Review

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Ferroptosis Resistance: Redundant Antioxidant Networks Is a Barrier to Cancer Therapy

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Abstract

Ferroptosis is an iron-dependent, lipid peroxidation–driven form of regulated cell death that has emerged as a promising strategy to eliminate therapy-resistant cancers. However, both intrinsic and acquired resistance to ferroptosis-inducing agents (FINs) limit their clinical efficacy. From this perspective, an integrated model is proposed in which ferroptosis resistance emerges through coordinated redox, metabolic, and transport adaptations that collectively suppress lipid peroxidation and support tumor cell survival. Central to this defense is the cysteine–glutathione–glutathione peroxidase 4 (GPX4) axis, supported by parallel CoQ10-dependent antioxidant systems including ferroptosis suppressor protein 1 (FSP1), dihydroorotate dehydrogenase (DHODH), NAD(P)H quinone oxidoreductase 1 (NQO1), and the GCH1–tetrahydrobiopterin (BH4) pathway. These systems are further reinforced by NrF2-mediated transcriptional programs, iron sequestration and export mechanisms, lipid remodeling that limits polyunsaturated fatty acid availability, and ATP-binding cassette (ABC) transporters that regulate drug and glutathione flux. Tumor heterogeneity—including differences in differentiation state, epithelial–mesenchymal plasticity, and metabolic reprogramming—generates subpopulations with distinct ferroptosis sensitivities and facilitates therapeutic escape. Emerging strategies that simultaneously target multiple resistance nodes, including GPX4 or FSP1 inhibition, combination chemotherapy, and nanoparticle-based delivery systems, may enhance ferroptosis-based therapies. A deeper understanding of oxidant–antioxidant networks governing ferroptosis resistance will enable the rational design of next-generation anticancer strategies to overcome drug resistance.

Keywords: resistance; ferroptosis; antioxidants; GPX4; FSP1; DHODH

Introduction

Ferroptosis is a form of iron-dependent, non-apoptotic programmed cell death characterized by the lethal accumulation of lipid peroxides, distinct from apoptosis or necrosis [1–3]. It is triggered by the failure of glutathione-dependent antioxidant defenses (specifically GPX4) and is associated with iron-dependent lipid peroxidation. In the context of cancer treatment, the induction of apoptosis through conventional therapeutic methods and immunotherapy has often been hindered by drug resistance, highlighting the urgent necessity to investigate alternative pathways of cell death.

The induction of ferroptosis not only suppresses tumor growth but also enhances the efficacy of immunotherapeutic responses and mitigates resistance to existing cancer therapies [4]. Notably, mesenchymal, de-differentiated, and therapy-resistant tumors often display increased susceptibility to ferroptosis [5–7]. These observations position ferroptosis as a promising strategy for targeting drug-resistant cancers. However, improving the specificity of ferroptosis inducers and controlling their dosage while minimizing toxicity to normal tissues remain major challenges. Nanocarrier-based delivery systems offer a potential solution by enhancing the solubility, stability, and targeted delivery of ferroptosis modulators.

Drug resistance remains one of the most significant barriers to effective cancer therapy and is responsible for a large proportion of cancer-related deaths. Clinically, resistance manifests as

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treatment failure, disease relapse, and tumor progression. Tumor cells frequently develop multidrug resistance (MDR) through adaptive mechanisms such as increased drug efflux, metabolic detoxification, or target modification. Because ferroptosis represents a mechanistically distinct form of cell death, inducing ferroptosis may eliminate cancer cells that are refractory to conventional therapies and help overcome immune evasion.

Several drugs already used in the clinic, such as Sorafenib (liver cancer) and Sulfasalazine (anti-inflammatory), are strong inducers of ferroptosis [8,9]. Currently, several clinical trials are investigating Sulfasalazine for solid tumors in combinations with new iron-based nanoparticles designed to trigger ferroptosis [10,11]. These studies highlight the growing clinical interest in ferroptosis-based therapeutic strategies.

Beyond its direct cytotoxic effects, ferroptosis also interacts with antitumor immunity. Ferroptosis can eliminate immunosuppressive cells within the tumor microenvironment and enhance immune-mediated tumor clearance [12,13]. Among various components of metabolic heterogeneity in cancer cells, iron-catalyzed pathways in lipid metabolism are more abundant in cancer cells. By identifying how cancer cells evade treatments, e.g., through efflux pumps, drug activation/detoxification, or target modification—we can rationally design new, more effective therapies, optimize current regimens. Inducing ferroptosis offers an alternative avenue to eliminate drug resistant cancer cells that become refractory to chemotherapy.

Additionally, not only can ferroptosis kill cancer cells, but it also releases factors (e.g., PGE2) that affect the tumor microenvironment, suggesting a complex role in immune response. Ferroptosis induction facilitates MHC-1 expression, releases DAMPS and IFNγ, which can activate immune cell activity including T cells and macrophages [14]. Furthermore, the release of IFNγ from T cells inhibits xCT system (glutamine/cystine antiporter), leading to enhanced ferroptosis sensitivity [15,16]. Thus, ferroptosis has dual immunological role—enhancing antitumor immunity while potentially compromising T-cell viability—necessitating carefully designed combination regimens.

Cisplatin has been shown to induce both apoptosis and ferroptosis by depleting glutathione (GSH) and combining it with erastin results in a strong synergistic effect [17]. Similarly, low-dose erastin has been shown to sensitize acute myeloid leukemia (AML) cells to these first-line treatments. Ferroptosis induction has been used to sensitize glioblastoma cells to Temozolomide, the drug of choice for this disease [18]. Furthermore, several *in vitro* studies have shown that triple-negative breast cancer (TNBC), are extremely sensitive to ferroptosis because these cells are naturally "iron-rich" and are vulnerable to lipid peroxidation [19,20]. This is currently being explored as a primary therapeutic strategy in the clinic [21]. At the molecular level, FINs (ferroptosis inducing agents) induce ferroptosis by suppressing the system xCT, leading to inhibition of cellular cystine uptake and inhibiting glutathione synthesis [22,23]. System xCT, which is composed of the light chain SLC7A11 and the heavy chain SLC3A2, has been shown to be the key regulator of cellular redox homeostasis. It mediates the uptake of extracellular cystine in exchange for intracellular glutamate, supplying cystine for its intracellular reduction to cysteine, the rate-limiting precursor for glutathione (GSH) synthesis. By maintaining GSH levels, system xCT supports the activity of antioxidant enzymes e.g., GPX4 and protecting cells from lipid peroxidation and oxidative stress. Inhibition of system xCT results in a rapid drop in intracellular GSH levels, causing cell death from the accumulation of lipid-derived reactive oxygen species (L-ROS). Studies have shown that inhibiting GPX4 can lead to ferroptosis in cancer cells and inhibit cancer growth both *in vitro* and *in vivo* [24,25]. GPX4 activity is also subject to post-translational regulation by non-coding RNAs and was shown that miR-324-3p inhibits GPX4 and induces ferroptosis, reversing cisplatin resistance in NSCLC cells [26].

Here, it is proposed that ferroptosis resistance is governed by an integrated, multi-layered network consisting of four major functional modules that buffer lipid peroxidation through compartmentalized and compensatory pathways. These include (A) Redox detoxification (GPX4, FSP1, DHODH, NQO1, GCH1) (B) Metabolic rewiring (NADPH, pentose phosphate pathway, lipid remodeling) (C) Transport regulation (xCT, ABC transporters), and (D) Iron/lipid substrate control.

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Together, these interconnected pathways maintain membrane integrity, suppress lipid peroxidation, and enable tumor survival under ferroptotic stress.

Tumor resistance mechanisms are numerous and complicated. Tumors are defined by genetic diversity and selective evolution, causing emergence of drug-resistant tumor cells. As a result, whether it is primary or acquired, drug resistance is a separate and irreversible phenomenon. Clinical resistance is defined by lack of tumor shrinkage or remission following first-line therapy [27]. It is typically triggered by a genetic mutation, aberrant behavior of tumor cells, or a rapid response of tumor cells to treatment. Acquired resistance is more common and relates to the resistance that develops throughout therapy. The two primary hypotheses of acquired resistance today are pre-existing and evolutionary [28,29]. Studies indicate that tumors exhibit several types of clonal heterogeneity and that subclones may already be drug resistant before treatment starts. Following treatment, these resistant subclones still proliferate, leading to tumor recurrence.

Tumor Heterogeneity and Ferroptosis Resistance

Tumor heterogeneity (TMH) exists both at cellular and tissue levels and is responsible for survival, cell death, and resistance to cancer drugs [30]. Resistance to conventional anticancer drugs is due to a complex and evolving nature of tumors [27]. Emergence of drug-resistance in cancer cells provides distinctive advantages for proliferation, survival, evasion of immune destruction and plasticity. In recent years, abnormal or deregulated cancer cell metabolisms in lipid metabolisms, and iron lead to ferroptosis resistance [31]. Heterogeneity contributes significantly to ferroptosis resistance by generating a subpopulation of cells within a tumor that may possess intrinsic or acquired defenses against lipid peroxidation, allowing cells to escape treatment-induced cell death. These resistant subpopulations often have distinct metabolic or differentiation states to survive and cause relapses [32]. Key aspects of the role of heterogeneity in ferroptosis resistance include:

Distinct Cellular Differentiation and Phenotypes

Tumor subpopulations with different differentiation states exhibit varying sensitivity to ferroptosis. In breast cancer, scRNA-seq revealed that luminal-differentiated cells were significantly more resistant to ferroptosis compared to basal-like, more proliferative cells [33]. The transcription factor GATA3, which drives luminal differentiation, promotes resistance by reducing the expression of Human Integrin $\alpha 1\beta 1$ [34]. It has been reported that this results in a higher expression of ACSL4 (acyl-CoA synthetase long-chain family member 4), making membranes more susceptible to lipid peroxidation. In contrast, in resistant subpopulations, high GATA3 suppresses integrin $\alpha 1\beta 1$ expression, decreasing ACSL4 expression and rendering cells resistant to ferroptosis [34].

Metabolic Heterogeneity

Heterogeneity in metabolic pathways allows certain cells to maintain redox homeostasis, protecting them from ferroptosis [35]. Subpopulations (e.g., in melanoma) can reprogram metabolism to consume lactate, increasing intracellular NADH/NADPH levels and enhancing antioxidant defenses [36]. Increased pentose phosphate activity in specific sub-clusters produces the NADPH necessary to fuel ferroptosis defense systems, such as the GPX4/GSH pathway or the FSP1/CoQ10 system [36]. Heterogeneity drives resistance through specific molecular mechanisms that reduce ferroptotic vulnerability. Treatments that induce ferroptosis can select for pre-existing resistant subpopulations within a heterogeneous tumor, leading to a rapid recurrence. Understanding the heterogeneity allows for targeted approaches, such as combining ferroptosis inducers (e.g., GPX4 inhibitors) with inhibitors of specific resistance mechanisms (e.g., immunotherapy, lactate uptake inhibitors) to eradicate both sensitive and resistant subpopulations.

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ABC Transporter-Mediated Resistance

ATP-binding cassette (ABC) transporters utilize ATP hydrolysis to transport various compounds across cell membranes against concentration gradients [37]. Drug resistant cancer cells usually express these transporters. Furthermore, heterogeneous tumors e.g., cancer stem cells, also express these transporters making them difficult to eradicate during chemotherapy. ABC transporters often contribute to ferroptosis resistance by actively eliminating FINs or by regulating lipid peroxidation. Frye et al. (2023) have reported that P-glycoprotein (P-gp, ABCB1) confers resistance to several erastin-derivatives offering protection from ferroptotic cell death [38]. Erastin has been reported to inhibit functions of ABC transporters, resulting in increased intracellular concentrations of drug and enhance drugs-induced ferroptosis [39,40].

Wang et. al. have shown that high ABCC2 (MRP2) plays a significant role in amino acid metabolism and ferroptosis by mediating GSH efflux in gastric cancer, resulting in alterations in redox status, and increasing the cell's susceptibility to ferroptosis [41]. De Souza et al. have reported that NrF2 positively correlates with ABCC1 expression in tumor tissues of glioma patients, which can be associated with tumor aggressiveness, drug resistance, and poor overall survival [42]. High NrF2 levels promote chemotherapy resistance by upregulating ABCC1, which then acts as an efflux pump to remove drugs from cancer cells. Altogether, studies indicate that high levels of NrF2 result in collateral sensitivity on glioblastoma via the expression of its pro-ferroptotic target ABCC1, leading to GSH depletion when the system xCT is blocked by erastin, weakening the cell's antioxidant defenses. Thus, ferroptosis induction could be an important therapeutic strategy to reverse drug resistance in gliomas with high NRF2 and ABCC1 expressions.

Huang et al. have identified that ABCC5 is a critical regulator and a promising therapeutic target of acquired sorafenib resistance in human hepatocellular carcinoma cells [43]. The expression of ABCC5 was dramatically induced in sorafenib-resistant HCC cells and was associated with poor clinical prognoses. The downregulation of ABCC5 expression significantly reduced the resistance of sorafenib to HCC cells. ABCC5 increased intracellular glutathione and attenuated lipid peroxidation accumulation by stabilizing SLC7A11 protein, inhibiting ferroptosis. Inhibition of ABCC5 enhanced the anti-cancer activity of sorafenib *in vitro* and *in vivo*, indicating role of ABCC5 in ferroptosis resistance.

A redox network model of ferroptosis resistance centers on balancing iron-dependent lipid peroxidation with robust antioxidant systems, primarily the system-GSH-GPX4 axis. Resistance is maintained by preventing excessive reactive oxygen species (ROS) accumulation and maintaining membrane integrity through GPX4 activity, which reduces lipid peroxides. There are several components of redox network that play significant role in ferroptosis resistance, and these are discussed below.

System-GSH-GPX4 Axis in Ferroptosis Resistance

The primary defense, importing cystine via glutathione synthesis, which GPX4 uses to reduce lipid hydroperoxides and has been studied extensively [44]. It is a chloride-dependent and sodium-independent antiporter of Cys and Glu, consisting of catalytic subunit xCT/Solute Carrier Family 7 Member 11 (SLC7A11) and regulatory subunit 4F2 (4F2hc)/Solute Carrier Family 3 Member 2 (SLC3A2) connected by disulfide bonds [45,46]. Activation of SLC7A11 expression enables cells to restore redox homeostasis and maintain survival under stressful conditions such as oxidative stress, amino acid starvation, metabolic stress, and genotoxic stress [22]. Thus, System xCT functions as the upstream determinant of GPX4-dependent redox capacity [47,48]. There are many compounds that interfere with System xCT, such as erastin and its analogues, that can lead to cysteine deprivation, glutathione depletion, endoplasmic reticulum stress, and cell death [49,50]. If System xCT is an important target for inducing ferroptosis and provides a new direction for the treatment of drug-resistant solid tumors [51]. This is summarized in Figure 1.

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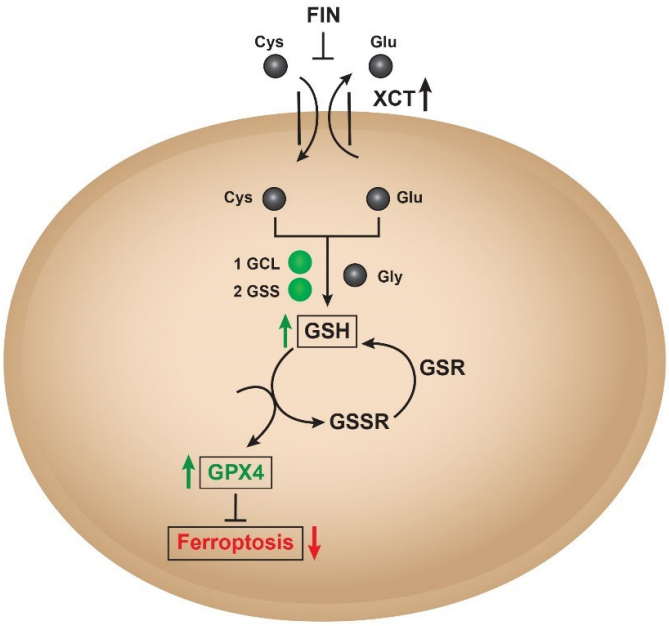

Figure 1. System xCT–GSH–GPX4 axis in ferroptosis resistance. Glutathione- dependent ferroptosis in tumor cells through inhibition of the xCT–GSH–GPX4 axis. Upregulation of xCT and GSH enhances GPX4-dependent detoxification resulting in ferroptosis resistance.

Extracellular cystine is imported in exchange for intracellular glutamate (Glu) via the cystine/glutamate antiporter system (xCT) for glutathione (GSH) synthesis that supports GPX4 to detoxify lipid peroxides, thereby suppressing ferroptosis. High expression or activity of the GSH-GPX4 axis, confer resistance to FINS. Interestingly, several drug-resistant cancer cells have been found to be more sensitive to lipid peroxidation, and inhibitors of the System xCT/GSH/GPX4 axis have been shown to be cytotoxic to these cells [40,52,53]. Cheng et al. found that inhibiting with erastin enhances the antitumor effect of cisplatin [17].

FSP1-CoQ10H2 Pathway in Resistance

A parallel, glutathione-independent system, Ferroptosis Suppressor Protein 1 (FSP1, also known as AIFM2), acts as a potent oxidoreductase enzyme and protects against ferroptosis by reducing extra-mitochondrial CoQ10 to its active antioxidant form, $CoQ10H_2$, using NAD(P)H as a cofactor at the plasma membrane [54] This reduced CoQ10H2 acts as a lipophilic radical-trapping antioxidant that intercepts phospholipid peroxyl radicals, preventing lethal lipid peroxidation and conferring resistance to ferroptosis [55]. FSP1 uses NADPH to regenerate reduced CoQ10 from its oxidized form, sustaining the antioxidant capacity. Importantly, FSP1 combats lethal peroxidation and ferroptosis in the absence of GPX4. Myristoylated FSP1 is tethered to the plasma membrane and acts as the critical enzyme to reduce ubiquinone to ubiquinol, thereby restoring the reduced pool. FSP1 is considered a critical, druggable target in cancer therapy [56]. Consistent with we observed that FSP1 expression correlates with erastin resistance in MCF-7 human breast cancer cells [53]. Pharmacological inhibition of FSP1 with various inhibitors of FSP1 restored sensitivity of erastin confirming that FSP1 played a major role in resistance. Roles of FSP1 and CoQ10H2 in ferroptosis resistance is shown in Figure 2.

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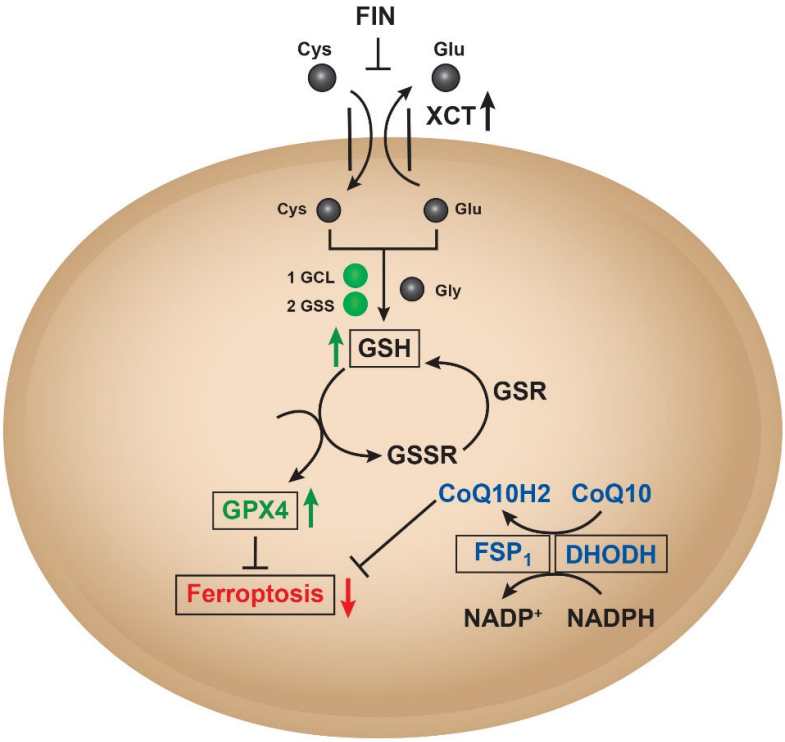

Figure 2. Dual antioxidant systems drive ferroptosis resistance. System xCT imports cystine in exchange for glutamate, supporting glutathione (GSH) synthesis. GSH sustains GPX4 activity to detoxify lipid peroxides and inhibits ferroptosis. In parallel, FSP1 reduces coenzyme Q10 (CoQ10) to $CoQ10H_2$ using NADPH, providing an independent lipid antioxidant pathway. Upregulation of both GPX4- and FSP1-dependent systems enhances ferroptosis resistance.

Dihydroorotate Dehydrogenase (DHODH) -CoQ10H 2 and GCH1-BH4 Systems

DHODH-CoQ10H2 is a recently discovered antioxidant defense system located in mitochondria that compensates for the loss of GPX4 in detoxifications of mitochondrial lipid peroxides [57]. DHODH is an enzyme involved in pyrimidine synthesis that can reduce CoQ10 to CoQ10H2 in the inner mitochondrial membrane. When GPX4 is inactivated, the flow through DHODH is increased, resulting in increased generation of CoQ10H2 that neutralizes lipid peroxidation and defends against ferroptosis in the mitochondria [58].

Cells have developed at least four defense systems that collectively form compartmentalized CoQ10-dependent defenses with different subcellular localizations to detoxify lipid peroxides and protect cells from ferroptosis. Cytosolic GPX4 (GPX4cyto) collaborates with FSP1 on the plasma membrane (and other non-mitochondrial membranes), and mitochondrial GPX4 (GPX4 mito) collaborates with DHODH in mitochondria to neutralize lipid peroxides [59]. Notably, mitochondrial GPX4 and DHODH can functionally compensate for one another to suppress mitochondrial lipid peroxidation. In contrast, cytosolic GPX4 and FSP1 lack this capacity, likely due to their absence from the mitochondrial compartment and consequent inability to detoxify lipid peroxides within the inner mitochondrial membrane. These observations underscore the critical importance of subcellular compartmentalization in ferroptosis defense. Beyond its canonical metabolic role, DHODH regenerates CoQ10H2 to suppress mitochondrial lipid peroxidation and ferroptosis. Elevated DHODH expression in colorectal, hepatocellular, breast, renal, and brain cancers correlates with poor prognosis, therapy resistance, and immune evasion [60]. Pharmacological inhibition of DHODH disrupts pyrimidine synthesis and redox defense, sensitizing GPX4-low tumors to ferroptosis. Preclinical studies demonstrate synergy between DHODH inhibitors and chemotherapy,

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radiotherapy, or immune checkpoint blockade [61,62]. DHODH serves as both a metabolic and redox checkpoint in cancer, linking ferroptosis suppression to proliferation and immune escape. Targeting DHODH offers a promising strategy to dismantle cancer resilience, particularly in combination with ferroptosis inducers and immunotherapies [60]. Its role in ferroptosis inhibition suggests that DHODH inhibitors could have two complementary mechanisms of action against tumors: inhibiting de novo pyrimidine nucleotide biosynthesis and enhancing ferroptosis. However, the link between mitochondrial function and ferroptosis, and the involvement of DHODH in the electron transfer chain suggests that its role in ferroptosis could be modulated by the Warburg effect [63]. Furthermore, emerging evidence suggests a link between DHODH and the cellular GSH pool, which may contribute to the rational design of ferroptosis-based anticancer therapies [63].

Kraft et. al. [64] reported on another highly potent endogenous ferroptosis suppressor, GTP cyclohydrolase 1 (GCH1), which is the rate-limiting enzyme for synthesis of the antioxidant tetrahydrobiopterin (BH4). Like FSP1 and CoQ10, GCH1 and BH4 act entirely independently of GPX4 to block ferroptosis. Also, elevated levels of GCH1 are linked to ferroptosis resistance, and therefore, suggesting GCH1 as a potential novel target for cancer therapy.

The NQO1-NADPH axis acts as a crucial, non-canonical defense mechanism against ferroptosis by maintaining reduced coenzyme CoQ10H2 and mitigating lipid peroxidation [65]. NQO1 acts as an oxidoreductase, reducing CoQ10 to CoQ10H2 which serves as an antioxidant to neutralize lipid peroxides in the plasma membrane. NQO1 requires abundant supply of NADPH, which is essential for maintaining the cell's reduced state and supporting other antioxidant systems like GPX4 and FSP1. In many cancers, NQO1 is up-regulated (often via NrF2 signaling) to protect cells from ferroptosis, contributing to chemotherapy resistance [66]. While high NQO1 generally promotes resistance, it can exhibit complex, expression-level-dependent effects on mitochondrial function. Pharmacological NADPH-dependent activation of NQO1 leads to inhibition of ferroptosis in certain models. High NQO1 expression confers resistance, particularly in KEAP1-deficient cancers, while inhibiting this axis sensitizes cells to ferroptosis [65]. Conversely, targeting NQO1 with specific inhibitors or leveraging NQO1-mediated ROS generation can induce ferroptosis in resistant cancer cells [67]. This axis operates independently of, but complementary to, the canonical system xCT−GSH-GPX4 pathway [68,69]. Although both NQO1 and FSP1 contribute to CoQ10-dependent antioxidant defense, their relationship to NrF2 and ferroptosis resistance is fundamentally different (Table 1). NQO1 is a canonical NrF2 target whose expression tightly tracks NrF2 activation and primarily supports general redox homeostasis through cytosolic quinone detoxification [70–72].

In contrast, FSP1 functions as a ferroptosis suppressor by reducing CoQ10 to $CoQ10H_2$ directly at cellular membranes, where lipid peroxidation occurs. While FSP1 expressions can be enhanced by NrF2 in some contexts, it is not strictly NrF2-dependent and can remain functional even when NrF2-regulated glutathione and detoxification pathways are compromised [73]. As a result, NrF2 activation significantly amplifies antioxidant capacity, whereas FSP1 provides a GPX4-independent, spatially optimized mechanism that leads to the inhibition of lipid peroxidation. This distinction explains why NQO1 induction alone often confers only partial protection, while FSP1 upregulation is more strongly associated with robust resistance to ferroptosis-inducing agents such as erastin. FSP1, on the other hand, sits directly at membranes and continuously regenerates $CoQ10H_2$ exactly where lipid radicals form. Even though NrF2 can increase FSP1 expression in some cells, FSP1 doesn't depend on NrF2 to function [73]. Once FSP1 is present in cells it acts independently of glutathione and GPX4. It is believed, therefore, that ferroptosis resistance persists even when NrF2-driven pathways are weakened—as FSP1 provides a more direct, localized, and GPX4-independent defense against lipid peroxidation. Together, these systems form spatially compartmentalized antioxidant defenses in cytosol (GPX4 and NQO1), membrane (FSP1) and mitochondria (DHODH and GPX4mito) protecting tumor cells from ferroptosis and is summarized in Table 1.

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Table 1. NrF2-based Resistance Mechanisms in Tumor Cells.

Pathway	Localization	NrF2 Dependence	Consequences	References
GPX4	Cytosol and Mitochondria	Yes	Reduction in Lipid Peroxides	[74,75]
FSP1	Membrane	Partial	Regeneration of CoQ10H2	[73]
DHODH	Mitochondria	No	CoQ10H2mito	[57,60]
NQO1	Cytosol	Yes	NADPH-Quinone Reduction	[70,71]

NrF2 is a master regulator of antioxidant defenses and iron metabolism that provides robust resistance to ferroptosis [76]. NrF2 coordinates redox and iron homeostasis through transcriptional upregulation of genes involved in glutathione synthesis (SLC7A11, GPX4), iron storage (ferritin), and iron export (ferroportin) [74,75,77,78]. NrF2 enhances cysteine uptake and glutathione synthesis by activating the SLC7A11 subunit of the system xCT transporter, ensuring a steady supply of cysteine for GSH synthesis. NrF2 also directly regulates GPX4 expression [75] and integrates antioxidant, iron and lipid metabolic programs [78,79]. It also enhances the activity of enzymes like glutathione-S-transferases (GSTs) [76]. In many cancers, high NrF2 activation drives resistance to therapies by preventing the accumulation of iron and oxidative damage [78,80]. Consequently, targeting the NrF2 pathway can sensitize resistant cancer cells to ferroptosis-based therapies.

Iron Metabolism in Ferroptosis Resistance

Iron plays a critical role in redox reactions and mediates oxidative stress, which is considered a driving force in evolution. Dysregulation of iron levels, whether elevated or reduced, can result in cellular and tissue damage, leading to various pathological conditions. Iron is a central driver of ferroptosis, and resistance to this form of cell death is achieved by maintaining low levels of cytoplasmic labile iron (Fe^{2+}) and promoting its storage or efflux [81]. Resistance mechanisms include reducing iron uptake (TfR1), enhancing iron storage (ferritin), and reducing iron-dependent lipid peroxidation via the GSH-GPX4 pathway.

Key aspects of iron in resisting ferroptosis include limiting Labile Iron Pool (LIP) and maintaining a low level of intracellular Fe^{2+} is crucial [82]. The LIP is directly involved in the Fenton reaction, generating toxic hydroxyl radicals. Increased expression of ferritin, which stores iron, reduces the free iron available for lipid peroxidation. In some senescent cells, trapping iron within lysosomes prevents it from triggering oxidative damage in the cytoplasm [83,84]. The iron exporter ferroportin (FPN) reduces intracellular iron levels, thereby reducing the sensitivity to ferroptosis inducers. It has been suggested that iron metabolism works closely with antioxidant systems, such as GPX4, which neutralizes lipid peroxides formed in iron-dependent processes [85]. Strategies that reduce iron availability decrease oxidative stress and accumulation of lipid peroxides.

Lipid Metabolism in Ferroptosis Resistance

Because lipid peroxidation is considered the execution step of ferroptosis, remodeling membrane lipid composition is a dominant resistance mechanism. Lowering polyunsaturated fatty acid (PUFA) content or modifying membrane compositions (e.g., via ACSL4 inhibition) reduces substrate availability for lipid peroxides. In cancer cells, ELOVL5 (Elongation of Very Long Chain Fatty Acids Protein 5) regulates ferroptosis resistance primarily by modulating the synthesis of long-chain polyunsaturated fatty acids (LC-PUFAs), which are substrates for lipid peroxidation [86,87]. In many cancer cells, high ELOVL5 expression promotes sensitivity to ferroptosis by producing arachidonic acid (AA) and adrenic acid (AdA), while its downregulation or silencing leads to resistance [87,88]. In breast cancer cells, knockdown or low expression of ELOVL5 decreases polyunsaturated fatty acids in the cell, preventing the formation of toxic lipid peroxides and thus

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protecting against ferroptosis [89]. ELOVL5 generally promotes ferroptosis sensitivity through PUFA synthesis, although in certain oncogenic contexts it can contribute to therapy resistance via lipid signaling pathways (e.g., AKT–mTOR activation) [90]. ACSL4 is a key proponent of ferroptosis, while ACSL3 often plays a protective role against it [91,92]. ELOVL5-derived fatty acids are incorporated into membrane phospholipids and lipid droplets via ACSL3 and ACSL4, influencing ferroptosis susceptibility [93]. Studies show that when ELOVL5 is silenced, the levels of arachidonic acid and eicosapentaenoic acid decrease, directly affecting the substrate availability for ACSL4-mediated activation [94]. ELOVL5-derived PUFAs are esterified into phospholipids by ACSL4, while ACSL3 promotes MUFA incorporation into lipid pools, including lipid droplets, collectively shaping ferroptosis susceptibility [95].

While ACSL4 promotes ferroptosis by enabling accumulation of oxidized phospholipids in cellular membranes, SCD1 (Stearoyl-CoA desaturase 1) protects against ferroptosis by converting saturated fatty acids (SFAs) into monounsaturated fatty acids (MUFAs), reducing the accumulation of lipid peroxides [96]. SCD1 is responsible for the biosynthesis of monounsaturated fatty acids for maintaining membrane fluidity, cellular signaling, and gene expression [97,98]. SCD1 catalyzes the D9-cis desaturation of a range of fatty acyl-CoA substrates. The preferred substrates are palmitoyl- and stearoyl-CoA, which are converted into palmitoleoyl- and oleoyl-CoA respectively. Endogenous synthesis is the key driver in cancer cells of oleate and is the most abundant monounsaturated fatty acid [99]. SCD1 has been reported to be involved in cancer stem cells in various types of cancer and therefore, SCD1 has been suggested as a novel therapeutic target for cancer treatment [100]. Various natural products can inhibit SCD1 expression/activity, thereby suppressing cancer cell survival and self-renewal activity [101]. Mechanistically, upregulated expression of the monounsaturated fatty acid (MUFA) stearoyl-CoA desaturase, alters the ratio of MUFA-PLs to PUFA-PLs leading to ferroptosis resistance.

Overexpression of LPCAT1 (lysophosphatidylcholine acyltransferase 1) is associated with various cancers, including colorectal, prostate, and renal cancers, where it promotes tumor growth, migration, and invasion (REF). LPCAT1 catalyzes the conversion of lysophosphatidylcholine (LPC) to phosphatidylcholine (PC) by adding a palmitoyl group. Interestingly, LPCAT1 has been shown to be involved in ferroptosis resistance by enhancing membrane phospholipid saturation through the Lands cycle [102]. Furthermore, inhibition of LPCAT1 in presence of ferroptosis inducers, synergistically enhanced ferroptosis and suppressed tumor growth in preclinical models, suggesting that LPCAT1 could be a target for ferroptosis-inducing therapies in cancer treatment [102]. Inhibition of LPCAT1 then results in the reduction in polyunsaturated fatty acids in cellular membranes, protecting cells from lipid peroxidation and inhibiting ferroptosis [103]. Roles of lipid pathways and metabolism in ferroptosis resistance are summarized in Table 2.

Table 2. Summary of Lipid Metabolism in Ferroptosis Resistance.

Pathway	Biological Process	Effect on Ferroptosis	References
ELOVL5	PUFA Synthesis	↑ Sensitivity	[86,87]
ACSL4	PAFU Incorporation	↑ Sensitivity	[93]
ACSL3	MUFA Incorporation	↓ Sensitivity	[95]
SCD1	MUFA Synthesis	↓ Sensitivity	[95] [101]
LPCAT1	Phospholipid Saturation	↓ Sensitivity	[102,103]

The integrated model of ferroptosis resistance is summarized in Figure 3.

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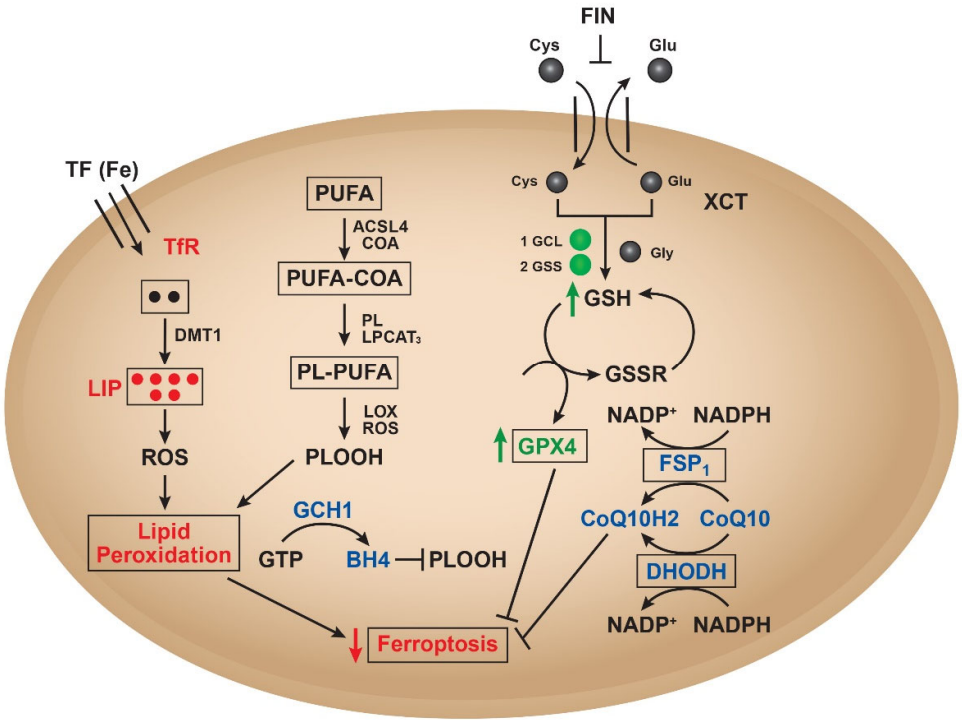

Figure 3. Integrated model of ferroptosis resistance in cancer. Canonical and non-canonical antioxidant pathways suppress lipid peroxidation and ferroptotic cell death. The xCT–GSH–GPX4 axis detoxifies phospholipid hydroperoxides, while FSP1–CoQ10H$_2$ and mitochondrial DHODH–CoQ10H$_2$ provide GPX4-independent protection. The GCH1–BH4 pathway further limits lipid peroxidation. Iron uptake through TfR and the labile iron pool promotes ROS generation and PUFA-containing phospholipid oxidation. Ferroptosis inhibitors (FIN) block cystine uptake through xCT. Together, these pathways regulate ferroptosis sensitivity and tumor cell survival.

Future and Therapeutic Considerations

A number of issues remain in ferroptosis research besides deciphering mechanisms of resistance that must also be addressed. These include need for suitable models for studying resistance *in vitro* and *in vivo*, development of biomarkers of ferroptosis resistance and targeted delivery of FINs and inhibitors without off target toxicity. It has been suggested that conditional GPX4 knockout mice can be utilized to study how cells adapt or resist ferroptosis through alternative pathways [104]. Also, one can utilize NrF2-overexpressing models that mimic the high resistance observed in some cancers [105,106]. Additionally, tumor or xenograft models overexpressing SLC7A11 for resistance due to cystine-deprivation-induced ferroptosis can be utilized [107]. However, tumors *in vivo* are more complex and often show more than one pathway for resistance e.g., tumors may express high levels/activity of both GPX4 and FSP1 as we found in certain breast cancer cells [53]. It is also possible that *in vivo* resistance may result from the presence of both ABC transporters and enhanced metabolic detoxification of FINs. These scenarios further complicate choice of models of ferroptosis resistance. Furthermore, it has recently been reported that both 3D and in vivo tumor models show significant resistance to lipid peroxidation due to extensive lipid remodeling [108], adding additional complications for studying mechanism of resistance.

With regards to biomarkers, at this time there are no valid biomarkers that can be utilized as predicative of ferroptosis resistance. However, levels of 4-HNE or MDA, phospholipid hydroperoxides (PLOOH), or reduced glutathione can be measured by mass spectrometers. The Western Blots or RT-PCR methods can also be utilized to detect elevated levels of GPX4, FSP1, or

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SLC7A11 in both *in vitro* and *in vivo*. However, these limitations highlight the need for standardized ferroptosis-resistance models and validated biomarkers to enable clinical translation.

Targeted delivery of FINs or inhibitors of FSP1 presents another difficult task as high concentrations of these compounds are toxic, resulting in serious adverse effects [109]. Doxorubicin (DOX) is extremely effective drug for the treatment of many human cancers in the clinic [110]. Doxorubicin is a well-known ROS generator and induces lipid peroxidation for both its antitumor activities and cardiotoxicity [111,112]. Liposomal encapsulation of DOX has been shown to decrease its cardiotoxicity and enhance its anti-tumor activity, especially in liposomes prepared from unsaturated phospholipids which get incorporated and provide an abundance of lipid molecules for lipid peroxidation [113,114]. It is believed that nanoparticle-based delivery systems enhance therapeutic efficacy by simultaneously targeting multiple ferroptosis defense arms while reducing toxicity. Encapsulation of various FINs not only can improve their solubility but may also result in delivering a higher concentration directly to the cellular membrane, resulting in enhanced effects. Similarly, encapsulated inhibitors of FSP1 can also be effectively delivered to tumor sites increasing their selectivity and simultaneously decreasing off target toxicity.

In this perspective, I propose that ferroptosis resistance in cancer is governed by an integrated network of redox-regulatory, metabolic, and transport adaptations that suppress lipid peroxidation and sustain tumor cell survival. Collectively, these pathways form a spatially and functionally compartmentalized network that suppresses lipid peroxidation through redundant antioxidant buffering. These antioxidant pathways are further supported by NrF2-mediated transcriptional programs, iron sequestration and lipid remodeling that reduces polyunsaturated fatty acid availability, and ABC transporters that regulate drug and glutathione flux.

Tumor heterogeneity—including differences in differentiation state, epithelial–mesenchymal plasticity, and metabolic reprogramming—generates subpopulations with distinct ferroptosis sensitivities and facilitates therapeutic escape. Importantly, ferroptosis also intersects with antitumor immunity, providing opportunities for synergistic therapeutic strategies that combine ferroptosis induction with immunotherapy.

Our recent work further demonstrated that ferroptosis resistance can arise through distinct pathway-specific antioxidant programs. In parental MCF-7 breast cancer cells, resistance to erastin is largely mediated by activation of the FSP1–CoQ10–NADPH pathway together with upregulation of the GSH–GPX4 antioxidant system, resulting in reduced lipid peroxidation and suppression of ferroptotic death. In contrast, the multidrug-resistant MXR derivative relies predominantly on the xCT–GSH–GPX4 axis, making these cells more susceptible to erastin-induced ferroptosis. These findings identify FSP1 as a critical regulator of ferroptosis resistance and suggest that co-targeting GPX4 and FSP1 may represent an effective strategy to sensitize resistant breast cancer cells to ferroptosis-inducing agents.

Overall, these insights highlight the context-dependent nature of ferroptosis resistance and underscore the importance of targeting multiple antioxidant defense systems simultaneously. A deeper understanding of the oxidant–antioxidant networks that govern ferroptosis will be essential for the development of next-generation therapeutic strategies designed to overcome drug resistance and improve cancer treatment outcomes. Given the complexity and redundancy of ferroptosis resistance pathways, key mechanisms and their corresponding therapeutic targeting strategies are summarized in Table 3, emphasizing the need for combinatorial approaches targeting multiple ferroptosis defense systems to effectively overcome tumor resistance.

Table 3. Major ferroptosis resistance mechanisms and corresponding therapeutic targeting strategies.

Category	Resistance Mechanism	Component & Pathway	Therapeutic Strategy	Representative Inhibitors	Reference
Antioxidants Defense Systems	GPX4-dependent Pathway	GSH-GPX4-Axis	Direct GPX4 Inhibition	RSL3, ML210	[115,116]

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	FSP1-CoQ10 System	FSP1-CoQ10-NADPH	FSP1 Inhibition	iFSP1	[54,117]
	DHODH-Mediated defense	Mitochondrial CoQ10 reduction	DHODH Inhibition	Brequinar	[118]
Cystine Transport & Redox Balance	xCT antiporter System	SLC7A11 (Cystine uptake)	xCT Inhibition	Sulfasalazine	[119,120]
Drug Efflux	ABC Transporters	FINS and GSH	Transport Inhibition	Tariquidar, Cyclosporine, PSC833	[121,122]
Lipid Metabolism	**Remodeling & Metabolism**	PUFA Depletion, MUFA Enrichment	Promote PUFA synthesis/Inhibit lipid desaturation	ACSL4 Activation, SCD1 Inhibition	[91,96]
Iron Metabolism	Iron Handling & ROS generation	Labile Iron Pool increase	Iron-based Therapies	Iron nanoparticles, Artesunate, Dihydroartemisinin	[11] [123,124]

Abbreviations

GPX4, Glutathione Peroxidase 4; CoQ10H2, Ubiquinol; FSP1, Ferroptosis Suppressor Protein 1; DHDOH, Dihydroorotates Dehydrogenase; NQO1, NADPH Quinone Reductase 1; BH4, Tetrahydrobiopterin; GCH, GTP cyclohydrolase 1; NrF2, Nuclear factor erythroid 2-related factor 2; ABC, ATP-binding Cassette, System xCT, glutamine/cysteine antiporter; FIN, ferroptosis inducing agents; ROS, Reactive oxygen species; L-ROS, lipid-derived reactive oxygen species; GATA3, GATA binding protein 3; ACSL3, Acetyl-CoA Synthetase Long Chain family member 3; ACSL4, Acetyl-CoA Synthetase Long Chain family member 4; SLC7A11, Solute Carrier Family 7 Member 11; LIP, Labile iron pool; PUFA, polyunsaturated fatty acid; ELOVL5, elongation of very long chain fatty acids 5; SCD1, Stearoyl-CoA-desaturate; LPCAT1, lysophosphatidylcholine acyl-transferase; DOX, doxorubicin.

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