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MOLECULAR MECHANISMS OF FERROPTOSIS IN ISCHEMIA-REPERFUSION INJURY

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ABSTRACT Background: Ischemia-reperfusion injury (IRI) is a complex pathological process characterized by metabolic disturbances, mitochondrial dysfunction, oxidative stress, inflammatory activation, and regulated cell death. Although restoration of blood circulation is essential for maintaining tissue viability, reperfusion may paradoxically aggravate cellular damage through excessive generation of reactive oxygen species and disruption of intracellular redox homeostasis. Ferroptosis, an iron-dependent form of regulated cell death driven by the accumulation of oxidized membrane phospholipids, has emerged as an important mechanism contributing to ischemia-reperfusion-associated tissue injury. **Objective:** To investigate the molecular and pathophysiological mechanisms of ferroptosis during ischemia-reperfusion injury, evaluate the interactions among iron metabolism, lipid peroxidation, mitochondrial dysfunction, and antioxidant defense pathways, and analyze contemporary therapeutic strategies targeting ferroptotic cell death.

Materials and Methods: A narrative review of international scientific publications, original experimental studies, and contemporary mechanistic investigations available through November 2026 was conducted. The analysis focused on the system Xc^-/glutathione/glutathione peroxidase 4 pathway, acyl-CoA synthetase long-chain family member 4, iron-dependent lipid oxidation, ferritinophagy, mitochondrial oxidative stress, and alternative ferroptosis defense mechanisms.

Results: The reviewed evidence indicates that ischemic energy depletion and subsequent reperfusion-associated oxidative stress create conditions favorable for iron-dependent phospholipid peroxidation. Reduced glutathione availability, impaired GPX4 activity, increased intracellular labile iron, and ACSL4-dependent enrichment of cellular membranes with polyunsaturated fatty acids contribute to ferroptotic injury. Experimental studies demonstrate that genetic and pharmacological inhibition of ferroptosis may reduce myocardial, cerebral, renal, and hepatic injury. A 2026 investigation published in Cell demonstrated an early increase in lipid peroxidation in human liver transplant samples and promising protective effects of a ferroptosis inhibitor in preclinical and ex vivo organ preservation models.

Conclusion: Ferroptosis represents an important molecular component of ischemia-reperfusion injury and a potential therapeutic target. Nevertheless, further clinical studies are required to establish reliable diagnostic biomarkers, determine organ-specific treatment windows, and confirm the safety and effectiveness of ferroptosis-targeted interventions in patients.

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Keywords: ferroptosis, ischemia-reperfusion injury, pathological physiology, iron metabolism, lipid peroxidation, GPX4, ACSL4, mitochondrial dysfunction, oxidative stress, regulated cell death, organ transplantation.

INTRODUCTION

Ischemia-reperfusion injury represents a fundamental pathological process occurring when the blood supply to a tissue or organ is temporarily interrupted and subsequently restored. Although reperfusion is necessary to prevent irreversible tissue necrosis and maintain organ viability, the rapid reintroduction of oxygen and metabolic substrates may initiate additional biochemical disturbances that aggravate cellular injury. This phenomenon is clinically relevant to acute myocardial infarction, ischemic stroke, acute kidney injury, organ transplantation, hepatic surgery, shock, and other conditions associated with temporary impairment of tissue perfusion. During the ischemic period, oxygen deprivation reduces mitochondrial oxidative phosphorylation, impairs adenosine triphosphate synthesis, and initiates alterations in intracellular ionic balance, membrane transport, and metabolic regulation. Progressive ATP depletion compromises the activity of energy-dependent ion pumps, contributing to intracellular sodium and calcium accumulation, cellular swelling, and disturbances in the mitochondrial membrane potential. Simultaneously, anaerobic glycolysis and altered intermediary metabolism promote intracellular acidification and accumulation of metabolites that may influence the response to subsequent reperfusion. Restoration of oxygen supply can reverse some of these abnormalities, but it may also stimulate excessive production of reactive oxygen species, mitochondrial permeability disturbances, inflammatory signaling, and microvascular dysfunction. Chouchani and colleagues (2014) demonstrated that succinate accumulation during ischemia contributes to rapid mitochondrial ROS generation upon reperfusion through reverse electron transport at respiratory complex I [3]. Their findings established a molecular relationship between ischemic metabolic adaptation and the oxidative injury that occurs after restoration of circulation. However, ischemia-reperfusion injury involves several interconnected mechanisms, and mitochondrial ROS production alone does not explain the diversity of cellular death pathways observed in different tissues.

Regulated cell death contributes substantially to the pathogenesis of ischemia-reperfusion injury, but its molecular characteristics vary according to cell type, metabolic status, and the intensity of injury. Apoptosis, necroptosis, pyroptosis, and ferroptosis represent distinct but potentially interacting mechanisms that may be activated during tissue ischemia and subsequent reperfusion. Among these processes, ferroptosis has attracted particular attention because it links iron homeostasis, lipid metabolism, antioxidant defense, and cellular membrane integrity. Dixon and colleagues first introduced the term ferroptosis in 2012 to describe an iron-dependent form of nonapoptotic cell death characterized by oxidative membrane injury and susceptibility to inhibition by iron chelators and lipid radical-trapping compounds [1]. Subsequent investigations established that the defining biochemical feature of ferroptosis is the uncontrolled accumulation of phospholipid hydroperoxides containing polyunsaturated

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fatty acid residues. Unlike classical apoptosis, ferroptosis does not require the canonical caspase-mediated execution program, and its molecular regulation is closely associated with the balance between lipid oxidation and membrane-protective antioxidant pathways. Stockwell and colleagues (2017) emphasized that ferroptosis represents a convergence point between cellular metabolism, redox biology, iron handling, and pathological tissue injury [2]. The sensitivity of cells to ferroptosis depends not only on their exposure to reactive oxygen species but also on the availability of redox-active iron, the lipid composition of cellular membranes, and the functional capacity of antioxidant defense systems. These features make ferroptosis particularly relevant during ischemia-reperfusion injury, when iron homeostasis and lipid oxidation may be disrupted simultaneously.

Recent scientific developments have identified several molecular pathways regulating ferroptosis, including the cystine/glutamate antiporter system Xc^-, glutathione peroxidase 4 (GPX4), acyl-CoA synthetase long-chain family member 4 (ACSL4), ferroptosis suppressor protein 1 (FSP1), and mechanisms controlling ferritin degradation and intracellular iron availability. Experimental evidence suggests that activation or inhibition of these pathways can influence the severity of injury in the heart, brain, kidneys, and liver. Friedmann Angeli and colleagues (2014) provided direct genetic evidence that inactivation of GPX4 can trigger severe renal injury and demonstrated the protective properties of the ferroptosis inhibitor liproxstatin-1 in experimental models [4]. Fang and colleagues (2019) subsequently identified ferroptosis as a contributor to cardiomyocyte injury in models of myocardial ischemia-reperfusion and cardiomyopathy [8]. More recently, investigations examining organ transplantation have expanded the translational relevance of ferroptosis. Veeckmans and colleagues (2026) identified an early increase in lipid peroxidation in human liver transplant samples and demonstrated the potential of a ferroptosis inhibitor to preserve organ function in experimental perfusion models [16]. These findings suggest that ferroptosis is not merely an experimental phenomenon observed in isolated cell cultures but a potentially relevant mechanism of tissue injury in clinically important conditions. Nevertheless, the contribution of ferroptosis varies across organs, and its inhibition has not yet been established as a standard clinical treatment for ischemia-reperfusion injury. **The aim of this study is to** analyze the molecular mechanisms of ferroptosis during ischemia-reperfusion injury, evaluate its contribution to organ-specific pathology, and examine emerging therapeutic approaches directed toward iron-dependent lipid peroxidation.

MATERIALS AND METHODS

The present study was conducted as a narrative review of international scientific literature concerning ferroptosis and its involvement in ischemia-reperfusion injury. Scientific publications available through November 2026 were examined, including original experimental investigations, mechanistic studies, translational research, and contemporary reviews published in internationally recognized medical and biomedical journals. Particular attention was given to publications in Cell, Nature, Nature Cell Biology, Nature Chemical Biology, Molecular Cell, Proceedings of the National Academy of Sciences, Molecular Psychiatry, Cell Research, and other peer-reviewed journals

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addressing cellular injury and regulated cell death. The analysis focused on the molecular mechanisms responsible for iron-dependent lipid peroxidation, intracellular iron trafficking, glutathione metabolism, antioxidant defense, mitochondrial dysfunction, and the regulation of cellular susceptibility to ferroptosis. The roles of GPX4, ACSL4, LPCAT3, SLC7A11, NCOA4, FSP1, GCH1, and dihydroorotate dehydrogenase were considered in relation to the initiation, amplification, and inhibition of ferroptotic injury. Experimental findings were evaluated in the context of myocardial, cerebral, renal, and hepatic ischemia-reperfusion models, including organ preservation and transplantation research. Descriptive and comparative analytical methods were used to synthesize the literature, with particular attention to differences between in vitro experiments, animal investigations, ex vivo organ studies, and clinical observations. The interpretation of therapeutic findings considered the specificity of ferroptosis-related interventions, their reported biological effects, and the limitations of translating experimental results into human clinical treatment. No original patient recruitment, tissue sampling, laboratory investigation, experimental intervention, or independent statistical meta-analysis was performed. Therefore, the results represent a critical narrative synthesis of published evidence rather than an original experimental investigation.

RESULTS

Analysis of the reviewed scientific literature demonstrated that ferroptosis is regulated through interactions among intracellular iron availability, polyunsaturated phospholipid metabolism, and the capacity of cellular antioxidant systems to prevent uncontrolled lipid oxidation. Iron is essential for numerous physiological functions, including oxygen transport, mitochondrial respiration, DNA synthesis, and the activity of iron-containing enzymes. However, poorly regulated intracellular iron may participate in redox reactions that generate highly reactive oxidative intermediates. Under normal physiological conditions, iron homeostasis is maintained through the coordinated activity of transferrin, transferrin receptors, intracellular transport proteins, ferritin, and ferroportin. Transferrin-bound iron enters cells through receptor-mediated endocytosis, while ferritin stores iron in a relatively stable form that limits its availability for damaging redox reactions. Disturbances in these mechanisms may increase the intracellular labile iron pool, particularly the availability of ferrous iron capable of participating in Fenton chemistry. During such reactions, hydrogen peroxide interacts with redox-active iron to generate highly reactive hydroxyl radicals, promoting the oxidation of nearby biological molecules. In membranes containing polyunsaturated fatty acid residues, these oxidative reactions may initiate lipid radical formation and propagate lipid peroxidation. Gao and colleagues (2015) demonstrated that transferrin-mediated iron uptake and glutaminolysis contribute to ferroptotic cell death, thereby identifying important interactions among extracellular iron availability, cellular metabolism, and oxidative injury [5]. Their experiments also showed that interference with glutaminolysis could reduce ischemia-reperfusion-associated cardiac injury in an experimental model, suggesting that metabolism-dependent regulation of ferroptosis may influence tissue survival. These findings demonstrate that ferroptotic susceptibility depends on the intracellular availability of iron and metabolic substrates rather

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than simply on an increase in total tissue iron concentration. Consequently, the regulation of iron uptake, storage, utilization, and export represents a central component of ferroptosis pathophysiology.

The accumulation of oxidized membrane phospholipids is a defining biochemical mechanism of ferroptosis. Cellular membranes contain phospholipids with different fatty acid compositions, and those enriched in polyunsaturated fatty acids are particularly susceptible to oxidation because of the presence of multiple double bonds and reactive hydrogen atoms. ACSL4 contributes to the activation of selected long-chain polyunsaturated fatty acids, allowing their incorporation into phospholipids through pathways involving enzymes such as lysophosphatidylcholine acyltransferase 3 (LPCAT3). Doll and colleagues (2017) demonstrated that ACSL4 influences cellular susceptibility to ferroptosis by shaping membrane lipid composition, with increased incorporation of long-chain polyunsaturated fatty acids promoting sensitivity to oxidative membrane injury [6]. The investigators used genetic approaches to demonstrate that loss of ACSL4 substantially reduced ferroptotic susceptibility in experimental cellular systems. Complementary work by Kagan and colleagues (2017) identified oxidized phosphatidylethanolamine species containing arachidonic and adrenic acid residues as important participants in the execution of ferroptosis [7]. Their lipidomic investigations demonstrated that ferroptosis involves relatively specific patterns of phospholipid oxidation rather than an entirely nonspecific increase in lipid peroxidation. These findings suggest that the vulnerability of cells to ferroptosis depends on both the biochemical properties of membrane lipids and the activity of enzymes responsible for their synthesis and oxidation. During ischemia-reperfusion injury, the sudden increase in oxidant availability may accelerate the oxidation of susceptible phospholipids, particularly when antioxidant defense mechanisms have already been compromised by ischemic metabolic disturbances. As lipid hydroperoxides accumulate, they may generate additional reactive intermediates and impair membrane integrity, ultimately contributing to irreversible cellular dysfunction. Nevertheless, lipid peroxidation can occur in several pathological conditions, and the detection of lipid oxidation alone does not necessarily establish ferroptosis as the dominant mechanism of cell death.

The system Xc^-/glutathione/GPX4 pathway represents one of the principal cellular defense systems against ferroptotic injury. System Xc^- is a membrane-associated cystine/glutamate antiporter composed of the transporter subunits SLC7A11 and SLC3A2. Its activity supports intracellular cysteine availability, which is essential for the synthesis of glutathione, a major cellular antioxidant. GPX4 is a selenium-containing enzyme that uses reduced glutathione to convert potentially damaging phospholipid hydroperoxides into less reactive lipid alcohols. This function is particularly important because GPX4 can act on membrane-associated lipid peroxides that may otherwise propagate oxidative chain reactions. Inhibition of cystine uptake, depletion of intracellular glutathione, or loss of GPX4 activity may therefore permit uncontrolled phospholipid oxidation and increase cellular susceptibility to ferroptosis. Dixon and colleagues (2012) demonstrated that inhibition of cystine transport through system Xc^- could trigger iron-dependent nonapoptotic cell death, establishing a fundamental relationship between amino acid transport and redox regulation [1]. Friedmann Angeli and colleagues

HSR (LONDON),
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(2014) subsequently demonstrated that GPX4 has a critical protective role in normal tissues, since genetic inactivation of the enzyme resulted in severe renal injury and death in experimental mice [4]. During ischemia, disturbances in energy metabolism and cellular substrate availability may compromise glutathione homeostasis, while reperfusion-associated oxidant production increases the demand for lipid peroxide detoxification. This imbalance can create conditions in which the protective capacity of GPX4 becomes insufficient relative to the rate of lipid peroxide generation. Nevertheless, the relationship between GPX4 expression and ferroptotic injury is not entirely determined by protein abundance, because enzyme activity also depends on selenium availability, glutathione concentration, and the metabolic environment. Consequently, evaluation of the GPX4 pathway requires consideration of both protein expression and functional antioxidant capacity.

Recent investigations have demonstrated that GPX4 is not the only mechanism protecting cells against ferroptosis. Alternative antioxidant systems can suppress lipid peroxidation through pathways that operate partly independently of glutathione metabolism. Bersuker and colleagues (2019) identified ferroptosis suppressor protein 1, also known as AIFM2, as an important regulator of ferroptotic resistance [11]. FSP1 functions as an oxidoreductase capable of regenerating the reduced form of coenzyme Q10, thereby supporting a membrane-associated antioxidant defense mechanism that limits lipid radical propagation. This process operates in parallel with the GPX4-dependent pathway and provides an additional mechanism through which cells can maintain membrane integrity during oxidative stress. Kraft and colleagues (2020) identified another protective system involving GTP cyclohydrolase 1 (GCH1) and tetrahydrobiopterin (BH4), demonstrating that changes in lipid composition and antioxidant metabolism can modify cellular sensitivity to ferroptosis [12]. The GCH1–BH4 pathway contributes to ferroptosis resistance through mechanisms involving lipid remodeling and the regulation of antioxidant metabolites. A further mitochondrial defense pathway was identified by Mao and colleagues (2021), who demonstrated that dihydroorotate dehydrogenase (DHODH) can reduce ubiquinone to ubiquinol within the inner mitochondrial membrane and thereby limit mitochondrial lipid peroxidation [13]. Although this mechanism was initially characterized primarily in cancer cell models, it provides important evidence that ferroptosis resistance involves several compartment-specific antioxidant systems. The relative contribution of GPX4, FSP1, GCH1, and DHODH may depend on cell type, metabolic activity, and the localization of oxidative injury. These observations suggest that effective inhibition of ferroptosis during ischemia-reperfusion may require attention to multiple protective pathways rather than exclusive manipulation of one antioxidant enzyme. However, the precise roles of these systems in different human organs remain incompletely defined, and their protective effects in experimental cellular models do not automatically establish clinical therapeutic efficacy.

Iron storage and selective ferritin degradation represent additional mechanisms influencing susceptibility to ferroptosis. Ferritin normally limits the intracellular availability of redox-active iron by storing excess iron in a relatively stable protein complex. However, ferritin can be transported to

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lysosomes and degraded through a selective autophagic pathway known as ferritinophagy, which involves the cargo receptor nuclear receptor coactivator 4 (NCOA4). Although ferritinophagy contributes to physiological iron mobilization, excessive activation under pathological conditions may increase the labile iron pool and promote oxidative lipid injury. This mechanism has attracted attention in ischemia-reperfusion research because cellular iron trafficking may become disturbed during hypoxia and subsequent reoxygenation. Shen and colleagues (2024) investigated the role of N-acetyltransferase 10 (NAT10) in renal ischemia-reperfusion injury and demonstrated that NAT10 promoted NCOA4-dependent ferroptosis through N4-acetylcytidine modification of NCOA4 messenger RNA [10]. The investigators reported that inhibition or conditional deletion of NAT10 reduced renal injury in experimental models, while changes in RNA acetylation influenced NCOA4 messenger RNA stability and ferroptosis-associated abnormalities in renal tubular epithelial cells. These findings provide evidence that post-transcriptional regulation of iron metabolism may contribute to ferroptotic injury. The relationship between ferritinophagy and ferroptosis also demonstrates that autophagy can have context-dependent effects on cellular survival. Although autophagic processes are frequently protective through removal of damaged organelles and maintenance of metabolic homeostasis, excessive ferritin degradation may increase iron availability and thereby facilitate lipid peroxidation. Consequently, the biological effects of autophagy during ischemia-reperfusion injury depend on the specific cargo, cellular context, and balance between protective recycling and pathological iron mobilization.

Mitochondrial dysfunction contributes to the development of ferroptosis through alterations in cellular energy metabolism, reactive oxygen species generation, and iron-dependent biochemical reactions. During ischemia, impaired oxygen availability limits electron transport and ATP synthesis, while disturbances in the tricarboxylic acid cycle promote the accumulation of metabolites that can influence the response to reperfusion. Chouchani and colleagues (2014) demonstrated that succinate accumulation during ischemia provides a substrate for rapid mitochondrial ROS production when oxygen supply is restored [3]. This process involves succinate oxidation and reverse electron transport at mitochondrial complex I, producing an early burst of oxidant activity that can contribute to tissue injury. However, mitochondrial oxidative stress and ferroptosis are related but distinct processes, and the generation of mitochondrial ROS does not automatically establish ferroptotic cell death. Ferroptosis specifically requires the accumulation of damaging phospholipid hydroperoxides under conditions in which relevant antioxidant defenses are insufficient. Mitochondria may contribute to this process through redox disturbances, altered substrate metabolism, calcium imbalance, and changes in intracellular iron handling. Morphological changes associated with ferroptosis in certain experimental systems include smaller mitochondria, increased membrane density, reduction or loss of mitochondrial cristae, and alterations in membrane integrity. Nevertheless, these features are not universally present in every cell type or disease model. Recent literature emphasizes that the contribution of mitochondria to ferroptosis varies according to the initiating stimulus and cellular metabolic state [14]. During ischemia-reperfusion injury, mitochondrial dysfunction may therefore act as an amplifier of lipid

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peroxidation, but its relationship with ferroptosis should be evaluated using specific biochemical, genetic, and functional evidence rather than inferred solely from increased oxidative stress.

The involvement of ferroptosis in myocardial ischemia-reperfusion injury has been supported by experimental investigations examining cardiomyocyte death, iron accumulation, and oxidative damage following restoration of coronary blood flow. Cardiomyocytes are highly dependent on mitochondrial oxidative phosphorylation and possess substantial requirements for continuous ATP production. During ischemia, energy depletion and impaired calcium regulation compromise cardiac contractile function, while reperfusion may produce rapid oxidant generation and additional cellular injury. Gao and colleagues (2015) demonstrated that inhibition of glutaminolysis could reduce ischemia-reperfusion-associated injury in an experimental cardiac model, suggesting that metabolic pathways supporting ferroptosis may influence myocardial damage [5]. Fang and colleagues (2019) subsequently investigated ferroptosis in experimental models of ischemia-reperfusion-associated cardiomyopathy and demonstrated that iron-dependent lipid oxidative injury contributed to cardiomyocyte dysfunction [8]. Their findings supported the involvement of ferroptotic mechanisms in cardiac injury and suggested that pharmacological inhibition of ferroptosis may provide protection in selected experimental conditions. However, myocardial ischemia-reperfusion injury is characterized by the simultaneous activation of several cell death mechanisms, including necrotic injury, apoptosis, and other regulated processes. Therefore, ferroptosis should be considered a contributing mechanism rather than the exclusive explanation for cardiomyocyte death. The clinical significance of these findings lies in the possibility that interventions targeting iron-dependent lipid peroxidation could complement established strategies for restoring myocardial perfusion and limiting secondary injury. Nevertheless, no ferroptosis-specific treatment has yet demonstrated sufficient clinical evidence to become a standard therapy for patients with acute myocardial infarction.

Cerebral ischemia-reperfusion injury represents another pathological condition in which iron-dependent lipid oxidation may contribute to cellular death and neurological dysfunction. Neurons are particularly vulnerable to disturbances in mitochondrial energy metabolism because of their high ATP requirements, complex membrane structure, and dependence on regulated calcium signaling. Cerebral ischemia reduces oxygen and glucose availability, leading to energy depletion, excitotoxic neurotransmitter release, and disturbances in intracellular ionic balance. Reperfusion may further increase oxidative injury through mitochondrial ROS generation, inflammatory activation, and altered iron metabolism. Tuo and colleagues (2017) investigated interactions between tau protein, cerebral iron handling, and ferroptosis in experimental ischemic stroke models [9]. Their findings demonstrated that alterations in tau-dependent iron regulation influenced vulnerability to ischemia-reperfusion injury, with effects varying according to age and tissue iron status. This research established an important connection between neuronal iron trafficking and ferroptotic susceptibility. Fei and Leng (2026) subsequently reviewed molecular mechanisms of ferroptosis in cerebral infarction, emphasizing the roles of GPX4 deficiency, iron overload, ACSL4-dependent phospholipid oxidation, mitochondrial dysfunction, and

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inflammatory signaling [15]. Their synthesis also described interactions between ferroptotic neuronal injury, microglial activation, and blood–brain barrier dysfunction. However, the available evidence derives predominantly from experimental stroke models, and differences in animal age, ischemia duration, reperfusion protocols, and molecular interventions limit direct clinical generalization. Although ferroptosis inhibition has reduced infarct volume or improved neurological outcomes in selected experimental investigations, sufficiently validated clinical evidence remains unavailable to recommend specific ferroptosis inhibitors for routine management of ischemic stroke.

Renal ischemia-reperfusion injury provides particularly important evidence for the role of ferroptosis in tissue damage because renal tubular epithelial cells are highly dependent on oxidative metabolism and are vulnerable to alterations in oxygen availability and intracellular iron regulation. Ischemic injury may occur during renal transplantation, major surgery, shock, and other conditions associated with impaired renal perfusion. Following reperfusion, renal tubular cells may experience increased ROS production, mitochondrial dysfunction, inflammatory activation, and disturbances in membrane integrity. Friedmann Angeli and colleagues (2014) demonstrated that genetic inactivation of GPX4 caused acute renal failure in mice, providing direct evidence of the importance of lipid peroxide detoxification for renal cell survival [4]. Subsequent investigations have examined the relationship between ferritinophagy and renal ferroptosis. Shen and colleagues (2024) identified the NAT10–NCOA4 pathway as a potential regulator of renal ischemia-reperfusion injury and demonstrated that manipulation of this pathway could reduce experimental renal tissue damage [10]. These findings suggest that renal ferroptosis is regulated by interactions among iron mobilization, antioxidant defense, RNA modifications, and intracellular metabolic stress. Nevertheless, acute kidney injury involves additional mechanisms, including hemodynamic abnormalities, endothelial dysfunction, inflammation, and direct tubular damage. Consequently, reduced expression of GPX4 or increased lipid peroxidation should be interpreted alongside functional and genetic evidence when evaluating the contribution of ferroptosis. The available investigations provide a strong experimental rationale for further research, but they do not establish the clinical effectiveness of ferroptosis-targeted treatment in patients with acute kidney injury.

Hepatic ischemia-reperfusion injury is another important area of ferroptosis research because temporary interruption of hepatic blood flow occurs during liver transplantation, hepatic resection, and certain forms of circulatory failure. Hepatocytes are involved in complex iron, lipid, and energy metabolic processes, making them susceptible to disturbances in intracellular redox regulation. During ischemia and reperfusion, mitochondrial dysfunction, inflammatory activation, and changes in iron availability may promote oxidative injury and impair hepatocyte survival. Friedmann Angeli and colleagues (2014) demonstrated that liproxstatin-1 could suppress ferroptosis and reduce tissue injury in a preclinical model of hepatic ischemia-reperfusion [4]. A broader review by Wei and colleagues (2025) summarized experimental findings linking ferroptosis with myocardial, cerebral, hepatic, and renal ischemia-reperfusion injury and identified GPX4, ACSL4, transferrin receptor 1, and NCOA4 as

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HOUGHTON STREET REVIEW JOURNAL
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potential regulatory targets [14]. Particularly important translational evidence was reported by Veeckmans and colleagues in 2026, who investigated ferroptosis inhibition in organ transplantation research [16]. The researchers identified an early and transient increase in lipid peroxidation in human liver transplant samples, with evidence that the increase was concentrated during the initial period following reperfusion. They also developed FXT-001, an experimental ferroptosis inhibitor with combined radical-trapping and iron-targeting properties, and investigated its protective activity in preclinical models involving liver and lung grafts. Ex vivo perfusion studies involving porcine organs and declined human donor lungs demonstrated promising effects on graft viability and function. These findings represent an important advance because they extend ferroptosis research beyond isolated cells and small-animal studies toward more clinically relevant organ preservation models. However, ex vivo improvements in donor organ function do not demonstrate that treatment improves postoperative survival, long-term graft function, or patient outcomes following transplantation. Further clinical research is therefore necessary before ferroptosis inhibitors can be incorporated into standard transplant medicine.

The development of targeted ferroptosis inhibitors has created several potential therapeutic directions for ischemia-reperfusion injury. Experimental compounds such as ferrostatin-1 and liproxstatin-1 suppress lipid radical propagation and can reduce ferroptotic cell death in selected laboratory and animal models. Iron chelators may limit the availability of redox-active iron, while modulation of GPX4, system Xc^-, FSP1, and related antioxidant pathways may strengthen cellular resistance to phospholipid oxidation. Other experimental approaches include reducing ACSL4-dependent membrane susceptibility, regulating ferritinophagy, modifying mitochondrial ROS production, and targeting specific metabolic pathways associated with ferroptosis. Nevertheless, the therapeutic consequences of these interventions depend on their molecular specificity, pharmacokinetic characteristics, and effects on normal physiological functions. Iron is essential for erythropoiesis, mitochondrial respiration, and immune defense, making indiscriminate iron depletion potentially harmful. Similarly, excessive inhibition of lipid oxidation or modification of glutathione metabolism may interfere with physiological signaling and cellular adaptation. The results reported by Veeckmans and colleagues (2026) suggest that organ preservation during ex vivo perfusion may provide a particularly valuable opportunity for targeted intervention because the timing of reperfusion and exposure to protective compounds can be controlled more precisely [16]. However, effective clinical translation will require carefully designed studies evaluating tissue delivery, treatment duration, adverse effects, and long-term outcomes. At present, experimental protection against ferroptosis should be distinguished from clinically proven treatment efficacy.

DISCUSSION

The present literature review demonstrates that ferroptosis represents an important molecular mechanism contributing to ischemia-reperfusion-associated cellular injury through the interaction of iron metabolism, lipid peroxidation, and antioxidant defense pathways. The pathological process

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develops when the rate of damaging phospholipid oxidation exceeds the ability of cellular protective mechanisms to maintain membrane integrity. Ischemia creates conditions favorable for metabolic disturbances, reduced energy production, and disruption of cellular homeostasis, while reperfusion provides oxygen and other factors that may accelerate oxidative reactions. However, the relationship between ischemia, reperfusion, and ferroptosis is more complex than a simple increase in reactive oxygen species. Ferroptotic susceptibility depends on the presence of oxidizable membrane phospholipids, intracellular iron availability, and the functional activity of protective pathways such as GPX4 and FSP1. The discoveries reported by Doll and colleagues and Kagan and colleagues established that lipid composition and specific phospholipid oxidation patterns are fundamental determinants of ferroptosis [6,7]. This distinction has important implications for the interpretation of experimental studies because increased malondialdehyde, 4-hydroxynonenal, or other nonspecific oxidative stress markers does not independently demonstrate ferroptotic cell death. Such markers may be elevated during several forms of tissue injury, including inflammation, necrosis, and mitochondrial oxidative stress. Similarly, changes in GPX4 or ACSL4 expression should be interpreted in relation to functional outcomes and the effects of genetic or pharmacological manipulation. More convincing evidence of ferroptosis requires integration of iron-dependent lipid oxidation measurements, relevant molecular alterations, and demonstrations that interruption of ferroptosis-associated pathways protects cells or tissues. Contemporary research therefore increasingly emphasizes the need for standardized experimental criteria and mechanistically specific biomarkers. Such approaches are essential for distinguishing ferroptosis from other regulated cell death pathways that may be activated simultaneously during ischemia-reperfusion injury.

The clinical significance of ferroptosis is supported by experimental evidence from multiple organs, but the contribution of individual molecular pathways varies considerably. Cardiac tissue is characterized by high mitochondrial activity and continuous energy requirements, while neuronal tissue possesses complex membrane lipid composition and particularly sensitive mechanisms of calcium and iron regulation. Renal tubular epithelial cells depend on oxidative metabolism and may experience substantial disturbances in iron homeostasis during reperfusion, whereas hepatocytes participate in systemic lipid and iron metabolism and are exposed to complex inflammatory and metabolic signals during organ preservation. These differences suggest that a therapeutic approach effective in one organ may not produce equivalent benefits in another. The temporal characteristics of ferroptotic injury also require attention. Reperfusion-associated oxidant generation may develop rapidly, while subsequent inflammatory activation, organelle dysfunction, and metabolic disturbances may continue over longer periods. The 2026 study by Veeckmans and colleagues demonstrated the importance of the early reperfusion interval for lipid peroxidation in human liver transplant samples [16]. This observation suggests that treatment timing could be a major determinant of therapeutic effectiveness. However, it remains uncertain whether pharmacological inhibition after the initial phase of oxidative injury can prevent established cellular damage or improve long-term organ recovery. Further investigations should

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therefore examine the time-dependent activity of ferroptosis pathways and identify therapeutic windows that differ according to the affected organ and underlying pathological condition.

Another important consideration concerns the interaction between ferroptosis and other mechanisms of cellular injury. Ischemia-reperfusion injury involves mitochondrial dysfunction, calcium overload, inflammatory signaling, endothelial abnormalities, and several regulated cell death pathways. Ferroptotic lipid oxidation may aggravate these processes, but its inhibition is unlikely to eliminate all pathological consequences of interrupted and restored blood circulation. The protective effects of ferroptosis inhibitors observed in experimental models may reflect inhibition of a particular component of tissue injury rather than complete prevention of cellular death. Consequently, future therapeutic approaches may require integration of ferroptosis modulation with established reperfusion strategies, mitochondrial protection, and appropriate management of inflammation and microcirculatory disturbances. The identification of alternative ferroptosis defense systems, including FSP1–coenzyme Q10, GCH1–tetrahydrobiopterin, and DHODH-related mitochondrial protection, provides additional molecular targets for future investigation [11–13]. Nevertheless, the physiological roles of these pathways must be carefully considered because they also participate in essential metabolic processes unrelated to ferroptosis. Modulation of iron handling or antioxidant systems may produce unintended consequences when applied systemically, particularly in patients with complex comorbidities. The development of tissue-selective delivery systems, short-duration interventions, or localized treatment during ex vivo organ preservation may provide opportunities to improve efficacy while limiting adverse effects.

The translation of ferroptosis research into clinical practice will also depend on the development of reliable diagnostic and prognostic indicators. Experimental investigations frequently evaluate GPX4 activity, ACSL4 expression, intracellular iron, oxidized phospholipids, and other markers associated with ferroptosis. However, no universally validated clinical biomarker currently identifies ferroptotic injury with sufficient specificity to guide routine treatment across different human diseases. Circulating iron concentrations may not reflect the intracellular labile iron pool in affected tissues, while systemic oxidative stress markers may be influenced by inflammation, infection, nutritional status, and several other conditions. Advanced lipidomic methods capable of identifying specific oxidized phospholipid species may provide greater mechanistic specificity, but their availability and standardization remain limited. Similarly, molecular imaging and tissue-specific gene expression profiles may offer potential approaches for characterizing ferroptosis in research settings. For pathological physiology research in Uzbekistan, experimental or clinical observational investigations examining ferroptosis-related pathways in myocardial ischemia, acute kidney injury, and liver pathology could provide valuable information about the relevance of these mechanisms in local patient populations. However, such studies should employ clearly defined research objectives, validated laboratory methods, appropriate comparison groups, and careful interpretation of the relationship between molecular markers and clinical outcomes. The present review is limited by its narrative design and by the predominance of

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experimental evidence in the analyzed literature. Although the recent transplantation research provides encouraging translational findings, sufficiently powered clinical studies demonstrating improved patient outcomes with ferroptosis-specific treatment remain unavailable. Therefore, the most important future priorities include development of specific biomarkers, identification of suitable patient populations, determination of optimal treatment timing, and rigorous clinical evaluation of potential ferroptosis inhibitors.

CONCLUSION

Ferroptosis represents a distinct form of regulated cell death characterized by iron-dependent accumulation of oxidized membrane phospholipids and failure of cellular mechanisms responsible for maintaining lipid redox homeostasis. During ischemia-reperfusion injury, disturbances in mitochondrial metabolism, intracellular iron handling, antioxidant defense, and phospholipid composition create conditions that may promote ferroptotic cellular damage. The system Xc^-/glutathione/GPX4 pathway plays a central protective role by limiting phospholipid peroxide accumulation, while ACSL4-dependent lipid metabolism and ferritinophagy influence cellular susceptibility to oxidative membrane injury. Alternative defense mechanisms involving FSP1, coenzyme Q10, GCH1, and DHODH contribute additional regulation of ferroptosis in specific cellular compartments. Experimental investigations demonstrate that ferroptosis participates in myocardial, cerebral, renal, and hepatic ischemia-reperfusion injury and that its inhibition may reduce tissue damage under selected conditions. Recent translational research involving human liver transplant samples and ex vivo organ preservation models provides further evidence supporting ferroptosis as a potentially relevant therapeutic target. Nevertheless, the contribution of ferroptosis is influenced by tissue-specific metabolic characteristics, the duration and severity of ischemia, and the timing of reperfusion. Current evidence remains insufficient to recommend ferroptosis-targeted agents as standard clinical treatment for ischemia-reperfusion injury. Future investigations should prioritize the validation of specific molecular biomarkers, clarification of interactions between ferroptosis and other cell death pathways, and the development of safe, targeted interventions capable of improving clinically meaningful outcomes. A deeper understanding of iron-dependent lipid peroxidation may contribute to advances in pathological physiology and support the development of new strategies for protecting tissues against ischemia-reperfusion-associated injury.

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