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Ferroptosis and Notch Signaling Drive Tumor Progression and Therapeutic Vulnerability

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Abstract

Ferroptosis is an iron-dependent form of regulated cell death characterized by unchecked lipid peroxidation and redox imbalance, which makes cancer cells vulnerable. The Notch signaling pathway is involved in cell survival, proliferation, differentiation, and helps cells adapt to metabolic and oxidative stress. Notch signaling intersects with ferroptosis through specific mechanisms: it modulates iron homeostasis by altering iron transport and storage proteins, influences lipid metabolism by regulating enzymes that modify membrane phospholipids, and affects antioxidant defenses by controlling the expression of genes such as SLC7A11 that regulate glutathione levels. As a result, Notch activity can sensitize cells to ferroptotic death by encouraging iron accumulation and lipid remodeling or confer resistance by increasing antioxidant capacity and reducing oxidative damage. In cancer, alterations in both ferroptosis and Notch signaling contribute to tumor initiation, progression, metastasis, and therapeutic resistance, in part through mechanistic interactions.

Recent studies report a link between ferroptosis and Notch signaling in several tumor types. However, this relationship likely varies by cancer type and experiment. Studying how these pathways connect could reveal new therapeutic targets, particularly in cancers that rely upon Notch-dependent metabolic programs or resist ferroptosis. Future work should address practical concerns. Selecting appropriate cellular targets, refining delivery methods, and understanding the tumor microenvironment will be important before demonstrating clinical benefits. Ultimately, more targeted ways to exploit the ferroptosis-Notch link may expand precision oncology tools. However, this remains under investigation and has not yet been approved as a therapy.

Keywords: Ferroptosis, Notch, Lipid Peroxidation, Cancer Therapeutic Targets, Metabolic Reprogramming, Immunogenic Cell Death (ICD), Iron metabolism, Precision oncology.

1. Introduction

Dixon and colleagues first reported on ferroptosis in 2012. They identified erastin, a molecule that induces a unique cell death in RAS-mutant cancer cells. This iron-dependent process involved severe lipid peroxidation but did not exhibit features of apoptosis or other forms of cell death (1). In the 2000s, research linked glutathione peroxidase 4 (GPX4) to the breakdown of lipid peroxides. This showed a specific role for GPX4 (2). In 2003, Yant et al. found that GPX4 is vital for mouse embryonic development. GPX4-deficient embryos died from severe oxidative damage. This indicated a novel form of cell death caused by uncontrolled lipid peroxidation, although it had not yet been named (3).

Advances in genome-wide screening and chemical biology have further uncovered key regulators and features of ferroptosis, including LPCAT3 and ACSL4. Both enzymes alter the phospholipid composition of membranes, increasing the proportion of PUFAs and making lipids more susceptible to oxidation. LPCAT3 and ACSL4 define cell sensitivity to ferroptosis, linking lipid metabolism to cell death. Inhibitors of ferroptosis, such as ferrostatin-1 (Fer-1), liproxstatin-1, and vitamin E derivatives, have been used in vivo to link ferroptosis to diseases such as ischemia-reperfusion injury, neurodegeneration, and kidney failure. Notably, one study using adult mice lacking the GPX4 gene showed rapid, severe lipid peroxidation, kidney failure, and death. Administration of liproxstatin-1 prevented this damage, clearly demonstrating for the first time that ferroptosis directly causes tissue injury. These findings highlight that targeting ferroptosis may help treat certain diseases.

The study of Notch signaling began in fruit flies when scientists found a mutant with notched wings. This discovery demonstrated that Notch was required for proper development and survival, thereby establishing it as a master developmental regulator. Subsequent studies have shown that Notch is a conserved cell-cell signaling pathway. It regulates cell-type selection, boundary formation, and tissue health in many animals. Cloning Notch revealed it to be a large membrane receptor with multiple EGF-like repeats. Soon after, Delta was identified as a Notch ligand, demonstrating that Notch is activated by cell-cell contact. This clarified Notch's developmental role and revealed it to be a juxtacrine signaling system. Additional studies explained the interactions between Notch and DSL ligands. High-resolution work detailed the EGF-like repeats and protein binding. This explained how ligand binding exposes the Notch regulatory region for proteolysis, releasing the active Notch domain. These findings established the modern model of Notch activation. Notch has also been shown to be a key regulator of stem cell function, tissue maintenance, and lineage decisions. Notch errors have been linked to cancer and developmental disorders. Genome-wide ChIP-seq mapped Notch's transcription targets and revealed its complex networks. Results showed that Notch works with other pathways and chromatin factors to guide cell fates. This prompted searches for drugs to block the pathway, such as γ-secretase inhibitors (GSIs) and monoclonal antibodies. These are being tested for cancers and inherited disorders linked to Notch. Research also uncovered noncanonical Notch signaling, such as ligand-independent activation and metabolic roles. These advances show the broad role of Notch in cell communication and disease.

Several studies have begun to describe direct interactions between Notch signaling and cellular systems that influence ferroptosis. For instance, activating Notch1 can increase SLC7A11 expression, a key component of the system Xc^- transporter, thereby increasing cysteine uptake and supporting glutathione synthesis. These changes enhance a cell's antioxidant defenses against ferroptosis. In this way, Notch1 maintains redox homeostasis and can reduce tumor cell sensitivity to ferroptotic triggers. Conversely,

when Notch1 activity is reduced, SLC7A11 support diminishes, thereby lowering glutathione synthesis and increasing cell susceptibility to ferroptosis. Loss of Notch1 signaling thus contributes to glutathione depletion, lipid peroxide accumulation, and increased vulnerability to ferroptotic damage in multiple cancer models. These findings suggest that Notch pathway status regulates ferroptosis sensitivity primarily by modulating iron balance, antioxidant defense, and lipid composition, rather than through a single-step process. Here, we review studies on the interplay between ferroptosis and Notch signaling in cancer. We discuss why context matters, why pathways behave differently in tumors, and what questions remain before clinical use.

2. Ferroptosis: Mechanisms, Regulators, and Oncogenic Context

Ferroptosis is fundamentally distinct from other forms of regulated cell death because it is driven by iron-dependent lipid peroxidation, rather than caspase activation or mitochondrial dysfunction. A central mechanism underlying this process is intracellular iron overload. Elevated levels of ferrous iron (Fe^{2+}) catalyze the Fenton reaction, in which Fe^{2+}species, including hydroxyl radicals, are produced. Reactive oxygen species (ROS) can damage membrane components by oxidizing polyunsaturated fatty acids (PUFAs), often triggering a broader lipid peroxidation cascade that disrupts membrane stability. When these oxidized lipids rise beyond what the cell's antioxidant defenses can manage, ferroptotic death becomes more likely. Unlike apoptosis or necroptosis, which engage distinct enzymatic programs, ferroptosis unfolds through iron-dependent oxidative reactions that reshape the cell's metabolic and redox environment. In this setting, lipid peroxidation does not simply stop once initiated; oxidized phospholipids can generate additional reactive lipid species that continue to attack neighboring lipids, gradually undermining membrane integrity. Without sufficient buffering systems, particularly those involving GPX4 or glutathione metabolism, cells struggle to halt this feedback loop, leaving them vulnerable to a point of no return. Initially, ROS strips hydrogen atoms from PUFAs within membrane phospholipids, generating lipid radicals. These radicals rapidly react with molecular oxygen to form lipid peroxyl radicals, propagating oxidative damage throughout the membrane. As lipid peroxides accumulate, antioxidant defenses become overwhelmed. In particular, loss of GPX4 activity disables the cell's ability to detoxify lipid peroxides, accelerating the peroxidation cascade. In parallel, impaired cystine uptake through SLC7A11 or SLC3A2 diminishes intracellular cysteine availability, limiting glutathione synthesis and further compromising the cell's redox buffering capacity (22-24)

Beyond the well-characterized components of ferroptosis, some additional regulators also shape a cell's susceptibility to this form of death. One example is acyl-CoA synthetase long-chain family member 4 (ACSL4), which modifies membrane phospholipids by incorporating PUFA substrates. Cells that accumulate these lipid species tend to be more vulnerable to oxidative damage, thereby sensitizing them to peroxidation and promoting ferroptosis (25). Likewise, arachidonate 15-lipoxygenase (ALOX15) catalyzes the oxygenation of PUFA-containing phospholipids (PUFA-PL), thereby driving lipid peroxide accumulation (26-28). Conversely, two independent antioxidant systems counteract ferroptotic stress: ferroptosis suppressor protein 1 (FSP1), which regenerates coenzyme Q10 (CoQ10) to trap lipid radicals at the plasma membrane, and dihydroorotate dehydrogenase (DHODH), which performs a similar protective function within mitochondria (29-31). These parallel pathways underscore the complex multilayered control of lipid peroxidation beyond the classical GPX4-GSH axis.

Ferroptosis is also modulated by the tumor suppressor p53, which exerts context-dependent effects on this cell-death pathway. On one hand, p53 can promote ferroptosis by repressing SLC7A11 transcription, thereby reducing cystine import and limiting glutathione synthesis, conditions that weaken antioxidant defenses and sensitize cells to lipid peroxidation. On the other hand, p53 can also act as a negative regulator of ferroptosis under certain physiological or stress conditions. It achieves

this by inducing p21, which slows cell-cycle progression and conserves intracellular redox capacity, or by reprogramming cellular metabolism to restrain excessive ROS production. These dual roles highlight p53 as a nuanced regulator that can either facilitate or suppress ferroptosis depending on cellular context, stress intensity, and metabolic state (32-34) (Figure 1).

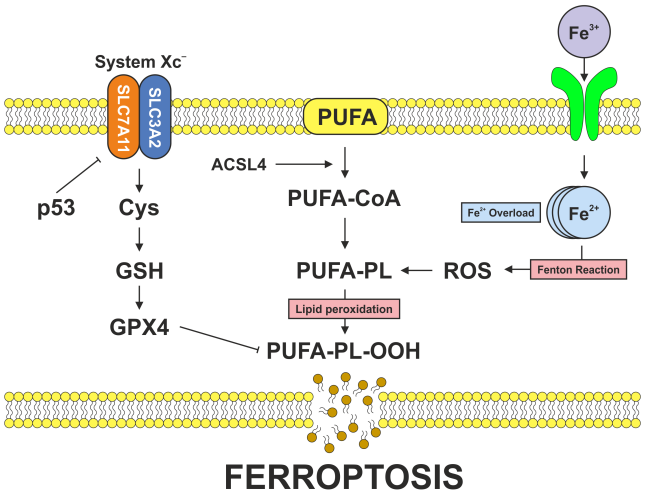

Figure 1. Mechanisms of ferroptosis. *Schematic illustration showing the dual roles of the tumor suppressor p53 in ferroptotic cell death. p53 can promote ferroptosis by transcriptionally repressing SLC7A11, thereby limiting cystine uptake, depleting glutathione, weakening antioxidant defenses, and sensitizing cells to lipid peroxidation. Conversely, under specific physiological or stress conditions, p53 can suppress ferroptosis by inducing p21, which slows cell-cycle progression and preserves redox homeostasis, or by promoting metabolic reprogramming that limits excessive reactive oxygen species (ROS) production. Together, these opposing activities underscore p53 as a finely tuned regulator of ferroptosis whose net effect depends on cellular context, stress intensity, and metabolic state.*

Moreover, beyond these canonical mechanisms, epigenetic and metabolic determinants play crucial roles in regulating ferroptosis sensitivity. Histone-modifying enzymes such as SETD1A, KDM5A, and HDAC3 reshape chromatin accessibility at ferroptosis-related loci, including GPX4, SLC7A11, and ACSL4, thereby influencing redox balance and therapy response (35,36). DNA methylation at the promoters of SLC7A11 and FSP1 confers ferroptosis resistance in hepatocellular and breast cancers, whereas demethylating agents can restore ferroptotic sensitivity (37).

Non-coding RNAs (ncRNAs) have emerged as important post-transcriptional regulators of ferroptosis. Some microRNAs, miR-137 and miR-9, for instance, appear to limit ferroptotic activity by targeting SLC7A11, which influences cystine import and the availability of glutathione. Other ncRNAs behave differently. The long non-coding RNA LINC00336 has been reported to protect cells from ferroptosis, either by stabilizing GPX4 or by acting as a competing endogenous RNA that diverts microRNAs that promote ferroptotic signaling. Taken together, these examples illustrate how ncRNAs create an additional layer of regulation that can shift redox homeostasis and influence whether a cell undergoes ferroptotic death (38-40). These epigenetic and metabolic interactions integrate chromatin, transcriptional, and redox control to fine-tune ferroptotic thresholds, suggesting that combined targeting of epigenetic modulators and ferroptosis inducers may provide refined therapeutic opportunities (41).

3. Notch Signaling in Cancer: A Dual-Role Developmental Pathway

Notch signaling is a highly conserved pathway that governs a wide range of developmental and homeostatic processes. Canonical Notch signaling is initiated when a Delta-like or Jagged ligand on one cell makes contact with a Notch receptor on an adjacent cell. This binding event leads to ligand endocytosis, which exerts mechanical force to expose the receptor's negative regulatory region, thereby making it accessible to proteolytic cleavage. Processing by ADAM metalloproteases and the γ-secretase complex releases the Notch intracellular domain (NICD), which translocates to the nucleus. NICD binds the transcription factor CSL/RBPJ and recruits co-activators, such as Mastermind-like proteins, to increase the expression of canonical target genes that regulate differentiation, stemness, and tissue-specific programs.

Despite its conserved mechanism, the biological consequences of Notch activation are context-dependent. In some tissues, Notch functions as an oncogene, while in others it acts as a tumor suppressor. Oncogenic roles are well documented in human leukemias, where activating Notch1 mutations drive proliferation and block differentiation. Similar pro-tumorigenic effects have been observed in triple-negative breast cancer (TNBC), certain lung cancers, and subsets of colorectal cancers (CRC), where Notch promotes survival and resistance to therapy. Conversely, in tissues such as the skin, liver, and myeloid compartment, Notch signaling limits excessive proliferation and supports differentiation, thereby acting as a barrier to transformation. Loss-of-function mutations within the Notch gene can contribute to tumorigenesis. This duality reflects the pathway's reliance on cellular context, microenvironmental cues, and the transcriptional landscape in which NICD operates. As a result, therapeutic targeting of Notch requires careful consideration of tissue-specificity to avoid unintended effects.

Although Notch signaling is best known for its role in directing cell-fate decisions, it also exerts broad metabolic effects across many cell types. Activation of the pathway can alter how cells manage energy production, reshaping metabolic circuits to meet the demands of growth or differentiation. Evidence from cancer studies indicates that Notch activity can push cells toward increased glycolysis, greater reliance on glutamine, and changes in mitochondrial behavior, adjustments that help sustain proliferation. The pathway also extends its influence to lipid metabolism, affecting the synthesis and remodeling of membrane phospholipids and potentially altering cellular responses to oxidative stress. Notch is also linked to antioxidant defenses; when active, it promotes the expression of genes that maintain redox balance, limit reactive oxygen species, and enable cells to cope with metabolic stress. When Notch activity is reduced, these protective functions are weakened, and cells become more susceptible to lipid peroxidation and, ultimately, ferroptotic death. Collectively, these observations suggest that Notch does not simply shape identity and lineage; it also helps coordinate the metabolic and redox landscape that determines a cell's vulnerability to stress.

4. Crosstalk between ferroptosis and Notch signaling in cancer

Notch activity does not influence ferroptosis in isolation; it intersects with processes that shape a cell's identity, energy use, and oxidative handling. When these elements align in particular ways, they can leave the cell markedly more or less sensitive to death triggered by lipid peroxidation. While these processes were once viewed as distinct, emerging studies demonstrate that they are tightly integrated through three shared biological frameworks: redox and antioxidant regulation, lipid metabolism and membrane vulnerability, and cellular stress signaling (42-44). Together, these domains establish a context-dependent "Notch-ferroptosis rheostat" that tunes ferroptotic susceptibility in response to metabolic needs, tumor microenvironment stresses, and oncogenic mutations.

Notch signaling modulates ferroptosis primarily by regulating lipid metabolism, antioxidant defenses, and iron homeostasis. By regulating enzymes such as ACSL4 and, indirectly, LPCAT3, Notch signaling can modulate the synthesis of PUFAs, key substrates for lipid peroxidation and ferroptotic cell death (45). Simultaneously, Notch regulates oxidative stress responses by modulating NRF2-dependent antioxidant genes, thereby fine-tuning the cellular redox balance and determining ferroptotic sensitivity (46,47).

Despite these common mechanisms, context-specific outcomes are evident across cancer types. For instance, in hepatocellular carcinoma (HCC), the Notch modulator NELL2 promotes ferroptosis by suppressing epithelial-mesenchymal transition (EMT), increasing intracellular ROS, iron, and malondialdehyde (MDA), and reducing glutathione (GSH) (48). In contrast, in non-small cell lung

cancer (NSCLC), Notch3 activation protects against ferroptosis by maintaining the expression of GPX4 and PRDX6, key antioxidant enzymes, whereas Notch3 inhibition sensitizes tumor cells to ferroptosis inducers such as erastin (49). Similarly, in liver fibrosis, the IGF2BP3-Jag1-Notch axis stabilizes Notch signaling and elevates GPX4 expression, thereby suppressing ferroptosis (50).

When considered in context, the data imply that Notch does more than participate in isolated steps of ferroptosis; it also helps coordinate several processes that determine whether ferroptotic death will occur. By transcriptionally enhancing SLC7A11 and GPX4, Notch sustains glutathione synthesis and detoxifies lipid peroxides, opposing ferroptotic stress (51). It can also cooperate with Nrf2 to amplify antioxidant responses, thereby conferring a protective advantage in oxidative microenvironments, such as those found in tumors or fibrotic tissues. However, under stress or in specific genetic contexts, such as elevated mitochondrial ROS levels or TP53 mutations, Notch signaling may no longer suppress ferroptosis, leaving cancer cells more vulnerable to ferroptosis-inducing therapies.

This vulnerability is particularly relevant in hematologic malignancies, where ferroptosis-based interventions have shown considerable therapeutic promise. Studies in acute lymphoblastic leukemia (ALL) have demonstrated that ferroptosis inducers, such as RSL3, erastin, and sulfasalazine, can significantly reduce leukemic cell burden in experimental models. Furthermore, selective inhibition of GPX4 has been shown to target acute myeloid leukemia (AML) preferentially, stem cells, while sparing normal hematopoietic stem cells, indicating that modulating the Notch-ferroptosis axis may open a unique therapeutic window for leukemia treatment (26,52).

Similar principles apply to solid tumors such as TNBC. Pharmacological targeting of SLC7A11 or GPX4 can re-sensitize TNBC cells to ferroptosis and suppress tumor progression, as shown in preclinical studies. TNBC represents an aggressive breast cancer subtype characterized by the absence of estrogen receptor, progesterone receptor, and HER2 expression, and is particularly susceptible to ferroptotic cell death. These tumors often exhibit elevated levels of PUFAs and have dysregulated iron metabolism, making them more vulnerable to lipid peroxidation. Moreover, SLC7A11, an essential component of the system Xc^- antiporter, is often overexpressed in breast cancer, where it enhances glutathione synthesis and supports GPX4 activity, thereby conferring resistance to ferroptosis (53-55).

Glioblastoma multiforme (GBM) is one of the deadliest and most treatment-resistant types of brain tumors. GBM cells frequently exhibit elevated iron absorption and altered metabolism, rendering them more susceptible to ferroptosis under stress. Notably, Notch1 has been shown to suppress SLC7A11 expression, thereby weakening cystine import and sensitizing cells to ferroptotic death. These findings suggest that ferroptosis-inducing agents may be especially effective in GBM tumors with impaired Notch signaling or diminished antioxidant capacity. This vulnerability is even more pronounced in glioblastoma stem-like cells (GSCs), which depend heavily on robust antioxidant systems, including GPX4 and FSP1, to maintain survival and stemness. When these protective pathways are disrupted, GSCs undergo ferroptosis, resulting in reduced self-renewal and impaired tumor-initiating potential (56-59).

Ferroptosis has been shown to exert a tumor-suppressing effect in colorectal cancer (CRC), and compounds such as genistein or sulfasalazine can trigger ferroptosis by downregulating SLC7A11 and GPX4 expression (60,61). However, many CRC cells exhibit inherent resistance to ferroptosis, driven in part by activation of antioxidant pathways, including the NRF2-HO1 axis, and by metabolic adaptations that reshape lipid composition. Given that Notch signaling can enhance oxidative stress resistance and promote fatty acid oxidation, it is reasonable to speculate that Notch activation may contribute to ferroptosis resistance in CRC. Supporting this idea, research in other tumor types has shown that Notch3-mediated fatty acid oxidation reduces lipid peroxide accumulation, indicating that a similar mechanism might be involved in colorectal tumors (62).

Another example is prostate cancer (PCa) driven by hormones, distinguished by its metabolic adaptability, redox changes, and resistance to treatment. High-grade and castration-resistant prostate cancer (CRPC) frequently exhibits elevated Notch signaling, driven predominantly by the Notch1 and Notch3 receptors. Jagged1/2 and Delta-like ligands trigger this signaling pathway, which results in the transcriptional upregulation of Hes1, Hey1, and Myc. These factors collectively promote the EMT and stress-tolerant survival (63). In parallel, the androgen receptor (AR) signaling pathway controls genes involved in glutathione homeostasis and lipid metabolism, which, in turn, directly affect ferroptotic sensitivity. Notably, AR has been reported to transcriptionally repress ACSL4 in prostate cancer, leading to reduced synthesis of PUFA-CoA and the ensuing PUFA-phospholipids, such as PE (phosphatidylethanolamine), which are substrates for lipid peroxidation in ferroptosis (64).

Table 1. Role of Ferroptosis and Notch Signaling in Selected Cancer Types.

Cancer Type	Ferroptosis Roles	Notch Roles
Breast Cancer	Promotes metastasis through mechanisms like PUFAs accumulation and resistance to ferroptosis-inducing conditions. Suppressing tumor growth and improving the effectiveness of conventional therapies, while also being a potential target for new treatments	Oncogenic
Glioblastoma	Influence proliferation, invasion, and the tumor's immunosuppressive microenvironment.	Oncogenic
Acute Lymphoblastic Leukemia	Facilitates metastasis by providing metastatic cells with resistance to ferroptosis, partly through the accumulation of fatty acids and glutathione.	Oncogenic
Acute Myeloid Leukemia	Involved in the development and progression of the disease.	Context dependent
Colorectal Cancer	Can contribute to progression and metastasis. The expression of ferroptosis-related genes correlates with chemosensitivity to certain drugs, suggesting a role in resistance mechanisms.	Context dependent
Hepatocellular Carcinoma	Can be a therapeutic target, with some drugs like sorafenib inducing cell death via ferroptosis.	Oncogene (primarily)
Gynecological Cancers	Contributes to tumor progression, invasion, and metastasis through the regulation of lipid metabolism and oxidative stress	Context dependent
Prostate Cancer	Influences invasion and migration through the regulation of lipid metabolism and ferroptosis key regulators like ACSL4	Context dependent

5. The Role of Ferroptotic Cells in Activating Antitumor Immunity

Ferroptosis, in addition to its innate ability to suppress tumors, has been recognized as a key modulator of the immune response within the TME (Figure 2) (65,66). Unlike apoptosis, which is generally immunologically silent, ferroptotic cell death can exhibit immunogenic features under specific conditions. The interplay between ferroptotic tumor cells and immune components underscores their dual roles as both a cell death mechanism and a potential trigger of antitumor immunity (Table 2) (67,68).

A hallmark of immunogenic cell death (ICD) is the release of damage-associated molecular patterns (DAMPs), which serve as danger signals. Ferroptotic cells release various DAMPs, including ATP, HMGB1, and calreticulin, which promote dendritic cell (DC) recruitment and maturation, enhance cross-presentation of tumor antigens to $CD8^+$ T cells, and elicit robust antitumor responses (69-71). Conversely, $CD8^+$ T cells can actively induce ferroptosis in tumor cells. Interferon-γ (IFN-γ) released by activated T cells downregulates SLC3A2 and SLC7A11, key components of the cystine/glutamate antiporter system Xc^-, thereby impairing glutathione synthesis and increasing susceptibility to ferroptosis (72).

Ferroptosis is also characterized by extensive lipid peroxidation, producing oxidized phospholipids and 4-hydroxynonenal (4-HNE), which activate DCs via TLR4-STING signaling, stimulate type I interferon secretion, and promote $CD8^+$ T-cell activation (73). These lipid peroxidation products further modulate immune cell behavior, serving as chemoattractants or triggers for innate immune responses. Notably, lipid peroxide accumulation in the TME can influence macrophage recruitment and polarization, with pro- or antitumor outcomes depending on tumor type and context (74-76). From a therapeutic perspective, inducing ferroptosis offers the dual benefit of direct tumor cell killing and enhancement of immune-mediated clearance. Preclinical studies combining ferroptosis inducers with immune checkpoint inhibitors, such as anti-PD-1 or anti-CTLA-4 antibodies, have demonstrated promising results in overcoming immune resistance in tumors with low inherent immunogenicity (77,78).

Table 2. Immune processes influenced by ferroptosis in the tumor context.

Key Process	Mechanism	Immune Cell Type	Effect on Immunity
Release of DAMPs	ATP, HMGB1, calreticulin released from ferroptotic cells	Dendritic cells	Promotes DC maturation and antigen presentation
Lipid Peroxidation Products	Generation of oxidized phospholipids, 4-HNE	Macrophages	Context-dependent activation or suppression
IFN-γ–mediated ferroptosis	IFN-γ from $CD8^+$ T cells downregulates system Xc^- (SLC7A11/SLC3A2), sensitizing tumor cells	$CD8^+$ T cells	Enhances tumor cell ferroptosis and immune clearance
Antigen cross-presentation	Mature DCs present tumor antigens released from ferroptotic cells	$CD8^+$ T cells	Stimulates cytotoxic T cell activation
Temporal context	Early ferroptosis promotes immunity; late-stage can induce immunosuppression	Multiple	Determines overall immune outcome
Therapeutic implications	Combination of ferroptosis inducers with immune checkpoint inhibitors	Immunotherapy strategies	Potential synergistic antitumor effects

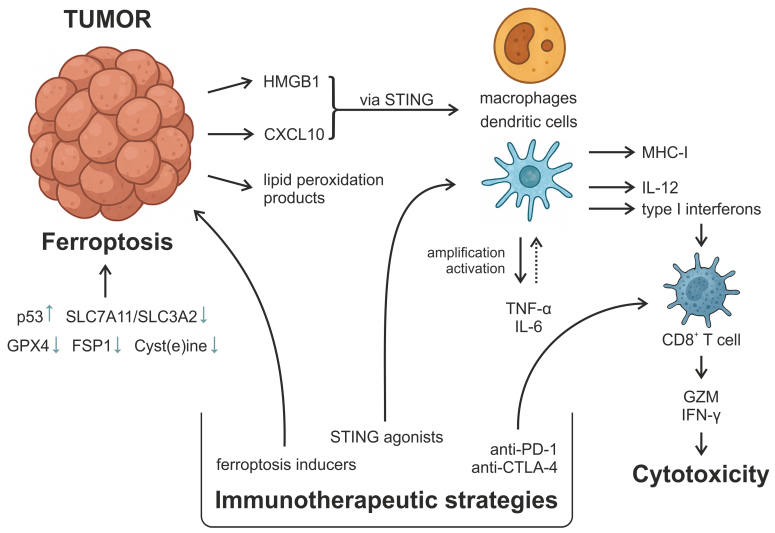

Figure 2. The role of ferroptotic cell death in triggering antitumor immunity. *This schematic illustrates the immunogenic cascade initiated by ferroptotic tumor cells and its implications for antitumor immunity and therapeutic intervention. Ferroptosis is induced by the suppression of antioxidant defenses, including GPX4 and the ferroptosis suppressor protein 1 (FSP1), and by disruption of cyst(e)ine metabolism, processes often regulated by p53 and the SLC7A11/SLC3A2 transporter system. Ferroptotic cells release damage-associated molecular patterns (DAMPs), such as HMGB1 and lipid peroxidation*

products, as well as chemokines, including CXCL10. These DAMPs engage pattern-recognition pathways, including Toll-like receptor 4 (TLR4)-dependent signaling and, in some contexts, cGAS-STING activation by oxidized nucleic acids, thereby promoting dendritic cell (DC) maturation and enhancing antigen processing and MHC class I cross-presentation. Mature DCs produce cytokines, such as interleukin-12 (IL-12) and type I interferons, which support the priming of cytotoxic $CD8^+$ T cells. Activated $CD8^+$ T cells secrete granzyme B and interferon-γ (IFN-γ), amplifying antitumor cytotoxicity and promoting further ferroptotic stress within tumor cells. Inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), contribute to the recruitment and activation of additional immune cells within the tumor microenvironment. Therapeutically, ferroptosis inducers can enhance tumor immunogenicity and synergize with immunotherapies, including immune checkpoint blockade (anti–PD-1 and anti–CTLA-4) and STING agonists, to overcome resistance and improve tumor eradication.

6. Therapeutic Implications of Targeting the Notch-Ferroptosis Axis

Targeting the Notch-ferroptosis axis represents a promising therapeutic approach. Combining Notch inhibitors with ferroptosis inducers may yield synergistic antitumor effects in cancers where Notch signaling suppresses ferroptosis and promotes tumor survival. Given the high activity of Notch3- or Jag1-mediated pathways in NSCLC and liver tumors, this strategy may be particularly effective in these malignancies.

6.1 Targeting Ferroptosis

Some molecular markers serve as indicators of ferroptosis sensitivity in cancer. Elevated expression of SLC7A11 (xCT) is a widely recognized biomarker, as it reflects enhanced cystine uptake and glutathione synthesis, both of which suppress lipid peroxidation and promote ferroptosis resistance. High GPX4 protein levels indicate strong antioxidant capacity that protects cells against phospholipid oxidation. In contrast, increased expression of ACSL4 and LPCAT3 is associated with increased ferroptotic vulnerability, as these enzymes drive the incorporation of PUFAs into membrane phospholipids, the substrates required for lethal lipid peroxidation. Additionally, the activity of FSP1 and genes involved in CoQ10 metabolism provides an alternative, GPX4-independent defense system; reduced expression of these components often correlates with increased ferroptosis sensitivity. Collectively, these biomarkers help define the ferroptotic landscape of tumor cells and guide the development of targeted therapeutic strategies.

Building on these insights, several therapeutic approaches aim to exploit ferroptosis in cancer treatment. GPX4 is a key regulator of ferroptosis, and its inhibition has emerged as a potential anticancer strategy. GPX4 inhibitors, including (1S,3R)-RSL3, FINO2, and FSP1, are being evaluated preclinically for their ability to induce ferroptosis in tumor cells, particularly those resistant to conventional therapies (79,80). System Xc^-, a cystine/glutamate antiporter, maintains intracellular glutathione levels and protects against ferroptosis. Inhibitors such as sulfasalazine and erastin disrupt this system, depleting glutathione and sensitizing cancer cells to ferroptosis. Their efficacy is being assessed in clinical trials across several cancer types, including glioblastoma, NSCLC, and other malignancies (81,82). Combination strategies are under active investigation, with ferroptosis inducers being paired with immune checkpoint inhibitors or standard chemotherapies to enhance antitumor efficacy. For example, GPX4 inhibitors combined with PD-1/PD-L1 blockade have shown promising results in preclinical models of TNBC (83,84).

6.2 Targeting Notch Signaling

Several molecular indicators can be used to assess the functional status of the Notch signaling pathway in cancer cells. Expression levels of the Notch1, Notch2, and Notch3 receptors serve as primary biomarkers, reflecting the pathway's activation potential at the cell surface. Similarly, the abundance of Jagged and Delta-like (DLL) ligands provides insight into upstream signaling cues within the TME. Downstream, transcriptional targets such as Hes1 and Hey1 are readouts of canonical Notch pathway activation. In addition, mutations in Notch genes, whether activating or inactivating, can alter pathway

dynamics and are increasingly used as clinically relevant biomarkers that influence tumor behavior and therapeutic response. Collectively, these markers help define the Notch signaling landscape and guide intervention strategies.

γ-Secretase inhibitors (GSIs), such as nirogacestat (Ogsiveo), block Notch signaling by preventing the cleavage of Notch receptors. These inhibitors have shown efficacy in treating desmoid tumors and are being tested in other malignancies (85). Since Notch signaling is essential for maintaining the balance between absorptive and secretory cells in the intestinal epithelium, the use of GSI is frequently associated with side effects. These can be alleviated by intermittent dosing schedules, lower doses with targeted combinations, or more selective Notch-sparing approaches (e.g., monoclonal antibodies, DLL4 inhibitors, or ADAM inhibitors). Monoclonal antibodies targeting Notch receptors or their ligands are used to prevent tumor growth and overcome resistance mechanisms driven by dysregulated Notch signaling. For instance, early-phase clinical trials for pancreatic and small-cell lung malignancies have assessed the anti-Notch2/3 antibody tarextumab (OMP-59R5). Brontictuzumab (OMP-52M51), which targets Notch1, has also shown early anticancer activity in hematologic malignancies and solid cancers that have relapsed or are resistant. Furthermore, phase I trials have been conducted in solid tumors, such as colorectal and pancreatic cancer, using demcizumab (OMP-21M18), an antibody targeting the Notch ligand DLL4 (86-88).

6.3 Synthetic Lethality and Drug Resistance

Tumor cells can acquire resistance to ferroptosis through multiple mechanisms, including upregulation of antioxidant pathways (e.g., GPX4, FSP1), alterations in lipid metabolism, and activation of survival signaling networks. These adaptive responses limit the efficacy of ferroptosis-based therapies and represent a significant barrier to clinical translation. Dihydroorotate dehydrogenase (DHODH), a key mitochondrial enzyme, has been shown to protect cancer cells from ferroptosis by maintaining mitochondrial redox homeostasis. Pharmacological inhibition of DHODH, either alone or in combination with GPX4 inhibitors, has emerged as a potentially important strategy to overcome ferroptosis resistance in chemoresistant tumors (89,90).

Combining Notch pathway inhibition with ferroptosis induction offers a promising synthetic-lethal therapeutic strategy. Notch signaling supports the maintenance of cancer stem-cell populations, and its blockade can sensitize tumor cells to ferroptotic death. In NSCLC, Notch3 knockdown increases ROS levels, enhances lipid peroxidation, and reduces GPX4 and PRDX6 expression, collectively driving ferroptotic cell death. Conversely, overexpression of the Notch3 intracellular domain protects cells from erastin-induced ferroptosis and provides ferroptosis resistance (49). Similarly, disruption of the Jag1/Notch1/3 axis in hepatic stellate cells decreased GPX4 levels and promoted ferroptosis (50). These findings support the therapeutic potential of co-targeting Notch signaling and ferroptosis regulators to eliminate tumor cells. While preclinical evidence is compelling, clinical validation is required to determine the safety and efficacy of these synthetic-lethal strategies (91-93). PI3K-AKT-mTOR signaling, which can be activated downstream of EGFR, promotes lipid biosynthesis and supports cell survival. Consequently, inhibition of this pathway increases cellular vulnerability to ferroptotic stress. Synthetic-lethality strategies target these resistance nodes. GPX4 inhibitors (such as RSL3 or ML162) block detoxification of lipid peroxides, whereas system Xc^- inhibitors (such as Erastin or Sulfasalazine) deplete cystine and GSH. Modulators of MAPK/ERK, AMPK, and PARP1 signaling can further influence ferroptotic sensitivity by altering lipid metabolism and stress-response pathways. Combination therapies, particularly ferroptosis inducers paired with immune checkpoint blockade (anti-PD-1 or anti-CTLA-4) or with STING agonists, enhance tumor immunogenicity and can overcome resistance to monotherapies in preclinical models (77,78). These integrated therapeutic designs highlight opportunities to exploit ferroptosis vulnerabilities across diverse tumor subtypes.

Despite these combination strategies, tumor cells frequently resist ferroptosis through multiple pathways. SLC7A11-mediated cystine uptake supports glutathione synthesis, which detoxifies lipid peroxides via GPX4. NRF2 activation upregulates antioxidant genes, including SLC7A11; ML385 inhibition sensitizes cells to ferroptosis. Parallel resistance mechanisms include the FSP1-CoQ10 pathway, which provides GSH-independent suppression of lipid peroxidation, and the GCH1-BH4 axis, which stabilizes phospholipid membranes and protects against oxidative damage. Figure 3 illustrates the molecular mechanisms by which cancer cells evade ferroptosis and highlights synthetic lethality strategies designed to restore ferroptotic sensitivity.

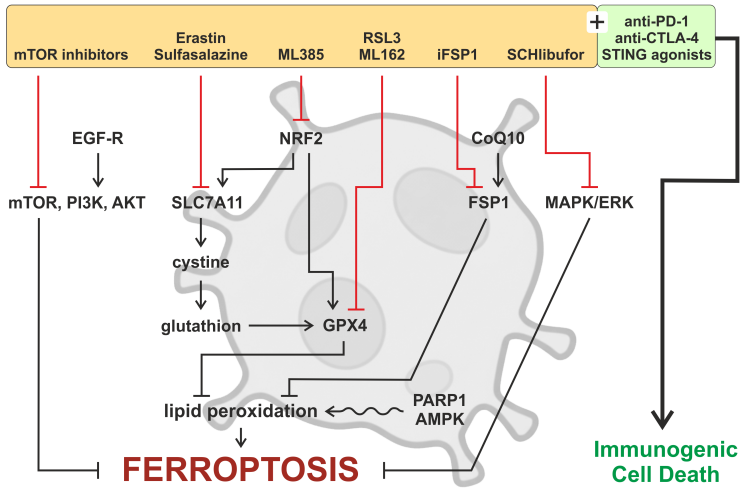

Figure 3. Drug resistance and synthetic lethality to overcome ferroptosis resistance. *This schematic illustrates the molecular networks governing ferroptotic cell death and the therapeutic strategies used to overcome ferroptosis resistance in cancer. Inhibition of cyst(e)ine uptake via SLC7A11, depletion of glutathione, and direct suppression of glutathione peroxidase 4 (GPX4) promote lipid peroxidation and ferroptosis. Resistance mechanisms mediated by NRF2 signaling, the FSP1–CoQ10 axis, and oncogenic pathways, including mTOR–PI3K–AKT and MAPK/ERK, limit ferroptotic sensitivity. Targeting these compensatory pathways with small-molecule inhibitors (e.g., erastin, sulfasalazine, ML385, RSL3, ML162, iFSP1, and mTOR inhibitors) establishes synthetic lethal vulnerabilities that restore ferroptosis. Ferroptotic tumor cell death can further induce immunogenic cell death, which is enhanced by combination with immunotherapies such as immune checkpoint blockade (anti–PD-1 and anti–CTLA-4) and STING agonists, thereby amplifying antitumor immune responses.*

6.4. Therapeutic considerations

Favorable therapeutic windows for ferroptosis-based interventions arise in tumors that naturally accumulate high levels of polyunsaturated phospholipids (PUFA-PLs), exhibit elevated ROS, or display increased iron influx, particularly when these features coincide with weakened antioxidant defenses. Such conditions create an intrinsic vulnerability to lipid peroxidation and ferroptotic stress. These windows tend to be particularly pronounced in tumor types such as TNBC, KRAS-mutant pancreatic cancer, GBM, hepatocellular carcinoma (HCC), and Notch3-driven NSCLC, all of which exhibit metabolic or redox profiles that increase ferroptosis susceptibility.

Toxicity remains a significant concern when manipulating ferroptosis or blocking Notch signaling for therapeutic purposes. Uncontrolled ferroptosis can injure organs that are particularly sensitive to oxidative stress, including the kidney, liver, and heart. Notch inhibition presents its own challenges: because the pathway helps maintain epithelial integrity, patients may experience gastrointestinal side effects, vascular complications, or changes in goblet cell populations. Adding ferroptosis inducers to immune-based treatments introduces an additional layer of risk, as heightened immune activation and elevated reactive oxygen species may drive responses beyond a tolerable range. To address these issues,

researchers are investigating approaches such as nanoparticle-guided delivery for better tumor targeting, treatment schedules that limit continuous exposure, and biomarker-driven selection of patients who are more likely to tolerate and benefit from these interventions.

Nanoparticle-based delivery systems are being developed to enhance ferroptosis induction specifically within tumors while minimizing systemic toxicity. For example, PD-1 membrane-coated polymeric nanoparticles encapsulating the ferroptosis inducer RSL3 have been shown to promote lipid peroxidation-mediated tumor cell death and simultaneously activate antitumor immunity in breast cancer models (94). Similarly, nanocarrier formulations such as liposomes, metal-organic frameworks, and polymeric micelles improve the pharmacokinetic stability and tumor-specific accumulation of ferroptosis inducers, enhancing therapeutic efficacy while reducing off-target effects (95).

Recently, CRISPR-based functional genomic screens have been used to identify regulators of ferroptosis sensitivity. Large-scale activation screens revealed that SWI/SNF chromatin-remodeling ATPases, including SMARCA2 and SMARCA4, act as key suppressors of ferroptosis, protecting tumor cells from lipid peroxidation-induced death (96). Targeting these ATPases or other chromatin-regulatory mechanisms may enhance ferroptosis induction and improve therapeutic responses. Moreover, CRISPR technology enables systematic mapping of ferroptosis gene networks, facilitating the rational design of drug combinations that exploit ferroptosis-Notch vulnerabilities.

Finally, integrative multi-omics analyses encompassing genomics, transcriptomics, proteomics, and metabolomics are increasingly used to classify patients based on ferroptosis-related gene signatures (e.g., ACSL4, FSP1, NFE2L2) (97). Machine learning algorithms trained on these datasets can predict ferroptosis sensitivity and inform therapeutic strategies (98). By combining genomic, transcriptomic, and proteomic data, researchers can identify ferroptosis-associated signatures across cancer cohorts, enabling patient stratification and the development of personalized therapies targeting ferroptosis and related pathways (99,100).

Discussion

Future research should define the precise cellular and molecular contexts regulating ferroptosis. Targeting NRF2 or downstream antioxidant pathways may increase tumor susceptibility to ferroptosis-inducing therapies. Next-generation preclinical platforms, including patient-derived organoids (PDOs) and organoid xenografts (PDOXs), will be essential for assessing ferroptosis within physiologically relevant tumor microenvironments (110). In parallel, single-cell RNA sequencing and spatial transcriptomics can uncover heterogeneity in ferroptosis sensitivity and distinct metabolic and redox states across tumors (111). Integrating CRISPR-based screens, multi-omics analyses, and AI-driven modeling may establish robust frameworks for predicting ferroptosis responsiveness and informing personalized therapeutic strategies. Collectively, these efforts aim to translate ferroptosis and Notch pathway modulation into clinically viable approaches that advance precision oncology.

Despite growing interest in therapeutically modulating ferroptosis and Notch signaling, clinical translation remains challenging. A significant challenge is the context-dependent nature of Notch signaling. In some cancers, Notch acts as an oncogene, promoting proliferation and metastasis (101-103); in others, it functions as a tumor suppressor by promoting differentiation or restricting growth. This dual role depends on cancer type, cellular context, genetic background, and specific cell populations within a tumor. Consequently, while Notch inhibition is effective in T-cell acute lymphoblastic leukemia (T-ALL) driven by gain-of-function NOTCH1 mutations, the development of broad-spectrum Notch inhibitors is complicated (104).

Tumor heterogeneity also generates a complex landscape of ferroptosis sensitivity. For example, hyperactivation of NRF2 in hepatocellular carcinoma (HCC) and lung adenocarcinoma enhances antioxidant defenses, including GPX4 and SLC7A11, reducing susceptibility to ferroptosis inducers (105). Adaptive resistance mechanisms further challenge both ferroptosis and Notch-targeted therapies. Prolonged induction of ferroptosis can upregulate FSP1, thereby bypassing GPX4 dependence, whereas resistance to γ-secretase inhibitors (GSIs) may arise through alternative survival pathways, such as PI3K/AKT or Wnt signaling (106,107). Additionally, cancer stem cells (CSCs), often regulated by Notch, can adapt to ferroptotic stress, promoting recurrence and metastasis (108,109). Most current data are derived from in vitro studies, underscoring the need for additional in vivo validation, particularly in models that reflect TME dynamics and drug resistance.

Taken together, current evidence indicates that Notch signaling is an essential regulator of ferroptosis in both malignant and normal tissues, in part by shaping antioxidant capacity and iron handling. When this pathway remains active, cells are often better equipped to avoid ferroptotic death, a feature that can undermine the effectiveness of specific therapies. For this reason, several groups are now exploring whether blocking Notch while inducing ferroptosis might enhance therapeutic responses in tumors that are resistant to standard treatment. As more datasets integrate genomic, transcriptomic, and metabolic information, the molecular links between these pathways are becoming clearer, which may eventually guide the development of more selective therapeutic approaches. Although much remains to be determined, adjusting ferroptosis alongside Notch activity could alter how some cancers are managed and may expand treatment options for patients with difficult-to-treat disease.

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