Review

Discovery Medicine 2026; 38(207): 987–1006
https://doi.org/10.24976/Discov.Med.202638207.80

The Main Molecular Mechanisms and Key Signaling Pathways of Ferroptosis

Renhe Lu[1,†], Longlong Su[1,†], Yong Ma[1], Hang Wang[1], Yu Shi[1], Xu Ma[1], Longcheng Shang[1,*], Shaozhong Ni[1,*]

[1]Department of General Surgery, Nanjing First Hospital, The Affiliated Nanjing Hospital of Nanjing Medical University, 210006 Nanjing, Jiangsu, China

*Correspondence: njushanglc@126.com (Longcheng Shang); nsznjmu@126.com (Shaozhong Ni)

[†]These authors contributed equally.

Submitted: 16 January 2026 Revised: 4 February 2026 Accepted: 16 March 2026 Published: 20 April 2026

Since ferroptosis was first described in 2012, it has attracted considerable attention in the medical community as an emerging mode of cell death driven by iron-dependent lipid peroxidation, distinct from apoptosis, necrosis, and autophagy. This unique cell death mode is regulated by multiple pathways, including the classical System Xc–glutathione peroxidase 4 (GPX4) and ferroptosis suppressor protein 1 (FSP1)-CoQ10 systems, as well as lipid metabolism, mitochondrial metabolism, cholesterol metabolism, sex hormone metabolism, and other auxiliary pathways. Notably, the cholesterol biosynthesis pathway exhibits bidirectional regulation—7-dehydrocholesterol (7-DHC) acts as a "sacrificial antioxidant" to inhibit ferroptosis, whereas elevated cholesterol levels promote it. Sex hormones regulate MBOAT1/2 to remodel membrane phospholipids and reduce ferroptosis susceptibility. Key signaling pathways, such as P53/SLC7A11, Nrf2-Keap1, and Hippo-YAP/TAZ, further fine-tune ferroptosis through iron homeostasis and redox balance regulation. Crosstalk exists between ferroptosis and other cell death modalities: copper chelators sensitize cells to ferroptosis, while lipid peroxidation products activate pyroptosis via the NLRP3 inflammasome. Novel inhibitors, including JKE-1674 (FSP1-targeted) and SRS11-92 (lipid radical scavenger), show improved pharmacokinetics and tissue specificity, while nanoparticle-based delivery systems enhance targeting efficacy. Multiple cancer cells are highly susceptible to ferroptosis, and ferroptosis is implicated in neurodegenerative diseases, ischemia-reperfusion injury, and metabolic disorders. This review systematically summarizes the molecular mechanisms, regulatory networks, novel modulators, and clinical translation progress of ferroptosis, highlighting its potential as a therapeutic target for various diseases and providing insights for future research and clinical application.

Keywords: ferroptosis; reactive oxygen species; cholesterol metabolism; cell death cross-talk; clinical translation; tissue specificity

What Is Ferroptosis?

Ferroptosis is a form of cell death driven by iron-dependent lipid peroxidation, distinct from apoptosis, necrosis, and autophagy in terms of morphology, biochemistry, and genetics [1,2]. Oxidative stress is a central component of ferroptosis, characterized by an imbalance between intracellular antioxidants and free radicals. This imbalance triggers a cascade of lipid reactions in the cell membrane, involving complex mechanisms such as reactive oxygen species (ROS) production and dysfunction of defense systems, including glutathione peroxidase 4 (GPX4) and ferroptosis suppressor protein 1 (FSP1, formerly known as flavoprotein apoptosis-inducing factor mitochondria-associated 2, AIFM2) [3,4].

Mechanism of Induction of Ferroptosis

Ferroptosis is initiated by excessive ROS production, which overwhelms cellular antioxidant defenses and triggers lipid peroxidation.

Generation of ROS

Mitochondria

Mitochondria are the "energy factories" of cells and major sources of ROS [5]. During electron transport chain (ETC) - mediated energy production, free radicals are generated and mostly exist as ROS (H_2O_2, HO•, O_2•$^-$) [6,7]. The production rate of ROS is closely related to mitochondrial membrane potential ($\Delta\psi$m) and ETC complex activity [8]. Mitochondrial enzymes such as aconitase and pyruvate dehydrogenase also contribute to ROS production [9]. In cancer cells, mitochondrial mutations create a "vicious cycle" of ROS overproduction, genomic instability, and cancer progression [10,11].

Fenton Reaction

As a key trace element, iron plays an indispensable role in human metabolism (Fig. 1). The total iron content in the human body is approximately 3–5 g, with an estimated daily loss of 1–2 mg through sweat, excretion, and shedding

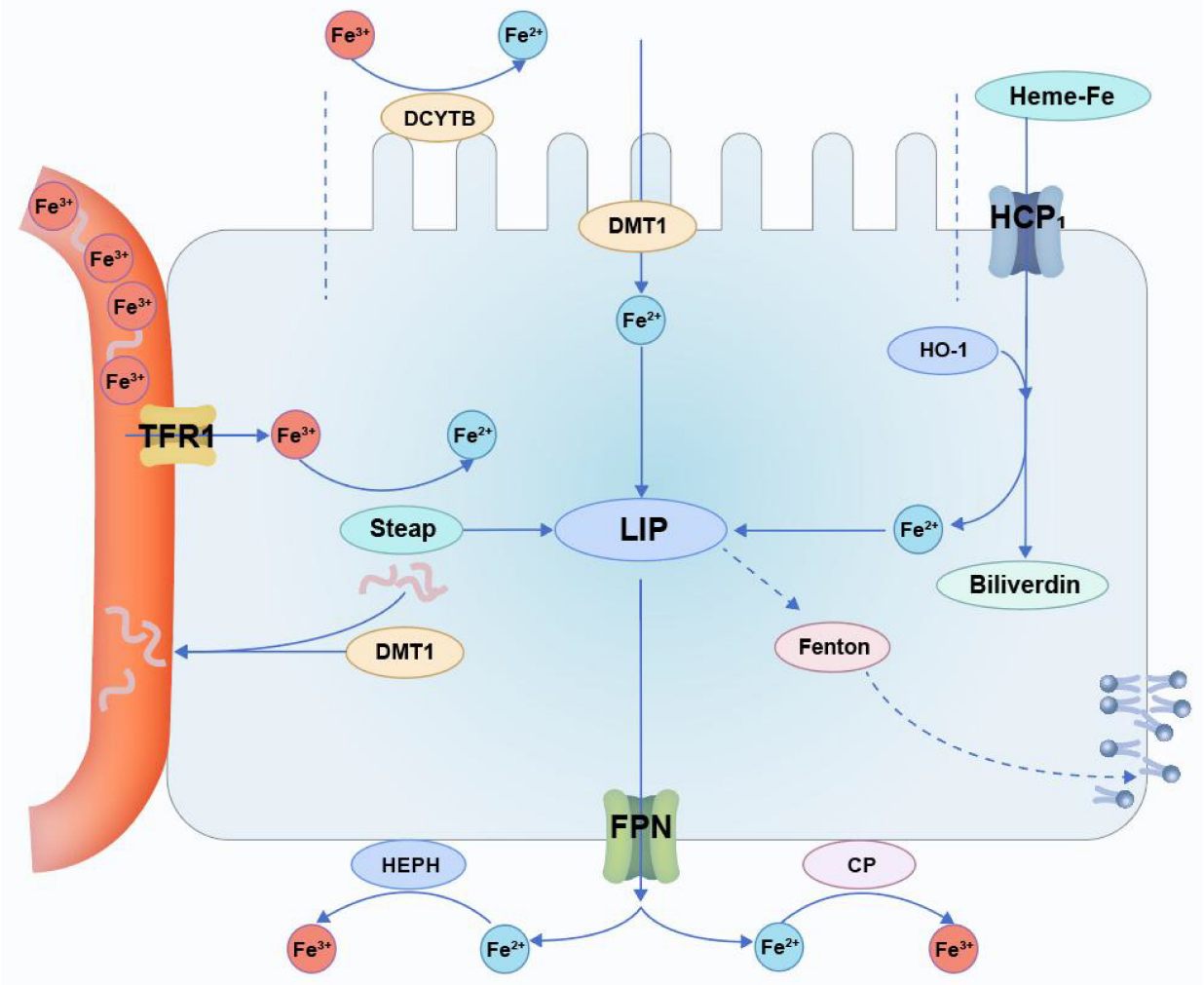

Fig. 1. Iron metabolism. All figures were created using Adobe Illustrator (Adobe Inc., San Jose, CA, USA). DCYTB, Duodenal cytochrome b; HCP1, Heme carrier protein 1; DMT1, Divalent metal transporter 1; HO-1, Heme oxygenase 1; TFR1, Transferrin receptor 1; LIP, Labile iron pool; FPN, Ferroportin; CP, Ceruloplasmin.

of intestinal epithelial cells. Iron metabolism is a dynamic and complex process involving the absorption, storage, utilization, and excretion of iron. Iron is absorbed through two pathways [12–14]. Heme iron (Fe^{2+}) in food can be transferred directly to intestinal epithelial cells via heme carrier protein 1 (HCP1), after which heme oxygenase 1 (HO-1) releases Fe and catabolizes heme into biliverdin. Fe^{3+}, which cannot be directly absorbed in humans, needs to be reduced to Fe^{2+} by the ferric reductase Cybrd1 (also known as DcytB) before being transported into the cell by divalent metal transfer protein 1 (DMT1, SLC11A2) [15–18]. After Fe^{2+} is taken up, it is translocated into the cytoplasmic lysate and may be released through HO-1 [19]. Intracellular iron can be bound to ferritin for storage [20,21]. Iron export from enterocytes into the circulation requires FPN, the only known iron efflux protein, together with iron oxidase. Iron oxidases contain Hephaestin (HEPH) and ceruloplasmin (Cp), which oxidize Fe^{2+} to Fe^{3+} [22,23]. In plasma, Fe^{3+} combines with transferrin (Tf), a glycoprotein that allows iron to remain soluble for transportation in the blood [24]. Cellular iron uptake occurs as Tf binds to TfR1 on the surface of macrophages and is brought in through endocytosis. STEAP proteins facilitate the reduction of Fe^{3+} to Fe^{2+} and promote the release of iron from Tf, after which the iron is re-transported out of the cell to form a cycle via DMT1 [25]. It is noteworthy that some cells also express another transferrin receptor, TfR2, but TfR2 is considered to be a mode of transferrin regulation, as TfR2 has a much lower affinity for transferrin than TfR1 [26–28]. Iron taken up by the cell forms the labile iron pool (LIP); a portion is bound by ferritin for storage, while another fraction enters the mitochondria for heme synthesis via MFRN [29]. In conditions of LIP overload, iron-mediated Fenton reactions convert hydrogen peroxide into hydroxyl radicals, which then induce lipid peroxidation [30], which in turn triggers ferroptosis [31].

Lipid Peroxidation Process

By incorporating PUFAs into membrane phospholipids, ACSL4 and LPCAT3 enable ROS to trigger widespread membrane disintegration during ferroptosis [32], while MUFAs offer structural resistance and may support repair mechanisms, possibly in coordination with sex hormones [33,34].

Lipid peroxidation arises through two mechanisms: non-enzymatic spontaneous oxidation and enzyme-mediated oxidation [35–38] (Fig. 2). In non-enzymatic spontaneous oxidation, the reaction begins when •OH attacks the bis-allylic hydrogen of PUFA-PL in the bilayer, resulting in a carbon-centered radical (L·) that reacts with molecular oxygen to produce LOO·. The lipid peroxyl radical will further react with the unsaturated fatty acid (LH) to form lipid peroxides (LOOH) and new lipid radicals (L·). The new lipid-free radicals will rejoin the peroxidation reaction, resulting in the accumulation of secondary products and disruption of membrane integrity, ultimately leading to the breakdown of organelle membranes and cell membranes [39–42]. Enzyme-mediated oxidation requires the interaction of lipoxygenase (LOX) and phosphatidylethanolamine-binding protein 1 (PEBP1). LOX directly connects to PUFA and catalyzes the formation of lipid peroxyl radicals (LOOH), which are involved in ferroptosis [43]. The human genome encodes six LOX genes, which may contribute to ferroptosis in different cell types. The oxidation of free PUFAs is primarily catalyzed by LOX, though its mechanism of action on membrane phospholipids is not well defined. Fleming MD *et al*. [44] discovered that PEBP1 stably binds to 15-LOX, enabling 15-LOX to oxidize PE-associated PUFAs and produce 15-hydroperoxyeicosatetraenoic-acid-phosphatidylethanolamine 15-HpETE-PE, thereby triggering ferroptosis.

Protective Mechanisms of Ferroptosis

A variety of protective mechanisms exist throughout the ferroptosis process, the two most prominent being the mitigation of iron overload and the enhancement of antioxidant capacity.

Reducing Ferroptosis by Relieving Iron Overloads

Ferroptosis is closely related to intracellular iron overload, and iron overload can be reduced by regulating cellular iron metabolism, which in turn reduces the occurrence of ferroptosis. Liver is an important organ in the systemic regulation of iron metabolism, and it is the main site of Hepcidin production [45,46]. Hepcidin regulates iron homeostasis by inhibiting iron release from duodenal intestinal epithelial cells, macrophages and hepatocytes [47,48]. On one hand, Hepcidin can inhibit cellular iron efflux by binding and sequestering FPN [49]. On the other hand, it can also induce conformational changes in FPN, which can lead to its ubiquitylation and to endocytosis and degradation of the ubiquitylated FPN [50,51]. Nemeth E *et al*. [51] suggested that Hepcidin exhibits various mechanisms of action related to its own concentration: at high plasma concentration, Hepcidin mainly combines with FPN and inhibits iron release. When the concentration of Hepcidin decreases significantly, it predominantly induces the endocytosis and degradation of FPN [48]. Iron and Hepcidin constitute a classical negative feedback regulatory system. When plasma iron concentration rises, the concentration of Hepcidin decreases, and vice versa. Meanwhile, Hepcidin is also regulated by other biological factors, among which erythropoietin and IL-6 are the most well-defined. Armitage AE *et al*. [52] considered erythroferrone as a key erythropoietic factor mediating the decreased secretion of Hepcidin. IL-6, on the other hand, has been suggested to increase the production of Hepcidin through the STAT-3 signaling pathway [53,54]. Rayatpour A *et al*. [55] experimentally demonstrated that ATV (Atorvastatin Calcium) mediated Hepcidin secretion via the SMAD7/Hepcidin pathway to attenuate ferroptosis in ischemia-reperfusion cardiomyocytes.

There are other ways to deal with intracellular iron overload. Iron chelators, deferoxamine and deferiprone, can both help reduce cellular iron levels. Deferiprone chelates with almost all iron, including iron pools in cells, and transferrin in plasma [56]. Guo Z *et al*. [57] have found that topical treatment with Deferiprone attenuates lysophosphatidylcholine-induced demyelinating lesions of the optic nerve. Desferrioxamine is slightly more specific in that it mainly removes iron from ferritin and hemosiderin without affecting iron bound to transferrin or hemoglobin [58]. Zhou Y *et al*. [59] found that deferoxamine injections reduced the concentration of iron in the joint cavity, which in turn reduced the risk of osteoarthritis. Yang C *et al*. [60] demonstrated that DFO-mediated inhibition of ferroptosis attenuated radiation-induced fibrosis. Additional drugs, including Deferasirox and curcumin, are gradually supported by corresponding experiments for their roles in regulating iron and ferroptosis [61–63].

Reduces Ferroptosis by Increasing Antioxidant Capacity

GPX4

We first focus on the System Xc- and GPX4 systems. System Xc- is a heterodimeric cystine/glutamate counter-transporter protein on cells, consisting of two core components: SLC7A11 and SLC3A2. This amino acid counter-transporter protein maintains the intracellular reducing environment by importing cystine and exporting glutamate. System Xc- facilitates the conversion of cystine to cysteine by thioredoxin (TXNRD1), which is then converted to glutathione (GSH) by glutamate cysteine synthetase and glutathione synthetase (GCL). Glutathione has its own oxidized form called oxidized glutathione (GSSG). By the

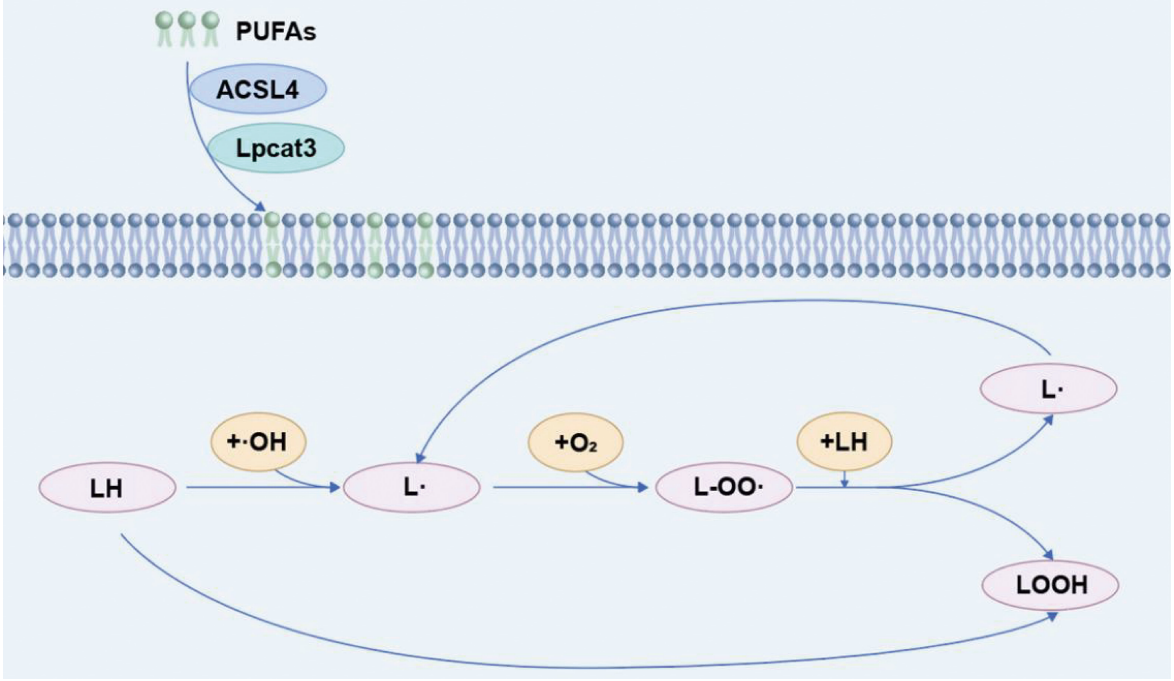

Fig. 2. Lipid peroxidation process. All figures were created using Adobe Illustrator (Adobe Inc., San Jose, CA, USA).

consumption of ATP, GSSG can be converted to GSH, which can also be converted to GSSG by GPX4. Reduced GSH acts as a cofactor for GPX enzymes in converting lipid hydroperoxides to lipid alcohols on phospholipids, thereby limiting intracellular peroxidation levels [64,65]. It is also noteworthy that cystine can be converted from methionine via the transsulfuration pathway and its direct extracellular uptake by System Xc-, thus bypassing the need for cystine input via the cystine/glutamate antitransporter system [66]. These cells are resistant to ferroptosis induced by System Xc- inhibitors. In the transsulfuration pathway, methionine is converted to S-adenosylmethionine by methionine adenosyltransferase, then to S-adenosylhomocysteine by methyltransferase, which then generates homocysteine. Homocysteine is either remethylated to methionine by methyltetrahydrofolate or irreversibly converted to cysteine by the transsulfuration pathway, which has its own regulatory enzymes called pyridoxal-phosphate-dependent enzymes—cystathionine-β-synthase (adding homocysteine) enzyme and cysteine-γ-cleaving enzyme. A complete System Xc- with GPX4 system is shown below (Fig. 3).

FSP1

FSP1, previously designated flavoprotein AIFM2, localizes primarily to the periphery of lipid droplets and the plasma membrane [67,68] (Fig. 4). It inhibits ferroptosis through three distinct glutathione-independent pathways [69,70]. First, FSP1 converts CoQ10 to its reduced form $CoQ10H_2$, a lipophilic antioxidant that traps free radicals to prevent lipid peroxidation and indirectly regenerates α-tocopherol. Second, it functions as a vitamin K reductase, participating in the atypical redox pathway of vitamin K to maintain VKH_2 (reduced vitamin K), which also acts as an antioxidant. Third, FSP1 promotes ESCRT-III-dependent membrane repair—ESCRT-III complexes mediate the repair of ferroptosis-induced plasma membrane damage, with CHMP5 and CHMP6 serving as key subunits [71,72]. Targeting FSP1 downregulates CHMP5/6 expression at the plasma membrane, abrogating this repair mechanism [73].

DHODH

Dihydroorotate dehydrogenase (DHODH), an iron-containing mitochondrial enzyme and rate-limiting step in *de novo* pyrimidine synthesis, inhibits ferroptosis by regenerating $CoQ10H_2$ while catalyzing the oxidation of dihydroorotic acid (DHO) to orotate (OA) [74]. A "see-saw" relationship exists between DHODH and GPX4: DHODH inhibitors induce ferroptosis in GPX4-low cells and enhance the sensitivity of GPX4-high cells to ferroptosis inducers [75]. GPX4 inhibition enhances pyrimidine metabolic flux via DHODH upregulation, while exogenous DHO suppresses GPX4 inhibitor-induced ferroptosis. Additionally, DHODH depletion reduces intracellular pyrimidines, slowing ribonucleotide reductase (RNR)-mediated conversion of NTPs to dNTPs. Inhibiting RNR increases GSH levels and enhances GPX4-mediated peroxidation resistance [76,77].

GTPCH-BH4-NOS

Tetrahydrobiopterin (BH4), a potent free radical scavenger, protects lipids from peroxidation and regulates ni-

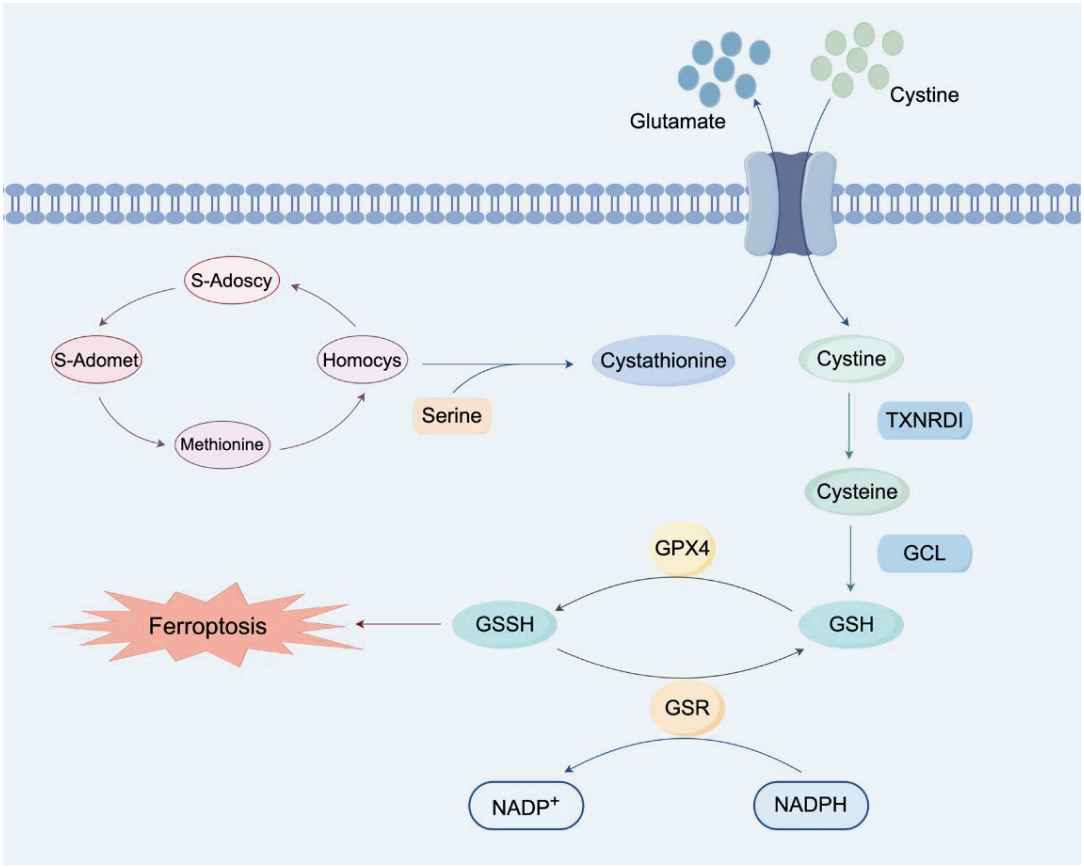

Fig. 3. System Xc- and GPX4 systems. All figures were created using Adobe Illustrator (Adobe Inc., San Jose, CA, USA). GPX4, glutathione peroxidase 4.

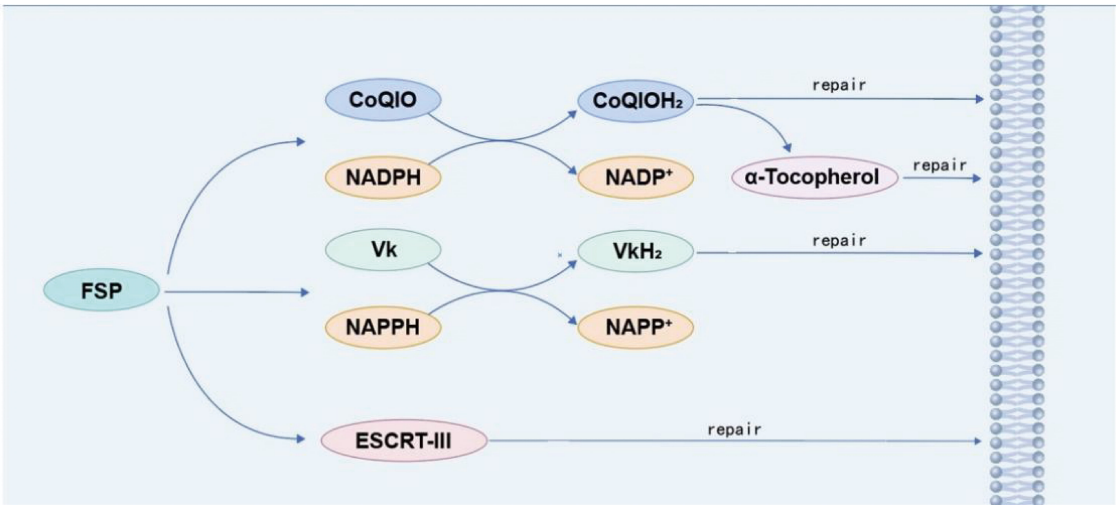

Fig. 4. FSP1 and its associated membrane repair systems. All figures were created using Adobe Illustrator (Adobe Inc., San Jose, CA, USA). FSP1, ferroptosis suppressor protein 1.

tric oxide synthase (NOS) function [78,79]. BH4 is synthesized via *de novo* (rate-limiting enzyme: GTP cyclohydrolase, GTPCH) and remedial pathways (dihydrofolate reductase, DHFR, regenerates BH4 from oxidized BH2) [80,81]. GTPCH expression is upregulated in response to oxidative stress-derived H_2O_2, increasing BH4 levels to mitigate ROS accumulation [82]. As a NOS cofactor, BH4 stabilizes NOS structure and regulates its catalytic activity [83,84]. Under BH4 deficiency, NOS produces ROS instead of NO [85], and the resulting ROS further oxidizes BH4 to BH2, forming a vicious cycle of oxidative stress [86] (Fig. 5).

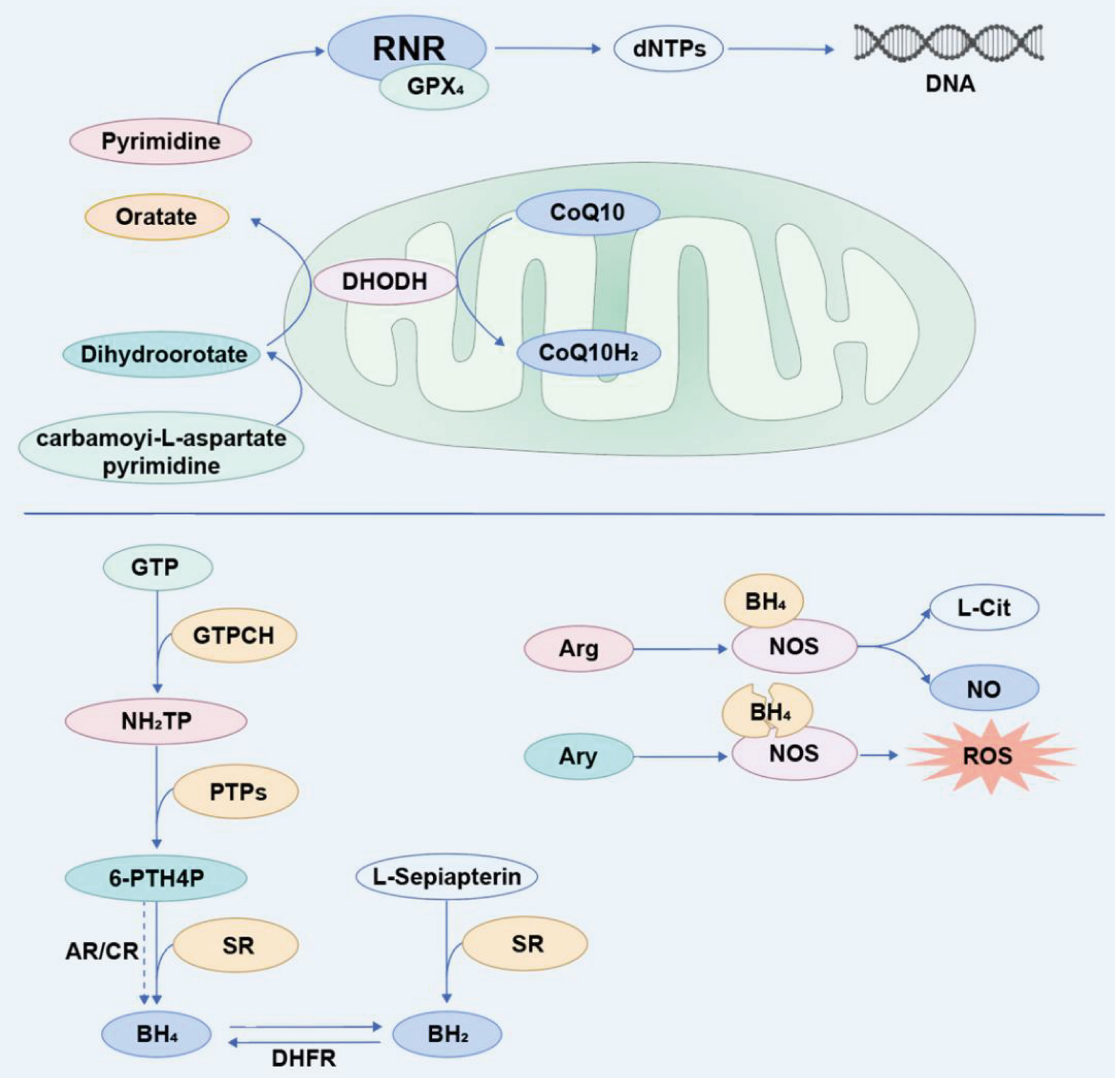

Fig. 5. DHODH and BH4 systems. All figures were created using Adobe Illustrator (Adobe Inc., San Jose, CA, USA). DHODH, Dihydroorotate dehydrogenase; BH4, Tetrahydrobiopterin.

Cholesterol Pathways

Metabolites of the cholesterol biosynthesis pathway regulate cellular sensitivity to ferroptosis. A preliminary cellular screening showed that Hashimoto sterols (Desmo), cholesterol (CH), and 7-dehydrocholesterol (7-DHC) significantly inhibited RSL3-induced lipid peroxidation and ferroptosis, with 7-DHC being the strongest protective effect [87,88]. 7-DHC is the most easily oxidized substance known, approximately 200 times more so than cholesterol [89]. Additional mechanistic studies of CH and Desmo have concluded that the upregulation of squalene and CoQ10 via sterol-linked SQLE degradation may enhance cellular resistance to iron-mediated oxidative damage [90]. A possible model is shown below. Cells constitutively express cytosqualene and CoQ10 at basal levels to neutralize low-level lipid peroxidation and avert ferroptosis [91]. The stability is vulnerable to multiple stimuli, any of which can initiate ferroptosis. Cellular overabundance of CH and Desmo triggers accelerated turnover of SQLE, thus preventing the conversion from squalene to cholesterol and relatively increasing CoQ10 production [92]. 7-DHC works via a distinct mechanism. CH and Desmo gradually lost activity over time, with Desmo retaining about 50% inhibition after 9 hours of washing [93]. In contrast, 7-DHC almost entirely inhibited iron prolapse after 24 hours, indicating differences in the mechanism of action or metabolic stability [94]. A study has suggested that 7-DHC functions as a free radical trapping agent, protecting cells against ferroptosis [95]. 7-DHC is more like a “sacrificial molecule” in that the presence of an extra double bond in the B ring makes 7-DHC structurally flatter than cholesterol, which increases the interaction with the fatty acid side chains of phospholipids, depleting ROS by self-oxidation and thus protecting normal membrane phospholipids [96]. In summary, metabolites of the cholesterol biosynthesis pathway exhibit a complex, bidirectional role in regulating cellular

sensitivity to ferroptosis. While certain intermediates protect against ferroptosis, the end product, cholesterol, can exert pro-ferroptotic effects under specific conditions [97]. The anti-ferroptotic effects of 7-DHC and Desmo are attributed to their potent antioxidant properties; 7-DHC functions as a "sacrificial molecule" that scavenges free radicals due to its high oxidation, while Desmo and CH can promote the degradation of squalene monooxygenase (SQLE), leading to the accumulation of squalene and CoQ10, both of which possess antioxidant properties [98]. In contrast, cholesterol itself can promote ferroptosis, as high levels of cholesterol can increase membrane rigidity and alter the distribution of PUFAs, making them more susceptible to peroxidation [99]. Furthermore, cholesterol can be oxidized to form oxysterols, such as 7-ketocholesterol, which are potent inducers of oxidative stress and can increase cellular susceptibility to ferroptosis [100]. This dual role highlights the importance of the cholesterol metabolic flux and the specific intermediates involved, rather than the pathway as a whole, in determining ferroptosis sensitivity.

Sex Hormone Pathway

MBOAT1 and MBOAT2 are independent of GPX4 and FSP1, and exert inhibitory functions in ferroptosis through remodeling cell membrane phospholipids [101]. The action of MBOAT1/2 involves transferring monounsaturated fatty acids (MUFA) to lysophosphatidylethanolamine (lyso-PE), which increases cellular PE-MUFA and decreases PE-PUFA, thus reducing the risk of oxidation by the ROS cascade [102,103]. The transcriptional upregulation of MBOAT1 and MBOAT2 is mediated by estrogen receptor (ER) and androgen receptor (AR), respectively [104].

Critical Signaling Pathways

The scope of ferroptosis is extensive, with different signaling systems governing each of the molecules involved. Here, we briefly discuss several well-established regulators.

P53/SLC7A11

P53 is a well-known tumor suppressor locus that mediates cellular life processes such as cell cycle arrest, senescence and apoptosis. However, it has been found that the P53 protein achieves its diverse cellular outcomes by acting as a DNA-binding transcription factor that selectively regulates the expression of certain P53 transcriptional target genes. Even acetylation-deficient p53, which loses its ability to regulate the cell cycle, among other things, retains its tumor suppressor function and its ability to regulate the expression of metabolic targets [105]. It has been reported that p53 binds to the p53-responsive element in the SLC7A11 promoter, leading to reduced expression and increased sensitivity of cancer cells to ferroptosis inducers like erastin [106]. Yang Y *et al.* [107] also inhibited P53 acetylation and restored SLC7A11 expression via STAT6, which ultimately reduced ferroptosis-associated lung injury. Nakamura T *et al.*'s [108] research also revealed that Gankyrin suppresses ferroptosis in TNBC by degrading p53. These findings suggest that p53 acts as an independent regulator that reduces the efficiency of the GPX4 system by inhibiting SLC7A11 expression, thereby promoting ferroptosis.

The effects of p53 on ferroptosis are not limited to those described above. FDXR, a mitochondrial flavoprotein, mediates electron flow from NADPH to FDX1 and FDX2, and subsequently to cytochrome P450, which is used for steroidogenesis as well as the synthesis of the Fe-S clusters and heme A synthesis [109]. FDXR is a target protein of P53. p53 induces the transcription of FDXR, which in turn can regulate the expression of P53 through a feedback mechanism [110]. This result suggests that P53 can also perturb iron homeostasis via FDXR, but the exact mechanism requires further investigation. In addition, P53 also regulates non-coding RNAs to induce ferroptosis, including miRNAs and LncRNAs. Meanwhile, various non-coding RNAs have been shown to negatively regulate p53 [111–113].

However, evidence also suggests that p53 can suppress ferroptosis in cells. Schade DS *et al.* [114] identified that the interaction between p53 and DPPP4 leads to NOX1 dissociation, thereby reducing lipid peroxidation and ferroptosis. Freitas FP *et al.* [115] found that p21 mediates p53 activity to inhibit cystine deprivation-induced ferroptosis in HT-1080 cells. Previous studies have suggested that the relationship between p53 and ferroptosis is intricate and warrants further elucidation.

The nRF2 Antioxidant Pathway

Nuclear factor-erythroid factor 2-related factor 2(NFE2L2/NRF2) acts as a pivotal regulator of cellular redox equilibrium and exogenous detoxification [116,117]. It regulates ROS homeostasis in three different pathways [118]: metal metabolism, intermediary metabolism, and GSH metabolism. NRF2 plays an important role in metal metabolism, especially iron metabolism. The iron transporter protein, SLC40A1(FPN), and the iron storage protein, ferritin, are both regulated by NRF2 [119,120]. Anandhan A *et al.* [121] demonstrated, using HERC2/VAMP8 double knockout cells, that NRF2 regulates ferritin synthesis and degradation via the HECT and RLD domains, with HERC2, VAMP8, and NCOA4 serving as key components. These proteins influence the intracellular LIP and the susceptibility of cancer cells to ferroptosis [122]. Nrf2 is also associated with the regeneration of NADPH, which is an important electron donor in redox reactions [123]. Finally, glutathione synthase (GSS), SLC7A11 and other important proteins in the GSH cycle are all modulated by NRF2 [124,125].

In cells, Nrf2 acts through the Keap1/Nrf2/ARE pathway. Keap1 and Nrf2 are bound in the cytoplasm and remain inactive. Under basal conditions, Nrf2 is ubiquitinated and degraded. In response to a specific stimulus, the Keap1-Nrf2 binding will be destabilized. Nrf2 will be released and translocated to the nucleus, where it binds to the ARE. It will subsequently trigger the transcription of downstream genes, followed by the production of proteins that induce antioxidant enzymes such as heme oxygenase 1 (HO-1), quinone oxidoreductase 1 (NQO1), superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT) [126].

Hippo-YAP/TAZ Pathway

The Hippo-YAP/TAZ pathway is a key regulator of tissue growth found in Drosophila melanogaster. YAP/TAZ is a well-characterized transcriptional effector of Hippo signaling involved in a variety of physiopathological processes, including tumorigenesis and tissue regeneration [127]. Recently, these two effectors have also been found to be associated with ferroptosis [128]. In both renal and ovarian cancers, TAZ is overexpressed. Knockdown of TAZ confers resistance to ferroptosis, whereas TAZ overexpression increases cellular susceptibility to ferroptosis [129]. The study by Yang WH *et al.* [130] indicated that TAZ modulates ferroptosis via the epithelial membrane protein 1 (EMP1)-NADPH oxidase 4 (NOX4) axis in renal cancer and angiopoietin-like 4 (ANGPTL4)-NADPH oxidase 2 (NOX2) axis in ovarian cancer. YAP upregulation can promote ferroptosis by upregulating multiple iron death regulators (e.g., ASCL4 and ferritin) [131]. However, the underlying mechanisms of YAP/TAZ signaling in ferroptosis are unclear and necessitate additional research.

Crosstalk Between Ferroptosis and Other Cell Death Modalities

The intricate interplay between ferroptosis and other forms of regulated cell death, such as cuproptosis and pyroptosis, has emerged as a critical area of research, revealing complex regulatory networks that challenge the traditional view of these pathways as independent entities. Grasping these interactions is essential for developing effective therapeutic strategies, as targeting one form of cell death may inadvertently modulate others, leading to unexpected outcomes.

Ferroptosis and Cuproptosis

Cuproptosis is a copper-dependent form of cell death characterized by the aggregation of lipoylated proteins in the tricarboxylic acid (TCA) cycle and the loss of iron-sulfur cluster proteins [132]. This process is initiated when excess copper binds to lipoylated components of the pyruvate dehydrogenase (PDH) complex, leading to protein aggregation and proteotoxic stress [133,134]. While distinct, ferroptosis and cuproptosis share a common reliance on transition metals, achieving a delicate balance within the cell. Recent studies have identified a potential antagonistic relationship between these two pathways. For instance, the depletion of intracellular copper using copper chelators, such as tetrathiomolybdate (TTM), can increase cellular susceptibility to ferroptosis inducers like erastin and RSL3 [135]. The sensitization suggests that copper may compete with iron for binding sites on enzymes critical for lipid peroxidation, such as lipoxygenases (LOXs) and cytochrome P450 oxidoreductases (POR) [136]. Alternatively, copper may modulate the activity of these enzymes through allosteric regulation or by affecting their expression levels [137]. Copper is also a cofactor for superoxide dismutase 1 (SOD1), which converts superoxide to hydrogen peroxide, a precursor for hydroxyl radical generation via the Fenton reaction [138,139]. Thus, copper depletion may reduce SOD1 activity, decreasing ROS production and potentially protecting against ferroptosis, although the net effect appears to be context-dependent. Conversely, the induction of ferroptosis may influence copper homeostasis. Lipid peroxidation products generated during ferroptosis can alter the expression and activity of copper transporters, such as copper transporter 1 (CTR1) and ATP7A/B, which regulate copper uptake and efflux, respectively [140,141]. Additionally, the oxidative stress associated with ferroptosis may affect the redox state of copper, shifting it between Cu+ and Cu2+, which have different biological activities [142,143]. However, the precise mechanisms by which ferroptosis impacts copper metabolism and whether this contributes to cuproptosis induction remain to be fully elucidated.

Ferroptosis and Pyroptosis

This inflammatory cell death, pyroptosis, is mediated by gasdermin proteins that create pores in the plasma membrane, resulting in cell lysis and the release of pro-inflammatory cytokines [121]. Accumulating evidence suggests extensive crosstalk between ferroptosis and pyroptosis, particularly in the context of sterile inflammation and tissue damage. Ferroptosis leads to lipid peroxidation, resulting in products like 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), which can activate the NLRP3 inflammasome, a key component of the pyroptosis pathway [144,145]. Lipid peroxidation-generated DAMPs are identified by PRRs, which trigger the assembly of the NLRP3 inflammasome complex [146]. The activation causes the cleavage of pro-caspase-1 into active caspase-1, which then processes pro-IL-1β and pro-IL-18 into mature forms and cleaves gasdermin D (GSDMD) to produce the N-terminal fragment (GSDMD-NT) [147]. The GSDMD-NT fragment oligomerizes and inserts into the plasma membrane, forming pores that enable the release of IL-1β, IL-18, and other inflammatory mediators [148]. This synergistic effect amplifies cellular damage and inflammation, which is particularly relevant in the context of ischemia-reperfusion in-

jury, neurodegenerative diseases, and acute kidney injury [149]. For example, in myocardial infarction, ferroptosis-induced lipid peroxidation in cardiomyocytes can trigger pyroptosis, thereby exacerbating myocardial damage and promoting adverse cardiac remodeling [150]. Similarly, in Alzheimer's disease, ferroptosis in neurons may lead to the release of DAMPs that activate microglial NLRP3 inflammasomes, contributing to neuroinflammation and disease progression [151]. Furthermore, certain ferroptosis inducers have been shown to trigger both lipid peroxidation and GSDMD activation, highlighting the interconnected nature of these cell death pathways. For instance, erastin treatment not only induces ferroptosis but also promotes GSDMD cleavage and IL-1β release in macrophages, suggesting that ferroptosis can directly engage the pyroptosis machinery [152]. This crosstalk may involve the activation of caspase-1 or other proteases that can process both GSDMD and proteins involved in ferroptosis execution [153].

Novel Ferroptosis Inhibitors

Beyond the classical inhibitors like Ferrostatin-1 and Liproxstatin-1, recent research has identified novel compounds with potent anti-ferroptosis activity, offering improved pharmacokinetic properties and distinct mechanisms of action. JKE-1674 is a highly potent and metabolically stable inhibitor of ferroptosis that targets the FSP1-CoQ10 pathway [154]. Unlike Ferrostatin-1 and Liproxstatin-1, which primarily act as radical-trapping antioxidants, JKE-1674 inhibits FSP1, an oxidoreductase that uses NAD(P)H to regenerate reduced CoQ10 and suppress lipid peroxidation [155]. JKE-1674 exhibits excellent oral bioavailability and brain penetration, making it a promising candidate for the treatment of neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease, where ferroptosis plays a critical role [156]. In preclinical models, JKE-1674 has shown significant neuroprotective effects without apparent toxicity [157]. SRS11-92 is a novel compound that inhibits ferroptosis by directly scavenging lipid radicals, offering a distinct mechanism of action from traditional inhibitors. SRS11-92 is a lipophilic antioxidant that localizes to cellular membranes, where it efficiently quenches lipid peroxyl radicals and terminates the chain reaction of lipid peroxidation [158]. Unlike Ferrostatin-1, which requires metabolic activation to exert its antioxidant effects, SRS11-92 is active in its parent form, providing rapid protection against ferroptosis. Additionally, SRS11-92 has been shown to protect against ischemia-reperfusion injury in the heart and kidney, suggesting its potential therapeutic utility in acute organ damage [159]. Nanoparticle-based inhibitors represent an innovative approach to overcome the limitations of conventional ferroptosis inhibitors, such as poor solubility, short half-life, and lack of tissue specificity. Engineered nanoparticles, such as those loaded with curcumin [160], resveratrol [161], or other antioxidants [162], have been developed to target specific tissues (e.g., the brain), thereby enhancing the bioavailability and efficacy of ferroptosis inhibitors. For example, liposomes decorated with transferrin receptor-targeting ligands can selectively deliver ferroptosis inhibitors to cancer cells that overexpress transferrin receptors, minimizing off-target effects [163]. Similarly, nanoparticles that respond to the acidic tumor microenvironment or specific enzymes can release their payload in a controlled manner, improving therapeutic efficacy [164]. These nanocarriers can also be designed to co-deliver multiple agents, such as a ferroptosis inducer and an immunomodulator, to achieve synergistic anti-tumor effects [165,166]. Other emerging inhibitors include iFSP1, a specific inhibitor of FSP1 that has shown potent anti-ferroptosis activity *in vitro* and *in vivo* [167], and DHODH inhibitors that target the dihydroorotate dehydrogenase pathway, which has been implicated in ferroptosis resistance [168]. These novel compounds expand the therapeutic arsenal for targeting ferroptosis in various pathological conditions and provide valuable tools for dissecting the molecular mechanisms of this cell death pathway. The following tables present the classification, names, and underlying mechanism of action of common ferroptosis inducers and inhibitors (Table 1, Ref. [169–190]); Table 2, Ref. [23,61,191–203]).

Clinical Translation and Challenges of Ferroptosis Modulators

Clinical Progress

Cancer: Sorafenib (System Xc- inhibitor) is approved for renal cell carcinoma and hepatocellular carcinoma, inducing ferroptosis in tumors with high ACSL4 expression [204,205]. Phase I/II trials of erastin analogs (e.g., imidazole ketone erastin) in lymphoma show tumor growth inhibition [172]. A combination of ferroptosis inducers with immune checkpoint inhibitors enhances anti-tumor immunity [206].

Neurodegenerative diseases: Deferiprone (phase II trial) reduces iron accumulation in patients with Parkinson's disease, improving motor function [207]. Liproxstatin-1 derivatives capable of crossing the blood-brain barrier are currently in preclinical development for the treatment of Alzheimer's disease [208].

Ischemia-reperfusion injury: SRS11-92 reduces myocardial infarction size in animal models, and clinical trials of nanoparticle-delivered ferroptosis inhibitors for acute kidney injury are ongoing [209,210].

Challenges and Solutions

Pharmacokinetic issues: First-generation inhibitors (e.g., Ferrostatin-1) have poor solubility and short half-life. Structural optimization (e.g., Liproxstatin-1 derivatives) and nanoparticle delivery improve stability and tissue targeting [210,211].

Table 1. Ferroptosis inducers.

Ferroptosis inducers			Reference
1 Suppression of Sys Xc	Erastin	Inhibits cystine absorption	[169–172]
	Auranofin	Inhibit thioredoxin reductase activity	[173,174]
	Acetaminophen	Deplete intracellular glutathione	[175]
	L-Buthionine-Sulfoximine	Inhibit intracellular glutathione formation	[176,177]
	Sulfasalazine	Inhibits cystine absorption	[178]
2 Degradation of GPX4	RSL3, ML162, ML210	Competition for the active site of bound GPX4	[179–181]
	FIN56	Induction of GPX4 degradation	[182,183]
	Cisplatin	Inactivates GPX4	[184]
3 Consumption of CoQ10	iFSP1	Inhibition of FSP1 activity	[185,186]
4 Induction of lipid peroxidation	Artemisinin, artesunate	Induction of ferritin autophagy and release of unstable iron	[187,188]
	Lapatinib	Catalyzing the generation of LIP-ROS	[189]
	FINO2	ferrous oxide	[190]

GPX4, glutathione peroxidase 4; CoQ10, Coenzyme Q10; iFSP1, Inhibitor of ferroptosis suppressor protein 1; FINO2, Ferroptosis inducer 2; RSL3, Ras-selective lethal 3; ML162, Molecular Libraries Small Molecule Repository 162; FSP1, ferroptosis suppressor protein 1; LIP, labile iron pool; ROS, reactive oxygen species.

Table 2. Ferroptosis inhibitors.

Ferroptosis inhibitors				Reference
1	Iron chelators	deferoxamine	Reduction of unstable iron in cells and inhibition of the Fenton reaction	[23]
		deferiprone		[23,191]
		Deferasirox		[192]
		Curcumin		[61,193]
2	Antioxidant	Ferrostain-1	Scavenges ROS and reduces unstable iron in cells	[194]
		Liproxstain-1	Clears ROS, activates Nrf2 pathway, restores GPX4 levels	[195,196]
		Trolox	Inhibits lipid peroxidation	[197]
		XJB-5-131	Targeting mitochondria to scavenge ROS	[198]
3	LOX inhibitors	Zileuton	Inhibition of 5-LOX	[199]
		PD146176	Inhibition of 15-LOX	[200]
		Scutellarin	Inhibition of 12/15-LOX	[201]
4	ACSL4 inhibitor	Troglitazone Rosiglitazone and Pioglitazone	Inhibition of ACSL4 function blocks PUFA activation and phosphorylation processes	[202]
5	Nitrogen oxide	TEMPO	Blocking the Fenton reaction	[203]

Nrf2, Nuclear factor-erythroid 2-related factor 2; LOX, lipoxygenase; ACSL4, Acyl-CoA synthetase long-chain family member 4.

Safety concerns: Long-term use of iron chelators causes anemia; broad-spectrum antioxidants disrupt normal redox signaling. Low-dose combination therapies reduce toxicity [207,212].

Tissue specificity: Transferrin receptor-targeted liposomes deliver inhibitors to cancer cells, minimizing off-target effects [169].

The Role of Ferroptosis in Disease

Organ and Cell Type Specificity of Ferroptosis

The susceptibility to ferroptosis is not uniform across all cell types and organs, a phenomenon that is crucial for understanding its physiological and pathological roles. This specificity is governed by the differential expression of key regulatory molecules, including those involved in iron metabolism, lipid composition, and antioxidant defense systems [213]. For instance, many cancer cells exhibit a heightened sensitivity to ferroptosis due to their altered metabolism, characterized by high levels of polyunsaturated fatty acids (PUFAs) in their membranes, increased iron demand to support rapid proliferation, and elevated basal levels of ROS [214,215]. Furthermore, mutations in tumor suppressors can directly or indirectly increase the cellular susceptibility to ferroptosis by downregulating SLC7A11 or promoting iron accumulation, making it a promising therapeutic target [216]. In contrast, neurons' susceptibility to ferroptosis is linked to their intense oxygen dependence, rich lipid content [217,218], and relatively low expression of antioxidant defense systems like GPX4, a piv-

Table 3. Key Ferroptosis Regulatory Targets, Therapeutic Strategies and Clinical Progress in Major Diseases.

Disease type	Key regulatory targets	Therapeutic strategy	Clinical progress
Cancer	SLC7A11, GPX4, ACSL4	Induce ferroptosis (erastin, RSL3)	Sorafenib approved; erastin analogs in phase II
Neurodegenerative Diseases	FSP1, BH4, iron chelators	Inhibit ferroptosis (deferiprone, JKE-1674)	Deferiprone phase II (Parkinson's)
Ischemia-Reperfusion Injury	LOX, NOX4, GPX4	Inhibit ferroptosis (SRS11-92, Liproxstatin-1)	Nanoparticle inhibitors in preclinical trials
Metabolic Disorders (NASH, Diabetes)	DHODH, cholesterol metabolism	Modulate ferroptosis (curcumin, statins)	Preclinical efficacy demonstrated

BH4, Tetrahydrobiopterin; NOX4, NADPH oxidase 4; NASH, non-alcoholic steatohepatitis; DHODH, Dihydroorotate dehydrogenase.

otal factor that drives the pathological processes in diseases such as Alzheimer's and Parkinson's [219]. Similarly, the kidney and heart are highly sensitive to ferroptosis, especially in the context of ischemia-reperfusion injury, where the sudden restoration of blood flow leads to a burst of ROS and iron overload, triggering ferroptosis in tubular epithelial cells and cardiomyocytes [220]. Conversely, hepatocytes possess robust antioxidant systems, but these can be overwhelmed in conditions such as drug-induced liver injury or non-alcoholic steatohepatitis (NASH), where lipid peroxidation plays a central role [221,222]. Understanding the molecular basis for this organ- and cell type-specific ferroptosis, such as the roles of lipid-metabolizing enzymes like ACSL4 and LPCAT3, is essential for developing targeted therapies that can induce ferroptosis in cancer cells while protecting healthy tissues [223], or, conversely, inhibit ferroptosis in vulnerable organs during disease.

Comparative Analysis of Therapeutic Targets Across Diseases

Ferroptosis features disease-specific regulatory patterns and molecular targets, which underpins the development of tailored therapeutic strategies. Variations in ferroptosis susceptibility across cancer, neurodegenerative diseases, ischemia-reperfusion injury and metabolic disorders are associated with each disease's unique cellular metabolism, tissue microenvironment and expression of ferroptosis-related regulators. Accordingly, core therapeutic targets and intervention strategies for ferroptosis modulation exhibit distinct disease specificity, with clinical research progress differing based on translation difficulty, drug development maturity and pathological complexity. Table 3 summarizes the key regulatory targets, therapeutic strategies and clinical progress of ferroptosis modulation in major diseases, intuitively reflecting the link between disease characteristics and ferroptosis-based therapeutic design. Cross-disease comparison of these targets also informs ferroptosis modulator repurposing and pan-disease strategy development, while highlighting the need to consider tissue and cell target specificity to avoid off-target effects in clinical practice.

Ferroptosis in Specific Diseases

Cancer: P53 and BAP1 promote ferroptosis by inhibiting SLC7A11 expression [224,225]. FH-deficient renal cancer cells exhibit heightened sensitivity to ferroptosis inducers [226].

Neurodegenerative diseases: Aβ (Alzheimer's) and α-synuclein (Parkinson's) induce iron accumulation and ferroptosis [227,228]. Ferroptosis inhibitors reduce neuronal loss in animal models [229,230].

Ischemia-reperfusion injury: Restoring blood flow triggers iron overload and ROS burst, inducing ferroptosis in cardiomyocytes and renal tubular epithelial cells [231,232]. Liproxstatin-1 reduces infarct size [233].

Metabolic disorders: NASH hepatocytes undergo ferroptosis due to lipid accumulation [234]. Diabetes-related hyperglycemia promotes ferroptosis via advanced glycation end products [235].

Conclusion

This review provides a comprehensive overview of the molecular mechanisms, regulatory networks, and clinical applications of ferroptosis. Core induction mechanisms involve ROS generation (mitochondria, Fenton reaction) and lipid peroxidation, while protective systems include classical pathways, such as System Xc–GPX4, FSP1-CoQ10, as well as auxiliary pathways involving cholesterol, sex hormone metabolism. Key signaling pathways and crosstalk with other forms of cell death further refine ferroptosis regulation. Novel modulators and delivery systems are being explored to overcome challenges in clinical translation. Ferroptosis exhibits disease- and cell type-specific regulatory features, and targeted therapies show promise in cancer, neurodegenerative diseases, and ischemia-reperfusion injury. Future research should focus on clarifying cell type-specific regulatory mechanisms, optimizing clinical trial design, and developing disease-specific ferroptosis modulators to bridge the gap between preclinical research and clinical utility.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

RHL, LLS, SZN and LCS designed the research study. YM, XM and RHL performed the research. HW, YS and LLS analyzed the literature. SZN and LCS drafted this article. All authors contributed to important 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 received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, *et al*. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012; 149: 1060–1072. https://doi.org/10.1016/j.cell.2012.03.042.

[2] Skouta R, Dixon SJ, Wang J, Dunn DE, Orman M, Shimada K, *et al*. Ferrostatins inhibit oxidative lipid damage and cell death in diverse disease models. Journal of the American Chemical Society. 2014; 136: 4551–4556. https://doi.org/10.1021/ja411006a.

[3] Lee JY, Kim WK, Bae KH, Lee SC, Lee EW. Lipid Metabolism and Ferroptosis. Biology. 2021; 10: 184. https://doi.org/10.3390/biology10030184.

[4] Kuang F, Liu J, Tang D, Kang R. Oxidative Damage and Antioxidant Defense in Ferroptosis. Frontiers in Cell and Developmental Biology. 2020; 8: 586578. https://doi.org/10.3389/fcell.2020.586578.

[5] Bock FJ, Tait SWG. Mitochondria as multifaceted regulators of cell death. Nature Reviews. Molecular Cell Biology. 2020; 21: 85–100. https://doi.org/10.1038/s41580-019-0173-8.

[6] Angelova PR, Abramov AY. Role of mitochondrial ROS in the brain: from physiology to neurodegeneration. FEBS Letters. 2018; 592: 692–702. https://doi.org/10.1002/1873-3468.12964.

[7] Matés JM, Segura JA, Alonso FJ, Márquez J. Oxidative stress in apoptosis and cancer: an update. Archives of Toxicology. 2012; 86: 1649–1665. https://doi.org/10.1007/s00204-012-0906-3.

[8] Votyakova TV, Reynolds IJ. DeltaPsi(m)-Dependent and -independent production of reactive oxygen species by rat brain mitochondria. Journal of Neurochemistry. 2001; 79: 266–277. https://doi.org/10.1046/j.1471-4159.2001.00548.x.

[9] Yang Y, Karakhanova S, Hartwig W, D'Haese JG, Philippov PP, Werner J, *et al*. Mitochondria and Mitochondrial ROS in Cancer: Novel Targets for Anticancer Therapy. Journal of Cellular Physiology. 2016; 231: 2570–2581. https://doi.org/10.1002/jcp.25349.

[10] Gibson GE, Blass JP, Beal MF, Bunik V. The alpha-ketoglutarate-dehydrogenase complex: a mediator between mitochondria and oxidative stress in neurodegeneration. Molecular Neurobiology. 2005; 31: 43–63. https://doi.org/10.1385/MN:31:1-3:043.

[11] Starkov AA, Fiskum G, Chinopoulos C, Lorenzo BJ, Browne SE, Patel MS, *et al*. Mitochondrial alpha-ketoglutarate dehydrogenase complex generates reactive oxygen species. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2004; 24: 7779–7788. https://doi.org/10.1523/JNEUROSCI.1899-04.2004.

[12] Lambert AJ, Brand MD. Superoxide production by NADH:ubiquinone oxidoreductase (complex I) depends on the pH gradient across the mitochondrial inner membrane. The Biochemical Journal. 2004; 382: 511–517. https://doi.org/10.1042/BJ20040485.

[13] Henning Y, Blind US, Larafa S, Matschke J, Fandrey J. Hypoxia aggravates ferroptosis in RPE cells by promoting the Fenton reaction. Cell Death & Disease. 2022; 13: 662. https://doi.org/10.1038/s41419-022-05121-z.

[14] Catapano A, Cimmino F, Petrella L, Pizzella A, D'Angelo M, Ambrosio K, *et al*. Iron metabolism and ferroptosis in health and diseases: The crucial role of mitochondria in metabolically active tissues. The Journal of Nutritional Biochemistry. 2025; 140: 109888. https://doi.org/10.1016/j.jnutbio.2025.109888.

[15] Canonne-Hergaux F, Gruenheid S, Ponka P, Gros P. Cellular and subcellular localization of the Nramp2 iron transporter in the intestinal brush border and regulation by dietary iron. Blood. 1999; 93: 4406–4417.

[16] Turi JL, Wang X, McKie AT, Nozik-Grayck E, Mamo LB, Crissman K, *et al*. Duodenal cytochrome b: a novel ferrireductase in airway epithelial cells. American Journal of Physiology. Lung Cellular and Molecular Physiology. 2006; 291: L272–L280. https://doi.org/10.1152/ajplung.00342.2005.

[17] Ferris CD, Jaffrey SR, Sawa A, Takahashi M, Brady SD, Barrow RK, *et al*. Haem oxygenase-1 prevents cell death by regulating cellular iron. Nature Cell Biology. 1999; 1: 152–157. https://doi.org/10.1038/11072.

[18] Arosio P, Levi S. Cytosolic and mitochondrial ferritins in the regulation of cellular iron homeostasis and oxidative damage. Biochimica et Biophysica Acta. 2010; 1800: 783–792. https://doi.org/10.1016/j.bbagen.2010.02.005.

[19] Theil EC. Ferritin: at the crossroads of iron and oxygen metabolism. The Journal of Nutrition. 2003; 133: 1549S–53S. https://doi.org/10.1093/jn/133.5.1549S.

[20] Vulpe CD, Kuo YM, Murphy TL, Cowley L, Askwith C, Libina N, *et al*. Hephaestin, a ceruloplasmin homologue implicated in intestinal iron transport, is defective in the sla mouse. Nature Genetics. 1999; 21: 195–199. https://doi.org/10.1038/5979.

[21] Schade AL, Caroline L. An Iron-binding Component in Human Blood Plasma. Science (New York, N.Y.). 1946; 104: 340–341. https://doi.org/10.1126/science.104.2702.340.

[22] Ohgami RS, Campagna DR, McDonald A, Fleming MD. The Steap proteins are metalloreductases. Blood. 2006; 108: 1388–1394. https://doi.org/10.1182/blood-2006-02-003681.

[23] Yan R, Xie E, Li Y, Li J, Zhang Y, Chi X, *et al*. The structure of erastin-bound xCT-4F2hc complex reveals

molecular mechanisms underlying erastin-induced ferroptosis. Cell Research. 2022; 32: 687–690. https://doi.org/10.1038/s41422-022-00642-w.

[24] Johnson MB, Enns CA. Diferric transferrin regulates transferrin receptor 2 protein stability. Blood. 2004; 104: 4287–4293. https://doi.org/10.1182/blood-2004-06-2477.

[25] Kawabata H, Yang R, Hirama T, Vuong PT, Kawano S, Gombart AF, *et al*. Molecular cloning of transferrin receptor 2. A new member of the transferrin receptor-like family. The Journal of Biological Chemistry. 1999; 274: 20826–20832. https://doi.org/10.1074/jbc.274.30.20826.

[26] Robb A, Wessling-Resnick M. Regulation of transferrin receptor 2 protein levels by transferrin. Blood. 2004; 104: 4294–4299. https://doi.org/10.1182/blood-2004-06-2481.

[27] Shaw GC, Cope JJ, Li L, Corson K, Hersey C, Ackermann GE, *et al*. Mitoferrin is essential for erythroid iron assimilation. Nature. 2006; 440: 96–100. https://doi.org/10.1038/nature04512.

[28] Park CH, Valore EV, Waring AJ, Ganz T. Hepcidin, a urinary antimicrobial peptide synthesized in the liver. The Journal of Biological Chemistry. 2001; 276: 7806–7810. https://doi.org/10.1074/jbc.M008922200.

[29] Pigeon C, Ilyin G, Courselaud B, Leroyer P, Turlin B, Brissot P, *et al*. A new mouse liver-specific gene, encoding a protein homologous to human antimicrobial peptide hepcidin, is overexpressed during iron overload. The Journal of Biological Chemistry. 2001; 276: 7811–7819. https://doi.org/10.1074/jbc.M008923200.

[30] Han X. Lipidomics for studying metabolism. Nature Reviews. Endocrinology. 2016; 12: 668–679. https://doi.org/10.1038/nrendo.2016.98.

[31] Yuan H, Li X, Zhang X, Kang R, Tang D. Identification of ACSL4 as a biomarker and contributor of ferroptosis. Biochemical and Biophysical Research Communications. 2016; 478: 1338–1343. https://doi.org/10.1016/j.bbrc.2016.08.124.

[32] Kagan VE, Mao G, Qu F, Angeli JPF, Doll S, Croix CS, *et al*. Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. Nature Chemical Biology. 2017; 13: 81–90. https://doi.org/10.1038/nchembio.2238.

[33] Dixon SJ, Winter GE, Musavi LS, Lee ED, Snijder B, Rebsamen M, *et al*. Human Haploid Cell Genetics Reveals Roles for Lipid Metabolism Genes in Nonapoptotic Cell Death. ACS Chemical Biology. 2015; 10: 1604–1609. https://doi.org/10.1021/acschembio.5b00245.

[34] Conrad M, Pratt DA. The chemical basis of ferroptosis. Nature Chemical Biology. 2019; 15: 1137–1147. https://doi.org/10.1038/s41589-019-0408-1.

[35] Yin H, Xu L, Porter NA. Free radical lipid peroxidation: mechanisms and analysis. Chemical Reviews. 2011; 111: 5944–5972. https://doi.org/10.1021/cr200084z.

[36] Shintoku R, Takigawa Y, Yamada K, Kubota C, Yoshimoto Y, Takeuchi T, *et al*. Lipoxygenase-mediated generation of lipid peroxides enhances ferroptosis induced by erastin and RSL3. Cancer Science. 2017; 108: 2187–2194. https://doi.org/10.1111/cas.13380.

[37] Zheng J, Conrad M. The Metabolic Underpinnings of Ferroptosis. Cell Metabolism. 2020; 32: 920–937. https://doi.org/10.1016/j.cmet.2020.10.011.

[38] Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. Nature Reviews. Molecular Cell Biology. 2021; 22: 266–282. https://doi.org/10.1038/s41580-020-00324-8.

[39] Forcina GC, Dixon SJ. GPX4 at the Crossroads of Lipid Homeostasis and Ferroptosis. Proteomics. 2019; 19: e1800311. https://doi.org/10.1002/pmic.201800311.

[40] Yang WS, Kim KJ, Gaschler MM, Patel M, Shchepinov MS, Stockwell BR. Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis. Proceedings of the National Academy of Sciences of the United States of America. 2016; 113: E4966–E4975. https://doi.org/10.1073/pnas.1603244113.

[41] Xie LH, Fefelova N, Pamarthi SH, Gwathmey JK. Molecular Mechanisms of Ferroptosis and Relevance to Cardiovascular Disease. Cells. 2022; 11: 2726. https://doi.org/10.3390/cells11172726.

[42] Wenzel SE, Tyurina YY, Zhao J, St Croix CM, Dar HH, Mao G, *et al*. PEBP1 Wardens Ferroptosis by Enabling Lipoxygenase Generation of Lipid Death Signals. Cell. 2017; 171: 628–641.e26. https://doi.org/10.1016/j.cell.2017.09.044.

[43] Gunshin H, Mackenzie B, Berger UV, Gunshin Y, Romero MF, Boron WF, *et al*. Cloning and characterization of a mammalian proton-coupled metal-ion transporter. Nature. 1997; 388: 482–488. https://doi.org/10.1038/41343.

[44] Fleming MD, Trenor CC, 3rd, Su MA, Foernzler D, Beier DR, Dietrich WF, *et al*. Microcytic anaemia mice have a mutation in Nramp2, a candidate iron transporter gene. Nature Genetics. 1997; 16: 383–386. https://doi.org/10.1038/ng0897-383.

[45] Chifman J, Laubenbacher R, Torti SV. A systems biology approach to iron metabolism. Advances in Experimental Medicine and Biology. 2014; 844: 201–225. https://doi.org/10.1007/978-1-4939-2095-2_10.

[46] Nemeth E, Ganz T. Hepcidin and Iron in Health and Disease. Annual Review of Medicine. 2023; 74: 261–277. https://doi.org/10.1146/annurev-med-043021-032816.

[47] Aschemeyer S, Qiao B, Stefanova D, Valore EV, Sek AC, Ruwe TA, *et al*. Structure-function analysis of ferroportin defines the binding site and an alternative mechanism of action of hepcidin. Blood. 2018; 131: 899–910. https://doi.org/10.1182/blood-2017-05-786590.

[48] Qiao B, Sugianto P, Fung E, Del-Castillo-Rueda A, Moran-Jimenez MJ, Ganz T, *et al*. Hepcidin-induced endocytosis of ferroportin is dependent on ferroportin ubiquitination. Cell Metabolism. 2012; 15: 918–924. https://doi.org/10.1016/j.cmet.2012.03.018.

[49] Wilbon AS, Shen J, Ruchala P, Zhou M, Pan Y. Structural basis of ferroportin inhibition by minihepcidin PR73. PLoS Biology. 2023; 21: e3001936. https://doi.org/10.1371/journal.pbio.3001936.

[50] Ganz T, Nemeth E. Hepcidin and disorders of iron metabolism. Annual Review of Medicine. 2011; 62: 347–360. https://doi.org/10.1146/annurev-med-050109-142444.

[51] Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pedersen BK, *et al*. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. The Journal of Clinical Investigation. 2004; 113: 1271–1276. https://doi.org/10.1172/JCI20945.

[52] Armitage AE, Eddowes LA, Gileadi U, Cole S, Spottiswoode N, Selvakumar TA, *et al*. Hepcidin regulation by innate immune and infectious stimuli. Blood. 2011; 118: 4129–4139. https://doi.org/10.1182/blood-2011-04-351957.

[53] Peng Y, Liao B, Zhou Y, Zeng W, Zeng ZY. Atorvastatin Inhibits Ferroptosis of H9C2 Cells by regulatingSMAD7/Hepcidin Expression to Improve Ischemia-Reperfusion Injury. Cardiology Research and Practice. 2022; 2022: 3972829. https://doi.org/10.1155/2022/3972829.

[54] Nemeth E, Ganz T. Hepcidin-Ferroportin Interaction Controls Systemic Iron Homeostasis. International Journal of Molecular Sciences. 2021; 22: 6493. https://doi.org/10.3390/ijms22126493.

[55] Rayatpour A, Foolad F, Heibatollahi M, Khajeh K, Javan M. Ferroptosis inhibition by deferiprone, attenuates myelin damage and promotes neuroprotection in demyelinated optic nerve. Scientific Reports. 2022; 12: 19630. https://doi.org/10.1038/s41598-022-24152-2.

[56] Zhu J, Dai X, Wang Y, Cui T, Huang B, Wang D, *et al*. Molybdenum and cadmium co-induce apoptosis and ferroptosis through inhibiting Nrf2 signaling pathway in duck (Anas platyrhyncha) testes. Poultry Science. 2024; 103: 103653. https://doi.org/10.1016/j.psj.2024.103653.

[57] Guo Z, Lin J, Sun K, Guo J, Yao X, Wang G, *et al*. Deferoxamine Alleviates Osteoarthritis by Inhibiting Chondrocyte Ferroptosis and Activating the Nrf2 Pathway [Erratum in: Frontiers in Pharmacology. 2023; 14: 1199951. doi: 10.3389/fphar.2023.1199951]. Frontiers in Pharmacology. 2022; 13: 791376. https://doi.org/10.3389/fphar.2022.791376.

[58] Tevlin R, Longaker MT, Wan DC. Deferoxamine to Minimize Fibrosis During Radiation Therapy. Advances in Wound Care. 2022; 11: 548–559. https://doi.org/10.1089/wound.2021.0021.

[59] Zhou Y, Jia Z, Wang J, Huang S, Yang S, Xiao S, *et al*. Curcumin reverses erastin-induced chondrocyte ferroptosis by upregulating Nrf2. Heliyon. 2023; 9: e20163. https://doi.org/10.1016/j.heliyon.2023.e20163.

[60] Yang C, Han M, Li R, Zhou L, Zhang Y, Duan L, *et al*. Curcumin Nanoparticles Inhibiting Ferroptosis for the Enhanced Treatment of Intracerebral Hemorrhage. International Journal of Nanomedicine. 2021; 16: 8049–8065. https://doi.org/10.2147/IJN.S334965.

[61] Liu Z, Ma H, Lai Z. The Role of Ferroptosis and Cuproptosis in Curcumin against Hepatocellular Carcinoma. Molecules (Basel, Switzerland). 2023; 28: 1623. https://doi.org/10.3390/molecules28041623.

[62] Ursini F, Maiorino M, Valente M, Ferri L, Gregolin C. Purification from pig liver of a protein which protects liposomes and biomembranes from peroxidative degradation and exhibits glutathione peroxidase activity on phosphatidylcholine hydroperoxides. Biochimica et Biophysica Acta. 1982; 710: 197–211. https://doi.org/10.1016/0005-2760(82)90150-3.

[63] Ingold I, Berndt C, Schmitt S, Doll S, Poschmann G, Buday K, *et al*. Selenium Utilization by GPX4 Is Required to Prevent Hydroperoxide-Induced Ferroptosis. Cell. 2018; 172: 409–422.e21. https://doi.org/10.1016/j.cell.2017.11.048.

[64] McBean GJ. The transsulfuration pathway: a source of cysteine for glutathione in astrocytes. Amino Acids. 2012; 42: 199–205. https://doi.org/10.1007/s00726-011-0864-8.

[65] Yue M, Wei J, Chen W, Hong D, Chen T, Fang X. Neurotrophic Role of the Next-Generation Probiotic Strain *L. lactis* MG1363-pMG36e-GLP-1 on Parkinson's Disease via Inhibiting Ferroptosis. Nutrients. 2022; 14: 4886. https://doi.org/10.3390/nu14224886.

[66] Nguyen HP, Yi D, Lin F, Viscarra JA, Tabuchi C, Ngo K, *et al*. Aifm2, a NADH Oxidase, Supports Robust Glycolysis and Is Required for Cold- and Diet-Induced Thermogenesis. Molecular Cell. 2020; 77: 600–617.e4. https://doi.org/10.1016/j.molcel.2019.12.002.

[67] Doll S, Freitas FP, Shah R, Aldrovandi M, da Silva MC, Ingold I, *et al*. FSP1 is a glutathione-independent ferroptosis suppressor. Nature. 2019; 575: 693–698. https://doi.org/10.1038/s41586-019-1707-0.

[68] Li W, Liang L, Liu S, Yi H, Zhou Y. FSP1: a key regulator of ferroptosis. Trends in Molecular Medicine. 2023; 29: 753–764. https://doi.org/10.1016/j.molmed.2023.05.013.

[69] Yoshioka H, Kawamura T, Muroi M, Kondoh Y, Honda K, Kawatani M, *et al*. Identification of a Small Molecule That Enhances Ferroptosis via Inhibition of Ferroptosis Suppressor Protein 1 (FSP1). ACS Chemical Biology. 2022; 17: 483–491. https://doi.org/10.1021/acschembio.2c00028.

[70] Hendricks JM, Doubravsky CE, Wehri E, Li Z, Roberts MA, Deol KK, *et al*. Identification of structurally diverse FSP1 inhibitors that sensitize cancer cells to ferroptosis. Cell Chemical Biology. 2023; 30: 1090–1103.e7. https://doi.org/10.1016/j.chembiol.2023.04.007.

[71] Dai E, Meng L, Kang R, Wang X, Tang D. ESCRT-III-dependent membrane repair blocks ferroptosis. Biochemical and Biophysical Research Communications. 2020; 522: 415–421. https://doi.org/10.1016/j.bbrc.2019.11.110.

[72] Ren X, Luo F, Li X, Yi S, Yang B, Jiang Z. Structural characteristics and catalytic cycle of dihydroorotate dehydrogenase-a review. Sheng Wu Gong Cheng Xue Bao = Chinese Journal of Biotechnology. 2020; 36: 2732–2740. https://doi.org/10.13345/j.cjb.200166.

[73] Mao C, Liu X, Zhang Y, Lei G, Yan Y, Lee H, *et al*. DHODH-mediated ferroptosis defence is a targetable vulnerability in cancer. Nature. 2021; 593: 586–590. https://doi.org/10.1038/s41586-021-03539-7.

[74] Sengupta R, Coppo L, Mishra P, Holmgren A. Glutathione-glutaredoxin is an efficient electron donor system for mammalian p53R2-R1-dependent ribonucleotide reductase. The Journal of Biological Chemistry. 2019; 294: 12708–12716. https://doi.org/10.1074/jbc.RA119.008752.

[75] Levring TB, Kongsbak M, Rode AKO, Woetmann A, Ødum N, Bonefeld CM, *et al*. Human CD4+ T cells require exogenous cystine for glutathione and DNA synthesis. Oncotarget. 2015; 6: 21853–21864. https://doi.org/10.18632/oncotarget.5213.

[76] Desler C, Durhuus JA, Hansen TLL, Anugula S, Zelander NT, Bøggild S, *et al*. Partial inhibition of mitochondrial-linked pyrimidine synthesis increases tumorigenic potential and lysosome accumulation. Mitochondrion. 2022; 64: 73–81. https://doi.org/10.1016/j.mito.2022.03.005.

[77] Tarangelo A, Rodencal J, Kim JT, Magtanong L, Long JZ, Dixon SJ. Nucleotide biosynthesis links glutathione metabolism to ferroptosis sensitivity. Life Science Alliance. 2022; 5: e202101157. https://doi.org/10.26508/lsa.202101157.

[78] Cronin SJF, Seehus C, Weidinger A, Talbot S, Reissig S, Seifert M, *et al*. The metabolite BH4 controls T cell proliferation in autoimmunity and cancer. Nature. 2018; 563: 564–568. https://doi.org/10.1038/s41586-018-0701-2.

[79] Kraft VAN, Bezjian CT, Pfeiffer S, Ringelstetter L, Müller C, Zandkarimi F, *et al*. GTP Cyclohydrolase 1/Tetrahydrobiopterin Counteract Ferroptosis through Lipid Remodeling. ACS Central Science. 2020; 6: 41–53. https://doi.org/10.1021/acscentsci.9b01063.

[80] Soula M, Weber RA, Zilka O, Alwaseem H, La K, Yen F, *et al*. Metabolic determinants of cancer cell sensitivity to canonical ferroptosis inducers. Nature Chemical Biology. 2020; 16: 1351–1360. https://doi.org/10.1038/s41589-020-0613-y.

[81] Vasquez-Vivar J, Shi Z, Tan S. Tetrahydrobiopterin in Cell Function and Death Mechanisms. Antioxidants & Redox Signaling. 2022; 37: 171–183. https://doi.org/10.1089/ars.2021.0136.

[82] Chuaiphichai S, Crabtree MJ, Mcneill E, Hale AB, Trelfa L, Channon KM, *et al*. A key role for tetrahydrobiopterin-dependent endothelial NOS regulation in resistance arteries: studies in endothelial cell tetrahydrobiopterin-deficient mice. British Journal of Pharmacology. 2017; 174: 657–671. https://doi.org/10.1111/bph.13728.

[83] Thöny B, Auerbach G, Blau N. Tetrahydrobiopterin biosynthesis, regeneration and functions. The Biochemical Journal. 2000; 347: 1–16.

[84] Crabtree MJ, Tatham AL, Hale AB, Alp NJ, Channon KM. Critical role for tetrahydrobiopterin recycling by dihydrofolate reductase in regulation of endothelial nitric-oxide synthase coupling: relative importance of the de novo biopterin synthesis versus salvage pathways. The Journal of Biological Chemistry. 2009; 284: 28128–28136. https://doi.org/10.1074/jbc.M109.041483.

[85] Vásquez-Vivar J. Tetrahydrobiopterin, superoxide, and vascular dysfunction. Free Radical Biology & Medicine. 2009; 47: 1108–

1119. https://doi.org/10.1016/j.freeradbiomed.2009.07.024.
[86] Kwon NS, Nathan CF, Stuehr DJ. Reduced biopterin as a cofactor in the generation of nitrogen oxides by murine macrophages. The Journal of Biological Chemistry. 1989; 264: 20496–20501.
[87] Rodríguez-Crespo I, Moënne-Loccoz P, Loehr TM, Ortiz de Montellano PR. Endothelial nitric oxide synthase: modulations of the distal heme site produced by progressive N-terminal deletions. Biochemistry. 1997; 36: 8530–8538. https://doi.org/10.1021/bi970192j.
[88] Klatt P, Schmid M, Leopold E, Schmidt K, Werner ER, Mayer B. The pteridine binding site of brain nitric oxide synthase. Tetrahydrobiopterin binding kinetics, specificity, and allosteric interaction with the substrate domain. The Journal of Biological Chemistry. 1994; 269: 13861–13866.
[89] Ghosh DK, Wu C, Pitters E, Moloney M, Werner ER, Mayer B, *et al*. Characterization of the inducible nitric oxide synthase oxygenase domain identifies a 49 amino acid segment required for subunit dimerization and tetrahydrobiopterin interaction. Biochemistry. 1997; 36: 10609–10619. https://doi.org/10.1021/bi9702290.
[90] Schmidt K, Kolesnik B, Gorren ACF, Werner ER, Mayer B. Cell type-specific recycling of tetrahydrobiopterin by dihydrofolate reductase explains differential effects of 7,8-dihydrobiopterin on endothelial nitric oxide synthase uncoupling. Biochemical Pharmacology. 2014; 90: 246–253. https://doi.org/10.1016/j.bcp.2014.05.010.
[91] Vásquez-Vivar J, Kalyanaraman B, Martásek P, Hogg N, Masters BS, Karoui H, *et al*. Superoxide generation by endothelial nitric oxide synthase: the influence of cofactors. Proceedings of the National Academy of Sciences of the United States of America. 1998; 95: 9220–9225. https://doi.org/10.1073/pnas.95.16.9220.
[92] Alderton WK, Cooper CE, Knowles RG. Nitric oxide synthases: structure, function and inhibition. The Biochemical Journal. 2001; 357: 593–615. https://doi.org/10.1042/0264-6021:3570593.
[93] Kaufman S. New tetrahydrobiopterin-dependent systems. Annual Review of Nutrition. 1993; 13: 261–286. https://doi.org/10.1146/annurev.nu.13.070193.001401.
[94] Fanet H, Capuron L, Castanon N, Calon F, Vancassel S. Tetrahydrobioterin (BH4) Pathway: From Metabolism to Neuropsychiatry. Current Neuropharmacology. 2021; 19: 591–609. https://doi.org/10.2174/1570159X18666200729103529.
[95] Yamada N, Karasawa T, Ito J, Yamamuro D, Morimoto K, Nakamura T, *et al*. Inhibition of 7-dehydrocholesterol reductase prevents hepatic ferroptosis under an active state of sterol synthesis. Nature Communications. 2024; 15: 2195. https://doi.org/10.1038/s41467-024-46386-6.
[96] Li J, Zhan S, Yang W, Zhang H, Ma X, Chen F, *et al*. Radiation-induced ferroptosis via liposomal delivery of 7-Dehydrocholesterol. Journal of Nanobiotechnology. 2025; 23: 249. https://doi.org/10.1186/s12951-025-03303-3.
[97] Lee J, Roh JL. Cholesterol-ferroptosis nexus: Unveiling novel cancer therapeutic avenues. Cancer Letters. 2024; 597: 217046. https://doi.org/10.1016/j.canlet.2024.217046.
[98] Cui S, Ye J. 7-Dehydrocholesterol: A sterol shield against an iron sword. Molecular Cell. 2024; 84: 1183–1185. https://doi.org/10.1016/j.molcel.2024.03.003.
[99] Noguchi N, Saito Y, Niki E. Lipid peroxidation, ferroptosis, and antioxidants. Free Radical Biology & Medicine. 2025; 237: 228–238. https://doi.org/10.1016/j.freeradbiomed.2025.05.393.
[100] Xu H, Zhou S, Tang Q, Xia H, Bi F. Cholesterol metabolism: New functions and therapeutic approaches in cancer. Biochimica et Biophysica Acta. Reviews on Cancer. 2020; 1874: 188394. https://doi.org/10.1016/j.bbcan.2020.188394.
[101] Yue K, Wu H, Li K, Yang S, Bai X, Zhang W, *et al*. HSF4 alleviates ferroptosis in colorectal cancer through transcriptional regulation of MBOAT1/2. Functional & Integrative Genomics. 2026; 26: 35. https://doi.org/10.1007/s10142-026-01822-2.
[102] Wiseman H. Vitamin D is a membrane antioxidant. Ability to inhibit iron-dependent lipid peroxidation in liposomes compared to cholesterol, ergosterol and tamoxifen and relevance to anticancer action. FEBS Letters. 1993; 326: 285–288. https://doi.org/10.1016/0014-5793(93)81809-e.
[103] Liang D, Feng Y, Zandkarimi F, Wang H, Zhang Z, Kim J, *et al*. Ferroptosis surveillance independent of GPX4 and differentially regulated by sex hormones. Cell. 2023; 186: 2748–2764.e22. https://doi.org/10.1016/j.cell.2023.05.003.
[104] Gijón MA, Riekhof WR, Zarini S, Murphy RC, Voelker DR. Lysophospholipid acyltransferases and arachidonate recycling in human neutrophils. The Journal of Biological Chemistry. 2008; 283: 30235–30245. https://doi.org/10.1074/jbc.M806194200.
[105] Belavgeni A, Tonnus W, Linkermann A. Cancer cells evade ferroptosis: sex hormone-driven membrane-bound O-acyltransferase domain-containing 1 and 2 (MBOAT1/2) expression. Signal Transduction and Targeted Therapy. 2023; 8: 336. https://doi.org/10.1038/s41392-023-01593-3.
[106] Li W, Li W, Leng Y, Xu H, Xia Z, Wang Y. ALKBH5-Mediated M^6A Demethylation of G3BP1 Attenuates Ferroptosis Via Cytoplasmic Retention of YBX1/p53 in Diabetic Myocardial Ischemia-Reperfusion Injury. Advanced Science (Weinheim, Baden-Wurttemberg, Germany). 2025; 12: e07254. https://doi.org/10.1002/advs.202507254.
[107] Yang Y, Ma Y, Li Q, Ling Y, Zhou Y, Chu K, *et al*. STAT6 inhibits ferroptosis and alleviates acute lung injury via regulating P53/SLC7A11 pathway. Cell Death & Disease. 2022; 13: 530. https://doi.org/10.1038/s41419-022-04971-x.
[108] Nakamura T, Hipp C, Santos Dias Mourão A, Borggräfe J, Aldrovandi M, Henkelmann B, *et al*. Phase separation of FSP1 promotes ferroptosis. Nature. 2023; 619: 371–377. https://doi.org/10.1038/s41586-023-06255-6.
[109] Xian M, Wang Q, Xiao L, Zhong L, Xiong W, Ye L, *et al*. Leukocyte immunoglobulin-like receptor B1 (LILRB1) protects human multiple myeloma cells from ferroptosis by maintaining cholesterol homeostasis. Nature Communications. 2024; 15: 5767. https://doi.org/10.1038/s41467-024-50073-x.
[110] Li Y, Ran Q, Duan Q, Jin J, Wang Y, Yu L, *et al*. 7-Dehydrocholesterol dictates ferroptosis sensitivity. Nature. 2024; 626: 411–418. https://doi.org/10.1038/s41586-023-06983-9.
[111] Yoshioka H, Coates HW, Chua NK, Hashimoto Y, Brown AJ, Ohgane K. A key mammalian cholesterol synthesis enzyme, squalene monooxygenase, is allosterically stabilized by its substrate. Proceedings of the National Academy of Sciences of the United States of America. 2020; 117: 7150–7158. https://doi.org/10.1073/pnas.1915923117.
[112] Liu J, Kang R, Tang D. Signaling pathways and defense mechanisms of ferroptosis. The FEBS Journal. 2022; 289: 7038–7050. https://doi.org/10.1111/febs.16059.
[113] Sun Q, Liu D, Cui W, Cheng H, Huang L, Zhang R, *et al*. Cholesterol mediated ferroptosis suppression reveals essential roles of Coenzyme Q and squalene. Communications Biology. 2023; 6: 1108. https://doi.org/10.1038/s42003-023-05477-8.
[114] Schade DS, Shey L, Eaton RP. Cholesterol Review: A Metabolically Important Molecule. Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2020; 26: 1514–1523. https://doi.org/10.4158/EP-2020-0347.
[115] Freitas FP, Alborzinia H, Dos Santos AF, Nepachalovich P, Pedrera L, Zilka O, *et al*. 7-Dehydrocholesterol is an endogenous suppressor of ferroptosis. Nature. 2024; 626: 401–410.

https://doi.org/10.1038/s41586-023-06878-9.

[116] Ryoo IG, Kwak MK. Regulatory crosstalk between the oxidative stress-related transcription factor Nfe2l2/Nrf2 and mitochondria. Toxicology and applied pharmacology. 2018; 359: 24–33. https://doi.org/10.1016/j.taap.2018.09.014.

[117] Jung KA, Lee S, Kwak MK. NFE2L2/NRF2 Activity Is Linked to Mitochondria and AMP-Activated Protein Kinase Signaling in Cancers Through miR-181c/Mitochondria-Encoded Cytochrome c Oxidase Regulation. Antioxidants & Redox signaling. 2017; 27: 945–961. https://doi.org/10.1089/ars.2016.6797.

[118] Tsakiri EN, Gumeni S, Vougas K, Pendin D, Papassideri I, Daga A, *et al*. Proteasome dysfunction induces excessive proteome instability and loss of mitostasis that can be mitigated by enhancing mitochondrial fusion or autophagy. Autophagy. 2019; 15: 1757–1773. https://doi.org/10.1080/15548627.2019.1596477.

[119] Horniblow RD, Pathak P, Balacco DL, Acharjee A, Lles E, Gkoutos G, *et al*. Iron-mediated epigenetic activation of NRF2 targets. The Journal of Nutritional Biochemistry. 2022; 101: 108929. https://doi.org/10.1016/j.jnutbio.2021.108929.

[120] Kerins MJ, Ooi A. The Roles of NRF2 in Modulating Cellular Iron Homeostasis. Antioxidants & Redox signaling. 2018; 29: 1756–1773. https://doi.org/10.1089/ars.2017.7176.

[121] Anandhan A, Dodson M, Shakya A, Chen J, Liu P, Wei Y, *et al*. NRF2 controls iron homeostasis and ferroptosis through HERC2 and VAMP8. Science Advances. 2023; 9: eade9585. https://doi.org/10.1126/sciadv.ade9585.

[122] Nishizawa H, Yamanaka M, Igarashi K. Ferroptosis: regulation by competition between NRF2 and BACH1 and propagation of the death signal. The FEBS journal. 2023; 290: 1688–1704. https://doi.org/10.1111/febs.16382.

[123] Luchkova A, Mata A, Cadenas S. Nrf2 as a regulator of energy metabolism and mitochondrial function. FEBS Letters. 2024; 598: 2092–2105. https://doi.org/10.1002/1873-3468.14993.

[124] Han Q, Shi J, Yu Y, Yuan H, Guo Y, Liu X, *et al*. Calycosin alleviates ferroptosis and attenuates doxorubicin-induced myocardial injury via the Nrf2/SLC7A11/GPX4 signaling pathway. Frontiers in Pharmacology. 2024; 15: 1497733. https://doi.org/10.3389/fphar.2024.1497733.

[125] Tang D, Kang R. NFE2L2 and ferroptosis resistance in cancer therapy. Cancer Drug Resistance. 2024; 7: 41. https://doi.org/10.20517/cdr.2024.123.

[126] Lin D, Zhang M, Luo C, Wei P, Cui K, Chen Z. Targeting Ferroptosis Attenuates Inflammation, Fibrosis, and Mast Cell Activation in Chronic Prostatitis. Journal of Immunology Research. 2022; 2022: 6833867. https://doi.org/10.1155/2022/6833867.

[127] Hishikawa D, Shindou H, Kobayashi S, Nakanishi H, Taguchi R, Shimizu T. Discovery of a lysophospholipid acyltransferase family essential for membrane asymmetry and diversity. Proceedings of the National Academy of Sciences of the United States of America. 2008; 105: 2830–2835. https://doi.org/10.1073/pnas.0712245105.

[128] Jiang L, Kon N, Li T, Wang SJ, Su T, Hibshoosh H, *et al*. Ferroptosis as a p53-mediated activity during tumour suppression. Nature. 2015; 520: 57–62. https://doi.org/10.1038/nature14344.

[129] Li T, Kon N, Jiang L, Tan M, Ludwig T, Zhao Y, *et al*. Tumor suppression in the absence of p53-mediated cell-cycle arrest, apoptosis, and senescence. Cell. 2012; 149: 1269–1283. https://doi.org/10.1016/j.cell.2012.04.026.

[130] Yang WH, Ding CKC, Sun T, Rupprecht G, Lin CC, Hsu D, *et al*. The Hippo Pathway Effector TAZ Regulates Ferroptosis in Renal Cell Carcinoma. Cell Reports. 2019; 28: 2501–2508.e4. https://doi.org/10.1016/j.celrep.2019.07.107.

[131] Lei M, Zhang YL, Huang FY, Chen HY, Chen MH, Wu RH, *et al*. Gankyrin inhibits ferroptosis through the p53/SLC7A11/GPX4 axis in triple-negative breast cancer cells. Scientific Reports. 2023; 13: 21916. https://doi.org/10.1038/s41598-023-49136-8.

[132] Punziano C, Trombetti S, Grosso M, Tornesello ML, Faraonio R. The Molecular Interplay Between p53-Mediated Ferroptosis and Non-Coding RNAs in Cancer. International Journal of Molecular Sciences. 2025; 26: 6588. https://doi.org/10.3390/ijms26146588.

[133] Hwang PM, Bunz F, Yu J, Rago C, Chan TA, Murphy MP, *et al*. Ferredoxin reductase affects p53-dependent, 5-fluorouracil-induced apoptosis in colorectal cancer cells. Nature Medicine. 2001; 7: 1111–1117. https://doi.org/10.1038/nm1001-1111.

[134] Wang M, Mao C, Ouyang L, Liu Y, Lai W, Liu N, *et al*. Long noncoding RNA LINC00336 inhibits ferroptosis in lung cancer by functioning as a competing endogenous RNA. Cell Death and Differentiation. 2019; 26: 2329–2343. https://doi.org/10.1038/s41418-019-0304-y.

[135] Lu J, Xu F, Lu H. LncRNA PVT1 regulates ferroptosis through miR-214-mediated TFR1 and p53. Life Sciences. 2020; 260: 118305. https://doi.org/10.1016/j.lfs.2020.118305.

[136] Olivero CE, Martínez-Terroba E, Zimmer J, Liao C, Tesfaye E, Hooshdaran N, *et al*. p53 Activates the Long Noncoding RNA Pvt1b to Inhibit Myc and Suppress Tumorigenesis. Molecular Cell. 2020; 77: 761–774.e8. https://doi.org/10.1016/j.molcel.2019.12.014.

[137] Xie Y, Zhu S, Song X, Sun X, Fan Y, Liu J, *et al*. The Tumor Suppressor p53 Limits Ferroptosis by Blocking DPP4 Activity. Cell Reports. 2017; 20: 1692–1704. https://doi.org/10.1016/j.celrep.2017.07.055.

[138] Tarangelo A, Magtanong L, Bieging-Rolett KT, Li Y, Ye J, Attardi LD, *et al*. p53 Suppresses Metabolic Stress-Induced Ferroptosis in Cancer Cells. Cell Reports. 2018; 22: 569–575. https://doi.org/10.1016/j.celrep.2017.12.077.

[139] Zhang DD. Mechanistic studies of the Nrf2-Keap1 signaling pathway. Drug Metabolism Reviews. 2006; 38: 769–789. https://doi.org/10.1080/03602530600971974.

[140] Rojo de la Vega M, Chapman E, Zhang DD. NRF2 and the Hallmarks of Cancer. Cancer Cell. 2018; 34: 21–43. https://doi.org/10.1016/j.ccell.2018.03.022.

[141] Dodson M, Castro-Portuguez R, Zhang DD. NRF2 plays a critical role in mitigating lipid peroxidation and ferroptosis. Redox Biology. 2019; 23: 101107. https://doi.org/10.1016/j.redox.2019.101107.

[142] Agyeman AS, Chaerkady R, Shaw PG, Davidson NE, Visvanathan K, Pandey A, *et al*. Transcriptomic and proteomic profiling of KEAP1 disrupted and sulforaphane-treated human breast epithelial cells reveals common expression profiles. Breast Cancer Research and Treatment. 2012; 132: 175–187. https://doi.org/10.1007/s10549-011-1536-9.

[143] Harada N, Kanayama M, Maruyama A, Yoshida A, Tazumi K, Hosoya T, *et al*. Nrf2 regulates ferroportin 1-mediated iron efflux and counteracts lipopolysaccharide-induced ferroportin 1 mRNA suppression in macrophages. Archives of Biochemistry and Biophysics. 2011; 508: 101–109. https://doi.org/10.1016/j.abb.2011.02.001.

[144] Itoh K, Mimura J, Yamamoto M. Discovery of the negative regulator of Nrf2, Keap1: a historical overview. Antioxidants & Redox Signaling. 2010; 13: 1665–1678. https://doi.org/10.1089/ars.2010.3222.

[145] Chan JY, Kwong M. Impaired expression of glutathione synthetic enzyme genes in mice with targeted deletion of the Nrf2 basic-leucine zipper protein. Biochimica et Biophysica Acta. 2000; 1517: 19–26. https://doi.org/10.1016/s0167-4781(00)00238-4.

[146] Sasaki H, Sato H, Kuriyama-Matsumura K, Sato K, Maebara K, Wang H, *et al*. Electrophile response element-mediated induction of the cystine/glutamate exchange transporter gene expression. The Journal of Biological Chemistry. 2002; 277:

44765–44771. https://doi.org/10.1074/jbc.M208704200.

[147] Kwak MK, Itoh K, Yamamoto M, Kensler TW. Enhanced expression of the transcription factor Nrf2 by cancer chemopreventive agents: role of antioxidant response element-like sequences in the nrf2 promoter. Molecular and Cellular Biology. 2002; 22: 2883–2892. https://doi.org/10.1128/MCB.22.9.2883-2892.2002.

[148] Li J, Jia B, Cheng Y, Song Y, Li Q, Luo C. Targeting Molecular Mediators of Ferroptosis and Oxidative Stress for Neurological Disorders. Oxidative Medicine and Cellular Longevity. 2022; 2022: 3999083. https://doi.org/10.1155/2022/3999083.

[149] Ma S, Meng Z, Chen R, Guan KL. The Hippo Pathway: Biology and Pathophysiology. Annual Review of Biochemistry. 2019; 88: 577–604. https://doi.org/10.1146/annurev-biochem-013118-111829.

[150] Lin CC, Yang WH, Lin YT, Tang X, Chen PH, Ding CKC, *et al*. DDR2 upregulation confers ferroptosis susceptibility of recurrent breast tumors through the Hippo pathway. Oncogene. 2021; 40: 2018–2034. https://doi.org/10.1038/s41388-021-01676-x.

[151] Yang WH, Chi JT. Hippo pathway effectors YAP/TAZ as novel determinants of ferroptosis. Molecular & Cellular Oncology. 2019; 7: 1699375. https://doi.org/10.1080/23723556.2019.1699375.

[152] Chen L, Min J, Wang F. Copper homeostasis and cuproptosis in health and disease. Signal Transduction and Targeted Therapy. 2022; 7: 378. https://doi.org/10.1038/s41392-022-01229-y.

[153] Liu R, Tang F, Zhang X, Fan J, Xiao D. Pyruvate dehydrogenase complex component B: A Gene Associated with Cuproptosis and Encoding the Beta Subunit of Pyruvate Dehydrogenase Is Involved in the Oxidative Decarboxylation Reaction. DNA and Cell Biology. 2025; 44: 537–547. https://doi.org/10.1177/10445498251365934.

[154] Huang Z, Liu Y, Zeng Y, Wang J, Sun S, Heng Tan CS, *et al*. Mitochondrial thermal proteome profiling reveals aberrant activation of pyruvate dehydrogenase upon cuproptosis. Cell Reports. 2025; 44: 115937. https://doi.org/10.1016/j.celrep.2025.115937.

[155] Huo S, Wang Q, Shi W, Peng L, Jiang Y, Zhu M, *et al*. ATF3/SPI1/SLC31A1 Signaling Promotes Cuproptosis Induced by Advanced Glycosylation End Products in Diabetic Myocardial Injury. International Journal of Molecular Sciences. 2023; 24: 1667. https://doi.org/10.3390/ijms24021667.

[156] Teschke R, Eickhoff A. Wilson Disease: Copper-Mediated Cuproptosis, Iron-Related Ferroptosis, and Clinical Highlights, with Comprehensive and Critical Analysis Update. International Journal of Molecular Sciences. 2024; 25: 4753. https://doi.org/10.3390/ijms25094753.

[157] Liu WQ, Lin WR, Yan L, Xu WH, Yang J. Copper homeostasis and cuproptosis in cancer immunity and therapy. Immunological Reviews. 2024; 321: 211–227. https://doi.org/10.1111/imr.13276.

[158] Ling W, Li S, Zhu Y, Wang X, Jiang D, Kang B. Inducers of Autophagy and Cell Death: Focus on Copper Metabolism. Ecotoxicology and Environmental Safety. 2025; 290: 117725. https://doi.org/10.1016/j.ecoenv.2025.117725.

[159] Herman S, Lipiński P, Ogórek M, Starzyński R, Grzmil P, Bednarz A, *et al*. Molecular Regulation of Copper Homeostasis in the Male Gonad during the Process of Spermatogenesis. International Journal of Molecular Sciences. 2020; 21: 9053. https://doi.org/10.3390/ijms21239053.

[160] Lin C, He J, Tong X, Song L. Copper homeostasis-associated gene PRNP regulates ferroptosis and immune infiltration in breast cancer. PloS One. 2023; 18: e0288091. https://doi.org/10.1371/journal.pone.0288091.

[161] Jiayi H, Ziyuan T, Tianhua X, Mingyu Z, Yutong M, Jingyu W, *et al*. Copper homeostasis in chronic kidney disease and its crosstalk with ferroptosis. Pharmacological Research. 2024; 202: 107139. https://doi.org/10.1016/j.phrs.2024.107139.

[162] Wang J, Zou Y, Guan R, Tan S, Su L, Zhao Z, *et al*. Copper supplementation alleviates hypoxia-induced ferroptosis and oxidative stress in neuronal cells. International Journal of Molecular Medicine. 2024; 54: 117. https://doi.org/10.3892/ijmm.2024.5441.

[163] Li H, Du X. Ferroptosis based on metal-organic frameworks for tumor therapy. Chemical Communications (Cambridge, England). 2025; 61: 17975–17988. https://doi.org/10.1039/d5cc05169j.

[164] Rao Z, Zhu Y, Yang P, Chen Z, Xia Y, Qiao C, *et al*. Pyroptosis in inflammatory diseases and cancer. Theranostics. 2022; 12: 4310–4329. https://doi.org/10.7150/thno.71086.

[165] Xiao Y, Zhao C, Tai Y, Li B, Lan T, Lai E, *et al*. STING mediates hepatocyte pyroptosis in liver fibrosis by Epigenetically activating the NLRP3 inflammasome. Redox Biology. 2023; 62: 102691. https://doi.org/10.1016/j.redox.2023.102691.

[166] Li X, Zhang Z, Han Y, Zhang M. NLRP3 inflammasome and pyroptosis: implications in inflammation and multisystem disorders. PeerJ. 2025; 13: e19887. https://doi.org/10.7717/peerj.19887.

[167] Xu Z, Kombe Kombe AJ, Deng S, Zhang H, Wu S, Ruan J, *et al*. NLRP inflammasomes in health and disease. Molecular Biomedicine. 2024; 5: 14. https://doi.org/10.1186/s43556-024-00179-x.

[168] Olsen MB, Gregersen I, Sandanger Ø, Yang K, Sokolova M, Halvorsen BE, *et al*. Targeting the Inflammasome in Cardiovascular Disease. JACC. Basic to Translational Science. 2021; 7: 84–98. https://doi.org/10.1016/j.jacbts.2021.08.006.

[169] Chen Y, Zeng D, Wei G, Liao Z, Liang R, Huang X, *et al*. Pyroptosis in Osteoarthritis: Molecular Mechanisms and Therapeutic Implications. Journal of Inflammation Research. 2024; 17: 791–803. https://doi.org/10.2147/JIR.S445573.

[170] Luo T, Zhou X, Qin M, Lin Y, Lin J, Chen G, *et al*. Corilagin Restrains NLRP3 Inflammasome Activation and Pyroptosis through the ROS/TXNIP/NLRP3 Pathway to Prevent Inflammation. Oxidative Medicine and Cellular Longevity. 2022; 2022: 1652244. https://doi.org/10.1155/2022/1652244.

[171] Wang XD, Kang S. Ferroptosis in myocardial infarction: not a marker but a maker. Open Biology. 2021; 11: 200367. https://doi.org/10.1098/rsob.200367.

[172] Zheng M, Zhang Q, Siebert HC, Loers G, Wen M, Wang Q, *et al*. Semaglutide attenuates Alzheimer's disease model progression by targeting microglial NLRP3 inflammasome-mediated neuroinflammation and ferroptosis. Experimental Neurology. 2026; 396: 115537. https://doi.org/10.1016/j.expneurol.2025.115537.

[173] Shao J, Bai Z, Zhang L, Zhang F. Ferrostatin-1 alleviates tissue and cell damage in diabetic retinopathy by improving the antioxidant capacity of the Xc^--GPX4 system. Cell Death Discovery. 2022; 8: 426. https://doi.org/10.1038/s41420-022-01141-y.

[174] Tong J, Lan XT, Zhang Z, Liu Y, Sun DY, Wang XJ, *et al*. Ferroptosis inhibitor liproxstatin-1 alleviates metabolic dysfunction-associated fatty liver disease in mice: potential involvement of PANoptosis. Acta Pharmacologica Sinica. 2023; 44: 1014–1028. https://doi.org/10.1038/s41401-022-01010-5.

[175] Wang ME, Chen J, Lu Y, Bawcom AR, Wu J, Ou J, *et al*. RB1-deficient prostate tumor growth and metastasis are vulnerable to ferroptosis induction via the E2F/ACSL4 axis. The Journal of Clinical Investigation. 2023; 133: e166647. https://doi.org/10.1172/JCI166647.

[176] Zhan M, Xu H, Yu G, Chen Q, Yang R, Chen Y, *et al*. Androgen receptor deficiency-induced TUG1 in suppressing ferroptosis to promote benign prostatic hyperplasia through the miR-188-3p/GPX4 signal pathway. Redox Biology. 2024; 75: 103298.

https://doi.org/10.1016/j.redox.2024.103298.

[177] Chen Y, He W, Wei H, Chang C, Yang L, Meng J, *et al*. Srs11-92, a ferrostatin-1 analog, improves oxidative stress and neuroinflammation via Nrf2 signal following cerebral ischemia/reperfusion injury. CNS Neuroscience & Therapeutics. 2023; 29: 1667–1677. https://doi.org/10.1111/cns.14130.

[178] Itoh H, Tani K, Sunahara H, Nemoto Y, Nakaichi M, Horikirizono H, *et al*. Sulfasalazine, a potent cystine-glutamate transporter inhibitor, enhances osteogenic differentiation of canine adipose-derived stem cells. The Journal of Veterinary Medical Science. 2023; 85: 1237–1244. https://doi.org/10.1292/jvms.22-0525.

[179] Lei L, Yuan J, Yang Q, Tu Q, Yu H, Chu L, *et al*. Curcumin-polydopamine nanoparticles alleviate ferroptosis by iron chelation and inhibition of oxidative stress damage. RSC Advances. 2024; 14: 14934–14941. https://doi.org/10.1039/d4ra02336f.

[180] Han R, Lan X, Han Z, Ren H, Aafreen S, Wang W, *et al*. Improving outcomes in intracerebral hemorrhage through microglia/macrophage-targeted IL-10 delivery with phosphatidylserine liposomes. Biomaterials. 2023; 301: 122277. https://doi.org/10.1016/j.biomaterials.2023.122277.

[181] Wang L, Zhu Y, Huang C, Pan Q, Wang J, Li H, *et al*. Targeting ferroptosis in cancer stem cells: A novel strategy to improve cancer treatment. Genes & Diseases. 2025; 12: 101678. https://doi.org/10.1016/j.gendis.2025.101678.

[182] Wong KH, Wang Y, Wang X, Yin Y, Feng K, Chen M. Unsaturated fatty acid-doped liposomes deliver piperine to deactivate defensive mechanism for ferroptosis in cancer therapy. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2025; 382: 113656. https://doi.org/10.1016/j.jconrel.2025.113656.

[183] Ruan Y, Zhuang H, Zeng X, Lin L, Wang X, Xue P, *et al*. Engineered Microbial Nanohybrids for Tumor-Mediated NIR II Photothermal Enhanced Ferroptosis/Cuproptosis and Immunotherapy. Advanced Healthcare Materials. 2024; 13: e2302537. https://doi.org/10.1002/adhm.202302537.

[184] Deng W, Shang H, Tong Y, Liu X, Huang Q, He Y, *et al*. The application of nanoparticles-based ferroptosis, pyroptosis and autophagy in cancer immunotherapy. Journal of Nanobiotechnology. 2024; 22: 97. https://doi.org/10.1186/s12951-024-02297-8.

[185] Zaffaroni N, Beretta GL. Nanoparticles for Ferroptosis Therapy in Cancer. Pharmaceutics. 2021; 13: 1785. https://doi.org/10.3390/pharmaceutics13111785.

[186] Miao H, Meng H, Zhang Y, Chen T, Zhang L, Cheng W. FSP1 inhibition enhances olaparib sensitivity in BRCA-proficient ovarian cancer patients via a nonferroptosis mechanism. Cell Death and Differentiation. 2024; 31: 497–510. https://doi.org/10.1038/s41418-024-01263-z.

[187] Hai Y, Fan R, Zhao T, Lin R, Zhuang J, Deng A, *et al*. A novel mitochondria-targeting DHODH inhibitor induces robust ferroptosis and alleviates immune suppression. Pharmacological Research. 2024; 202: 107115. https://doi.org/10.1016/j.phrs.2024.107115.

[188] Yang WH, Huang Z, Wu J, Ding CKC, Murphy SK, Chi JT. A TAZ-ANGPTL4-NOX2 Axis Regulates Ferroptotic Cell Death and Chemoresistance in Epithelial Ovarian Cancer. Molecular Cancer Research: MCR. 2020; 18: 79–90. https://doi.org/10.1158/1541-7786.MCR-19-0691.

[189] Wu J, Minikes AM, Gao M, Bian H, Li Y, Stockwell BR, *et al*. Intercellular interaction dictates cancer cell ferroptosis via NF2-YAP signaling [Erratum in: Nature. 2019; 572: E20. doi: 10.1038/s41586-019-1480-0]. Nature. 2019; 572: 402–406. https://doi.org/10.1038/s41586-019-1426-6.

[190] Li Y, Zeng X, Lu D, Yin M, Shan M, Gao Y. Erastin induces ferroptosis via ferroportin-mediated iron accumulation in endometriosis. Human Reproduction (Oxford, England). 2021; 36: 951–964. https://doi.org/10.1093/humrep/deaa363.

[191] Wei X, Huang Q, Huang J, Yu L, Chen J. Erastin induces ferroptosis in cervical cancer cells via Nrf2/HO-1 signaling pathway. International Journal of Immunopathology and Pharmacology. 2023; 37: 3946320231219348. https://doi.org/10.1177/03946320231219348.

[192] Yang L, Wang H, Yang X, Wu Q, An P, Jin X, *et al*. Auranofin mitigates systemic iron overload and induces ferroptosis via distinct mechanisms. Signal Transduction and Targeted Therapy. 2020; 5: 138. https://doi.org/10.1038/s41392-020-00253-0.

[193] Qi X, Wan Z, Jiang B, Ouyang Y, Feng W, Zhu H, *et al*. Inducing ferroptosis has the potential to overcome therapy resistance in breast cancer. Frontiers in Immunology. 2022; 13: 1038225. https://doi.org/10.3389/fimmu.2022.1038225.

[194] Chu J, Jiang Y, Zhou W, Zhang J, Li H, Yu Y, *et al*. Acetaminophen alleviates ferroptosis in mice with sepsis-associated encephalopathy via the GPX4 pathway. Human & Experimental Toxicology. 2022; 41: 9603271221133547. https://doi.org/10.1177/09603271221133547.

[195] Luo Y, Yan P, Li X, Hou J, Wang Y, Zhou S. pH-Sensitive Polymeric Vesicles for GOx/BSO Delivery and Synergetic Starvation-Ferroptosis Therapy of Tumor. Biomacromolecules. 2021; 22: 4383–4394. https://doi.org/10.1021/acs.biomac.1c00960.

[196] Huan H, Lyamzaev KG, Panteleeva AA, Chernyak BV. Mitochondrial lipid peroxidation is necessary but not sufficient for induction of ferroptosis. Frontiers in Cell and Developmental Biology. 2024; 12: 1452824. https://doi.org/10.3389/fcell.2024.1452824.

[197] Zhao C, Yu Y, Yin G, Xu C, Wang J, Wang L, *et al*. Sulfasalazine promotes ferroptosis through AKT-ERK1/2 and P53-SLC7A11 in rheumatoid arthritis. Inflammopharmacology. 2024; 32: 1277–1294. https://doi.org/10.1007/s10787-024-01439-6.

[198] Zhang Y, Huang Z, Cheng J, Pan H, Lin T, Shen X, *et al*. Platelet-Vesicles-Encapsulated RSL-3 Enable Anti-Angiogenesis and Induce Ferroptosis to Inhibit Pancreatic Cancer Progress. Frontiers in Endocrinology. 2022; 13: 865655. https://doi.org/10.3389/fendo.2022.865655.

[199] Cheff DM, Huang C, Scholzen KC, Gencheva R, Ronzetti MH, Cheng Q, *et al*. The ferroptosis inducing compounds RSL3 and ML162 are not direct inhibitors of GPX4 but of TXNRD1. Redox Biology. 2023; 62: 102703. https://doi.org/10.1016/j.redox.2023.102703.

[200] Wang H, Wang C, Li B, Zheng C, Liu G, Liu Z, *et al*. Discovery of ML210-Based glutathione peroxidase 4 (GPX4) degrader inducing ferroptosis of human cancer cells. European Journal of Medicinal Chemistry. 2023; 254: 115343. https://doi.org/10.1016/j.ejmech.2023.115343.

[201] Sun Y, Berleth N, Wu W, Schlütermann D, Deitersen J, Stuhldreier F, *et al*. Fin56-induced ferroptosis is supported by autophagy-mediated GPX4 degradation and functions synergistically with mTOR inhibition to kill bladder cancer cells. Cell Death & Disease. 2021; 12: 1028. https://doi.org/10.1038/s41419-021-04306-2.

[202] Costa I, Barbosa DJ, Benfeito S, Silva V, Chavarria D, Borges F, *et al*. Molecular mechanisms of ferroptosis and their involvement in brain diseases. Pharmacology & Therapeutics. 2023; 244: 108373. https://doi.org/10.1016/j.pharmthera.2023.108373.

[203] Lin Q, Li S, Jin H, Cai H, Zhu X, Yang Y, *et al*. Mitophagy alleviates cisplatin-induced renal tubular epithelial cell ferroptosis through ROS/HO-1/GPX4 axis. International Journal of Biological Sciences. 2023; 19: 1192–1210. https://doi.org/10.7150/ijbs.80775.

[204] Zheng J, Sato M, Mishima E, Sato H, Proneth B, Conrad M. Sorafenib fails to trigger ferroptosis across a wide range of cancer cell lines. Cell Death & Disease. 2021; 12: 698. https://doi.org/10.1038/s41419-021-03998-w.

[205] Xavier da Silva TN, Schulte C, Alves AN, Maric HM, Friedmann Angeli JP. Molecular characterization of AIFM2/FSP1 inhibition by iFSP1-like molecules. Cell Death & Disease. 2023; 14: 281. https://doi.org/10.1038/s41419-023-05787-z.

[206] Shi Y, Fan G, Yang E, Zhang Y, Ding H, Tian J, *et al*. Enhanced efficacy of immune checkpoint inhibitors by folate-targeted multifunctional drug through synergistic therapy inducing ferroptosis and immunogenic cell death in bladder cancer. Materials Today. Bio. 2025; 31: 101584. https://doi.org/10.1016/j.mtbio.2025.101584.

[207] Yong Y, Yan L, Wei J, Feng C, Yu L, Wu J, *et al*. A novel ferroptosis inhibitor, Thonningianin A, improves Alzheimer's disease by activating GPX4. Theranostics. 2024; 14: 6161–6184. https://doi.org/10.7150/thno.98172.

[208] Kalishwaralal K, Patil P, Mali A. Ferroptosis-targeting compounds modulate cancer cell cytotoxicity and migration: Insights from in vitro and in silico analyses. Journal of Trace Elements in Medicine and Biology: Organ of the Society for Minerals and Trace Elements (GMS). 2025; 92: 127770. https://doi.org/10.1016/j.jtemb.2025.127770.

[209] Cotticelli MG, Xia S, Lin D, Lee T, Terrab L, Wipf P, *et al*. Ferroptosis as a Novel Therapeutic Target for Friedreich's Ataxia. The Journal of Pharmacology and Experimental Therapeutics. 2019; 369: 47–54. https://doi.org/10.1124/jpet.118.252759.

[210] Xie J, Luo D, Xing P, Ding W. The Dual Roles of STAT3 in Ferroptosis: Mechanism, Regulation and Therapeutic Potential. Journal of Inflammation Research. 2025; 18: 4251–4266. https://doi.org/10.2147/JIR.S506964.

[211] Shi W, Yuan S, Cheng G, Zhang H, Liu KJ, Ji X, et al. Blood brain barrier-targeted lipid nanoparticles improved the neuroprotection of Ferrostatin-1 against cerebral ischemic damage in an experimental stroke model. Experimental neurology. 2024; 379: 114849. https://doi.org/10.1016/j.expneurol.2024.114849.

[212] Srinivasamurthy SK, Mittal P, Goyal A, Ballal S, Maharana L, Goyal K, *et al*. Ferroptosis and iron homeostasis in chronic obstructive pulmonary disease: Therapeutic opportunities of iron chelators. Journal of Trace Elements in Medicine and Biology: Organ of the Society for Minerals and Trace Elements (GMS). 2025; 92: 127766. https://doi.org/10.1016/j.jtemb.2025.127766.

[213] Zou Y, Henry WS, Ricq EL, Graham ET, Phadnis VV, Maretich P, *et al*. Plasticity of ether lipids promotes ferroptosis susceptibility and evasion. Nature. 2020; 585: 603–608. https://doi.org/10.1038/s41586-020-2732-8.

[214] Morgan PK, Pernes G, Huynh K, Giles C, Paul S, Smith AAT, *et al*. A lipid atlas of human and mouse immune cells provides insights into ferroptosis susceptibility. Nature Cell Biology. 2024; 26: 645–659. https://doi.org/10.1038/s41556-024-01377-z.

[215] Ma XH, Liu JHZ, Liu CY, Sun WY, Duan WJ, Wang G, *et al*. ALOX15-launched PUFA-phospholipids peroxidation increases the susceptibility of ferroptosis in ischemia-induced myocardial damage. Signal Transduction and Targeted Therapy. 2022; 7: 288. https://doi.org/10.1038/s41392-022-01090-z.

[216] Bi G, Liang J, Bian Y, Shan G, Ren S, Shi H, *et al*. Targeting ALDH16A1 mediated thioredoxin lysosomal degradation to enhance ferroptosis susceptibility in SMARCA4-deficient NSCLC. Nature Communications. 2025; 16: 8181. https://doi.org/10.1038/s41467-025-63687-6.

[217] Rui T, Wang H, Li Q, Cheng Y, Gao Y, Fang X, *et al*. Deletion of ferritin H in neurons counteracts the protective effect of melatonin against traumatic brain injury-induced ferroptosis. Journal of Pineal Research. 2021; 70: e12704. https://doi.org/10.1111/jpi.12704.

[218] Lin XM, Pan MH, Sun J, Wang M, Huang ZH, Wang G, *et al*. Membrane phospholipid peroxidation promotes loss of dopaminergic neurons in psychological stress-induced Parkinson's disease susceptibility. Aging Cell. 2023; 22: e13970. https://doi.org/10.1111/acel.13970.

[219] Shahid MM, Hohman G, Eldeeb M. Fine-Tuning Ferroptosis by Modulating GPX4 and Its Potential in Mitigating Neuronal Degeneration in Parkinson's Disease. Chembiochem: a European Journal of Chemical Biology. 2025; 26: e202401052. https://doi.org/10.1002/cbic.202401052.

[220] Packer M. Iron homeostasis, recycling and vulnerability in the stressed kidney: A neglected dimension of iron-deficient heart failure. European Journal of Heart Failure. 2024; 26: 1631–1641. https://doi.org/10.1002/ejhf.3238.

[221] He F, Zhang P, Liu J, Wang R, Kaufman RJ, Yaden BC, *et al*. ATF4 suppresses hepatocarcinogenesis by inducing SLC7A11 (xCT) to block stress-related ferroptosis. Journal of Hepatology. 2023; 79: 362–377. https://doi.org/10.1016/j.jhep.2023.03.016.

[222] Yu Y, Jiang L, Wang H, Shen Z, Cheng Q, Zhang P, *et al*. Hepatic transferrin plays a role in systemic iron homeostasis and liver ferroptosis. Blood. 2020; 136: 726–739. https://doi.org/10.1182/blood.2019002907.

[223] Gupta G, Bhat AA, Goyal A, Singla N, Gupta S, Sharma S, *et al*. Exploring ACSL4/LPCAT3/ALOX15 and SLC7A11/GPX4/NFE2L2 as potential targets in ferroptosis-based cancer therapy. Future Medicinal Chemistry. 2023; 15: 1209–1212. https://doi.org/10.4155/fmc-2023-0125.

[224] Zhang X, Zhang Y, Wei J, Li X, Jiang A, Shen Y, et al. The Role of SLC7A11 in Tumor Progression and the Regulation Mechanisms Involved in Ferroptosis. Cancer management and research. 2025; 17: 2393–2401. https://doi.org/10.2147/CMAR.S551549.

[225] Wang J, Wang M, Wu S, Zhu Y, Fan K, Chen Y, *et al*. Tumor suppressor BAP1 suppresses disulfidptosis through the regulation of SLC7A11 and NADPH levels. Oncogenesis. 2024; 13: 31. https://doi.org/10.1038/s41389-024-00535-0.

[226] Cheng P, Xia R, Wang X. Ferroptosis: a promising target for fumarate hydratase-deficient tumor therapeutics literature review. Translational Cancer Research. 2024; 13: 3126–3141. https://doi.org/10.21037/tcr-24-21.

[227] Wang F, Chen Z, Zhou Q, Sun Q, Zheng N, Chen Z, *et al*. Implications of liquid-liquid phase separation and ferroptosis in Alzheimer's disease. Neuropharmacology. 2024; 259: 110083. https://doi.org/10.1016/j.neuropharm.2024.110083.

[228] Zhou M, Xu K, Ge J, Luo X, Wu M, Wang N, *et al*. Targeting Ferroptosis in Parkinson's Disease: Mechanisms and Emerging Therapeutic Strategies. International Journal of Molecular Sciences. 2024; 25: 13042. https://doi.org/10.3390/ijms252313042.

[229] Yi Y, Jia P, Xie P, Peng X, Zhu X, Yin S, *et al*. Beyond oxidative stress: Ferroptosis as a novel orchestrator in neurodegenerative disorders. Frontiers in Immunology. 2025; 16: 1683876. https://doi.org/10.3389/fimmu.2025.1683876.

[230] Sheng YC, Huang JN, Wu WL, Wan XR, Wang J, Qin ZH, *et al*. TIGAR plays neuroprotective roles in MPP^+/MPTP-induced Parkinson's disease by alleviating ferroptosis. European Journal of Pharmacology. 2025; 995: 177430. https://doi.org/10.1016/j.ejphar.2025.177430.

[231] Chen KJ, Zhang Y, Zhu XY, Yu S, Xie Y, Jin CJ, *et al*. GSTM1 suppresses cardiac fibrosis post-myocardial infarction through inhibiting lipid peroxidation and ferroptosis. Military Medical Research. 2025; 12: 26. https://doi.org/10.1186/s40779-025-00610-6.

[232] Gong S, Zhang A, Yao M, Xin W, Guan X, Qin S, *et al*.

REST contributes to AKI-to-CKD transition through inducing ferroptosis in renal tubular epithelial cells. JCI Insight. 2023; 8: e166001. https://doi.org/10.1172/jci.insight.166001.

[233] Lillo-Moya J, Rojas-Solé C, Muñoz-Salamanca D, Panieri E, Saso L, Rodrigo R. Targeting Ferroptosis against Ischemia/Reperfusion Cardiac Injury. Antioxidants (Basel, Switzerland). 2021; 10: 667. https://doi.org/10.3390/antiox10050667.

[234] Guan Q, Wang Z, Hu K, Cao J, Dong Y, Chen Y. Melatonin Ameliorates Hepatic Ferroptosis in NAFLD by Inhibiting ER Stress via the MT2/cAMP/PKA/IRE1 Signaling Pathway. International Journal of Biological Sciences. 2023; 19: 3937–3950. https://doi.org/10.7150/ijbs.85883.

[235] Huang Y, Jin Y, Hu J, Li M, Tian M, Zeng G, *et al*. Ferritinophagy Is Involved in the Advanced Glycation End Products-Induced Ferroptosis of Vascular Endothelial Cells in Diabetes Mellitus. Journal of Cellular and Molecular Medicine. 2025; 29: e70857. https://doi.org/10.1111/jcmm.70857.