Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2025**; 30(7): 39675
https://doi.org/10.31083/FBL39675

Review

Iron Fist in a Velvet Glove: Class IV Ferroptosis Inducers as a Novel Strategy to Target Ovarian Cancer

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Academic Editor: Sung Eun Kim
Submitted: 11 April 2025 Revised: 30 May 2025 Accepted: 23 June 2025 Published: 24 July 2025

Abstract

Epithelial ovarian cancer (EOC) is a highly lethal gynecological malignancy characterized by frequent late-stage diagnosis, high rates of chemoresistance, and poor long-term survival. Emerging evidence underscores the central role of iron metabolism dysregulation in EOC pathogenesis, progression, and treatment resistance. Ovarian cancer cells and cancer stem cells exhibit an "iron-addicted" phenotype, characterized by increased iron uptake, reduced export, and enhanced storage, which sustains proliferative signaling, redox imbalance, and metastatic potential. Recent advances have illuminated ferroptosis, a regulated form of iron-dependent cell death driven by lipid peroxidation, as a promising therapeutic target for overcoming resistance to platinum-based chemotherapy. This review provides a comprehensive synthesis of the mechanisms governing iron metabolism and ferroptosis in EOC, with a particular focus on Class IV ferroptosis inducers (FINs). These agents act by disrupting iron homeostasis and promoting labile iron pool accumulation, thereby triggering oxidative stress and ferroptotic death. Preclinical studies demonstrate that Class IV FINs, including iron nitroprusside, superparamagnetic iron oxide nanoparticles, ferric ammonium citrate, and Ferlixit, exhibit potent antitumor activity in EOC models, particularly in chemoresistant and stem-like tumor subpopulations. Furthermore, Class IV FINs show synergistic effects when combined with other ferroptosis modulators or immunotherapeutic agents. Despite their promise, clinical translation remains limited by challenges in bioavailability, delivery specificity, and potential systemic toxicity. Ongoing efforts in nanotechnology, biomarker discovery, and tumor stratification offer new avenues for refining ferroptosis-based interventions. Ultimately, this review highlights Class IV FINs as a mechanistically distinct and clinically actionable strategy to target metabolic vulnerabilities in EOC, with the potential to reshape therapeutic paradigms and improve patient outcomes.

Keywords: epithelial ovarian cancer; ferroptosis; metabolism; iron compounds

1. Introduction

Epithelial ovarian cancer (EOC) remains a formidable challenge in gynecological oncology. Despite advances in the conventional treatment paradigm, involving surgical debulking followed by platinum and taxane-based chemotherapeutic regimens, the persistence of high recurrence rates and the frequent development of chemoresistance continue to compromise patient prognosis [1]. These limitations underscore the pressing need for innovative therapeutic strategies to combat this challenging disease [2,3]. Recently, the induction of ferroptosis, an iron-dependent form of regulated cell death mechanistically distinct from apoptosis, has emerged as a promising approach to overcome treatment resistance and impede EOC progression [4]. Preclinical studies have increasingly revealed that ovarian cancer cells often exhibit dysregulated iron metabolism, a characteristic that renders them uniquely susceptible to ferroptosis induction. This intrinsic metabolic vulnerability, coupled with the inherent ability of ferroptosis to bypass traditional drug resistance mechanisms that often plague conventional therapies, positions it as a compelling approach to overcome the limitations of current treatment modalities [5,6]. Furthermore, the growing understanding of the capacity of ferroptosis to modulate the tumor immune microenvironment offers potential avenues for the rational design of synergistic combinations with immunotherapeutic interventions, thus potentially amplifying anti-tumor responses [7]. By strategically exploiting the unique biochemical dependencies of ovarian cancer cells, ferroptosis-based therapies hold the potential to improve treatment outcomes, address the unmet clinical needs in EOC, and ultimately enhance patient survival [8].

In this review, we aim to provide a comprehensive and critical overview of ferroptosis in the context of EOC. Specifically, we will (i) discuss the intricate molecular and biochemical mechanisms that govern ferroptosis, (ii) elucidate the multifaceted role of ferroptosis in the com-

plex pathogenesis of EOC, from early tumorigenesis to advanced disease progression, and (iii) critically evaluate the therapeutic potential of targeting ferroptosis to treat EOC, including the current state of preclinical and clinical investigations, and the challenges and opportunities that lie ahead.

2. Ferroptosis: A Specific Iron-Dependent Form of Regulated Cell Death

2.1 Brief History and Definition

Ferroptosis, a distinct form of regulated cell death (RCD), was initially described by Dixon *et al.* in 2012 [9]. In contrast to other cell death modes, ferroptosis is characterized by the dependence on iron and the accumulation of lipid peroxides, culminating in cellular demise. This process is intricately associated with the expansion of the labile iron pool (Fe^{2+}, LIP), underscoring the critical role of iron in this unique form of cell death [10]. As a non-apoptotic RCD, ferroptosis diverges significantly from apoptosis, necrosis, and autophagy, exhibiting unique morphological, biochemical, and genetic features [11]. Morphologically, ferroptosis is characterized by alterations in mitochondrial ultrastructure, including decreased size and increased membrane density, while the nucleus remains relatively preserved [12,13]. Biochemically, the process is driven by the iron-dependent generation of reactive oxygen species (ROS) and the peroxidation of polyunsaturated fatty acids (PUFAs) within cellular membranes, a process that is relatively refractory to inhibition by classical antioxidant enzymes [14,15]. Genetically, ferroptosis is regulated by a complex network of genes involved in iron metabolism, lipid metabolism, and antioxidant defense, with glutathione peroxidase 4 (GPX4) functioning as a key regulatory enzyme [16]. The discovery of ferroptosis has broadened our understanding of cell death mechanisms and provided new potential targets for therapeutic intervention in diverse pathologies, including cancer.

2.2 The Basic Characteristics of Ferroptosis

As a distinct form of RCD, ferroptosis is characterized by specific morphological and biochemical features that differentiate it from other cell death routes.

Morphologically, ferroptosis is distinguished by alterations in mitochondrial morphology, typically involving mitochondrial shrinkage, increased membrane density, and cristae condensation. In contrast to apoptosis, ferroptosis does not exhibit plasma membrane blebbing, pseudopod retraction, reduction in cell and nuclear volume, apoptotic body formation, or nuclear fragmentation. Furthermore, ferroptosis differs from necrosis and autophagy by lacking plasma membrane rupture, cellular swelling, or a marked accumulation of autophagic vacuoles, respectively [17]. Biochemically, ferroptosis is fundamentally driven by iron-dependent lipid peroxidation, a process that initiates oxidative damage to cellular membranes. This involves the oxidation of PUFAs esterified within membrane phospholipids, and is categorized as either non-enzymatic (auto-oxidation) or enzymatic. Non-enzymatic lipid peroxidation, or auto-oxidation, is a free radical-mediated chain reaction fueled by ROS, with iron acting as a critical catalyst. The pivotal role of iron in ferroptosis arises from its redox cycling between ferrous (Fe^{2+}) and ferric (Fe^{3+}) states, enabling ROS generation via the Fenton reaction. Specifically, Fe^{2+} catalyzes the conversion of hydrogen peroxide (H_2O_2) into highly reactive hydroxyl radicals (•OH), potent initiators of lipid peroxidation [18]. Consequently, dysregulation of genes governing iron uptake (e.g., transferrin receptor, *TfR1*), storage (e.g., ferritin heavy subunit, *FtH1*), and export (e.g., ferroportin, *FPN*) resulting in LIP accumulation, can precipitate membrane lipid peroxidation and culminate in ferroptosis [19,20]. Enzymatic lipid peroxidation is mediated by lipoxygenase (LOX), cyclooxygenase, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzymes activity, which catalyzes the formation of lipid hydroperoxides from PUFAs [16]. While PUFAs are essential components of the phospholipid bilayer, contributing to membrane fluidity, they, particularly arachidonic acid, are susceptible to the Fenton reaction, leading to peroxide formation that compromises membrane integrity and function. The dynamic balance between lipid peroxidation and cellular repair mechanisms is a critical determinant of cell fate. Unlike classical antioxidant enzymes like superoxide dismutase and catalase, which exhibit limited efficacy in preventing ferroptosis, GPX4 plays a central and indispensable role. GPX4 reduces phospholipid hydroperoxides to phospholipids, thereby safeguarding cells from ferroptosis. This process is dependent on glutathione (GSH), a tripeptide composed of three amino acids (γ-glutamyl-cysteinyl-glycine), with potent antioxidant properties, serving as a cofactor. System Xc^-, a heterodimeric amino acid antiporter composed of solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2 (SLC3A2), facilitates the exchange of extracellular cystine for intracellular glutamate. Intracellular cystine is subsequently utilized for GSH synthesis, a process catalyzed by glutamate-cysteine ligase and glutathione synthetase. When system Xc^- functions correctly, it guarantees a constant supply of cystine, allowing the cell to produce enough GSH to neutralize free radicals. However, when this system is inhibited, there is conversely a deficiency of cysteine within the cell, which in turn drastically reduces GSH levels. This results in ROS beginning to accumulate and damage the cell membrane.

Beyond the canonical GPX4-dependent pathway, cells have evolved alternative defense mechanisms to counteract ferroptosis, primarily by preventing lipid peroxidation. These GPX4-independent systems converge on the generation and recycling of lipophilic antioxidants capable of neutralizing lipid-derived ROS. Among these, ubiquinol ($CoQ10H_2$) and tetrahydrobiopterin (BH4) have emerged as critical mediators of ferroptosis resistance [21].

Coenzyme Q10 (ubiquinone, CoQ10) and its reduced form $CoQ10H_2$ are essential lipid-soluble molecules involved in mitochondrial electron transport and lysosomal membrane stabilization. Importantly, $CoQ10H_2$ serves as an effective free radical scavenger, suppressing lipid peroxidation and conferring protection against ferroptosis [22]. Pharmacological approaches aimed at increasing $CoQ10H_2$ levels, including supplementation with farnesyl pyrophosphate, a precursor of CoQ10, or idebenone, a water-soluble CoQ10 analog, have been shown to prevent ferroptosis induced by Class III ferroptosis inducers (FINs), such as FIN56. In contrast, inhibition or genetic disruption of CoQ10 biosynthesis sensitizes cells to ferroptotic death [23].

A pivotal regulator of $CoQ10H_2$-mediated ferroptosis suppression is ferroptosis suppressor protein 1 (FSP1), formerly known as apoptosis-inducing factor mitochondria-associated 2 (AIFM2). FSP1, primarily localized to the outer mitochondrial membrane, undergoes N-myristoylation-dependent translocation to the plasma membrane, where it catalyzes the NADPH-dependent reduction of CoQ10 to $CoQ10H_2$, thereby preventing lipid ROS accumulation and ferroptosis independently of the glutathione-GPX4 axis [24].

Another crucial ferroptosis-modulating antioxidant is BH4, a cofactor essential for the activity of nitric oxide synthases (NOS) and enzymes involved in dopamine and melatonin synthesis [25]. Both dopamine and melatonin have been reported to attenuate ferroptosis. Notably, nitric oxide (NO), a product of NOS activity, has a dual role in ferroptosis regulation. Homma *et al*. [26] demonstrated that NO can inhibit ferroptosis by disrupting the propagation of lipid peroxyl radicals. However, this effect is highly context-dependent. In some settings, inhibition of NO production or blockade of inducible nitric oxide synthase (iNOS) suppresses ferroptosis, as shown in palmitoyl-lysine (PAL)-treated multiple myeloma cells. These observations highlight the pleiotropic role of NO, which can either promote or inhibit ferroptosis depending on the cellular microenvironment and stress conditions [26,27].

The biosynthesis of BH4 is regulated by GTP cyclohydrolase 1 (GCH1), the rate-limiting enzyme in this pathway. Recent studies have implicated the GCH1-BH4 axis as a potent ferroptosis suppressor, acting through the inhibition of lipid peroxidation. Targeting this antioxidant pathway has been proposed as a promising therapeutic strategy in specific malignancies, including gynecological cancers [28–30].

Moreover, dihydroorotate dehydrogenase (DHODH), a mitochondrial flavoprotein and rate-limiting enzyme in *de novo* pyrimidine biosynthesis, has emerged as an additional regulator of ferroptosis. Beyond its canonical role in nucleotide metabolism, DHODH catalyzes the oxidation of dihydroorotate to orotate, coupled with the reduction of ubiquinone to ubiquinol within the inner mitochondrial membrane. Through this mechanism, DHODH contributes to the detoxification of mitochondrial lipid peroxides, thereby limiting ferroptosis. Pharmacological inhibition of DHODH has shown potential in cancer therapy by simultaneously impairing pyrimidine biosynthesis and promoting ferroptotic cell death, particularly in tumors with high oxidative stress dependency [31–33]. The main biochemical and regulatory mechanisms underlying ferroptosis are summarized in Table 1.

3. Iron Metabolism in EOC

3.1 Regulation of Cellular Iron Homeostasis

Iron is an essential trace element that supports a broad range of vital cellular functions. Its unique ability to alternate between two oxidation states, Fe^{3+} and Fe^{2+}, underpins its critical role in redox biology and the catalytic activity of numerous proteins and enzymes. Iron contributes to the formation of coordination complexes such as heme, which is integral to oxygen transport in hemoglobin, and iron-sulfur (Fe-S) clusters, which are key components of enzymes involved in the citric acid cycle and electron transport chain, thereby supporting mitochondrial oxidative phosphorylation (OXPHOS) and ATP production. Moreover, iron acts as a cofactor for a variety of enzymes, including catalases, peroxidases, nitric oxide synthases [34], and ribonucleotide reductase [35]. It also supports essential cellular processes such as DNA repair, telomere maintenance, and ribosome biogenesis [36].

Given its indispensable functions, the maintenance of intracellular iron homeostasis is crucial and requires tight regulation of iron uptake, storage, utilization, and export. Cells primarily acquire iron from the plasma via transferrin (Tf), the major iron transport protein in circulation. Iron-loaded transferrin (holo-transferrin) binds to transferrin receptor 1 (TfR1), which is ubiquitously expressed on cell membranes. The Tf–TfR1 complex undergoes clathrin-mediated endocytosis, and the acidic environment of the endosome facilitates the release of Fe^{3+} from transferrin. The metalloreductase (Six-Transmembrane Epithelial Antigen of the Prostate 3) STEAP3 then reduces Fe^{3+} to Fe^{2+}, which is subsequently transported into the cytosol via the divalent metal transporter 1 (DMT1) [37,38]. In conditions where transferrin becomes saturated, non-transferrin-bound iron can be directly imported into cells through DMT1 or solute carrier family 39 member 14 (ZIP14) [39,40]. Once in the cytosol, iron is utilized for biosynthetic pathways including heme synthesis and the assembly of Fe-S clusters within mitochondria. To prevent the deleterious effects of excess iron, such as Fenton reaction-driven ROS formation, cells employ multiple regulatory mechanisms. Excess cytosolic iron can be exported via FPN, the only known cellular iron exporter, a process facilitated by ferroxidases such as ceruloplasmin, which oxidize Fe^{2+} back to Fe^{3+} for loading onto Tf [41]. Intracellular iron can also be stored safely in ferritin, a 24-subunit protein complex

Table 1. Key molecular mechanisms and regulators of ferroptosis.

Trigger	Mechanisms	Key Molecules/Pathways
Iron Metabolism Dysregulation	Iron overload or labile iron pool (LIP) accumulation; Fe^{2+}/Fe^{3+} redox cycling promotes reactive oxygen species (ROS) generation	Transferrin receptor (*TfR1*), Ferritin heavy subunit (*FtH1*), Ferroportin (*FPN*)
Non-enzymatic Lipid Peroxidation	Auto-oxidation of PUFAs; free radical chain reaction	ROS (•OH), PUFAs (e.g., arachidonic acid)
Enzymatic Lipid Peroxidation	Direct enzymatic oxidation of phospholipids	Lipoxygenases (LOX), Cyclooxygenases, NADPH oxidases
Main Execution Pathway	Description	Key Molecules
Cysteine Supply for GSH Synthesis	System Xc^- antiporter exchanges extracellular cystine for intracellular glutamate	SLC7A11, SLC3A2
Coenzyme Q10 (CoQ10) Pathway	$CoQ10H_2$ scavenges lipid radicals	FSP1/AIFM2 (reduces CoQ10 using NADPH)
Tetrahydrobiopterin (BH4) Pathway	BH4 directly neutralizes lipid radicals	GCH1 (synthesizes BH4), NO, dopamine, melatonin
Mitochondrial DHODH Pathway	Reduces CoQ10 in mitochondria to prevent lipid peroxidation	DHODH (in inner mitochondrial membrane)

ROS, reactive oxygen species; PUFAs, polyunsaturated fatty acids; NADPH, nicotinamide adenine dinucleotide phosphate; GSH, glutathione; SLC7A11, solute carrier family 7 member 11; SLC3A2, solute carrier family 3 member 2; $CoQ10H_2$, ubiquinol; FSP1, ferroptosis suppressor protein 1; AIFM2, apoptosis-inducing factor mitochondria-associated 2; GCH1, GTP cyclohydrolase 1; NO, nitric oxide; DHODH, dihydroorotate dehydrogenase.

composed of heavy (H, FtH1) and light (L, FtL) chains. Ferritin can sequester up to 4500 iron atoms per molecule, with the H-chain catalyzing Fe^{2+} oxidation and the L-chain contributing to iron nucleation and structural stability [42]. Intracellular iron metabolism is post-transcriptionally regulated by the iron regulatory protein/iron-responsive element (IRP/IRE) system. This system modulates the expression of key iron-handling proteins, including DMT1, TfR1, ferritin, and FPN. Two IRPs-IRP1 and IRP2-are ubiquitously expressed but exhibit distinct regulatory properties. Under iron-replete conditions, IRP1 binds a [4Fe–4S] cluster and functions as cytosolic aconitase. When intracellular iron levels are low, the cluster is disassembled, converting IRP1 into an RNA-binding protein. Unlike IRP1, IRP2 lacks aconitase activity and is primarily regulated via proteasomal degradation in response to iron availability. IRPs bind to IREs, which are conserved stem-loop structures located in the untranslated regions (UTRs) of target mRNAs. Binding of IRPs to IREs in the 5′-UTR of ferritin or ferroportin transcripts inhibits their translation, thereby limiting iron storage and export under iron-deficient conditions. Conversely, IRP binding to 3′-UTR IREs in transcripts such as TfR1 and DMT1 stabilizes these mRNAs, promoting iron uptake. In iron-replete conditions, the displacement of IRPs from IREs leads to decreased TfR1 and DMT1 expression and increased ferritin and FPN synthesis, thereby restoring iron homeostasis [43]. More recently, autophagic degradation of ferritin, termed ferritinophagy, has emerged as a key regulatory mechanism of intracellular iron mobilization. This process is mediated by nuclear receptor coactivator 4 (NCOA4), which binds ferritin and directs it to lysosomes, where iron is released in response to hypoxia or iron deficiency. Under conditions of diminished NCOA4 expression or activity, ferritin accumulates, contributing to iron sequestration and cellular iron deficiency [44].

3.2 Dysregulation of Iron Metabolism in EOC

Iron metabolism plays a critical role in the pathogenesis and progression of EOC, influencing tumor growth, metastasis, chemoresistance, and overall disease aggressiveness. Ovarian cancer cells exhibit an “iron-addicted” phenotype, characterized by a heightened dependency on iron to support rapid proliferation, metabolic reprogramming, DNA synthesis, and mitochondrial activity. This increased demand is met through the upregulation of iron acquisition mechanisms, notably the TfR1, which mediates cellular iron uptake from circulating Tf. In contrast, the expression of FPN, the only known iron exporter, is often downregulated in high-grade serous ovarian carcinoma (HGSOC), leading to intracellular iron accumulation (see Fig. 1A).

This dysregulated iron homeostasis not only fuels cellular proliferation and spheroid formation but also promotes migration and metastatic potential [45]. The excess intracellular ferrous iron (Fe^{2+}) contributes to the generation of ROS via Fenton chemistry, which in turn activates oncogenic signaling pathways (e.g., rat sarcoma protein (RAS), mitogen-activated protein kinase (MAPK), inhibits tumor suppressors such as p53 and phosphatase and tensin homolog (PTEN), and induces DNA damage, including the formation of 8-hydroxy-2′-deoxyguanosine, a biomarker of oxidative stress associated with poor prog-

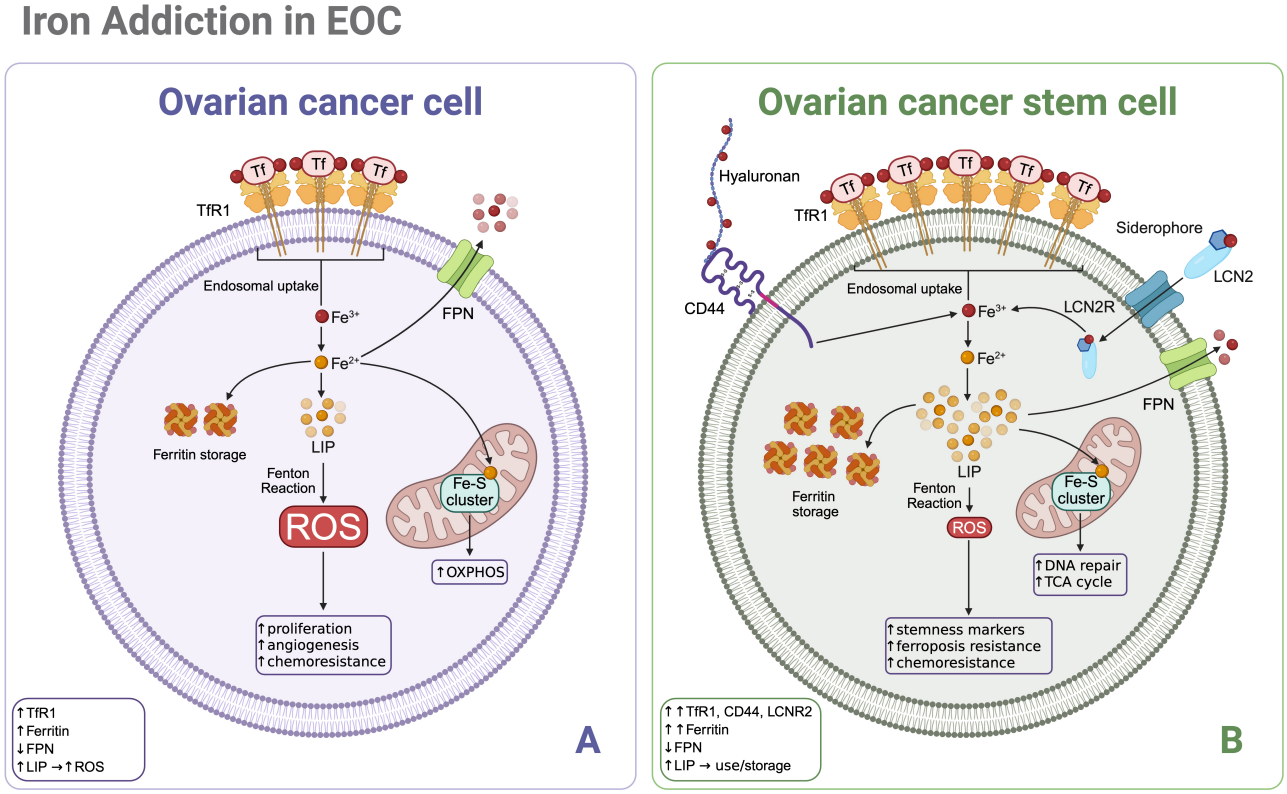

Fig. 1. Schematic representation of the iron addiction in EOC cells and CSCs. (A) EOC cells: Tf-bound iron (Fe^{3+}) is imported through TfR1 and released into the cytosolic LIP as Fe^{2+} after endosomal reduction. Excess iron is sequestered in ferritin nanocages, whereas a limited fraction is exported by the sole iron exported FPN. When iron influx exceeds storage/export capacity, Fe^{2+} participates in Fenton chemistry, generating ROS that act as secondary messengers to activate MAPK/ERK, NF-κB, and HIF-1α pathways, driving proliferation, angiogenic factor production, and chemoresistance. Fe^{2+} is also imported into mitochondria, where it contributes to Fe-S cluster biogenesis, thereby supporting mitochondrial enzyme function and sustaining oxidative phosphorylation. (B) Ovarian CSCs: these cells intensify iron intake by (i) further upregulating TfR1, (ii) expressing the hyaluronan receptor CD44, which stabilizes TfR1 at the membrane, and (iii) recruiting the LCN2/LCNR2 axis. LCN2 captures endogenous iron-siderophore complexes that are internalized via LCNR2, adding an alternative iron source. Despite low FPN, ovarian CSCs sort the increased LIP into ferritin and mitochondrial Fe-S cluster to fuel DNA repair and TCA-cycle enzymes while limiting cytotoxic ROS accumulation. The iron-supported metabolic rewiring reinforces stemness pathways (i.e., STAT3, NOTCH, and NANOG) and bolsters resistance to ferroptosis and chemotherapy. The schematic underscores that both EOC cells and CSCs are iron addicted, but CSCs deploy additional uptake mechanisms and signaling circuits that couple iron metabolism to self-renewal, survival, and therapy resistance, highlighting multiple points for therapeutic intervention. Abbreviations: Tf, transferrin; TfR1, transferrin receptor 1; FPN, ferroportin; CD44, cluster of differentiation 44; LCN2, lipocalin-2; LCN2R, lipocalin-2 receptor; LIP, labile iron pool; TCA, tricarboxylic acid cycle; EOC, epithelial ovarian cancer; CSCs, cancer stem cells; ROS, reactive oxygen species; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; NF-κB, Nuclear Factor Kappa B; HIF, hypoxia-inducible factor; Fe-S, iron-sulfur; STAT3, Signal Transducer and Activator of Transcription 3; NOTCH, Notch receptor; NANOG, Nanog homeobox. Created using BioRender.com.

nosis in HGSOC patients. Iron-driven genomic instability and oxidative stress have also been implicated in the malignant transformation of precursor lesions, such as endometriotic cysts, into endometrioid and clear cell carcinomas, largely due to sustained ROS exposure and mutation accumulation. Some studies demonstrated that the modulation of iron metabolism can interfere with chemotherapy response [46]. Indeed, Zhang *et al.* [47] highlighted that iron addition decreased the carboplatin-mediated DNA damage in ovarian cancer cells by downregulating the expression of DNA polymerase theta (POLQ). By downregulating POLQ, iron disrupt its interaction with recombinase (RAD51), promotes RAD51-mediated DNA double-strand breaks repair, thus leading to enhanced cell survival and reduced platinum sensitivity [47,48]. Conversely, the iron chelator deferoxamine (DFO) increased nuclear POLQ-RAD51 co-localization, thus amplifying DNA damage and restoring platinum sensitivity.

In the tumor microenvironment, iron modulates immune function by impairing macrophage cytotoxicity and promoting immunosuppression, partly through the upregulation of interleukin-6 (IL-6) and the inhibition of NO production. Tumor-associated macrophages may adopt an iron-donating phenotype, further enriching the local iron supply to support cancer cell survival [49].

Therapeutically, iron metabolism represents a compelling target in EOC. Iron chelators such as DFO have demonstrated antitumor efficacy by depleting the labile iron pool, inducing apoptosis, and sensitizing cancer cells to chemotherapy. Moreover, the induction of ferroptosis, the iron-dependent form of regulated cell death driven by lipid peroxidation, offers a promising strategy to overcome resistance in EOC, although cancer cells often deploy antioxidant defenses such as GPX4 to evade this fate. Notably, different histological subtypes of EOC, including HGSOC, endometrioid carcinoma, clear cell carcinoma, and mucinous carcinoma, exhibit distinct expression patterns of iron-regulating genes (e.g., *TfR1*, *FPN*, *FtH1*) suggesting that subtype-specific metabolic vulnerabilities may be exploited for targeted therapy [50].

3.3 Iron Addiction of EOC Cancer Stem Cells (CSCs)

Ovarian CSCs, a subpopulation within epithelial ovarian tumors, are defined by their capacity for self-renewal, pluripotency, and long-term tumor propagation. These cells have been strongly implicated in disease relapse and resistance to standard therapies.

Recent findings have highlighted iron metabolism as a central regulator of ovarian CSC biology, contributing to their survival, proliferation, and therapeutic evasion. Elevated iron concentrations are a hallmark of the ovarian tumor microenvironment, with iron-rich conditions preferentially supporting CSC expansion. Ovarian CSCs exhibit increased iron uptake, a phenomenon driven by the overexpression of TfR1, the primary receptor mediating cellular iron acquisition from circulating Tf. This elevated iron influx fulfills the heightened metabolic requirements of CSCs, supporting DNA synthesis, mitochondrial respiration, and epigenetic regulation. Simultaneously, these cells show increased expression of ferritin, an iron storage protein, which protects against iron-induced oxidative stress by sequestering excess iron and limiting ROS accumulation [51]. The balance between iron availability and oxidative stress appears to be tightly maintained through modulation of the LIP, enabling CSCs to exploit iron without succumbing to cytotoxic damage (see Fig. 1B). IRP1 and IRP2, which modulate post-transcriptional control of iron metabolism-related genes via IREs, also play a pivotal role in CSCs. Overexpression of *IRP2*, frequently observed in HGSOC, enhances TfR1 expression and augments intracellular iron uptake, thereby promoting CSC maintenance and proliferation. Meanwhile, IRP1 activity may be altered in CSCs, shifting from its role as cytosolic aconitase to an RNA-binding protein under iron-deficient conditions, with implications for redox homeostasis and iron-related gene expression. In this regard, Basuli *et al.* [45], reported HGSOCs and their associated CSC populations display decreased expression of FPN and elevated levels of TfR1, contributing to intracellular iron accumulation. This imbalance favors tumor aggressiveness, as excessive iron has been shown to upregulate matrix metalloproteinases and IL-6, facilitating invasion and metastasis [45]. In preclinical models, depletion of intracellular iron in ovarian CSCs inhibited their proliferation, reduced tumor growth, and limited peritoneal dissemination, supporting the notion that iron is a non-redundant cofactor for ovarian tumor-initiating capacity [52,53].

To further meet their iron demands, recent studies highlighted that ovarian CSCs utilize cluster of differentiation 44 (CD44)-mediated iron endocytosis [54–56]. CD44, a transmembrane glycoprotein broadly expressed across various cell types, has been extensively characterized as a principal receptor for hyaluronic acid (HA) and a marker of CSCs. Beyond its canonical roles in cell adhesion, motility, and matrix interaction, recent evidence implicates CD44 as a central player in iron metabolism within the CSC compartment. In CSCs, CD44 facilitates the endocytosis of iron in at least two major ways. First, CD44 directly binds to HA, which can form complexes with iron ions or iron-binding proteins, allowing CD44-mediated internalization of iron-containing HA structures. Second, and perhaps more significantly, CD44 interacts with the lipocalin-2 (LCN2)/lipocalin-2 receptor (LCN2R) axis. LCN2 is an iron-trafficking protein that binds siderophore-bound iron with high affinity. The LCN2–siderophore–iron complex is internalized via CD44–LCN2R-mediated endocytosis, delivering bioavailable iron into the cytosol of CSCs. This process enhances the intracellular LIP, fueling mitochondrial respiration, nucleotide biosynthesis, and epigenetic regulation, all of which are essential for the maintenance of stemness and tumorigenicity [54]. The upregulation of CD44 in CSCs corresponds with increased iron uptake and storage, often accompanied by elevated expression of TfR1 and ferritin, suggesting a cooperative network that tightly controls iron availability and detoxification [55,56]. Importantly, CD44 also intersects with key signaling pathways involved in cancer progression and iron regulation, including (phosphatidylinositol 3-kinase/protein kinase B) PI3K/Akt, Wnt/β-catenin, and hypoxia-inducible factor (HIF) signaling. These pathways may synergize with CD44 to regulate the expression of iron metabolism-related genes and sustain CSC properties under stress conditions such as hypoxia or chemotherapy. For example, HIF-1α can induce *TfR1* expression under hypoxic conditions, while PI3K/Akt signaling modulates ferritin levels and iron-dependent ROS production. Interestingly, while CD44 promotes iron uptake, CD133, another key surface expression marker of CSCs, has been identified as a neg-

Table 2. Ferroptosis regulatory roles of p53 in HGSOC *vs* OCCC.

Aspect	Epithelial ovarian cancer-EOC (normal condition)	High-grade serous ovarian cancer (HGSOC)	Ovarian clear cell carcinoma (OCCC)
p53 status	*p53*-wild-type	Mutated in ~96% of cases	*p53*-wild-type in >80% of cases
p53 function	*p53*-wild-type represses solute carrier family 7 member 11 (SLC7A11), promoting ferroptosis	*p53* mutation fails to repress SLC7A11, reducing ferroptosis sensitivity	*p53*-wild-type, but ferroptosis resistance due to other mechanisms
Impact on ferroptosis	Ferroptosis sensitivity due to *p53*-wild-type	Ferroptosis resistance due to *p53* mutation	Ferroptosis resistance despite *p53*-wild-type
Tumor progression	Reduced tumorigenesis	Increased tumor resilience	Poor prognosis, increased metastasis and recurrence
Therapeutic implications	Restore p53 function or enhance p53 ability to induce ferroptosis	Targeting SLC7A11 or restoring *p53*-wild-type	Targeting alternative ferroptosis pathways

ative regulator of TfR1-mediated iron entry, suggesting a nuanced and possibly context-dependent regulation of iron metabolism by stemness-associated surface proteins [44].

Given the heterogeneity of epithelial ovarian cancer, stratification of patients based on iron metabolic profiles may aid in identifying those most likely to benefit from iron-targeted therapies. Plus, the integration of iron-targeted strategies with conventional chemotherapy and novel CSC-directed agents offers a promising avenue to improve outcomes in patients with advanced ovarian cancer.

4. Ferroptosis: An Emerging Therapeutic Target in EOC

Advances in cancer research and cell biology have progressively revealed the significant involvement of ferroptosis in tumorigenesis, tumor progression, and antineoplastic therapy across various malignancies. The role of ferroptosis in EOC can be conceptualized within four key aspects: (i) its participation in EOC tumorigenesis and progression, (ii) its potential for prognostic prediction, (iii) the development of related therapeutic strategies, and (iv) its capacity to reverse chemotherapy resistance [57]. Despite significant advances in understanding the pathogenesis of EOC, key molecular mechanisms underlying its progression remain incompletely defined. One emerging area of interest is the role of ferroptosis, a form of regulated, iron-dependent cell death, in the biology of EOC. Disruptions in iron metabolism is indeed a hallmark of EOC, critically influencing tumorigenesis and disease progression. In particular, HGSOC cells and tumor-initiating cells exhibit increased expression of *TfR1* and downregulation of *FPN*, leading to an accumulation of intracellular iron. This iron overload creates a pro-oxidant state that renders cells particularly vulnerable to ferroptosis, offering a unique therapeutic vulnerability termed “iron addiction” [45,58,59].

The interplay between ferroptosis and genetic mutations further accentuates its role in EOC progression. Central to this process is the tumor suppressor protein p53, which exerts multifaceted roles in cell fate regulation. Under normal conditions, *p53*-wild-type promotes ferroptosis by transcriptionally repressing solute carrier family 7 member 11 (SLC7A11), a gene encoding a subunit of system Xc^-, which is responsible for cystine uptake and glutathione synthesis, both critical for antioxidant defense [59–61]. By downregulating *SLC7A11*, *p53* lowers cellular antioxidant capacity, thereby facilitating lipid peroxidation and ferroptotic cell death, ultimately suppressing tumor growth. However, recent findings indicate that *p53* can be functionally inactivated through the action of proteins such as Mex-3 RNA binding family member A (MEX3A), which contains both a ring finger domain and an RNA-binding domain. Overexpression of *MEX3A* has been shown to promote tumorigenesis by enhancing *p53* degradation, thereby impairing its ability to trigger ferroptosis. This mechanism may contribute to the survival and expansion of malignant cells, particularly in *p53*-wild-type settings [62,63].

Notably, mutations in *p53* are present in approximately 96% of HGSOC, the most common and aggressive EOC subtype. In these cases, *p53* mutation often fails to repress SLC7A11, resulting in reduced sensitivity to ferroptosis and increased tumor resilience. Conversely, in ovarian clear cell carcinoma (OCCC), a distinct EOC subtype, over 80% of tumors retain *p53*-wild-type, yet paradoxically exhibit poorer prognosis, enhanced drug resistance, and increased rates of metastasis and recurrence [59]. This suggests that, in OCCC, mechanisms other than *p53* mutation may contribute to ferroptosis resistance and tumor aggressiveness. Hence, the impact of p53 on ferroptosis varies significantly across EOC subtypes. While *p53* mutation is a major driver of ferroptosis suppression and tumor progression in HGSOC, alternative regulatory pathways may be more relevant in *p53*-wild-type cancers such as OCCC. These findings underscore the potential of targeting ferroptosis-related pathways, including SLC7A11 and p53 regulators, as a therapeutic strategy in EOC [64]. Table 2 summarizes the ferroptosis regulatory roles of p53 in EOC under normal condition, HGSOC and OCCC.

Importantly, ferroptosis not only contributes to tumor cell death but also actively shapes the tumor microenvironment (TME), promoting a more immunogenic and inflam-

matory landscape. The oxidative stress intrinsic to ferroptosis triggers the release of damage-associated molecular patterns (DAMPs) such as adenosine triphosphate (ATP), high mobility group box 1 (HMGB1), and calreticulin. These molecules serve as potent immunostimulatory signals, enhancing the recruitment and activation of dendritic cells and cytotoxic T lymphocytes within the TME. Ferroptotic tumor cells have also been shown to increase type I interferon signaling, further augmenting antitumor immunity by enhancing antigen presentation and T cell priming. In ovarian cancer, which is often characterized by an immunosuppressive microenvironment, the induction of ferroptosis may act as a strategic lever to reprogram immune dynamics. For instance, ferroptosis can reverse immune evasion by reducing the activity of regulatory T cells and myeloid-derived suppressor cells, while promoting the infiltration of $CD8^+$ T cells. This immune-permissive reconfiguration has important therapeutic implications, especially in HGSOC, where traditional immunotherapies have had limited efficacy [65].

Furthermore, emerging evidence suggests that combining FINs with immune checkpoint inhibitors (e.g., anti-programmed cell death protein 1/programmed death-ligand 1(PD-1/PD-L1) therapies) results in synergistic antitumor effects, enhancing both direct cytotoxicity and immune-mediated clearance of cancer cells. In preclinical models of EOC, such combinations have been shown to increase tumor antigen visibility, stimulate pro-inflammatory cytokine production (such as IL-6 and TNF-α), and suppress metastatic potential. The dynamic interaction between ferroptosis and the immune system not only enhances immunosurveillance but also offers a strategy to convert "cold" tumors into "hot" ones, thus improving their sensitivity to immunotherapy [65,66].

The integration of bioinformatic approaches into ferroptosis and ovarian cancer research has opened new avenues for the discovery of diagnostic and prognostic biomarkers, as well as for the stratification of patients based on their molecular and metabolic profiles. In particular, the application of multi-omics analyses, including proteomics, metabolomics, and bioenergetics, has revealed distinct metabolic heterogeneity within HGSOC [67]. These studies have identified two major tumor subgroups: high-OXPHOS and low-OXPHOS phenotypes, distinguished by their reliance on oxidative phosphorylation. Notably, high-OXPHOS tumors are characterized by elevated mitochondrial activity, chronic oxidative stress, and a higher propensity for ferroptosis. Interestingly, this subgroup correlates with a favorable prognosis, suggesting that ferroptosis susceptibility linked to oxidative metabolism may serve as a clinically relevant prognostic indicator in EOC [67,68]. In parallel, transcriptomic analyses using data from public repositories such as The Cancer Genome Atlas (TCGA) and the Gene Expression Omnibus (GEO) have led to the identification of novel ferroptosis-related gene (FRG) signatures with strong prognostic implications. One such signature includes three key FRGs, HIC ZBTB transcriptional repressor 1 (*HIC1*), lysophosphatidylcholine acyltransferase 3 (*LPCAT3*), and dual oxidase 1 (*DUOX1*), whose expression patterns have been used to construct a risk score model capable of stratifying EOC patients into high- and low-risk groups. This model has been robustly validated and reveals that high-risk patients exhibit enhanced enrichment of immune-related pathways, increased infiltration of M2-polarized macrophages, and upregulation of immune checkpoint molecules, such as PD-1 and cytotoxic T-lymphocyte associated protein 4 (CTLA-4). These features are consistent with a more immunosuppressive tumor microenvironment and a poorer clinical outcome, underscoring the importance of ferroptosis-related immune modulation in EOC pathophysiology [67]. Additionally, ferroptosis-related long non-coding RNAs (FRLs) have emerged as valuable components of the tumor transcriptome, capable of influencing ferroptotic sensitivity and immune interactions. A recent study has developed and validated a nine-FRL signature that effectively stratifies EOC patients by risk and predicts overall survival. These FRLs may modulate ferroptosis by regulating the expression of FRGs, redox balance, and iron metabolism, providing insight into non-coding RNA–mediated control of cell death and immune evasion mechanisms [69].

Together, these findings highlight the critical role of ferroptosis-associated molecular signatures in defining tumor subtypes, predicting prognosis, and potentially guiding personalized therapeutic strategies. The continued application of bioinformatic and systems biology tools will be essential in refining these models and integrating ferroptosis-based metrics into clinical decision-making frameworks for ovarian cancer.

5. FINs and Relative Mechanisms of Action

Ovarian cancer remains one of the most lethal gynecological malignancies, primarily due to its frequent diagnosis at advanced stages. This diagnostic delay is largely attributed to an initial asymptomatic course and the absence or underutilization of effective screening strategies [70]. Compounding this issue, the emergence of resistance to conventional therapies, particularly platinum-based chemotherapy, significantly worsens patient prognosis and contributes to high mortality rates [71]. Recent research has identified ferroptosis as a critical biological process with substantial therapeutic implications in cancer, including ovarian cancer, where preclinical studies have shown encouraging results. Of particular interest is the vulnerability of ovarian CSCs to ferroptosis. These cells, known for driving tumor initiation, progression, metastasis, and recurrence, exhibit a pronounced dependency on iron, often referred to as "iron addiction". This metabolic trait creates a unique vulnerability: the elevated LIP and intrinsic redox imbalance in CSCs can be leveraged by FINs to induce selective ferroptotic death. In HGSOC, where

CSCs are central to disease aggressiveness and therapeutic resistance, targeting ferroptosis may represent a powerful strategy to eliminate this treatment-refractory population. Moreover, emerging evidence suggests that the activation of ferroptosis not only contributes to tumor cell death but also modulates the TME. Inducing ferroptosis in ovarian cancer cells has been shown to enhance antitumor immune responses, potentially improving the efficacy of immunotherapies [59]. This immunomodulatory effect opens new avenues for combination therapies, integrating FINs with immune checkpoint inhibitors or other immunotherapeutic modalities [72,73].

So far, several FINs have been developed to pharmacologically activate ferroptotic pathways in cancer cells. These small molecules act on various molecular targets to promote intracellular iron accumulation, inhibit antioxidant defenses, or trigger lipid peroxidation. Mechanistically, FINs can be subdivided into four main classes, each characterized by a distinct mechanism of action. Class I FINs inhibit the system Xc^-, reducing GSH synthesis and compromising GPX4 activity. Class II FINs act directly by inhibiting GPX4, preventing lipid peroxides detoxification and promoting ROS accumulation. Class III FINs target the FSP1-CoQ10 system or induce GPX4 depletion, making tumor cells more vulnerable to ferroptosis. Class IV FINs directly modulate iron metabolism, increasing LIP through release from storage compartments or inhibition of efflux, leading to free radical generation and lipid peroxidation [74].

5.1 Class I FINs: GSH Depletion

Class I FINs represent a promising class of small molecules that selectively induce ferroptotic cell death by targeting the cystine/glutamate antiporter system Xc^-. This membrane-bound transporter, composed primarily of the subunits SLC7A11 and SLC3A2, plays a crucial role in maintaining cellular redox homeostasis. By facilitating the import of cystine, an essential precursor for GSH biosynthesis, system Xc^- ensures adequate antioxidant defense against ROS. GSH, a tripeptide composed of glutamate, cysteine, and glycine, is vital for neutralizing lipid peroxides via GPX4. Inhibition of system Xc^- disrupts cystine uptake, leading to GSH depletion, accumulation of lipid ROS, and ultimately ferroptosis [75].

In the context of EOC, Class I FINs have gained increasing attention for their ability to circumvent traditional resistance mechanisms. Among these, preclinical studies have demonstrated that erastin, the prototypical Class I FIN, exerts selective cytotoxicity against platinum-resistant ovarian cancer cell lines such as SKOV3 and OVCAR8, and enhances the efficacy of cisplatin in combination therapy [76–78]. Consistent with these findings, additional *in vitro* and *in vivo* studies confirmed that erastin, when combined with cisplatin, induces ferroptosis and significantly enhances tumor growth inhibition [79]. Metabolomic analyses further reveal that erastin-treated ovarian carcinoma cells display alterations in sulfur amino acid metabolism, accumulation of pro-inflammatory eicosanoids, and dysregulation of arachidonic acid metabolism, underscoring the oxidative and metabolic vulnerabilities induced by ferroptosis [80]. Additionally, erastin inhibits the ATP binding cassette subfamily B member 1 (ABCB1) transporter, reducing efflux of chemotherapeutics such as docetaxel, restoring drug sensitivity, and synergistically increasing tumor cell death in resistant models [81]. Notably, a recent study revealed that EOC cell sensitivity to erastin correlates with intracellular LIP levels, with resistance observed when LIP remains low despite the presence of FINs (i.e., erastin). Consistently, co-treatment with exogenous iron intensifies intracellular ROS production, thereby enhancing sensitivity to erastin-induced ferroptosis in EOC resistant cells [82]. In a recent study, our group further demonstrated that EOC cells evade ferroptosis by exporting iron-loaded ferritin via CD63-mediated multivesicular body (MVB)/extracellular vescicle (EV) trafficking. Notably, inhibition of EV biogenesis re-sensitizes cells to ferroptosis *in vitro*, revealing a novel resistance mechanism and potential therapeutic target in ovarian cancer [83].

Erastin's activity extends beyond cytotoxicity, as it also modulates the TME. In *in vivo* models of ovarian carcinoma, erastin administration in combination with oncolytic virus therapy was shown to potentiate immunogenic cell death, characterized by DAMPs release, increased $CD8^+$ T cell infiltration, and suppression of metastasis, pointing toward synergistic potential with immunotherapies [73].

Another Class I FIN, sulfasalazine, also targets system Xc^- and has demonstrated therapeutic relevance in ovarian cancer. In paclitaxel-resistant uterine serous carcinoma cells, sulfasalazine showed greater cytotoxicity than in sensitive cells, inducing cell death through c-Jun N-terminal kinase (JNK)-mediated ferroptosis [84]. Furthermore, combination of sulfasalazine with Poly(ADP-Ribose) polymerase (PARP) inhibitors in breast cancer (BRCA)-proficient ovarian cancer significantly enhanced ferroptotic responses. PARP inhibition suppresses SLC7A11 expression and reduces GSH biosynthesis, thereby sensitizing cells to sulfasalazine-induced ferroptosis [85].

Sorafenib, another Class I FIN, has also shown promise in ovarian carcinoma. A recent study identified that oxidative stress induced growth inhibitor 1 (*OSGIN1*) deletion activates the ataxia telangiectasia mutated (ATM)–AMP-activated protein kinase (AMPK) axis, leading to the upregulation of SLC2A3, a glucose transporter that enhances cell survival by mitigating ferroptosis. However, pharmacological blockade of SLC2A3 using neutralizing antibodies sensitized tumor cells to sorafenib, enhancing ferroptotic cell death and reducing tumor burden in xenograft models [86].

5.2 Class II FINs: GPX4 Inactivation

Rather than targeting the system Xc^-, Class II FINs directly inhibit GPX4, a selenoenzyme critical for detoxifying lipid hydroperoxides and maintaining redox balance in cancer cells. By blocking GPX4 activity, these agents disrupt the cellular antioxidant defense, leading to the accumulation of lethal lipid peroxides and triggering ferroptosis, a non-apoptotic form of cell death.

In the context of EOC, Class II FINs offer considerable therapeutic potential, particularly in tumors that exhibit resistance to platinum-based chemotherapy. Ovarian cancer cells frequently enhance GPX4 expression as a survival mechanism to counteract oxidative stress. However, pharmacological inhibition of GPX4 disables this defense, re-sensitizing tumor cells to oxidative damage and promoting ferroptosis. Notably, this strategy may also remodel the TME, enhancing immune responses and improving the efficacy of chemotherapy and immunotherapy.

Among the most studied Class II FINs are RAS-selective lethal 3 (RSL3), ML162, ML210, altretamine, and withaferin A. RSL3 has shown significant activity in *in vitro* and *in vivo* models of ovarian carcinoma. Luo *et al*. [87] demonstrated that inhibition of paired box 8 (PAX8), a transcription factor regulating GSH synthesis, sensitizes ovarian cancer cells to RSL3-induced ferroptosis through enhanced lipid peroxidation. The combination of *PAX8* knockdown with RSL3 treatment resulted in substantial growth suppression in both cell culture and xenograft models.

Lipid peroxidation is a hallmark of ferroptosis, and LOXs play a pivotal role in this process. RSL3 efficacy in ovarian cancer is critically dependent on LOX activity, as demonstrated by a study showing that LOX inhibition impairs ferroptotic cell death induced by GPX4 blockade [88].

Another key regulator of ferroptosis in ovarian cancer is the nuclear factor erythroid 2-related factor 2 (NRF2) transcription factor, which modulates antioxidant responses. Co-targeting NRF2 and GPX4 has emerged as a promising combinatorial strategy. Inhibition of NRF2 using ML385, in conjunction with RSL3, significantly increased ROS and 4-hydroxynonenal (4-HNE) accumulation, leading to ferroptosis and suppressed tumor growth *in vivo* [89]. High expression of junctional adhesion molecule 3 (JAM3) activates the NRF2/FSP1 axis, conferring resistance to RSL3. JAM3 inhibition re-sensitizes ovarian cancer cells to ferroptosis, further emphasizing the role of NRF2 in therapeutic resistance [90].

Additional resistance mechanisms involve the sphingosine kinase 1 (SPHK1)–Nuclear Factor Kappa B (NFκB)–NRF2 pathway, particularly in olaparib-resistant ovarian cancer. SPHK1 overexpression reduces RSL3 sensitivity, whereas its inhibition restores ferroptosis induction [91]. Similarly, targeting the peptidylprolyl cis/trans isomerase, NIMA-interacting 1 (PIN1)–NRF2–GPX4 axis enhances RSL3-mediated cytotoxicity and increases tumor sensitivity to cisplatin, suggesting the potential for synergy between ferroptosis induction and DNA-damaging agents [92].

Crucially, ovarian CSCs also exhibit sensitivity to GPX4 inhibition. Combined knockdown of frataxin (*FXN*), which regulates mitochondrial redox homeostasis, and GPX4 blockade via RSL3 enhances ferroptosis in CSCs, offering a strategy to eliminate these treatment-refractory cells [93]. MicroRNAs (miRNAs) are emerging as modulators of ferroptosis sensitivity [94]. For instance, miR-424-5p suppresses ferroptosis by targeting ACSL4, an enzyme involved in lipid remodeling. Overexpression of miR-424-5p decreases sensitivity to RSL3, while its inhibition restores ferroptotic cell death [95]. Conversely, miR-1-3p promotes ferroptosis by targeting frizzled class receptor 7 (*FZD7*), with overexpression enhancing RSL3 efficacy in ovarian tumor models [96].

Resistance to PARP inhibitors in homologous recombination (HR)-proficient ovarian cancers presents a major clinical challenge. Recent findings suggest that GPX4 inhibition via RSL3 enhances PARP inhibitor efficacy, promoting ferroptosis and overcoming resistance [97].

Beyond RSL3, ML162 and ML210 are widely used as GPX4 inhibitors in research settings to confirm ferroptosis involvement. These compounds have been applied in ovarian carcinoma studies to validate ferroptotic cell death, including in eribulin-treated OCCC, where GPX4 inhibition enhanced cytotoxicity [98]. In parallel, machine learning-based modeling has been applied to predict ferroptosis sensitivity in cancer cells. ML210 and ML162 have been used to experimentally validate these predictions, reinforcing their utility in biomarker discovery and personalized therapy development [99].

Altretamine (hexamethylmelamine), a Food and Drug Administration (FDA)-approved drug for recurrent ovarian cancer, has recently been shown to act as a GPX4 inhibitor, suggesting that its antineoplastic effects may be partially mediated by ferroptosis [100,101]. Nevertheless, further research is warranted to establish its role in ferroptosis induction in ovarian carcinoma.

Finally, withaferin A, a steroidal lactone derived from withania somnifera, possesses known antitumor properties. While direct evidence of its ferroptosis-inducing activity in ovarian cancer is lacking, studies in other malignancies suggest potential involvement. Withaferin A has been shown to activate oxidative stress pathways, such as Kelch-like ECH-associated protein 1 (KEAP1)/NRF2, and promote ROS accumulation, mechanisms compatible with ferroptosis induction [16,102,103].

5.3 Class III FINs: GPX4 Depletion

Class III FINs are mechanistically distinct from classes I and II, as they primarily act by promoting proteasomal degradation of GPX4 and by disrupting CoQ10, also

known as ubiquinone, metabolism. Both GPX4 and CoQ10 are pivotal components of the cellular antioxidant defense system, essential for neutralizing lipid peroxides and maintaining redox homeostasis. Inhibiting these systems leads to uncontrolled accumulation of lipid radicals, culminating in ferroptosis.

The prototypical compound in this class, FIN56, induces ferroptosis via a dual mechanism: it promotes GPX4 degradation while simultaneously depleting CoQ10, leading to excessive lipid peroxidation and oxidative stress. A preclinical study has demonstrated the efficacy of FIN56 in various cancer models, including glioblastoma and bladder carcinoma [104]. Though direct studies in ovarian cancer are currently limited, the mechanistic underpinnings of Class III FINs suggest potential applicability. Ovarian tumors, particularly high-grade serous subtypes, frequently exhibit oxidative stress adaptation and elevated GPX4 activity, making them theoretically vulnerable to FIN56-mediated ferroptosis. Additionally, *KEAP1* mutations, common in certain tumors, can upregulate NRF2 and FSP1, which maintains CoQ10 in its reduced form. By targeting CoQ10 degradation, FIN56 may overcome FSP1-mediated ferroptosis resistance even in tumors with NRF2 pathway activation [105].

Statins, widely used lipid-lowering drugs, also intersect with CoQ10 metabolism. They inhibit 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase, impairing mevalonate pathway activity and consequently reducing CoQ10 synthesis. This renders tumor cells more susceptible to ferroptosis, particularly when oxidative stress is amplified or iron metabolism is dysregulated. Moreover, recent data suggest that statins like simvastatin may also influence GPX4 expression, contributing further to ferroptotic susceptibility [106,107]. Although most studies focus on triple-negative breast cancer, these findings provide a rationale for exploring statin-based combinations in ovarian cancer models as well.

5.4 Class IV FINs: Lipid Peroxidation by Increasing the LIP or Oxidizing Iron

Class IV FINs act by directly disrupting iron metabolism, thereby increasing intracellular LIP and promoting lipid peroxidation. These agents enhance ferroptosis by exploiting the cancer cell's intrinsic dependence on iron homeostasis, a hallmark of highly proliferative and therapy-resistant tumors such as ovarian cancer. Their mechanisms include: (i) upregulation of iron uptake, primarily via increased expression of TfR1, (ii) inhibition of iron export, through downregulation or blockade of FPN, (iii) release of iron from intracellular stores, including FtH1 via NCOA4-mediated ferritinophagy, and from heme via heme oxygenase-1 (HO-1) activity, (iv) mobilization of mitochondrial iron, contributing to cytosolic iron overload and ROS generation [16,108].

Recent research has demonstrated that iron oxide nanoparticles (IONPs) can serve as Class IV FINs by selectively targeting CSCs in ovarian tumors. IONPs are internalized by CSCs, where they release ferrous ions, elevate intracellular iron, promote ROS accumulation, and induce lipid peroxidation, ultimately resulting in ferroptosis [109]. Importantly, IONPs also modulate the expression of key iron-handling proteins such as ferritin and ferroportin, further perturbing iron homeostasis.

Additionally, modulation of iron chaperones such as Poly(RC) binding protein 1 (PCBP1), which facilitate iron storage within ferritin, has emerged as a novel regulatory axis. Silencing *PCBP1* disrupts this process, increasing free iron and enhancing ferroptosis sensitivity [110]. Overall, Class IV FINs represent an innovative and versatile therapeutic avenue, capable of directly exploiting iron dependency of EOC, particularly in its aggressive and chemoresistant subtypes.

However, their therapeutic application must be approached cautiously, as excess free iron can cause collateral damage to healthy tissues. Therefore, advanced targeting strategies, such as nanoparticle-based delivery systems or CSC-specific ligands, are critical for clinical translation.

A comprehensive summary of the main FINs used in the EOC treatment is provided in Table 3 (Ref. [73,77,80,82,84,86,88,93,97,98,101,103,104,106,111–118]).

6. Class IV FINs as Promising Approach for Overcoming Chemoresistance in EOC

Despite advances in treatment, EOC remains a leading cause of gynecological cancer-related mortality. One of the primary challenges in managing EOC is the development of resistance to platinum-based chemotherapy, which occurs in most patients and significantly impairs prognosis. A key mechanism underlying this resistance is the reduced susceptibility to apoptosis, which limits the efficacy of conventional therapies. As a result, non-apoptotic cell death pathways, particularly ferroptosis, have gained increasing attention as alternative therapeutic targets [119].

Among ferroptosis-inducing agents, Class IV FINs, which act by modulating intracellular iron homeostasis, have shown exceptional promise. These compounds promote the accumulation of LIP and stimulate lipid peroxidation, thereby inducing ferroptotic cell death. This approach is especially relevant in EOC, where dysregulated iron metabolism and iron addiction confer a unique vulnerability to ferroptosis induction (see Fig. 2) [108].

6.1 Iron Nitroprusside (FeNP)

FeNP, initially proposed for chemodynamic therapy, exerts a dual ferroptotic effect by generating •OH through Fenton-like reactions and simultaneously depleting GPX4, a key antioxidant enzyme. Unlike traditional agents requiring delivery systems, FeNP exploits endogenous H_2O_2 in the tumor microenvironment to selectively kill cancer cells while sparing normal tissues. Recent *in vitro* and *in vivo* st-

Table 3. FINs used in EOC and their mechanism of action.

Class of ferroptosis inducers (FINs)	Drugs/Molecules	Target and Mechanism of Action	Reference
Class I FINs (System Xc^- inhibition)	Erastin	Increases cisplatin sensitivity in combination therapy; alters amino acid and lipid metabolism towards oxidative phenotype; inhibits the ATP-binding cassette sub-family B member 1 (ABCB1) transporter; enhance intracellular labile iron pool (LIP) levels; releases damage-associated molecular patterns (DAMPs) potentiating immunogenic cell death	[73,77,80,82]
	Sulfasalazine	Induces c-jun N-terminal kinase (JNK)-mediated ferroptosis in paclitaxel-resistant epithelial ovarian cancer (EOC)	[84]
	Sorafenib	Sensitizes cells via solute carrier family 2 member 3 (SLC2A3) modulation	[86]
Class II FINs (glutathione peroxidase 4 inhibition)	RAS-selective lethal 3 (RSL3)	Enhance lipid peroxidation and ROS accumulation, depending on LOX activity; enhances ferroptosis in cancer stem cells (CSCs), in combination with frataxin (*FXN*) knockdown; enhances Poly(ADP-Ribose) polymerase (PARP) inhibitor efficacy in homologous recombination (HR)-proficient ovarian cancers	[88,93,97]
	ML162, ML210	Oxidative stress pathway activation	[98]
	Altretamine	GPX4 inhibition	[101]
	Withaferin A	Activation of oxidative stress pathways, such as Kelch-like ECH-associated protein 1 (KEAP1)/nuclear factor erythroid 2-related factor 2 (NRF2)	[103]
Class III FINs (GPX4 depletion)	FIN56	GPX4 degradation and CoQ10 depletion	[104]
	Statins	Inhibit 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase , impairing mevalonate pathway, and reduce CoQ10 synthesis	[106]
Class IV FINs (Lipid peroxidation promotion)	Iron nitroprusside (FeNP)	Generates •OH radicals via Fenton-like reaction	[111]
	Superparamagnetic iron oxide nanoparticles (SPIONs)	Generate ROS, disrupts autophagy flux, downregulate GPX4 and SLC7A11	[112,113]
	Ferric ammonium citrate (FAC)	Promotes ROS generation, increases intracellular Fe^{2+}, promotes autophagic vacuolation and lysosomal iron storage	[114]
	Ferlixit	Restores sensitivity to ferroptosis, in cisplatin/Erastin resistant or Kirsten rat sarcoma viral oncogene homolog (*KRAS*)-mutant EOC cells; induces ferroptosis during extracellular matrix (ECM) detachment	[82,115]
	FINO2	Promotes iron oxidation and lipid peroxidation	[116]
	Sodium Molybdate	Increases LIP, promotes glutathione (GSH) depletion	[117]
	Artesunate	ROS generation, along with cell cycle impairment	[118]

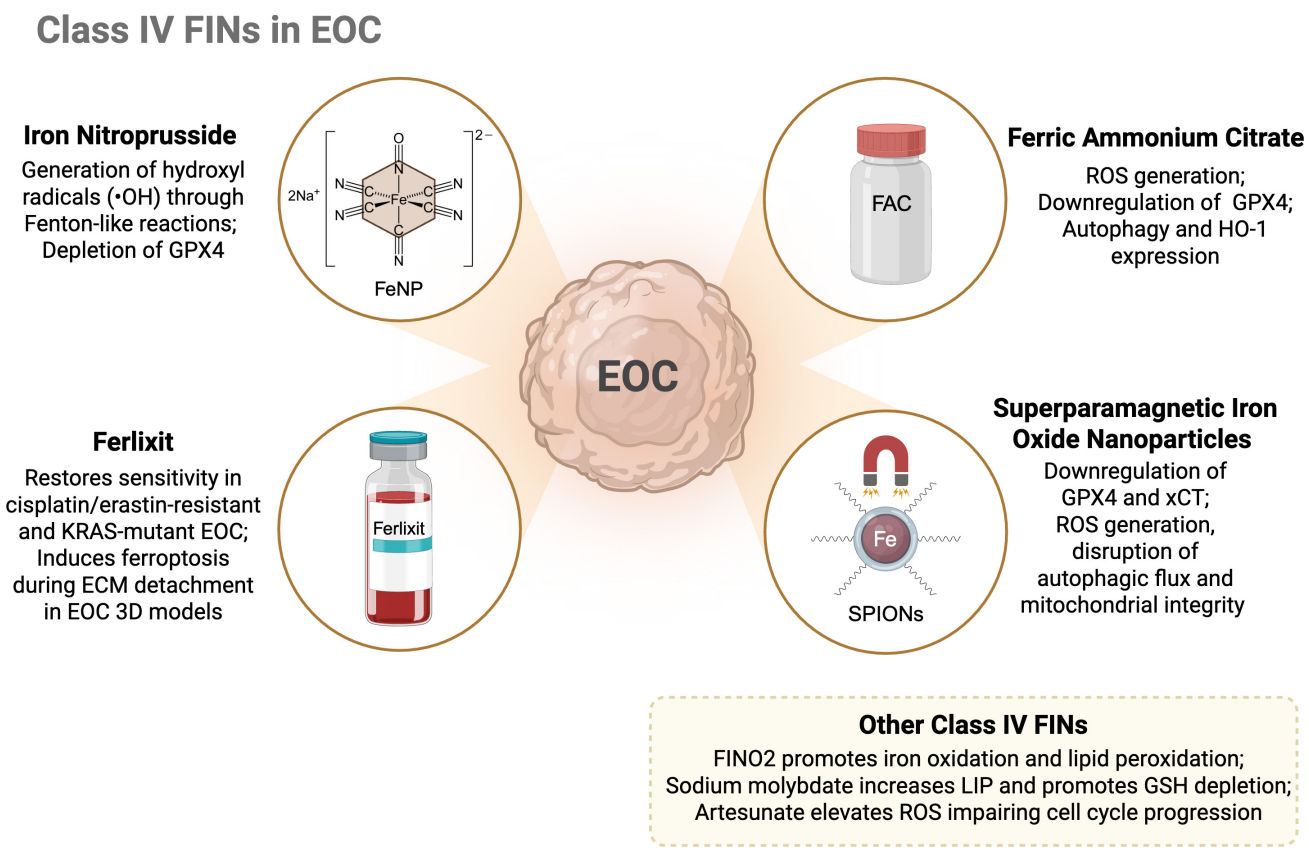

Fig. 2. Mechanisms of action of Class IV FINs in EOC. The schematic shows the main Class IV FINs and their respective mechanisms that promote ferroptosis in EOC cells through iron overload. These agents include iron-based compounds such as FAC, Ferlixit, and FeNP, as well as iron nanoparticle such as SPIONs. The accumulation of LIP induced by these agents contributes to enhanced oxidative stress and ferroptotic cell death. Abbreviations: FINs, ferroptosis inducers; LIP, labile iron pool; ROS, reactive oxygen species; FAC, ferric ammonium citrate; FeNP, iron nitroprusside; SPIONs, superparamagnetic iron oxide nanoparticles; EOC, epithelial ovarian cancer; GPX4, glutathione peroxidase 4; HO-1, heme oxygenase-1; ECM, extracellular matrix. Created using BioRender.com.

udies in SKOV3, A2780, and A2780cis ovarian cancer cells demonstrated that FeNPs bypass lysosomal degradation, accumulate in the cytoplasm, and induce potent ferroptotic responses. In HGSOC-derived organoid models, FeNP exhibited significant therapeutic efficacy, highlighting its potential in overcoming chemoresistance in EOC [111].

6.2 Superparamagnetic Iron Oxide Nanoparticles (SPIONs)

SPIONs are nanomaterials widely used as drug delivery systems but have also emerged as potent Class IV FINs [112]. Studies show that SPIONs induce ferroptosis in ovarian cancer by generating ROS, disrupting autophagic flux, and downregulating tumor stemness and proliferation markers. *In vivo*, SPION-treated cells exhibited diminished tumorigenic potential and reduced chemoresistance. Further, SPION-serum complexes were shown to downregulate GPX4 and SLC7A11, disrupt mitochondrial integrity, and induce p53-dependent ferroptotic cell death, positioning SPIONs as potent agents for targeting chemoresistant and stem-like EOC populations [112,113].

6.3 Ferric Ammonium Citrate (FAC)

FAC, an iron salt complex, increases intracellular Fe^{3+} levels, promoting ROS generation and ferroptosis. In ovarian cancer models, FAC reduced proliferation, enhanced inflammation, and downregulated GPX4 [120]. Importantly, FAC selectively induced ferroptosis in kirsten rat sarcoma viral oncogene homolog (*KRAS*)-mutated ovarian cancer cells while sparing normal epithelial and endometriotic cells. Additionally, it promoted autophagic vacuolation and lysosomal iron storage, suggesting that iron overload can induce stress-related pathways, such as autophagy and heme oxygenase-1 (HO-1) expression, contributing to tumor cell death. These findings underscore the importance of iron metabolism modulation as a therapeutic strategy [114].

6.4 Ferlixit

Ferlixit, an iron-based compound commonly used to treat anemia [121], has recently been repurposed as a Class IV FIN in EOC. It enhances the efficacy of erastin, a Class I FIN, by increasing intracellular LIP and restoring sensi-

tivity to ferroptosis, even in cisplatin-resistant or *KRAS*-mutant EOC cells. Ferlixit thus offers a viable strategy to overcome erastin resistance [82]. Moreover, in non-adherent 3D culture models, EOC cells displayed a reliance on ferritin-mediated iron storage to avoid ferroptosis. Disruption of this protective mechanism via Ferlixit or *FtH1* silencing sensitized cells to ferroptotic death, especially during detachment and metastasis [115,122]. These findings support a combinatorial approach involving iron supplementation and FINs to target both adherent and metastatic tumor cells.

6.5 Other Class IV FINs: FINO2, Sodium Molybdate, and Artesunate

Ferroptosis-inducing agent 2 (FINO2) has been shown to inhibit the growth of ovarian cancer cells (e.g., IGROV-1) by promoting iron oxidation and lipid peroxidation [116]. Sodium molybdate increases LIP and promotes GSH depletion via NO production, causing mitochondrial dysfunction, reduced ATP synthesis, and ultimately ferroptosis. *In vivo*, it reduces tumor volume, increases ferritin expression, and elevates lipid peroxidation products such as 4-hydroxynonenal (4-HNE) [117].

Artesunate (ART), a derivative of artemisinin, induces ferroptosis by elevating ROS and impairing cell cycle progression in ovarian cancer cells. ART exerts dose-dependent cytotoxicity and DNA damage through both ROS-dependent and -independent mechanisms, including mammalian target of rapamycin (mTOR) inhibition and the modulation of cyclin D3 and p21 expression. Inhibition of ART-induced cytotoxicity by ferroptosis inhibitors further confirms its mechanism of action [118].

7. Weighing the Pros and Cons: Class IV vs. Classes I, II, and III Ferroptosis Inducers

Class IV FINs show unique advantages by directly targeting iron metabolism, making them especially promising for overcoming chemoresistance in ovarian cancer. However, despite their therapeutic potential, excessive iron accumulation can trigger non-specific lipid peroxidation, oxidative stress, and tissue damage in organs with high iron uptake, such as the liver and heart. To mitigate these risks, several targeted delivery strategies are under investigation, including tumor-specific nanoparticles, pH- or ROS-responsive drug release systems [23,109,123,124]. Additionally, prodrug formulations and selective ferroptosis protection of healthy tissues offer promising avenues to enhance therapeutic precision while minimizing off-target effects.

Furthermore, like other FIN classes, they face challenges in terms of delivery, toxicity, and clinical viability. Many FINs suffer from chemical and physical limitations, including low solubility, poor pharmacokinetics, and metabolic instability, which hinder their therapeutic use. While progress has been made, significant barriers still limit the full exploitation of ferroptosis-based therapies [125].

There is a pressing need to develop more potent and bioavailable FINs suitable for *in vivo* use. Promising examples include nanoparticle-formulated imidazole ketone erastin and cyst(e)inase, which have shown strong anti-tumor effects in mouse models. For GPX4-targeting FINs, compounds like ML210 and its derivatives (e.g., JKE-1674) have demonstrated selective inhibition of GPX4 but still require optimization for use in living systems [126]. Another major concern is toxicity to healthy organs such as the kidneys, liver, and brain. Preclinical data suggest that careful dose control and treatment scheduling will be essential. Identifying predictive biomarkers to stratify patients and guide ferroptosis-based treatments is also crucial for minimizing adverse effects and improving efficacy. To address these concerns, protective agents such as DFO (an iron chelator) have been used to buffer excessive ferroptosis, although their short half-life limits clinical utility [28]. More advanced strategies are under development. Nanomaterials have emerged as an effective strategy to improve the performance of FINs. For example, cisplatin-loaded iron oxide nanoparticles can be selectively activated in tumors using a magnetic field, enhancing tumor targeting while reducing systemic toxicity. However, nanomaterials carry their own risks, such as potential cytotoxicity and the unintended activation of autophagy, which may reduce therapeutic effects. Therefore, the design of ferroptosis-driven nanotherapies must balance efficacy with safety, ensuring precise control over drug delivery and action [127].

8. Conclusions

Among the diverse landscape of ferroptosis-inducing agents, Class IV FINs, which act by modulating intracellular iron metabolism, have emerged as particularly promising candidates for the treatment of EOC, especially in the context of platinum-resistant and stem-like tumor populations. These compounds harness the intrinsic “iron addiction” of EOC cells and CSCs, exploiting their elevated LIP and redox imbalance to selectively trigger ferroptotic cell death. This mechanism is of particular relevance in HGSOC, where dysregulated iron homeostasis and ferroptosis resistance are tightly linked to disease aggressiveness and recurrence.

Preclinical studies with iron-based agents such as FeNP, SPIONs, FAC, and Ferlixit have demonstrated the capacity of Class IV FINs to overcome chemoresistance, reduce tumorigenicity, and selectively eliminate therapy-refractory CSC populations. Notably, these agents do not rely on apoptosis, thereby bypassing one of the major resistance mechanisms in recurrent EOC. Furthermore, several Class IV FINs exhibit dual mechanisms of action, combining iron oxidation, GPX4 depletion, and modulation of autophagy to amplify ferroptotic stress. This multipronged activity positions them as ideal candidates for combinatorial

regimens with other ferroptosis inducers, DNA-damaging agents, or immune checkpoint inhibitors.

Despite these encouraging findings, the clinical translation of Class IV FINs requires careful consideration of their pharmacokinetics, selectivity, and potential off-target toxicity, particularly in iron-rich or ROS-sensitive organs. Nanotechnology-based delivery platforms, such as iron oxide nanoparticles functionalized for tumor targeting, represent a promising approach to enhance therapeutic precision while minimizing systemic exposure. Additionally, further investigation into tumor subtype-specific vulnerabilities, such as variations in ferritinophagy, FPN expression, or CD44-mediated iron uptake, may facilitate the development of biomarker-driven strategies for patient selection.

Looking ahead, key research priorities include: (i) refining Class IV FIN formulations for clinical use, including nanoparticle-enhanced and prodrug-based systems, (ii) elucidating resistance mechanisms to ferroptosis in EOC subtypes with *p53*-wild-type or altered redox networks, (iii) identifying predictive biomarkers, such as TfR1, FPN, or (FRG)/(FRL) signatures, to enable personalized ferroptosis-targeted therapies, (iv) validating combinatorial regimens that integrate Class IV FINs with immunotherapy, chemotherapy, or metabolic reprogramming agents in both 2D and 3D EOC models.

In conclusion, Class IV FINs offer a compelling and mechanistically distinct therapeutic avenue for overcoming chemoresistance and targeting EOC. With continued refinement and translational innovation, these agents have the potential to reshape the therapeutic landscape of ovarian cancer by addressing some of its most intractable clinical challenges.

Abbreviations

EOC, epithelial ovarian cancer; FINs, ferroptosis inducers; RCD, regulated cell death; LIP, labile iron pool; ROS, reactive oxygen species; PUFAs, polyunsaturated fatty acids; GPX4, glutathione peroxidase 4; H_2O_2, hydrogen peroxide; •OH, hydroxyl radicals; TfR1, transferrin receptor; FtH1, ferritin heavy subunit; FPN, ferroportin; LOX, lipoxygenase; GSH, glutathione; SLC7A1, solute carrier family 7 member 11; SLC3A2, solute carrier family 3 member 2; $CoQ10H_2$, ubiquinol; BH4, tetrahydrobiopterin; CoQ10, Coenzyme Q10; FSP1, ferroptosis suppressor protein 1; NOS, nitric oxide synthases; NO, nitric oxide; GCH1, GTP cyclohydrolase 1, DHODH, dihydroorotate dehydrogenase; Fe-S, iron-sulfur; Tf, transferrin, DMT1, divalent metal transporter 1; ZIP14, solute carrier family 39 member 14; FtL, ferritin light chain; IRP, iron regulatory protein; IRE, iron-responsive element; UTR, untranslated region; NCOA4, nuclear receptor coactivator 4; HGSOC, high-grade serous ovarian carcinoma; POLQ, polymerase theta; IL-6, interleukin-6; DFO, deferoxamine; CSCs, cancer stem cells; HA, hyaluronic acid; LCN2, lipocalin-2; LCN2R, lipocalin-2 receptor; HIF, hypoxia-inducible factor; MEX3A, Mex-3 RNA Binding Family Member A; OCCC, ovarian clear cell carcinoma; TME, tumor microenvironment; DAMPs, damage-associated molecular patterns; OXPHOS, oxidative phosphorylation; TCGA, The Cancer Genome Atlas; GEO, Gene Expression Omnibus; FRG, ferroptosis-related gene; FRLs, ferroptosis-related long non-coding RNAs; MVB, multivescicular boby; EV, extracellular vescicle; PARP, Poly(ADP-Ribose) Polymerase; RSL3, RAS-selective lethal 3; NRF2, Nuclear Factor Erythroid 2-Related Factor 2; 4-HNE, 4-hydroxynonenal; JAM3, junctional adhesion molecule 3; miRNAs, microRNAs; HR, homologous recombination; FDA, Food and Drug Administration; HO-1, heme oxygenase-1; IONPs, iron oxide nanoparticles; PCBP1, Poly(RC) binding protein 1; FeNP, iron nitroprusside; SPIONs, Superparamagnetic Iron Oxide Nanoparticles; FAC, ferric ammonium citrate; ART, artesunate.

Author Contributions

FC, FB, AMB, LP, EG and CMF designed the study; LP, EG, CMF, FC, FB and AMB drafted the manuscript; GN, CG and SRF performed literature selection and drew the figures. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research was funded by the European Union-Next Generation Eu, Mission 4 Component 1, CUP F53D23003840006. PRIN-Research Projects of National Interest-Call 2022-Prot. 2022R85H27.

Conflict of Interest

Given her role as the Guest Editor, Flavia Biamonte had no involvement in the peer-review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Sung Eun Kim.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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