



The subcellular landscape of ferroptosis: A cellular organelle perspective

Junren Dai^{1,2}, Xingfeng Du³, Ying Hu^{1,2,3,*}

¹School of Life Science and Technology, Harbin Institute of Technology, Harbin 150001, Heilongjiang, China.

²Key Laboratory of Science and Technology and Intelligent Equipment for the Prevention and Control of Major Chronic Diseases, Ministry of Industry and Information Technology, Harbin Institute of Technology, Harbin 150001, Heilongjiang, China.

³Zhengzhou Advanced Research Institute, Harbin Institute of Technology, Zhengzhou 450000, Henan, China.

***Correspondence to:** Ying Hu, School of Life Science and Technology, Harbin Institute of Technology, Harbin 150001, Heilongjiang, China. E-mail: huying@hit.edu.cn

Received: July 05, 2026 **Accepted:** September 16, 2026 **Published:** September 16, 2026

Cite this article: Dai J, Du X, Hu Y. The subcellular landscape of ferroptosis: A cellular organelle perspective. *Ferroptosis Oxid Stress*. 2027;3:202632. <https://doi.org/10.70401/fos.2026.0043>

Abstract

Ferroptosis is a regulated form of cell death driven by iron-dependent lipid peroxidation. Its execution depends not only on the amount of lipid peroxides, but also on where oxidizable lipids, redox-active iron, reactive oxygen species, and antioxidant defenses are distributed within cells. This review summarizes current evidence for organelle-resolved regulation of ferroptosis and oxidative stress, with emphasis on the endoplasmic reticulum, peroxisomes, mitochondria, lysosomes, lipid droplets, and phase-separated condensates. We discuss how lipid remodeling, ether lipid synthesis, mitochondrial metabolism and local antioxidant defense, ferritinophagy, lysosomal lipid peroxidation, and lipid droplet-mediated fatty acid buffering influence ferroptosis sensitivity. We also summarize how organelle-specific redox defenses and stress-adaptive signaling pathways may shape therapeutic responses. Together, these studies show that ferroptosis is regulated by coordinated changes in lipid metabolism, iron handling, and antioxidant capacity across distinct subcellular compartments.

Keywords: Ferroptosis, lipid peroxidation, organelles, spatiotemporal specificity

1. Introduction

Ferroptosis is typically defined as a lipid-dependent regulated cell death driven by lipid peroxidation^[1-4]. The lipid reactive oxygen species (lipid ROS) referred to in this article generally encompass free radicals from lipid sources and oxidized membrane lipids, including phospholipid hydroperoxides. Lipid ROS are not uniformly produced within the cell, and their biological effects largely depend on the specific location and timing of their generation and accumulation. Only when oxidizable phospholipids, pro-oxidative reactions, iron with redox activity, and insufficient antioxidant defense occur simultaneously in a local subcellular region can membrane lipid peroxidation more easily accumulate and damage membrane integrity. Therefore, understanding how these factors aggregate and change in different subcellular regions from a temporal and spatial perspective helps explain why lipid peroxidation may first appear in specific membrane structures and then spread to other membrane regions, as well as how cells limit this process within a controllable range in most cases.

Overall, the lipid peroxidation related to ferroptosis requires several basic conditions. First, there must be oxidizable polyunsaturated fatty acid (PUFA) phospholipids in the cell membrane. Phospholipids containing arachidonic acid (AA) or adrenic acid (AdA) are the most extensively studied substrates in the classical ferroptosis model^[5,6]. In addition, the type of PUFA and its combination in phospholipids also affect ferroptosis sensitivity. Linoleic acid and conjugated PUFA can enhance ferroptosis induced by Ras-selective lethal 3 (RSL3)^[7]; phospholipids with both acyl chains as PUFA also show a strong pro-ferroptosis effect^[8]. Secondly, these susceptible phospholipids need to be oxidized. The initiation reaction can be catalyzed by enzymes or occur through non-enzymatic free radical reactions^[4]. Once lipid peroxidation is formed, it can also be further amplified. Zhang *et al.* found that PKC β II can sense early lipid peroxidation and phosphorylate acyl-CoA synthetase long-chain family member 4 (ACSL4) at the Thr328 site, thereby enhancing ACSL4 activity and the generation of phospholipids containing PUFA, further promoting lipid peroxidation^[9]. At the same time, labile iron can promote lipid oxidation through the Fenton reaction and related free radical chemical processes^[1,4]. Finally, lipid peroxidation will only continue to accumulate after exceeding the local clearance capacity of the cell. These defenses include glutathione peroxidase 4 (GPX4)-mediated reduction of phospholipid hydroperoxides using glutathione (GSH)^[2], as well as FSP1-coenzyme Q (CoQ)-dependent, GPX4-independent defense^[10,11] and lipid remodeling mediated by GTP cyclohydrolase 1 (GCH1)-tetrahydrobiopterin (BH₄) pathway^[12]. Therefore, ferroptosis essentially reflects the loss of balance between local lipid



© The Author(s) 2026. This is an Open Access article licensed under a Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

peroxide generation and clearance.

These pro-oxidative factors and defense mechanisms are not uniformly distributed in various organelles. The endoplasmic reticulum is an important site for lipid synthesis and phospholipid remodeling, and ACSL4/lysophosphatidylcholine acyltransferase 3 (LPCAT3)-mediated lipid remodeling can affect the supply of oxidizable membrane lipids^[5,13,14], while cytochrome P450 oxidoreductase (POR)-mediated oxidation reactions provide the pro-oxidative mechanism related to the endoplasmic reticulum^[15]. In some models, the endoplasmic reticulum-mitochondria contact site can also be an area where phospholipid peroxidation occurs earlier^[16]. Mitochondria provide metabolic input for ferroptosis through glutaminolysis and the tricarboxylic acid (TCA) cycle^[17,18], and also have local defense mechanisms such as dihydroorotate dehydrogenase (DHODH) and mitochondrial GPX4, which can limit mitochondrial membrane lipid peroxidation under specific conditions^[19]. Lysosomes regulate the availability of intracellular iron through ferritin turnover^[20,21]; the lysosome-targeted compound fentomycin-1 (Fento-1) activates reactive lysosomal iron^[22], and in some models, lipid peroxidation in lysosomes can further promote lysosomal membrane permeabilization^[23]. Peroxisomes mainly change the composition of oxidizable lipid substrates through ether lipid synthesis^[24,25]. Lipid droplets can regulate the distribution of PUFA between neutral storage lipids and membrane phospholipids, and their effects vary with metabolic state and cellular background^[26-30]. Besides membrane organelles, phase separation also provides another spatial regulatory mechanism. Ferroptosis suppressor protein 1 (FSP1) condensation can alter the subcellular localization of this antioxidant protein^[31], sequestosome 1 (p62) condensates can regulate the antioxidant signaling of Kelch-like ECH-associated protein 1 (KEAP1)-nuclear factor erythroid 2-related factor 2 (NRF2)^[32,33], and nuclear receptor coactivator 4 (NCOA4)-dependent ferritin condensation participates in ferritin turnover^[34].

There have been reviews summarizing ferroptosis regulation from the perspective of organelles and establishing a relatively complete cellular biology framework in this field^[3,35]; recently, there have also been mini-reviews focusing on lysosomal iron metabolism and its relationship with tumor plasticity^[36]. Based on this, this article pays more attention to a specific issue: where exactly do lipid peroxidation, iron mobilization, and antioxidant defense occur within the cell, and how these spatial differences affect the initiation, amplification, and propagation of ferroptosis. Besides traditional organelles, we also incorporate recent progress such as organelle contact sites, lysosomal membrane damage, lipid droplet regulation with significant context dependence, and phase separation condensates, and try to distinguish direct evidence of early local lipid oxidation, subsequent amplification or propagation processes, and only reflecting changes in ferroptosis sensitivity. **Figure 1** summarizes the main distribution of PUFA phospholipids, ROS, Fe²⁺, and antioxidant defense in different subcellular regions and their interrelationships. The following sections will discuss various organelles and related subcellular structures, focusing on how they provide lipid substrates, regulate redox reactions, organize local defense, or participate in the early occurrence and subsequent expansion of lipid peroxidation under specific conditions.

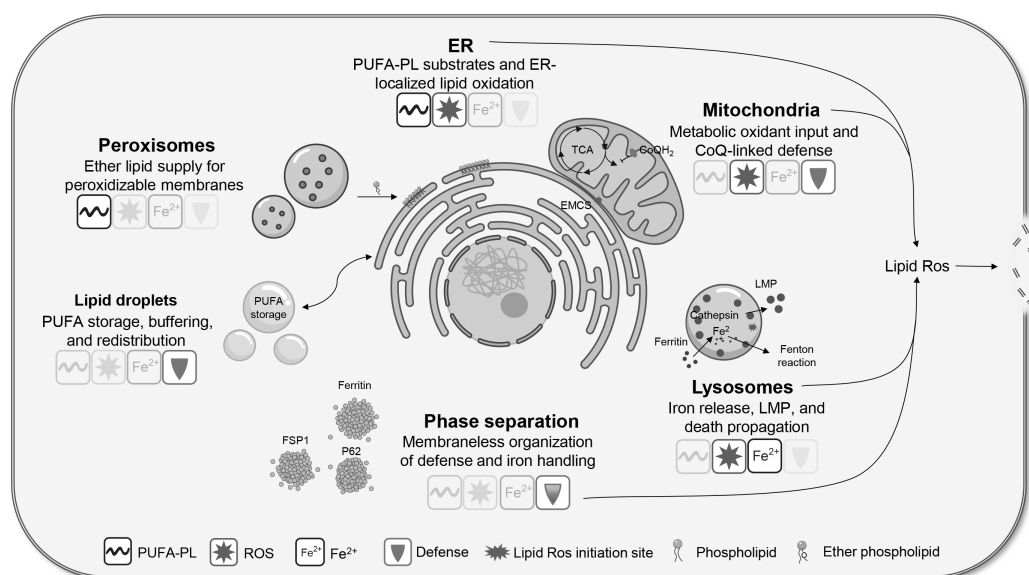


Figure 1. Subcellular landscape of lipid peroxidation and ferroptosis control. Ferroptosis depends on the coordinated distribution of PUFA-PLs, ROS, Fe²⁺, and antioxidant defenses across organelles. The ER supplies and remodels PUFA-containing phospholipids, mitochondria contribute metabolic redox input and CoQ-linked defense, lysosomes regulate iron and LMP-associated damage, and peroxisomes support ether lipid metabolism. Lipid droplets buffer exogenous PUFAs, while phase-separated condensates may regulate defense protein localization, NRF2-related antioxidant signaling, and ferritin turnover. Together, these organelles determine where lipid peroxidation is initiated, amplified, or restrained. CoQ: coenzyme Q; CoQH₂: ubiquinol; EMCS: ER-mitochondria contact site; ER: endoplasmic reticulum; FSP1: ferroptosis suppressor protein 1; LMP: lysosomal membrane permeabilization; lipid ROS: lipid reactive oxygen species; NRF2: nuclear factor erythroid 2-related factor 2; p62: sequestosome 1; PUFA: polyunsaturated fatty acid; PUFA-PL: polyunsaturated fatty acid-containing phospholipid; ROS: reactive oxygen species; TCA: tricarboxylic acid.

2. Endoplasmic Reticulum

The endoplasmic reticulum (ER) plays a crucial role in maintaining calcium ion and protein homeostasis, as well as in membrane lipid synthesis and remodeling^[35]. During ferroptosis, the ER functions through processes such as phospholipid remodeling^[5,13,14], POR-dependent phospholipid peroxidation^[15], stress signal transduction^[37,38], and regulation of the contact sites between the ER and mitochondria^[16].

One of the established functions of the endoplasmic reticulum is to generate and remodel the lipid substrates that support ferroptosis. Long-chain ACSL4 first activates long-chain PUFAs, particularly arachidonic acid and adrenic acid, at membrane-associated sites, generating PUFA-CoA^[5]. Although ACSL4 is not a specific marker of the endoplasmic reticulum, the activated PUFA-CoA can enter the endoplasmic reticulum-related phospholipid remodeling process. LPCAT3 is the endoplasmic reticulum-related lysophospholipid acyltransferase in the Lands cycle, and subsequently transfers these polyunsaturated acyl chains to lysophospholipids, generating phospholipids containing PUFA^[13,14]. The resulting phospholipid composition alters the pool of easily oxidizable substrates, thereby affecting the sensitivity to ferroptosis^[13,14].

These lipid remodeling events provide easily oxidizable substrates in the ER-related membranes^[6,13,14]. Redox lipidomics showed that GPX4 inhibition leads to the accumulation of oxidized arachidonoyl- and adrenoyl-phosphatidylethanolamines in ER-associated compartments^[6]. The endoplasmic reticulum may also promote lipid peroxidation through local redox enzymes. POR is an ER-associated, reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent oxidoreductase identified by genome-wide clustered regularly interspaced short palindromic repeats-CRISPR-associated protein 9 (CRISPR-Cas9) screens as a contributor to ferroptosis across multiple cancer lineages, cell states, and induction mechanisms. Systematic lipidomic profiling mapped POR activity to the phospholipid-peroxidation step^[15], indicating that the endoplasmic reticulum can not only provide oxidizable substrates but also provide redox activity promoting the peroxidation reaction. At ER-mitochondria contact sites, locally formed phospholipid peroxides were subsequently detected toward mitochondria, together with increased mitochondrial ROS and fission^[16].

ER stress and unfolded protein response pathways add another layer of regulation, but their role is context-dependent. Ferroptosis inducers can activate protein kinase R-like ER kinase (PERK)-eukaryotic translation initiation factor 2 α (eIF2 α)-activating transcription factor 4 (ATF4)-C/EBP homologous protein (CHOP) signaling and interact with apoptotic pathways^[37]. However, ATF4 can also induce solute carrier family 7 member 11 (SLC7A11), maintain glutathione synthesis, and suppress ferroptosis-associated tissue damage in liver disease models^[38]. Therefore, ER stress should be viewed as a modifier of ferroptosis sensitivity, not as a universal initiating event.

3. Mitochondria

Mitochondria support the TCA cycle and the electron transport chain (ETC), linking the oxidation of nutrients with adenosine triphosphate (ATP) production. Electron transfer also generates ROS, and the mitochondrial antioxidant system removes these ROS^[39]. These metabolic and redox functions can affect ferroptosis, but the involvement of mitochondria is not fixed. In the model tested by Gao *et al.*, mitochondria are necessary for cystine deprivation-induced ferroptosis, while the death caused by GPX4 inhibition requires much less mitochondrial involvement^[17]. The inducing conditions determine which mitochondrial processes are associated with it.

System xc⁻ is a cystine/glutamate antiporter that can provide extracellular cystine for the synthesis of intracellular cysteine^[2]. Inhibiting system xc⁻ or removing cystine will limit the supply of cysteine and reduce the synthesis of GSH^[2,17]. The resulting depletion of GSH will gradually weaken the ability of GPX4 to remove phospholipid hydroperoxides^[2,17]. In the cystine deprivation model used by Gao *et al.*, blocking glutaminolysis, the TCA cycle, or the ETC can reduce the accumulation of lipid peroxides and protect cells from ferroptosis^[17]. Glutaminolysis converts glutamine into glutamate and α -ketoglutarate, providing a carbon source for the TCA cycle^[18]. During cystine deprivation, inhibiting glutaminolysis can inhibit ferroptosis, and when this pathway is blocked, supplementing downstream TCA cycle intermediates will restore cell death^[18].

GPX4 reduces phospholipid hydroperoxides to the corresponding phospholipid alcohols. RSL3 and ML162 directly inhibit this detoxification step^[2]. Gao *et al.* compared the effects of cystine deprivation and GPX4 inhibition in mouse embryonic fibroblasts and HT1080 cells. Elimination or inhibition of mitochondrial function has a strong protective effect on cystine deprivation, but HT1080 cells with depleted mitochondria remain sensitive to RSL3^[17]. Therefore, under these experimental conditions, the absence or inhibition of GPX4 can lead to lipid peroxidation, independent of mitochondrial metabolism. Mitochondria may still alter downstream events. Mitochondrial respiration is not required for ferroptosis induced by direct GPX4 inhibition.

DHODH is an enzyme of de novo pyrimidine synthesis located in the mitochondrial inner membrane^[19]. During the oxidation of dihydroorotate to orotate, DHODH reduces ubiquinone (CoQ) to ubiquinol (CoQH₂)^[19]. CoQH₂ is the reduced form of CoQ and acts as a radical-trapping antioxidant that suppresses lipid-radical propagation in the mitochondrial inner membrane^[19]. Mao *et al.* demonstrated that DHODH acts in parallel with mitochondrial GPX4 to limit mitochondrial lipid peroxidation^[19]. Supplementation with dihydroorotate or orotate, the substrate and product of DHODH, attenuated or potentiated GPX4-inhibitor-induced ferroptosis,

respectively^[19]. Inactivation of DHODH can induce ferroptosis in cancer cells with low GPX4 expression and enhance the ferroptosis triggered by GPX4 inhibition in cells with high GPX4 expression^[19].

In HT-22 neuronal-like cells, glutamate-induced oxytosis or erastin treatment caused BH3-interacting domain death agonist (BID), a BH3-only member of the BCL-2 family, to translocate to mitochondria^[40]. BID inhibition limited mitochondrial ROS and preserved membrane potential. ATP loss was attenuated, while release of apoptosis-inducing factor (AIF) was blocked^[40]. These experiments were performed in HT-22 cells and related neuronal cultures. BID has not been tested broadly in cancer cells or with other ferroptosis inducers.

Mitochondria provide pro-ferroptotic metabolic input during cystine limitation and also contain DHODH- and mitochondrial GPX4-dependent defenses. Their requirement was lower after direct GPX4 inhibition in the tested models^[17,19]. The HT-22 BID pathway shows that cell type can change the contribution of mitochondrial injury^[40]. Mitochondrial involvement therefore differs across experimental systems. Understanding the role of mitochondria in ferroptosis requires correlation with inducers, cell models, and measurement times.

4. Peroxisomes

The peroxisome is a single-membrane organelle that participates in fatty acid oxidation, reactive oxygen metabolism, and ether phospholipid biosynthesis. According to current research, peroxisomes mainly alter susceptibility through ether phospholipid biosynthesis rather than serving as the primary site for lipid reactive oxygen generation^[24,25,41].

The synthesis of ether phospholipids begins in the peroxisomes and is completed in the endoplasmic reticulum^[24,25]. This pathway generates ether phospholipids, including alkyl-ether phospholipids and plasmalogens, which may contain PUFA chains at the sn-2 position^[42]. These lipids can serve as substrates for lipid peroxidation^[24,25]. Genome-wide CRISPR-Cas9 screens in renal and ovarian cancer cells identified peroxisome biogenesis genes and ether-lipid biosynthesis genes, including peroxisomal biogenesis factor 3 (PEX3), PEX10, alkylglycerone phosphate synthase (AGPS), and fatty acyl-CoA reductase 1 (FAR1), as determinants of ferroptosis sensitivity. The deletion of these genes reduces the abundance of peroxisomes, depletes polyunsaturated ether phospholipids, and protects cells from ferroptosis induced by GPX4 inhibition^[24,25]. In contrast, ferroptosis-sensitive cancer cells can acquire resistance *in vivo*, while the abundance of polyunsaturated ether phospholipids is reduced^[24].

However, the relationship between ether lipids and ferroptosis is not a simple linear one. FAR1-dependent fatty alcohol production and peroxisome-driven ether phospholipid biosynthesis can promote ferroptosis, but different types of ether lipids may have different effects^[24,25]. TMEM189 converts alkyl-ether phospholipids to alkenyl-ether phospholipids, also known as plasmalogens. In the tested model, plasmalogen synthesis counteracted FAR1-driven ferroptosis^[25]. Depending on their molecular species and cellular context, plasmalogens may provide oxidizable PUFA-containing phospholipids or display radical-scavenging properties^[42].

Therefore, peroxisomes affect ferroptosis susceptibility by providing or restricting specific ether-linked lipid substrates^[24,25]. Whether these lipids are oxidized on peroxisomal membranes, endoplasmic reticulum-related membranes, plasma membrane regions, or organelle contact sites may depend on the inducer, cell type, lipid composition, and local redox environment. Moreover, there is currently no direct evidence to prove that peroxisomes are the initiation site of lipid ROS.

5. Lysosomes

Lysosomes are acidic degradation organelles that are responsible for participating in the degradation of recyclable macromolecules, as well as autophagy and intracellular iron processing^[20-23,35]. These functions make lysosomes closely related to the two key elements of ferroptosis: redox-active iron and membrane lipid oxidation. In current research, lysosomes affect ferroptosis through ferritin turnover and iron release^[20-22,43], lysosomal lipid peroxidation and membrane permeabilization^[23], or collective propagation after glutathione depletion^[44].

Ferritinophagy is an important pathway through which lysosomes participate in ferroptosis^[20,21]. Ferritin stores iron in a relatively inert state, and its selective autophagic degradation can release iron and expand the labile iron pool within the cell^[20,21,43]. NCOA4 is a key cargo receptor in this process, responsible for recognizing ferritin and promoting its entry into the autophagic degradation pathway, ultimately being degraded in the lysosome^[20]. In ferroptosis models, genetic inhibition of autophagy-related 5 (ATG5), ATG7, or NCOA4 can reduce ferritin degradation and intracellular Fe²⁺ accumulation, while also lowering lipid peroxidation levels and inhibiting erastin-induced ferroptosis^[21].

In recent years, some studies have begun to further investigate whether the lysosome itself can also be an early site of lipid oxidation. It has been found that liproxstatin-1 and its related probes preferentially accumulate in lysosomes and exert protective effects by inactivating the active iron within the lysosome^[22]. In RSL3-treated cancer cells, lipid oxidation signals first appear in lysosomes and then extend to other membrane structures including the endoplasmic reticulum^[22]. The study further showed that Fento-1 promotes the oxidative degradation of phospholipids and induces ferroptosis in iron-rich cancer cells^[22]. These results suggest that under specific experimental conditions, iron with redox activity within the lysosome may be involved in the early membrane lipid oxidation.

Lysosomal lipid peroxidation may further amplify ferroptosis by damaging the lysosomal membrane. After tracking with lipid free radical probes, it was found that lysosomal lipid peroxidation is accompanied by increased lysosomal membrane permeability, changes in intracellular pH, release of cathepsins, and iron leakage, and is further associated with enhanced lipid peroxidation throughout the cell^[23]. However, this process is not the same in all cells. In some cell lines that are relatively insensitive to RSL3-induced ferroptosis, although lysosomal lipid peroxidation can be detected, there is no obvious lysosomal membrane permeabilization (LMP). In these cell models, combining chloroquine treatment can induce LMP and increase the sensitivity of cells to GPX4 inhibitor-induced ferroptosis^[23].

In addition, the lysosome may also affect the spread of ferroptosis in the cell population. Recent studies have shown that glutathione depletion can change the death pattern after GPX4 inhibition, transforming previously isolated single-cell death into collective necrosis^[44]. A related Preview further proposed that lysosomal rupture may be an important link connecting single-cell ferroptosis and the spread of the population^[45]. This collective propagation state is accompanied by obvious lysosomal rupture and may present a mixed cell death phenotype^[44]. Therefore, lysosomal damage may not only affect whether individual cells enter ferroptosis, but also participate in determining whether ferroptosis stress can spread in the cell population.

Overall, the lysosome mainly participates in ferroptosis regulation through iron mobilization and membrane damage^[20-23,44]. Among them, ferritinophagy and lysosomal iron have been well supported by genetic and biochemical evidence^[20-22,43]; in contrast, lysosomal lipid peroxidation and membrane rupture are more likely to participate in the early initiation or subsequent amplification of ferroptosis under specific conditions^[22,23,44]. As for whether lysosomal damage occurs before endoplasmic reticulum, mitochondria, or plasma membrane damage, it is still difficult to generalize, and the sequence relationship may be affected by factors such as ferroptosis induction mode, cell type, iron load, glutathione level, lipid probes, and detection time.

6. Lipid Droplets

Lipid droplets are neutral lipid storage organelles derived from the endoplasmic reticulum, which can buffer the intracellular fatty acid flux by regulating the storage and release of fatty acids. In the process of ferroptosis, one of the important roles of lipid droplets is to determine whether PUFAs enter the triacylglycerol storage pool or are integrated into membrane phospholipids, thereby changing the possibility of lipid peroxidation^[26-30].

Numerous studies have shown that lipid droplet formation has a protective effect under certain conditions. In cancer cells adapted to the acidic extracellular environment, n-3 and n-6 long-chain PUFA are more likely to accumulate in lipid droplets^[26]. When the PUFA intake exceeds the storage capacity of lipid droplets or the activity of diacylglycerol acyltransferase (DGAT) is inhibited, excess PUFA cannot be adequately stored in neutral lipids, and lipid peroxidation increases, thereby promoting ferroptosis^[26]. Additionally, cell cycle arrest can induce DGAT-dependent lipid droplet formation, causing more excess PUFA to enter triacylglycerol, thereby reducing ferroptosis sensitivity^[27]. However, lipid droplets do not always play the same role in all conditions. Recent studies have shown that the effect of DGAT-mediated lipid droplet formation on ferroptosis depends on the PUFA load and the cell's own ferroptosis defense ability, and may even show opposite effects under different experimental conditions^[28].

The fatty acid composition also alters the relationship between lipid droplets and ferroptosis. Exogenous monounsaturated fatty acids can enhance ferroptosis resistance through ACSL3-dependent lipid metabolism, accompanied by a decrease in membrane lipid ROS and a reduction in oxidizable PUFA phospholipids^[29]. However, the role of ACSL3 cannot be simply summarized as anti-ferroptosis. In clear cell renal cell carcinoma, ACSL3 not only participates in lipid droplet formation and supports tumor growth, but its inhibition can instead reduce the cell's sensitivity to ferroptosis, suggesting that ACSL3-dependent fatty acid metabolism also helps maintain a lipid composition prone to peroxidation in specific tumor contexts^[30].

The oxidation state of the lipids within lipid droplets themselves may further affect this process. Kump *et al.* found in lung adenocarcinoma cells that FSP1 deficiency enhances lipid peroxidation within lipid droplets, suggesting that lipid peroxidation produced by lipid droplets may further promote the diffusion of lipid ROS to other cellular compartments^[28]. This result indicates that lipid droplets do not merely store and buffer fatty acids in the process of ferroptosis; when local antioxidant defense is weakened, the lipid peroxidation that has already occurred within lipid droplets may also participate in the expansion of subsequent oxidative damage.

Overall, the influence of lipid droplets on the sensitivity to ferroptosis is highly context-dependent. Their effect largely depends on how fatty acids are allocated between neutral storage lipids and membrane phospholipids, and is also influenced by factors such as DGAT activity, fatty acid composition, cell state, and antioxidant capacity^[26-30].

7. Organelle Contact Sites

The organelle contact sites refer to the structures formed when the membranes of two organelles are closely adjacent to each other but do not undergo membrane fusion^[46]. This narrow spatial distance is conducive to the direct exchange of substances such as lipids and ions, or the completion of transport through related proteins, and can also form a localized signaling environment^[46]. In this

article, ER-mitochondria contact sites (EMCSs) mainly refer to the contact structures that can be observed or experimentally manipulated in intact cells. In contrast, mitochondria-associated membranes (MAMs) usually refer to the specialized ER membrane domains located at these contact interfaces; in biochemical research, MAM is also often used to describe the corresponding membrane components obtained by subcellular fractionation^[47]. Therefore, although EMCSs and MAMs have similar concepts, they are not exactly the same^[46,47].

Currently, studies linking organelle contact sites with ferroptosis mainly focus on EMCSs. Super-resolution imaging combined with oxidative lipidomics has revealed that after ferroptosis induction, phospholipid peroxidation can occur earlier at the ER-mitochondria interface. Experimental alterations in the degree of connection between ER and mitochondria also affect the sensitivity of cells to ferroptosis. Subsequently, local lipid peroxidation signals can further extend to mitochondria, accompanied by increased ROS in mitochondria and mitochondrial fission^[16]. These results indicate that in the corresponding experimental models, EMCSs can be the regions where lipid oxidation occurs earlier, but this phenomenon may not apply to other ferroptosis conditions and requires further verification.

The ER-mitochondrial interface not only participates in the pro-oxidative process but can also organize anti-ferroptosis signals. In the local signal regions enriched with MAMs, A-kinase anchoring protein 1 (AKAP1)-anchored protein kinase A (PKA) can phosphorylate glucose-regulated protein 75 (GRP75), thereby promoting the stabilization of NRF2 and enhancing the expression of anti-ferroptosis-related genes^[48]. Therefore, the influence of EMCSs on ferroptosis is not fixed but depends on the specific proteins aggregated at the contact site and the activated signaling pathways.

In addition to ER-mitochondrial contact, mitochondrial-lysosomal contacts (MLCs) can also affect ferroptosis by regulating the distribution of iron within the cell^[49]. In melanoma cells, BDH2 can be recruited to MLCs and generate the iron-binding metabolite 2,5-dihydroxybenzoic acid (2,5-DHBA), thereby promoting the transfer of Fe(II) from lysosomes to mitochondria^[49]. After the deletion of BDH2, mitochondrial iron content decreases, while more iron accumulates in lysosomes, accompanied by abnormal contact dynamics and lysosomal pH, and the sensitivity of cells to ferroptosis also increases. Re-expression of BDH2 or supplementation of 2,5-DHBA can restore MLC structure and reduce this ferroptosis sensitivity^[49]. These results suggest that MLCs can affect ferroptosis by regulating the distribution of iron between lysosomes and mitochondria.

Another study tracked the changes in lysosomes and ER during the ferroptosis process over time. Within 15 minutes after RSL3 treatment, the GSH level in lysosomes decreased, and the hydroxyl radical signal increased; approximately 1 hour later, the oxidative membrane lipid signal mainly appeared in lysosomes, and by 4 hours, most of the signals were associated with ER. Inhibition of lysosomal acidification can reduce the reactive iron level in lysosomes and weaken lipid oxidation^[22]. These results suggest that lysosomes and the ER may successively participate in lipid peroxidation during ferroptosis, but there is currently no direct evidence to observe that the lysosome-ER contact site is the initial starting point of lipid ROS.

8. Phase Separation and Membraneless Condensates

Liquid-liquid phase separation can be driven by multivalent molecular interactions, often involving intrinsically disordered regions or low complexity regions^[31]. The resulting aggregates do not have a lipid bilayer but can alter the spatial distribution of proteins within the cell and their functional locations. For ferroptosis, this means that cells can reorganize antioxidant defenses or iron homeostasis-related processes without forming new membrane compartments. Existing evidence more supports the regulation of ferroptosis sensitivity by such aggregates, but is not sufficient to consider them as the universal lipid ROS initiation sites.

FSP1 is a relatively direct example of this spatial regulation. FSP1 typically binds to the membrane and inhibits lipid radical amplification through its CoQ oxidoreductase activity, which does not rely on GPX4. The small molecule icFSP1 does not primarily exert its effect by competitively inhibiting FSP1 enzyme activity *in vitro*, but rather causes FSP1 to leave its original membrane environment and reaggregate to form aggregates with phase separation characteristics. This process depends on the N-terminal myristoylation of FSP1 and specific sequence features, including disordered regions or low complexity regions. After FSP1 detaches from the membrane, its anti-ferroptosis effect weakens, and cells become more sensitive to GPX4 inhibition. This study also observed FSP1 aggregate formation in tumor models and found that icFSP1 treatment can inhibit tumor growth^[31]. Therefore, the key revealed by this study is that phase separation alters the membrane localization of FSP1 and its anti-ferroptosis function, rather than demonstrating that the aggregates themselves can produce lipid peroxides.

p62 participates in ferroptosis regulation through another mechanism. Ferroptosis induction can promote PRMT6-dependent asymmetric dimethylarginine modification of p62, thereby enhancing p62 oligomerization and promoting aggregate formation. The formed p62 bodies can recruit KEAP1, stabilizing NRF2 and increasing the expression of antioxidant genes. Interfering with PRMT6 or p62 can enhance the sensitivity of pancreatic cancer cells to ferroptosis, and *in vivo* experiments also support this effect^[32]. Additionally, neighbor of BRCA1 gene 1 (NBR1) can promote p62 droplet formation and enhance the KEAP1-NRF2 signal, but related studies mainly focus on oxidative stress and autophagy rather than directly studying ferroptosis^[33].

Phase separation can also link immune signals to ferroptosis. In melanoma models, interferon-gamma (IFN- γ) induces

guanylate-binding protein 2 (GBP2) expression and promotes GBP2 aggregate formation through its inherent disordered regions. Src homology region 2 domain-containing phosphatase-1 (SHP1) is then recruited to these aggregates, allowing signal transducer and activator of transcription 1 (STAT1) signaling to persist and reducing SLC7A11 expression. Destruction of GBP2 phase separation leads to a decrease in lipid ROS levels and a weakening of T-cell-mediated ferroptosis killing. In the experimental models used, this change also weakens the tumor-suppressing effect of anti-PD-L1 treatment^[50]. Therefore, GBP2 aggregates mainly affect ferroptosis by altering IFN- γ signal transmission, and their effect is likely to depend on the specific immune and cell signaling background.

NCOA4 links aggregate formation to intracellular iron turnover. NCOA4 can promote the formation of liquid-like ferritin aggregates and facilitate ferritin degradation through macroferritinophagy and microferritinophagy pathways^[34]. Studies have shown that ferritin degradation can expand the labile iron pool and increase ferroptosis sensitivity^[20,21], so NCOA4-mediated aggregate formation may indirectly affect subsequent lipid peroxidation by regulating iron supply. Overall, the current role of phase separation in ferroptosis is mainly manifested as spatial regulation of antioxidant defense, signal transduction, and iron turnover, and is more upstream of lipid membrane damage.

Table 1 summarizes representative rather than exhaustive mechanisms. Initiation-site assessments refer to direct compartment-resolved evidence in the cited experimental models and do not imply a universal requirement. “Not established” indicates insufficient direct evidence for local initiation, rather than absence of a ferroptosis-related role.

Table 1. Major compartment-associated mechanisms and functional contributions to ferroptosis.

Subcellular compartment or structure	Evidence for local lipid-peroxidation initiation	Major mechanisms and molecular players	Principal contribution to ferroptosis
Endoplasmic reticulum	Not established	ACSL4/LPCAT3: PUFA-PL synthesis and remodeling ^[5,13,14] POR: ER-associated phospholipid peroxidation ^[15] PERK-ATF4-SLC7A11: context-dependent stress adaptation ^[37,38]	PUFA-PL supply; local lipid oxidation; adaptive GSH response
Mitochondria	Not established	Glutaminolysis/TCA cycle/ETC: metabolic contribution under cystine limitation ^[17,18] DHODH-mediated CoQH₂ production: mitochondrial inner-membrane defense acting in parallel with mitochondria-localized GPX4 ^[19]	Metabolic redox input; CoQ-linked defense; model-dependent amplification
Peroxisomes	Not established	PEX3/PEX10/AGPS/FAR1: polyunsaturated ether-lipid synthesis ^[24,25] TMEM189/plasmalogen remodeling: context-dependent modification of ether-lipid effects ^[25,42]	Ether-lipid substrate supply
Lysosomes	Supported in specific experimental models	NCOA4-mediated ferritinophagy: labile iron mobilization ^[20,21,43] Reactive lysosomal Fe²⁺: local iron-dependent phospholipid oxidation ^[22] Lysosomal lipid peroxidation/LMP: damage amplification ^[23,44]	Fe ²⁺ mobilization; local lipid oxidation; LMP-dependent amplification
Lipid droplets	Not established	DGAT-dependent lipid storage: PUFA sequestration and availability ^[26-28] ACSL3-dependent fatty-acid handling: context-dependent resistance or sensitization ^[29,30]	PUFA storage, buffering and remobilization
Organelle contact sites	Supported at EMCSs	EMCS-localized phospholipid peroxides: localized formation and propagation ^[16] AKAP1-PKA-GRP75: anti-ferroptotic signaling ^[48] BDH2-dependent mitochondria-lysosome contacts: Fe ²⁺ transfer and sensitivity ^[49]	Localized peroxide formation or transfer; iron exchange; defense signaling
Membraneless condensates	Not established	FSP1 condensation: removal from functional membrane context ^[31] GBP2 condensates: SHP1 sequestration sustains STAT1 signaling and promotes T-cell-induced ferroptosis ^[50]	Context-dependent weakening or strengthening of ferroptosis defense;

		p62/NBR1 condensates: enhancement of KEAP1-NRF2 antioxidant signaling ^[32,33]	ferritin turnover
		NCOA4-ferritin condensation: ferritin turnover and potential iron mobilization ^[20,21,34]	
Golgi apparatus	Not established	Golgi disruption and altered trafficking: ACBD3 downregulation and TfR1 relocalization have been associated with ferroptosis-related phenotypes ^[51-53]	Possible modulation of ferroptosis sensitivity; local initiation not established

ACBD3: acyl-CoA-binding domain-containing protein 3; ACSL3/4: acyl-CoA synthetase long-chain family members 3 and 4; AGPS: alkylglycerone phosphate synthase; AKAP1: A-kinase anchoring protein 1; ATF4: activating transcription factor 4; BDH2: 3-hydroxybutyrate dehydrogenase 2; CoQ: coenzyme Q; CoQH₂: ubiquinol; DGAT: diacylglycerol acyltransferase; DHODH: dihydroorotate dehydrogenase; EMCS: ER-mitochondria contact site; ER: endoplasmic reticulum; ETC: electron transport chain; FAR1: fatty acyl-CoA reductase 1; Fe²⁺: ferrous iron; FSP1: ferroptosis suppressor protein 1; GBP2: guanylate-binding protein 2; GPX4: glutathione peroxidase 4; GRP75: glucose-regulated protein 75; GSH: glutathione; LMP: lysosomal membrane permeabilization; LPCAT3: lysophosphatidylcholine acyltransferase 3; NCOA4: nuclear receptor coactivator 4; NRF2: nuclear factor erythroid 2-related factor 2; p62: sequestosome 1; PERK: protein kinase R-like ER kinase; PEX3/10: peroxisomal biogenesis factors 3 and 10; PKA: protein kinase A; POR: cytochrome P450 oxidoreductase; PUFA: polyunsaturated fatty acid; PUFA-PL: polyunsaturated fatty acid-containing phospholipid; SLC7A11: solute carrier family 7 member 11; SHP1: Src homology region 2 domain-containing phosphatase-1; STAT1: signal transducer and activator of transcription 1; TCA: tricarboxylic acid; TfR1: transferrin receptor 1; TMEM189: transmembrane protein 189; KEAP1: Kelch-like ECH-associated protein 1; NBR1: neighbor of BRCA1 gene 1.

9. Therapeutic Implications

Currently, most therapeutic strategies based on ferroptosis are still in the stage of cell and animal experiments^[54,55]. In tumor treatment, the core idea is usually to weaken the local antioxidant defense or increase iron with redox activity, thereby promoting the accumulation of lipid peroxidation; while in non-malignant tissue damage, the treatment goal is the opposite, that is, to block this process as much as possible and protect normal tissues.

DHODH is located in the inner mitochondrial membrane and can reduce CoQ to CoQH₂, thereby limiting mitochondrial membrane lipid peroxidation^[49]. Mao *et al.* reported that the DHODH inhibitor brequinar can induce ferroptosis and inhibit the growth of tumors with low expression of GPX4; in the tumor model with high expression of GPX4, brequinar combined with sulfasalazine could further enhance ferroptosis and inhibit tumor growth^[49]. However, subsequent studies found that several DHODH inhibitors, when reaching the required concentration for cell sensitization, would also simultaneously inhibit FSP1^[56]. Mao *et al.* subsequently provided evidence that DHODH still has an independent contribution in this process^[57]. Therefore, although brequinar can be used to intervene in this pathway, it cannot be regarded as a highly specific tool for studying the anti-ferroptosis function of mitochondrial DHODH.

The anti-ferroptosis activity of FSP1 also depends on its correct membrane localization. icFSP1 can detach FSP1 from the membrane environment and promote its formation of aggregates; A375 and H460 cells with knocked out GPX4 showed higher sensitivity to this compound. Two animal experiments used artificially constructed GPX4-deficient tumor models. In this context, icFSP1 could increase lipid peroxidation and slow down the growth of xenograft tumors^[31]. These results indicate that disrupting the membrane localization of FSP1 is expected to weaken the local anti-ferroptosis defense of tumor cells, but the current *in vivo* evidence mainly comes from the specific model of GPX4 deficiency.

Targeting lysosomal iron provides another idea. Fento-1 is designed to activate Fe(II) in acidic lysosomes, thereby inducing phospholipid oxidation and ferroptosis^[22]. The primary tumor and pancreatic ductal adenocarcinoma cells used in the study were directly derived from patient samples, and cells rich in reactive iron and high CD44 expression were particularly sensitive to Fento-1. The compound can also kill resistant persisting cells *in vitro*. In the mouse model, Fento-1 was administered intralymphatically into the tumour-bearing lymph node every other day. Treatment increased tumour lipid oxidation and reduced intranodal tumour growth^[22]. However, this study did not assess the drug exposure after systemic administration and the toxicity of normal tissues, so the treatment window still needs to be further determined.

The mechanism of phase separation-related processes is currently more at the stage of genetic verification. In melanoma models, researchers manipulated GBP2 through genetic methods, but did not test drugs that directly target GBP2. After IFN- γ stimulation, GBP2 aggregates can recruit SHP1 and maintain the STAT1 signal within tumor cells, causing a decrease in SLC7A11 expression, while enhancing T-cell-induced lipid ROS and ferroptosis. GBP2 deficiency reduces tumor lipid ROS and weakens the anti-PD-L1 treatment effect; conversely, GBP2 overexpression can improve these phenotypes. After neutralizing IFN- γ , the therapeutic benefit brought by GBP2 overexpression disappears^[50]. These results suggest that the immune signal regulation related to phase separation may affect the response of tumors to ferroptosis and immunotherapy, but there is currently no evidence of direct pharmacological targeting of GBP2.

In non-malignant tissue damage, the treatment direction is to inhibit ferroptosis. Conditional deletion of Gpx4 in adult forebrain neurons caused hippocampal degeneration and cognitive impairment. Vitamin E deficiency further exacerbates this phenotype, while Liproxstatin-1 can alleviate neurodegenerative changes^[58]. In another inducible Gpx4 deletion model, Liproxstatin-1 can also protect mice from acute renal failure and alleviate liver ischemia/reperfusion injury^[59]. Ferrostatin-1 and Liproxstatin-1 act as

radical-trapping antioxidants that intercept lipid peroxyl radicals and suppress lipid-peroxidation propagation^[60]. However, these early studies did not clearly indicate where the main effect occurs in the subcellular compartment. Recent studies have found that a clickable Liproxstatin-1 analogue can accumulate in lysosomes and exert protective effects by inactivating the reactive iron within lysosomes^[22], suggesting that organelle localization may affect the mode of action of some ferroptosis inhibitors.

From a translational perspective, current evidence is not sufficient to support the use of only cell-level ROS or iron indicators for patient screening. A more realistic approach is to first confirm that the targeted organelle-related mechanisms still exist in patient-derived materials and can be effectively regulated by corresponding interventions; then evaluate whether the drug will damage normal tissues at an effective exposure level through systemic administration. Only when a clear connection is established between mechanism retention, drug exposure, and tissue safety can the cell-type-specific ferroptosis-targeted strategies have the basis for further clinical advancement.

10. Conclusion

Cell ferroptosis is not determined solely by a single organelle, but is the result of the spatiotemporal interaction of multiple organelles^[3,4]. Different subcellular compartments respectively provide lipid substrates, pro-oxidative reactions, iron sources or antioxidant defenses, jointly influencing whether lipid peroxidation can accumulate continuously. ACSL4/LPCAT3-mediated lipid remodeling increases phospholipids containing easily oxidizable PUFA^[5,6,13,14], and POR further promotes the oxidation of these membrane lipids^[15]; meanwhile, peroxisomes change the composition of available oxidizable lipid substrates through ether lipid synthesis^[24,25]. Lysosomes release iron through ferritin turnover^[20,21,43], and the redox-active iron within them can directly promote lipid oxidation^[22]. In some models, subsequent lysosomal membrane damage further amplifies ferroptosis^[23,44]. The role of mitochondria is more dependent on inducing conditions. Under cystine deprivation, glutaminolysis and TCA-cycle activity can promote ferroptosis, whereas mitochondrial involvement is less consistently required after direct GPX4 inhibition^[2,17,18]. On the other hand, DHODH located in the inner mitochondrial membrane constitutes a local anti-ferroptosis defense^[19]. Lipid droplets can also limit or maintain ferroptosis sensitivity under different conditions by regulating the distribution of fatty acids between stored lipids and membrane lipids^[26-30]. Phase separation provides another spatial regulatory mechanism. FSP1 and p62 condensates can affect ferroptosis by altering protein localization or antioxidant signaling, without forming new membrane compartments^[31-34].

The exact location of the earliest lipid damage during ferroptosis in the subcellular compartments remains inconclusive. In some models, lipid peroxidation products can appear earlier at the EMCs; however, it is worth noting that the AKAP1-PKA-GRP75 signal enriched at the same interface plays an anti-ferroptosis role^[16,48]. Other studies suggest that lysosomes are the earliest sites of lipid peroxidation, and that ferritin turnover and lysosomal reactive iron are closely related to early lipid oxidation^[20-22,43]. In contrast, lysosomal membrane damage occurs later in some experimental systems and is more likely to participate in the subsequent amplification process^[23,44]. The differences between these results are not necessarily contradictory, but may be related to the different induction methods and detection times of ferroptosis.

For lipid droplets and Golgi apparatus, it is currently more difficult to determine their position in the temporal sequence of lipid peroxidation. Studies have observed lipid oxidation within lipid droplets, but it cannot be proven that this event occurs earlier than lipid peroxidation in other membrane structures^[28]. Golgi apparatus damage or acyl-CoA-binding domain-containing protein 3 (ACBD3) downregulation can change ferroptosis-related phenotypes^[51,52], and the relocalization of TfR1 is also related to the ferroptosis process, but these results do not yet provide evidence that the Golgi apparatus is the initiating site of lipid damage^[53].

To truly determine where ferroptosis begins, comparing ROS levels in different organelles is not sufficient. What is more crucial is to track the spatial changes in lipid oxidation in the same cell and at the same time point, while confirming the accuracy of the localization of organelle-targeted probes, and clarifying which type of lipid is actually being detected. The causal relationship also needs to be further demonstrated through specific perturbation of the corresponding subcellular compartments to show that such intervention can both change the early local oxidative signals and affect the subsequent cell death. Only by establishing this continuous mechanism connection can the relevant intervention be suitable for further verification in patient-derived materials. At present, changes in ROS or iron content levels at the cellular organelle level alone are not sufficient as a basis for patient screening.

Declarations

Acknowledgements

We thank members of our laboratory for helpful discussions during the preparation of this Mini Review.

The authors declare that ChatGPT was used solely for language polishing during the manuscript preparation process. After AI-assisted language polishing, the entire manuscript was carefully reviewed and further revised by the authors. The scope and organization of the review, literature evaluation, scientific reasoning, interpretation, and conclusions were developed by the authors. ChatGPT was not used to generate the figure or table, determine scientific claims, or independently produce the scholarly content of the manuscript. The authors reviewed, revised, and approved the final manuscript and take full responsibility for its content.

Authors contribution

Dai J: Writing-original draft, investigation.

Du X: Visualization.

Hu Y: Supervision, conceptualization, project administration.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

This work was supported by the Heilongjiang Provincial Natural Science Foundation Doctoral Student Project (Grant No. BS2025C011).

Copyright

© The Author(s) 2026.

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(5):1060-1072. [DOI][PubMed][PMC]
2. Yang WS, SriRamaratnam R, Welsch ME, Shimada K, Skouta R, Viswanathan VS, et al. Regulation of ferroptotic cancer cell death by GPX4. *Cell*. 2014;156(1-2):317-331. [DOI][PubMed][PMC]
3. Dixon SJ, Olzmann JA. The cell biology of ferroptosis. *Nat Rev Mol Cell Biol*. 2024;25(6):424-442. [DOI][PubMed][PMC]
4. Stockwell BR, Jiang X. The chemistry and biology of ferroptosis. *Cell Chem Biol*. 2020;27(4):365-375. [DOI][PubMed][PMC]
5. Doll S, Proneth B, Tyurina YY, Panzilius E, Kobayashi S, Ingold I, et al. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. *Nat Chem Biol*. 2017;13(1):91-98. [DOI][PubMed][PMC]
6. Kagan VE, Mao G, Qu F, Angeli JPF, Doll S, Croix CS, et al. Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. *Nat Chem Biol*. 2017;13(1):81-90. [DOI][PubMed][PMC]
7. Do Q, Zhang R, Hooper G, Xu L. Differential contributions of distinct free radical peroxidation mechanisms to the induction of ferroptosis. *JACS Au*. 2023;3(4):1100-1117. [DOI][PubMed][PMC]
8. Qiu B, Zandkarimi F, Bezjian CT, Reznik E, Soni RK, Gu W, et al. Phospholipids with two polyunsaturated fatty acyl tails promote ferroptosis. *Cell*. 2024;187(5):1177-1190.e18. [DOI][PubMed][PMC]
9. Zhang HL, Hu BX, Li ZL, Du T, Shan JL, Ye ZP, et al. PKC β II phosphorylates ACSL4 to amplify lipid peroxidation to induce ferroptosis. *Nat Cell Biol*. 2022;24(1):88-98. [DOI]
10. Bersuker K, Hendricks JM, Li Z, Magtanong L, Ford B, Tang PH, et al. The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis. *Nature*. 2019;575(7784):688-692. [DOI][PubMed][PMC]
11. 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(7784):693-698. [DOI][PubMed]
12. Kraft VAN, Bezjian CT, Pfeiffer S, Ringelstetter L, Müller C, Zandkarimi F, et al. GTP cyclohydrolase 1/tetrahydrobiopterin counteract ferroptosis through lipid remodeling. *ACS Cent Sci*. 2020;6(1):41-53. [DOI][PubMed][PMC]
13. Reed A, Ichu TA, Milosevich N, Melillo B, Schafer MA, Otsuka Y, et al. LPCAT3 inhibitors remodel the polyunsaturated phospholipid content of human cells and protect from ferroptosis. *ACS Chem Biol*. 2022;17(6):1607-1618. [DOI][PubMed]
14. Zhang Q, Yao D, Rao B, Jian L, Chen Y, Hu K, et al. The structural basis for the phospholipid remodeling by lysophosphatidylcholine acyltransferase 3. *Nat Commun*. 2021;12(1):6869. [DOI][PubMed][PMC]
15. Zou Y, Li H, Graham ET, Deik AA, Eaton JK, Wang W, et al. Cytochrome P450 oxidoreductase contributes to phospholipid peroxidation in ferroptosis. *Nat Chem Biol*. 2020;16(3):302-309. [DOI][PubMed][PMC]

16. Sassano ML, Tyurina YY, Diokmetzidou A, Vervoort E, Tyurin VA, More S, et al. Endoplasmic reticulum-mitochondria contacts are prime hotspots of phospholipid peroxidation driving ferroptosis. *Nat Cell Biol.* 2025;27(6):902-917. [DOI][PubMed][PMC]
17. Gao M, Yi J, Zhu J, Minikes AM, Monian P, Thompson CB, et al. Role of mitochondria in ferroptosis. *Mol Cell.* 2019;73(2):354-363.e3. [DOI][PubMed][PMC]
18. Gao M, Monian P, Quadri N, Ramasamy R, Jiang X. Glutaminolysis and transferrin regulate ferroptosis. *Mol Cell.* 2015;59(2):298-308. [DOI][PubMed][PMC]
19. 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(7860):586-590. [DOI][PubMed][PMC]
20. Mancias JD, Wang X, Gygi SP, Harper JW, Kimmelman AC. Quantitative proteomics identifies NCOA4 as the cargo receptor mediating ferritinophagy. *Nature.* 2014;509(7498):105-109. [DOI][PubMed][PMC]
21. Hou W, Xie Y, Song X, Sun X, Lotze MT, Zeh HJ 3rd, et al. Autophagy promotes ferroptosis by degradation of ferritin. *Autophagy.* 2016;12(8):1425-1428. [DOI][PubMed][PMC]
22. Cañeque T, Baron L, Müller S, Carmona A, Colombeau L, Versini A, et al. Activation of lysosomal iron triggers ferroptosis in cancer. *Nature.* 2025;642(8067):492-500. [DOI][PubMed][PMC]
23. Saimoto Y, Kusakabe D, Morimoto K, Matsuoka Y, Kozakura E, Kato N, et al. Lysosomal lipid peroxidation contributes to ferroptosis induction via lysosomal membrane permeabilization. *Nat Commun.* 2025;16(1):3554. [DOI][PubMed][PMC]
24. 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(7826):603-608. [DOI][PubMed][PMC]
25. Cui W, Liu D, Gu W, Chu B. Peroxisome-driven ether-linked phospholipids biosynthesis is essential for ferroptosis. *Cell Death Differ.* 2021;28(8):2536-2551. [DOI][PubMed][PMC]
26. Dierge E, Debock E, Guilbaud C, Corbet C, Mignolet E, Mignard L, et al. Peroxidation of n-3 and n-6 polyunsaturated fatty acids in the acidic tumor environment leads to ferroptosis-mediated anticancer effects. *Cell Metab.* 2021;33(8):1701-1715.e5. [DOI][PubMed]
27. Lee H, Horbath A, Kondiparthi L, Meena JK, Lei G, Dasgupta S, et al. Cell cycle arrest induces lipid droplet formation and confers ferroptosis resistance. *Nat Commun.* 2024;15(1):79. [DOI][PubMed][PMC]
28. Kump A, Perne L, Koren Š, Jovičić EJ, Feguš N, Kozmus CP, et al. Opposing roles of DGAT-mediated lipid droplet biogenesis in the regulation of ferroptosis sensitivity. *FEBS J.* 2026;293(15):4508-4532. [DOI][PubMed][PMC]
29. Magtanong L, Ko PJ, To M, Cao JY, Forcina GC, Tarangelo A, et al. Exogenous monounsaturated fatty acids promote a ferroptosis-resistant cell state. *Cell Chem Biol.* 2019;26(3):420-432.e9. [DOI][PubMed][PMC]
30. Klasson TD, LaGory EL, Zhao H, Huynh SK, Papandreou I, Moon EJ, et al. ACSL3 regulates lipid droplet biogenesis and ferroptosis sensitivity in clear cell renal cell carcinoma. *Cancer Metab.* 2022;10(1):14. [DOI][PubMed][PMC]
31. 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(7969):371-377. [DOI][PubMed][PMC]
32. Feng L, Chen L, Wang W, Wei Q, Chen M, Jiang X, et al. PRMT6-mediated ADMA promotes p62 phase separation to form a negative feedback loop in ferroptosis. *Theranostics.* 2024;14(10):4090-4106. [DOI][PubMed][PMC]
33. Sánchez-Martín P, Sou YS, Kageyama S, Koike M, Waguri S, Komatsu M. NBR1-mediated p62-liquid droplets enhance the Keap1-Nrf2 system. *EMBO Rep.* 2020;21(3):e48902. [DOI][PubMed][PMC]
34. Ohshima T, Yamamoto H, Sakamaki Y, Saito C, Mizushima N. NCOA4 drives ferritin phase separation to facilitate macroferritinophagy and microferritinophagy. *J Cell Biol.* 2022;221(10):e202203102. [DOI]
35. Chen X, Kang R, Kroemer G, Tang D. Organelle-specific regulation of ferroptosis. *Cell Death Differ.* 2021;28(10):2843-2856. [DOI][PubMed][PMC]
36. Rizzollo F, Agostinis P. The lysosomal iron rheostat: Orchestrating ferroptosis in cancer plasticity. *Ferroptosis Oxid Stress.* 2026;2(4):202612. [DOI]
37. Lee YS, Lee DH, Choudry HA, Bartlett DL, Lee YJ. Ferroptosis-induced endoplasmic reticulum stress: Cross-talk between ferroptosis and apoptosis. *Mol Cancer Res.* 2018;16(7):1073-1076. [DOI][PubMed][PMC]
38. 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. *J Hepatol.* 2023;79(2):362-377. [DOI][PubMed][PMC]
39. Liu YE, Lu S, Wu LL, Yang L, Yang L, Wang J. The diversified role of mitochondria in ferroptosis in cancer. *Cell Death Dis.* 2023;14(8):519. [DOI][PubMed][PMC]
40. Neitemeier S, Jelinek A, Laino V, Hoffmann L, Eisenbach I, Eying R, et al. BID links ferroptosis to mitochondrial cell death pathways. *Redox Biol.* 2017;12:558-570. [DOI]
41. Tang D, Kroemer G. Peroxisome: The new player in ferroptosis. *Signal Transduct Target Ther.* 2020;5(1):273. [DOI][PubMed][PMC]
42. Astudillo AM, Balboa MA, Balsinde J. Compartmentalized regulation of lipid signaling in oxidative stress and inflammation: Plasmalogens, oxidized lipids and ferroptosis as new paradigms of bioactive lipid research. *Prog Lipid Res.* 2023;89:101207. [DOI][PubMed]
43. Liu J, Kuang F, Kroemer G, Klionsky DJ, Kang R, Tang D. Autophagy-dependent ferroptosis: Machinery and regulation. *Cell Chem Biol.* 2020;27(4):420-435. [DOI][PubMed][PMC]
44. Das J, Hombalkar SK, Klein AD, Nsara E, Vasandani M, Petrucci K, et al. Ferroptosis induces heterogeneous death profiles that are controlled by lysosome rupture. *Dev Cell.* 2026;61(4):760-772.e4. [DOI][PubMed][PMC]
45. Zhang W, Dai J, Hu Y. Lysosomal rupture: An emerging switch for collective ferroptosis. *Dev Cell.* 2026;61(4):709-710. [DOI]

46. Scorrano L, De Matteis MA, Emr S, Giordano F, Hajnóczky G, Kornmann B, et al. Coming together to define membrane contact sites. *Nat Commun.* 2019;10(1):1287. [DOI][PubMed][PMC]
47. Wieckowski MR, Giorgi C, Lebedzinska M, Duszynski J, Pinton P. Isolation of mitochondria-associated membranes and mitochondria from animal tissues and cells. *Nat Protoc.* 2009;4(11):1582-1590. [DOI][PubMed]
48. Liu H, Zheng S, Hou G, Dai J, Zhao Y, Yang F, et al. AKAP1/PKA-mediated GRP75 phosphorylation at mitochondria-associated endoplasmic reticulum membranes protects cancer cells against ferroptosis. *Cell Death Differ.* 2025;32(3):488-505. [DOI]
49. Rizzollo F, Escamilla-Ayala A, Fattorelli N, Lysiak NB, More S, Hernández Varas P, et al. BDH2-driven lysosome-to-mitochondria iron transfer shapes ferroptosis vulnerability of the melanoma cell states. *Nat Metab.* 2025;7(9):1851-1870. [DOI][PubMed][PMC]
50. Liu X, Fang S, Ren X, Hong Y, Guo J, Liu X, et al. GBP2 condensates promote ferroptosis to sensitize anti-PD-L1 immunotherapy in melanoma. *Nat Commun.* 2026;17:964. [DOI]
51. Alborzinia H, Ignashkova TI, Dejure FR, Gendarme M, Theobald J, Wölfl S, et al. Golgi stress mediates redox imbalance and ferroptosis in human cells. *Commun Biol.* 2018;1:210. [DOI]
52. Qian Y, Ma S, Qiu R, Sun Z, Liu W, Wu F, et al. Golgi protein ACBD3 downregulation sensitizes cells to ferroptosis. *Cell Biol Int.* 2024;48(10):1559-1572. [DOI]
53. Feng H, Schorpp K, Jin J, Yozwiak CE, Hoffstrom BG, Decker AM, et al. Transferrin receptor is a specific ferroptosis marker. *Cell Rep.* 2020;30(10):3411-3423.e7. [DOI][PubMed][PMC]
54. Lei G, Gan B. Exploring ferroptosis-inducing therapies for cancer treatment: Challenges and opportunities. *Cancer Res.* 2024;84(7):961-964. [DOI][PubMed][PMC]
55. Zhou Q, Meng Y, Li D, Yao L, Le J, Liu Y, et al. Ferroptosis in cancer: From molecular mechanisms to therapeutic strategies. *Signal Transduct Target Ther.* 2024;9(1):55. [DOI][PubMed][PMC]
56. Mishima E, Nakamura T, Zheng J, Zhang W, Mourão ASD, Sennhenn P, et al. DHODH inhibitors sensitize to ferroptosis by FSP1 inhibition. *Nature.* 2023;619(7968):E9-E18. [DOI][PubMed]
57. Mao C, Liu X, Yan Y, Olszewski K, Gan B. Reply to: DHODH inhibitors sensitize to ferroptosis by FSP1 inhibition. *Nature.* 2023;619(7968):E19-E23. [DOI]
58. Hambright WS, Fonseca RS, Chen L, Na R, Ran Q. Ablation of ferroptosis regulator glutathione peroxidase 4 in forebrain neurons promotes cognitive impairment and neurodegeneration. *Redox Biol.* 2017;12:8-17. [DOI]
59. Friedmann Angeli JP, Schneider M, Proneth B, Tyurina YY, Tyurin VA, Hammond VJ, et al. Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice. *Nat Cell Biol.* 2014;16(12):1180-1191. [DOI]
60. Zilka O, Shah R, Li B, Friedmann Angeli JP, Griesser M, Conrad M, et al. On the mechanism of cytoprotection by ferrostatin-1 and liproxstatin-1 and the role of lipid peroxidation in ferroptotic cell death. *ACS Cent Sci.* 2017;3(3):232-243. [DOI]

Publisher's Note

Science Exploration remains a neutral stance on jurisdictional claims in published maps and institutional affiliations. The views expressed in this article are solely those of the author(s) and do not reflect the opinions of the Editors or the publisher.