International Journal of Cell and Biomedical Science (2026) 5: (14) 516-532
https://doi.org/10.59278/cbs.v5i14.108

REVIEW ARTICLE OPEN ACCESS

Ferroptosis in Human Diseases: Molecular Mechanisms, Biomarkers Evidence, and Translational Therapeutic Strategies

Ghea Farmaning Thias Putri[1], Dwi Widiyanti[2*]

*Correspondence:
dwi.widyawati@untirta.ac.id

[1]Departement of Medical Biology, Faculty of Medicine and Health Sciences, Universitas Sultan Ageng Tirtayasa, Serang, Banten, Indonesia
[2]Department of Physiology, Faculty of Medicine and Health Sciences, Universitas Sultan Ageng Tirtayasa, Serang, Banten, Indonesia

Submission July 21, 2026
Accepted August 18, 2026
Available online on October 31, 2026

©2026 The Authors. Published by Stem Cell and Cancer Research, Semarang, Indonesia. This is an open-access article under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike License (CC BY-NC-SA 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

ABSTRACT

Background: Ferroptosis is a distinct form of regulated cell death characterized by iron-dependent lipid peroxidation and disruption of cellular redox homeostasis. Unlike apoptosis, necroptosis, and pyroptosis, ferroptosis is primarily driven by dysregulated iron metabolism, excessive reactive oxygen species generation, and impaired antioxidant defense systems, making it a critical mechanism in the pathogenesis of numerous human diseases. **Aim:** This narrative review summarizes current advances in the molecular mechanisms, biomarkers, and emerging therapeutic strategies targeting ferroptosis. **Methods:** Relevant literature published between 2021 and 2026 was retrieved from PubMed, Scopus, and ScienceDirect and qualitatively analyzed. **Results:** Current evidence indicates that ferroptosis is regulated by coordinated interactions among iron metabolism, lipid remodeling, mitochondrial function, and antioxidant defense pathways, including the System Xc^-/glutathione/glutathione peroxidase 4 (GPX4) axis, ferroptosis suppressor protein 1 (FSP1), dihydroorotate dehydrogenase (DHODH), and GTP cyclohydrolase 1 (GCH1). Dysregulation of these pathways contributes to cancer, neurodegenerative, cardiovascular, kidney, liver, metabolic, and inflammatory diseases. Several ferroptosis-associated molecular and biochemical indicators, including GPX4, SLC7A11, ACSL4, transferrin receptor 1, ferritin, malondialdehyde, and 4-hydroxynonenal, have been investigated in experimental and clinical disease contexts; however, their specificity for ferroptotic cell death remains insufficiently established. **Conclusion:** Although ferroptosis-targeted interventions have demonstrated promising effects in experimental and preclinical models, clinical translation remains limited by disease heterogeneity, the absence of standardized ferroptosis-specific biomarkers, uncertainties regarding therapeutic selectivity and toxicity, and limited clinical evidence.

Keywords: *Ferroptosis; Iron metabolism; Lipid peroxidation; Biomarkers; Oxidative stress; Therapeutic strategies.*

INTRODUCTION

Programmed cell death (PCD) is a fundamental biological process that maintains tissue homeostasis by eliminating damaged, aged, or dysfunctional cells while preserving normal physiological function[1–3]. Beyond its essential role in embryonic development and tissue remodeling, PCD is critical for regulating immune responses, maintaining genomic stability, and preventing the accumulation of cells that may contribute to malignant transformation or chronic inflammatory disorders [1–3]. Dysregulation of cell death pathways has been implicated in numerous human diseases, including cancer, neurodegenerative disorders, cardiovascular diseases, metabolic syndrome, and chronic inflammatory conditions. Consequently, understanding the molecular mechanisms underlying different forms of cell death has become an important focus of biomedical research, providing new opportunities for disease prevention, diagnosis, and therapeutic intervention [2,4,5].

International Journal of Cell and Biomedical Science (2026) 5: (14) 516-532
https://doi.org/10.59278/cbs.v5i14.108

For decades, apoptosis was considered the predominant form of regulated cell death and has been extensively investigated as a therapeutic target in various pathological conditions. Subsequently, additional regulated cell death modalities, including necroptosis, pyroptosis, autophagy-dependent cell death, and immunogenic cell death, were identified, highlighting the complexity of cellular responses to stress and injury[2,4,6].

Although these pathways differ in their molecular mediators and biological outcomes, they primarily involve activation of proteolytic enzymes, inflammatory signaling, or lysosomal degradation pathways. Nevertheless, increasing evidence suggests that these classical forms of cell death cannot fully explain the cellular damage observed in several pathological conditions characterized by severe oxidative stress, iron overload, and lipid membrane destruction, indicating the existence of distinct regulatory mechanisms[6–9].

The discovery of ferroptosis in 2012 introduced a novel paradigm in regulated cell death that is mechanistically, morphologically, and biochemically distinct from previously recognized forms of cell death. Ferroptosis is an iron-dependent form of regulated cell death driven by excessive lipid peroxidation resulting from the imbalance between reactive oxygen species (ROS) production and antioxidant defense systems (Dixon, 2024; Jiang, 2021). Unlike apoptosis, ferroptosis does not involve caspase activation, chromatin condensation, or DNA fragmentation. Instead, it is characterized by intracellular iron accumulation, depletion of glutathione (GSH), inactivation of glutathione peroxidase 4 (GPX4), overwhelming lipid peroxide formation, and profound mitochondrial structural alterations, including mitochondrial shrinkage, increased membrane density, and reduced cristae. These unique characteristics have established ferroptosis as an independent biological process with significant implications for human health and disease[8–10].

At the molecular level, ferroptosis is tightly regulated through the interaction of iron metabolism, lipid metabolism, and multiple antioxidant defense pathways. Cellular iron homeostasis determines the availability of ferrous iron (Fe^{2+}), which catalyzes the Fenton reaction and promotes the generation of highly reactive hydroxyl radicals capable of initiating lipid peroxidation. Polyunsaturated fatty acids (PUFAs) within cellular membranes serve as primary substrates for oxidative damage, while enzymes such as acyl-CoA synthetase long-chain family member 4 (ACSL4) and lipoxygenases (ALOXs) facilitate the incorporation and oxidation of membrane lipids [8,11,12].

Under physiological conditions, the cystine/glutamate antiporter System Xc^- maintains intracellular cysteine availability for glutathione synthesis, enabling GPX4 to detoxify phospholipid hydroperoxides. Failure of this antioxidant defense system results in uncontrolled lipid peroxidation, membrane disruption, and ultimately ferroptotic cell death. Recent studies have also identified additional regulatory mechanisms involving ferroptosis suppressor protein 1 (FSP1), dihydroorotate dehydrogenase (DHODH), GTP cyclohydrolase 1 (GCH1), nuclear factor erythroid 2-related factor 2 (NRF2), and p53, further demonstrating the complexity of ferroptosis regulation [8,12].

Accumulating experimental and observational evidence supports a potential contribution of ferroptosis to the pathophysiology of numerous human diseases, although the strength of evidence and degree of causal inference vary substantially across disease contexts[8,16,29,37]. In neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, excessive iron accumulation and lipid peroxidation accelerate neuronal degeneration and cognitive decline[8,13–15]. Similarly, ferroptosis has been implicated in myocardial ischemia-reperfusion injury, heart failure, acute kidney injury, chronic kidney disease, metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated steatohepatitis

(MASH), diabetes mellitus, and inflammatory disorders, highlighting its broad pathological relevance across multiple organ systems [8,16–19].

The growing recognition of ferroptosis has stimulated investigation of molecular and biochemical indicators associated with ferroptotic susceptibility and lipid oxidative injury. Parameters such as GPX4, ACSL4, SLC7A11, transferrin receptor 1 (TfR1), ferritin, MDA, 4-HNE, and lipid reactive oxygen species have been investigated in experimental and clinical disease contexts [16,20,36,44]. However, these parameters differ substantially in their biological meaning and specificity, and changes in individual markers alone are insufficient to establish ferroptotic cell death[4,16,20]. Furthermore, pharmacological modulation of ferroptosis using inhibitors, including ferrostatin-1, liproxstatin-1, deferoxamine, vitamin E, and coenzyme Q10, as well as ferroptosis inducers such as erastin, RSL3, sorafenib, and FIN56, has demonstrated encouraging preclinical outcomes, particularly in cancer therapy and ischemia-reperfusion injury. These findings suggest that ferroptosis-targeted interventions may represent a new generation of precision medicine strategies capable of addressing diseases driven by oxidative stress and iron dysregulation [15,17,21,22].

Despite remarkable advances in ferroptosis research, several important challenges remain unresolved. The molecular interactions among ferroptosis and other regulated cell death pathways are incompletely understood, validated biomarkers suitable for routine clinical application are still limited, and most therapeutic approaches remain confined to experimental and preclinical studies. In addition, inconsistencies in biomarker assessment, disease-specific regulatory mechanisms, and the lack of standardized clinical protocols continue to impede successful clinical translation[4,8,12,16,17].

Therefore, this narrative review aims to comprehensively summarize the current understanding of ferroptosis in human diseases by integrating recent evidence on its molecular mechanisms, emerging biomarkers, and novel therapeutic strategies. Furthermore, this review discusses current translational challenges and future research directions that may facilitate the development of ferroptosis-based precision medicine for a broad spectrum of human diseases.

While recent literature extensively covers ferroptosis mechanisms, disease involvement, biomarkers, and therapeutic modalities, critical translational and conceptual gaps persist. Crucially, studies frequently conflate ferroptosis-associated molecular alterations with true biomarkers, overlooking fundamental differences between core pathway machinery, markers of lipid peroxidation, experimental surrogates of cell death, and clinically validated diagnostics. Additionally, the strength of causative evidence and the clinical readiness of targeted therapies remain highly heterogeneous across distinct disease settings. To address these issues, this review offers a critical, integrative synthesis linking fundamental ferroptosis biology with disease-specific data, biomarker limitations, experimental validation standards, and key translational hurdles. By doing so, we establish a rigorous framework to separate true mechanistic causality from mere association, ultimately highlighting key research priorities to advance clinical translation.

To bridge the gap between preclinical discovery and clinical application, this review critically evaluates the role of ferroptosis across human pathologies by integrating core molecular mechanisms, disease-specific evidence, biomarker reliability, experimental validation standards, and targeted therapeutic approaches.

MATERIALS AND METHODS

Literature Search Strategy

This narrative review was conducted to synthesize recent evidence on ferroptosis in human diseases, with particular emphasis on its molecular mechanisms, disease-specific roles, associated molecular and biochemical indicators, experimental validation, and therapeutic strategies. Literature searches were performed using three electronic databases: PubMed, Scopus, and ScienceDirect.

The search strategy was specifically developed according to the objectives and scope of this ferroptosis-focused review. The search terms were related exclusively to ferroptosis, its regulatory mechanisms, disease associations, biomarkers, and therapeutic approaches. The primary search strategy combined ("ferroptosis" OR "ferroptotic cell death") with terms related to iron metabolism, lipid peroxidation, ferroptosis-regulatory pathways, biomarkers, and therapeutic strategies, including *"iron metabolism," "lipid peroxidation," "GPX4," "SLC7A11," "FSP1," "ACSL4," "ferroptosis biomarker*," "ferroptosis inhibitor*," and "ferroptosis inducer*."*

Additional disease-specific searches were performed by combining "ferroptosis" with terms related to individual disease categories, including cancer, neurodegenerative diseases, cardiovascular diseases, kidney diseases, liver diseases, metabolic disorders, and inflammatory diseases. The search was limited to English-language publications published between January 2021 and July 21, 2026. The final database search was conducted on July 21, 2026.

The search strategy did not include search concepts related to stem cells or stem cell-derived exosomes because these topics were outside the scope of the present review.

Inclusion and Exclusion Criteria

Publications were considered eligible when they addressed one or more of the following ferroptosis-related topics: (1) molecular mechanisms regulating ferroptosis; (2) experimental or clinical evidence linking ferroptosis to human diseases; (3) molecular or biochemical indicators associated with ferroptosis; (4) experimental approaches for detecting or validating ferroptotic cell death; or (5) pharmacological and emerging therapeutic strategies targeting ferroptosis.

Original research articles, systematic reviews, narrative reviews, consensus or guideline papers, and other relevant peer-reviewed publications were considered eligible when they provided information directly relevant to the objectives of this ferroptosis-focused review.

Publications were excluded when ferroptosis was mentioned only incidentally without mechanistic or disease relevance, when the article did not provide sufficient information relevant to the scope of this review, or when the publication focused primarily on topics unrelated to ferroptosis, including stem cell-derived exosome research without a direct and substantive focus on ferroptosis.

Study Screening and Selection

Retrieved records were screened according to their relevance to the objectives and scope of this ferroptosis-focused narrative review. Titles and abstracts were initially assessed, followed by full-text evaluation when necessary. Particular attention was given to publications providing mechanistic evidence, disease-specific evidence, biomarker-related evidence, or therapeutic evidence directly relevant to ferroptosis.

Because this study was designed as a narrative review rather than a systematic review or meta-analysis, study selection was based on thematic relevance, recency, and scientific contribution to the review objectives. Recent mechanistic studies, consensus recommendations, and publications providing direct evidence of ferroptotic cell death were prioritized.

International Journal of Cell and Biomedical Science (2026) 5: (14) 516-532
https://doi.org/10.59278/cbs.v5i14.108

Data Extraction and Analysis

Relevant information was extracted from the selected publications according to predefined thematic categories. The extracted information included disease context, proposed ferroptosis-related mechanisms, iron metabolism, lipid metabolism and peroxidation, antioxidant defense systems, ferroptosis-associated molecular and biochemical indicators, experimental evidence supporting ferroptotic cell death, therapeutic interventions, and translational status.

The extracted information was synthesized thematically across four major domains: (1) molecular mechanisms of ferroptosis; (2) disease-specific roles of ferroptosis; (3) ferroptosis-associated molecular and biochemical indicators and their clinical relevance; and (4) therapeutic strategies and translational challenges.

Particular emphasis was placed on distinguishing associations with ferroptosis from evidence demonstrating ferroptotic cell death. Changes in individual ferroptosis-associated molecules or oxidative stress markers were not considered sufficient evidence of ferroptosis in isolation. Where available, greater weight was given to studies incorporating complementary biochemical, molecular, morphological, and pharmacological evidence.

Rationale for the Narrative Review Approach

A narrative review approach was selected because the literature on ferroptosis encompasses heterogeneous experimental models, disease contexts, molecular endpoints, biomarkers, and therapeutic strategies that cannot readily be combined quantitatively. The purpose of this review was therefore to provide a critical and integrative synthesis of the available evidence rather than a quantitative estimate of effect sizes.

To reduce selection bias, the literature search was based on predefined ferroptosis-related concepts and search terms, explicit inclusion and exclusion criteria, and thematic evidence categories. The synthesis emphasized recent mechanistic studies, consensus or guideline publications, and evidence directly relevant to the identification, interpretation, and therapeutic modulation of ferroptotic cell death.

RESULTS

Molecular Basis of Ferroptosis

Ferroptosis is a distinct form of regulated cell death characterized by iron-dependent lipid peroxidation and overwhelming oxidative damage that ultimately compromises membrane integrity [8]. Unlike apoptosis, necroptosis, or pyroptosis, ferroptosis is not mediated by caspase activation or inflammatory pore formation but instead results from a disruption of intracellular redox homeostasis[8]. The initiation and progression of ferroptosis are orchestrated through the interplay of iron metabolism, lipid metabolism, antioxidant defense systems, and mitochondrial function, which together determine cellular susceptibility to ferroptotic cell death[14,23].

International Journal of Cell and Biomedical Science (2026) 5: (14) 516-532
https://doi.org/10.59278/cbs.v5i14.108

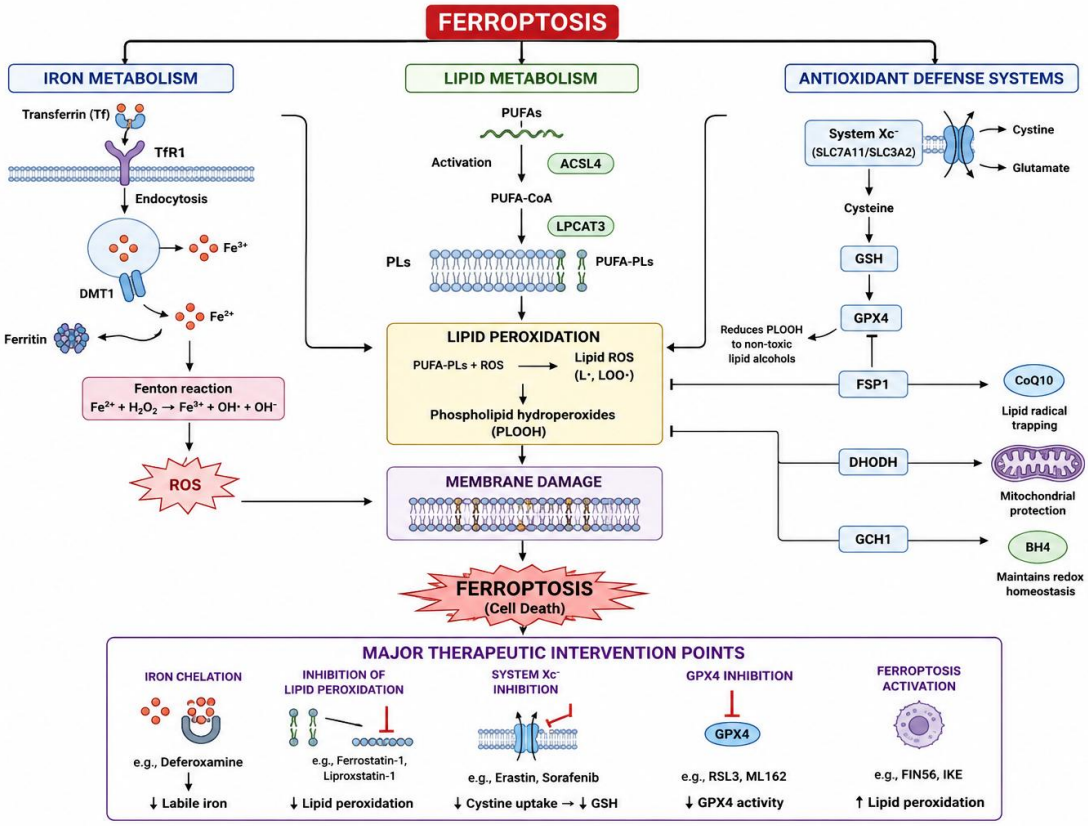


Figure 1. Integrated molecular mechanisms of ferroptosis and major therapeutic intervention points. Ferroptosis results from the interplay between iron metabolism, lipid metabolism, and antioxidant defense systems, leading to iron-dependent lipid peroxidation and phospholipid hydroperoxide accumulation. The System Xc^-/GSH/GPX4, FSP1-CoQ10, DHODH, and GCH1-BH4 pathways act as complementary defense mechanisms against lipid peroxidation. Disruption of these protective pathways promotes membrane damage and ferroptotic cell death, while major therapeutic strategies target iron availability, lipid peroxidation, System Xc^-, and GPX4.

Iron Metabolism and Ferroptosis

Iron homeostasis plays a central role in ferroptosis by regulating the availability of intracellular ferrous iron (Fe^{2+}), the principal catalyst of reactive oxygen species (ROS) generation through the Fenton reaction[16]. Under physiological conditions, circulating ferric iron (Fe^{3+}) binds to transferrin and enters cells via transferrin receptor 1 (TfR1)-mediated endocytosis[16]. Following endosomal acidification, ferric iron is reduced to ferrous iron by six-transmembrane epithelial antigen of the prostate 3 (STEAP3) and subsequently transported into the cytoplasm through divalent metal transporter 1 (DMT1)[16].

Disruption of these regulatory mechanisms results in the accumulation of the labile iron pool (LIP), increasing intracellular Fe^{2+} availability and promoting ROS generation via the Fenton reaction[4,12,16]. Elevated ROS subsequently initiate oxidative damage to polyunsaturated phospholipids within cellular membranes, a hallmark event in ferroptosis[20]. Several studies have demonstrated that increased TfR1 expression, ferritin degradation through ferritinophagy mediated by nuclear receptor coactivator 4 (NCOA4), and impaired ferroportin-mediated iron export significantly enhance ferroptosis susceptibility across multiple disease models[14,16].

International Journal of Cell and Biomedical Science (2026) 5: (14) 516-532
https://doi.org/10.59278/cbs.v5i14.108

Lipid Peroxidation

Lipid peroxidation represents the biochemical hallmark of ferroptosis. Polyunsaturated fatty acids (PUFAs) incorporated into membrane phospholipids are particularly susceptible to oxidative attack because of their multiple double bonds[8,25]. The incorporation of arachidonic acid and adrenic acid into phospholipids is primarily catalyzed by acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3), generating phospholipid substrates that are susceptible to oxidation[8,25].

Both enzymatic and non-enzymatic pathways contribute to lipid peroxide formation. Lipoxygenases (ALOXs) can catalyze the oxidation of PUFA-containing phospholipids, whereas iron-dependent reactions can promote non-enzymatic lipid oxidation[8,25,26]. Progressive accumulation of phospholipid hydroperoxides can disrupt membrane integrity and contribute to irreversible cellular injury[8,10]. However, commonly measured products of lipid peroxidation, including malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), are not specific to ferroptosis because they can also arise from other forms of oxidative lipid damage[26,36,44]. Therefore, increased MDA or 4-HNE should be interpreted as evidence of lipid oxidative injury rather than definitive evidence of ferroptotic cell death. More direct assessment of lipid reactive oxygen species or phospholipid hydroperoxides may provide stronger evidence of ferroptosis, but these parameters should likewise be interpreted together with evidence of iron dependence and appropriate pharmacological or genetic validation[10,27,36].

Antioxidant Defense Systems

Under physiological conditions, ferroptosis is prevented by multiple antioxidant defense systems that detoxify lipid hydroperoxides and maintain cellular redox balance[12]. The best-characterized protective mechanism involves the System Xc^-/glutathione (GSH)/glutathione peroxidase 4 (GPX4) axis[20]. System Xc^-, composed of SLC7A11 and SLC3A2, imports extracellular cystine in exchange for intracellular glutamate[20]. Intracellular cystine is subsequently reduced to cysteine, which serves as the rate-limiting substrate for glutathione synthesis[12].

GPX4 utilizes reduced glutathione as a cofactor to convert phospholipid hydroperoxides into non-toxic lipid alcohols, thereby preventing excessive lipid peroxidation[12]. Pharmacological inhibition of System Xc^- or direct inactivation of GPX4 rapidly depletes antioxidant capacity and represents one of the principal mechanisms triggering ferroptosis[20].

Recent evidence has identified additional ferroptosis defense pathways independent of GPX4[2412,25]. Ferroptosis suppressor protein 1 (FSP1) reduces coenzyme Q10 (CoQ10) to ubiquinol, which functions as a potent lipophilic antioxidant capable of preventing membrane lipid oxidation[12]. Likewise, dihydroorotate dehydrogenase (DHODH) protects mitochondrial membranes against oxidative damage, while the GTP cyclohydrolase 1 (GCH1)-tetrahydrobiopterin (BH4) pathway has emerged as another endogenous antioxidant system contributing to ferroptosis [26,27]. Together, these complementary pathways demonstrate that ferroptosis is regulated through a highly integrated antioxidant network rather than a single molecular mechanism[28].

Evidence for Establishing Ferroptotic Cell Death

Ferroptosis should not be identified solely on the basis of changes in a single molecular or biochemical marker. Increased reactive oxygen species (ROS), iron accumulation, altered GPX4, SLC7A11, or ACSL4 expression, and elevated malondialdehyde (MDA) or 4-hydroxynonenal (4-HNE) may occur during ferroptosis but can also reflect broader forms of oxidative or metabolic stress; therefore, these findings alone are insufficient to establish ferroptotic cell death[27,36,44]. The defining biochemical feature of ferroptosis is iron-dependent phospholipid peroxidation, and

International Journal of Cell and Biomedical Science (2026) 5: (14) 516-532
https://doi.org/10.59278/cbs.v5i14.108

experimental interpretation should therefore integrate evidence of lipid peroxidation with complementary molecular and functional findings[8,10,44].

A more rigorous assessment of ferroptosis should incorporate multiple complementary lines of evidence. Molecular alterations in established ferroptosis-regulatory pathways, such as impairment of the System Xc^-/GSH/GPX4 axis or increased ACSL4-dependent incorporation of polyunsaturated fatty acids into membrane phospholipids, can provide mechanistic support[10,12,25]. However, these molecular changes should be interpreted together with evidence of increased lipid peroxidation and cell death rather than as independent diagnostic criteria.

Pharmacological or genetic rescue provides an additional important layer of evidence. When feasible, cell death attributed to ferroptosis should be attenuated by established ferroptosis inhibitors or iron-chelating interventions, while alternative regulated cell-death pathways should be considered and appropriately controlled[10,15,36]. The use of multiple complementary approaches is particularly important because currently available methods for detecting ferroptosis, including measurements of ROS, MDA, pathway-related proteins, cell viability, and mitochondrial alterations, are individually insufficiently specific [27,36].

Morphological findings may provide supportive evidence, particularly when characteristic mitochondrial alterations are observed, but morphology should not be interpreted independently of biochemical and molecular evidence[10,32,33]. Accordingly, a combination of biochemical, molecular, pharmacological, and, where appropriate, morphological evidence provides a more reliable basis for identifying ferroptotic cell death than measurement of any single ferroptosis-associated marker[27,36,44].

Mitochondrial Contribution to Ferroptosis

Mitochondria can influence ferroptosis through their effects on cellular metabolism, redox homeostasis, reactive oxygen species production, and mitochondrial antioxidant defense; however, mitochondrial dysfunction should not be regarded as a defining requirement for ferroptotic cell death[31,34,35]. The central biochemical event distinguishing ferroptosis is iron-dependent phospholipid peroxidation, whereas the contribution of mitochondria varies according to cell type, metabolic state, and experimental context[8,10,31].

Mitochondrial morphological alterations, including mitochondrial shrinkage, increased membrane density, and reduction or loss of cristae, have been reported in experimental models of ferroptosis[32,33]. Nevertheless, these morphological features should be considered supportive rather than independently diagnostic evidence, because mitochondrial damage can occur in other forms of cellular stress and regulated cell death[32,34,36].

Mitochondria may also modulate ferroptotic susceptibility through metabolic and antioxidant mechanisms. In particular, mitochondrial dihydroorotate dehydrogenase (DHODH) has been identified as a ferroptosis defense pathway that protects mitochondrial membranes from lipid peroxidation[29,31,35]. These findings indicate that mitochondria can function as both modulators of ferroptotic sensitivity and components of cellular defense, depending on the biological context[31,34,35].

Therefore, mitochondrial alterations should be interpreted as context-dependent contributors to ferroptosis rather than defining characteristics of the process. This distinction is important when morphological findings are used to support the identification of ferroptotic cell death[31,32,34].

International Journal of Cell and Biomedical Science (2026) 5: (14) 516-532
https://doi.org/10.59278/cbs.v5i14.108

DISCUSSION

Ferroptosis as a Central Mechanism in Human Disease Pathogenesis

Accumulating experimental and observational evidence supports a potential contribution of ferroptosis to the pathophysiology of multiple human diseases, although the strength of mechanistic and causal evidence varies across disease contexts[16,21]. Unlike traditional forms of regulated cell death, ferroptosis is uniquely driven by iron-dependent lipid peroxidation, placing oxidative membrane damage at the center of cellular injury[29]. This distinctive mechanism provides a unifying explanation for pathological conditions characterized by excessive oxidative stress and disrupted iron homeostasis, which cannot be fully explained by apoptosis or necroptosis alone[16,30].

The findings summarized in this review demonstrate that ferroptosis is regulated through a highly integrated network involving iron metabolism, lipid remodeling, antioxidant defense systems, and mitochondrial function[8]. Rather than acting independently, these molecular pathways interact dynamically to determine cellular susceptibility to ferroptotic injury[12]. Consequently, disturbances in one regulatory component frequently amplify dysfunction in other pathways, ultimately accelerating disease progression [16]. This interconnected regulation explains why ferroptosis has been implicated in diverse pathological conditions affecting multiple organ systems[16,21].

Integration of Molecular Regulatory Networks

One of the most important advances in ferroptosis research is the recognition that ferroptotic cell death is controlled by multiple complementary defense mechanisms rather than a single molecular pathway[31]. Although the System Xc^-/GSH/GPX4 axis remains the principal antioxidant system preventing lipid peroxidation, recent discoveries have identified additional protective mechanisms, including FSP1-CoQ10, DHODH, and GCH1-BH4 pathways[12,32]. These parallel defense systems provide redundancy that enables cells to maintain redox homeostasis under varying physiological conditions[31].

Similarly, signaling pathways such as NRF2, p53, AMPK, PI3K/AKT, mTOR, and Hippo signaling coordinate antioxidant responses, metabolic adaptation, and iron metabolism [33]. The extensive crosstalk among these pathways suggests that ferroptosis should not be considered an isolated biological process but rather an integrated component of cellular stress responses[8]. This complexity also explains why therapeutic strategies targeting a single molecule frequently produce variable responses across different diseases and patient populations [14].

Disease-Specific Roles of Ferroptosis

The contribution of ferroptosis to human disease is highly context-dependent, and the available evidence varies substantially across disease categories[16,29,37]. In several degenerative and ischemic conditions, ferroptosis has been proposed as a contributor to tissue injury through the interaction of iron dysregulation, impaired antioxidant defense, and excessive lipid peroxidation[16,17,41,42]. However, the strength of evidence is not uniform, and findings from experimental models should not automatically be interpreted as evidence that ferroptosis is a primary causal mechanism in human disease.

In neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease, abnormalities in iron homeostasis and increased oxidative lipid damage have been associated with neuronal dysfunction and degeneration[41]. Experimental studies suggest that disruption of ferroptosis-regulatory pathways may contribute to neuronal vulnerability, while pharmacological inhibition of ferroptosis can provide neuroprotective effects in experimental models[41]. Nevertheless, much of the

International Journal of Cell and Biomedical Science (2026) 5: (14) 516-532
https://doi.org/10.59278/cbs.v5i14.108

available evidence remains based on preclinical studies, and the extent to which ferroptosis independently drives disease progression in patients remains uncertain.

In ischemic and cardiovascular conditions, including ischemic stroke and myocardial ischemia-reperfusion injury, restoration of blood flow can generate substantial oxidative stress and promote lipid peroxidation, creating a cellular environment compatible with ferroptotic injury[17,42]. Experimental studies have reported protective effects of ferroptosis inhibition in these settings[17,42]. However, ischemia-reperfusion injury involves multiple interacting forms of regulated cell death and inflammatory responses, making it difficult to attribute tissue injury exclusively to ferroptosis[17,42,50].

Ferroptosis has also been implicated in kidney diseases, particularly acute kidney injury and chronic kidney disease, where altered iron handling, oxidative stress, and impaired antioxidant defenses may increase susceptibility to lipid peroxidation[18,19]. Experimental evidence supports a potential pathogenic role for ferroptosis in renal injury, and ferroptosis-targeted interventions have shown protective effects in preclinical models[18,19]. However, the clinical relevance of these findings remains to be established, particularly because renal injury is characterized by substantial metabolic, inflammatory, and vascular interactions.

In liver and metabolic diseases, ferroptosis may represent a link between disturbed lipid metabolism, iron homeostasis, oxidative stress, and hepatocellular injury[16,17]. This relationship is particularly relevant to metabolic dysfunction-associated steatotic liver disease (MASLD), in which increased lipid availability and oxidative stress may promote the accumulation of oxidized phospholipids[16]. Nevertheless, the contribution of ferroptosis may vary according to disease stage, metabolic phenotype, and the balance between lipid peroxidation and endogenous antioxidant defenses. Therefore, ferroptosis should be considered a potential disease-modifying mechanism rather than a uniform driver of all forms of metabolic liver injury[16,29].

Cancer represents a distinct disease context because ferroptosis may be therapeutically activated rather than inhibited. Many cancer cells exhibit altered iron metabolism, increased oxidative stress, and dependence on antioxidant systems such as GPX4 and SLC7A11, which can create selective vulnerabilities to ferroptosis induction[13,20,21]. Experimental studies have demonstrated that pharmacological induction of ferroptosis can suppress tumor growth and may be particularly relevant to cancers that have developed resistance to apoptosis-based therapies[13,20,21]. However, ferroptosis can also contribute to treatment resistance or adverse tissue injury depending on the molecular context, demonstrating that its role in cancer is not uniformly beneficial[13,20,43].

Taken together, these findings indicate that ferroptosis should not be considered a universal pathogenic mechanism that should simply be inhibited across all diseases. Rather, its biological and therapeutic significance depends on disease context, cell type, metabolic state, and the balance between ferroptosis-promoting and ferroptosis-suppressing mechanisms[29,37,43]. Importantly, most evidence linking ferroptosis to human disease remains experimental or observational, and stronger causal and clinical evidence is required before ferroptosis can be considered a disease-independent therapeutic target.

Critical Synthesis of Current Evidence and Conflicting Findings

Although ferroptosis has been increasingly implicated in multiple human diseases, the strength of evidence supporting its role is not uniform across disease contexts. A recurring finding across experimental studies is the presence of iron dysregulation, oxidative lipid damage, and alterations in ferroptosis-related regulatory pathways. However, these findings do not necessarily indicate that ferroptosis is the primary cause of tissue injury. Changes in iron homeostasis, lipid peroxidation, GPX4, SLC7A11, or ACSL4 may also occur as consequences of broader oxidative, metabolic, inflammatory, or cellular stress. Therefore, the interpretation of ferroptosis-related

findings should consider whether the available evidence demonstrates a causal contribution to ferroptotic cell death or merely an association with a ferroptosis-compatible cellular state [24,34].

Differences in the strength of evidence are particularly apparent across disease settings. In neurodegenerative diseases and ischemia-reperfusion injury, experimental studies have reported protective effects following ferroptosis inhibition, supporting a potential pathogenic contribution of ferroptotic mechanisms. Nevertheless, these conditions also involve multiple interacting processes, including mitochondrial dysfunction, inflammation, oxidative stress, apoptosis, and other regulated cell death pathways [17,35]. Consequently, the beneficial effects of ferroptosis inhibitors cannot always be interpreted as evidence that ferroptosis is the exclusive or dominant mechanism of tissue injury. Similar considerations apply to kidney and metabolic liver diseases, in which iron dysregulation and lipid peroxidation may contribute to disease progression but occur within complex metabolic, inflammatory, and vascular environments [16–19].

Cancer represents a contrasting context in which ferroptosis is generally investigated as a mechanism that can be therapeutically activated. Experimental studies have demonstrated that tumor cells with altered iron metabolism or increased dependence on antioxidant pathways such as GPX4 and SLC7A11 may exhibit increased ferroptotic vulnerability[2120]. However, the response to ferroptosis-inducing strategies is not uniform across cancer models. Differences in cellular metabolism, iron availability, lipid composition, antioxidant capacity, and genetic background may contribute to variable therapeutic responses. In addition, several commonly investigated ferroptosis-inducing compounds have pharmacological effects beyond ferroptosis, which makes attribution of their effects specifically to ferroptotic cell death challenging [2220,36].

The apparent differences among studies may therefore reflect differences in experimental models, disease stage, cellular context, and methods used to define ferroptosis rather than true biological contradictions [3724]. This is particularly relevant when individual molecular or biochemical indicators are used as evidence of ferroptosis. For example, MDA and 4-HNE reflect lipid oxidative damage but are not specific to ferroptosis, whereas GPX4, SLC7A11, ACSL4, FSP1, TfR1, and ferritin provide information about ferroptosis-related regulatory or susceptibility states but cannot independently establish ferroptotic cell death [24,37,38]. Stronger evidence is obtained when these findings are combined with lipid peroxidation measurements, evidence of iron dependence, cell death assessment, and pharmacological or genetic rescue by appropriate ferroptosis-targeting interventions [24,37].

The added value of the present review is therefore the integration of these different levels of evidence rather than simply summarizing ferroptosis-related findings across diseases. By distinguishing ferroptosis-associated molecular alterations, ferroptotic susceptibility, and evidence supporting actual ferroptotic cell death, this review provides a framework for interpreting the heterogeneous literature more critically [3724]. This perspective also emphasizes that the therapeutic relevance of ferroptosis is disease- and context-dependent, and that future studies should prioritize multiparametric validation, standardized biomarkers, and stronger causal evidence before ferroptosis-targeted approaches can be translated into routine clinical practice [24,37].

Emerging Biomarkers and Clinical Translation

The increasing interest in ferroptosis has led to the identification of numerous molecular and biochemical parameters associated with ferroptotic susceptibility or lipid oxidative damage[20,36,44]. However, these parameters should not be considered interchangeable as specific biomarkers of ferroptosis. A distinction should be made between molecular components of the ferroptosis regulatory network, experimental indicators of ferroptotic activity, and clinically validated biomarkers[27,36].

International Journal of Cell and Biomedical Science (2026) 5: (14) 516-532
https://doi.org/10.59278/cbs.v5i14.108

Molecular components such as GPX4, SLC7A11, ACSL4, FSP1, transferrin receptor 1 (TfR1), and ferritin are mechanistically involved in pathways regulating ferroptosis susceptibility[10,12,16,28]. Alterations in their expression or activity may therefore provide information about cellular susceptibility or changes in ferroptosis-related pathways. However, changes in these proteins alone do not establish that ferroptotic cell death has occurred[27,36]. For example, increased ACSL4 may indicate enhanced availability of polyunsaturated phospholipid substrates for oxidation, whereas reduced GPX4 or SLC7A11 activity may indicate impaired antioxidant defense; neither finding independently demonstrates ongoing ferroptotic cell death[10,12,25].

Similarly, MDA and 4-HNE are frequently measured as indicators of lipid peroxidation, but their elevation is not specific to ferroptosis because both can arise from diverse forms of oxidative stress and lipid membrane damage[26,44]. Thus, these parameters should be interpreted as indicators of lipid oxidative injury rather than as standalone biomarkers of ferroptosis[36,44].

The current evidence therefore supports a multiparametric approach to ferroptosis assessment. Stronger evidence is obtained when alterations in ferroptosis-associated pathways are accompanied by increased phospholipid peroxidation, evidence of iron dependence, loss of cellular viability, and attenuation of cell death following treatment with ferroptosis inhibitors or appropriate iron-chelating interventions[10,27,36]. The international consensus literature emphasizes the importance of integrating complementary experimental approaches when defining and interpreting ferroptotic cell death[27].

Table 1. Ferroptosis-associated molecular and biochemical indicators and their limitations

Category	Examples	What the parameter indicates	Major limitation
Ferroptosis regulatory components	GPX4, SLC7A11, ACSL4, FSP1	Ferroptosis susceptibility or regulatory state[10,12,28]	Not independently diagnostic of ferroptosis[27,36]
Iron-related indicators	TfR1, ferritin, labile iron	Altered iron handling and ferroptotic susceptibility[16,]	Iron accumulation is not specific to ferroptosis[16,36]
Lipid peroxidation indicators	MDA, 4-HNE	Oxidative lipid damage[26,44]	Not specific to ferroptosis[36,44]
Lipid peroxidation-related evidence	Lipid ROS, phospholipid hydroperoxides	More direct evidence of lipid oxidation relevant to ferroptosis[10,25,36]	Requires complementary evidence
Functional/pharmacological evidence	Cell death + ferroptosis inhibitor rescue	Supports causal involvement of ferroptosis[15,27,36]	Requires appropriate experimental controls
Morphological evidence	Mitochondrial shrinkage, dense membranes, reduced cristae	Supportive ultrastructural evidence[32,33]	Not independently diagnostic[32,34,36]
Clinically validated universal biomarker	**None currently established**	—	Requires prospective validation[36]

Importantly, the translational status of ferroptosis-related biomarkers remains limited. Although ferroptosis-associated proteins and lipid peroxidation products have been investigated in experimental and clinical disease contexts, their association with disease severity does not establish specificity for ferroptosis[20,36,44]. Consequently, no individual molecular or biochemical parameter currently provides sufficient evidence to serve as a universal, clinically validated bioerroptosis-associated molecular indicator across different human diseases[36].

International Journal of Cell and Biomedical Science (2026) 5: (14) 516-532
https://doi.org/10.59278/cbs.v5i14.108

Future biomarker development should therefore focus on integrated panels combining complementary domains, including iron availability, phospholipid peroxidation, antioxidant defense, and disease-specific molecular characteristics. Such approaches may improve the specificity of ferroptosis assessment, although prospective clinical validation, standardized analytical methods, clinically relevant thresholds, and demonstration of diagnostic or prognostic utility remain necessary before ferroptosis-related biomarker panels can be incorporated into routine clinical practice[20,36]. Because individual molecular or biochemical parameters are not sufficiently specific to establish ferroptotic cell death, the major ferroptosis-associated indicators, their biological significance, and their limitations for ferroptosis identification are summarized in Table 1.

Overall, assessing ferroptosis requires moving beyond single molecular markers toward an integrated, multiparametric framework. Differentiating ferroptosis-associated indicators from validated biomarkers is crucial for clinical translation; molecular or biochemical changes seen in experimental models often signal susceptibility or general oxidative stress rather than definitive ferroptotic cell death[27,36].

Therapeutic Opportunities and Translational Challenges

Therapeutic modulation of ferroptosis can theoretically follow two opposing strategies: inhibition of ferroptosis to protect normal tissues from pathological injury or induction of ferroptosis to eliminate susceptible malignant cells[15,17,22]. This context-dependent therapeutic strategy is an important distinction because systemic inhibition or activation of ferroptosis may produce substantially different consequences across tissues.

Ferroptosis inhibitors such as ferrostatin-1 and liproxstatin-1 have demonstrated protective effects against ferroptotic injury in experimental models, while iron-chelating agents such as deferoxamine can reduce ferroptosis by limiting the availability of catalytically active iron[15,45]. Antioxidant pathways involving vitamin E and coenzyme Q10 can also suppress lipid peroxidation and contribute to ferroptosis resistance[8,15]. However, most of these compounds remain experimental tools or preclinical candidates, and their pharmacokinetic properties, tissue distribution, dose-response relationships, and long-term safety require further investigation before clinical application can be considered[15,32,45].

Conversely, ferroptosis induction has attracted considerable interest in cancer therapy. Agents such as erastin and RSL3 can promote ferroptosis by disrupting cystine-dependent antioxidant defense or directly impairing GPX4 activity, respectively[13,22]. Sorafenib has also been investigated in relation to ferroptosis, although its pharmacological effects are pleiotropic and cannot be attributed exclusively to ferroptosis induction[20,22]. These observations highlight an important translational issue: an agent that produces a ferroptosis-compatible phenotype in experimental systems should not automatically be considered a specific ferroptosis-targeted therapy.

The therapeutic window represents another major challenge. Because ferroptosis is closely linked to iron metabolism, lipid metabolism, and redox homeostasis, systemic modulation of these pathways may affect normal tissues as well as diseased cells[16,32]. Potential toxicity is particularly relevant in tissues characterized by high metabolic activity, substantial iron turnover, or dependence on antioxidant defense systems[32,34]. Therefore, therapeutic development requires not only demonstration of efficacy but also careful assessment of selectivity, off-target effects, pharmacokinetics, tissue distribution, and dose-dependent toxicity.

An additional limitation is the gap between experimental models and human clinical disease. Most ferroptosis-targeted interventions have been evaluated in cultured cells or animal models, where drug exposure, disease homogeneity, and experimental conditions differ substantially from those encountered in patients[15,17,22]. Furthermore, the absence of standardized clinical

biomarkers makes it difficult to determine whether a therapeutic response in humans is specifically associated with modulation of ferroptosis[36]. Consequently, preclinical efficacy should be interpreted as evidence of therapeutic potential rather than proof of clinical effectiveness.

Emerging approaches, including nanomedicine, targeted drug delivery, RNA-based approaches, CRISPR-mediated modulation, and exosome-based delivery, may improve tissue specificity and reduce systemic toxicity[46–49]. Nevertheless, these technologies remain largely experimental in the context of ferroptosis and introduce additional translational challenges related to delivery efficiency, manufacturing, immunogenicity, pharmacokinetics, and regulatory approval[46–49]. Future therapeutic development should therefore prioritize disease-specific targeting and selective modulation of ferroptosis rather than nonspecific systemic activation or inhibition.

Current Challenges and Future Research Directions

Despite remarkable progress, several important challenges continue to limit the clinical translation of ferroptosis-targeted therapies[37]. One major obstacle is the incomplete understanding of the molecular interactions between ferroptosis and other regulated cell death pathways, including apoptosis, necroptosis, pyroptosis, and autophagy[39]. Increasing evidence suggests that these pathways exhibit substantial crosstalk during disease progression, yet the precise regulatory mechanisms remain incompletely understood[34].

Table 2. Ferroptosis-targeting therapeutic strategies, mechanisms, evidence level, and translational limitations

Strategy	Representative agents/approaches	Mechanism and evidence	Key translational limitation
Ferroptosis inhibition	Ferrostatin-1, liproxstatin-1[15,45]	Suppress lipid peroxidation; mainly experimental/preclinical[15,45]	Limited clinical evidence; pharmacokinetic and tissue-delivery challenges[15,45]
Iron chelation	Deferoxamine[15,16]	Reduces available iron and iron-dependent lipid peroxidation; preclinical[15,16]	Systemic effects of iron depletion[16,32]
Antioxidant protection	Vitamin E, CoQ10[8,15]	Suppress lipid oxidation; experimental/preclinical[8,15]	Limited specificity for ferroptosis[15,36]
System Xc^- inhibition	Erastin[12,22]	Cystine deprivation → GSH depletion → impaired GPX4 defense; preclinical[12,22]	Selectivity and toxicity[22,32]
GPX4 inhibition	RSL3[12,22]	GPX4 inhibition → phospholipid peroxide accumulation; preclinical[12,22]	Potency, selectivity, and systemic toxicity[22,32]
Repurposed agents	Sorafenib[20,22]	Modulates ferroptosis-related pathways; experimental evidence	Ferroptosis is not its sole mechanism[20,22]
Targeted delivery	Nanomedicine, exosomes[46–49]	Improve tissue-specific delivery; experimental/preclinical[46–49]	Delivery, manufacturing, safety, and regulatory barriers[46–49]

Additional limitations include the lack of standardized biomarkers, variability in experimental methodologies, disease-specific regulatory differences, and the limited number of clinical trials evaluating ferroptosis-targeted interventions[40]. Furthermore, the long-term safety of pharmacological ferroptosis modulation remains uncertain, particularly regarding potential effects on normal tissues with high iron turnover or elevated oxidative metabolism [20,36]. Addressing these challenges will require multidisciplinary collaboration integrating molecular biology, pharmacology, systems biology, biomarker discovery, and clinical investigation [12,26].

Overall, current evidence indicates that ferroptosis represents far more than an additional form of regulated cell death [10]. Instead, it constitutes a central biological process linking oxidative

stress, iron metabolism, lipid peroxidation, and metabolic dysfunction across numerous human diseases[16]. Continued advances in mechanistic understanding, biomarker development, and targeted therapeutics are expected to accelerate the translation of ferroptosis research from experimental models into precision medicine, ultimately providing novel diagnostic and therapeutic opportunities for a wide spectrum of human diseases [14].

Ferroptosis-targeting interventions differ substantially in their mechanisms, experimental evidence, and translational readiness. Representative ferroptosis inhibitors, inducers, and emerging delivery approaches, together with their mechanisms and major translational limitations, are summarized in Table 2.

Table 2 highlights that the majority of ferroptosis-targeted strategies are still at the preclinical stage, with limited clinical validation to date[15,17,22,45]. Bridging this translational divide requires rigorous characterization of their pharmacokinetic properties, therapeutic windows, target selectivity, and long-term safety profiles prior to clinical implementation[15,32,36].

CONCLUSION

Ferroptosis is an iron-dependent form of regulated cell death that may contribute to the pathophysiology of various human diseases, although the strength of mechanistic and causal evidence varies across disease contexts. Ferroptosis-associated molecules and oxidative lipid products may provide useful information but are not sufficiently specific to serve as universal biomarkers of ferroptotic cell death. Therapeutic modulation of ferroptosis remains largely at the experimental and preclinical stage, highlighting the need for standardized multiparametric detection, disease-specific validation, and further evaluation of therapeutic safety and clinical efficacy.

Acknowledgements

We would like to thank the our colleagues for their encouragement and help during the preparation of this project.

Authors' contributions

All authors contributed equally to this research, including conceptualization, data acquisition and analysis, literature review, manuscript preparation, and revision.

Funding

None.

Conflict of interest

The authors declare that there are no conflicts of interest related to this work.

REFERENCES

1. Hughes LD, Wang Y, Meli AP, Rothlin C V., Ghosh S. Decoding Cell Death: From a Veritable Library of Babel to Vade Mecum? *Annu Rev Immunol*. 2021;39(1):791-817. doi:10.1146/annurev-immunol-102819-072601
2. Qian S, Long Y, Tan G, et al. Programmed cell death: molecular mechanisms, biological functions, diseases, and therapeutic targets. *MedComm*. 2024;5(12). doi:10.1002/mco2.70024
3. Snyder AG, Oberst A. The Antisocial Network: Cross Talk Between Cell Death Programs in Host Defense. *Annu Rev Immunol*. 2021;39(1):77-101. doi:10.1146/annurev-immunol-112019-072301

4. Chen Y, Li X, Yang M, Liu SB. Research progress on morphology and mechanism of programmed cell death. *Cell Death Dis*. 2024;15(5):327. doi:10.1038/s41419-024-06712-8
5. Wang S, Guo S, Guo J, et al. Cell death pathways: molecular mechanisms and therapeutic targets for cancer. *MedComm*. 2024;5(9). doi:10.1002/mco2.693
6. Yuan J, Ofengeim D. A guide to cell death pathways. *Nat Rev Mol Cell Biol*. 2024;25(5):379-395. doi:10.1038/s41580-023-00689-6
7. Glover HL, Schreiner A, Dewson G, Tait SWG. Mitochondria and cell death. *Nat Cell Biol*. 2024;26(9):1434-1446. doi:10.1038/s41556-024-01429-4
8. Dixon SJ, Olzmann JA. The cell biology of ferroptosis. *Nat Rev Mol Cell Biol*. 2024;25(6):424-442. doi:10.1038/s41580-024-00703-5
9. Zhang DD. Ironing out the details of ferroptosis. *Nat Cell Biol*. 2024;26(9):1386-1393. doi:10.1038/s41556-024-01361-7
10. Dai E, Chen X, Linkermann A, et al. A guideline on the molecular ecosystem regulating ferroptosis. *Nat Cell Biol*. 2024;26(9):1447-1457. doi:10.1038/s41556-024-01360-8
11. Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. *Nat Rev Mol Cell Biol*. 2021;22(4):266-282. doi:10.1038/s41580-020-00324-8
12. Zheng J, Conrad M. Ferroptosis: when metabolism meets cell death. *Physiol Rev*. 2025;105(2):651-706. doi:10.1152/physrev.00031.2024
13. Nakamura T, Conrad M. Exploiting ferroptosis vulnerabilities in cancer. *Nat Cell Biol*. 2024;26(9):1407-1419. doi:10.1038/s41556-024-01425-8
14. Zhou Q, Meng Y, Le J, et al. Ferroptosis: mechanisms and therapeutic targets. *MedComm*. 2024;5(12). doi:10.1002/mco2.70010
15. Zhang L, Luo YL, Xiang Y, et al. Ferroptosis inhibitors: past, present and future. *Front Pharmacol*. 2024;15. doi:10.3389/fphar.2024.1407335
16. Ru Q, Li Y, Chen L, Wu Y, Min J, Wang F. Iron homeostasis and ferroptosis in human diseases: mechanisms and therapeutic prospects. *Signal Transduct Target Ther*. 2024;9(1):271. doi:10.1038/s41392-024-01969-z
17. Maremonti F, Tonnus W, Gavali S, et al. Ferroptosis-based advanced therapies as treatment approaches for metabolic and cardiovascular diseases. *Cell Death Differ*. 2024;31(9):1104-1112. doi:10.1038/s41418-024-01350-1
18. Jiang M, Wu S, Xie K, Zhou G, Zhou W, Bao P. The significance of ferroptosis in renal diseases and its therapeutic potential. *Heliyon*. 2024;10(16):e35882. doi:10.1016/j.heliyon.2024.e35882
19. Mao ZH, Gao ZX, Pan SK, Liu DW, Liu ZS, Wu P. Ferroptosis: a potential bridge linking gut microbiota and chronic kidney disease. *Cell Death Discov*. 2024;10(1):234. doi:10.1038/s41420-024-02000-8
20. Zhou Q, Meng Y, Li D, et al. Ferroptosis in cancer: from molecular mechanisms to therapeutic strategies. *Signal Transduct Target Ther*. 2024;9(1):55. doi:10.1038/s41392-024-01769-5
21. Wang X, Ren X, Lin X, et al. Recent progress of ferroptosis in cancers and drug discovery. *Asian J Pharm Sci*. 2024;19(4):100939. doi:10.1016/j.ajps.2024.100939
22. Ma W, Hu N, Xu W, Zhao L, Tian C, Kamei K ichiro. Ferroptosis inducers: A new frontier in cancer therapy. *Bioorg Chem*. 2024;146:107331. doi:10.1016/j.bioorg.2024.107331
23. Kong Y, Li J, Lin R, et al. Understanding the unique mechanism of ferroptosis: a promising therapeutic target. *Front Cell Dev Biol*. 2024;11. doi:10.3389/fcell.2023.1329147
24. Chen X, Tsvetkov AS, Shen HM, et al. International consensus guidelines for the definition, detection, and interpretation of autophagy-dependent ferroptosis. *Autophagy*. 2024;20(6):1213-1246. doi:10.1080/15548627.2024.2319901
25. Li W, Liang L, Liu S, Yi H, Zhou Y. FSP1: a key regulator of ferroptosis. *Trends Mol Med*. 2023;29(9):753-764. doi:10.1016/j.molmed.2023.05.013

26. Chen F, Kang R, Tang D, Liu J. Ferroptosis: principles and significance in health and disease. *J Hematol Oncol*. 2024;17(1):41. doi:10.1186/s13045-024-01564-3
27. Li Z, Lange M, Dixon SJ, Olzmann JA. Lipid Quality Control and Ferroptosis: From Concept to Mechanism. *Annu Rev Biochem*. 2024;93(1):499-528. doi:10.1146/annurev-biochem-052521-033527
28. Xie X, Pang Q, Luo L. Post-translational modifications in ferroptosis: mechanisms and therapeutic potential. *Int J Biol Sci*. 2026;22(4):1868-1905. doi:10.7150/ijbs.120624
29. Sun K, Zhi Y, Ren W, et al. The mitochondrial regulation in ferroptosis signaling pathway and its potential strategies for cancer. *Biomed Pharmacother*. 2023;169:115892. doi:10.1016/j.biopha.2023.115892
30. Jin X, Tang J, Qiu X, et al. Ferroptosis: Emerging mechanisms, biological function, and therapeutic potential in cancer and inflammation. *Cell Death Discov*. 2024;10(1):45. doi:10.1038/s41420-024-01825-7
31. Alves F, Lane D, Nguyen TPM, Bush AI, Ayton S. In defence of ferroptosis. *Signal Transduct Target Ther*. 2025;10(1):2. doi:10.1038/s41392-024-02088-5
32. Ge A, He Q, Zhao D, et al. Mechanism of ferroptosis in breast cancer and research progress of natural compounds regulating ferroptosis. *J Cell Mol Med*. 2024;28(1). doi:10.1111/jcmm.18044
33. Pang Q, Tang Z, Luo L. The crosstalk between oncogenic signaling and ferroptosis in cancer. *Crit Rev Oncol Hematol*. 2024;197:104349. doi:10.1016/j.critrevonc.2024.104349
34. Saxena R, Welsh CM, He YW. Targeting regulated cell death pathways in cancers for effective treatment: a comprehensive review. *Front Cell Dev Biol*. 2024;12. doi:10.3389/fcell.2024.1462339
35. Soni P, Ammal Kaidery N, Sharma SM, et al. A critical appraisal of ferroptosis in Alzheimer's and Parkinson's disease: new insights into emerging mechanisms and therapeutic targets. *Front Pharmacol*. 2024;15. doi:10.3389/fphar.2024.1390798
36. Liu Y, Lu S, Wu L lei, Yang L, Yang L, Wang J. The diversified role of mitochondria in ferroptosis in cancer. *Cell Death Dis*. 2023;14(8):519. doi:10.1038/s41419-023-06045-y
37. Chen Z, Lin H, Wang X, et al. The application of approaches in detecting ferroptosis. *Heliyon*. 2024;10(1):e23507. doi:10.1016/j.heliyon.2023.e23507
38. Veeckmans G, Van San E, Vanden Berghe T. A guide to ferroptosis, the biological rust of cellular membranes. *FEBS J*. 2024;291(13):2767-2783. doi:10.1111/febs.16993
39. Ai Y, Meng Y, Yan B, Zhou Q, Wang X. The biochemical pathways of apoptotic, necroptotic, pyroptotic, and ferroptotic cell death. *Mol Cell*. 2024;84(1):170-179. doi:10.1016/j.molcel.2023.11.040
40. Berndt C, Alborzinia H, Amen VS, et al. Ferroptosis in health and disease. *Redox Biol*. 2024;75:103211. doi:10.1016/j.redox.2024.103211