-dihydrofolate reductase (DHFR) pathway. A previous study has identified the GCH1-BH4-DHFR pathway

as an alternative compensatory mechanism for the System Xc^--GSH-GPX4 pathway (120). GCH1 is the rate-limiting enzyme for BH4 biosynthesis, which promotes ferroptosis via the metabolites BH4 and dihydrobiopterin (BH2). BH4 acts as a free radical trapping antioxidant that can be recycled by DHFR for redox cycling, and BH4 has antioxidant degradation effects on phospholipids containing two PUFA tails and prevents lipid peroxidation and thus ferroptosis by inhibiting the production of specific LPOs (120,121).

Through the direct trapping of antioxidant free radicals and the production of CoQ10 (120), when GCH1 is upregulated, it promotes BH4 production and abrogates the deleterious effects of RSL3-induced cellular ferroptosis. Additionally, overexpression of GCH1 has been shown to decrease the sensitivity of drug-resistant cancer cells to ferroptosis, which in turn further ameliorated the progression of ferroptosis in cancer cells through the regulation of CoQ10 (122).

In addition, relevant studies have shown that BH4 is involved in the synthesis of dopamine, nitric oxide synthase and melatonin (123), whereas exogenous dopamine or melatonin can inhibit ferroptosis (124). Several studies have shown that nitric oxide can induce or inhibit ferroptosis in tumor cells depending on environmental conditions (125-127). DHFR reduces BH2 through the involvement of NADPH, thereby promoting BH4 synthesis. If DHFR is inhibited, ferroptosis of tumor cells is promoted via the synergistic action of GPX4 inhibitors (87).

Therefore, the GCH1-BH4-DHFR pathway serves a role in regulating the balance between oxidative damage and antioxidant defense during ferroptosis and interacts with the System Xc^--GSH-GPX4 pathway and the FSP1-CoQ10-NADPH pathway in a synergistic or complementary manner. Although other specific mechanisms and potential therapeutic targets remain to be determined, the identified pathways may serve as potential therapeutic targets for overcoming resistance to chemotherapy in OC.

Mitochondrial DHODH-CoQ10H_2 pathway. The mitochondrial DHODH-CoQ10H_2 pathway and the FSP1-CoQ10-NADPH pathway are the two major lipid antioxidant systems in mitochondria. If one system is inhibited, the cell becomes more dependent on the other antioxidant system, and if both systems are inhibited, mitochondrial lipid peroxidation occurs, resulting in ferroptosis (128).

CoQ10H_2, a free radical trapping antioxidant with anti-ferroptotic activity. DHODH is located on the outer surface of the inner mitochondrial membrane and inhibits cellular ferroptosis by converting CoQ10 to CoQ10H_2 to reduce lipid ROS in mitochondria. In addition, supplementation with dihydroorotate or orotate, substrates or products of DHODH, attenuates or enhances the inhibitory effect of GPX4, respectively, thereby modulating cellular ferroptosis (129).

The mitochondrial DHODH-CoQ10H_2 pathway and the FSP1-CoQ10-NADPH pathway function independently of each other, but they both reduce CoQ10 to CoQ10H_2 to enhance the mitochondrial defense mechanism against ferroptosis.

3. ERS in OC

When tumor cells are challenged by intrinsic factors such as oncogenic activation, altered chromosome numbers or enhanced secretory capacity, as well as by extrinsic factors such as hypoxia, nutrient deprivation and acidosis, protein homeostasis is altered, resulting in the accumulation of unfolded or misfolded proteins in the lumen of the ER, activating the ERS and the UPR, thus restoring homeostasis to the cell (32). However, when ERS is prolonged or the stimulus is too strong, exceeding the tolerance threshold of the UPR leads to cell death, which in turn causes the development of cancer (130).

UPR is initiated by three major ERS sensors located in the ER membrane, including inositol-requiring protein 1α (IRE1α), protein kinase RNA-like ER kinase (PERK) and activating transcription factor 6 (ATF6) (131). The ER-resident chaperone binding immunoglobulin protein (BiP) acts as a master regulator of the UPR by binding to and inactivating three ERS sensors, IRE1α, PERK and ATF6, negatively regulating them and keeping them in an inactive state. When misfolded proteins accumulate in the ER, they bind to the inhibitory chaperone BiP and sequester it, which activates the ERS sensors to initiate UPR signaling (132). An overview of the mechanisms of ERS is shown in Fig. 2.

IRE1 pathway. IRE1 consists of two isoforms, IRE1α and IRE1β; IRE1β is primarily expressed in the respiratory and gastrointestinal tracts, whereas IRE1α is more widely expressed (133). The cytoplasmic tail of IRE1α has two domains, a serine/threonine kinase structural domain and a ribonuclease (RNase) structural domain, which work together (134). The kinase of IRE1α is activated upon binding to misfolded proteins and undergoes dimerization/coupling and trans-autophosphorylation, leading to ectopic activation of the structural domain of RNase (135). Under the catalysis of active RNase, the intron containing 26 nucleotides is excised from the mRNA encoding the homeostasis transcription factor X-box protein 1 (XBP1). Then, two mRNA fragments are cleaved by RNA splicing ligase RNA 2',3'-cyclic phosphate and 5'-OH ligase, thereby generating the stable active transcription factor XBP1s (spliced form) (136,137). XBP1s (spliced form) is involved in the expression of genes encoding ER membrane biogenesis, ER protein folding, ER-associated degradation and multiple UPR targets (138). C/EBP homologous protein (CHOP), a major regulator of ERS-induced apoptosis, is activated by activating transcription factor 4 (ATF4) through the PERK-ATF4-CHOP pathway (139). In addition, IRE1α promotes apoptosis by activating the apoptosis signal-regulating kinase 1/JNK pathway, and by binding to tumor necrosis factor receptor-associated factor 2 (140). In addition, regulated IRE1-dependent decay is a novel UPR-regulated pathway that has been identified to control cell fate under ERS. Activated RNase can target other mRNAs and microRNAs (miRs) by regulating this pathway (141).

Zundell *et al* (142) showed that pharmacological inhibition of the IRE1α/XBP1 pathway may serve as a novel therapeutic strategy for Arid1a-mutant cancers, and that knockdown of the XBP1 gene improved survival in mice harboring Arid1a-inactivated ovarian clear cell carcinomas. Song *et al* (143) demonstrated that controlling ERS or targeting IRE1α-XBP1 signaling modulated mitochondrial activity, and thus, may help control T-cell metabolic adaptations

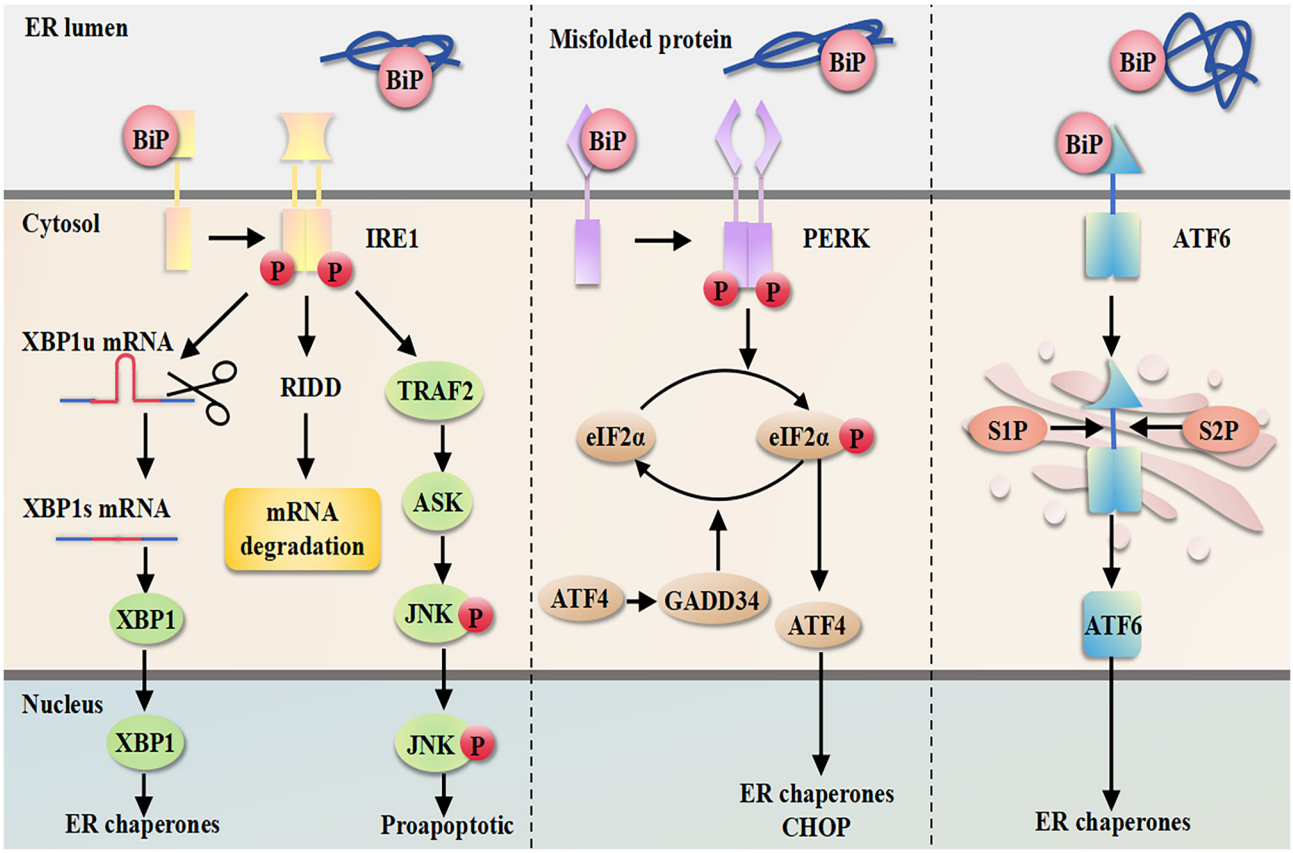

Figure 2. Mechanisms of ERS. Accumulation of unfolded or misfolded proteins in the lumen of the ER activates three transmembrane proteins of the unfolded protein response (IRE1, PERK and ATF6) and thereby restores cellular homeostasis. IRE1: Activation of IRE1 kinase results in the excision of an intron in the mRNA encoding the XBP1 transcription factor, and ligase mediates the linking of two mRNA fragments to produce stably active XBP1s. Stable XBP1s activity is involved in subsequent ER biogenesis. PERK: GADD34 forms a loop by regulating eIF2α dephosphorylation, thereby modulating ATF4-mediated ER biogenesis. ATF6: ATF6 is translocated to the Golgi under conditions of ERS and is sequentially hydrolyzed by S1P and S2P proteins, thereby regulating ER biogenesis. ATF4, activating transcription factor 4; ASK, apoptosis signal-regulating kinase; ATF6, activating transcription factor 6; BiP, binding immunoglobulin protein; eIF2α, eukaryotic translation initiation factor 2α; ER, endoplasmic reticulum; ERS, ER stress; GADD34, growth arrest DNA-damage 34; IRE1, inositol-requiring protein 1α; P, phosphorylated; PERK, protein kinase RNA-like ER kinase; RIDD, regulated IRE1-dependent decay; S1P, serine protease site 1; S2P, metalloprotease site 2; TRAF2, tumor necrosis factor receptor-associated factor 2; XBP1, homeostasis transcription factor X-box protein 1.

and anti-tumorigenic capacity in patients with OC. The mitochondria-associated ER membrane can also serve as an important link between the mitochondria and the ER (144). Cubillos-Ruiz *et al* (145) showed that the IRE1α-XBP1 pathway of dendritic cells in the OC microenvironment was continuously activated due to sustained ERS, which disrupted the antigen-presenting capacity and metabolic homeostasis of the dendritic cells and diminished their protective function in supporting of T cells against tumors, highlighting a unique immunotherapeutic approach for the management of OC. OC cells utilize ERS for survival through activation of the IRE1α/XBP1s pathway among other pathways, and coactivator associated arginine methyltransferase 1 (CARM1), which is typically upregulated in OC cells, has been revealed to regulate the expression of XBP1s target genes and to be selectively sensitive to the inhibition of the IRE1α/XBP1s pathway, providing a potential therapeutic strategy for the treatment of CARM1-expressing OC (146).

PERK pathway. PERK is a type I transmembrane protein with similarities to IRE1, which has an ER lumenal dimerization structural domain and a cytoplasmic kinase structural domain. The tubulin dimerization structural domain of PERK has less sequence similarity to IRE1 but is structurally and functionally similar to the structural domain of IRE1. The cytoplasmic kinase structural domain of PERK also undergoes trans-autophosphorylation in response to ERS, but it differs from IRE1 in that PERK also phosphorylates the eukaryotic translation initiation factor 2α (eIF2α) at serine 51, and phosphorylated eIF2α inhibits overall translation of proteins, and thus, reduces the amount of proteins entering the lumen of the ER (147,148). In addition, phosphorylation of eIF2α alters the utilization efficiency of the AUG start codon (149), which results in preferential translation of the ATF4 mRNA (148).

ATF4 is a transcription factor that activates downstream UPR target genes, such as the expression of growth arrest DNA-damage 34 (GADD34), which induces CHOP expression (148,150). CHOP promotes DNA damage, inhibits cell proliferation and activates apoptosis by upregulating the pro-apoptotic members of the B-cell lymphoma-2 family of proteins (151). Therefore, ATF4 serves an important role in ER-functional gene expression, ERS-mediated ROS production and ERS-induced apoptosis. ATF4 can also regulate the dephosphorylation of eIF2α through GADD34 to form an inhibitory feedback loop to reverse PERK-mediated translational decay (152). In addition, PERK phosphorylates nuclear

factor erythroid 2-related factor 2 (Nrf2), thereby upregulating antioxidants to promote cellular antioxidation (153). Overall, the PERK-eIF2α pathway first mediates the promotion of cell survival during ERS but shifts to the promotion of apoptosis when ERS is sustained and maintains cellular homeostatic balance by activating ATF4 and NRF2. Therefore, the PERK pathway is an attractive therapeutic target in OC therapy.

ATF6 pathway. ATF6 is a type II transmembrane protein with a carboxy-terminal stress-sensing lumenal structural domain and an amino-terminal bZip transcription factor structural domain (154). ATF6 is transported to the Golgi under conditions of ERS, where it is sequentially hydrolyzed by serine protease site 1 and metalloprotease site 2 (S2P) proteins to release its amino-terminal transcription factor structural domain, which, synergistically with XBP1, upregulates genes involved in protein folding and ER amplification, as well as genes involved in ER-associated degradation pathway components (155). It has been shown that ATF6 expression in OC tumor tissues is higher than that in normal ovarian tissues (156), and under irreversible ERS, it downregulates the levels of anti-apoptotic proteins (157). In addition, by regulating ATF6, the sensitivity of OC cells to chemotherapeutic agents can be altered (158). However, the role of ATF6 in ER-induced cell death and co-targeting of chemotherapeutic agents to improve survival in OC still needs to be explored further.

4. Ferroptosis and ERS interactions in OC

With the gradual increase in interest in ferroptosis and ERS, an increasing number of studies have shown that ferroptosis and ERS have an important impact on OC and that there is a close relationship between the two (35,159-161).

Chen *et al* (162) found that regulating ferroptosis in OC cells increased the anti-proliferative effect of cannabidiol derivatives and induced ferroptosis in OC cells, both *in vitro* and *in vivo*, effectively inhibiting the development of OC (163). Liu *et al* (164) used organoids to show that ovarian tumorigenesis was effectively inhibited by targeting ferroptosis. In addition, ferroptosis-related mechanisms can also reverse cisplatin resistance in OC (14), affecting drug resistance and prognosis in patients with OC (165,166). Li *et al* (25) facilitated the possible clinical transition of targeting ferroptosis for OC diagnosis and synergistic treatment by combining the ferroptosis mechanism with nanotechnology, MRI and cisplatin-based chemotherapeutic treatment (167,168).

ERS also serves a crucial role in the development and prognosis of OC. Studies have shown that activation of UPR sensors, and thus, induction of ERS can lead to apoptosis of OC cells (169), and regulation of ERS-associated targets influences drug resistance in OC treatment (170,171), highlighting potentially novel targets for the management of OC. Zhang *et al* (172) developed promising medical aids for the prognostic assessment of patients with epithelial OC by establishing a risk classifier for differentially expressed genes associated with ERS. Ma *et al* (173) utilized nanotechnology to accurately and durably induce ERS through photodynamic responses, thus inducing an antitumor effect in a mouse model of OC.

A growing body of research has shown a link between ferroptosis and ERS, which share common pathways (174-176), and that ROS, a byproduct of ERS, may exacerbate ferroptosis, while the ER is a key site for lipid peroxidation during ferroptosis, and conversely ROS produced during ferroptosis further exacerbate ERS. However, ferroptosis and ERS have been discussed separately regarding OC, and, to the best of our knowledge, there are no studies assessing their interactions in OC. In the present review, the potential therapeutic targets for OC treatment are examined based on a potential association between ERS and ferroptosis in OC using the existing literature. An overview of interactions between ferroptosis and ERS is shown in Fig. 3 and an overview of mechanisms associated with ferroptosis and ERS is shown in Table I.

A study has shown that ERS is modulated by regulation of ferroptosis (34). Zhong *et al* (34) demonstrated that ferroptosis and ferroptosis-mediated ERS cause damage to prefrontal cortex neurons, and that ferroptosis in prefrontal cortex neurons activates the ERS-associated PERK-ATF4-CHOP pathway. The ferroptosis inhibitor liproxstatin-1 and the iron ion chelator deferoxamine reduced the expression levels of partially restored ferroptosis-related proteins, upregulated Nrf2 expression, downregulated phosphorylated-PERK, ATF4 and CHOP, and reduced ERS by inhibiting ferroptosis. This resulted in the attenuation of chronic intermittent hypoxia-induced neuronal damage and cognitive dysfunction, providing a potential therapeutic target for neurocognitive dysfunction induced by exposure to chronic intermittent hypoxia (34). ERS serves an important role in the etiology of obesity-associated myocardial malformations, and ERS markers are upregulated in persistent obesity. Taurine deoxycholic acid attenuates obesity-associated ERS-induced myocardial dysfunction, whereas ferroptosis induces the elimination of the beneficial effects provided by taurine deoxycholic acid and enhances the effects of ERS (177). Yang *et al* (176) found that activation of ferroptosis signaling in tumor cells promoted the formation and secretion of exosomes containing unfolded and misfolded proteins, inhibited ERS, and improved the survival rate of tumor cells. Additionally, it has been shown that the ERS-ferroptosis signaling-exosome pathway induced ERS drug resistance, highlighting a potentially key intracellular signaling mechanism that may be involved in ER signaling, ER homeostasis and drug resistance in cancer (176). Dihydroartemisinin (DHA) can induce ferroptosis of immunogenic cells in lung cancer by accumulating LPO, and at the same time induce cellular ERS. Further analysis showed that ferroptosis inhibitors eliminate the DHA-induced ERS, highlighting a potential novel therapeutic avenue for the management of cancer with traditional Chinese medicines in cancer immunotherapy (178).

Similarly, the regulation of ERS can also affect ferroptosis. Han *et al* (179) showed that polydatin ameliorated early brain injury after subarachnoid hemorrhage by inhibiting ERS through upregulation of sirtuin 1 (SIRT1) expression, and thus, inhibiting ferroptosis in neuronal cells. Wang *et al* (180) revealed that the ERS inhibitor 4-phenylbutyric acid inhibited ferroptosis in airway epithelial cells to prevent acute lung injury by downregulating ERS, reversing the lipopolysaccharide-induced decrease in GSH, and inhibiting the expression of ferroptosis-associated proteins, Acyl-CoA synthetase long-chain family member 4, cyclooxygenase-2

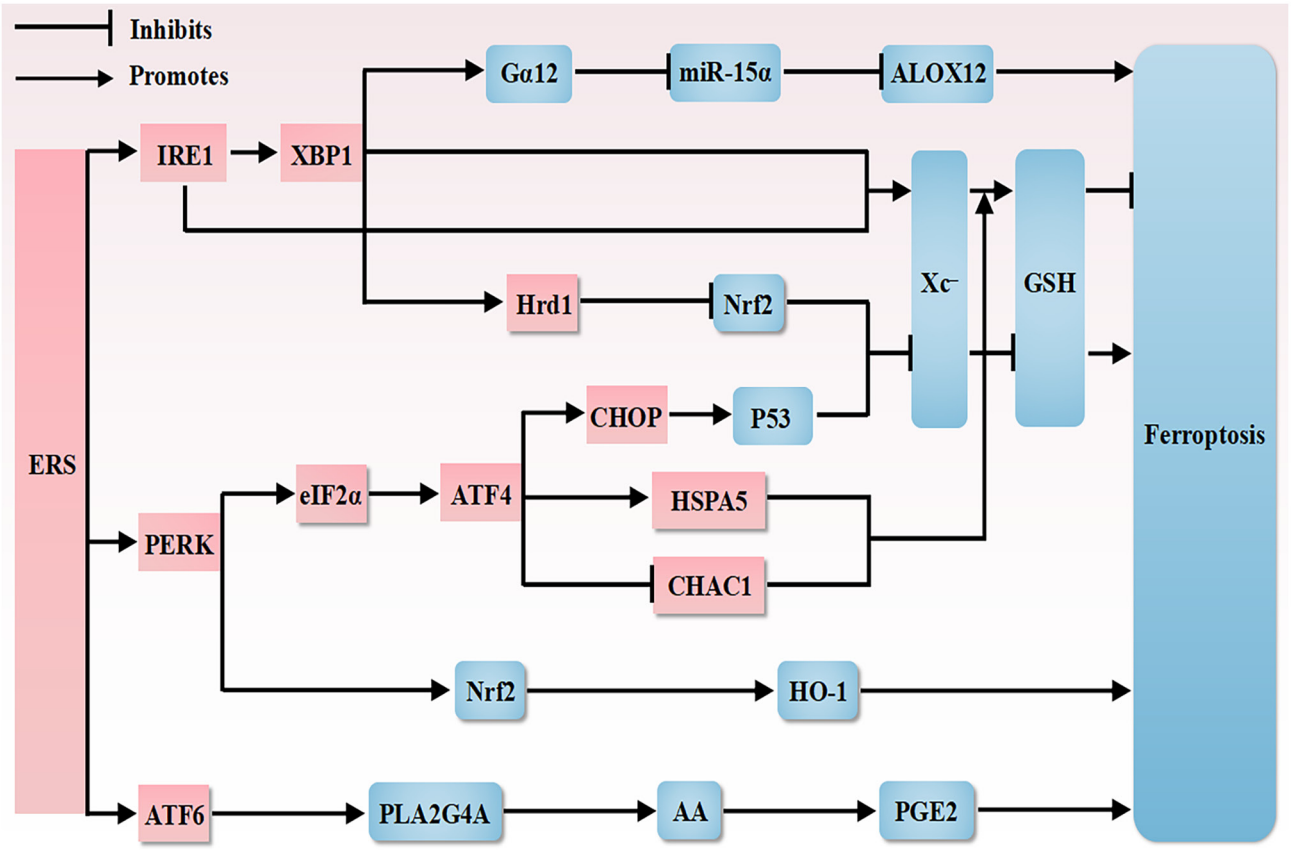

Figure 3. Interactions between ferroptosis and ERS. ERS induces ferroptosis. ERS activates the IRE1α-XBP1s-Gα12, PERK-eIF2α-ATF4-CHOP, PERK-Nrf2-HO-1, PERK-P53-System Xc^- and ATF6-PLA2G4A-AA-PGE2 pathways to induce ferroptosis. ERS inhibits ferroptosis. ERS inhibits ferroptosis by activating the PERK-eIF2α-ATF4-HSPA5 and PERK-eIF2α-ATF4-CHAC1 pathways. AA, arachidonic acid; ALOX12, arachidonate 12-lipoxygenase, 12S type; ATF4, activating transcription factor 4; ATF6, activating transcription factor 6; CHAC1, cation transport regulator homolog 1; CHOP, C/EBP homologous protein; eIF2α, eukaryotic translation initiation factor 2α; ERS, endoplasmic reticulum stress; Gα12, G protein subunit α 12; GSH, glutathione; HO-1, heme oxygenase-1; Hrd1, E3 ligase; HSPA5, heat shock 70 kDa protein 5; IRE1α, inositol-requiring protein 1α; miR, microRNA; Nrf2, nuclear factor erythroid 2-related factor 2; PERK, protein kinase RNA-like ER kinase; PGE2, prostaglandin E2; PLA2G4A, phospholipase A2 group IVA; XBP1, homeostasis transcription factor X-box protein 1.

and ferritin heavy chain 1, thus highlighting a potential means of intervention for management of acute lung injury. *In vitro* experiments on ovarian granulosa cells revealed elevated ROS production, lipid peroxidation and intracellular iron content in testosterone-treated cells. The expression levels of SLC7A11, a key protein of System XC^-, were also altered, resulting in reduced intracellular GSH synthesis and cystine deficiency. This led to a decrease in the activity of GPX4, the primary intracellular antioxidant, thereby inducing ferroptosis in granulosa cells. However, the testosterone-induced ferroptosis process was reduced by ERS inhibitors (181). Jiang *et al* (182) found that IRE1α, a regulatory protein that serves an important role in UPR, also determines susceptibility to ferroptosis by regulating GSH synthesis, suggesting that inhibition of IRE1α is a promising therapeutic strategy for ameliorating pathologies associated with ferroptosis. In addition, it has been demonstrated that exogenous melatonin, a drug candidate for the treatment of hepatocyte ferroptosis in non-alcoholic fatty liver disease, inhibits hepatocyte ferroptosis by reducing ERS through the regulation of the type 1B/cAMP/protein kinase A/IRE1 pathway (183). The high-risk heavy metal cadmium induces hepatocyte ferroptosis, causing liver injury, and the occurrence of ferroptosis is often accompanied by activation of the PERK-eIF2α-ATF4-CHOP signaling pathway, which can be countered by inhibition of ERS to reduce ferroptosis; therefore, cadmium-induced ferroptosis is dependent on ERS (184). Cadmium also regulates ferroptosis and induces nephrotoxicity in renal tubular epithelial cells through the same aforementioned mechanisms, resulting in kidney injury (185). Data from an ulcerative colitis study suggest that ERS is involved in the development of ferroptosis. eIF2α is a key component of the PERK branch of the ERS response, and phosphorylated NF-κBp65 inhibits ERS, and thus, protects the intestinal epithelium from ferroptosis in ulcerative colitis by directly interacting with eIF2α (186).

Colorectal cancer is a common digestive malignancy in which both surgery and chemotherapy exhibit limited therapeutic efficacy (187). Tagitinin C, a natural product, induces ERS production, which results in nuclear translocation of Nrf2 and upregulation of HO-1. HO-1 is a downstream effector of Nrf2, which leads to an increase in the pool of unstable iron, and thus, promotes lipid peroxidation. This increase in the pool of unstable iron together with erastin exerts synergistic antitumor effects in inducing ferroptosis in colorectal cancer cells. Thus, tagitinin C has been identified as a novel ferroptosis inducer and potent sensitizer (188). Furthermore, in a prostate cancer

Table I. Mechanisms associated with ferroptosis and ERS.

First author/s, year	Drug/active ingredient	Experimental model		Role in ferroptosis and ERS	Pathways/targets affecting ferroptosis/ERS	Role as a potential therapeutic target	(Refs.)
		In vitro	*In vivo*				
Dixon *et al*, 2012	Erastin	HT-1080	-	Induction of ferroptosis	System Xc^-	Leads to non-apoptotic destruction of tumor cells	(38)
Sun *et al*, 2016	Sorafenib	HepaG2, Hep3B	Nude mice	Induction of ferroptosis	System Xc^-	Modulating drug resistance in hepatocellular carcinoma cells	(106)
Guan *et al*, 2009	Sulfasalazine	NCI-H69, NCI-H82	-	Induction of ferroptosis	System Xc^-	Inhibition of small cell lung cancer cell proliferation	(107)
Jiang *et al*, 2015	p53	H1299, U2OS, MCF7	Nude mice	Induction of ferroptosis	System Xc^-	Inhibition of tumor cell proliferation	(108)
Luo *et al*, 2024	PAX8 inhibitor	-	Xenograft mouse model	Induction of ferroptosis	GPX4	Inhibits the proliferation of OC cells	(110)
Yang *et al*, 2024	Chitosan-ferrocene-sodium alginate crosslinked nanogels	-	Mouse breast model	Induction of ferroptosis	FSP1-CoQ10-NADPH	Producing effective tumor ablation in a mouse model of breast cancer	(118)
Liu *et al*, 2023	Sorafenib	HepG2, Huh-7	Nude mice	Induction of ferroptosis	FSP1	Novel opportunities for the development of ferroptosis-associated cancer therapies	(119)
Zundell *et al*, 2021	IRE1α inhibitor	OVCA429, OVTOKO, SKOV3, OVISE, TOV21G	Mouse model	Induction of ERS	IRE1α-XBP1	A novel therapeutic strategy for ARID1A-mutant OC	(142)
Song *et al*, 2018	-	Stage III-IV human OC tumors and malignant ascites	Transgenic mice	Adjustment of ERS	IRE1α-XBP1	Contributes to the restoration of antitumor capacity and metabolic adaptation of cancer host T cells	(143)

Table I. Continued.

First author/s, year	Drug/active ingredient	Experimental model		Role in ferroptosis and ERS	Pathways/targets affecting ferroptosis/ERS	Role as a potential therapeutic target	(Refs.)
		In vitro	*In vivo*				
Lin *et al*, 2021	IRE1α inhibitor	HGSOC, ID8, UPK10	Six-week-old female immunodeficiency gamma (NSG) mice	Adjustment of ERS	IRE1α-XBP1	A novel therapeutic strategy for CARM1-expressing cancers	(146)
Meng *et al*, 2020	DNA binding inhibitor	HEY, HEY A8, SKOV3, SKOV3 ip1, OVCA420, OVCA429, OVCA433, A2780	Nude mice	Induction of ERS	ATF6	Improving chemotherapy resistance in cancer cells	(158)
Zhong *et al*, 2024	Liproxstatin-1 and the iron chelator deferoxamine	-	CIH model in 4-week-old male mice	Induction of ferroptosis, and thus, ERS	Nrf2, PERK-ATF4-CHOP	Attenuating chronic intermittent hypoxia-induced neuronal damage and cognitive dysfunction	(34)
Han *et al*, 2024	Polydatin	-	Male C57BL/6 mice	Inhibition of ERS and ferroptosis	SIRT1	Improving early brain injury after subarachnoid hemorrhage	(179)
Wang *et al*, 2024	4-Phenylbutyric acid	BEAS-2B	-	Inhibition of ERS, and thus, ferroptosis	GSH, ACSL4, COX-2, FTH1	Prevention of acute lung injury	(180)
Tak *et al*, 2022	Acetaminophen or other ERS inducers	-	*Gna12* KO mice	Induction of ERS, and thus, ferroptosis	IRE1α-XBP1, $G\alpha_{12,}$ miR-15α, ALOX12	A promising strategy for constituting acute liver injury	(190)
Liu *et al*, 2023	Ferrostatin-1	-	DN mice	Induction of ERS, and thus, ferroptosis	XBP1-Hrd1-Nrf2, SLC7A11, GSH	Providing insights into potential mechanisms that delay epithelial-mesenchymal transition in renal tubular epithelial cells	(35)

Table I. Continued.

First author/s, year	Drug/active ingredient	Experimental model		Role in ferroptosis and ERS	Pathways/targets affecting ferroptosis/ERS	Role as a potential therapeutic target	(Refs.)
		In vitro	*In vivo*				
Ji *et al*, 2024	Esculin	HCT116	Colorectal cancer mouse model	Induction of ERS, and thus, ferroptosis	PERK, Nrf2/HO-1, eIF2α/CHOP	Inhibition of colon cancer development and progression	(191)
Guo *et al*, 2024	Tanshinone IIA	HepG2	H22-bearing mice	Inhibition of ERS, and thus, ferroptosis	PERK-ATF4-HSPA5	Inhibits tumor growth in mice	(192)
Xu *et al*, 2023	Salidroside	-	male C57BL/6 J mice	Inhibition of ERS, and thus, ferroptosis	AMPK-SIRT1, ATF4-CHAC1	Mitigation of acetaminophen-induced acute liver injury	(193)
Chen *et al*, 2019	Dihydroartemisinin	U251, U373	-	Induction of ERS, and thus, ferroptosis	PERK, ATF4, GPX4	Potentially novel anticancer mechanism in gliomas	(194)

ACSL4, acyl-CoA synthetase long chain family member 4; ALOX12, arachidonate 12-lipoxygenase, 12S type; ARID1A, AT-rich interaction domain 1A; ATF4, activating transcription factor 4; ATF6, activating transcription factor 6; CARM1, coactivator associated arginine methyltransferase 1; CHAC1, cation transport regulator homolog 1; CHOP, C/EBP homologous protein; CIH, chronic intermittent hypoxia; CoQ10, coenzyme Q10; COX-2, cyclooxygenase-2; eIF2α, eukaryotic translation initiation factor 2α; ERS, endoplasmic reticulum stress; FSP1, ferroptosis suppressor protein 1; FTH1, ferritin heavy chain 1; Gα12, G protein subunit alpha 12; GPX4, glutathione peroxidase 4; GSH, glutathione; HO-1, heme oxygenase-1; Hrd1, E3 ligase; HSPA5, heat shock 70 kDa protein 5; IRE1α, inositol-requiring protein 1α; miR, microRNA; Nrf2, nuclear factor erythroid 2-related factor 2; OC, ovarian cancer; PAX8, paired box 8; PERK, protein kinase RNA-like ER kinase; SIRT1, sirtuin 1; SLC7A11, solute carrier family 7 member 11; XBP1, homeostasis transcription factor X-box protein 1.

study, the mediation of arachidonic acid release and prostaglandin E2 production via ATF6α-phospholipase A2 group IVA was found to protect prostate cancer cells from ferroptosis (189). Upregulation of Gα12 through the IRE1α-XBP1 pathway after ERS in hepatocytes thereby promotes hepatic ferroptosis and exacerbates acute liver injury through Rho associated coiled-coil containing protein kinase 1-mediated dysregulation of 12-lipoxygenase and miR-15α (190). Furthermore, in a study related to diabetic nephropathy, ERS downregulated SLC7A11 expression through the XBP1-E3 ligase-Nrf2 pathway, which decreased GSH antioxidant levels and enhanced cellular sensitivity to ferroptosis, thereby inducing ferroptosis, providing insights into the potential mechanism of delaying epithelial-mesenchymal transition in renal tubular epithelial cells (35).

In addition, several studies have demonstrated that herbal components can also improve cellular ferroptosis by modulating ERS. Esculin, a compound extracted from the cortex of the willow bark, inhibits the development and progression of colon cancer by activating the ERS PERK signaling pathway, and inducing apoptosis and ferroptosis through the Nrf2/HO-1 and eIF2α/CHOP pathways (191). Tanshinone IIA, the primary active ingredient of the traditional Chinese medicine Danshen, has been shown to exert antitumor effects primarily in the ER-mediated ferroptosis signaling pathway, downregulating the ferroptosis of tumor cells through the PERK-ATF4-heat shock 70 kDa protein 5 pathway (192). Acetaminophen overdose is a major cause of drug-induced liver injury. Salidroside inhibits ER stress-mediated ferroptosis via the ATF4-cation transport regulator homolog 1 axis by activating AMPK-SIRT1 signaling, and serves an important role in alleviating acetaminophen-induced acute liver injury (193). In a study on glioma, DHA-induced ERS upregulated ATF4 via PERK, thereby increasing the expression and activity of GPX4, thus inhibiting DHA-induced lipid peroxidation and protecting glioma cells from ferroptosis, highlighting a novel anticancer mechanism in glioma (194).

In addition, ERS induces Ca^{2+} release, and TF transport is regulated by cytoplasmic Ca^{2+} levels, thus affecting intracellular iron content and inducing ferroptosis in colon cancer cells (195). Ferroptosis therapy, which is centered on increased intracellular ROS production and LPO accumulation, has emerged as a novel treatment modality for lung cancer. A ferroptosis nano-inducer consisting of DHA and pH-responsive calcium phosphate is delivered to the lungs by nebulization. The burst of Ca^{2+} can mediate ERS, thereby promoting the accumulation of ROS and leading to the intensification of ferroptosis, providing a novel research direction for the treatment of lung cancer (196).

It has been shown that ERS and ferroptosis are also related in terms of tumor angiogenesis. In a glioma-related study, elevated expression of ATF4, a transcription factor that activates downstream UPR target genes, promoted angiogenesis by facilitating tumor shaping of vascular structures in a System Xc^--dependent manner, and erastin, a ferroptosis inducer, and RSL3, a GPX4 inhibitor, could reduce ATF4-induced angiogenesis (197).

Drug development research on natural compounds and their derivatives is a popular research topic for cancer treatment. Research on novel drugs also takes into consideration the side effects and off-target effects, which can negatively affect the quality of life of patients. Drugs with high specificity and selectivity need to be developed to minimize off-target effects and their potential toxicities (198). In OC, reducing off-target effects during treatment can help improve patient outcomes and prognosis (199). Studies have shown that off-target effects are strongly linked to ferroptosis and ERS. Dahlmanns *et al* (200) found that adjusting the mechanism of ferroptosis improved tumor therapy, but that interfering with the induction of ferroptosis produced an off-target effect, and thus, a reduction in therapeutic efficacy. Similarly, it has been shown that ERS may modulate off-target effects in glioblastoma multiforme (201). Inhibitors of ROS, which are closely related to ferroptosis and ERS, likewise have some degree of influence on off-target effects (202). Recent advances in research on coupled drug delivery systems (203), liposomes (204) and nanotechnology (205) in combination with bioactive agents for the treatment of a wide range of diseases, including cancer, may lead to improved efficacy through the localized and precise delivery of drugs, thereby reducing off-target effects.

In summary, ERS interacts with ferroptosis in several diseases through various pathways, regulatory proteins and related factors to regulate disease development, highlighting potential therapeutic targets and strategies for disease treatment and prevention. However, the specific mechanisms by which ERS interacts with ferroptosis in the development, treatment and prevention of OC remain to be investigated.

5. Conclusions and future perspectives

Ferroptosis and ERS are both increasingly popular topics in relation to cancer research, and studies have shown that ferroptosis and ERS are related to the development and potential treatment of gynecological tumors (13,20,32,206,207). OC, as the gynecological malignant tumor with the highest mortality rate, has attracted attention; however, there is no relevant research on the potential mechanism of the interaction between ERS and ferroptosis in OC. In the present review, the pathogenesis of ERS and ferroptosis in OC, and the common pathways and related links between the two in liver, lung and colorectal cancer, are discussed, with the aim of providing novel strategies for the prevention, treatment and prognosis of OC in the future.

Numerous studies (208-212) have shown that ferroptosis and ERS serve as potential therapeutic targets for preventing the occurrence and development of OC, as well as in the treatment and prognostic prediction of patients with OC, while the combination with other drugs and novel technologies has also achieved favorable therapeutic effects, and has provided novel avenues for OC research. In particular, the proliferation and growth of OC cells can be inhibited by regulating the levels of iron in OC cells, and ferroptosis can thus be induced in the cells (105), which affects the occurrence and development of OC. Additionally, the induction of ferroptosis can also be achieved to counter chemoresistance (213). ERS can inhibit cell proliferation by regulating relevant pathways (214) and targeting chemoresistant cancer cells, and ERS-induced apoptosis has been shown to improve the sensitivity of OC cells to paclitaxel, thereby improving the prognosis of patients with OC (215).

There is also an association between the two, with ERS inducing ferroptosis by causing Fe^{2+} accumulation and lipid peroxidation through related pathways (195), and the ER, which contains more than half of all the lipid bilayers in any given cell, being the source of lipids for the majority of the cytosolic membranes, thus being critical for the initiation of ferroptosis (216). Ferroptosis can maintain ER homeostasis by signaling and regulating the degree of ERS. Ferroptosis can also be positively regulated by inducing ERS through various pathways.

However, ferroptosis and ERS have different and complex mechanistic pathways, and several novel mechanisms, pathways and potential targets are gradually being identified, although it is likely that more remain to be uncovered. For example, the detailed mechanisms of the four pathways associated with lipid antioxidation, particularly the GCH1-BH4-DHFR pathway and the DHODH-CoQ10H_2 pathway in OC, still remain to be explored. Oxidative stress in mitochondria is closely associated with related processes in ferroptosis and ERS, and the mechanisms involved in mitochondria are not fully understood at present. Furthermore, the early onset of OC is insidious, and regarding diagnostic accuracy, there is still a lack of research on the difference in iron content between OC tissues of different stages and normal ovarian tissues (55). Interfering with iron metabolism during early OC may inhibit the further development of OC (104). The occurrence, progression and treatment of OC is a complex process, and there is a complex connection between ERS and ferroptosis. Whether the relevant pathways present in other diseases have the same role in OC, whether there are obvious differences in the roles in different cells at different stages of OC, and whether they have the same regulatory role in the different stages of OC occurrence, development, and recurrence remain to be determined. Furthermore, the prognostic prediction of OC still has major deficiencies and lacks the support of clinical data. Although current studies on various diseases have shown that the crosstalk between ferroptosis and ERS has a related improvement effect on the diseases (34,217-219), there is still a lack of relevant research regarding mechanisms for the crosstalk between ERS and ferroptosis in terms of OC.

Based on the clearer understanding of potential targets of ERS and ferroptosis, the role of the mechanistic pathways in the process of OC, the impact of the crosstalk between the two, and how to translate the results of research and experiments into clinical practice is an important and challenging aspect. In terms of clinical index detection, the aforementioned mechanism and modern scientific technologies such as nano-molecular materials, MRI and X-ray may be combined to detect the pathological factors of OC before the onset of the disease, and analyze the efficacy or assess prognosis during and following treatment of the disease. Assessment of iron metabolism levels during relevant clinical testing may allow for earlier detection of OC, potentially improving treatment options and patient outcomes. The direction of these studies, which await further translation to the clinic, may serve as a means of assessing patients to improve prevention, and assess efficacy and recurrence. In terms of drug development, for the commonly used chemotherapeutic regimens, there are obvious side effects alongside drug resistance. Thus, additional screening of safe and effective therapeutic drugs is required. Whether ferroptosis inhibitors and inducers of ERS can be used clinically or as references for future drug development remains to be explored. In addition, several studies (14,80,192,220) have found that traditional Chinese herbs are effective in regulating the crosstalk between ferroptosis and ERS-related mechanisms in relation to OC, thus the dosage and clinical safety of these options should be investigated. Whether the combination of various drugs, chemotherapeutic treatments and modern technologies will have a synergistic effect or inhibit resistance to chemotherapy and side effects also needs to be tested.

The present review highlights the potential therapeutic promise of crosstalk between ferroptosis and ERS in OC, suggesting that the intricate interactions merit deeper exploration. In addition, several potential treatments have shown therapeutic potential and efficacy in combination with conventional chemotherapy for the treatment of OC in preclinical testing, and future studies are required to determine the detailed molecular mechanisms of these compounds and to assess their efficacy in the clinic. To address these unknown challenges, it is necessary to draw on the results of existing research to help understand the focus and direction of the research. After clarifying the mechanism of each target and pathway, it is necessary to screen for important links or representative factors and more precise biomarkers. For drug development, a large amount of clinical data is required.

Overall, understanding ferroptosis and ERS, and the potential crosstalk between them, may provide novel therapeutic approaches for the management of OC.

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Authors' contributions

JY wrote and revised the manuscript. YW revised the manuscript. FL revised the manuscript. YZ and FH conceived the topic of study. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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