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Review Article

Advances in ferroptosis research in ovarian cancer: molecular mechanisms and therapeutic perspectives

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Abstract: Ovarian cancer is one of the most aggressive malignancies in the female genital system and presents a poor prognosis. Its high rate of recurrence and emergence of acquired resistance to the current chemotherapeutic approaches significantly restrict its long-term therapeutic efficacy. While treatment strategies including cytoreductive surgery (CRS) plus platinum (Pt)-based chemotherapy and poly(ADP-ribose) polymerase inhibitors (PARP inhibitors) have brought clinical benefits to a proportion of patients, the majority eventually suffer cancer relapse post-treatment. This finding suggests that classical forms of cell death may not fully explain treatment outcomes, survival, and resistance in ovarian cancer. Ferroptosis is a nonapoptotic mode of cell death that results from the iron-dependent and lethal peroxidation of lipids. Its onset and progression are contextually regulated by iron homeostasis, lipid metabolism, and redox balance, and also tightly involved in the tumor metabolic reprogramming and adaptation to the tumor microenvironment (TME). Under therapeutic pressure, ovarian cancer cells may become more susceptible to ferroptosis while simultaneously suppressing ferroptotic cell death through multilayered regulatory systems, including glutathione peroxidase 4 (GPX4) and the cystine/glutamate antiporter system (system Xc^-) antioxidant defenses, acyl-CoA synthetase long-chain family member 4 (ACSL4)-mediated lipid peroxidation (LPO), and nuclear receptor coactivator 4 (NCOA4)-dependent ferritinophagy, in order to survive. This biphasic behaviour is strongly linked to treatment resistance and disease recurrence. In this review, the molecular mechanisms by which ferroptosis operates in ovarian cancer are systematically reviewed, and a profile of regulatory factors - genetic, epigenetic, metabolic, and microenvironmental - is presented. Special attention is given to a summary of current literature on the cross-talk between ferroptosis and the sensitivity of Pt-based chemotherapy and PARP inhibitors, cancer stem cell properties within ovarian cancer, as well as the TME. In addition, the current progress in ferroptosis-inducing strategies, nanodelivery systems, and related biomarkers for precision therapy and therapeutic response prediction is comprehensively discussed.

Keywords: Ovarian cancer, ferroptosis, lipid peroxidation, iron homeostasis, therapeutic resistance, precision therapy

Introduction

Ovarian cancer is one of the deadliest cancers in the female reproductive system [1]. The poor prognosis of ovarian cancer is mainly due to its often late detection, limited early screening options, and the development of resistance to standard therapeutic schemes [2]. Treatment approaches based on CRS combined with platinum-based chemotherapy have evolved over

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time. Moreover, the introduction of targeted agents such as PARP inhibitors has significantly prolonged progression-free survival in ovarian cancer patients, particularly those harboring breast cancer (BRCA) 1/2 mutations or homologous recombination deficiency (HRD) [3]. However, most patients relapse after treatment and subsequently develop increasingly drug-resistant disease, leading to only modest gains in overall survival [4, 5]. An increasing amount of clinical and molecular evidence indicates that resistance to therapy in ovarian cancer is not based on a single oncogenic event. Instead, it probably mirrors an evolutionary process in which tumor cells dynamically adjust their survival tactics by multilevel adaptation to long-term therapeutic pressure and microenvironmental stress. As a result, the traditional view that focuses on classical oncogenic mutations, DNA repair deficiency, or activation of apoptotic machinery is not in itself enough to account for variations in clinical outcome in ovarian cancer [6, 7].

For a long time, programmed cell death has been assumed to be a central biological itinerary limiting tumor growth and guiding therapy responses [8]. Progress in cell biology research has characterized additional forms of cell death beyond traditional pathways, such as autophagic cell death, necroptosis, and inflammation-associated programmed cell death [9]. Ferroptosis is an iron-dependent form of regulated cell death mediated by LPO. Major molecular mediators are GPX4 as a fundamental antioxidant defense enzyme and NCOA4-mediated ferritinophagy to regulate labile Fe^{2+}, which allows the accumulation of lipid reactive oxygen species (ROS) [10]. The molecular events downstream of changes in these components contribute to oxidative stress-induced ferroptotic death, and also determine the fate of tumor cells under therapeutic conditions.

The signaling pathways associated with ferroptosis, especially GPX4 and system Xc^- antioxidant defense, are important for therapeutic response and Pt resistance in ovarian cancer [11]. SLC7A11 upregulation and GPX4-dependent antioxidant defenses confer ferroptosis resistance to drug-resistant and stem cell-like subpopulations, while inhibition of ferritinophagy probably occurs alongside this event, with polyunsaturated fatty acids (PUFA)-enriched apoptotic tumor cells remaining partially sensitive [12-14]. The existence of such phenotypic heterogeneity is mainly regulated by a constantly changing interplay between pro-ferroptosis signals, such as LPO due to the inhibition of SLC7A11, and ferroptosis defensive mechanisms, especially via the SLC7A11-glutathione (GSH)-GPX4 axis that centralizes cellular protection against oxidative injury [15]. Thus, a comprehensive investigation of the molecular mechanisms and regulatory networks underlying ferroptosis in ovarian cancer and its interplay with current treatment regimens should not only contribute to a better comprehension of the biological aspects driving this disease but also establish valuable translational platforms for the identification of novel predictive biomarkers of treatment response and precision-based intervention strategies.

Core mechanisms of ferroptosis and its role in ovarian physiology and pathophysiology

Overview of the canonical ferroptosis pathway: from dysregulated iron metabolism to LPO

Ferroptosis refers to a form of regulated cell death characterized by lethal, iron-dependent, LPO. Ferroptosis resistance in ovarian cancer is closely associated with the maintenance of the GSH-dependent antioxidant system, particularly through glutamate-cysteine ligase catalytic subunit (GCLC)-mediated regulation of GSH synthesis [16]. Unlike classical modalities of cell death such as apoptosis or autophagy, ferroptosis is largely driven by metabolic perturbation and features cellular accumulation of labile Fe^{2+}, continual production of ROS, and cascade amplification of membrane lipid peroxidative damage [17]. In ovarian cancer cells, increased iron uptake and induction of ferritinophagy provide substrates for the Fenton reaction that promote chain reactions of LPO, leading to ferroptotic cell death [18]. These processes are iron-dependent Fenton chemistry, whereby Fe^{2+} stimulates the formation of ROS that initiate membrane phospholipid LPO in PUFA-rich membranes [19]. Simultaneously, NCOA4-mediated ferritinophagy causes an increase in intracellular labile iron pool (LIP) due to increased degradation of ferritin and triggers ROS generation and also leads to iron-dependent LPO during the course of ferroptosis [20]. The combined damage in different regions ulti-

mately can lead to the irreversible damage of the membrane and necrosis at the cellular level that indicates ferroptotic cell death.

The susceptibility of ovarian cancer cells to ferroptosis is largely attributed to the regulation of a dynamic equilibrium between iron metabolism, lipid metabolism, and antioxidant defense systems (ADS). An important pathway in the cellular responses to oxidative and ferroptosis-related stress is activation of the nuclear factor erythroid 2-related factor 2 (NRF2) signaling pathway through transcriptional activation of antioxidant genes, such as heme oxygenase 1 (HMOX1) and NAD(P)H quinone dehydrogenase 1 (NQO1) [21]. It is important to note that NRF2 usually does not function as an antioxidant due to a constitutively activated response, but rather as an adaptive target under oxidative and metabolic perturbations. Degradation or functional inhibition of Kelch-like ECH-associated protein 1 (KEAP1) results in the stabilization and nuclear translocation of NRF2 and activation of downstream antioxidant signaling pathways [22]. NRF2 binds to the promoter region of SLC7A11 to activate transcription, augmenting cystine uptake and GSH synthesis, thereby supporting GPX4 activity and lipid peroxide detoxification [23]. NRF2 activation reduces oxidative stress and restrains LPO through the synergistic regulation of antioxidant and ferroptosis-related pathways, which enhances cellular resistance to ferroptosis [24]. As examples, the NRF2-HMOX1 axis along with other NRF2-regulated antioxidant genes such as NQO1 has emerged in ischemia/reperfusion injury (IR) to play an important role in cellular antioxidative stress response homeostasis and regulation of iron metabolism [25], although HMOX1 may exert context-dependent pro- or anti-ferroptotic effects depending on iron sequestration capacity and redox status. Moreover, serum/glucocorticoid-regulated kinase 1 (SGK1) may regulate membrane lipid content in an NRF2-independent manner through the mechanistic target of rapamycin (mTOR)/sterol regulatory element-binding protein 1 (SREBP1)/SCD1-driven lipogenic pathway to promote lipid remodeling, thereby decreasing further oxidation of membrane lipids. This suggests that ACSL4 enhances the inclusion of PUFAs into membrane phospholipids, which are more readily oxidized and thus also key to the ferroptosis sensitivity of tumor cells [26]. In addition, SCD1-mediated lipid metabolic reprogramming promotes ferroptosis resistance through modulation of membrane lipid composition and decreased LPO [27, 28]. On the contrary, when the cystine/glutamate antiporter (system Xc^-)-GPX4 antioxidant defense axis is inhibited or downregulated, ovarian cancer cells are sensitized to ferroptosis [29]. These changes are accompanied by significant increases in Fe^{2+}, ROS, and lipid peroxides, along with a decreased ratio of reduced GSH/oxidized glutathione (GSSG) levels and downregulation of SLC7A11 and GPX4 expression. Ferroptosis can be directly triggered by specific stimuli, or it has been reported to function as an effector mechanism contributing to the antitumor activity exerted by $CD8^+$ tumor-infiltrating lymphocytes in certain contexts. Importantly, the above process can be reversed by treatment with the ferroptosis inhibitor, ferrostatin-1 [30, 31].

Ferroptosis induction in ovarian cancer is not an independent process, but a coordinated process involving the induced imbalance of intracellular iron homeostasis, a persistent rise of LPO level and GPX4-mediated antioxidant detoxification system [32]. Previous work shows that modulation of cellular iron levels through the use of chelators, potentiation of oxidative stress by iron loading, or direct blockade of GPX4-mediated clearance of lipid peroxides can have profound effects on ovarian cancer cell survival and therapeutic stress responses [32]. Altogether, these results consistently delineate the 'iron load-LPO-GPX4 axis' as a pivotal regulatory pathway governing ovarian cancer ferroptosis execution, validate its central significance in treatment sensitivity modulation, and present it as a solid platform for future investigation of non-canonical ferroptosis regulators and their relation to therapeutic responses [32]. Combining the above, ferroptosis of ovarian cancer can be regarded as a dynamic regulatory network centered on the balance between iron homeostasis, lipid remodeling, and antioxidant defense. Increased ferritinophagy-mediated iron overload enhances the LIP and drives Fenton chemistry, whilst ACSL4-mediated incorporation of PUFAs into membrane phospholipids serves as substrates for LPO [33]. These processes are opposed by the antioxidant axis of system Xc^--GSH-GPX4, which detoxifies lipid peroxides and

maintains cellular redox homeostasis [34]. Overall, ferroptosis in ovarian cancer is generally modulated by the balance between iron-dependent LPO and ADS. ACSL4 increases the total pool of lipid peroxides to promote ferroptosis by remodeling PUFAs, while the GPX4/system Xc^- axis protects against lipid peroxidation and inhibits ferroptotic cell death [35, 36]. This balance is tipped under therapeutic stress, resulting in either lethal ferroptotic death or preferential tumor survival as mediated by the regulation of these pathways. Significantly, these findings suggest that ferroptosis is regulated by a fine balance among iron metabolism, LPO, and antioxidant defenses, which collectively determine cellular sensitivity to ferroptotic cell death.

Biological specificities of ovarian tissue: an iron-rich microenvironment and susceptibility to oxidative stress

Being a distinctly dynamic reproductive endocrine organ, the ovary experiences repetitive ovulation and constant tissue remodeling, which collectively lead to significant region-specific regulation of iron metabolism and redox balance [37]. Recurrent follicular rupture, inflammatory reactions, and micro-hemorrhagic events contribute to the deposition and accumulation of iron-derived molecules (e.g., ferritin and labile iron) in the ovarian microenvironment, creating a local, relatively iron-enriched metabolic milieu [38, 39]. At the same time, the reliance on mitochondrial oxidative metabolism for steroidogenesis makes ovarian cells more vulnerable to an elevated basal level of ROS. Under this physiological "iron-rich-high oxidative stress" state, disturbances in iron homeostasis could easily augment LPO through the Fenton reaction, reducing the cellular threshold for oxidative damage and ferroptotic cell death in ovarian tissue [40].

Emerging evidence demonstrates that excess ROS production, resulting from ovarian iron homeostatic dysregulation, depletes the ovarian reserve and damages oocytes [37]. Conversely, interventions like iron chelation or interventions counteracting LPO and chronic inflammation as well as boosting mitochondrial function can successfully restore ovarian redox equilibrium and attenuate histopathological changes. These results demonstrate the synergistic pathological effects of iron overload, oxidative stress, and ferroptosis on ovarian aging and metabolism-endocrine disorders [37, 41]. At the cellular defense level, ovarian cells rely heavily on antioxidant response systems. Of these, NRF2 is a central regulator that has essential protective effects for the maintenance of iron homeostasis and the restriction of LPO [42].

Tumor cell-mediated reprogramming of iron metabolism and mitochondrial function in ovarian cancer exacerbates this innate tissue susceptibility. In ovarian clear cell carcinoma with the most oxidative metabolic phenotype, tumor cells respond to iron-sulfur cluster insufficiency by stimulating the influx of iron into mitochondria [43]. While such adaptation may be able to temporarily satisfy the metabolic requirements, it eventually causes excess iron overload and more oxidative damage as well as mitochondrial dysfunction, which finally increase susceptibility to ferroptosis. This phenomenon illuminates an endogenous vulnerability in ovarian cancer cells, achieving a balance between the survival advantage in iron-rich conditions and the vulnerability to ferroptotic risk [43].

The iron-rich microenvironment in ovarian tissue and its increased susceptibility to oxidative stress are not entirely passive physiological conditions [44]. Instead, spanning from physiological condition to aging and tumor pathology, these factors gradually adjust both the ferroptosis threshold and its event landscape. This continuum offers a cohesive mechanism for the abnormal hyper-activation of ferroptosis implicated in ovarian-related diseases and provides a fundamental theoretical basis for future research aiming to design targeted intervention strategies through modulating iron homeostasis and oxidative stress regulators. In addition, this framework serves as a novel starting point for future studies involving the selective exploitation of ferroptosis in ovarian cancer treatment [45].

Crosstalk between ferroptosis and other cell death pathways, including apoptosis and autophagy, in ovarian cancer

Ferroptosis is closely linked with apoptosis, autophagy, and pyroptosis through shared molecular nodes and signaling axes in ovarian can-

cer. In ovarian cancer cells, ferroptosis-induced accumulation of ROS and lipid peroxides induces mitochondrial dysfunction, which can crosstalk with apoptotic pathways, leading to cytochrome c release, followed by downstream caspase-dependent signaling [27, 46]. NCOA4-mediated ferritinophagy induces the degradation of ferritin and release of bioavailable iron, which facilitates LPO by the Fenton reaction and then boosts ferroptosis in an autophagy-dependent manner so that it connects iron metabolism with autophagic regulation [20]. Damage-associated molecular patterns generated during ferroptosis activate the NLRP3 inflammasome, leading to caspase-1-dependent pyroptotic signaling [47]. Collectively, these pathways establish a dynamic network in which ferroptosis may cooperate with apoptosis and pyroptosis in the promotion of cell death under high oxidative stress conditions or be inhibited by elevated antioxidant defenses and autophagy-mediated lipid clearance to facilitate tumor cell survival.

Mechanistically, oxidative stress-induced mitochondrial dysfunction mediates crosstalk between ferroptosis and apoptosis. Increased production of ROS and LPO products in ferroptosis leads to the loss of mitochondrial membrane integrity, resulting in mitochondrial outer membrane permeabilization (MOMP). This process is accompanied by the activation of pro-apoptotic proteins such as BCL2 associated X protein (BAX) and BCL2 antagonist/killer 1 (BAK) with associated cytochrome c release and subsequent caspase activation [48]. Excessive accumulation of ROS accelerates LPO and causes mitochondrial dysfunction, leading to loss of mitochondrial membrane potential (MMP) together with cytochrome c release in this type of cell death [27]. Mitochondrial dysfunction associated with ferroptosis can promote the release of cytochrome c and activate apoptotic signaling through activating caspase-dependent apoptosis, which involves mechanistic crosstalk between ferroptosis and apoptosis [46]. Of these molecules, those related to unfolded protein response and inflammatory signaling axes are regarded as the most crucial nodes that bridge ferroptosis and apoptosis, which could act cooperatively to enhance cell death stimuli in some stresses [36, 49]. The autophagic pathway is associated with the upregulation or downregulation of ferroptosis, and iron homeostasis and lipid metabolism are the main focuses in regulating this process. Selective autophagic degradation of ferritin, so-called ferritinophagy, is mediated by NCOA4 and promotes the release of iron stored in this protein into the cytosolic LIP in cancer cells [50]. NCOA4 can also increase the intracellular iron storage capacity by mediating ferritinophagy, leading to increased ROS generation through LPO [51]. In ovarian cancer and ovarian cancer stem cells (OCSCs), crosstalk within the autophagy-ferroptosis axis has been shown to be closely linked with inhibition of tumor cell proliferation, invasion, and drug resistance through transcriptional regulation by stress-responsive transcription factors [52-54]. Moreover, ferroptosis is capable of crosstalking with inflammatory cell death, underlying a more complicated regulatory network. Inflammatory signaling decreases the threshold for ferroptosis through promoting ROS production and, in return, the oxidized lipids and damage-associated molecular patterns (DAMPs) generated by ferroptosis can also regulate inflammatory pathways to form positive feedback circuits within the TME [55].

Ferroptosis is not an independent, terminal event in ovarian cancer but part of an interconnected network with intercellular interactions within the TME [56]. The particular biological effects of ferroptosis are constantly modulated by apoptosis resistance, the status of autophagy, and modifications in inflammation-related pathways [57]. Emerging evidence suggests that the ferroptotic signaling pathway may functionally crosstalk with apoptotic, autophagic, and inflammatory cell death pathways, hence collectively governing tumor cell survival or death in response to therapeutic stress [8]. The integrated molecular mechanisms of ferroptosis, including iron metabolism, lipid peroxidation, antioxidant defense, as well as crosstalk with apoptosis, autophagy, and pyroptosis, are summarized schematically in **Figure 1**. A systematic elucidation of these interactions will facilitate a more comprehensive understanding of the complex regulatory landscape governing cell death in ovarian cancer and provide novel perspectives for interpreting therapeutic resistance and heterogeneity in treatment responses.

Therefore, ferroptosis should be conceptualized not as an isolated death program but as a node within an integrated cell death network,

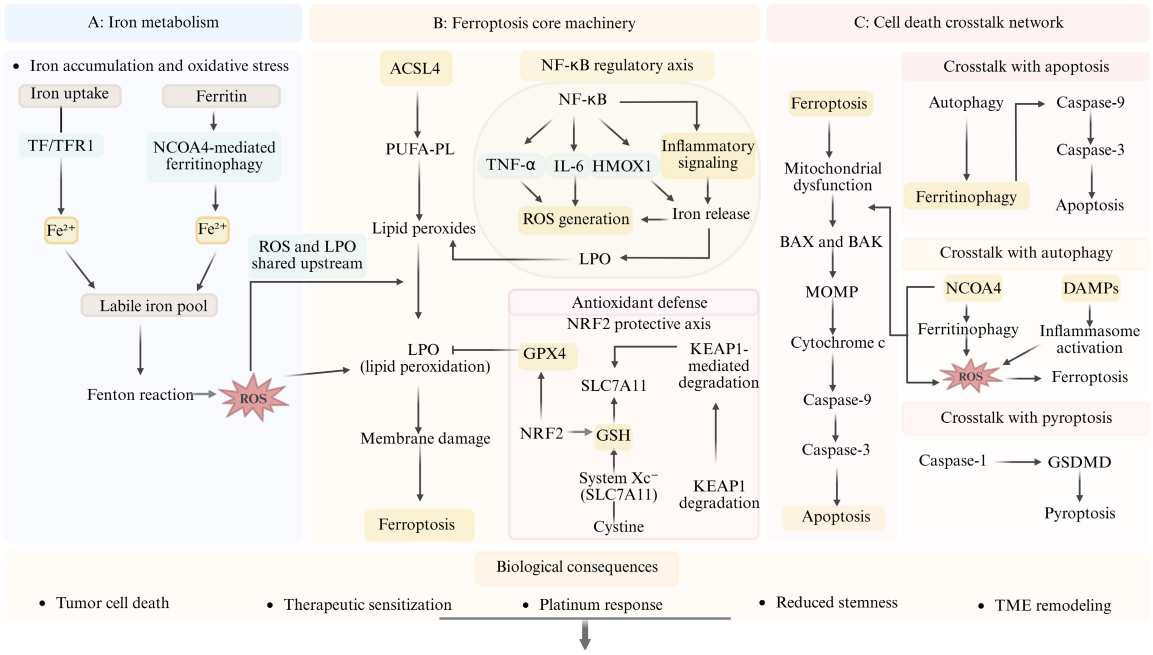

Figure 1. Integrated molecular mechanisms of ferroptosis and cell death crosstalk in ovarian cancer. Increased intracellular labile iron pool and ROS generation via the Fenton reaction due to cellular iron uptake through TF/TFR1 and NCOA4-mediated ferritinophagy promote lipid peroxidation and ferroptosis. The incorporation of polyunsaturated fatty acids into membrane phospholipids mediated by ACSL4 increases lipid peroxidation sensitivity, while the NRF2-system Xc^--GSH-GPX4 antioxidant axis protects against oxidative damage and ferroptotic cell death. Next, NF-κB-mediated inflammation promotes ROS production and iron-stimulated lipid peroxidation via downstream effector molecules such as TNF-α, IL-6, and HMOX1. Ferroptosis also involves interplay with apoptosis, autophagy, and pyroptosis via ROS-dependent signalling pathways linking mitochondrial dysfunction, ferritinophagy, and inflammasome activation, leading to synergistic effects in determining therapeutic responses and the biological fate of ovarian cancer.

where ROS-mediated signaling acts as a central integrator coordinating apoptosis, autophagy, and inflammatory responses under therapeutic stress.

A multidimensional regulatory network of ferroptosis in ovarian cancer

Genetic and epigenetic regulation: DNA methylation and histone modifications

In the context of ovarian cancer, corruption or repression of networks involved in ferroptosis not only originates from classical genetic events like gene mutations [58], but also involves epigenetic mechanisms. Reversible epigenetic control of ferroptosis susceptibility through DNA methyltransferase 1 (DNMT1)/DNA methylation and H3K36me3/histone methylation may contribute to shaping the gene transcription state during ferroptosis. Core processes - like iron metabolism, detoxification of lipid peroxides, and resistance to cellular stress adaptation - are epigenetically reprogrammed by ovarian cancer cells to dynamically regulate and maintain a balanced functional status of ferroptosis-associated pathways during enduring inflammation-related oxidative stress and selective pressure from therapy [59, 60].

Abnormal DNA methylation can regulate redox homeostasis in ovarian cancer through transcriptional modulation of genes associated with ferroptosis, such as SLC7A11 and GPX4 [11, 61]. Frizzled class receptor 7 (FZD7)/β-catenin/p63 signaling upregulates GPX4 and SLC7A11 in Pt-tolerant ovarian cancer cells, enhancing antioxidant defense and lipid peroxide detoxification, whereas knockdown of FZD7 enhances ferroptosis sensitivity [14]. The epigenetic repression of this shift results in an intracellular redox balance that moves toward a pro-oxidative state, enhances LPO, and ultimately leads to a decreased threshold for ferroptotic cell death, promoting the aggressiveness of tumor cells and resistance to therapy.

As an example, laminin subunit alpha 3 (LAMA3) hypermethylation negatively correlates with its expression and can be restored in chemoresistant ovarian cancer cells, where it antagonizes proliferation but promotes apoptosis, invasion, and migration [62]. In addition, targeting epigenetic regulatory complexes reinforces the importance of DNA methylation in the maintenance of tumor stemness and susceptibility to cell death [63]. Indeed, targeting of HOX transcript antisense intergenic RNA (HOTAIR) via peptide nucleic acid-mediated interference in cells to interfere with dysregulated enhancer of zeste homolog 2 (EZH2) binding, in combination with DNA methyltransferase inhibitors, greatly inhibited spheroid formation by OCSCs and reduced the population of aldehyde dehydrogenase-positive ($ALDH^+$) cells [64]. Modulation of upstream pathways, such as the MAGEA6-AMP-activated protein kinase (AMPK) axis, influences ferroptosis susceptibility through DNA methylation to converge on the SLC7A11/GPX4 antioxidant system [65]. In parallel, epigenetic regulation can also influence tumor cell biological properties such as the persistence of CSC states by modulating chromatin landscape and expression of stemness-associated genes [64]. Besides DNA methylation, histone modifications are also essential in the regulatory network of ferroptosis in ovarian cancer. Histone acetylation acts as a mark of chromatin accessibility and regulates transcriptional programs related to cell metabolism and stress responses [66]. However, sirtuin 1 (SIRT1)-mediated deacetylation of autophagy-related proteins (such as autophagy-related 5 and autophagy-related 2B) potently activates autophagy in ovarian cancer cells and has antitumor effects (e.g., by modulating non-histone deacetylation), suggesting that histone and non-histone deacetylation can potentially affect ferroptosis-related susceptibility and tumor cell survival by possibly modulating autophagy-associated stress responses [67]. Meanwhile, large-scale transcriptomic analyses have revealed that a substantial number of differentially expressed genes are closely associated with the regulation of the Wnt signaling pathway, which has been demonstrated to contribute to cisplatin resistance and to attenuate antitumor immune responses in ovarian cancer. These findings suggest that epigenetic reprogramming, by reshaping the transcriptional architecture of key signaling pathways, indirectly modulates ferroptosis-related stress adaptation and therapeutic responses [68]. This transcriptional reprogramming may mediate autophagy-associated adaptation to metabolic stress, thereby promoting cellular tolerance to oxidative stress and therapeutic pressure.

In brief, epigenetic regulation modifies ferroptosis susceptibility via the transcriptional accessibility of critical antioxidant and lipid metabolism-associated genes that rewire cellular redox homeostasis while establishing a new threshold for ferroptotic cell death. Collectively, these epigenetic mechanisms equip ovarian cancer cells to continuously adjust to oxidative stress and therapeutic pressure under the conditions they encounter, establishing a connection between ferroptosis regulation, drug resistance, and heterogeneous treatment responses [56]. In **Figure 2**, a schematic summary is provided of the most relevant epigenetic mechanisms that influence ferroptosis susceptibility and therapeutic adaptation in ovarian cancer.

Fine-tuned regulation of ferroptosis by non-coding RNAs

Besides DNA methylation and histone modifications, ncRNAs are another important layer of subtle adjustment in the ferroptosis regulatory network of ovarian cancer [69]. In a collaborative manner at the post-transcriptional level, versatile microRNAs and lncRNAs cooperate with one another in regulating iron metabolism, LPO, and antioxidant defense by coordinating to finely adjust the expression profiles of effector genes [70]. Through this coordinated regulation of these cellular processes, microRNAs and lncRNAs flexibly dictate the ferroptosis sensitivity of ovarian cancer cells at different pathological stages and in response to diverse stress cues, which collectively endow context-dependent control over ferroptotic vulnerability in ovarian cancer [71, 72].

Using lncRNA-related network analysis, some molecules have been reported to facilitate tumor progression by inhibiting ferroptosis-related pathways [73]. For example, tumor protein translationally controlled 1 antisense RNA 1 (TPT1-AS1) has been shown to promote the development of ovarian cancer through suppression of ferroptosis and elevation of transcription factor cAMP response element-bind-

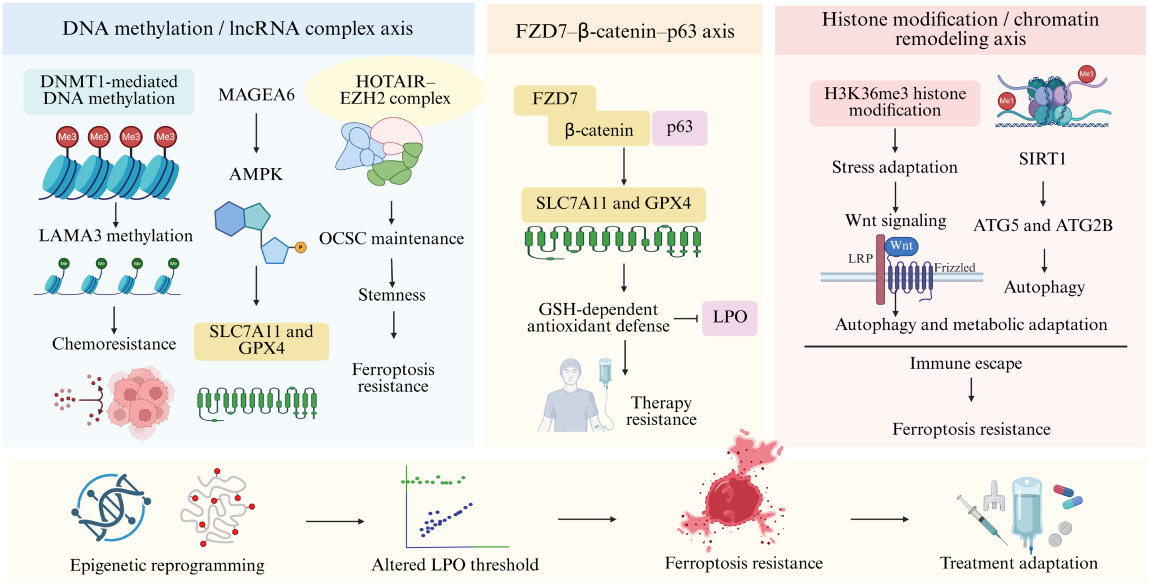

Figure 2. Epigenetic regulation of ferroptosis susceptibility and therapy adaptation in ovarian cancer. Summary of the roles of DNA methylation, lncRNA-associated regulatory complexes, and chromatin remodeling, which cooperatively modulate susceptibility to ferroptosis in ovarian cancer. Ferroptosis-related pathways are modulated by DNMT1-mediated DNA methylation, LAMA3 hypermethylation, the HOTAIR-EZH2 complex, and the MAGEA6-AMPK axis through SLC7A11 and GPX4 mechanisms. SLC7A11 and GPX4 are activated by the FZD7-β-catenin-p63 signaling axis to improve antioxidant defense, subsequently repressing lipid peroxidation. Pathways associated with histone modification, such as H3K36me3-mediated adaptation to stress, Wnt signaling, and SIRT1-dependent autophagy regulation, also play vital roles in ferroptosis resistance and therapy adaptation. These findings suggest that collective epigenetic reprogramming alters lipid peroxidation levels and dysregulates ferroptotic cell death, thereby promoting drug resistance and heterogeneous therapeutic responses in ovarian cancer.

ing protein 1 (CREB1), which relies on a regulatory network constituted with KH domain-containing RNA-binding, signal transduction-associated protein 3 (KHDRBS3). Further mechanistic studies revealed that TPT1-AS1 regulates GPX4 transcription by maintaining active CREB1 expression. Mechanistically, TPT1-AS1 binds to KHDRBS3, thereby preventing it from suppressing CREB1. Through this regulatory axis, TPT1-AS1 enhances antioxidant defense capacity and decreases the cell sensitivity to ferroptosis [74]. Additionally, the lncRNA CACNA1G-AS1 promotes ferritin heavy chain 1 (FTH1) expression in an insulin-like growth factor 2 mRNA-binding protein 1-dependent manner to promote iron storage and inhibit ferritinophagy-associated activities. This in turn restricts intracellular labile iron accumulation and suppresses ferroptosis, thereby facilitating ovarian cancer cell proliferation and migration [75]. In contrast, multiple ncRNAs have been shown to drive ovarian cancer cells toward ferroptosis by weakening antioxidant defenses or increasing iron burden and LPO [76]. For example, knockdown of lncRNA HCP5 markedly induces ferroptosis, characterized by reduced expression of GPX4, GSH, and SLC7A11, accompanied by elevated levels of LPO products (such as malondialdehyde [MDA] and 4-hydroxynonenal) and iron metabolism-related molecules (including ACSL4 and transferrin) [71]. Furthermore, the contribution of the ceRNA network to ferroptosis regulation has been widely acknowledged. For instance, the ADAMTS9-AS1/miR-587/SLC7A11 axis modulates ferroptosis response in epithelial ovarian cancer (EOC) cells by controlling the expression of SLC7A11 (a functional subunit of system Xc^-). This underscores the essential roles of ncRNAs in the post-transcriptional regulation of ferroptosis [70].

Overall, ncRNAs coordinate post-transcriptional control of critical pathways governing antioxidant defense, iron metabolism, and LPO to regulate ferroptosis. The ncRNA miR-424-5p directly binds to ACSL4, regulating its expression and enzyme activity, thus affecting lipid peroxide accumulation and intracellular redox

balance in ovarian cancer cells, thereby modulating the sensitivity of cells to ferroptosis [72].

A new perspective on the TME: immune cell involvement and metabolic reprogramming

In the setting of ovarian cancer, ferroptosis regulation is not solely through tumor cell-intrinsic molecular alterations but also extensively embedded through the immune-metabolic microenvironment [77]. The TME provides a highly heterogeneous immune and metabolic environment that shapes ferroptotic signaling through coordinated intercellular metabolic interactions, thereby contributing to context-dependent ferroptosis sensitivity. As a case, tumor-associated macrophage (TAM) polarization is correlated with the acceleration of iron metabolism in the local TME that affects the LIP in adjacent tumor cells as indicated by correlations with ferritin, hepcidin, and free iron levels [78]. Such intercellular trafficking of iron directly impacts the efficiency of Fenton reactions and the kinetics of LPO, offering a mechanistic explanation for spatial variability in susceptibility to ferroptosis.

Lipid metabolic reprogramming and the functional state of immune cells also crosstalk in a coordinated manner as core regulatory aspects of ferroptosis susceptibility in the TME [79]. The perturbed activation of fatty acid desaturation and membrane lipid remodeling pathways dramatically increases the PUFA content in membrane phospholipids, leading to higher levels of peroxidized membranes and lower thresholds for ferroptosis in ovarian cancer cells [26, 35].

TAMs are also pivotal regulators in the ferroptosis-immunity-metabolism axis at the immunological level. TGF-β1 secreted from ovarian cancer epithelial cells has been experimentally proven to activate multiple TAM subsets including $SPP1^+$, $FOLR2^+$ as well as $C1QC^+$ populations through the PI3K/AKT serine/threonine kinase (AKT)/NF-κB (p65) signaling pathway [80]. Moreover, NF-κB signaling may affect ferroptosis-associated metabolic pathways directly by regulating the transcription of key genes associated with iron homeostasis, antioxidant defense, and LPO. Increased NF-κB activation has been found to transcriptionally activate SLC7A11, resulting in increased cystine uptake and GSH de novo synthesis, thus promoting cellular antioxidant capability [81]. In the interim, NF-κB-driven inflammatory signaling can stimulate ROS formation that indirectly leads to increased iron-mediated oxidative stress and LPO under specific conditions. TNF-α and IL-6 are two important proinflammatory cytokines that serve as representative downstream mediators of NF-κB signaling pathways, which can promote ROS production and enhance oxidative stress levels. Second, due to HMOX1-mediated iron release, the intracellular labile iron pool may be augmented by this mechanism, ultimately promoting iron-dependent lipid peroxidation and ferroptotic signaling. Concomitant with these immune-remodeling effects, the elevated expression of HMOX1 in macrophages also modulates this immune-remodeling process via NF-κB signaling transduction [80]. Based on this, changes in intracellular iron handling in TAMs may significantly impact their polarization. Knockdown of cytochrome b-245 beta chain (CYBB) induces the expression levels of FTH1 and ferroptosis suppressor protein 1 (FSP1), along with inhibited M1 polarization and promoted M2 polarization. These results demonstrate that not only do ferroptosis-related molecules regulate tumor cell fate, but they are also engaged in the maintenance of an immunosuppressive TME [80, 82]. In addition to immune-metabolic control at the TME level, direct metabolic and iron homeostasis reprogramming within the tumor cells can subvert ferroptosis and establish an immunosuppressive environment for immune escape while promoting tumorigenesis. For example, the transcription factor MYC proto-oncogene, basic helix-loop-helix (bHLH) transcription factor (c-MYC) directly suppresses NCOA4 expression, thereby leading to hampered ferritinophagy activity, cellular labile iron depletion, and resistance to ferroptosis. Thus, c-MYC contributes to the maintenance of ovarian cancer cells' malignant phenotype and their immune escape potential [83].

Taken together, these results suggest that ferroptosis sensitivity in ovarian cancer cells is intimately linked to intracellular metabolic reprogramming that allows lipid metabolism and antioxidant capacity to cooperatively dictate the fate of oxidative stress; that is, whether LPO underlies cell death or whether it is buffered sufficiently to maintain cellular viability [84]. The iron metabolic and ROS crosstalk

between tumor cells and TAMs contributes to local heterogeneity and context-dependent regulation of ferroptotic processes within the TME [77]. Representative molecular regulators and mechanistic axes of ferroptosis regulation in ovarian cancer are summarized in **Table 1**. The dual functionality of ferroptosis regulators - governing both intrinsic tumor cell death and extrinsic immune remodeling - positions these molecules as central determinants of immune evasion and therapeutic failure in ovarian cancer.

Ferroptosis: a key mechanism underlying therapeutic failure in ovarian cancer

Mechanisms of 'ferroptosis evasion' in Pt-resistant ovarian cancer cells

In Pt-resistant ovarian cancer, the transition of tumor cells from a responsive to resistant state is not limited to their efficient DNA damage repair and upregulated apoptotic resistance; enhanced anti-ferroptotic defenses that inhibit iron-driven LPO are requisites and co-contributors to Pt resistance in Pt-resistant ovarian tumors [85]. Main point: Although ROS accumulation, together with LPO stress caused by Pt-based agents, is markedly increased in the treated cells, Pt-resistant ovarian cancer cells are often characterized as possessing decreased sensitivity to ferroptosis, which can be associated with impaired NCOA4-mediated ferritinophagy [86], leading to restricted release of stored iron and a diminished intracellular LIP that attenuates ferroptosis via iron-mediated LPO. At the same time, induction of SLC7A11 increases cystine uptake and promotes GSH biosynthesis in ovarian cancer cells [12], while FSP1 restores electrons to reduced CoQ10 (ubiquinol), which sequesters lipid peroxyl radicals, thereby inhibiting LPO [87], thus preventing both LPO and ferroptotic cell death. This coordinated response forms a durable 'ferroptosis-escape' phenotype that is emerging as a key metabolic/redox scaffold for Pt resistance pathogenesis and maintenance.

Reactivation of ferroptosis sensitizes cells to Pt-based chemotherapy under certain circumstances. For instance, co-treatment with shikonin and cisplatin enhances the expression of HMOX1 to facilitate iron release followed by Fe^{2+} accumulation in cells, particularly when cellular iron-buffering capacity is exceeded. The process boosts LPO and promotes GSH depletion, leading to sensitization of ovarian cancer cells to ferroptotic cell death [49]. On the other hand, upon prolonged Pt exposure, the Pt-resistant ovarian cancer cells trigger an acyl-CoA synthetase long-chain family member 1 (ACSL1)/FSP1 resistance side of ferroptosis. Increased ACSL1 expression may promote the transfer of FSP1 to the plasma membrane, leading to improved lipid peroxide scavenging ability and resistance to ferroptosis. Consequently, cellular susceptibility to Pt chemotherapy is decreased and the drug-resistant cells survive [85]. Apart from the metabolic defense mechanisms, ncRNAs and epigenetic control are also implicated in evading ferroptosis. These results demonstrate that silencing circASH1L releases its inhibitory effect on miR-515-5p, which in turn downregulates the CDCA7/RRM2 axis to induce ferroptosis, thereby contributing to the resensitization of cisplatin-resistant cells. Similarly, miR-1-3p sensitizes ovarian cancer cells to ferroptosis through repression of FZD7 signaling [88, 89]. In addition, epigenetic silencing of SREBF2 regulates cholesterol uptake and membrane lipid content, and thus alters GPX4-dependent redox homeostasis. This allows resistant cells to retain antioxidant ability in a state of high ROS and represses the efficiency of ferroptotic effectors [90].

The blunting of ferroptosis in Pt-resistant ovarian cancer is not a consequence of any single gene abnormality, but rather reflects a systemic adaptive response involving the coordinated reprogramming of iron homeostasis, metabolic rewiring of lipid pathways, reinforced antioxidant defenses, and integrated post-transcriptional and epigenetic regulation. The limitation of labile iron availability to the cytosol of an ovarian cell can be mediated by suppression of NCOA4-dependent ferritinophagy in Pt-resistant cells, thereby decreasing LPO [86], and by upregulation of antioxidant defenses that could support survival under Pt-induced oxidative stress. Consistently, the disruption of these anti-ferroptotic regulatory axes can reveal context-specific metabolic liabilities, thus identifying ferroptosis as a central modulatory node in the therapeutic response to Pt agents. This comprehensive view unveils potential mechanisms for maintaining Pt resistance.

Table 1. Multidimensional regulatory network of ferroptosis in ovarian cancer

Regulation Level	Key Molecules	Core Mechanism	Effect on Ferroptosis	Biological Effect	References
Molecular	NTX-301, stearoyl-CoA desaturase (SCD), unsaturated fatty acids (UFAs)	NTX-301 inhibits SCD, reduces unsaturated fatty acids, increases LPO	Promotes ferroptosis	Induces ferroptosis, inhibits tumor growth, targets ovarian CSCs	[63]
Molecular	miR-424-5p, ACSL4	miR-424-5p targets ACSL4, suppresses LPO	Suppresses ferroptosis	Reduces ferroptotic cell death, promotes tumor progression	[72]
Molecular	Icariside II, SLC7A11, GPX4, GSH, Fe^{2+}, lipid ROS	Downregulates SLC7A11, decreases GSH/GPX4, increases Fe^{2+} and lipid ROS	Promotes ferroptosis	Suppresses proliferation, migration, invasion	[29]
Molecular	miR-1-3p, FZD7	Targets FZD7, enhances LPO induced by Erastin/RAS-selective lethal 3 (RSL3)	Promotes ferroptosis	Increases sensitivity to ferroptotic cell death	[89]
Molecular	SREBP1, Nrf2, SLC7A11, GPX4, Keap1, PD-L1	SREBP1 knockdown decreases Nrf2, SLC7A11, GPX4, reduces PD-L1	Promotes ferroptosis	Induces ferroptosis, inhibits proliferation and invasion, modulates immune microenvironment	[114]
Molecular	C-MYC, NCOA4, FTH1, Beclin-1	C-MYC inhibits NCOA4, suppresses ferritin autophagy, decreases ROS	Suppresses ferroptosis	Promotes proliferation, invasion, immune evasion	[83]
Molecular	histone H3 lysine 18 lactylation (H3K18la), transformer 2 alpha homolog (TRA2A), STIL-L	H3K18la promotes TRA2A transcription, alters STIL splicing, suppresses iron metabolism	Suppresses ferroptosis	Increases resistance to ferroptosis, enhances cisplatin resistance	[115]
Molecular	Sodium citrate, calcium/calmodulin-dependent protein kinase kinase 2 (CAMKK2), AMPK, NCOA4, MCU, GPX4, FTH1	Chelates Ca^{2+}, inhibits CAMKK2/AMPK, increases ferritinophagy, ROS	Promotes ferroptosis	Induces ferroptosis, inhibits tumor growth, enhances chemotherapy sensitivity	[10]
Molecular	NRF2, HECT and RLD domain-containing E3 ubiquitin protein ligase 2 (HERC2), vesicle-associated membrane protein 8 (VAMP8), NCOA4, FTH1, FTL	NRF2 regulates HERC2/NCOA4/VAMP8, controls ferritin homeostasis and labile iron	Promotes ferroptosis	Enhances ferroptosis sensitivity, ROS and LPO	[116]
Molecular	ubiquitin specific peptidase 43 (USP43), fatty acid synthase (FASN), hypoxia-inducible factor 1 alpha (HIF1α), SLC7A11, Yin Yang 1 transcription factor (YY1)	YY1 activates USP43, stabilizes FASN and HIF1α, increases SLC7A11 transcription	Suppresses ferroptosis	Enhances proliferation, migration, cisplatin resistance; targeting SLC7A11 restores ferroptosis	[117]

Molecular associations between ferroptosis and sensitivity to PARP inhibitor therapy

PARP inhibitors are a promising targeted therapy for ovarian cancer, especially in BRCA mutated or HRD patients. The synthetic lethality resulting from defective DNA repair is predominantly considered to be their canonical antitumor activity. Here, the efficacy of PARP inhibitors is not only determined by DNA damage but also influenced by susceptibility to ferroptosis that is regulated by metabolic reprogramming and oxidative stress imbalance [15].

GPX-dependent removal of lipid peroxides protects cells from the accumulation of toxic LPO products, which mediate a critical bottleneck for oxidative stress-inducing therapeutic strategies including PARP inhibitors [91]. Inhibition of GPX4 substantially increases the sensitivity of BRCA1-deficient ovarian cancer cells to ferroptosis induced by PARP inhibitors, and combined use of these drugs exerts a synergistic antitumor effect in relevant models, indicating that the GPX4-ferroptosis pathway is a central regulatory unit for determining therapeutic response to PARP inhibitors [45]. In the meantime, lipid reprogramming remodels treatment sensitivity through regulation of the availability of ferroptosis substrates, while AMPKα-SCD1 signaling is critical in governing ovarian cancer energy metabolism and ferroptosis by perturbing the threshold for LPO via regulating fatty acid desaturation and membrane lipid composition. Furthermore, niraparib may induce the fatty acid transporter CD36 in an NRF2-dependent manner to accelerate excessive fatty acid uptake and lipid deposition, leading to ferroptosis under certain metabolic conditions. This suggests that PARP inhibitors are metabolic reprogramming drivers [92, 93]. It is worth noting that sensitivity to PARP inhibitor-induced ferroptosis is not only governed by intrinsic pathways in tumor cells, but also modulated by the antioxidant buffering capacity within the surrounding tumor ecosystem. In ovarian cancer and breast cancer-derived cancer-associated fibroblasts (CAFs), discoidin domain receptor tyrosine kinase 2 (DDR2) controls ferroptosis by the p62-KEAP1-NRF2 pathway. By regulating cystine uptake and GSH biosynthesis through the xCT transporter, this pathway indirectly upregulates antioxidant defenses in tumor cells. xCT (SLC7A11) thereby effectively negates the ferroptosis response triggered by PARP inhibitors [56].

Ferroptosis and its molecular correlation with PARP inhibitor sensitivity are multi-dimensional and contextual. The role of DNA damage accumulation in determining PARP-inhibitor efficacy is counterbalanced and dependent upon GPX4-mediated redox control of ferroptosis regulation in ovarian cancer [94]. Ferroptosis driven by oxidative stress is orchestrated through GPX4-dependent detoxification of lipid peroxides in combination with NRF2-mediated antioxidant and lipid metabolic regulation [95]. The relationship between the inherent metabolic status of tumor cells and ROS buffering capability in the microenvironment is the major determinant of PARP inhibitor sensitivity variability and resistance, suggesting that ferroptosis plays a central role in modulating PARP inhibitor treatment sensitivity.

The role of ovarian cancer stem cell characteristics and ferroptosis resistance in tumor recurrence

Ovarian cancer is highly recurrent, and this is thought to be due to a minor subpopulation of OCSCs with self-renewal ability as well as extensive phenotypic plasticity. This cell subset can survive long-term after initial treatment and regrow the tumor once the pressure is released. Recently, experimental evidence has also shown that altered ferroptosis signaling contributes to therapy resistance in ovarian cancer, and specifically, stem-like cell populations provide enhanced antioxidant defenses together with suppressed LPO [45, 96].

OCSCs control ferroptosis by dynamically rewiring iron homeostasis and redox balance, establishing a distinct regulatory phenotype compared to differentiated tumor cells. These stem-like cells commonly exhibit improved regulation of intracellular iron handling but a concomitant induction of antioxidant protective systems, thereby effectively restricting the generation of iron-dependent lipid peroxides. This capacity to adapt is likely to contribute to keeping the survival threshold under oxidative stress and under continuous treatment pressure high. Iron homeostasis factors are essential components of this process. Among these, the expression intensity of the iron-sulfur cluster-associated protein frataxin (FXN) is closely

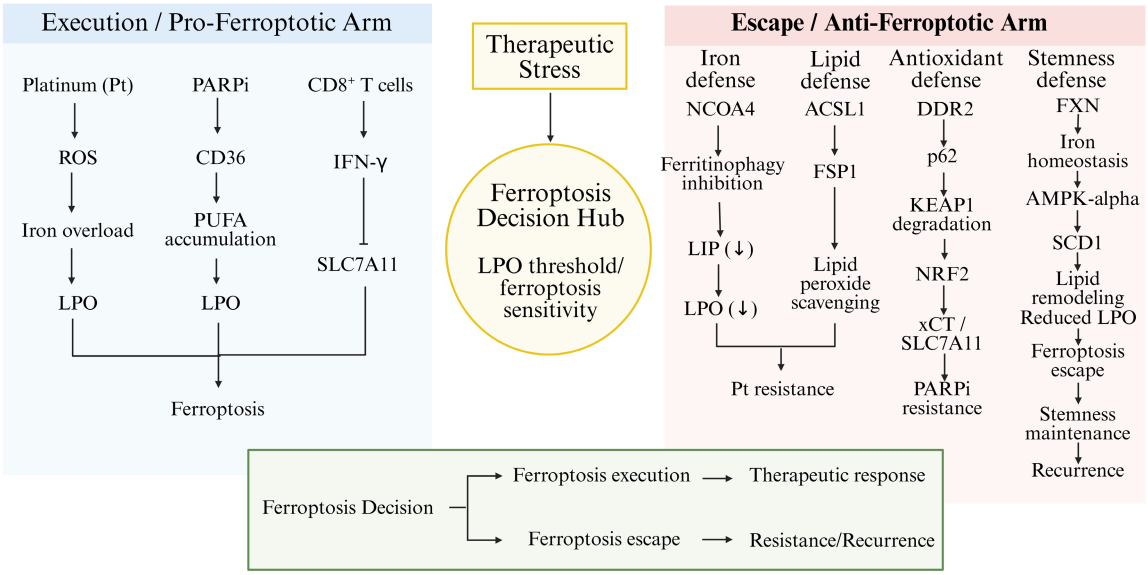

Figure 3. Ferroptosis decision networks underlying therapeutic response and resistance in ovarian cancer. Ferroptosis sensitivity is dictated by the balance between pro-ferroptotic execution pathways and anti-ferroptotic defense mechanisms in response to therapeutic stress. In turn, platinum agents, PARP inhibitors, and $CD8^+$ T cell-derived signals promote ferroptosis by increasing oxidative stress, iron overload, lipid peroxidation, or suppression of antioxidant defense through SLC7A11. In contrast, ovarian cancer cells escape from ferroptosis through orchestrated regulation of iron metabolism, lipid peroxide scavenging, antioxidant buffering, and stemness-associated metabolic adaptation. Examples of pathobiologically relevant resistance mechanisms include suppression of NCOA4-mediated ferritinophagy, activation of the ACSL1-FSP1 axis, DDR2-p62-KEAP1-NRF2-xCT signaling, and FXN-associated maintenance of iron homeostasis. Ferroptosis execution and ferroptosis escape are fine-tuned to determine therapeutic response, resistance, and tumor recurrence in ovarian cancer.

related to the sensitivity of OCSCs to ferroptosis [88, 96, 97]. Together, these results indicate that the inhibition of ferroptosis in OCSCs is not due to innate tolerance but to the active maintenance of iron homeostasis and oxidative status. Nevertheless, ferroptosis control on OCSCs is not a strict suppression but shows remarkable context specificity and plasticity. Under particular metabolic or pathological conditions, stem-like cell populations may exhibit differential sensitivity to ferroptosis [96, 98]. This negotiable state is additionally reinforced by post-transcriptional regulation which involves ncRNAs. Some circRNA-miRNA regulatory axes contribute to a trade-off between maintaining stemness and triggering ferroptosis, by influencing cell cycle progression or the expression of iron-metabolism-related genes. Modulation of these pathways can lead to sensitizing drug-resistant properties and paracrine stemness dominance [88, 96]. As a result, ferroptosis is not irreversibly silenced in OCSCs but remains in a latent state that can be reactivated and exploited. The biological consequence is determined by the balance between stemness signals, the metabolic setting, and oxidative stress.

The characteristics of OCSCs and ferroptosis regulation form a close functional network in tumor recurrence. OCSCs evade treatment by rewiring iron homeostasis and amplifying antioxidant defenses, and fine-tune the ferroptosis threshold through the ncRNA networks for tumor regeneration. Resistance to ferroptosis is both recognized in the maintenance of ovarian cancer stem-like cells and more generally in the development of chemoresistance, preventing curative treatment for a variety of malignancies [94, 96]. **Figure 3**, Schematic overview of the main ferroptosis-related mechanisms regulating therapeutic response, resistance, and tumor recurrence in ovarian cancer.

Precise therapeutic strategies and translational applications based on ferroptosis

Classification of Ferroptosis Inducers (FINs) and their research progress in ovarian cancer

Given that ferroptosis has now been recognized as a crucial hub regulating drug resistance

and relapse of ovarian cancer, the pharmacological maneuvers aiming to modulate this form of regulated cell death are starting to transition from proof-of-principle reports to mechanism-based personalized translational tactics. FINs are not panaceas for inducing ferroptosis; rather, they mediate ferroptosis through a progressive failure of cysteine import, ADS, and iron homeostasis, and by reducing the threshold for LPO to push tumor cells beyond the critical threshold for ferroptosis. In ovarian cancer, a disease critically depending on redox homeostasis and adaptation in lipid metabolism, such a regulatory axis operates under the condition of chronic stress.

The antioxidant system, in which system Xc^--GPX4 serves as a core regulatory node, is essential for the execution of ferroptosis. The classic ferroptosis inducer erastin reduces cysteine uptake through the suppression of SLC-7A11 and increases LPO, leading to the induction of ferroptosis in ovarian cancer cells. Its action was partially blocked by the inhibitory effect induced by miR-93-5p, indicating a functional interconnection between FIN activity and post-transcriptional regulation [69]. In the presence of cisplatin, erastin co-treatment further augments ROS production and LPO as a part of combination therapy. This is associated with a much more pronounced synergistic interaction with cisplatin both in vitro and in vivo. It increases antitumor activity without significantly increasing toxicity, thus presenting a potentially viable therapeutic approach to overcome Pt drug resistance [36].

In addition, transcriptional suppression upstream also affects cellular sensitivity to ferroptosis. Loss of snail family transcriptional repressor 2 (SNAI2) function or suppression of its activity can inhibit the progression of ovarian cancer by allowing basic processes related to ferroptosis to resume. This demonstrates that the FIN regulatory network is even more extensive than previously thought [99]. Beyond inhibiting the Xc^- system, modulating redox metabolism and iron metabolism-related pathways are two other major mechanisms of action of new FINs. NQO1 is a key node in the regulatory network controlling ferroptosis. The NQO1-targeting FIN, Daph, can induce ferroptosis in ovarian cancer cells. At the same time, a second FIN, BRU, shows strong therapeutic potential in ovarian cancer by simultaneously blocking both the AKT/mTOR signaling pathway and the NRF2/heme oxygenase 1 (HO-1)/NQO1 axis; in this way, it can broadly weaken antioxidant and survival signals [30, 100].

The research on ferroptosis in ovarian cancer has evolved from single-molecule verification to the global regulation of antioxidant defense, iron homeostasis, and LPO. The pivotal value of this strategy is the systematic disruption of the adaptive survival advantage gained by tumor cells through long-term treatment stress. This step provides the basis for future multi-modality chemo-, targeted-, and precision therapy efforts based on molecular profiling. **Table 2** summarizes ferroptosis-based precision therapeutic strategies and translational applications in ovarian cancer.

Nanotechnology-driven ferroptosis-targeted drug delivery system

While currently used FINs show good efficacy in ovarian cancer therapy, their clinical application may be limited by poor stability, short circulation time, systemic toxicity, and unsuitable targeting ability. Lipid-based nanoparticles are good in biocompatibility and drug loading, but they need surface modification for targeting purposes. Ultrasmall inorganic Fe_3O_4 nanomaterials could trigger ROS production and interfere with iron homeostasis, but their high reactivity gives rise to concerns regarding long-term toxicity and bioaccumulation [101]. Hybrid platforms combine both strategies to enable more accurate regulation of ferroptosis induction; however, they are cumbersome and expensive. Overall, these comparative analyses substantiate the systematic design of targeted nanotherapeutics for ferroptosis that exhibit enduring therapeutic effects with limited off-target responses. The accumulation of ROS induced by superparamagnetic iron oxide nanoparticles leads to the ferroptosis of ovarian cancer stem-like cells in vitro and inhibits tumorigenicity and drug resistance [53]. This is because it reframes ferroptosis from a potential liability that cells must escape to a therapeutic event that may be specifically and effectively warranted. Nanotechnology-based delivery systems directed to molecular targets of ferroptosis represent a potentially translatable approach that integrates materials engineering with can-

Table 2. Precision treatment strategies and translational applications of ferroptosis in ovarian cancer

Strategy Type	Core Mechanism	Key Molecules/Drugs	Effect on Ferroptosis	Therapeutic Effect	References
Targeting renalase (RNLS), signal transducer and activator of transcription 3 (STAT3) axis to overcome ferroptosis resistance	RNLS upregulates STAT3, activates PI3K/AKT, enhances antioxidant defense, suppresses ROS/LPO, inhibits ferroptosis	RNLS, STAT3, PI3K/AKT, GPX4, GSH, ROS	Inhibits ferroptosis	Promotes proliferation, migration, invasion of ovarian cancer cells; suppression of ferroptotic cell death; targeting RNLS, STAT3 can enhance ferroptosis and inhibit tumor growth in vivo	[118]
Ferroptosis inducers combined with iron homeostasis regulation	Erastin induces ferroptosis only when intracellular LIP is sufficient; ferlixit increases LIP and synergizes with erastin, induces mitochondrial dysfunction and ferroptotic cell death	Erastin, Ferlixit, voltage-dependent anion channel 2 (VDAC2), NCOA4, FTH	Promotes ferroptosis	Sensitizes ovarian cancer cells to ferroptosis; overcomes ferroptosis resistance; enhances cell death	[18]
Ferroptosis induction via AMPKα, SCD1 signaling modulation combined with chemotherapy	Olaparib + arsenic trioxide (ATO) activate AMPKα, suppress SCD1 and acyl-CoA synthetase long-chain family member 3 (ACSL3), increase LPO and ROS, induce ferroptosis in Pt, resistant ovarian cancer cells	Olaparib, Arsenic trioxide, AMPKα, SCD1, ACSL3, SLC7A11, GPX4, ROS	Promotes ferroptosis	Induces ferroptosis, induces apoptosis, suppresses tumor growth in Pt, resistant ovarian cancer	[92]
Natural product-based ferroptosis induction	Daphnetin inhibits NQO1, increases intracellular Fe^{2+} and ROS, decreases SLC7A11/GPX4 antioxidant defense, induces ferroptosis	Daphnetin, NQO1, GPX4, SLC7A11, Fe^{2+}, ROS	Promotes ferroptosis	Induces ferroptotic cell death, inhibits proliferation and migration of ovarian cancer cells; enhances sensitivity to cisplatin	[30]
Ferroptosis inducers combined with NRF2 inhibition	NRF2 inhibition, reduces HERC2/VAMP8, ferritinophagy blockage, NCOA4, mediated apoferritin accumulation, increases intracellular LIP, sensitizes cells to ferroptosis	IKE, BRU, NRF2, HERC2, VAMP8, NCOA4, FTH1/FTL	Promotes ferroptosis	Induces ferroptosis, suppresses tumor growth in 3D spheroids, xenografts, and PDX models; translationally relevant for treating refractory ovarian cancer	[116]
Transcription factor, targeted ferroptosis induction	Artesunate inhibits homeobox C11 (HOXC11), decreases prominin 2 (PROM2) transcription, suppresses PI3K/AKT signaling, reduces GPX4 and GSH, increases ROS and LPO, induces ferroptosis	Artesunate, HOXC11, PROM2, PI3K/AKT, GPX4, ROS, GSH	Promotes ferroptosis	Induces ferroptotic cell death, promotes apoptosis, inhibits proliferation and migration of ovarian cancer cells in vitro; suppresses tumor growth in xenograft mouse model	[119]
Ferroptosis activation via transcriptional regulation	CEBPG knockdown, decreases SLC7A11 transcription, increases LPO and ROS, induces ferroptosis	CEBPG, SLC7A11, Erastin, Ferr, 1	Promotes ferroptosis	Induces ferroptosis; inhibits ovarian tumor growth; potential therapeutic target	[106]
Ferroptosis inducers combined with UFA β, oxidation inhibition	ACSL4 and enoyl-CoA hydratase 1 (ECH1) regulate UFAs β, oxidation, maintain membrane fluidity and metastatic extravasation; dual inhibition blocks UFA metabolism, increases ferroptosis	ACSL4, ECH1, abhydrolase domain containing 6 (ABHD6), enoyl-CoA delta isomerase 1 (ECI1), malate dehydrogenase 1 (MDH1)	Promotes ferroptosis	Induces ferroptosis, suppresses ovarian cancer metastasis and tumor growth in vivo	[26]
Targeting sphingosine kinase 1 (SPHK1)/NF, κB/NRF2 axis to overcome PARP inhibitor resistance	SPHK1 activates NF, κB p65, transcriptionally upregulates NRF2, increases SLC7A11/GPX4, inhibits ferroptosis; SPHK1 inhibition or FINs restore ferroptosis	SPHK1, NF, κB p65, NRF2, SLC7A11, GPX4, PF-543, Erastin, RSL3	Promotes ferroptosis	Enhances Olaparib sensitivity, induces ferroptotic cell death, inhibits ovarian cancer growth	[120]

Nanoparticle, mediated ferroptosis induction via sonodynamic therapy	Bismuth-based material (BMO), MXene nanosheets + ultrasound, enhanced ROS generation, downregulates GPX4/SLC7A11, LPO increases, ferroptosis; DAMP release, immune activation	BMO, MXene, ROS, GPX4, SLC7A11, Fe^{2+}, DAMPs	Promotes ferroptosis	Inhibits ovarian cancer cell proliferation, induces ferroptotic cell death and ICD; reduces tumor growth in vivo	[121]
Targeting SELENOI to overcome Pt resistance via ferroptosis induction	Inhibition of SELENOI, decreases Akt phosphorylation, upregulates ACSL4, increases LPO & ROS, decreases GSH, induces ferroptosis	SELENOI, Akt/p, Akt, ACSL4, GSH, ROS, Cisplatin	Promotes ferroptosis	Reverses cisplatin resistance; induces ferroptotic cell death; suppresses tumor growth	[122]
Natural compound, based ferroptosis induction	Icariside II downregulates SLC7A11, decreases cystine uptake and GSH synthesis, reduces GPX4 activity, increases Fe^{2+}, ROS, LPO, induces ferroptosis	Icariside II, SLC7A11, GPX4, GSH, Fe^{2+}, Ptgs2, Chac1	Promotes ferroptosis	Inhibits proliferation, migration, and invasion of ovarian cancer cells; induces ferroptotic cell death; suppresses tumor growth in vivo	[29]
Targeting DNA topoisomerase II alpha (TOP2A)/tumor protein p53 (TP53)/GPX4/SLC7A11 axis to overcome Pt resistance	TOP2A knockdown increases TP53, decreases GPX4/SLC7A11, increases ROS & LPO, induces ferroptosis, inhibits epithelial-mesenchymal transition (EMT)	TOP2A, TP53, GPX4, SLC7A11, Erastin	Promotes ferroptosis	Reverses cisplatin resistance, inhibits EMT, proliferation, invasion and migration of ovarian cancer cells	[123]
Natural compound, based ferroptosis induction	Salidroside binds to and downregulates FSP1, increases Fe^{2+}, ROS, LPO, and decreases GSH/GPX4, induces ferroptosis in ovarian cancer cells	Salidroside, FSP1, Fe^{2+}, ROS, GSH, GPX4	Promotes ferroptosis	Inhibits OC cell proliferation, migration and invasion; suppresses tumor growth in vivo; reverses ferroptosis resistance	[124]
Targeting ferroptosis resistance pathways in iron, dependent cancers	tuberous sclerosis complex 2 (TSC2), deficiency upregulates NRF2 and FSP1, ferroptosis resistance; inhibition of NRF2 or FSP1 knockdown restores sensitivity, enhances iron, dependent LPO	NRF2, FSP1, RSL3, ML385, iFSP1, GSH, GPX4, SLC7A11	Promotes ferroptosis	Sensitizes ovarian and breast cancer cells to ferroptosis; overcomes resistance; potential precision therapy for iron, dependent tumors	[125]
Targeting CYBB to modulate ferroptosis and TAM polarization	CYBB regulates ferroptosis and macrophage polarization in OC; knockdown increases FTH1/FSP1 in TAMs and modulates M1/M2 balance	CYBB, FTH1, FSP1, Erastin, TAMs, OVCAR3, SKOV3	Promotes ferroptosis in TAMs; modulates ferroptosis sensitivity in OC cells	Induces ferroptosis, inhibits tumor progression, reshapes immune microenvironment	[82]
Targeting transcription factor nuclear receptor subfamily 1 group D member 2 (NR1D2) to enhance ferroptosis and modulate immune microenvironment	NR1D2 knockdown, decreases FSP1, increases LPO and Fe^{2+}, induces ferroptosis; simultaneously promotes M1 TAM polarization and inhibits M2 TAM	NR1D2, FSP1, Fe^{2+}, MDA, TAMs, Cisplatin	Promotes ferroptosis	Induces ferroptosis, increases chemosensitivity, reshapes TME, inhibits ovarian tumor progression	[126]
Ferroptosis inducers combined with redox modulation	Menin-MLL inhibitors induce ROS, dependent ferroptosis; combination with auranofin synergistically increases ferroptotic cancer cell death; SCD1 and HO, 1 modulate ferroptosis sensitivity	MI,463, MI,503, MI,2,2, Auranofin, thioredoxin reductase (TrxR), SCD1, HO-1, ROS, Fe^{2+}	Promotes ferroptosis	Induces ferroptosis, suppresses ovarian cancer cell viability, potential combination therapy for chemoresistant tumors	[127]

cer biology and molecular medicine for the treatment of ovarian cancer.

From a mechanistic perspective, nanomaterials can enhance ferroptosis execution signals through various direct or indirect routes. One method involves modifying iron homeostasis control and oxidative stress induced by nanoscale materials. This can be achieved by increasing iron release, enhancing the Fenton reaction, or perturbing redox homeostasis to drive forward the cascade of LPO. In ovarian cancer models, some Fe-based or metal oxide nanoparticles can produce a high level of ROS in tumor cells. These systems, together with stress-response pathways including p53, facilitate the transition of ferroptosis from a subthreshold state to overwhelming lethal execution [102, 103]. In the meantime, nanoparticle-based therapies targeting tumor metabolic properties also possess their own strengths. These interventions can disturb energy metabolism patterns, promote mitochondrial respiration, and decrease the Warburg effect, thus potentially making cancer cells more prone to ferroptosis at the metabolic level. This approach leads to greatly increased sensitivity to therapy and decreased drug resistance phenotypes [104].

Apart from iron balance and oxidative pressure, nanoplatforms could provide a flexible integrated platform to modulate lipid metabolism and antioxidant defense in a synergistic manner [105]. Moreover, the utilization of intelligent carriers responsive to hypoxia or oxidative stress enables synchronized and precise ferroptosis induction and lipid metabolism suppression spatiotemporally. For example, if FINs and SCD1 inhibitors (which block the synthesis of anti-ferroptotic monounsaturated fatty acids) are co-encapsulated in hypoxia-sensitive polymer micelles, the lipid reconstitution capability could be blocked and the LPO load could be increased simultaneously in the TME. Through this method, the compensatory defense mechanisms of tumor cells against ferroptosis are disrupted at a systemic level. On the other hand, in addition to the previously mentioned benefits of targeting cholesterol uptake or membrane lipid homeostasis at the nanoscale level, nanoplatforms can also indirectly facilitate LPO and ferroptosis by altering the balance of antioxidant capacity, specifically weakening GPX4-based antioxidant defense. This also highlights the critical role of lipid metabolism in tightly regulating ferroptosis induction [90].

From the perspective of the evolution of therapeutic norms, ferroptosis-targeted delivery systems facilitated by nanoparticles are reconstructing the rationale for applying ferroptosis as a therapy. They are not so much a novel material or pathway breakthrough as they are a means to spatially localize and integrate signals required to systematically dismantle multi-layered ferroptosis resistance networks that have been shaped in ovarian cancer cells throughout long-term therapeutic stress. Through the increasing integration of material science, tumor molecular subtyping, and biomarker screening, addressable delivery systems have the potential to convert ferroptosis from a bypassable potential risk into a precisely executable therapeutic event. These approaches are hypothesized to have greater therapeutic potential and higher clinical translational value, at least for high-risk ovarian cancer subtypes including Pt-resistant tumors, tumors enriched with stem cell-like cells, and peritoneal metastases.

The potential value of ferroptosis-related biomarkers in predicting treatment response

With the increasing incorporation of ferroptosis into the major mechanisms underlying differential chemo-sensitivity and resistance development in ovarian cancer, its accompanying molecular profiles have gained attention as potential predictive biomarkers for therapeutic response. In contrast to conventional predictive factors focusing on single gene mutation or signal pathway activation, ferroptosis-related biomarkers more comprehensively reflect the overall metabolic-redox balance in tumor cells, including iron homeostasis, LPO threshold, as well as antioxidant defense. These biomarkers are also functionally descriptive of the ability of therapeutic stress to be translated into lethal cellular injury. This feature endows them with the power to predict the heterogeneity of drug sensitivity (such as to Pt-based chemotherapy, PARP inhibitors, and ferroptosis-inducing strategies), thus demonstrating their multi-faceted predictive utility.

At molecular levels, several ferroptosis-related genes have been shown to be significantly correlated with clinical features and therapeutic efficacy of ovarian cancer patients. Evidence suggests that CCAAT/enhancer binding protein gamma (CEBPG) is an upstream regulatory node of ferroptosis in ovarian cancer cells. It can serve as a predictive biomarker and a potential therapeutic target, as its expression is significantly correlated with patient prognosis and treatment outcome [106]. Notably, the involvement of ncRNAs, and especially lncRNAs, in the ferroptosis regulatory network is emerging. Patients with overexpression of ferroptosis-related lncRNAs are more likely to benefit from conventional chemotherapy or ferroptosis-inducing agents. These lncRNAs can serve as potential biomarkers in patient stratification and efficacy prediction [107]. At the level of execution, the central metabolic axis of ferroptosis is also predictively informative. For example, overexpression of FZD7 may facilitate TP63 activation and targeting of the GSH metabolic pathway, which includes GPX4, to increase the tolerance of tumor cells to chemotherapy-derived oxidative stress. Suppressing the expression of GPX4 can sensitize $FZD7^{+}$ Pt-resistant ovarian cancer cells to ferroptosis, indicating that FZD7-associated signaling is an important functional indicator of response to ferroptosis-inducing agents [14].

At a systems level, the predictive model constructed by ferroptosis-related gene signatures could improve the clinical utility further. An integrated model of the ferroptosis and necroptosis signaling pathways has shown better prediction accuracy for advanced ovarian cancer patients treated with Pt-based therapy [108]. Moreover, multifactorial ferroptosis-related gene signatures, such as the 15-ferroptosis-related gene (FRG) signature, have been demonstrated to be independent predictors of overall survival and therapy response in ovarian cancer patients across different populations. They also partially overlap with immune regulatory states, providing a basis for stratification in precision immunotherapy [109, 110].

It should be noted that there are also some limitations to the use of ferroptosis-associated biomarkers in predicting therapeutic response. The prognostic or therapeutic value of a few ferroptosis molecules in different studies is not completely uniform. This more likely results from their highly context-dependent biological nature rather than from major discrepancies in outcomes. Ferroptosis signaling pathways in cell fate determination may be changed by distinct tumor molecular subtypes, treatment regimens, and extracellular matrix (ECM) environments. Thus, future approaches towards the clinical translation of these ferroptosis-related biomarkers should involve their inclusion in multiparametric and function-driven predictive models rather than as stand-alone signatures. Collectively, ferroptosis-associated biomarkers provide an alternative insight into functional state-based monitoring of treatment responses in ovarian cancer. They largely serve to determine whether therapeutic stress is sufficient to drive oxidative imbalance and ferroptotic cell death.

Conclusion and perspectives

In the last few years, accumulating evidence has indicated that ferroptosis is not a minor type of cell death in ovarian cancer cells but an important regulated process closely related to tumor cell metabolism and therapeutic resistance. Ferroptosis is induced by iron-dependent LPO, which interacts with metabolic reprogramming, redox homeostasis, and sensitivity to ferroptosis to define the life of tumor cells [111]. Systemic alterations in ferroptosis-related pathways, such as iron metabolism, lipid ROS thresholds, and ADS, have emerged repeatedly in the context of ovarian cancer progression, intratumoral response to therapy, and acquired resistance during therapy [12, 28]. Under a variety of therapeutic stress stimuli, tumor cells have the ability to delay ferroptosis execution or ameliorate therapy-imposed oxidative damage through enhancing antioxidant systems, reprogramming amino acid metabolism, and altering key regulatory nodes. Under certain key clinical circumstances, such as Pt resistance, heterogeneity in sensitivity to PARP inhibitors, and development of tumor recurrence, ferroptosis can emerge both as a potentially lethal vulnerability of tumor cells under conditions of metabolic and oxidative stress and as an actively repressed adaptive state. The dynamics of this susceptibility and resistance mechanism allow ferroptosis to function as a life-death rheostat to which tumor cells adapt in order to endure sustained

metabolic stress and therapeutic pressure through upregulation of SLC7A11/GPX4 signaling, iron metabolism, and ROS-mediated LPO, especially when co-targeting with PARP inhibitors [15].

It is worth noting that the biological meaning of ferroptosis in ovarian cancer and its clinical value remain relatively uncertain and controversial. Ferroptosis-related characteristic models based on different molecular levels have varied predictive powers for the prognosis and therapeutic efficacy [112], indicating that ferroptotic signaling at the population level is largely affected by the molecular subtype, metabolic status, and microenvironment heterogeneity of the tumors. It is more probable that such differences are attributable to different degrees of functional importance of ferroptosis in distinct biological settings rather than to the occasional limitations of individual research findings. In solid tumors, resistant cell populations, stem cell-like subpopulations, and components of the TME collectively counteract the efficient execution of ferroptosis signaling via multilevel metabolic and antioxidant bypass mechanisms [113], which consequently restricts the sustainability of therapeutic efficacy when targeting a single pathway. Furthermore, the functional cross-talk and hierarchical coordination between ferroptosis and other forms of cell death, including apoptosis, autophagy, and necroptosis/inflammation, for therapeutic purposes are still not fully addressed with systematic comparative and quantitative evaluations. This, in part, limits the clinical predictability and translatability of ferroptosis-related interventions.

The most difficult part of future research is not to find more molecules that mediate ferroptosis, but rather to find their functional context and discover relevant binding partners in those cases where they can be targeted therapeutically. Ferroptosis regulation in specific metabolic and redox contexts, where iron availability, lipid composition, and antioxidant capacity dictate whether oxidative stress leads to cell death or tumor survival, should be the focus of future studies. Inclusion of ferroptosis in multi-omics studies, the possibility of monitoring treatment longitudinally, and investigating molecular cancer subtypes are likely to allow discerning whether it represents an execution pathway or a buffering mechanism shaping tumor fate. Translational ferroptosis-based therapy should additionally surpass the tumor-adaptive suppression of ferroptosis as mediated by the SLC7A11/GSH/GPX4 axis but avoid nonspecific oxidative stress as shown in nanoplatform-based strategies including CuAp@GOx systems in ovarian cancer models [111]. Meticulous regulation of the ferroptosis threshold within specific molecular and therapeutic contexts offers a viable strategy to transition ferroptosis from a tumor-evaded stress pathway into a potent clinical modality for overcoming drug resistance and relapse in ovarian cancer.

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Disclosure of conflict of interest

None.

Abbreviations

ABHD6, abhydrolase domain containing 6; ACSL1, acyl-CoA synthetase long-chain family member 1; ACSL3, acyl-CoA synthetase long-chain family member 3; ACSL4, acyl-CoA synthetase long-chain family member 4; ADS, antioxidant defense systems; AKT, AKT serine/threonine kinase; $ALDH^+$, aldehyde dehydrogenase-positive cells; AMPK, AMP-activated protein kinase; ATO, arsenic trioxide; BMO, Bismuth-based material; BRCA, breast cancer susceptibility gene; CAFs, cancer-associated fibroblasts; CAMKK2, calcium/calmodulin-dependent protein kinase kinase 2; CEBPG, CCAAT/enhancer-binding protein gamma; c-MYC, MYC proto-oncogene, basic helix-loop-helix (bHLH) transcription factor; CREB1, cAMP response element-binding protein 1; CRS, cytoreductive surgery; CYBB, cytochrome b-245 beta chain;

DAMP, damage-associated molecular pattern; DDR2, discoidin domain receptor tyrosine kinase 2; DNMT1, DNA methyltransferase 1; ECH1, enoyl-CoA hydratase 1; ECI1, enoyl-CoA delta isomerase 1; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; EOC, epithelial ovarian cancer; EZH2, enhancer of zeste homolog 2; FASN, fatty acid synthase; FINs, ferroptosis inducers; FRG, ferroptosis-related gene; FSP1, ferroptosis suppressor protein 1; FTH1, ferritin heavy chain 1; FXN, frataxin; FZD7, frizzled class receptor 7; GCLC, glutamate-cysteine ligase catalytic subunit; GPX4, glutathione peroxidase 4; GSH, glutathione; GSSG, oxidized glutathione; H3K18la, histone H3 lysine 18 lactylation; HERC2, HECT and RLD domain-containing E3 ubiquitin protein ligase 2; HIF1α, hypoxia-inducible factor 1 alpha; HMOX1, heme oxygenase 1; HO-1, heme oxygenase 1; HOTAIR, HOX transcript antisense intergenic RNA; HOXC11, homeobox C11; HRD, homologous recombination deficiency; IR, ischemia/reperfusion injury; KEAP1, Kelch-like ECH-associated protein 1; KHDRBS3, KH domain-containing RNA-binding, signal transduction-associated protein 3; LAMA3, laminin subunit alpha 3; LIP, labile iron pool; LPO, lipid peroxidation; MDA, malondialdehyde; MDH1, malate dehydrogenase 1; MMP, mitochondrial membrane potential; MOMP, mitochondrial outer membrane permeabilization; mTOR, mechanistic target of rapamycin; NCOA4, nuclear receptor coactivator 4; NQO1, NAD(P)H quinone dehydrogenase 1; NR1D2, nuclear receptor subfamily 1 group D member 2; NRF2, nuclear factor erythroid 2-related factor 2; OCSCs, ovarian cancer stem-like cells; PARP inhibitors, poly(ADP-ribose) polymerase inhibitors; PROM2, prominin 2; Pt, platinum; PUFA, polyunsaturated fatty acid; RNLS, renalase; ROS, reactive oxygen species; RSL3, RAS-selective lethal 3; SCD, stearoyl-CoA desaturase; SGK1, serum/glucocorticoid-regulated kinase 1; SNAI2, snail family transcriptional repressor 2; SPHK1, sphingosine kinase 1; SREBP1, sterol regulatory element-binding protein 1; STAT3, signal transducer and activator of transcription 3; system Xc^-, cystine/glutamate antiporter system; TAM, tumor-associated macrophage; TME, tumor microenvironment; TOP2A, DNA topoisomerase II alpha; TP53, tumor protein p53; TPT1-AS1, tumor protein translationally controlled 1 antisense RNA 1; TRA2A, transformer 2 alpha homolog; TrxR, thioredoxin reductase; TSC2, tuberous sclerosis complex 2; UFAs, unsaturated fatty acids; USP43, ubiquitin specific peptidase 43; VAMP8, vesicle-associated membrane protein 8; VDAC2, voltage-dependent anion channel 2; YY1, Yin Yang 1 transcription factor.

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