Interactions between ferroptosis and tumour development mechanisms: Implications for gynaecological cancer therapy (Review)

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Abstract. Ferroptosis is a form of programmed cell death that is distinct from apoptosis. The mechanism involves redox-active metallic iron and is characterized by an abnormal increase in iron-dependent lipid reactive oxygen species, which results in high levels of membrane lipid peroxides. The relationship between ferroptosis and gynaecological tumours is complex. Ferroptosis can regulate tumour proliferation, metastasis and chemotherapy resistance, and targeting ferroptosis is a promising antitumour approach. Ferroptosis interacts with mechanisms related to tumorigenesis and development, such as macrophage polarization, the neutrophil trap network, mitochondrial autophagy and cuproptosis. The present review examines recent information on the interaction between the molecular mechanism of ferroptosis and other tumour-related mechanisms, as well as the involvement of ferroptosis in gynaecological tumours, to identify implications for gynaecological cancer therapy.

Contents

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1. Introduction

The high incidence of gynaecological malignancies threatens women's health and longevity. Depending on their origin, gynaecological malignancies are often categorized individually, and they present different risk factors, symptoms, growth predictions and treatments (1). As the leading cause of cancer death in women, breast cancer (BCa) remains a global public health problem (2). Cervical cancer is second after BCa and causes >300,000 deaths per year (3). The low 5-year survival rate (4-6) of ovarian cancer (OC) is because most patients are at the terminal stage when they are diagnosed, and some exhibit chemoresistance (7). In addition to the ovary and cervix, the endometrium may also be affected by malignant tumours. The development of endometrial cancer is mainly influenced by metabolic imbalance and genetic susceptibility (8,9). The main treatment options for gynaecological malignancies are surgery, chemotherapy and radiotherapy. Chemotherapy aims to induce apoptosis in tumour cells, selectively eliminating cancer cells without harming normal cells, but some patients develop escape from apoptosis and chemotherapy resistance. Regulatory cell death (RCD) can be modulated by pharmacological or genetic interventions and is controlled by specific signalling pathways. Exploring nonapoptotic RCD processes may provide another strategy for breaking through the anti-apoptotic characteristics of tumours to inhibit tumour growth.

The discovery of ferroptosis stems from the 2003 appearance of erastin (10), a compound with selective lethal effects on RAS-expressing cancer cells with different cell death patterns. In 2012, Dixon *et al* (11) named the process ferroptosis on the basis of its death characteristics. Iron accumulation catalyses the oxidation of phospholipids with polyunsaturated fatty

acid (PUFA) residues through the Fenton reaction (5), leading to an imbalance of oxidative and antioxidant systems and resulting in lipid peroxidation (12) and the formation of lipid ROS, which ultimately rupture the cell membrane and then lead to programmed cell death (6). There have been substantial breakthroughs in the research of ferroptosis in cancer. Cancer cells can mediate ferroptosis resistance through related signalling pathways (13) and tumour factors, which are conducive to occurrence, development, metastasis and treatment resistance (14). A high reactive oxygen species (ROS) load makes tumour cells vulnerable to ferroptosis treatment (15). Ferroptosis has been shown to be associated with a variety of gynaecological cancers (16), such as breast, cervical, ovarian and endometrial cancer. However, the potential importance of ferroptosis in the treatment of gynaecological malignancies has not been fully explored.

The vigorous metabolism and rapid proliferation of tumour cells cause a hypoxic tumour microenvironment (TME). Cancer cells undergo changes in signalling pathways and molecular expression to adapt to the hypoxic environment and escape immune surveillance, and hypoxia affects tumour biological behaviour and treatment effects (17). Hypoxia inducible factor (HIF) is the main regulator of the hypoxic microenvironment (18). It is activated under hypoxic conditions, and it promotes tumour angiogenesis, regulates metabolic reprogramming, and increases chemoradiotherapy resistance (19). Hypoxia directly affects the expression of ferroptosis-related molecules, upregulates the expression of iron oxidase and stearoyl-CoA desaturase 1 (SCD1), downregulates iron autophagy-related protein nuclear receptor coactivator 4 (NCOA4), limits intracellular $Fe^{2+,}$ and inhibits ferroptosis (20). Moreover, HIF and nuclear factor erythroid 2-related factor 2 (Nrf2) are involved in regulating and coordinating the antioxidant mechanisms of ferroptosis and iron homeostasis (21). HIF-1 increases the transcription of SLC7A11 and HO-1, inhibiting ferroptosis (22). Hypoxia increases Nrf2 activity, increases HO-1 expression, and inhibits ferroptosis (23,24). Inflammatory molecules released by cancer cells (such as IL-8, CXCL1 and CTSC) and cells in the TME, such as cancer-associated fibroblasts, can induce neutrophil extracellular trap (NET) formation, and cancer cells in a hypoxic environment may have an increased ability to induce NETs (25). Hypoxia-activated HIF-1α promotes M2 macrophage polarization by increasing the expression of VEGF, Arg1 and other M2-related genes (26). Hypoxia also affects mitochondrial behaviour, inducing the production of mitochondrial ROS (mtROS) through mitochondrial complex I dysfunction and the activation of the mitochondrial Na^+/Ca^{2+} exchanger NCLX (27). The increase in mtROS induces mitochondrial autophagy, which is related to the mTOR/AKT/HIF1α signalling axis (28), further improving the oxygen tolerance of cancer cells (29). Ferredoxin 1 (FDX1) and protein acylation are key regulators of cuproptosis. Tumour hypoxia significantly downregulates the expression of FDX1 in cells, thereby significantly inhibiting cuproptosis (30). Tumour cells are highly adaptable in hypoxic microenvironments; have heightened resistance to adverse factors such as ferroptosis and cuproptosis; and promote proliferation, oxygen resistance and invasion by inducing macrophages to polarize to M2 (protumour type), increasing NET release, and activating mitochondrial autophagy (Fig. 1).

To date, the intrinsic network between ferroptosis and other tumour-related mechanisms has not been fully characterized. Therefore, the latest research progress on the crosstalk between ferroptosis and macrophage polarization, NETs, mitochondrial autophagy and cuproptosis is reviewed. The role of ferroptosis in female cancers has gradually emerged in recent years. In the present review, research advances in the field of ferroptosis in gynaecological malignancies and the implications for gynaecological cancer therapy are discussed.

2. Overview of ferroptosis

Ferroptosis is a special type of regulated cell death characterized by intracellular iron overload, with excessive accumulation of lipid peroxides on the cell membrane damaging membrane integrity. It occurs when the ferroptosis defence mechanism is out of balance (Fig. 2). Thus, lipid peroxidation, iron metabolism and the anti-ferroptosis system constitute the cornerstones of ferroptosis; conversely, ferroptosis can be induced or inhibited by genetic or pharmacological intervention in these three aspects.

Lipid peroxidation. Polyunsaturated fatty acids (PUFAs), which are produced from food, acetyl-CoA carboxylase (ACC), or lipid phagocytes, are indispensable substrates for lipid peroxidation under iron overload conditions. They bind with specific membrane phospholipids (PLs) to form PUFA-PLs (12). Acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysolipid phosphatidylcholine acyltransferase 3 (LPCAT3) are crucial drivers of ferroptosis (31,32). ACSL4 attaches long-chain PUFAs to CoA, catalysing the conversion of free PUFAs to acyl-CoA derivatives (PUFA-CoAs) (33). The latter are further incorporated into membrane phospholipids by LPCAT3 and possibly other enzymes, such as AGPAT3, increasing the amount of long-chain PUFAs in cellular lipids and membranes. Lipid peroxides interact with Fe^{2+} to produce peroxide radicals, which extract hydrogen from adjacent acyl chains in the lipid membrane, propagating the lipid peroxidation process. This process is mediated by lipoxygenases (ALOXs) or cytochrome P450 oxidoreductases (34). The products of lipid peroxidation include initial lipid hydroperoxides (LOOHs) and subsequent reactive aldehydes such as malondialdehyde (MDA). The accumulation of lipid peroxides leads to membrane damage and instability, eventually resulting in cell death.

Iron accumulation. Iron metabolism is a static and dynamic regulatory process involving the absorption, storage, utilization and excretion of iron and the participation of numerous proteins and molecules. Iron absorption occurs mainly in the duodenum and upper jejunum, and dietary iron is absorbed in the form of Fe^{2+}. Non-haem iron in food is mainly in the form of insoluble Fe^{3+}, which binds to transferrin (TF) in serum and is subsequently recognized by the TF receptor (TFRC) on cell membranes (35). TF carrying Fe^{3+} binds to TFR1 to form a complex that is internalized into the endosome. In endosomes, prostate epithelial antigen 3 reduces Fe^{3+} to Fe^{2+}, which is then transported by ZIP8/14 (zinc transporter 8/14) or divalent metal transporter 1 (DMT1), thus promoting the formation of labile iron pools (LIP) (36). In addition to extracellular iron

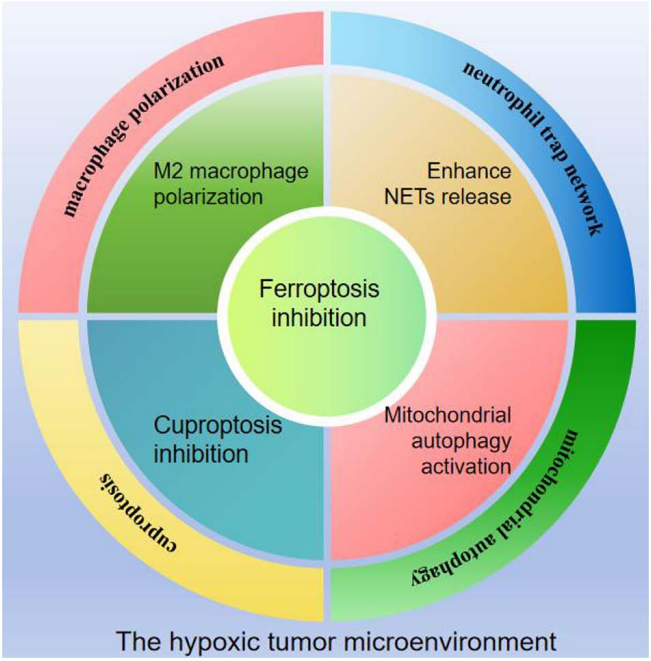

Figure 1. Adaptive regulation of tumor cells in the hypoxic tumor microenvironment.

transport, LIP expansion can be facilitated by haem degradation and ferritinophagy mediated by NCOA4 (37), which can be excreted from cells via the lysosome DMT1 (38). The iron in a cell's LIP can be used in the mitochondria, sequenced in ferritin, or excreted from the cell via ferritransporter (FPN). Iron plays a key role in the induction and propagation of lipid peroxidation, possibly by increasing the activity of ALOX or EGLN prolyl hydroxylase and promoting free radical production, which leads to lipid peroxidation and cell membrane damage, causing an imbalance of enzyme-regulated lipid peroxidation and oxygen homeostasis. In iron-overloaded cells, iron is released from these compartments and increases the intracytoplasmic iron concentration (39), thus promoting the Fenton reaction and enhancing cell ROS production.

Core pathway of anti-ferroptosis effects. The glutathione peroxidase 4 (GPX4)-glutathione (GSH) axis represents a pivotal pathway in countering ferroptosis. GPX4 effectively combats lipid peroxidation by utilizing GSH as a reducing agent. The synthesis of GSH relies on cystine, whose uptake is mediated by the cystine reverse transport system Xc-. This system comprises solute carrier family 7 member 11 (SLC7A11) and solute carrier family 7 member 11 (SLC3A2). The proteins encoded by the SLC7A11 and SLC3A2 genes form a transmembrane transporter that is responsible for importing cystine into cells, where it is then used to synthesize GSH. With GSH as a cofactor, GPX4 reduces LOOHs to lipid alcohols, protecting cells from the threat of ferroptosis. Additionally, nicotinamide adenine dinucleotide phosphate (NADPH) plays a vital role in the GPX4-GSH axis (11). As an electron donor, NADPH participates in the recycling of GSH, enabling it to continuously exert its antioxidant effects. Any disturbance to the GPX4-GSH axis may trigger excessive generation of ROS, leading to the occurrence of lipid peroxidation. These disturbances include the degradation of GPX4 through autophagy or the ubiquitin-proteasome system (40); the inhibition of system Xc- by drugs such as erastin and sorafenib; the direct inhibition of GPX4 by drugs such as RAS-synthetic lethal 3 (RSL3) and the nitro-isoxazole-containing compound (ML210); or defects in GSH, cysteine, or NADPH (41). Previously, scientists discovered a ferroptosis inhibition mechanism that is independent of the GPX4 antioxidant pathway (42). The FSP1-CoQ10-NAD(P)H system, which acts in parallel and independently, synergizes with GPX4 and glutathione to inhibit phospholipid peroxidation and ferroptosis. As a powerful ferroptosis inhibitor, FSP1 (ferroptosis suppressor protein 1) (43) exerts antioxidant effects via coenzyme Q10 (CoQ10) with NADPH to regenerate reduced CoQ10 (CoQ10H2). In the mitochondrial lipid protection system, dihydrolactate dehydrogenase (DHODH), an enzyme located on the outer surface of the inner mitochondrial membrane, is essential. It oxidizes dihydrolactate (DHO) to lactate (OA) in the inner mitochondrial membrane and simultaneously reduces CoQ to CoQH2 (44,45). Therefore, DHODH/CoQ can protect mitochondria from oxidative damage (46). Furthermore, GTP cyclohydrolase 1 plays a significant role in this antioxidant system. It produces tetrahydrobiopterin (BH4), which can capture lipid-derived peroxyl radicals and reduce oxidized lipids. Simultaneously, BH4 contributes to the production of CoQ10H2, further enhancing the resistance of cells to oxidative stress and ferroptosis (47). In summary, the combined dysregulation of iron metabolism and the redox system leads to the accumulation of LOOHs in cells, ultimately triggering ferroptosis. The GPX4-GSH axis and other related mechanisms play crucial roles in this life-and-death struggle, jointly maintaining cellular homeostasis and survival.

Inducers and inhibitors of ferroptosis. Ferroptosis is a regulated mode of cell death that can be induced or inhibited by targeting iron metabolism, lipid metabolism and the antioxidant system (GSH/GPX4 axis, CoQ/FSP1) (11,48-50). Erastin induces cell death in an iron-dependent manner. It targets voltage-dependent anion channels (VDACs) and binds to VDAC2, inducing lipid ROS production and mitochondrial dysfunction (48). RSL5 (49), which binds to VDAC3, acts similarly on VDACs. Additionally, diisothiocyanatostilbene-2',2-disulfonic acid (DIDS) (50) can block VDACs and inhibit DNA damage repair, thereby inducing ferroptosis. Temozolomide (TMZ) can disrupt intracellular iron levels and iron homeostasis by enhancing DMT1 (51), thereby inducing ferroptosis (52). MMRi62, a small-molecule quinolinol, induces the degradation of the ferritin heavy chain, disrupting intracellular iron homeostasis and leading to the accumulation of iron ions within cells and an increase in ROS, which ultimately induces ferroptosis (53). Ferroptosis is closely related to lipid metabolism, and disrupting lipid metabolism can also regulate ferroptosis. Sorafenib (54) is an antitumour drug, and the expression level of ACSL4 is associated with cellular sensitivity to sorafenib. The addition of sorafenib directly affects the metabolic pathway of lipid ROS generation in cells, leading to oxidative stress and DNA damage, which ultimately induces ferroptosis. The small-molecule compound tert-butyl hydroperoxide (55) can

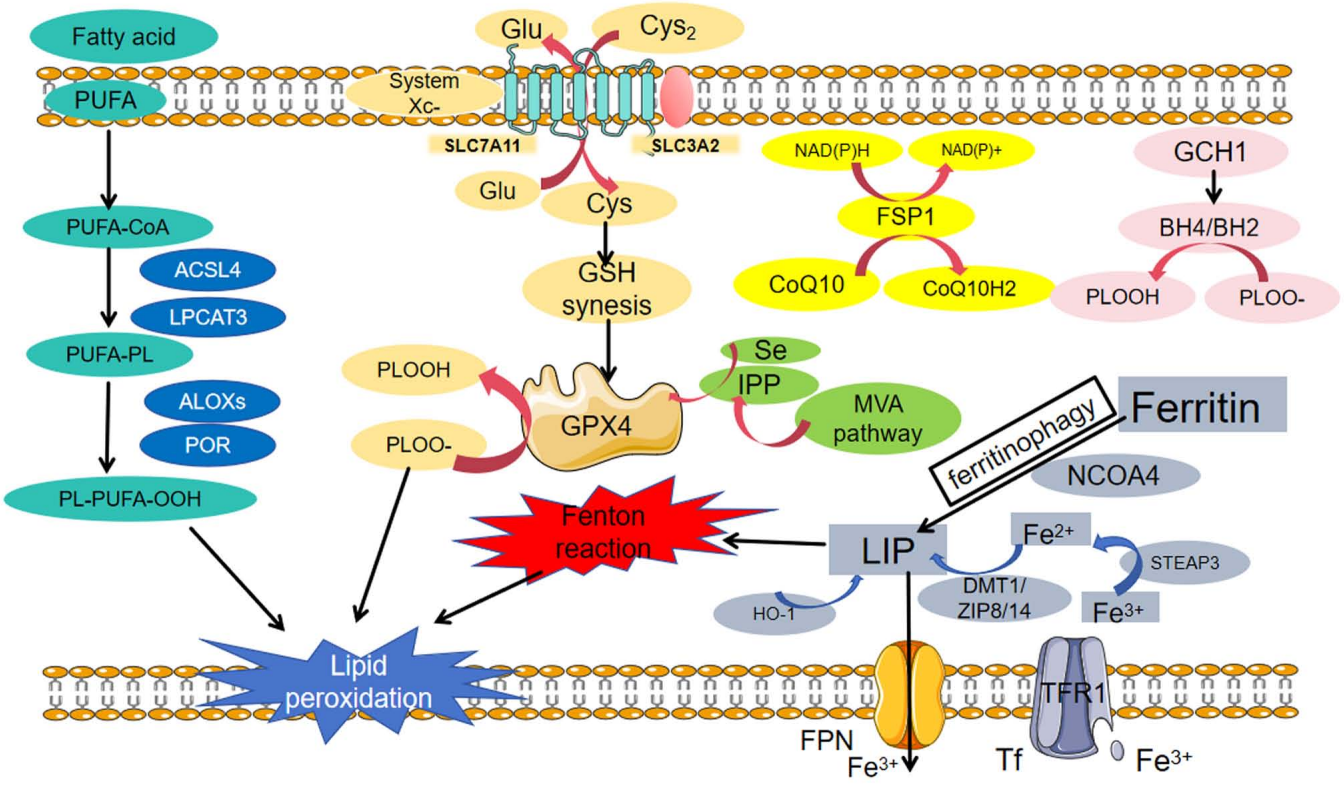

Figure 2. Molecular mechanism of ferroptosis. The figure shows the three core mechanisms of ferroptosis: i) Metabolic generation of PUFA-PLs as substrates for phospholipid peroxidation: Fat phagocytosis-mediated fatty acid release induces the accumulation of free fatty acids in cells, and ACSL4 and LPCAT3 promote the incorporation of PUFAs into PLs to form PUFA-PLs, which are susceptible to free radical-induced oxidation mediated by LOX or cytochrome. ii) Iron metabolism processes lead to the initiation and propagation of phospholipid peroxidation: multiple proteins, including serum transferrin, transferrin receptor, solute carrier family 40 member 1 and ferritin. iii) Monitoring mechanisms that can control phospholipid peroxidation: the cystine-glutamate transporter (also known as system xc^-) transports glutamate into cells, and cystine (Cys2) can be oxidized to cysteine (Cys) for the synthesis of GSH. GSH acts as a reducing cofactor, and GPX4 can reduce lipid hydroperoxides to lipid alcohols. The GSH-GPX4 antioxidant system plays an important role in protecting cells from ferroptosis. The FSP1-CoQ10-NAD(P)H and GCH1-BH4 systems can also inhibit ferroptosis. PUFA-PLs, polyunsaturated fatty acid-containing phospholipids; ACSL4, Acyl-CoA synthetase long-chain family member 4; LPCAT3, lysolipid phosphatidylcholine acyltransferase 3; LOX, lipoxygenase; GSH, glutathione; GPX4, glutathione peroxidase 4.

directly affect lipid ROS levels, causing abnormalities in the mitochondrial membrane potential and inducing ferroptosis. By targeting the GSH-GPX4 axis, multiple steps can be regulated. RSL3, ML162, diphenyleneiodonium (DPI) and ferroptosis-inducing 56 (FIN56) can induce ferroptosis by promoting the degradation of GPX4 (56,57). In addition to blocking VDAC, erastin depletes GSH to further weaken the antioxidant capacity of cells, simultaneously inducing GPX4 degradation, exacerbating lipid peroxidation, and inducing ferroptosis (58). By targeting the FSP1/CoQ-related pathway, NDP4928 binds and inhibits FSP1, enhancing the GSH-induced suppression of ferroptosis (59). FIN56 inhibits farnesyl diphosphate farnesyltransferase (SQS), reduces cholesterol synthesis, depletes CoQ, degrades GPX4, causes mitochondrial dysfunction, and promotes the induction of ferroptosis. Different compounds target different steps of the GSH-GPX4 axis, including promoting GPX4 degradation, depleting GSH, and inhibiting FSP1 and SQS, to induce ferroptosis through multiple mechanisms. The emergence of ferroptosis inhibitors has also advanced research on the regulation of ferroptosis. For example, cyclopyrrolone (11), deferoxamine, deferiprone and deferasirox (60) inhibit ferroptosis by chelating iron ions, whereas ferrostatin-1 (Fer-1) inhibits lipid peroxidation induced by aromatic amines. microRNA-522 inhibits ferroptosis by targeting arachidonate ALOX15 (61). β-ME helps to produce cystine, increases GPX4 expression, and inhibits ferroptosis by reacting with cystine to form mixed disulphide bonds (62). 2-Cyano-3,12-dioxooleana-1,9 (11)-dien-28-oic acid inhibits the function of heat shock protein (HSP) 90, thereby inhibiting the degradation of GPX4 and protecting cells from ferroptosis (58). These findings provide new strategies and ideas for cancer treatment, and they offer important clues for elucidating the regulatory network of ferroptosis and developing new anticancer strategies.

3. Ferroptosis and macrophage polarization

Macrophages can adopt distinct phenotypes (63), becoming M1 and M2 macrophages, in response to environmental stimuli in the TME (64). M1 macrophages typically suppress tumour growth by promoting inflammation and antibacterial activity. To promote antitumour immune responses, they can secrete proinflammatory cytokines such as IL-12 and TNF-α, attracting $CD8^+$ T cells as well as NK cells (65). M2 macrophages promote angiogenesis and produce growth factors such as TGF-β, which facilitate tumour cell proliferation and survival (66,67). Iron is an essential trace element for cellular

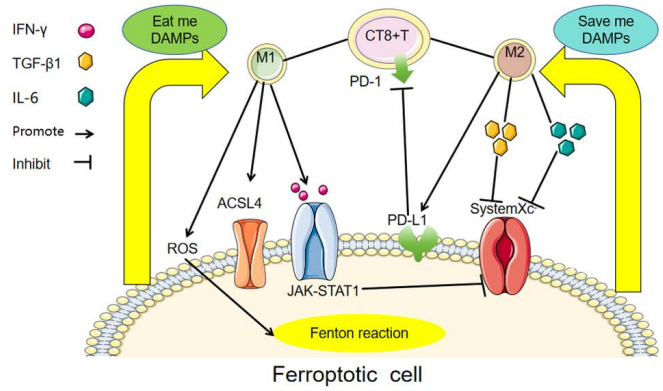

Figure 3. Interaction of TAMs with ferroptosis. Ferroptosis can induce polarization of TAMs, and TAMs exert a dual effect on ferroptosis. 1-stearoyl-2-15-HpETE-sn-glycero-3-phosphatidylethanolamine and HMGB1 are recognized by the corresponding pattern recognition receptors (Toll-like receptor 2 and HMGB1) and promote M1 polarization. Kirsten rat sarcoma 12D and 8-hydroxy-2'-deoxyguanosine mediate M2 polarization. M1-like TAMs can either downregulate the endogenous anti-ferroptosis system through the activation of $CD8^+$ CTLs, release proinflammatory cytokines to downregulate the expression of solute carrier family 3, member 2 and solute carrier family 7, member 11, or provide peroxides that lead to excessive production of ROS to accelerate the Fenton reaction. M2-like TAMs can indirectly inhibit ferroptosis by inactivating CTLs or upregulating oncogenic PD-L1 expression. TAMS, tumor-associated macrophages; HMGB1, high mobility group box 1; CTLs, cytotoxic T lymphocytes; ROS, reactive oxygen species; PD-L1, programmed cell death 1 ligand 1; ACSL4, Acyl-CoA synthetase long-chain family member 4; DAMPs, damage-associated molecular patterns.

proliferation and division and participates in various biological processes, including DNA synthesis and energy metabolism. Iron metabolism plays a crucial role in macrophage polarization and is linked to immunogenic cell death in tumour cells, thus potentially influencing the M1/M2 macrophage balance and consequently tumour growth and progression (68-70). M1 macrophages typically exhibit high levels of iron storage and low levels of iron release (71), whereas M2 macrophages display the opposite pattern. The activation of ferroptosis in the TME can contribute to the depletion of M2 macrophages (72) and facilitate the repolarization of M2 macrophages towards the M1 phenotype (68-70), which is associated with reduced tumour progression and metastasis (70,73). Crosstalk occurs between ferroptosis, the TME and macrophage polarization (Fig. 3). M1 macrophages can directly release peroxides, such as hydrogen peroxide (H_2O_2) (74), or they can release interferon gamma (IFNγ) and thereby downregulate the expression of glutamate-cystine antiporters via the JAK/STAT1 signalling pathway. Furthermore, M1 macrophages can activate ACSL4 to increase lipid peroxidation sensitivity (75), thereby facilitating ferroptosis in tumour cells (76). On the other hand, M2 macrophages participate in immune regulation through distinct mechanisms. They increase the expression of PD-L1 on tumour cells (77), and PD-L1 then binds to PD-1 on T cells, initiating programmed cell death in CTLs and thus increasing resistance to tumour ferroptosis (78). Additionally, M2 macrophages can activate the ERK signalling pathway by releasing IL-6, inhibiting the expression of system Xc- (79), which further modulates iron metabolism and immune responses in the TME. Similarly, NADPH oxidase 4 can be activated by TGF-β1 (80), which promotes the generation of ROS. In HeLa cells treated with IL-6 (81), the increase in phosphorylated ERK further corroborates this finding. Chen *et al* (82) reported that ACSL4 promotes the polarization of M2 macrophages towards the M1 phenotype, consequently reducing cell proliferation and invasion and inducing ferroptosis in nasopharyngeal carcinoma cells. Gu *et al* (68) utilized MIL88B nanoparticles containing RSL3 to activate ferroptosis in M2-polarized macrophages, resulting in a shift in cellular metabolic patterns and the repolarization of M2 cells towards the M1 phenotype. This process involves the inhibition of GPX4 expression and the promotion of lipid peroxidation. Notably, cancer cells may target ferroptosis in macrophages, thereby weakening their anticancer effects and causing immune resistance (83). Macrophage-associated exosomes in the TME inhibit ferroptosis in macrophages during lung metastasis, thereby promoting disease dissemination (73). Ferroptotic cell products can be divided into two categories of damage-associated molecular patterns (DAMPs), which bind to receptors on immune cells and transmit protective or aggressive signals to the adaptive immune system (84). 'Eat me' DAMPs such as High mobility group Box 1 (85) promote M1 polarization and assist immune clearance, whereas DAMPs such as Kirsten rat sarcoma 12D (86) promote M2 polarization and tumour progression. Therefore, the use of DAMPs to activate positive immune feedback can prevent tumour progression.

4. Ferroptosis and neutrophil trap network

NETs were discovered in 1996 (87). Unlike apoptosis and necrosis, NETs, an intricate meshwork of DNA strands and proteins that constitute a novel extracellular elimination mechanism by which neutrophils capture and destroy microorganisms, usually require the activation of neutrophils as well as the involvement of NADPH oxidases to produce ROS (88,89). NETs have primary tumorigenicity and promote angiogenesis, which mediates cancer proliferation, acts as an adhesion matrix to facilitate metastatic spread (90), and promotes endothelial-to-mesenchymal transition (91). Various cancer types, including breast (92), gastric (93) and colorectal cancer (94,95), are associated with NETs. Yang *et al* (96) reported that the coiled-coil domain containing 25 receptor on BCa cells can bind to NET DNA, serving as a chemoattractant and correlating with liver metastases. Therefore, NETs in patient serum may predict the incidence of early BCa liver metastases. Lee *et al* (97) reported similar findings in ovarian tumours, where inflammatory factors released by tumour cells stimulate neutrophils to become NET-like and capture circulating OC cells to promote tumour metastasis. The interaction between NETs and ferroptosis is closely related to metabolic reprogramming. Enhanced glycolysis is a characteristic of NET-induced proinflammatory and proangiogenic responses (98), which promote inflammation and ROS generation, whereas increased ROS and lipid peroxidation are characteristic of ferroptosis. It has been revealed that ferroptosis is one of the mechanisms of NET-induced sepsis-associated acute lung injury in alveolar epithelial cells (99). This process depends on methyltransferase-like 3-mediated HIF-1α m_6A modification and subsequent mitochondrial metabolic reprogramming, accompanied by increased glycolysis and decreased oxidative phosphorylation.

These metabolic changes promote the accumulation of ROS and the ferroptosis of alveolar epithelial cells. These findings provide a theoretical basis for the role of aerobic glycolysis in NET-induced ferroptosis. In addition, ferroptosis may partially explain the tumour-promoting characteristics of NETs. Necrotic tumour cells are initially immunogenic, but as the hypoxic and hypoglycaemic TME deteriorates, immune surveillance by immune cells decreases (100). Moreover, tumour-associated glycolysis increases, lactate and immunosuppressive metabolites accumulate, and necrotic cells gradually transform into immunosuppressive cells (101). NETs contribute to thrombosis and subsequent vascular occlusion (102), leading to hypoxia and nutrient deprivation in the TME, which further promotes immunosuppression and induces tumour cell resistance to ferroptosis. Merlin is considered a tumour suppressor. A recent study reported that NETs can inhibit Merlin phosphorylation through the TLR9/Merlin axis, leading to increased GPX4 expression, increasing the ferroptosis resistance of triple-negative BCa (TNBC) cells, and promoting the proliferation and invasion of TNBC cells (103). These findings indicate that blocking the key regulatory factors of NETs is beneficial for the treatment of TNBC.

5. Ferroptosis and mitochondrial autophagy

Mitochondrial autophagy refers to the selective removal of damaged or incomplete mitochondria through autophagy, which serves as a 'scavenger' for maintaining mitochondrial network homeostasis and functional integrity. Mitochondrial autophagy is a promising biomarker and potential therapeutic target (104) because its abnormal activity is associated with the growth and metastasis of cancers, particularly OC (105). In response to a certain level of oxidative stress, mitochondria can temporarily protect cells by promoting mitochondrial fusion (106), mitigating oxidative stress, inhibiting ferroptosis and maintaining their own stability (107). However, when damage exceeds the threshold for mitochondrial fusion, mitochondrial autophagy is activated (108), which helps maintain mitochondrial stability by reducing the accumulation of ROS, preserving iron homeostasis, activating cellular antioxidant systems, and enhancing cellular resistance to oxidative stress (109). Nevertheless, excessive activation of mitochondrial autophagy can have negative consequences. Sustained activation of mitochondrial autophagy can lead to the release of metal ions such as iron from mitochondria into the cytoplasm, providing an unstable iron source. Iron reacts with H_2O_2 in the subsequent Fenton reaction, generating large amounts of hydroxyl radicals (·OH), which are highly reactive oxidants that can initiate lipid peroxidation, damage cell membrane structures, impair functions, and promote ferroptosis (110). During tumour development, mitochondrial autophagy plays a dual role. On the one hand, it can eliminate dysfunctional mitochondria, alleviate oxidative stress, and prevent carcinogenesis (109). On the other hand, under adverse conditions (such as nutrient deprivation and hypoxia), mitochondrial autophagy can promote tumour cell survival and protect cells from apoptosis or necrosis. Therefore, mitochondrial autophagy is a crucial factor in controlling cancer cell quality.

6. Interaction between ferroptosis and cuproptosis

The concentration of copper is closely related to cellular activities such as cell proliferation and angiogenesis, as well as metabolic processes such as glycolysis and lipid transformation (111,112). Rapid cancer cell division and immune infiltration are inseparable from copper levels, and increased copper concentrations can be observed in various malignant tumours, including breast, gynaecological, lung, pancreatic, and gastric cancer (113-115). In 2022, Peter Tsvetkov first proposed the concept of 'cuproptosis', a type of regulated cell death that differs from apoptosis and follows ferroptosis. The process of cuproptosis involves the accumulation of copper-dependent fatty acid-acylated proteins and the reduction of Fe-S cluster proteins (116) (Fig. 4). Copper ions in the extracellular environment can be transported into cells by binding to copper ionophores such as elesclomol. The upstream regulator of protein acylation, FDX1/lipoyl synthase, is responsible for reducing Cu(II) to Cu(I) (117), which subsequently binds to lipoylated proteins within the tricarboxylic acid cycle (TCA) cycle in mitochondria, such as dihydrolipoamide S-acetyltransferase (118,119). During this process, lipoylated proteins accumulate, leading to increased ROS generation. Additionally, the stability of Fe-S clusters is disruptive, and the resulting protein toxicity stress serves as a trigger for cell death. This process can be reversed by copper chelators such as tetrathiomolybdate (120). Ferroptosis and cuproptosis involve similar regulatory processes, such as alterations in metal valence states, metabolism of macronutrients, and energy conversion, all of which affect cancer signalling pathways (121). There are also interactions between ferroptosis and cuproptosis. First, there are overlapping molecular components between these two modes of cell death. In a study investigating the pathogenesis of osteoarthritis, He *et al* (122) reported that 63 ferroptosis-related genes were closely related to 11 cuproptosis-related genes, and among these, they identified 40 novel characteristic genes associated primarily with inflammation, extracellular stimuli and autophagy. Luo *et al* (123) reported six ferroptosis genes (including TRIB3, PML and CD44) to be related to cuproptosis and were negatively correlated with survival rates. Second, copper can increase the ubiquitination and aggregation of GPX4, promoting its degradation and initiating ferroptosis. Copper chelators can specifically inhibit ferroptosis but have no effect on other forms of cell death, such as necrosis or apoptosis (124). Third, both forms of cell death can be triggered by the same stimuli, such as P53 activation and excessive ROS production (125,126). Finally, the progression of a single disease can involve both forms of cell death. In clear-cell renal cell carcinoma (ccRCC), the downregulation of FDX1, a key factor in cuproptosis, has been linked to tumorigenesis (123). The overexpression of Kruppel-like factor 2 downregulates GPX4 (127), increasing the sensitivity of ccRCC to ferroptosis and thereby hindering its growth and invasion (128).

7. Association of ferroptosis with gynaecological malignancies

Ferroptosis has dual effects on tumours. Resistance to ferroptosis is the nature of tumors. Inhibiting ferroptosis can promote cancer progression, whereas inducing ferroptosis has promising applications in tumour treatment.

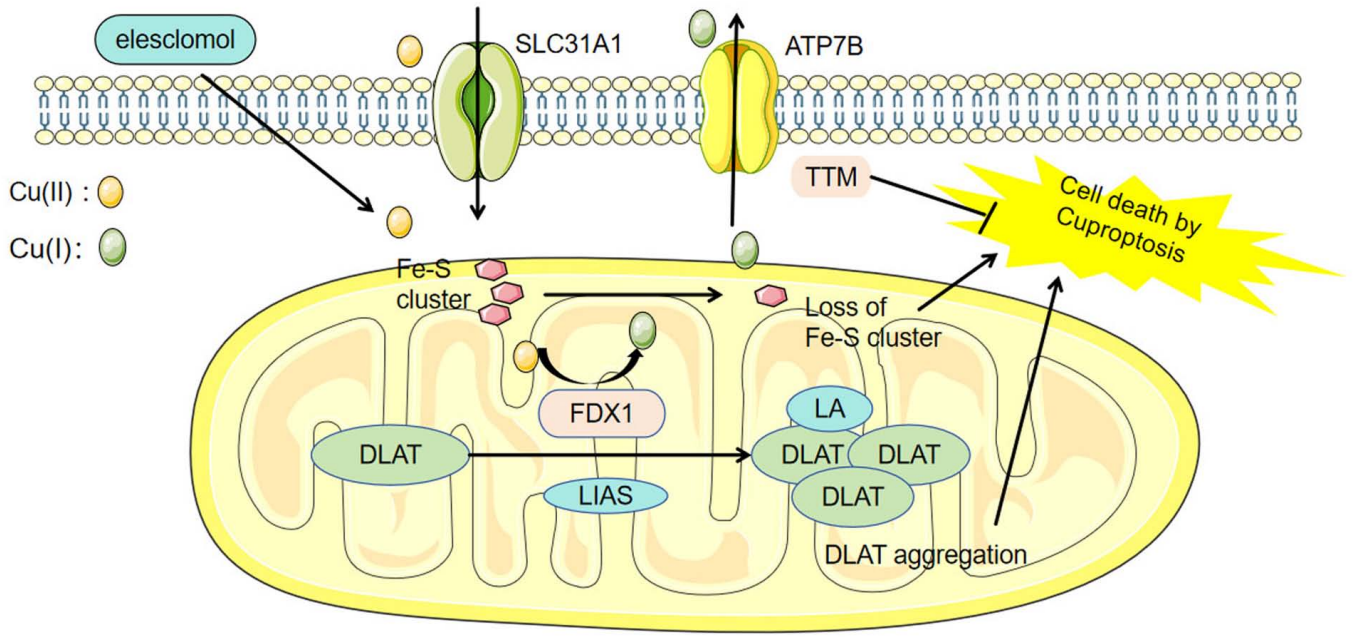

Figure 4. Mechanism of cuproptosis. Cellular Cu can bind to Cu ion carriers (such as elesclomol) and transport them into the cell. Excess intracellular Cu(II) can be transported to the mitochondria. FDX1/LIAS is an upstream regulator of protein fatty acid acylation. The mitochondrial enzyme ferredoxin 1 (FDX1) reduces Cu(II) to Cu(I), which leads to increased ROS levels. Increased Cu(I) directly binds to lipoylated proteins (such as DLAT) in the tricarboxylic acid cycle, leading to abnormal aggregation of lipoylated proteins and instability of Fe-S cluster proteins, causing in turn proteotoxic stress and, ultimately, cell death. Cu chelators (such as TTM) can inhibit cuproptosis. DLAT, dihydrolipoamide S-acetyltransferase; FDX1, ferredoxin-1; Fe-S iron-sulfur; LIAS, lipoate synthase; TTM, tetrathiomolybdate.

Ferroptosis can increase the sensitivity of tumour cells to traditional antitumour therapies such as chemotherapy and radiotherapy, providing a new strategy for targeting cancer cells that are difficult to eliminate with traditional treatments.

BCa. BCa is the most common malignant tumour in women, and non-surgical treatments for this disease include chemotherapy, human epidermal growth factor receptor 2-targeted therapy and endocrine therapy (129). Ferroptosis is involved in the drug resistance (130) and prognosis (131) of BCa. Zou *et al* (132) reported that VDAC3-derived crRNA binds to HSPB1 and inhibits its ubiquitination degradation, reducing the accumulation of ROS and LIP and thereby inhibiting ferroptosis in BCa cells with low levels of HER2, which in turn mediates trastuzumab deruxtecan resistance. Breast tissue has vigorous fatty acid metabolism, the expression of IL-6 and leptin is significantly increased in cancer-associated adipocytes, and these two substances are key factors in promoting tumour growth (133-135). Studies have shown that disrupting lipid metabolism reprogramming in BCa cells through ferroptosis can inhibit tumour activity and prevent tumour metastasis (136). Ferroptosis interferes with fatty acid metabolism by causing the oxidation of PUFAs to increase the production of $PLOO^{\cdot}$. This process damages the metabolism of cancer cells and thus promotes cancer cell death. Bobińskir *et al* (137) proposed that inducing ferroptosis causes an unbalanced fatty acid ratio in cancer cells, limiting the consumption and biosynthesis of BCa-related fatty acids and consequently leading to fatty acid deficiency and inhibiting tumour progression. In addition to interfering with fat metabolism, ferroptosis can reverse resistance to endocrine therapy in BCa. Tamoxifen (TAM) is a long-term endocrine drug for patients with oestrogen receptor $(ER)^{+}$ BCa (138). Unfortunately, TAM cannot escape the development of chemoresistance (139). shown It has been reported that ferroptosis and the non-canonical NF-κB pathway activated by RelB are involved in BCa-TAM resistance: Activated RelB inhibits TAM-induced ferroptosis by upregulating GPX4, thereby promoting TAM resistance (140). By contrast, sustained inhibition of RelB transcriptional activation re-sensitizes TAM-resistant cells by increasing ferroptosis. The development of drugs related to RelB inhibitors is expected to promote the reversal of BCa resistance. The overexpression of DNAJC12, a member of the HSP family (HSP40), is a negative predictor of the response to neoadjuvant concurrent chemoradiotherapy (141). It has been revealed that overexpression of DNAJC12 inhibits ferroptosis and apoptosis through the HSP70-AKT signalling axis, thereby promoting BC resistance to chemotherapy and azithromycin. Studies have also shown that AKT or HSP70 inhibitors can reverse this process by repairing broken caspase3 and reducing GPX4 and SLC7A11 levels, providing new treatments for BCa chemotherapy resistance (142). TNBC, characterized by the absence of ER, progesterone receptor (PR) and HER2 (143), is the subtype of BCa that is the most difficult to treat (144). TNBC is rich in iron and lipids, making the induction of ferroptosis a viable therapeutic strategy (31,145). Yu *et al* (146) reported that TFRC is highly expressed in ER^{+} tissues and that reduced ER expression can increase TFRC expression, suggesting that ER plays a regulatory role in TFRC expression. Timmerman *et al* (147) reported that TNBC cells rely on glutamine and that reducing intracellular glutamine or inhibiting system Xc-can increase ROS in TNBC, inhibiting tumour progression.

Cervical cancer. The incidence rate of cervical cancer among young women has been increasing, which is a cause of serious concern. The annual mortality rate of cervical cancer exceeds 300,000, making it one of the cancers with the highest mortality rate among women worldwide, along with BCa, colorectal and lung cancer (3). Research has revealed the involvement of ferroptosis in the transformation of normal cervical cells into squamous intraepithelial lesion (SIL), the progression of SIL, and its transformation into cervical squamous cell carcinoma (148). Cervical cancer cells can inhibit ferroptosis through circular RNAs (149,150), hypoxia (151) and the proliferation of M1 macrophages (152), enabling them to survive and proliferate under ferroptotic stress (153). Inducing ferroptosis by targeting the characteristics of cervical cancer that resist ferroptosis provides a new prospective therapeutic approach. Oleanolic acid (OA) is a natural anticancer agent (154). It has been identified that OA targets and promotes ACSL4-mediated ferroptosis, which promotes the biosynthesis of PUFA-PLs and increases lipid peroxidation, thereby inhibiting the proliferation of cervical cancer cells (155). Dihydroartemisinin (DHA) is the main active metabolite of artemisinin and its derivatives and has a variety of low-toxicity anticancer properties. DHA can induce NCOA4-mediated ferritin autophagy, thereby leading to an increase in the intracellular LIP, aggravating the Fenton reaction to produce excessive ROS, and consequently enhancing ferroptosis in cervical cancer. The combination of DHA and doxorubicin has a highly synergistic elimination effect on cervical cancer cells, which is also related to ferroptosis (156). In addition to chemotherapy, ferroptosis induction combined with radiotherapy has unexpected effects. Radiotherapy can not only activate NRF2-mediated GPX4 transcription but also inhibit lysosome-mediated GPX4 degradation, thereby inducing cancer cell tolerance to ferroptosis and radioresistance. Tubastatin A, a histone deacetylase 6 inhibitor, significantly promotes radiotherapy-induced lipid peroxidation and tumour suppression by inhibiting GPX4 enzyme activity, overcoming the ferroptosis resistance and radioresistance of cancer cells (157). Various ferroptosis inducers, such as sorafenib and sulfaquinoxaline, can act as radiosensitizers by inhibiting the activity of SLC7A11 and GPX4. Combining radiotherapy with ferroptosis inducers is expected to overcome radiotherapy resistance in patients with cervical cancer (158).

OC. In total, ~70% of patients are already in the advanced stage at the time of their first diagnosis of OC (159). Multiple mechanisms, including glycolysis, fatty acid synthesis and angiogenesis mimicry, collectively contribute to the development of OC (160-162). Platinum drugs combined with paclitaxel are the traditional first-line treatment options for OC, but chemotherapy resistance and high recurrence rates often occur during treatment (163,164). Studies have shown that both cisplatin and paclitaxel can act on the GPX4-GSH axis. The former forms a complex with glutathione (165), and the latter downregulates the expression of system Xc-. Both can reduce GSH levels, increase oxidative stress and lipid peroxidation, and effectively induce ferroptosis (166). The characteristics of platinum-resistant cancer cells may confer therapeutic benefits. Wang *et al* (167) reported that overexpression of the Wnt receptor frzzled-7 (FZD7) activates the oncogenic factor TP63, upregulates the glutathione metabolic pathway, increases GPX expression, and protects cancer cells from chemotherapy-induced peroxidative damage. After treatment with GPX4 inhibitors, $FZD7^+$ platinum-resistant OC cells become more sensitive to platinum drugs, filling the therapeutic gap in treating platinum-resistant cancers (168). Curcumin sensitizes cisplatin-resistant OC cells to cisplatin-induced apoptosis. However, its low bioavailability limits its application. The development of the curcumin derivative NLO1 has greatly improved the antitumour effects of curcumin. Ferroptosis is involved in this process (169). NLO1 can downregulate HCAR1/MCT1 expression, activate the AMPK-SREBP1 pathway, downregulate GPX4 expression, induce ferroptosis in the Anglne and HO8910PM OC cell lines, and inhibit OC proliferation. Erastin induces lipid ROS production and mitochondrial dysfunction, consumes GSH, weakens the antioxidant capacity of cells, and triggers ferroptosis. It has a synergistic effect with cisplatin in inducing ferroptosis to inhibit the growth of OC cells *in vitro* and *in vivo*, thereby increasing the cytotoxic effect of cisplatin while reducing side effects (170). In addition, it has been revealed that combined treatment with cisplatin and natural antitumour compounds isolated from the roots of *Lithospermum officinale* can increase the levels of the ferroptosis-related molecular markers ROS, LPO and Fe^{2+}, downregulate GPX4, induce ferroptosis, and synergistically reduce the viability of cisplatin-resistant OC cells (171). PARP is an important target for cancer treatment and is involved in DNA repair, methylation, transcriptional regulation and transcriptional metabolism (172,173). The pharmacological inhibition or genetic deletion of PARP promotes ferroptosis by inhibiting SLC7A11-mediated GSH biosynthesis in a p53-dependent manner. Olaparib is the most classic and effective PARP inhibitor (174,175). It is used in combination with a ferroptosis inducer (FIN) to sensitize BRCA-mutated OC cells to PARP inhibitors (176). Arsenic trioxide is used in combination with olaparib to activate the AMPKα pathway, inhibit SCD1 expression, promote lipid peroxidation, and ultimately induce ferroptosis, increasing the effect of olaparib on platinum-resistant OC (177). Targeted therapy against ferroptosis is expected to open new avenues for the treatment of platinum-resistant OC.

Carcinoma of the endometrium. Endometrial cancer (EC) is a type of cancer that arises from the malignant transformation of endometrial epithelial cells (178). Metabolic reprogramming is involved in the development of EC. Studies have shown that EC is dependent on glucose and glutamine and overexpresses SLC7A11 (179,180), which not only affects cellular antioxidant defence (181) but also influences the induction of ferroptosis in tumour cells. EC cells rely on glycolysis-lipogenesis metabolism (182). A high glycolytic rate inhibits the TCA cycle, reducing the production of NADH and ROS. Conversely, inhibiting glycolysis in ECs promotes the TCA cycle and oxidative phosphorylation, thereby inducing ferroptosis and inhibiting tumour progression (183). Glucose oxidase nanoparticles have been utilized to target tumour cells (184), where they catalyse glucose decomposition and increase H_2O_2 concentrations, thereby reducing glucose levels and increasing ROS in tumours (185). The glutamine dependency of EC can be exploited by upregulating the glutamine transporter ASCT2 in

Table I. Inducers and inhibitors of ferroptosis.

First author/s, year		Name	Mechanism	Targets	Ref.
Yagoda *et al*, 2007; Yang *et al*, 2008; Tomaskova *et al*, 2007; Song *et al*, 2021; Li *et al*, 2022	Ferroptosis inducers	Erastin, RSL5, DIDS, temozolomide, MMRi62	Target iron metabolism	VDACs, DMT1, Ferritin	(48-50, 52, 53)
Feng *et al*, 2021; Wenz *et al*, 2018		Sorafenib, tert-butyl hydroperoxide	Target lipid metabolism	ACSL4, Cardiolipins	(54,55)
Yang *et al*, 2014; Liu *et al*, 2018; Dixon *et al*, 2014		RSL3, ML162, DPI7, DPI10, FIN56, Sorafenib, Erastin	Target GSH/GPX4 axis	GPX4	(56,195,196)
Yoshioka *et al*, 2022; Liang *et al*, 2019; Yang *et al*, 2022		NDP4928, FIN56, Statins	Target CoQ/FSP1	FSP1, SQS, HMGCR	(59,197,198)
Radadiya *et al*, 2021; Yao *et al*, 2019; Zheng *et al*, 2021		cyclopyrrolone, deferoxamine, deferiprone, deferasirox	Reduce iron levels	Iron ions	(199-201)
Brown *et al*, 2019	Ferroptosis inhibitors	Ferritin		Prominin2	(202)
Zhang *et al*, 2020		ALOX15		microRNA-522	(61)
Dixon *et al*, 2012		Fer-1	Reduce lipid peroxides	Lipid	(11)
Wu *et al*, 2021		Nuclear enriched transcript 1		ACSL4	(203)
Dixon *et al*, 2012		β-ME	Effects on the GSH/GPX4 axis	Cystine	(11)
Alim *et al*, 2019		Se		TFAP2c, Sp1	(204)

RSL5, RAS synthetic lethal 5; DIDS, 4,4'-diisothiocyanostilbene-2,2'-disulfonic acid; RSL3, RAS-synthetic lethal 3; DPI7, diphenyleneiodonium; FIN56, ferroptosis inducing 56; VDACs, voltage-dependent anion channels; DMT1, divalent metal transporter 1; FSP1, ferroptosis suppressor protein 1; SQS, squalene synthase; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; TFAP2c, transcription factor activating protein 2 gamma; Sp1, specificity protein 1; ACSL4, Acyl-CoA synthetase long-chain family member 4; GSH, glutathione; GPX4, glutathione peroxidase 4.

ECs, which in turn reduces intracellular glutamine levels and inhibits EC cell proliferation (179). Given that SLC7A11 is a critical player in ferroptosis, therapies targeting SLC7A11 can also be applied to EC. The use of ferroptosis inducers (such as sulfasalazine, erastin and RSL3) to treat megestrol acetate (MPA)-resistant EC downregulates SLC7A11 and GPX4, significantly reducing the survival rate of MPA-resistant EC-1 cells (185). In addition, juglone (186) activates ferroptosis in EC cells by upregulating heme oxygenase 1, resulting in the release of free iron from haem in ECs, the production of lipid peroxides, and the reduction of MDA. These results suggest a new therapeutic approach for the treatment of EC.

8. Conclusions and future perspectives

The mechanism of ferroptosis involves iron homeostasis, lipid metabolism and antioxidant systems. Ferroptosis is a programmed cell death process that can be regulated by drugs or genetic means, either inducers or inhibitors. In the TME, tumour cells resist ferroptosis by activating hypoxia-related induction factors to reduce intracellular iron storage or by increasing antioxidant signals (187). In the tumour immune microenvironment, inducing M2 macrophage polarization is beneficial for tumour survival and progression. Ferroptotic cells can release DAMPs to activate the immune system, induce macrophage polarization, and initiate signals related to protection or resistance to ferroptosis. The depletion of M2 tumour-associated macrophages in the TME and M1 repolarization can activate ferroptosis and prevent tumour progression and metastasis (70,72). The polarization state and function of macrophages in the TME are significantly influenced by iron metabolism. Future research needs to further explore the specific mechanisms of iron metabolism in macrophage polarization and tumour immunotherapy and discover how to balance the anticancer and cancer-promoting effects of ferroptosis in macrophages and direct iron regulation in macrophages towards the inhibition of cancer progression to develop more effective therapeutic strategies. Inflammatory factors secreted by tumours can induce the formation of NETs, which protect tumour cells from cytotoxic immunity and impair tumour clearance (188). In BCa (92), they can act as chemokines to mediate the distant

metastasis of tumours and can also promote tumour progression by mediating ferroptosis resistance (103). Interestingly, in non-tumour cells, such as alveolar epithelial cells (189) and intestinal endothelial cells (190), NETs can cause disease phenotypes by inducing ferroptosis. The mechanism by which NETs resist ferroptosis in tumour tissues but induce ferroptosis in non-tumour tissues has not yet been elucidated. Abnormalities in mitochondrial structure and function lead to abnormal levels and distributions of metal ions (191). Mitochondrial autophagy contributes to mitochondrial quality control. The resulting autophagic mitochondria cannot only isolate abnormal mitochondria but also serve as new iron storage space to prevent the generation of ROS by the Fenton reaction from inducing further cell death (110). However, excessive mitochondrial autophagy is a sufficient source of iron for ferroptosis. Cuproptosis is another form of metal ion-dependent cell death that was discovered after ferroptosis and is closely related to multiple signalling pathways and tumour-related biological behaviours (192). The ferroptosis inducers sorafenib and erastin can increase cuproptosis in primary liver cancer, upregulate protein fatty acylation by blocking mitochondrial matrix-associated protease-mediated degradation of the FDX1 protein, and reduce the synthesis of the intracellular copper chelator GSH by inhibiting cystine import (193). Cuproptosis and ferroptosis can be induced by the same stimuli and share interacting molecules and genes, and cuproptosis can promote ferroptosis (194). These findings indicate that ferroptosis is not an independent pathway involved in disease. Ferroptosis combines mechanisms involved in tumour occurrence and development, such as cellular immunity-macrophage polarization, organelle defence-mitochondrial autophagy, the cell clearance-neutrophil capture network, and the interactions of other metal ions with copper. Among these mechanisms, whether ferroptosis is the main trunk or a side branch, has great application prospects in oncology research. Examples of inducers and inhibitors of ferroptosis are included in Table I.

At present, the drug resistance of gynaecological tumours is a worldwide problem that urgently needs to be solved. Ferroptosis has been found to be involved in tumorigenesis, the destruction of the immune microenvironment, tumour proliferation and metastasis, and the treatment of malignant gynaecological tumours. The current therapeutic strategies for inducing ferroptosis in tumour cells include targeting anti-iron oxidation pathways and ferroptosis metabolic pathways. The former weakens the antioxidant capacity of cancer cells mainly by inhibiting the GSH-GPX4 axis and inducing tumour cell death. The latter induces ferroptosis in cancer cells by regulating ferroptosis metabolic systems such as iron metabolism and lipid metabolism. Research on related drugs in female patients is also in full swing. Ferroptosis can supplement the therapeutic mechanisms of existing drugs, such as curcumin derivatives, or it can be combined with existing drugs, such as tamoxifen combined with RELB inhibitors, erastin combined with platinum, and FIN combined with olaparib, to promote the antitumour effect, reverse chemotherapy resistance or reduce adverse drug reactions. In addition, ferroptosis combined with radiotherapy is expected to reverse the radiotherapy resistance of tumour cells. Ferroptosis has the potential to overcome difficulties in the traditional treatment of gynaecological malignancies, inhibit tumour cell proliferation and metastasis, and resolve tumour resistance. However, the existing research on ferroptosis remains experimental, and further research is needed to enable clinical translation.

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Authors' contributions

PTW and YKL structured the ideas for the document and drafted the outline. PTW, JLC and HL were responsible for the writing of the original manuscript and the creation of figures and table. HYL and JZ reviewed and revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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