Al-imad Journal of Humanities and Applied Sciences (AJHAS)
مجلة العماد للعلوم الإنسانية والتطبيقية
ISSN: 3106-0323
Volume 2 – Issue 2 – 2026
Pages 702-714

Enzymatic Regulation of Ferroptosis: Molecular Mechanisms, Metabolic Interactions, and Therapeutic Opportunities: A Comprehensive Review

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التنظيم الأنزيمي للفروبتوزيس: الآليات الجزيئية، والتفاعلات الاستقلابية، والفرص العلاجية: مراجعة شاملة

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Received: 18-07-2026; Accepted: 23-08-2026; Published: 03-09-2026

Abstract:
Ferroptosis is an iron-dependent modality of regulated cell death precipitated by the liberated accumulation of phospholipid hydroperoxides within cellular membranes, and it is a precisely enzyme-governed metabolic system of considerable pathophysiological consequence across oncology, neurodegeneration, and inflammatory disease. While mechanistic discoveries around ferroptosis biology have rapidly proliferated, little is known about how enzymatic interplay ultimately regulates ferroptotic responses. This review aims to fill this gap by integrating these diverse components into a unified model, in which ferroptotic susceptibility is not determined solely by GPX4 but rather a functionally redundant, hormonally regulatable pool of parallel antioxidant and execution enzymes whose balance ultimately governs cell fate. By critically evaluating the translational potential of these axes and the evidence-based controversies that remain, particularly concerning enzymatic vs. autoxidative lipid peroxidation and recent editorial objections to some studies, we identify opportunities for co-targeting ferroptosis with immunotherapeutic, hormonal, or metabolic approaches in actionable combinatorial strategies while stressing the urgent need for validation of relevant in vivo biomarkers to advance their clinical translation.

Keywords: lipid peroxidation, GPX4, Iron metabolism, Oxidative stress.

الملخص
الفروبتوزيس هو نمط من الموت الخلوي المنظم المعتمد على الحديد، ينجم عن التراكم الحر لهيدروبيروكسيدات الفوسفوليبيد داخل أغشية الخلايا، وهو نظام استقلابي محكوم بالإنزيمات بدقة وذو عواقب مرضية فيزيولوجية كبيرة في مجالات طب الأورام، التنكس العصبي، والأمراض الالتهابية. وفي حين تزايدت الاكتشافات الآلية المتعلقة ببيولوجيا الفروبتوزيس بسرعة، إلا أنه لا يُعرف سوى القليل عن كيفية تنظيم التفاعل الأنزيمي للاستجابات الفروبتوزية في النهاية. تهدف هذه المراجعة إلى سد هذه الثغرة من خلال دمج هذه المكونات المتنوعة في نموذج موحد، لا تُحدد فيه القابلية للفروبتوزيس حصرياً بواسطة (*GPX4*)، بل بواسطة مجموعة متوازية ومتكررة وظيفياً وقابلة للتنظيم هرمونياً من الإنزيمات المضادة للأكسدة والإنزيمات المنفذة التي يحدد توازنها مصير الخلية في النهاية. ومن خلال التقييم النقدي

للإمكانيات الانتقالية لهذه المحاور والخلافات المستندة إلى الأدلة التي لا تزال قائمة، لا سيما فيما يتعلق بأكسدة الدهون الأنزيمية مقابل التلقائية والاعتراضات التحريرية الحديثة على بعض الدراسات، فإننا نحدد فرصاً للاستهداف المشترك للفروبتوزيس بنهج علاجية مناعية أو هرمونية أو استقلابية ضمن استراتيجيات تركيبية قابلة للتنفيذ، مع التأكيد على الحاجة الملحة للتحقق من صحة المؤشرات الحيوية ذات الصلة في الجسم الحي لتعزيز ترجمتها السريرية.

الكلمات المفتاحية: أكسدة الدهون، *GPX4*، استقلاب الحديد، الإجهاد التأكسدي.

1. Introduction

Ferroptosis is an iron-dependent form of regulated cell death defined by lipid peroxidation in polyunsaturated fatty acid (PUFA)-containing phospholipids integrated into cellular membranes, combined with loss of reduced glutathione and the subsequent inactivation of glutathione peroxidase 4 (GPX4). it is distinguished by shrunken mitochondria exhibiting condensed membranes and reduced, followed by plasma membrane rupture [1, 2]. While they were initially considered separate forms of cell death unrelated in their biochemical and genetic signatures, necroptosis and pyroptosis have been shown to extensively cross-talk with ferroptosis- a notion that continues to develop [3, 4].

The enzymes that govern ferroptosis constitute unique actionable vulnerabilities since many therapy-resistant, metastatic and dedifferentiated malignant cells are critically dependent on a lipid-peroxidase defence for survival [5-7]. By contrast, maladaptive ferroptosis drives tissue attrition in neurodegeneration, acute kidney injury and organ ischaemia–reperfusion injury; here once more these enzymes serve as cytoprotective drug targets within degenerative disease [8-10]. Therefore, a detailed mechanistic insight into the underlying enzymatic circuitry is an essential precursor to harnessing ferroptosis for any therapeutic application.

Despite this extraordinarily fast pace of obtaining mechanistic detail, the major obstacle that faces this field is that knowledge of the enzymatic machinery responsible for ferroptotic processes remains almost completely piecemeal. Indeed, most previous investigations have studied defensive enzymes and the execution enzymes (along with their upstream transcriptional and metabolic regulators) mostly in isolation. Figure 1 shows a schematic representation of the ferroptosis signaling pathway.

In this regard, the current review aims to (i) integrate key enzymatic defence and execution machinery into a single mechanistic model; (ii) anchor this machinery within the metabolic and iron-regulatory networks that dictate ferroptotic sensitivity; (iii) include transcriptional and epigenetic regulators (NRF2, p53, Hippo–YAP, ATF4), which are fundamental in contemporary thinking; and (iv) leverage their learnings into an assessment of therapeutic possibilities and limitations.

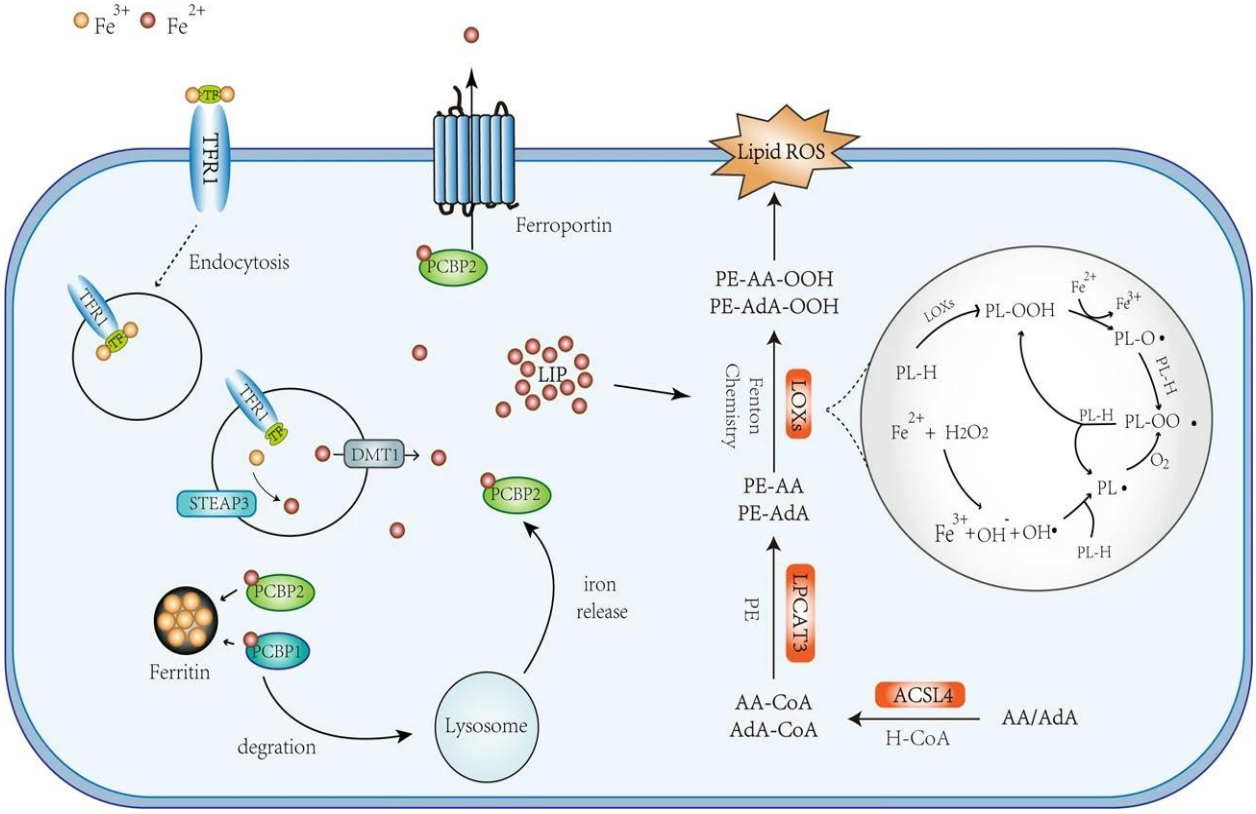

Figure 1. Schematic description of the signaling pathway of ferroptosis

2. Core Enzymatic Defense Mechanisms

When cells experience a constant bombardment of oxidants, they may survive due to any involvement of enzymatic surveillance systems that scavenge and remove lipid peroxides prior to generating lethal membrane damage. This is not simply a matter of redundancy, given that these defenses are operative in different subcellular compartments with distinct reducing factors and are clearly coupled to metabolic and hormonal signaling.

2.1 GPX4/GSH Pathway

The major protector against iron-induced damage is glutathione peroxidase 4 (GPX4). This can uniquely degrade esterified, membrane-bound phospholipid peroxides, and the electron donor is reduced glutathione (GSH) [11]. For example, a cystine/glutamate antiporter, or "System xc^-" is an important component of this axis and serves to drive the transport of cysteine for maintaining intracellular concentrations in concert with endogenous synthesis GSH (glutathione). Pharmacological inhibition of this system, either through glutamine deprivation via erastin or RSL3 (imidazole ketones) [12]. results in the depletion of glutathione and functional inhibition of the GPX4 enzyme. GPX4 is a selenic protein that relies on the incorporation of selenocysteine into its catalytic site, meaning the enzyme's activity is ultimately dependent on selenium availability and isopentenyl pyrophosphate-dependent maturation of selenocysteine tRNA [13, 14]. The biosynthesis of GPX4 is thus susceptible to small-molecule interference through mevalonate pathway interruption, placing GPX4 at the bifurcation between oxidative-reductive defense and intermediary metabolism. The outline in Figure 2 is (GPX4/GSH): System xc^- → cystine/glutamate exchange → GSH synthesis (GSR/GSSG cycle) → GPX4 reducing PL-OOH to PL-OH.

2.2 FSP1/CoQ10 Pathway

The main non-glutathione-dependent defensive factor is iron-dependent cell death inhibitor protein 1 (FSP1, AIFM2). It achieves this task through the reduction of ubiquinone

(coenzyme Q10) to its antioxidant form, ubiquinol, which acts as a lipophilic antioxidant able to neutralize free radicals and can prevent intramembrane peroxyl radical propagation in cellular membranes [15, 16]. The discovery of vitamin K followed this as another substrate of FSP1-dependent antioxidants, providing a dramatic increase in diversity to the functional potential of this pathway. We developed a series of first-generation FSP1 inhibitors that behaved as promoters of FSP1 phase separation/condensation, including icFSP1 [17, 18]. Panel B in figure 2 shows (FSP1/CoQ10): NAD(P)H/H$^+$ → FSP1 → ubiquinone regenerated to ubiquinol (the CoQ10 redox pair) neutralizing PL-OO/PL-OOH.

2.3 GCH1/BH4 Pathway

The enzyme GTP cyclohydrolase 1 (GCH1), is responsible for the first and rate-limiting step in the synthesis of tetrahydrobiopterin (BH4), a natural antioxidant that scavenges free radicals of membrane phospholipids. It also partially regenerates CoQ10 and lipid remodeling. Besides being a powerful pan-cancer factor defending against iron-induced cell death across multiple histological origins, our finding that GCH1 expression can uncouple cell survival from GPX4 activity highlights the biological relevance of such parallelism [19]. Panel C of Figure 2 illustrates the GCH1/BH4/BH2 cycle and mevalonate branch (FDFT1, squalene) topping up control of lipid peroxidation.

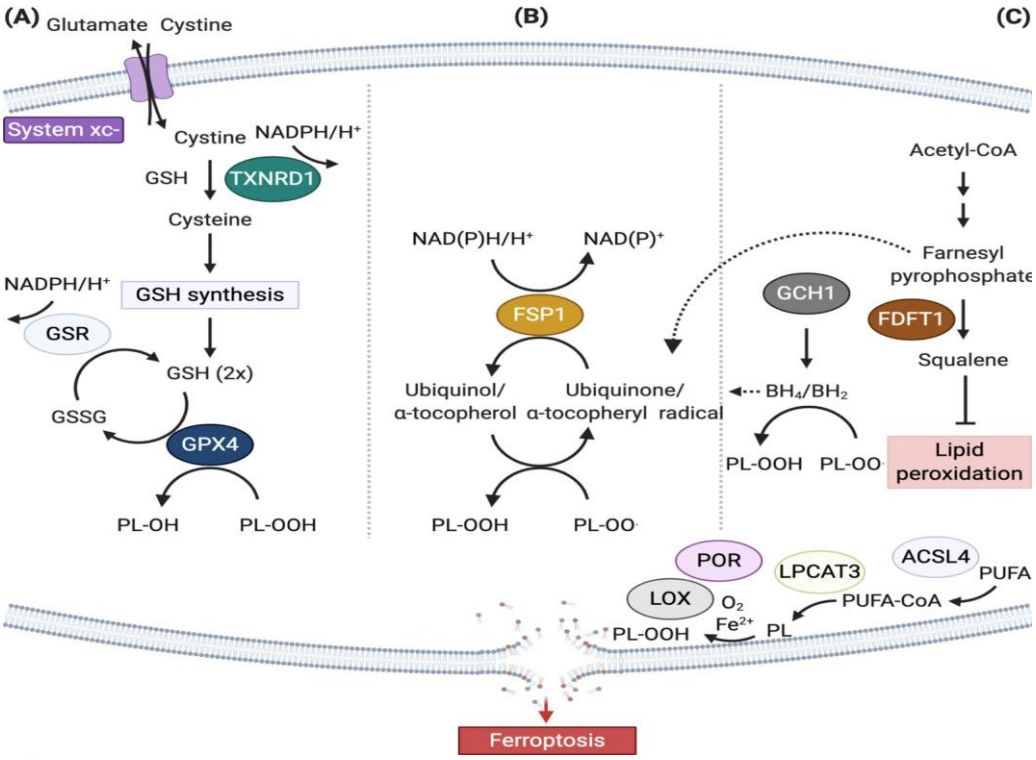

Figure 2. Pathways that suppress ferroptosis (GPX4/GSH, FSP1/CoQ10, GCH1/BH4)

2.4 DHODH and Mitochondrial Defense

The enzyme DHODH, embedded in the inner mitochondrial membrane, catalyzes a process that produces a localized stockpile of ubiquinol, which protects mitochondrial membranes from oxidation, along with the mitochondrial component of GPX4 [20]. Although this axis represents a potential vulnerability in low-GPX4 malignancies, its contribution via DHODH-derived ubiquinol remains poorly defined and is a subject of ongoing debate [20, 21].

2.5 Phospholipid Remodeling Axis by MBOAT1/2

In 2023, a major finding, independent of GPX4 or FSP1, was the identification of the membrane-associated acyltransferase enzymes MBOAT1 and MBOAT2 as novel inhibitors of iron-mediated cell death [22]. Through genome-wide CRISPR analysis, it was shown that

MBOAT1/2 remodels the membrane phospholipid structure by selectively transferring monounsaturated fatty acids (MUFAs) to the sn-2 position of lysophospholipids, thereby reducing the amount of oxidizable polyunsaturated fatty acids. It is important to note that MBOAT2 is a target of the androgen receptor, while MBOAT1 transcription is regulated by the estrogen receptor. This allows to identify a sex hormone-dependent pathway for the regulation of iron cell death and provides a rationale for the application of anti-androgen agents, as well as complementary cytotoxic agents, targeting iron cell death in androgen receptor-positive prostate cancers and estrogen receptor-positive breast cancers [23].

2.6 7-dehydrocholesterol (7-DHC) Regulatory System

The last steps of cholesterol synthesis can also regulate an iron-dependent form of cell death ferroptosis, 7-DHC functions as an endogenous repressor of ferroptosis. In this route, SC5D makes 7-dehydrocholesterol (7-DHC), and DHCR7 turns it into cholesterol. Due to its content of conjugated diene, which might trap lipid radicals and reduce membrane lipid oxidation [24, 25].

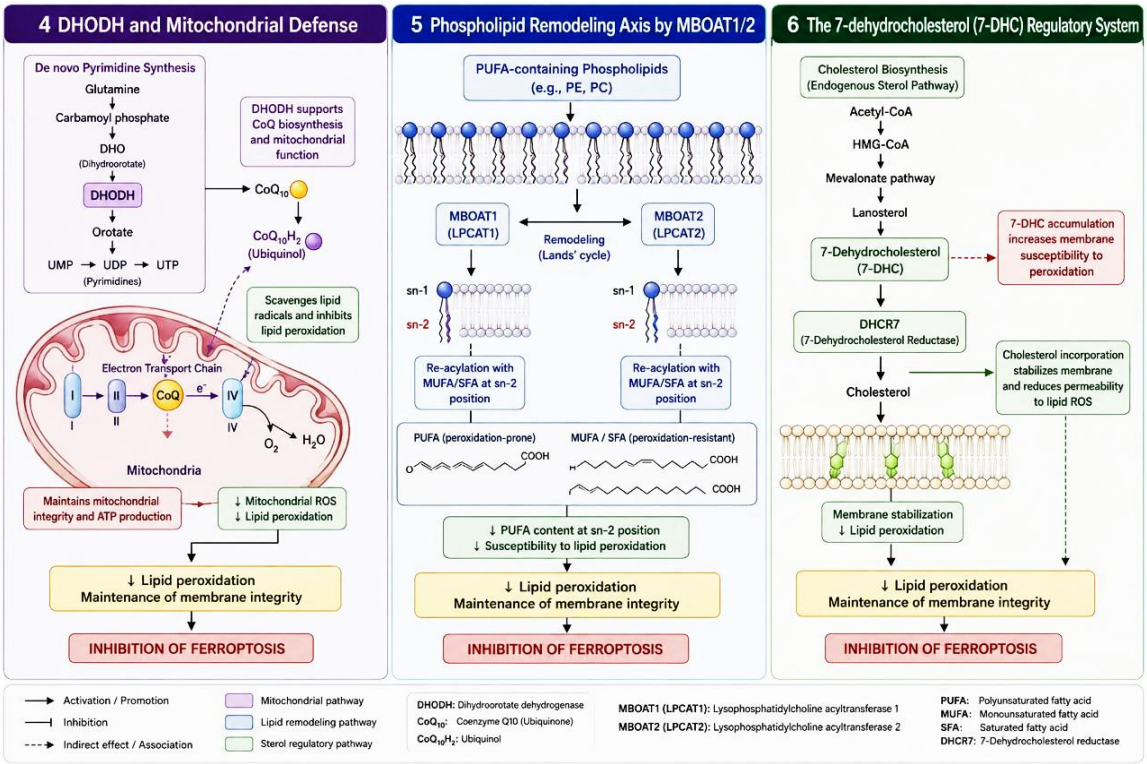

Figure 3. DHODH and Mitochondrial Defense, Phospholipid Remodeling Axis by MBOAT1/2, 7-dehydrocholesterol (7-DHC) Regulatory System pathways

3. Enzymatic Drivers of Lipid Peroxidation

If the above-described defensive systems make up the oxidative fortress of the cell, then a separate group of enzymes that actively construct and oxidise the vulnerable lipid substrate are ultimately responsible for ferroptosis. These drivers work in series first establishing the 706xidizable composition of the membrane, to which then catalysed peroxidation executes death—and their relative contribution, especially that from lipoxygenases, is one of the most hotly debated questions in the field.

3.1 ACSL4: Capitalizing on PUFAs in the Membrane

Acyl-CoA synthetase long-chain family member 4 (ACSL4) is distinguished in that it activates polyunsaturated fatty acids, most notably arachidonate and adrenate, to their CoA thioesters for incorporation into membrane phospholipids, thus committing them to the size

of the 707xidizable substrate pool [26]. Since ACSL4 fundamentally regulates the cellular lipid composition, it is a principal determinant of sensitivity to ferroptosis [27], and its expression has been established as an accurate predictive biomarker for therapy targeting ferroptosis [28].

3.2 LPCAT3: Esterification of PUFAs to phospholipids

Lysophosphatidylcholine acyltransferase 3 (LPCAT3), a gene that functions downstream of ACSL4, esterifies PUFA-CoA species into phospholipids in membrane preparations—primarily the phosphatidylethanolamines to finish building the pro-ferroptotic PUFA-PE substrates that lipoxygenases subsequently oxidize The combined ACSL4–LPCAT3 axis forms the biosynthetic machinery that predisposes a membrane to peroxidation and drives an activity threshold where protective systems may be compromised [29].

3.3 Lipoxygenases and the Enzymatic-versus-Hewing Controversy

Lipoxygenases—especially 15-LOX/ALOX15—can directly dioxygenate PUFA-PE to produce the lipid hydroperoxides that mediate ferroptosis and often act in concert with scaffold protein PEBP1 [30]. The essential need for the enzymes, however, is still under intense debate: strong evidence exists that non-enzymatic, iron-catalysed functional autoxidation via Fenton chemistry can drive membrane peroxidation independent of lipoxygenase activity. The mechanistic debate—enzymatic vs. spontaneous autoxidation—which remains to date one of the most persistent open questions in the field—has direct repercussions on whether lipoxygenase inhibition is a rational therapeutic strategy [31].

3.4 POR and Auxiliary Oxidoreductases

Cytochrome P450 oxidoreductase (POR) provides an alternative endogenous source for reactive oxygen species that activates membrane phospholipid peroxidation and, paired with lipoxygenase- and Fenton-driven pathways, generates electrons to sustain peroxyl-radical production [32]. In concert with the NADPH oxidase (NOX) family, POR is an essential component of generating a basal oxidative tone that in turn sets the critical threshold for lethal peroxidation and thereby integrates enzymatic radical generation with the non-enzymatic chemistry that perpetuates it [33].

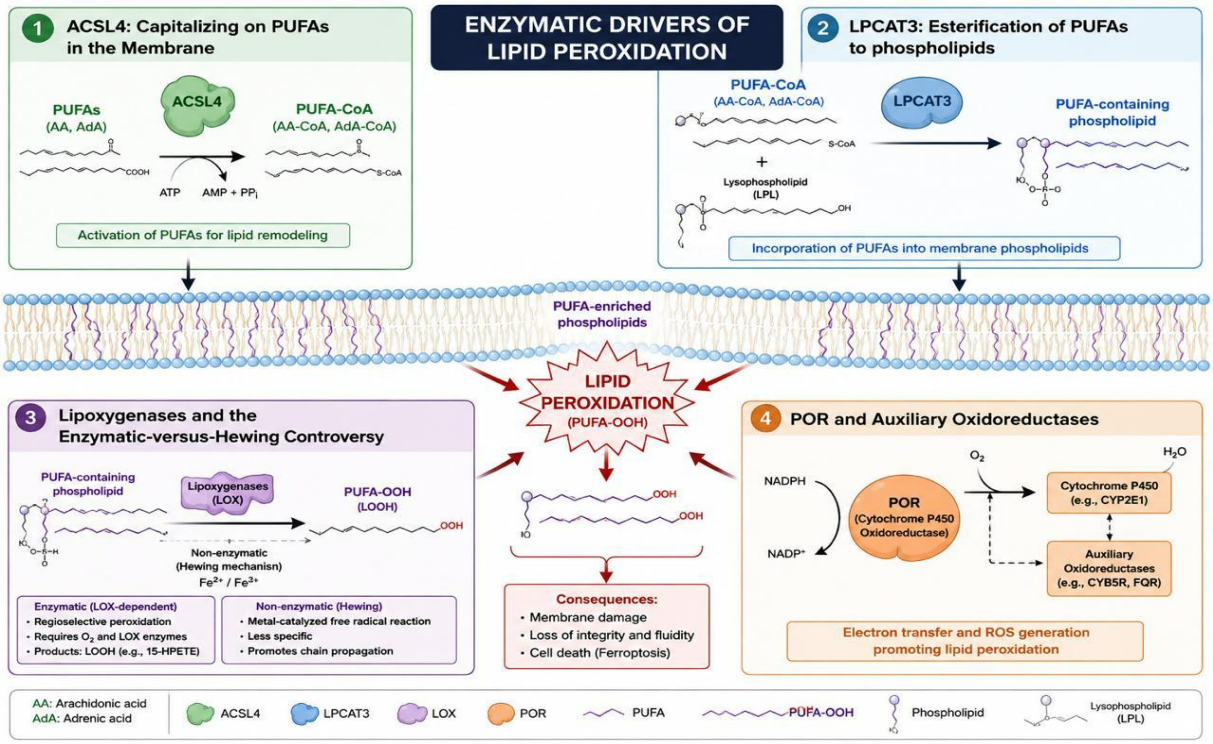

Figure 4. Enzymatic Drivers of Lipid Peroxidation

4. Metabolic Interactions and Iron Regulation

The ratio of defense to execution enzymes does not alone determine if a cell is susceptible to ferroptosis; this susceptibility is, more fundamentally, determined by the metabolic environment in which these enzymes work. Iron availability fuels radical generation, intermediary metabolism supplies the antioxidant cofactors, and a transcriptional and epigenetic landscape governs the near-complete abundance. This regulatory layer, largely neglected in earlier syntheses, is what bridges the gap between the enzymatic machinery and the physiological state of the cell.

4.1 Iron Homeostasis and Ferritinophagy

The labile iron pool responsible for the driving force behind the Fenton reaction is regulated by import (transferrin/TFR1, DMT1), export (ferroportin/SLC40A1), storage (ferritin), and autophagic resequestration [34]. The NCOA4-dependent mode of ferritinophagy is dependent on the canonical autophagic machinery composed of ATG5/ATG7, preferentially releasing stored iron, making cells more susceptible to ferroptosis and giving a strong mechanistic connection between autophagic flux and iron-driven cell death [35]. Heme oxygenase-1 (HMOX1) and the poly(rC)-binding proteins (PCBP1/2) partition the labile iron pool, which may be cytoprotective or lethal based on the fluxes present, in a caution against viewing iron handling as a universal pro-ferroptotic determinant [36].

4.2 The Mevalonate Pathway as a Metabolic Integrator

At several convergent nodes the mevalonate pathway integrates ferroptosis defences: it provides the farnesyl-pyrophosphate necessary for CoQ10 production — thus Fuelling both FSP1 and DHODH— supplies the cholesterol precursors which include protective 7-DHC, and produces isopentenyl-pyrophosphate, essential for selenocysteine-tRNA maturation and consequently efficient GPX4 selenoprotein synthesis. Sterol metabolism, due to this tripartite dependency, becomes a major cellular determinant of antioxidant capacity and thus provides a rational mechanistic rationale for the ferroptosis-modulating action of statins [37].

4.3 Energy Sensing and AMPK

Ferroptosis is the context-dependent role of the cellular energy sensor AMPK in ferroptosis. In conditions of energetic stress it can inhibit ferroptosis by targeting acetyl-CoA carboxylase and limiting PUFA-phospholipid biosynthesis, yet under different settings it induces death—an apparent paradox reconciled by the consideration that its net effect is determined by the cell's nutrient and redox state [38]. The associated BAP31-mediated and AMPK–BECN1 nodes connect this energy status to the activity of System Xc^-, thus linking bioenergetic status with cystine import [39].

4.4 Transcriptional Regulation

One strikingly underrepresented regulatory layer in previous models is that of the transcriptional network controlling the expression of ferroptotic enzymes. NRF2 and its repressor KEAP1 coordinate a comprehensive antioxidant program that includes SLC7A11, GPX4, FSP1, ferritin, and indeed the NADPH-generating enzymes—such that its hyperactivation is one of the main mediators of ferroptosis resistance in tumors [40, 41]. The tumor suppressor p53 acts in a bidirectional manner, repressing SLC7A11 to sensitise sensitivity while at select contexts restricting death through SAT1 and ALOX15 or controlling DPP4 activity [42, 43]. The Hippo–YAP/TAZ pathway connects cell density and adhesion signalling to ferroptosis through regulation of ACSL4 and TFR1, connecting tissue architecture with metabolic susceptibility [44, 45], while ATF4 and the integrated stress response reprogramme amino acid and glutathione metabolism to modulate sensitivity [46].

4.5 Epigenetic and Hormonal Modulation

Such transcriptional architecture is further eeyg6 comprised of an epigenetic layer, conferring broader tunability. BAP1-driven H2A deubiquitination at the SLC7A11 locus provides a selectable, but reversible means to epigenetically fine-tune expression of ferroptotic

determinants in conjunction with the emerging tools of lncRNAs and miRNAs [47, 48]. Steroid-hormone signalling also tunes the circuit: glucocorticoid-receptor-binding dexamethasone inhibits glutathione production through dipeptidase-1, making cells sensitive to ferroptosis [49]. Along with the hormone-responsive MBOAT1/2 axis, these findings provide evidence that endocrine and epigenetic states are bona fide determinants of ferroptotic fate that could be capitalized upon.

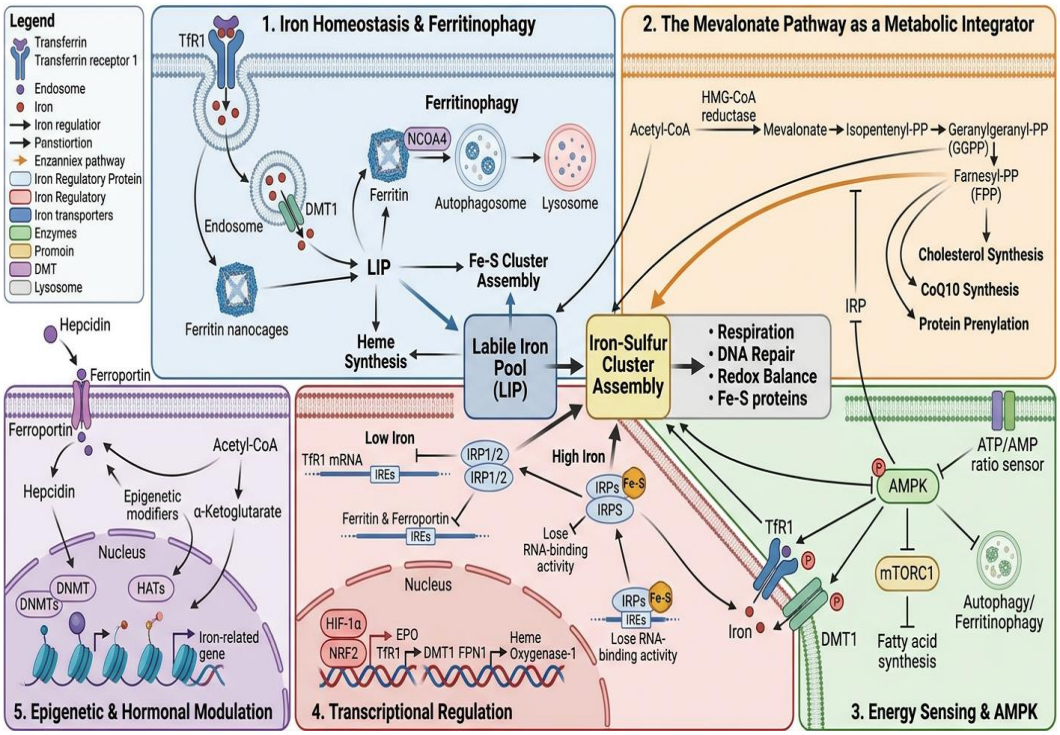

Figure 5. Metabolic Interactions and Iron Regulation

5. Therapeutic Opportunities & Clinical Translation

Positioning ferroptosis as either a lethal event in one cell context or a protective mechanism in another has directly translated into two opposing therapeutic imperatives. With regard to oncological approaches, the goal is to induce ferroptosis in cells that have become reliant on a lipid-peroxidase cytoprotective mechanism, and conversely, with this information at hand, for degenerative disease modalities, which look to inhibit it and subsequently protect susceptible tissue. Though the dearth of validated clinical agents and biomarkers moderated translational optimism, the newly defined enzymatic axes have markedly enlarged the actionable target space in both directions.

5.1 Ferroptosis Inducers in Cancer

Induction of ferroptosis is a particularly appealing approach to targeting therapy-resistant, drug-tolerant persister and dedifferentiated cancer-stem-like populations that depend on GPX4 for survival [50]. While erastin and RSL3 are prototypical tool compounds whose promise as clinical agents has not been fully realized, translational effort is shifting toward repurposed drugs—most notably sorafenib, sulfasalazine and derivatives of artesunate and the newly defined axes including antagonism of androgen- and estrogen-receptor (to disable MBOAT1/2), inhibitors of emopamil-binding proteins (i.e. EBP; to deplete protective 7-DHC pools), or GPX4-degrading or DHODH inhibiting strategies [51]. Ferroptosis induction is actively investigated as a mechanism to sensitize against targeted therapy and immunotherapy in melanoma or pancreatic and renal malignancies [52].

5.2 Inhibition of Ferroptosis in Degenerative Disease

Selective inhibitors (ferrostatin-1 and liproxstatin-1—both radical-trapping antioxidants) protect against organ damage in experimental models of neurodegeneration (Alzheimer's and Parkinson's disease), acute kidney injury, cardiomyopathy, and ischemia-reperfusion injury [53]. Newer strategies are emerging, which could capitalize on the endogenous 7-DHC system; inhibition of DHCR7 increases protective 7-DHC output while attenuating hepatic and renal ischemic injury [54]. Iron chelation and (D-PUFAs) that resist abstraction of the bis-allylic hydrogen, thereby blocking peroxidation, are complementary cytoprotective approaches [55].

5.3 Drug Delivery and Nanomedicine

There are also the nanoparticle platforms based on PLGA, iron, and metal-organic-framework nanocarriers that allow the targeted delivery of ferroptosis modulators to tumors, improving selectivity with less systemic toxicity, and being potential carriers to co-deliver ferroptosis inducers together with immune inhibitors, using the inherent immunogenic feature of ferroptotic death [56-58]. Fenton-reaction-amplifying and glutathione-depleting nanomaterials now represent a growing class of ferroptosis-inducing 'nanomedicines' [59].

5.4 The Ferroptosis–Immunity Interface

Ferroptotic cells are a common source of damage-associated molecular patterns—HMGB1, ATP, and oxidized lipids—that modify the tumor immune microenvironment, and type I IFNγ-secreting CD8+ T cells can also drive ferroptosis in neighboring tumor cells through SLC7A11 repression [60, 61]. However, this relationship is certainly double-edged: ferroptosis of immune effector cells, together with the release of immunosuppressive oxidized lipids by tumor-associated myeloid populations, could conversely inhibit antitumor immunity, giving a net positive or negative effect that is heavily context-dependent [62, 63]. This bidirectional crosstalk provides a strong justification for (but also cautions against) combining ferroptosis induction with immunotherapy and highlights the maintenance of effector-cell viability as an important design limitation for these strategies.

6. Discussion

This review sought to identify if the enzymes controlling ferroptosis can be reconciled into one mechanistic framework and facilitate therapeutic targeting. across the survey of literature, ferroptosis arises not from the loss of function of one single antioxidant enzyme, but as a synergetic output from multiple largely redundant enzymatic systems whose balance is constantly recalibrated by the interaction among metabolic, hormonal, and transcriptional inputs [64]. This synthesis in turn reconceptualizes ferroptosis as an emergent property of a distributed, multiply redundant enzymatic network rather than a linear GPX4-dependent pathway [65]. Many broader themes and their (if appropriate) controversies warrant close attention.

The most important conceptual novelty in the last couple of years is that GPX4 and ferroptotic fate are not one-to-one related. FSP1/CoQ10, GCH1/BH4, DHODH, and MBOAT1/2 (the Coordination of Membrane Lipids with the Mitochondrial Antioxidant System) each have unique membrane compartments and use different reducing equivalents to be largely self-sufficient from the glutathione axis.

While mechanistic discoveries happen at an unprecedented speed, clinical translation of ferroptosis modulation remains lamentably low. Ferroptotic inducers and inhibitors that are by far the most disseminated—erastin, RSL3, ferrostatin-1, and liproxstatin-1—remain basic research tools without pharmacokinetic properties required for human use; translational potential remains heavily qualified due to reliance on repurposed agents as fundamentally pleiotropic ferroptotic triggers and there are no dynamic in vivo readouts of ferroptosis in humans that have been validated for human use, and the absence of such readouts is a major limitation in interpreting ferroptosis-targeting clinical trials.

7. Conclusion

The ferroptosis paradigm, thus far, has extended well beyond the classical GPX4 axis to include GPX4-independent control (FSP1, GCH1/BH4, DHODH, MBOAT1/2), a sterol-derived antioxidant system (7-DHC), and an overarching transcriptional epigenetic/hormonal control architecture. Together, these systems constitute a versatile and context-tunable network whose inherent redundancy is simultaneously the biggest barrier to, but also the clearest path for, therapeutic manipulation. The advances will rely even more on the introduction of existing information into rational combination approaches, the resolution of the enzymatic-versus-autoxidation and 7-DHC controversies, and — above all — the validation of biomarkers to inform clinical translation than upon new individual nodes at this point.

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