**The international consensus on the molecular ecosystem regulating ferroptosis**

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**Abstract**

Ferroptosis, an intricately regulated form of cell death characterized by uncontrolled lipid peroxidation, has garnered substantial interest since its discovery in 2012. Recent years have witnessed remarkable progress in elucidating the detailed molecular mechanisms governing ferroptosis induction and defense, with particular emphasis on the roles of heterogeneity and plasticity, especially within the GPX4-dependent and -independent pathways. These advancements have substantially deepened our comprehension of ferroptosis and concomitantly unveiled promising therapeutic opportunities. Nevertheless, despite these accomplishments, several notable challenges persist, underscoring the urgent need for precisely targeted agents, reliable biomarkers, optimized drug delivery systems, and carefully designed clinical trial. Within the molecular ecosystem of ferroptosis, present and future advancements promise to unlock highly effective and nontoxic therapeutic strategies across a broad spectrum of diseases.

**Introduction**

Cellular demise is a fundamental process that determines cell numbers and encompasses various forms, including accidental cell death and regulated cell death (Galluzzi et al., 2018). Ferroptosis stands out as a notable form of regulated cell death, initially identified in 2012 as an iron-dependent modality observed in cancer cells (e.g., HT-1080, Calu-1, and BJeLR cells) harboring oncogenic *RAS* mutations (Dixon et al., 2012). Ferroptosis differs from apoptosis, which relies on caspase activation, and necroptosis, which involves mixed lineage kinase domain like pseudokinase (MLKL) signaling, because it does not involve caspases or MLKL (Dixon et al., 2012; Muller et al., 2017).

In recent times, remarkable progress has been made in the field of ferroptosis research, broadening its scope from cancer cells to encompass non-cancerous cells and tissues (Bayir et al., 2023; Chen et al., 2021c; Jiang et al., 2021; Lei et al., 2022; Stockwell, 2022; Tang et al., 2021). Ferroptosis is currently acknowledged as a form of regulated necrosis characterized by oxidative damage to cell membranes. Distinguishing itself from other lytic cell death mechanisms that depend on pore-forming proteins (e.g., the gasdermin family), ferroptosis is propelled by the accumulation of toxic lipids or their metabolic byproducts, including 4-hydroxynonenal (4HNE) (Chen et al., 2022b). Dysregulation of cellular iron and lipid metabolism contributes to all stages of ferroptosis. In particular, the compromised activity of antioxidant enzymes responsible for neutralizing lipid peroxides leads to the uncontrolled accumulation of these toxic products, resulting in severe membrane damage (Yang and Stockwell, 2016).

Phospholipids serve as the essential building blocks that form the structural framework of cell membranes (Dowhan, 2017). In the context of ferroptosis, the accumulation of lipid peroxides derived from phospholipids containing polyunsaturated fatty acids (PUFA) causes damage to the cell membranes (Mortensen et al., 2023; Yang et al., 2016). This damage disrupts the integrity and functionality of cells, resulting in various cellular dysfunctions (Riegman et al., 2020). Permeabilization of the cell membrane causes the release of cellular contents, including molecules known as damage-associated molecular patterns (DAMPs) (Wiernicki et al., 2022). DAMPs play a multifaceted role in signaling cellular damage and regulating immune responses, resulting in either immunostimulation or immunosuppression (Gong et al., 2020).

Ferroptosis holds extensive implications in preclinical studies encompassing various diseases, including cancer, neurodegenerative disorders, and conditions associated with ischemia-reperfusion injury (Chen et al., 2021c; Jiang et al., 2021; Yan et al., 2020b). The manipulation of ferroptosis has emerged as a promising therapeutic approach, particularly for the elimination of drug-resistant cancer cells with deficiencies in apoptosis (Hangauer et al., 2017; Viswanathan et al., 2017). Conversely, pharmacological inhibition of ferroptosis shows potential in mitigating infection-related diseases associated with iron overload or lipid toxicity (Amaral et al., 2019; Li et al., 2021d; Wang et al., 2022c; Yao et al., 2021b). Furthermore, beyond its role in pathological processes, ferroptosis is believed to play a crucial role in normal physiological functions, such as tissue homeostasis and development (Friedmann Angeli et al., 2014; Matsushita et al., 2015; Muri et al., 2019). Therefore, comprehending the intricate molecular mechanisms underlying ferroptosis, particularly its relationship with oxidative stress and the antioxidant defense, is essential for developing effective therapeutic strategies.

Oxidation is a chemical process that generates reactive free radicals, leading to cellular damage through the oxidation of essential components, such as DNA, proteins, and lipids. The body's antioxidant system, consisting of enzymes like glutathione peroxidase (GPX), superoxide dismutase (SOD), and catalase, as well as non-enzymatic antioxidants such as vitamin E, glutathione (GSH), and ubiquinol, plays a pivotal role in counteracting free radicals and mitigating their harmful effects. Recent studies have shed light on the involvement of multiple antioxidant systems in safeguarding against oxidative damage during ferroptotic stress. These systems include the classical glutathione peroxidase 4 (GPX4) pathway (Ingold et al., 2018; Yang et al., 2014) and alternative GPX4-independent pathways (Bersuker et al., 2019; Doll et al., 2019; Liang et al., 2023; Mao et al., 2021; Nakamura et al., 2023), highlighting the complexity and adaptability of the mechanisms involved.

In this review, our primary objective is to provide an updated overview of the fundamental mechanisms underlying ferroptosis, shedding light on its core processes as well as its heterogeneity and plasticity. Moreover, we will explore the evolving understanding of the pivotal role played by the integrated antioxidant and membrane system in regulating ferroptotic sensitivity. Additionally, we will delve into the potential disease implications, therapeutic opportunities, and challenges that emerge from targeting this interconnected ecosystem.

**The discovery and mechanism of ferroptosis**

Cell death research often relies on classical cell lines and stimulations to investigate the core mechanisms. With a near-diploid karyotype and a well-defined genetic background, human fibrosarcoma HT-1080 cells offer a relatively simple system for manipulating and analyzing specific genes, providing valuable insights into cell death pathways, including ferroptosis (Dixon et al., 2012). Erastin and RSL3 are the two most commonly used small molecule compounds to induce ferroptosis (Conrad and Pratt, 2019). Originally identified in screenings targeting *RAS* mutation cancer cells, these compounds trigger iron accumulation, leading to oxidative stress through the Fenton reaction (Dolma et al., 2003). This iron-dependent and non-apoptotic process coined the term "ferroptosis" (Dixon et al., 2012). These early findings have highlighted the potential of ferroptosis induction as a precise cancer therapy, selectively targeting *RAS* mutations while sparing normal cells.

Further research has revealed that the mechanism of ferroptosis is highly context-dependent. Phenotypes initially not considered to be associated with ferroptosis have been found to play a role in this form of cell death in specific conditions. For instance, zinc and copper, in addition to iron, induce ferroptosis in specific conditions. In a genome-wide RNAi screen investigating zinc-related genes and their association with ferroptosis, solute carrier family 39 member 7 (SLC39A7) was identified as a novel genetic determinant (Chen et al., 2021b). SLC39A7 encodes ZIP7, a protein responsible for transporting zinc from the endoplasmic reticulum (ER) to the cytosol. This discovery revealed that SLC39A7 drives zinc supplementation-induced ferroptosis in human breast adenocarcinoma MDA-MB-231 and HT-1080 cells (Chen et al., 2021b). In human pancreatic cancer cells, exogenous copper can increase the ubiquitination of GPX4 and the formation of GPX4 aggregates by directly binding to specific cysteines (C107 and C148) on the GPX4 protein (Xue et al., 2023). This interaction subsequently leads to Tax1 binding protein 1 (TAX1BP1)-dependent autophagic degradation of GPX4, contributing to ferroptosis (Xue et al., 2023). Thus, metal ions involved in ferroptosis are not only limited to the Fenton reaction. Consistently with this idea, iron can promote ferroptosis by activating iron-containing enzymes, such as the arachidonate lipoxygenases (ALOX) family (Sun et al., 2019).

Additionally, both *RAS* wild-type and *RAS* mutation cells, including cancer and non-cancer cells, can undergo ferroptotic death. Conditional knockout of *Gpx4* in certain tissues (e.g., kidney (Friedmann Angeli et al., 2014)) or cells (e.g., T cells (Matsushita et al., 2015) or B cells (Muri et al., 2019)) can cause ferroptotic damage in mice. Mitochondrial reactive oxygen species (ROS), rather than lipid ROS, also play a significant role in ferroptosis induction. For instance, the induction of ferroptosis in SV40-transformed fibroblast (MRC5-SV40) by erastin can be inhibited by mitochondrial ROS inhibitors like SkQ1, MitoTEMPO, and methylene blue (Lyamzaev et al., 2023). Of note in cancer and non-cancer cells, mitochondrial GPX4 may inhibit both ferroptosis and apoptosis induced by mitochondrial ROS (Azuma et al., 2022; Mao et al., 2021; Oh et al., 2022; Tadokoro et al., 2020), although cytosolic GPX4 is the predominant form in many cells or tissues. A challenge is that current GPX4 inhibitors (e.g., RSL3 and ML210 (Eaton et al., 2020)) cannot distinguish between the different subcellular forms of GPX4, including cytosolic, mitochondrial, and nuclear GPX4. Although the levels of mitochondrial and nuclear GPX4 are relatively low, it cannot be excluded that these pools of GPX4 play an important physiological and pathological role, requiring further investigation.

Ferroptosis is intricately connected to autophagy, and heightened levels of autophagy often correlate with increased sensitivity to ferroptosis. For instance, a screening involving 60 different cancer cell resources revealed that cells constitutively or inducibly expressing high levels of microtubule-associated protein 1 light chain 3 alpha/beta (MAP1LC3A/B-II), a marker of autophagosome (Kabeya et al., 2000), displayed heightened susceptibility to ferroptotic death (Li et al., 2021c). Specific types of selective autophagy, such as ferritinophagy (Gao et al., 2016; Hou et al., 2016), lipophagy (Bai et al., 2019; You et al., 2021), and clockophagy (Yang et al., 2019), can selectively degrade iron storage protein ferritin, lipid droplets, and circadian clock proteins, respectively. This degradation process favors iron accumulation and lipid peroxidation, leading to the induction of ferroptosis in cancer cells (e.g., human pancreatic cancer cells) or non-cancer cells (e.g., mouse embryonic fibroblasts or neuronal cells). Genome-wide CRISPRi/a screens in human neurons revealed that so-called autophagy-related (ATG) family members (e.g., beclin 1 [BECN1]) and lysosomal proteins (e.g., prosaposin [PSAP]) are involved in ferroptosis by triggering the formation of lipofuscin or increasing iron accumulation (Tian et al., 2021). Of note, certain forms of selective autophagy (e.g., reticulophagy (Liu et al., 2022d) and lysophagy (Li et al., 2022a)) can play a protective role against ferroptosis by selectively degrading pro-ferroptotic organelles or factors. In certain conditions, the depletion of *ATG* has no effect on cell death, including ferroptosis. These findings support the idea that autophagy plays a complex, context-dependent role in modulating stress responses (Kroemer et al., 2010).

While these findings emphasize the adaptable and context-dependent nature of ferroptosis, its ignition involves three essential elements, which will be elaborated below.

***Reactive oxygen species***

The first crucial element in ferroptosis induction is the presence of initiation signals that stimulate the production of ROS. ROS, which are byproducts of cellular metabolism, are generated from various sources (**Fig. 1**):

1) Mitochondria: Mitochondria serve as a major source of ROS. During oxidative phosphorylation, electron leakage from the electron transport chain leads to the generation of primary ROS, such as superoxide anion (O2•-). Mitochondrial SOD converts superoxide into other ROS, including hydrogen peroxide (H2O2). As mentioned earlier, mitochondrial ROS can trigger ferroptosis under certain conditions. The quality of mitochondria is regulated by a process called mitophagy, which involves the autophagic destruction of damaged or dysfunctional mitochondria. Increased mitophagy has a context-dependent dual role in promoting or inhibiting ferroptosis (Basit et al., 2017; Feng et al., 2022a; Li et al., 2023a; Li et al., 2021f; Yu et al., 2022). While mitochondrial fission promotes apoptosis (Lee et al., 2004), mitochondrial fusion can increase cellular sensitivity to ferroptosis (Li et al., 2021a). Although the exact mechanism underlying the impact of mitochondrial dynamics on ferroptosis is not yet fully understood, one hypothesis suggests that the activation of mitochondrial stimulator of interferon response CGAMP interactor 1 (STING1) promotes mitofusin 1/2 (MFN1/2)-dependent mitochondrial fusion (Li et al., 2021a). Excessive mitochondrial fusion, in turn, leads to the production of pro-ferroptotic ROS in pancreatic cancer cells (Li et al., 2021a). Mitochondrial energy stress inhibits ferroptosis through AMP-activated protein kinase (AMPK)-mediated phosphorylation of acetyl-CoA carboxylase alpha (ACACA, also known as ACC), an enzyme that catalyzes the conversion of acetyl coenzyme A to malonyl coenzyme A (Lee et al., 2020). However, AMPK can also promote ferroptosis by phosphorylating different substrates, such as BECN1 (Song et al., 2018) or by disrupting pyrimidinosome assembly, consequently inhibiting the synthesis of pyrimidine intermediates, namely dihydroorotate and orotate (Yang et al., 2023a). Further elucidation of the metabolic and dynamic roles of mitochondria may unmask their influence on ferroptosis and non-ferroptotic cell death (Bock and Tait, 2020; Gao et al., 2019b; Li et al., 2021b; Qiu et al., 2023).

2) NADPH oxidases (NOX): NOX enzymes, located in cell membranes, transfer electrons from NADPH to molecular oxygen, leading to the production of superoxide. These NOX-generated ROS serve critical functions in cell signaling, immune responses, and host defense mechanisms (Bedard and Krause, 2007). When NOX is overexpressed, it can deplete NADPH and increase the levels of oxidative free radicals, thereby heightening sensitivity to ferroptosis (Wang et al., 2020; Xie et al., 2017; Yang et al., 2020). The activity of NOX in ferroptosis is regulated by multiple factors. For example, tumor protein p53 (TP53), a tumor suppressor protein, can inhibit ferroptosis in human colorectal cancer cells by binding to dipeptidyl peptidase 4 (DPP4) (Xie et al., 2017). Conversely, *Tp53* deficiency promotes the accumulation of DPP4 on the cell membrane, where it forms a complex with NOX1, resulting in oxidative damage (Xie et al., 2017). Arachidonic acid also possesses the ability to enhance NOX1 activity through its phosphorylation by protein kinase C (PKC), thereby promoting the production of ROS (Shiose and Sumimoto, 2000). 4HNE, a byproduct of lipid peroxidation, further enhances NOX1 activity, inducing ferroptosis in HT-1080 and Calu1 lung cancer cells (Chen et al., 2022b). Interestingly, the ferroptosis-inducing effect of NOX1 activity can be inhibited by aldehyde dehydrogenase 1 family member B1 ALDH1B1 (Chen et al., 2022b). ALDH1B1 catalyzes the oxidation of aldehydes, converting them into their corresponding carboxylic acids. This process is related to colorectal and pancreatic tumor development (Feng et al., 2022b; Mameishvili et al., 2019). Given the diverse members of the NOX family (Bedard and Krause, 2007), further investigation is necessary to understand their selective modulation in different cellular contexts.

3) Enzymatic reactions: ROS can be generated as byproducts of various enzymatic reactions. One example is the cytochrome P450 enzyme family, which is involved in drug metabolism and detoxification, and can produce ROS during their catalytic cycles. An important member of this family, cytochrome P450 oxidoreductase (POR), has been identified through CRISPR-Cas9 screening as a pro-ferroptotic promoter of ROS production and lipid peroxidation (Yan et al., 2020a; Zou et al., 2020b). It is worth noting that not all cytochrome P450 enzymes promote ferroptosis. Thus, the expression of cytochrome P450 family 1 subfamily B member 1 (CYP1B1) in colorectal cancer cells results in ferroptosis inhibition (Chen et al., 2023a). This inhibition is believed to occur through the degradation of acyl-CoA synthetase long-chain family member 4 (ACSL4) mediated by the ubiquitin E3 ligase subunit F-box protein 10 (FBXO10) (Chen et al., 2023a).

4) The Fenton reaction. It involves the interaction between H2O2 and a transition metal, typically iron (Fe2+), leading to the generation of highly reactive hydroxyl radicals (•OH) (Abe et al., 2022). Cellular iron levels are tightly regulated at the levels of iron uptake, transformation, storage, and export. Deregulation of each of these steps of iron metabolism can result in iron accumulation, thereby activating the Fenton reaction and increasing susceptibility to ferroptosis (Chen et al., 2020). One extensively studied mechanism is ferritinophagy, which involves the degradation of the iron storage protein ferritin by autophagy (Mancias et al., 2014). Through the liberation of free iron, this process triggers the production of ROS and subsequently induces ferroptosis in cancer and non-cancer cells (Gao et al., 2016; Hou et al., 2016). Ferritinophagy has implications for the susceptibility of malignant cells to ferroptosis, as well as for inflammation and metabolic disorders associated with dysregulated iron homeostasis (Anandhan et al., 2023; Hong et al., 2022; Liu et al., 2023a; Qin et al., 2021; Wu et al., 2023a; Zhou et al., 2022; Zhu et al., 2023b).

The diverse origins of ROS concur to determine to the oxidative environment required for initiating ferroptosis. The exploration of the rules dictating ROS generation and detoxification in different subcellular compartments provides valuable insights into the mechanisms of ferroptotic cell death. An unanswered question is whether the threshold of ROS levels differs between ferroptosis and other oxidative cell death pathways.

***Oxidizable lipids***

The second essential element in ferroptosis is the presence of easily oxidizable (e.g., polyunsaturated) lipids (**Fig. 2**). Cell membranes, being the primary target of oxidative damage in ferroptosis, can be influenced by metabolic pathways that promote lipid synthesis, particularly the generation of PUFAs (Xin and Schick, 2023). Such pathways enhance cell sensitivity to ferroptotic inducers like erastin or RSL3. A key positive regulator involved in ferroptosis is ACSL4, an enzyme belonging to the ACSL family (Doll et al., 2017; Kagan et al., 2017; Yuan et al., 2016). ACSL4 drives the activation of long-chain fatty acids by converting them into acyl-CoA esters, which then can be introduced into in various metabolic pathways. ACSL4 specifically acts on long-chain fatty acids containing 12 to 20 carbon atoms and primarily localizes at the ER membrane. The acyl-CoA esters produced by ACSL4 can serve as substrates for lipid peroxidation, thereby contributing to the initiation of ferroptosis (Doll et al., 2017; Kagan et al., 2017; Yuan et al., 2016).

Two downstream pathways mediated by ACSL4 result in the production of different PUFA-related acyl-CoA esters. One pathway involves lysophosphatidylcholine acyltransferase 3 (LPCAT3), which incorporates PUFA into phosphatidylethanolamines (PEs) (Cui et al., 2023; Gupta et al., 2023; Kagan et al., 2017). The other pathway involves the activation of sterol O-acyltransferase 1 (SOAT1), leading to the production of PUFA-cholesteryl esters (CEs) instead of PUFA-Pes (Lin et al., 2022b). Both pathways contribute to lipid peroxidation, with PUFA-PEs and PUFA-CEs serving as substrates. Additionally, in human pancreatic cancer cells lacking the lipid flippase solute carrier family 47 member 1 (SLC47A1), ACSL4-mediated PUFA-CE production is particularly relevant (Lin et al., 2022b). Accordingly, activating ACSL4-dependent ferroptosis is a strategy to enhance the effectiveness of chemotherapy or immunotherapy in solid cancers (Liao et al., 2022; Wang et al., 2023c). The activity of ACSL4 can be enhanced by protein kinase C beta (PRKCB, also known as PKCβII), which catalyzes the phosphorylation of ACSL4 at Thr328 (Zhang et al., 2022a). Phosphorylation of hippocalcin like 1 (HPCAL1) on Thr149 by protein kinase C theta (PRKCQ) promotes ferroptosis by inducing autophagic degradation of cadherin 2 (CDH2), leading to alterations in membrane tension in cancer cells (Chen et al., 2023b). However, the activation of kinases of the PKC family can also inhibit oxytosis and ferroptosis in neuronal and malignant cells (Davis and Maher, 1994; Sun et al., 2015). This indicates that the phosphorylation of distinct protein substrates by different PKC family members can result in positive or negative modulation of ferroptosis.

ACSL3 plays a crucial role in synthesizing monounsaturated fatty acids (MUFAs) that competitively inhibit the peroxidation of polyunsaturated fatty acids (PUFAs) due to the structural inertness of MUFAs. This observation underscores the significant potential of ACSL3-mediated MUFA synthesis to counteract the initiation of ferroptosis by protecting against PUFA peroxidation (Ma et al., 2022; Magtanong et al., 2019). The mitochondrial glutamate transporter solute carrier family 25 member 22 (SLC25A22) inhibits ferroptosis in pancreatic cancer cells by remodeling lipid metabolism pathways and facilitating the production of GSH and MUFA (Liu et al., 2023d). SLC25A22 accomplishes this through the utilization of NADPH and the stimulation of enzyme stearoyl-CoA desaturase (SCD, also known as SCD1) activity (Liu et al., 2023d). Membrane bound O-acyltransferase domain containing 1 (MBOAT1) and membrane bound O-acyltransferase domain containing 2 (MBOAT2) are transcriptionally upregulated by sex hormone receptors, resulting in the inhibition of ferroptosis in cancer cells (Liang et al., 2023). These enzymes achieve this effect by remodeling the cellular phospholipid profile, leading to the production of MUFA in a manner dependent on SCD and ACSL3 (Liang et al., 2023). Furthermore, the existence of ACSL4-independent ferroptosis-modulatory pathways complicates the final comprehension of lipid metabolism in cell death regulation (Chu et al., 2019; Magtanong et al., 2022; Wang et al., 2022b).

Peroxisomes provide an additional resource of lipids that favor ferroptosis. Peroxisomes are involved in the breakdown of fatty acids and can generate hydrogen peroxide as a byproduct. They also contribute to the biosynthesis of plasmalogens, which are vulnerable to lipid peroxidation (Cui et al., 2021; Zou et al., 2020a). However, peroxisomes possess antioxidant enzymes, such as catalase (Hosoi et al., 2017), which can detoxify ROS and potentially inhibit ferroptosis, as well as other cell death modalities (Peng et al., 2023). This dual role of peroxisomes in promoting or inhibiting ferroptosis highlights their dynamic role in cell (death) biology.

Lipophagy, a selective form of autophagy, specifically targets and degrades lipid droplets within cells. Lipid droplets consist of a neutral lipid core surrounded by a phospholipid monolayer and serve as storage sites for lipids. The degradation of lipid droplets through lipophagy releases lipids that can undergo peroxidation, increasing the susceptibility of cells, particularly liver cancer cells, to ferroptosis (Bai et al., 2019). Increased lipid storage in lipid droplets favored by ACSL3 can limit ferroptosis in clear cell renal cell carcinoma cells (Klasson et al., 2022). Paclitaxel-resistant cancer cells exhibited upregulation of progesterone receptor membrane component 1 (PGRMC1), which stimulates lipophagy, thus increasing susceptibility to ferroptotic cell death (You et al., 2021).

A recent advancement in our understanding of the regulation of lipid metabolism in ferroptosis involves the discovery of transmembrane protein 164 (TMEM164) as a mediator of this cell death process. TMEM164 functions as an acyltransferase and is involved in the synthesis of C20:4 ether phospholipids (Reed et al., 2023). Moreover, TMEM164 promotes the formation of membrane-driven phagophores, which are required for the subsequent formation of autophagosomes in pancreatic cancer cells in response to ferroptotic stimuli, rather than starvation (Liu et al., 2023b). However, it remains to be demonstrated whether the catalytic activity of TMEM164 is directly involved in autophagy-dependent ferroptosis. Regardless, the involvement of TMEM164 expands our knowledge of the intricate network of lipid metabolism-related processes implicated in ferroptotic cell death.

***Lipid peroxidation***

The third essential element in ferroptosis is the execution of lipid peroxidation by several enzymes, including ALOXs, cyclooxygenases (COXs), and cytochrome P450 enzymes (**Fig. 3**).

ALOXs are a family of enzymes that catalyze the oxygenation of PUFAs, initiating lipid peroxidation. They introduce a peroxide group (-OOH) into the fatty acid chain, leading to the formation of lipid hydroperoxides. LOXs can act on various PUFAs, such as arachidonic acid, linoleic acid, and docosahexaenoic acid. The contribution of ALOXs to ferroptosis is context-dependent due to their cell and tissue-specific expression. In humans, six ALOX isoforms have been identified, namely ALOX5, ALOX12, ALOX12B, ALOX15, ALOX15B, and ALOXE3. Each isoform exhibits specific substrate preferences and catalytic activities, contributing to ferroptosis in different cells or tissues (Cai et al., 2023; Chen et al., 2021a; Chu et al., 2019; Dar et al., 2023; Dar et al., 2018; Friedmann Angeli et al., 2014; Kapralov et al., 2020; Li et al., 2021b; Nagasaki et al., 2022; Sun et al., 2021; Wenzel et al., 2017; Yang et al., 2016). Therefore, profiling ALOX expression in experimental models is important.

COXs are involved in prostaglandin synthesis but also catalyze lipid peroxidation. Like ALOXs, COXs oxygenate PUFAs, resulting in the generation of lipid hydroperoxides (Hajeyah et al., 2020). However, COXs primarily function in prostaglandin production and, compared to ALOXs, play a secondary role in lipid peroxidation. A recent study suggested that the production of prostaglandin E2 (PGE2) inhibits ferroptosis through its prostaglandin E receptor 1 (PTGER1) and prostaglandin E receptor 2 (PTGER2) receptors in cerebral ischemia-reperfusion (Xu et al., 2022). However, excessive PGE2 promotes ferroptosis in acute kidney injury (Liu et al., 2023f). Given the association of PGE2 release with immune suppression (Agard et al., 2013; Mandapathil et al., 2010), further investigation is warranted to explore the interplay between PGE2 and other DAMPs in determining the immune properties of ferroptotic cell death (Tang et al., 2023).

Cytochrome P450 enzymes constitute a superfamily of heme-containing enzymes involved in various metabolic reactions, including drug and fatty acid metabolism. Certain cytochrome P450 enzymes can catalyze lipid peroxidation by introducing an oxygen atom into the fatty acid chain (Rabe et al., 2010). This process generates lipid hydroperoxides and reactive aldehydes, such as 4HNE, which are known mediators of ferroptosis. In the context of ferroptosis, cytochrome P450 reductase plays a role by supplying electrons to cytochrome P450 enzymes involved in the production of lipid hydroperoxides (Yan et al., 2020a; Zou et al., 2020b).

Irrespective of the enzymes that catalyze lipid peroxidation, the resulting lipid hydroperoxides can initiate a chain reaction. Thus, hydroperoxides undergo further reactions, such as decomposition and rearrangement, generating highly reactive lipid radicals. These radicals then react with nearby lipids, fueling a self-propagating process that amplifies lipid peroxidation. Ultimately, this cascade of reactions inflicts extensive damage to cell membranes, culminating with ferroptotic plasma membrane permeabilization. Understanding the intricacies of lipid peroxidation and the involvement of specific enzymes provides valuable insights into the mechanisms underlying ferroptosis.

**Antioxidant systems in ferroptosis**

The antioxidant system involves multiple components that collectively function to defend against oxidative stress and uphold cellular homeostasis. Although there may not be a fixed sequential activation of these components, they interact and synergize with each other in a coordinated manner to counteract the oxidative damage associated with ferroptosis.

***Enzymatic antioxidants***

The key enzyme involved in the antioxidant defense against ferroptosis is GPX4, which has a unique ability to scavenge lipid hydroperoxides on biological membranes (Yang et al., 2014) (**Fig. 4**). GPX4 contains selenocysteine in its active center (Ingold et al., 2018; Yao et al., 2021b). When selenium levels are low, ribosome stalling occurs at the inefficiency decoded selenocysteine UGA codon within GPX4, leading to ribosome collisions, premature translation termination, and subsequent proteasomal clearance of the N-terminal GPX4 fragment (Li et al., 2022c). The R152H mutation in GPX4 can cause Sedaghatian-type spinal metaphyseal dysplasia (SSMD), a rare and fatal disease in newborns (Liu et al., 2022a). *In vitro* studies suggest that this R152H mutation does not affect the catalytic activity of the enzyme in a direct fashion but rather interferes with its allosteric activation by cardiolipin (Roveri et al., 2023). Further examination is needed to determine whether excessive cardiolipin peroxidation participates to the pathogenesis of SSMD.

Constitutive knockout of the *Gpx4* gene in mice leads to embryonic death at 7.5-8.5 days (Yant et al., 2003). The first evidence linking *Gpx4* deficiency to ferroptosis *in vivo* was obtained in mice bearing a conditional knockout of *Gpx4* in the kidney that, in addition, were fed a vitamin E-deficient diet (Friedmann Angeli et al., 2014). These mice displayed kidney damage, and the phenotype was reversed by supplementation with vitamin E or the ferroptosis inhibitor liproxstatin-1 (Friedmann Angeli et al., 2014). Under normal breeding conditions, conditional knockout of *Gpx4* in specific cell types (e.g., myeloid cells) or tissues (e.g., pancreas, intestine, or liver) is not lethal (Conche et al., 2023; Dai et al., 2020a; Kang et al., 2018; Mayr et al., 2020).

GSH, a tripeptide composed of glutamate, cysteine, and glycine, serves as a cofactor for GPX4. GSH plays a crucial role in cellular antioxidant defense, detoxification, and redox homeostasis. GSH can be synthesized within cells through various pathways and can also be obtained from extracellular sources. The intracellular concentration of cysteine, a critical precursor for GSH synthesis, can limit GSH production. Cysteine can be derived from the metabolism of methionine, an essential amino acid. Methionine is initially converted to s-adenosylmethionine, which can donate a methyl group to various substrates, generating s-adenosylhomocysteine. S-adenosylhomocysteine can be hydrolyzed to form homocysteine, which is ultimately converted to cysteine (Cho et al., 2021). In addition, and more importantly, cells take up extracellular cystine through transporters, such as the cystine/glutamate antiporter system xc-. This transporter, consisting of two subunits (SLC7A11 and SLC3A2), exchanges extracellular cystine for intracellular glutamate. Once imported, cystine then can be reduced to cysteine. The system xc- can be inhibited by pharmacological agents, such as erastin, sulfasalazine or sorafenib (Dixon et al., 2012; Dixon et al., 2014; Gao et al., 2021; Sun et al., 2016a; Xu et al., 2023b; Yin et al., 2023). At high concentrations, sorafenib reportedly inhibits the activity of system xc- in a direct fashion (Dixon et al., 2014), but a recent study challenges this notion because sorafenib fails to induce ferroptosis in multiple cancer cells (Zheng et al., 2021). However, this discrepancy has not been fully resolved, requiring further investigation.

GSH is synthesized within cells, primarily in the cytosol, through a series of enzymatic reactions (Forman et al., 2009). The first step involves the synthesis of gamma-glutamylcysteine that is catalyzed by the enzyme glutamate-cysteine ligase catalytic subunit (GCLC). Subsequently, glutathione synthetase (GSS) combines gamma-glutamylcysteine with glycine to form GSH. Of note, GCLC can also inhibit ferroptosis in a GSH-independent manner, through its noncanonical contribution to γ-glutamyl-peptide synthesis (Kang et al., 2021). The breakdown of GSH into cysteinylglycine and free amino acids is catalyzed by a family of enzymes called gamma-glutamyltransferases (GGTs) (Hanigan, 2014). Cysteinylglycine is then further broken down to release cysteine, which can be utilized for GSH resynthesis.

While GSH depletion contributes to ferroptosis, it is important to note that GPX4 is not the sole target of GSH, suggesting the existence of GPX4-independent pathways that protect against ferroptosis (**Fig. 4**). Among them, apoptosis inducing factor mitochondria associated 2 (AIFM2, also known as FSP1) has been identified in *Gpx4*-deficient cells as an inhibitor of ferroptosis (Bersuker et al., 2019; Doll et al., 2019). AIFM2 belongs to the apoptosis-inducing factor family and is localized in mitochondria. While AIFM1 is primarily involved in caspase-independent cell death pathways (Joza et al., 2001; Susin et al., 1999), AIFM2 has gained attention as a potent suppressor of ferroptosis due to its translocation from mitochondria to the cell membrane and its role in the reduction of coenzyme Q10 (CoQ10) (Bersuker et al., 2019; Doll et al., 2019). StAR-related lipid transfer domain-containing 7 (STARD7), which is dual-localized to the intermembrane space of mitochondria and the cytosol after cleavage by the rhomboid protease presenilin-associated rhomboid-like (PARL), is engaged in the synthesis and transport of CoQ10 to the plasma membrane, thereby inhibiting ferroptosis (Deshwal et al., 2023). Additionally, AIFM2-mediated membrane repair (Dai et al., 2020c) and its involvement in the canonical vitamin K cycle, including warfarin-resistant vitamin K reduction (Jin et al., 2023; Mishima et al., 2022; Nakamura et al., 2023), contribute to its antiferroptotic activity. The activity of AIFM2 in ferroptosis further depends on phase separation and can be triggered by AIFM2's N-terminal myristoylation, facilitated by a compound known as icFSP1 (Nakamura et al., 2023).

Dihydroorotate dehydrogenase (DHODH) is a pivotal enzyme involved in the de novo biosynthesis of pyrimidines, which are essential building blocks of DNA and RNA. DHODH has emerged as an attractive target for therapeutic interventions on various diseases. Thus, inhibitors of DHODH have been developed and studied as potential anticancer and immunosuppressive agents. The activity of DHODH has an influence on the ferroptotic susceptibility of cancer cells expression low levels of GPX4, likely due the DHODH-catalyzed utilization of CoQ10 as an electron acceptor (Mao et al., 2021). Inhibiting DHODH activity results in diminished CoQ10 levels, thus compromising antioxidant capacity and increasing vulnerability to lipid peroxidation and ferroptosis (Mao et al., 2021). However, a recent study suggests that DHODH inhibitors may exert off-target effects on AIFM2 in cancer cells (Mishima et al., 2023), challenging our current vision of the contribution of DHODH to mitochondrial antioxidant defenses (Mao et al., 2023).

Beyond this trio of well-studied enzymes, including GPX4, AIFM2, and DHODH, accumulating evidence indicates the involvement of additional antioxidant enzymes in suppressing ferroptosis. GTP cyclohydrolase 1 (GCH1) participates to the biosynthesis of tetrahydrobiopterin (BH4), a cofactor of various enzymatic reactions, including the synthesis of monamine neurotransmitters (Kraft et al., 2020). GCH1 contributes to maintaining cellular redox balance and antioxidant defenses, thereby inhibiting susceptibility to ferroptotic cell death (Kraft et al., 2020). Additionally, the activity of mitochondrial SOD, which can be increased by selenium, contributes to the defense against heat-stress-induced ferroptosis of mammary epithelial cells (Liu et al., 2021c).

Microsomal glutathione S-transferase 1 (MGST1), a member of the glutathione S-transferase (GST) family, localizes primarily at the ER and outer mitochondrial membranes. In response to ferroptotic activators, NFE2 like BZIP transcription factor 2 (NFE2L2, best known as NRF2)-mediated upregulation of MGST1 mediates cellular detoxification by binding to ALOX5 in pancreatic cancer cells (Kuang et al., 2021). Glutathione S-transferase zeta 1 (GSTZ1), also known as maleylacetoacetate isomerase, belongs to the GST superfamily and exhibits additional enzymatic activity. The antioxidant activity of GSTZ1 inhibits ferroptosis in bladder cancer cells (Wang et al., 2021b). Thioredoxin reductase 1 (TXNRD1) reduces thioredoxin using NADPH as a coenzyme. The reduced form of thioredoxin restricts ferroptosis in chronic myeloid leukemia or pancreatic cancer cells (Liu et al., 2021d; Rong et al., 2021). Intriguingly, a recent study suggests that classical ferroptotic activators RSL3 and ML162 directly inhibit TXNRD1 (Cheff et al., 2023), questioning previous assumptions that these compounds exclusively target GPX4.

The Ca2+-independent phospholipase A(2)beta (iPLA2β), encoded by the gene phospholipase A2 group VI (PLA2G6, also called patatin like phospholipase domain containing 9, PNPLA9), is a member of the patatin-like phospholipase (PNPLA) protein family and hydrolyzes peroxidized membrane phospholipids. Through this enzymatic activity, iPLA2β may eliminate the ferroptotic death signal caused by 15-HpETE-PE in H109 cells (Sun et al., 2021). Mice with a homozygous *Pnpla9R748W* loss-of-function mutation exhibit a Parkinsonian phenotype coupled to the accumulation of oxygenated PE in their midbrain (Sun et al., 2021). iPLA2β expression is regulated by TP53 in cancer cells, and its detoxification of peroxidized lipids blocks TP53-driven ferroptosis during ROS-induced stress, even in *GPX4*- or *AIFM2*-knockout cells (Chen et al., 2021a). It remains unknown whether other PNPLA family members have similar effects on ferroptosis.

Collectively, these findings emphasize the advancing comprehension of the complex interactions among antioxidant enzymes and the sophisticated regulation of ferroptosis.

***Non-enzymatic antioxidants***

Non-enzymatic antioxidants can effectively counteract and neutralize harmful ROS and reactive nitrogen species, thus playing a vital role in maintaining cellular redox balance and safeguarding cells against oxidative damage. Here are some examples of non-enzymatic antioxidants known to inhibit ferroptosis:

Vitamin E: Vitamin E encompasses a group of fat-soluble antioxidants, including alpha-tocopherol and gamma-tocopherol. Due to its lipophilie, vitamin E accumulates in cell membranes, effectively neutralizing lipid peroxyl radicals. In doing so, vitamin E protects against lipid peroxidation and inhibits ferroptosis in both *in vitro* and *in vivo* studies (Jian et al., 2021; Zhang et al., 2022b). In particular, studies using *Gpx4* conditional knockout mice have demonstrated the involvement of vitamin E in suppressing ferroptosis (Friedmann Angeli et al., 2014; Matsushita et al., 2015).

Vitamin K: Primarily known for its essential role in blood clotting and bone health, emerging evidence suggests that Vitamin K may possess additional antioxidant and anti-inflammatory properties that impact cellular processes associated with ferroptosis. The activity of Vitamin K is regulated by AIFM2, as discussed earlier, highlighting its potential involvement in the modulation of ferroptosis (Jin et al., 2023; Mishima et al., 2022).

GSH: As one of the most abundant antioxidants in cells, GSH plays a critical role in maintaining cellular redox homeostasis and protecting against ferroptosis (Yang et al., 2014). Due to its hydrophily, GSH cannot penetrate the lipid phase of cellular membranes and its addition to cells in culture usually fails to mediate cytoprotective effects. This difficulty can be overcome by the administration of lipophilic GSH monoethyl ester that enter cells and then are de-esterified to form free GSH (Liu et al., 2023e).

CoQ10: It is a fat-soluble compound predominantly found in mitochondria. It plays a role in cellular energy production, serving as a component of the electron transport chain in oxidative phosphorylation. Beyond its role in bioenergetic reactions, CoQ10 functions as a potent antioxidant, playing a role in safeguarding cells against oxidative stress-induced cell death, including ferroptosis. Notably, the anti-ferroptotic functions of AIFM2 and DHODH may partially depend on CoQ10, although this is controversial (Mao et al., 2023; Mishima et al., 2023).

NADPH: NADPH is the reduced form of NADP+ and plays a crucial role in cellular processes requiring reducing power. NADPH is essential for enzymatically reducing oxidized glutathione and serves as both a direct antioxidant and a biomarker for predicting sensitivity to ferroptosis (Shimada et al., 2016). The membrane associated ring-CH-type finger 6 (MARCHF6) E3 ubiquitin ligase acts as an NADPH sensor through its C-terminal regulatory region, regulating ferroptosis by degrading ACSL4 and TP53 (Nguyen et al., 2022).

Carotenoids: Carotenoids, such as beta-carotene, lycopene, and lutein, are natural pigments found in fruits and vegetables. These compounds possess potent antioxidant properties and play a crucial role in protecting against ferroptotic damage in various disease models, including in the pathogenic demise of cells induced by di(2-ethylhexyl) phthalate, (Dai et al., 2021). Hence, carotenoids present in the diet or food supplements may offer a cytoprotection against ferroptosis.

Flavonoids: Flavonoids are a diverse group of plant compounds found in fruits, vegetables, and beverages such as tea and wine. These compounds possess potent antioxidant properties and have been linked to numerous health benefits, inter alia by attenuating ferroptotic cell death (Huang et al., 2023; Wang et al., 2023b; Xie et al., 2016; Zhu et al., 2023a).

Melatonin: Melatonin, widely recognized for its regulatory role in sleep-wake cycles, exhibits potent antioxidant properties. Melatonin inhibits ferroptosis and delays age-related cataract development, partially through the suppression of ferritinophagy (Gao et al., 2023; Mi et al., 2023; Zhang et al., 2023a). Dysfunctions in the circadian clock can also increase sensitivity to ferroptosis in animal models of pancreatitis or carcinogenesis (Liu et al., 2020; Wang et al., 2023a), suggesting that melatonin may confer cellular protection through several mechanisms that warrant further preclinical exploration.

Alpha-lipoic acid: Alpha-lipoic acid functions as a multifaceted antioxidant by effectively scavenging free radicals and regenerating other essential antioxidants, such as vitamins C and E. Remarkably, the administration of alpha-lipoic acid inhibits cisplatin-induced ferroptosis in cancer cells (Cho et al., 2022). Studies in mouse models indicate that alpha-lipoic acid can protect against ferroptosis-related tauopathies (Zheng et al., 2023). It will be interesting to explore the potential of alpha-lipoic acid to act against other ferroptosis-linked diseases.

These non-enzymatic antioxidants act synergistically with enzymatic antioxidants to prevent or mitigate oxidative stress leading to ferroptosis. Molecules classified as antioxidants only scavenge toxic radicals when they are in their reduced form (which is oxidizable), while their oxidized form may actually amplify oxidative stress, underscoring the necessity to dynamically monitor redox reactions.

***Metal chelators***

Metal ions, such as iron and copper, engage in Fenton or Haber-Weiss reactions, leading to the generation of highly reactive hydroxyl radicals. Metal-binding proteins, such as transferrin and ferritin, sequester free iron to inhibit its participation in such detrimental reactions (Gao et al., 2016; Hou et al., 2016). Moreover, metallothioneins, which are small proteins, play a role in binding and regulating the availability of metal ions, thereby mitigating their contribution to oxidative damage and ferroptosis (Sun et al., 2016a).

In addition to proteins, several metal chelator drugs utilized in clinical settings have shown promising implications in the regulation of ferroptosis, as observed in preclinical studies. These chelators have demonstrated the capacity to counteract the lipid peroxidation processes associated with ferroptosis.

Deferoxamine: Deferoxamine is a pharmacological iron chelator that is clinically used and is primarily prescribed to treat conditions characterized by iron overload. These include transfusional hemosiderosis (excessive iron accumulation resulting from repeated blood transfusions) and chronic iron overload related to genetic disorders like thalassemia and hereditary hemochromatosis. By effectively reducing iron levels, deferoxamine inhibits lipid peroxidation-mediated ferroptosis. For instance, in studies involving mice with spinal cord injury and female diabetic rats experiencing poststroke memory impairment, deferoxamine has demonstrated notable benefits through the inhibition of ferroptosis and inflammation (Jia et al., 2023; Li et al., 2023b).

Deferiprone: Like deferoxamine, deferiprone is a wide used clinical iron chelator that forms stable stable complexes with iron that can be excreted through urine. Inhibition of ferroptosis by deferiprone has shown promising effects in various scenarios, for instance in promoting neuroprotection in a model of optic nerve demyelination (Rayatpour et al., 2022).

Deferasirox: Deferasirox is an oral iron chelator provides a treatment option for patients who require frequent blood transfusions, offering convenience compared to deferoxamine, which must be injected subcutaneously or intravenously. In preclinical studies, deferasirox or dietary supplementation with selenium or vitamin E alleviates colitis induced by dextran sulfate sodium (Panda et al., 2023; Wu et al., 2023c). Deferasirox mitigates colitis by inhibiting ferroptosis and by improving the composition of the intestinal microbiota (Panda et al., 2023; Wu et al., 2023c).

Cyclipirox: Ciclopirox is an antifungal drug that falls into the category of hydroxypyridones. It is primarily administered topically to treat fungal infections affecting the skin, hair, and nails. Through its ability to bind iron, ciclopirox also exhibits the potential to inhibit ferroptosis in cancer cells (Fernandez-Acosta et al., 2022), suggesting that this drug might be repurposed as a ferroptosis inhibitor. Like for any other metal celator, it will be important to weight the potential side effects of ciclopirox mediated by the rarefaction of free iron (with consequent iron deficiency anemia) against its desired effects as a cytoprotector.

***Heat shock proteins***

Heat stress can elicit homeostatic or hermetic responses that protect cells and organs against non-thermic damage. However, excessive heat stress can trigger cell death, including ferroptosis (Chen et al., 2022a; Distefano et al., 2017; Xu et al., 2023a). When cells encounter heat stress, they initiate a process known as the heat shock response, which leads to the upregulation of genes encoding heat shock proteins (HSPs) (Sorger, 1991). This response is mediated by a transcription factor called heat shock factor 1 (HSF1), which becomes activated upon exposure to heat stress. Activated HSF1 binds to specific regions called heat shock elements (HSEs) in the promoter regions of HSP genes, thereby enhancing their transcription and subsequent translation (Sorger, 1991). In cardiomyocytes, HSF1 inhibits ferroptosis, potentially due to its association with GPX4 levels (Wang et al., 2021a). *Hsf1*-deficient mice treated with palmitic acid exhibit reduced GPX4 levels and exacerbated cardiomyocyte loss due to ferroptosis compared to wild-type controls (Wang et al., 2021a).

HSPs aid in refolding damaged proteins, preventing protein aggregation, and facilitating the degradation of irreversibly damaged proteins. By maintaining proteostasis, HSPs ensure proper cellular function and promote cell survival under heat stress conditions (Sorger, 1991). Several specific HSPs have been linked to ferroptosis:

HSP70: HSP70 is the best-studied heat shock protein. Different forms of HSP70 include cytoplasmic constitutive HSPA8 (also known as HSC70 or HSP73), cytoplasmic inducible HSPA1A (also known as HSP72), mitochondrial HSPA9 (also known as mortalin), and ER HSPA5 (also known as BIP). Inducible expression of HSP70 family inhibits ferroptosis in various stress conditions (Liu et al., 2022c). Specifically, HSPA5 can directly interact with, and stabilize, GPX4, thereby inhibiting ferroptosis of cancer cells or neurons (Chen et al., 2019; Mun et al., 2023; Wang et al., 2022a; Zhu et al., 2017).

HSP90: HSP90 is primarily recognized for its role in safeguarding cells against harmful pro-apoptotic stimuli. However, HSP90 can stimulate the chaperone-dependent autophagic degradation of GPX4, meaning that the downregulation or pharmacological inhibition of HSP90 can protect against the toxic consequences of ferroptosis in mouse nerve cells and cancer cells (Wu et al., 2019b). This process can be inhibited by creatine kinase B (CKB)-mediated phosphorylation of GPX4 at serine residue 104, resulting in reduced HSP90 binding and inhibition of ferroptosis (Wu et al., 2023b). Furthermore, HSP90 can induce ferroptosis in glioma cells by modifying mitochondrial morphology secondary to the dephosphorylation of dynamin 1 like (DNM1L, also known as Drp1) at Ser637, thereby promoting the production of ROS (Miao et al., 2022).

HSPB1: Heat shock protein family B (small) member 1 (HSPB1), also known as HSP27 in humans and HSP25 in mice, is a small heat shock protein that inhibits ferroptosis. Phosphorylation of HSPB1 by PKC inhibits ferroptosis by reducing cytoskeleton-mediated iron uptake (Sun et al., 2015). Moreover, HSPB1 has a role in inhibiting the expression of transferrin receptor (TFRC, also known as TFR1) (Chen et al., 2006). Through these mechanisms HSPB1 inhibits the intracellular accumulation of free iron and subsequent ferroptosis (Dai and Hu, 2022; Yuan et al., 2022; Zhang et al., 2023b).

Other HSPs, such as HSP60, HSP40, and HSPB5, have also been suggested to inhibit ferroptosis, although their specific roles and mechanisms are not yet well-defined (Liu et al., 2022c).

***Transcriptional regulators***

Transcriptional factors regulate the expression of antioxidant enzymes and other components of the cellular antioxidant defense system. Here are some key transcriptional factors that have an impact on ferroptosis (**Fig. 5**):

NFE2L2: NFE2L2 is a member of the cap 'n' collar (CNC) family of transcription factors and plays a central role in activating the expression of various genes involved in antioxidant responses. Primarily located in the cytoplasm, it is bound to a protein called Kelch like ECH associated protein 1 (KEAP1), which facilitates its continuous degradation via the proteasome pathway. However, under conditions of oxidative stress or exposure to electrophilic compounds, NFE2L2 is released from KEAP1 and translocates into the nucleus (Ichimura et al., 2013; Komatsu et al., 2010). The levels of KEAP1 are regulated by sequestosome 1 (SQSTM1)-mediated protein degradation. Impaired autophagy leads to SQSTM1 accumulation, resulting in KEAP1 degradation and subsequent increased NFE2L2 protein stability (Ichimura et al., 2013; Komatsu et al., 2010). Once in the nucleus, NFE2L2 binds to specific DNA sequences known as antioxidant response elements (AREs) or electrophile response elements (EpREs) in the promoter regions of its target genes. This binding activates the transcription of a battery of genes, including GPX4-dependent and -independent pathways involved in inhibiting ferroptosis (Anandhan et al., 2023; Cahuzac et al., 2023; Sun et al., 2016b; Takahashi et al., 2020; Wang et al., 2022d). A key unanswered question is how NFE2L2 selectively activates target genes to inhibit ferroptosis, rather than other types of cell death.

TP53: TP53 has a dual role in regulating the susceptibility of cells to ferroptosis. For instance, the acetylation-deficient TP53 variant, TP533KR, lacks the ability to induce apoptosis and cell cycle arrest. However, it retains its capacity for tumor suppression similar to wild-type TP53 by suppressing SLC7A11 expression, thereby inducing ferroptosis in human breast cancer MCF7 cells, human osteosarcoma U2OS cells, and mouse embryonic fibroblasts (Jiang et al., 2015; Wang et al., 2016b). TP53-mediated downregulation of vitamin K epoxide reductase complex subunit 1 like 1 (VKORC1L1) also increases ferroptosis sensitivity in cancer cells through vitamin K metabolism (Yang et al., 2023c). Additionally, TP53 positively regulates ferroptosis by inducing the expression of spermidine/spermine N1-acetyltransferase 1 (SAT1), a rate-limiting enzyme in polyamine catabolism that can produce ROS (Ou et al., 2016). Conversely, under certain conditions, TP53 inhibits ferroptosis. For instance, in human colorectal cancer cells, *Tp53* deletion increases sensitivity to erastin-triggered ferroptosis through the activation of the DPP4-NOX1 pathway on the cell membrane (Xie et al., 2017). The classical TP53-inducible gene, cyclin dependent kinase inhibitor 1A (CDKN1A, also known as p21), also inhibits ferroptosis in cancer cells (Tarangelo et al., 2018). Furthermore, *TP53* mutation (R175H) yields a modified TP53 protein that functions as a suppressor of ferroptosis by preventing BTB domain and CNC homolog 1 (BACH1)-mediated downregulation of SLC7A11, thus promoting tumor growth (Su et al., 2023). These findings underscore the wide implications of TP53 in the modulation of ferroptosis.

HIF1A: hypoxia inducible factor 1 subunit alpha (HIF1A, also known as HIF-1α) is a key transcription factor involved in cellular responses to hypoxia, regulating genes associated with oxygen homeostasis, energy metabolism, and antioxidant defenses. HIF1A can upregulate antioxidant enzymes like heme oxygenase 1 (HMOX1, also known as HO-1) and SLC7A11, but downregulate the expression of ACSL4 (Lu et al., 2015; Wang et al., 2022e). In nasopharyngeal carcinoma, HIF1A also increases the expression of SCD, which inhibits ferroptosis by producing MUFAs, thereby protecting cells from ferroptosis (Su et al., 2022). On the other hand, endothelial PAS domain protein 1 (EPAS1, also known as HIF-2α) activation stimulates the hypoxia-induced expression of hypoxia-inducible lipid droplet associated (HILPDA) and selectively enriches PUFAs, thus incrementing the sensitivity of clear-cell carcinoma cells to ferroptosis (Zou et al., 2019). However, the relative weight of the potentially competing functions of HIF1A and EPAS1 in the regulation of ferroptosis remains to be determined.

NFKB: Nuclear factor-kappa B (NFKB, also known as NF-κB), a stress-related transcription factor, exerts a profound influence on cellular processes, including cell death. During quiescence, NFKB is constrained by its alliance with IκBα dimers, preventing uncontrolled activity. External signals trigger the degradation of IκBα, releasing NFKB dimers to the nucleus. NFKB has a dual function with respect to ferroptosis. It can repress the transcription of antioxidant enzymes (e.g., GPX4, NAD(P)H quinone dehydrogenase 1 [NQO1], and HMOX1), intensifying oxidative stress (Li et al., 2021e; Yan et al., 2021). The loss of LIF receptor subunit alpha (LIFR) tips the balance, enhancing NFKB activation and leading to increased iron exporter lipocalin 2 (LCN2) secretion, sequestering extracellular iron during sorafenib-induced ferroptosis in liver cancer cells (Yao et al., 2021a). Inhibitors of NFKB activation exemplified by BAY 11-7082 may counter ferroptosis, likely through this pathway (Li et al., 2021e). In contrast, nuclear transcriptional regulator protein 1 (NUPR1), another stress-inducible transcription factor, promotes LCN2 expression and inhibits ferroptosis in human pancreatic cancer cells (Liu et al., 2021b).

ATF4: Activating transcription factor 4 (ATF4) is a member of the larger family of ATF transcription factors and plays a crucial role in ER stress. When cells experience stress, such as an accumulation of misfolded proteins in the ER, ATF4 becomes activated through a signaling pathway known as the integrated stress response. Activated ATF4 binds to specific DNA sequences called ATF4 response elements (ATF4REs) within the regulatory regions of target genes. This leads to the upregulation of anti-ferroptotic genes, such as HSPA5 (Zhu et al., 2017) or SLC7A11 (Chen et al., 2017). The activation of ATF4 pathway protects against ferroptosis in cancer cells and mitochondrial cardiomyopathy (Ahola et al., 2022; He et al., 2023; Zhu et al., 2017). Moreover, sublethal cytochrome c (CYCS) release induced by pro-apoptotic BH3 mimetics (e.g., ABT-737 and S63845) can lead to ATF4-dependent chemotherapy resistance of cancer cells (Kalkavan et al., 2022). This phenomenon can be reversed by a GPX4 inhibitor RSL3 (Kalkavan et al., 2022). Considering the importance of ER as a critical organelle for ferroptosis (von Krusenstiern et al., 2023), ATF4 likely plays a specific role in transcriptional regulation, preserving cellular viability and conferring ferroptosis resistance.

**Membrane repair system**

The membrane repair system mitigates and reverses damage to the plasma membrane caused by mechanical stress, injury, or disruption. When the plasma membrane is damaged, intricate cellular processes become activated to repair and restore its integrity, thus reducing the propensity of cells to undergo ferroptosis.

Ca2+ signaling: Ca2+ serves as a primary trigger for initiating the membrane repair response (Cheng et al., 2015). When the plasma membrane is damaged, there is an influx of Ca2+ into the cytoplasm from extracellular sources or intracellular stores. The increase in intracellular Ca2+ concentration acts as a signal to activate downstream repair processes, such as endosomal sorting complexes required for transport (ESCRT)-III and exocytosis (Pedrera et al., 2021). Ca2+ signaling from different organelles has a dual role in the control of ferroptosis sensitivity (Nakamura et al., 2021; Stejerean-Todoran et al., 2022; Xin et al., 2022), emphasizing the need to monitor these signals in a timely manner.

ESCRT-III: This intricate protein complex plays a multifaceted role in various cellular processes, such as endosomal sorting, membrane remodeling, and vesicle formation (Liu et al., 2021a). Recent studies also suggest its contribution to the suppression of ferroptotic cell death (Dai et al., 2020b; Pedrera et al., 2021). During cellular stress, such as oxidative stress associated with ferroptosis, the components of the ESCRT-III molecular machinery can be recruited to the site of membrane damage to facilitate repair and restore membrane integrity before it becomes irreversible and results in ferroptosis.

Exocytosis: Another crucial process in the membrane repair system is exocytosis, where intracellular vesicles fuse with the plasma membrane, effectively mending it. Exocytosis is a fundamental cellular mechanism used for transporting and secreting various molecules, including proteins, lipids, neurotransmitters, and hormones (Wu et al., 2014). Autolysosomal exocytosis of lipids, in particular, has been found to protect neurons from ferroptosis (Ralhan et al., 2023).

Together, these components and processes coordinate the repair and restoration of the plasma membrane upon damage. They ensure the maintenance of cellular integrity, prevent the loss of cellular contents, and enable the cell to withstand mechanical stress or injury. The efficiency of the membrane repair system is crucial for the overall functionality of cells, and the disruption of membrane repair may constitute a point-of-no-return.

**Therapeutic opportunities and challenges**

Targeting ferroptosis as a therapeutic strategy presents a promising yet challenging endeavor. Here we summarize therapeutic opportunities and obstacles associated with harnessing ferroptosis for medical intervention.

***Therapeutic opportunities***

Preclinical studies have provided compelling evidence that targeting ferroptosis holds significant implications for a wide range of pathological conditions and diseases. Among these, the most extensively researched applications concern oncological indications, neurodegenerative disorders, and ischemia/reperfusion (I/R) injury, as discussed below.

Cancer cells frequently undergo metabolic reprogramming, leading to dysregulation in redox homeostasis and increased reliance on antioxidant systems, rendering them more susceptible to ferroptosis compared to their normal counterparts (Perillo et al., 2020). The upregulation of iron importers and higher rates of lipid peroxidation in cancer cells contribute to the accumulation of toxic lipid hydroperoxides, thereby promoting the process of ferroptosis. Exploiting this vulnerability offers a distinctive opportunity to selectively target and eliminate malignant cells while preserving healthy cells. Furthermore, cancer cells often acquire resistance to conventional therapeutic modalities, including chemotherapy-, radiation-, or immunotherapy-induced apoptosis (Mohammad et al., 2015). Inducing ferroptosis presents an innovative strategy to bypass such resistance mechanisms and overcome the limitations of current treatments (Alvarez et al., 2017; Badgley et al., 2020; Hong et al., 2021; Jiang et al., 2015; Lang et al., 2019; Liao et al., 2022; Minami et al., 2023; Sabatier et al., 2023; Song et al., 2022; Tan et al., 2021; Tsoi et al., 2018; Ubellacker et al., 2020; Viswanathan et al., 2017; Wang et al., 2019; Wu et al., 2019a; Zhang et al., 2018), despite the occasional presence of ferroptosis resistance mechanisms (e.g., due to enhanced biosynthesis of pyrimidines (Yang et al., 2023a) or hydropersulfides (Barayeu et al., 2023)). By precisely targeting the susceptibilities of cancer cells, ferroptosis-inducing agents, particularly GPX4 inhibitors, exhibit the potential to eradicate drug-resistant cancer cell populations (Hangauer et al., 2017; Rodriguez et al., 2022; Viswanathan et al., 2017). Moreover, drugs that stimulate ferroptosis can sensitize cancer cells to other treatment modalities, enabling the use of lower doses of conventional therapies, thus reducing associated side effects. Additionally, the intricate association between specific mutations in tumor-related genes (e.g., *KRAS* and *TP53*) and ferroptosis sensitivity in certain solid cancers opens up avenues for precision medicine approaches (Dixon et al., 2012; Jiang et al., 2015; Su et al., 2023).

Neurodegenerative disorders, such as Alzheimer's, Parkinson's, and Huntington's diseases, are hallmarked by the gradual destruction of neurons and the build-up of protein aggregates within the brain. Oxidative stress is a significant contributor to this degenerative process (Korovesis et al., 2023; Teleanu et al., 2022). This stress imbalance precipitates lipid peroxidation, resulting in neuronal damage and ferroptotic cell death. Therapeutic strategies aiming to ameliorate oxidative damage, focus on inhibiting ferroptosis, which, in turn, promotes the survival of neurons (Li et al., 2023c; Tian et al., 2020). The non-oxidatized, native form of dopamine can inhibit ferroptotic cell death, partly due to its ability to enhance GPX4 stability (Wang et al., 2016a). In contrast, aminochrome, which results from dopamine oxidation, can induce GPX4 protein degradation through the ubiquitination-proteasome system, leading to the activation of ferroptosis in dopaminergic neurons (Sun et al., 2023). Arsenite, a form of inorganic arsenic, has been associated with nerve loss, and diseases like Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis (Lee et al., 2021; Rahman et al., 2021). Numerous studies suggest that arsenite can induce nerve cell death by activating ferroptosis (Tang et al., 2018; Xiao et al., 2021). The GPX4 enzyme plays a critical role in the survival of parvalbumin-positive interneurons and the prevention of seizures, as well as in providing protection against ferroptosis in animal models (Ingold et al., 2018; Jia et al., 2020). Therefore, manipulating the pathways leading to ferroptosis may mitigate the accumulation of lipid peroxides, reactive aldehydes, and other harmful byproducts that accelerate neurodegeneration.

Ischemic events followed by reperfusion induce oxidative stress and subsequent cell death, emphasizing the therapeutic potential of targeting ferroptosis-relevant pathways. These strategies could mitigate oxidative damage and preserve tissue function in various I/R injury contexts, such as stroke, myocardial infarction, liver, and kidney damage. Ischemic stroke is often modeled in rodents by temporary occlusion of the middle cerebral artery, and ferroptosis contributes to brain I/R injuries (Tuo et al., 2017). The compound galangin can improve learning ability and memory in gerbils after I/R injury by inhibiting ferroptosis, likely through upregulation of SLC7A11 and GPX4 (Guan et al., 2021). Ferroptosis inhibitors, such as ferrostatin-1, also confer cardioprotection against I/R-induced injury (Fang et al., 2019). In liver transplantation, hepatic I/R injuries can be inhibited by ferrostatin-1 or vitamin E (Yamada et al., 2020). For kidney I/R injury, the third-generation ferrostatin, 16–86, prevents renal tubular cell death and protects against acute renal failure (Linkermann et al., 2014). These studies highlight the therapeutic potential of ferroptosis inhibitors in I/R-related diseases.

**Therapeutic challenges**

Specificity and selectivity: The development of agents selectively inducing ferroptosis in diseased cells, while sparing healthy ones, is crucial. High specificity and selectivity are required to minimize off-target effects and potential toxicity. For instance, recent research indicates that RSL3 and ML162 act as the TXNRD1 (not GPX4) inhibitor (Cheff et al., 2023). Notably, most current classical ferroptosis activators have been primarily investigated *in vitro*, with limited *in vivo* applications. The most widely used *in vivo* ferroptosis inducer is imidazole ketone erastin (also known as IKE) (Zhang et al., 2019), although its activity compared to other widely used *in vitro* ferroptosis activators remains understudied. In the living organism, drugs are often metabolized to distinct compounds, creating discrepancies between *in vitro* cell culture experiments and *in vivo* results. Another hurdle involves the complexity of disease models which often involved the simultaneous manifestation of various cell death pathways. Moreover, inhibition of ferroptosis by antioxidant mechanisms may impact non-ferroptotic pathways, including apoptosis (Muller et al., 2017; Sun et al., 2020). Hence, disentangling the overlapping regulation of alternate cell death pathways may be vital for successful drug development.

Drug delivery: The efficient delivery of ferroptosis-targeting agents to the desired site of action poses a significant challenge. To enhance therapeutic efficacy while minimizing systemic side effects, the development of strategies for targeted drug delivery systems is crucial. Recent studies have highlighted the potential of nanoparticles, including liposomes, micelles, and polymer-based carriers, in addressing these challenges (Gao et al., 2019a; Gao et al., 2020; Liu et al., 2023c; Yan et al., 2022). Nanoparticles offer several advantages in drug delivery, such as improved drug stability, solubility, and targeted delivery. Specifically, in the context of ferroptosis, nanoparticles can encapsulate ferroptosis-related drugs, providing protection against degradation and enabling controlled release kinetics (Kim et al., 2016; Song et al., 2023; Yu et al., 2023). These pharmacokinetic properties make nanoparticles a promising tool for enhancing the delivery of ferroptosis-targeting agents and optimizing their therapeutic effects. Further research and development in nanoparticle-based drug delivery systems hold promise for advancing the field of pharmacological ferroptosis modulation.

Biomarker identification: The identification of reliable biomarkers for assessing ferroptosis susceptibility and monitoring treatment responses is of paramount importance. Biomarkers play a crucial role in identifying those patients who are most likely to benefit from ferroptosis-targeting therapies and enable personalized treatment approaches. Several biomarkers, such as TFRC (Feng et al., 2020), ACSL4 (Yuan et al., 2016), and prostaglandin-endoperoxide synthase 2 (PTGS2) (Yang et al., 2014), have been measured at the mRNA or protein levels to predict ferroptosis responses. Theoretically, blood-based biomarkers offer the best translational potential in the clinical setting. In particular, the release of DAMPs, such as HMGB1 (Wen et al., 2019), ATP (Efimova et al., 2020), SQSTM1 (Yang et al., 2022), and decorin (DCN) (Liu et al., 2022b), may indicate plasma membrane rupture during ferroptosis. Among them, DCN, a small leucine-rich proteoglycan, stands out because it allows to distinguish between ferroptosis and non-ferroptotic cell death, at least in the early stages of cell death (Liu et al., 2022b). It appears plausible that the development of robust and sensitive biomarkers, including protein and lipid biomarkers, will contribute to the accurate diagnosis, prognosis, and monitoring of ferroptosis-related diseases. However, so far no tissue- or cell-specific biomarkers of ferroptosis have been identified, and further research is needed to explore this area.

Side effects: Modulating ferroptosis pathways can potentially impact normal physiological processes and lead to unintended adverse effects. Striking a balance between therapeutic benefits and potential off-target effects is crucial to ensure treatment safety and tolerability. It is important to note that currently widely used ferroptosis activators lack cell or tissue selectivity. As a result, treatment with these agents may lead to cell death not only in target cancer cells, but also in non-malignant cells, including various immune cell types, such as neutrophils (Kim et al., 2022), CD8+ T cells (Ma et al., 2021; Xu et al., 2021), natural killer cells (Poznanski et al., 2021), dendritic cells (Han et al., 2021), and macrophages (Kapralov et al., 2020). This unintended consequence highlights the need for strategies that selectively target tumor cells while preserving immune cell integrity and anticancer immunosurveillance. Adverse effects constitute another problem. In mice fed a high-fat, low-carbohydrate ketogenic diet, the induction of ferroptosis suppresses tumor growth, but also precipitates the onset of cachexia and shortens survival (Ferrer et al., 2023). Induction of ferroptosis can result in stem cell death and bone marrow injury, potentially affecting hematopoiesis and leading to bone marrow suppression (Song et al., 2016; Zhao et al., 2023). In addition, ferroptotic damage-initiated inflammation plays a significant role in stimulating tumorigenesis in *KrasG12D*-driven pancreatic cancer as well as in diethylnitrosamine-induced liver cancer (Conche et al., 2023; Dai et al., 2020a; He et al., 2023). Thus, secondary tumors might arise as a side effect of the pharmacological induction of ferroptosis, calling for long-term experiments assessing this possibility in suitable animal models.

Clinical translation: The translation of ferroptosis-targeting therapies from preclinical models to clinical settings necessitates rigorous testing and validation. Currently, no definitive gold standard drug is available to assess the efficacy of ferroptosis-targeting strategies in patients, although some FDA-approved drugs (such as sorafenib (Dixon et al., 2014), sulfasalazine (Sugiyama et al., 2020), and artesunate (Eling et al., 2015)) have shown potential to induce ferroptosis in preclinical studies, although such desired effects might be linked to adverse off-target effects. Therefore, it is crucial to identify and screen specific drugs that can be safely used in patients. Future studies should focus on this aspect to bridge the gap in our understanding of the pathological significance of ferroptosis in human diseases. To evaluate the effectiveness, safety, and long-term outcomes of ferroptosis-targeting agents in patients, well-designed clinical trials are essential. These trials should enroll carefully selected patient populations and monitor (yet-to-be-discovered) specific and reliable biomarkers.

**Conclusion and outlook**

In recent years, the field of ferroptosis research has witnessed a remarkable surge, spanning investigations into the underlying molecular mechanisms, development of related therapeutic agents, and exploration of potential applications. This surge reflects the establishment of a genuine ferroptosis-focused research era (Stockwell, 2022). However, the initial definition of ferroptosis as iron-dependent cell death is now recognized as incomplete. Although iron-induced oxidative stress remains a prominent trigger, other iron-independent stimuli or stresses are undoubtedly involved in ferroptosis. Considering that the core downstream feature of ferroptosis is structural damage to cellular membranes resulting from uncontrolled lipid peroxidation, the term ‘lipotoxicity’ may more accurately reflect its core mechanism (Piccolis et al., 2019; Schaffer, 2016).

The molecular mechanisms of ferroptosis have well expanded beyond the confines of the original GPX4 regulatory pathway. This review has amply discussed the battle between pro-ferroptotic and anti-apoptotic mechanisms that can be broadly classified as GPX4-dependent and GPX4-independent, encompassing historical perspectives and recent studies. Nevertheless, a central question remains unresolved: when, where and how are these different signaling pathways and molecular networks activated? Moreover, many of the regulatory molecules implicated in ferroptosis have also been involved in the regulation of other forms of cell death. This inherent heterogeneity and plasticity may reflect fundamental laws of the design of living organisms (Li et al., 2021c; Li et al., 2022b; Lin et al., 2022a; Yang et al., 2023b). Untangling the intricate cellular, molecular, and tissue mechanisms governing condition-dependent ferroptosis necessitates well-designed experiments incorporating stringent negative and positive controls, as well as the identification and validation of specific biomarkers (Dixon and Pratt, 2023; Liang et al., 2022).

The discovery of critical molecular regulatory mechanisms underlying ferroptosis has been facilitated by the identification of small molecule compounds as well as of their molecular targets. However, it is important to acknowledge that these compounds may have off-target effects, and further research aiming at target validation and the demonstration of target engagement, especially through *in vivo* experimentation, is crucial to unravel the mysteries of ferroptosis. Understanding the impact of physiological and pathogenic stressors on ferroptosis activity in real-world scenarios presents another significant challenge. Finally, the precise connections between stress pathways leading to ferroptotic and, or versus, non-ferroptotic cell death remain to be elucidated in all molecular details. Despite the occasional drawbacks of preclinical research and sometimes colliding hypotheses, we maintain optimism regarding the prospects. We anticipate that, well beyond their heuristic value, the principles of ferroptosis will eventually find clinical application.

**Author disclosure statement**

The authors declare no competing interests.

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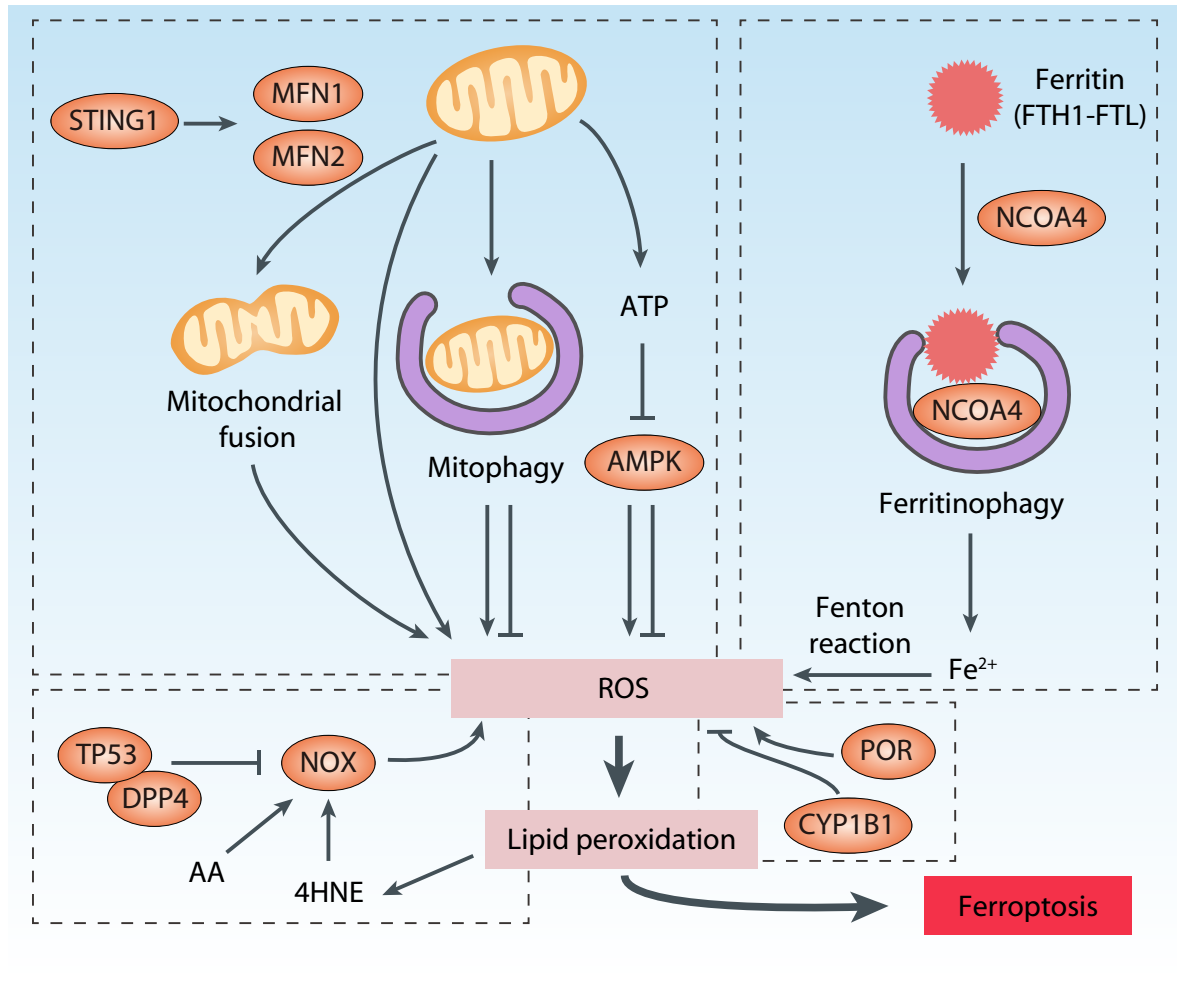
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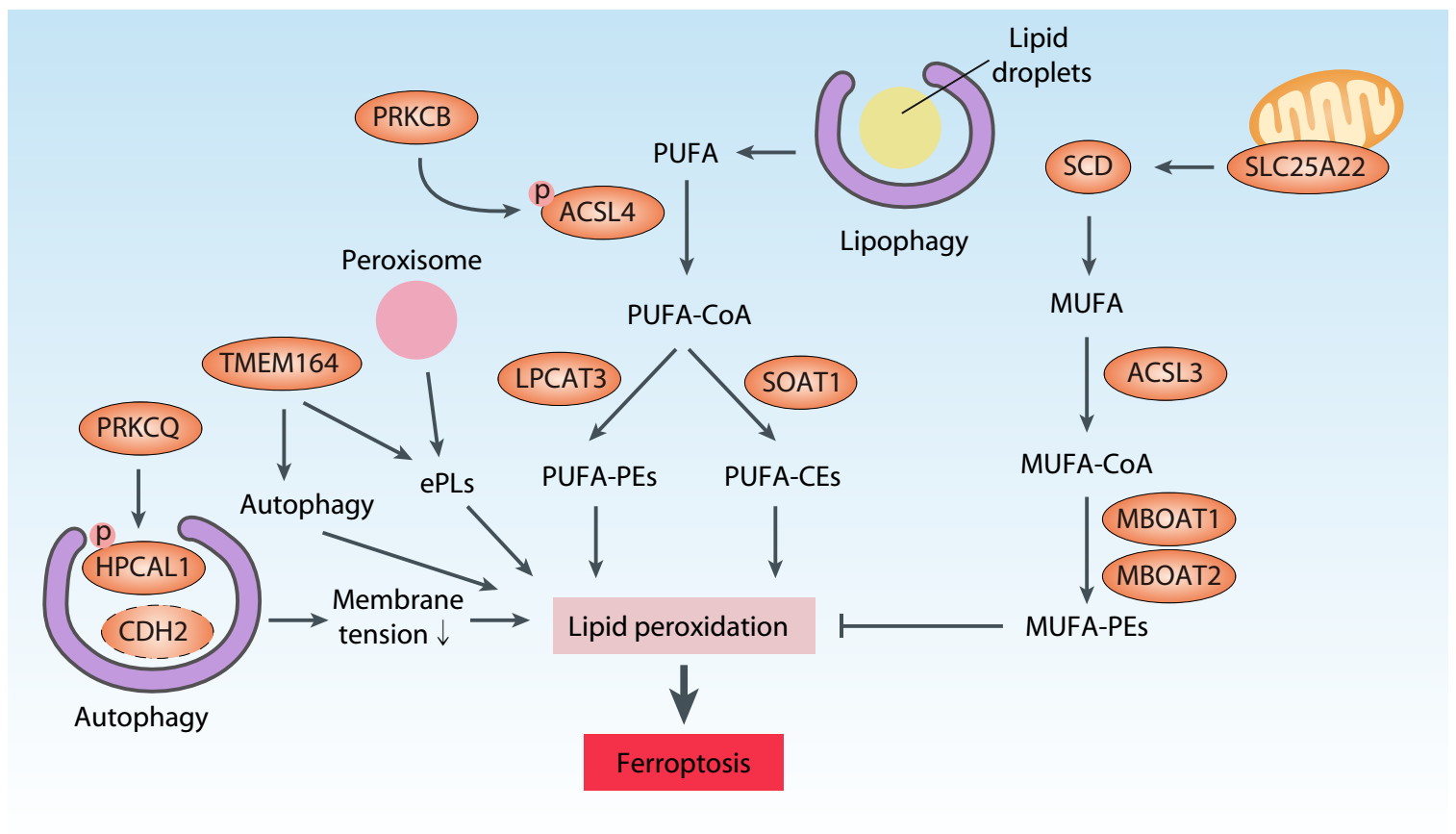
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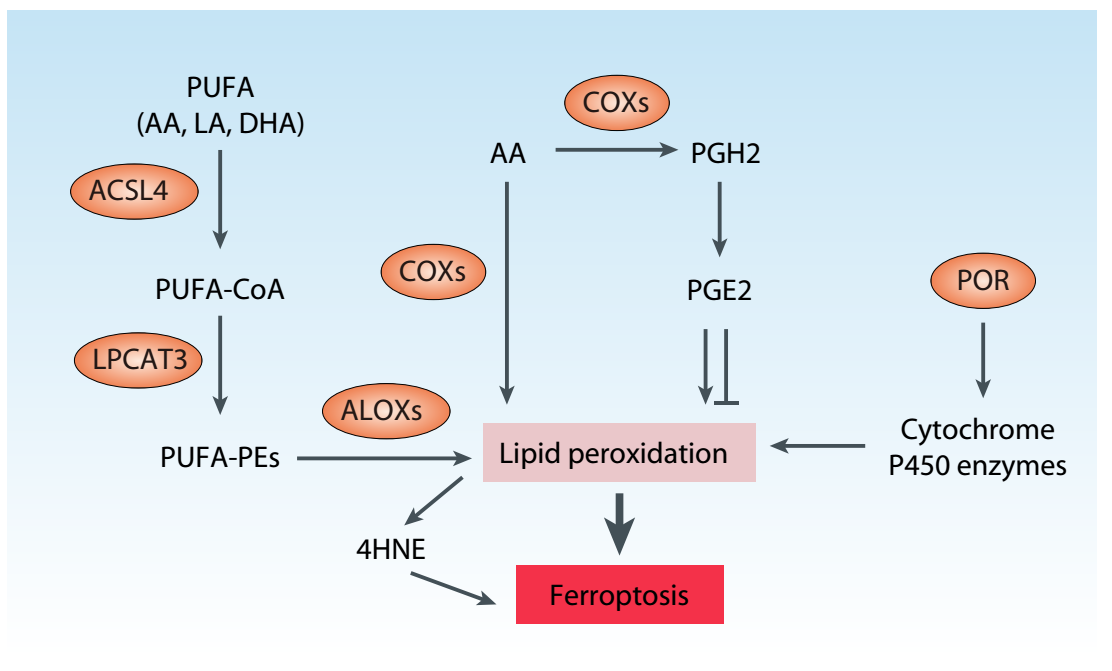
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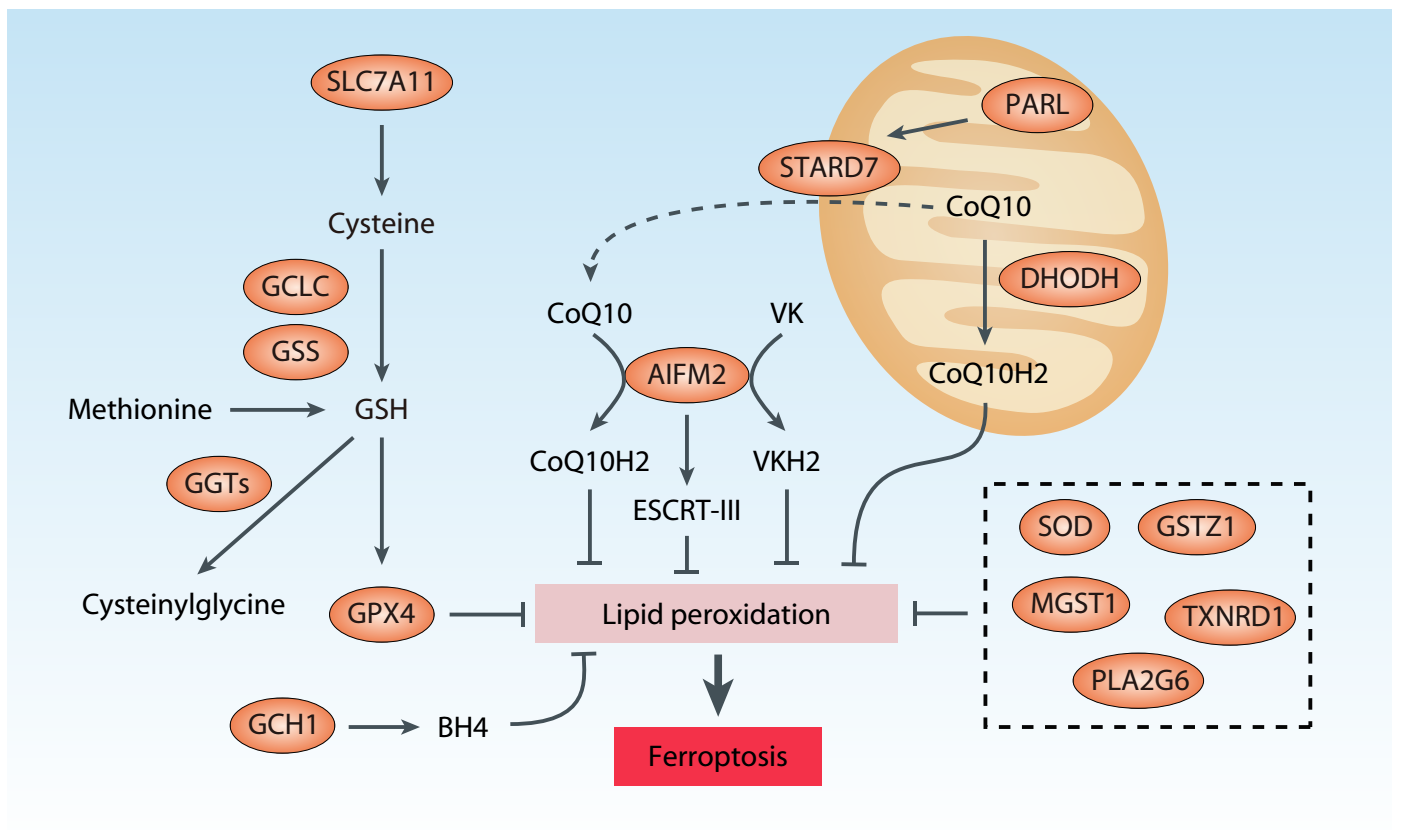
**Figure 1. The production of ROS in ferroptosis.** The initiation of ferroptosis requires an oxidative environment, facilitated by diverse sources of ROS. Mitochondrial ROS, primarily generated through the electron transport chain, can trigger ferroptosis in specific conditions. Mitophagy, involved in removing damaged mitochondria, has a dual role in promoting or inhibiting ferroptosis, while mitochondrial fusion increases cellular sensitivity to ferroptosis. Activation of the mitochondrial stimulator of interferon response CGAMP interactor 1 (STING1) may promote mitochondrial fusion, leading to ROS production implicated in ferroptosis. Mitochondrial energy stress activates AMP-activated protein kinase (AMPK), which can promote or inhibit ferroptosis by phosphorylating different substrates. NADPH oxidases (NOX) in cell membranes play a crucial role in generating ROS in ferroptosis. TP53 inhibits NOX-mediated ferroptosis by binding to dipeptidyl peptidase 4 (DPP4), while arachidonic acid (AA) and 4HNE enhance NOX1 activity to promote ROS production. The cytochrome P450 oxidoreductase (POR) promotes ROS production and ferroptosis, whereas cytochrome P450 family 1 subfamily B member 1 (CYP1B1) inhibits ferroptosis. Ferritinophagy involves the degradation of the iron storage protein ferritin, releasing Fe2+ that triggers ROS production through the Fenton reaction.



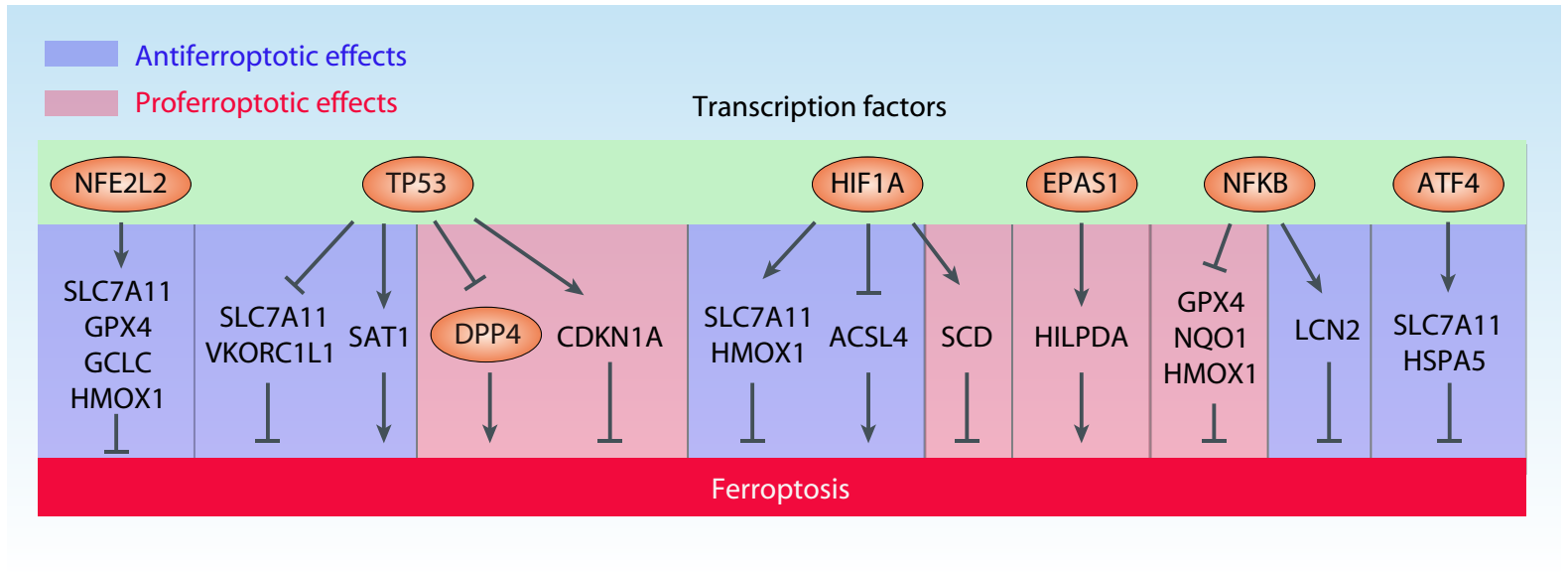
**Figure 2. The lipid supplements in ferroptosis.** Cell membranes are the primary target of oxidative damage in ferroptosis, influenced by processes and metabolic pathways that promote lipid synthesis. Acyl-CoA synthetase long-chain family member 4 (ACSL4) plays a critical role in activating polyunsaturated fatty acids (PUFA) by converting them into acyl-CoA esters (PUFA-CoA), which serve as substrates for lipid peroxidation, contributing to the initiation of ferroptosis. Two downstream pathways involve lysophosphatidylcholine acyltransferase 3 (LPCAT3)-mediated PUFA-PEs and sterol O-acyltransferase 1 (SOAT1)-mediated PUFA-CEs. The activity of ACSL4 in ferroptosis is further enhanced by protein kinase C beta (PRKCB)-mediated ACSL4 phosphorylation. Hippocalcin like 1 (HPCAL1) phosphorylation by protein kinase C theta (PRKCQ) promotes ferroptosis by inducing autophagic degradation of cadherin 2 (CDH2), leading to alterations in membrane tension in cancer cells. Monounsaturated fatty acid (MUFA) synthesis mediated by stearoyl-CoA desaturase (SCD) and acyl-CoA synthetase long-chain family member 3 (ACSL3) counteracts the initiation of ferroptosis by protecting against PUFA peroxidation. The mitochondrial transporter solute carrier family 25 member 22 (SLC25A22) plays a role in inhibiting ferroptosis by facilitating the production of SCD-mediated MUFA. Membrane bound O-acyltransferase domain containing 1 (MBOAT1) and membrane bound O-acyltransferase domain containing 2 (MBOAT2) inhibit ferroptosis by remodeling the cellular phospholipid profile to produce MUFA-PEs. Peroxisomes contribute to the biosynthesis of ether phospholipids (ePLs), which are vulnerable to lipid peroxidation. Transmembrane protein 164 (TMEM164) functions as an acyltransferase involved in ePLs synthesis or promotes the formation of autophagosomes. Lipophagy, the degradation of lipid droplets, releases lipids that can undergo peroxidation, increasing the susceptibility of cells to ferroptosis.



**Figure 3. The lipid peroxidation in ferroptosis.** Several key enzymes participate in lipid peroxidation, including lipoxygenases (ALOXs), cyclooxygenases (COXs), and cytochrome P450 enzymes. ALOXs are a family of enzymes that catalyze the oxygenation of polyunsaturated fatty acids (PUFAs), such as arachidonic acid (AA), linoleic acid (LA), and docosahexaenoic acid (DHA), leading to the formation of lipid hydroperoxides. On the other hand, COXs are enzymes involved in prostaglandin synthesis but can also catalyze lipid peroxidation. The production of prostaglandin E2 (PGE2) promotes or inhibits ferroptosis in a context-dependent manner. Additionally, POR plays a role by supplying electrons to cytochrome P450 enzymes involved in the production of lipid hydroperoxides. These hydroperoxides can undergo further reactions, such as decomposition and rearrangement, generating highly reactive lipid radicals. Ultimately, this cascade of reactions can disrupt membrane integrity and contribute to ferroptotic cell death.



**Figure 4. Enzymatic antioxidants in ferroptosis.** The main enzyme central to the antioxidant defense against ferroptosis is glutathione peroxidase 4 (GPX4), which requires a tripeptide cofactor glutathione (GSH), composed of glutamate, cysteine, and glycine. Solute carrier family 7 member 11 (SLC7A11) is a key component of the cystine/glutamate antiporter system xc-, responsible for allowing the uptake of cystine, which is then reduced to cysteine within the cells. The synthesis of the majority of cellular GSH involves the rate-limiting substrate cysteine, catalyzed by glutamate-cysteine ligase catalytic subunit (GCLC) and glutathione synthetase (GSS). Cysteine can also be derived from the metabolism of methionine. A family of enzymes called gamma-glutamyltransferases (GGTs) catalyze the breakdown of GSH into cysteinylglycine and free amino acids. Apoptosis inducing factor mitochondria associated 2 (AIFM2) and dihydroorotate dehydrogenase (DHODH) play pivotal roles in the reduction of coenzyme Q10 (CoQ10) to its antioxidant form, CoQ10H2, in the plasma membrane/cytoplasm and mitochondria, respectively. The cleavage of StAR-related lipid transfer domain-containing 7 (STARD7) by the rhomboid protease presenilin-associated rhomboid-like (PARL) is essential for the synthesis and transport of CoQ10 to the plasma membrane/cytoplasm, thereby inhibiting ferroptosis. Furthermore, AIFM2-mediated membrane repair and vitamin K (VK) reduction also contribute to its antiferroptotic activity. GTP cyclohydrolase 1 (GCH1) participates in the biosynthesis of tetrahydrobiopterin (BH4), a cofactor that helps maintain cellular redox balance and antioxidant defenses, thereby inhibiting susceptibility to ferroptotic cell death. Several other enzymes, such as mitochondrial superoxide dismutase (SOD), microsomal glutathione S-transferase 1 (MGST1), glutathione S-transferase zeta 1 (GSTZ1), thioredoxin reductase 1 (TXNRD1), and PLA2G6, have been found to inhibit ferroptosis in some cases.



**Figure 5. Transcription factors in ferroptosis.** Multiple transcription factors intricately regulate ferroptosis sensitivity and exert significant influence over the expression of diverse genes involved in the process. 1) NFE2 like BZIP transcription factor 2 (NFE2L2) activates the transcription of a battery of genes, including glutathione peroxidase 4 (GPX4)-dependent and independent pathways (e.g., solute carrier family 7 member 11 [SLC7A11], GPX4, glutamate-cysteine ligase catalytic subunit [GCLC], and heme oxygenase 1 [HMOX1]), involved in inhibiting ferroptosis. 2) Tumor protein p53 (TP53) has a dual role in regulating ferroptosis sensitivity. It can induce ferroptosis by suppressing SLC7A11 and vitamin K epoxide reductase complex subunit 1 like 1 (VKORC1L1) expression or inducing spermidine/spermine N1-acetyltransferase 1 (SAT1) expression. Conversely, TP53 inhibits ferroptosis by directly binding and sequestering dipeptidyl peptidase 4 (DPP4) in the nucleus. Furthermore, the classical TP53-inducible gene, cyclin dependent kinase inhibitor 1A (CDKN1A), also inhibits ferroptosis. 3) HIF1A can upregulate antioxidant enzymes like SLC7A11 and HMOX1 while inhibiting the expression of acyl-CoA synthetase long-chain family member 4 (ACSL4). It also increases the expression of stearoyl-CoA desaturase (SCD), which inhibits ferroptosis by producing monounsaturated fatty acids, thereby protecting cells from ferroptosis through enhanced antioxidant defenses. Conversely, the activation of transcription factor endothelial PAS domain protein 1 (EPAS1, also known as HIF-2α) stimulates the hypoxia-induced expression of hypoxia inducible lipid droplet associated (HILPDA) and selectively enriches polyunsaturated lipids to enhance ferroptosis. 4) Nuclear factor-kappa B (NFKB) can repress the transcription of antioxidant molecules (e.g., GPX4, NAD(P)H quinone dehydrogenase 1 [NQO1], and HMOX1), intensifying cellular oxidative stress. NFKB activation also leads to increased lipocalin 2 (LCN2) secretion, sequestering extracellular iron to induce ferroptosis. 5) Activating transcription factor 4 (ATF4) plays a crucial role in ER stress responses, leading to the upregulation of genes (such as SLC7A11 or heat shock protein family A (Hsp70) member 5 [HSPA5]) and inhibition of ferroptosis.