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Review Article

Ferroptosis in ischemia-reperfusion injury: molecular mechanisms and therapeutic strategies

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Abstract: Ferroptosis is a novel form of programmed cell death characterized by iron-dependent lipid peroxidation (LPO). It has been widely demonstrated in the last years to play a crucial pathogenic role in ischemia-reperfusion injury (IRI). The pathological basis for ferroptosis is established through disturbances in energy metabolism, iron homeostasis and mitochondrial injury during ischemic phase. During the following period of reperfusion, the surge in reactive oxygen species (ROS), along with the liberation of inflammatory mediators, and the aggravation of LPO, will further stimulate peroxidase 4 (GPX4) inactivation and augment iron load in the cells, which will greatly intensify bodily tissue injury. Ferroptosis, which operates through intricate cross-regulation with oxidative stress, immune-inflammatory responses, and autophagy, forms a multi-tiered positive feedback loop that actively contributes to injury-repair imbalance IRI pathogenesis across various organs, including the heart, brain, liver and kidney. Studies show that tissue damage and recovery can be improved by targeting system Xc^-, GPX4, ACSL4, TfR1, and NCOA4 in the body. This review summarizes the mechanisms, organ-specific manifestations, and current therapeutic strategies of ferroptosis in IRI. It is helpful for the theoretical foundation and potential direction of clinical targeted therapy.

Keywords: Ferroptosis, ischemia-reperfusion injury, lipid peroxidation, glutathione peroxidase 4, reactive oxygen species, system Xc^-, iron homeostasis, multi-organ injury, mitochondrial function, programmed cell death

Introduction

IRI is a shared pathological substrate for several life-threatening conditions that are clinically manifest, such as acute myocardial infarction, stroke, organ transplantation, hepatectomy, shock and acute kidney injury. IRI includes two phases, ischemia and reperfusion, the injury mechanisms of which have different stage-specific characteristics. During the ischemia phase, a sudden reduction in blood flow and oxygen supply leads to obstruction of the mitochondrial electron transport chain, rapid ATP depletion, intracellular acidification, electrolyte imbalance, and calcium overload, resulting in a comprehensive disruption of cellular homeostasis. In the reperfusion phase, the effects of oxygenation and replenishment of nutrients paradoxically increase the oxidative stress. There is also the release of inflammatory mediators and dysfunction of the endothelial cells. In addition, there is a reduction in perfusion within the microcirculation which leads to aggravated cell and tissue suffering [1]. Findings indicating that an immediate and intense postoperative neutrophil response is an independent predictor of pulmonary complication have been demonstrated clinically. Abundant evidence currently exists for the pathological significance of other tissue injury inflammatory burst [2]. Recent researches showed that SGLT-2 inhibitors can provide protec-

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tion against IRI to many organs by inhibiting oxidative stress and inflammatory responses, and improving endothelial function, providing new opportunities for its prevention and treatment [3]. Notably, studies on colorectal cancer models indicate that one notable consequence of the "release of inflammatory mediators" is profound "immunosuppression": specific tumor cells exploit macrophages via the MIF signaling axis to create a pro-tumor microenvironment which is linked to cardiac dysfunction and provides compelling evidence for similar immune dysregulation in IRI [4]. A multitude of studies have shown that IRI activates multiple modalities of regulated cell death, including apoptosis, necroptosis and pyroptosis, and organ-specific injury [5].

In the last few years, a novel cell death named ferroptosis, which refers to iron load and lipid peroxidation has gained considerable attention related to IRI. Ferroptosis represents a cell death pathway whose signature features include (i) increased levels of cellular free iron; (ii) depletion of GSH; (iii) diminished activity of GPX4; and (iv) lipid metabolism remodeling by ACSL4 and LPCAT3 that promote polyunsaturated fatty acids to undergo peroxidation. The major morphological features include decreased mitochondrial cristae, shrinkage of mitochondria, and impaired membrane potential [6]. In a wealth of studies, it has become evident that ferroptosis is a common key element in multi-organ ischemia-reperfusion injury (IRI) with suppressing Nrf2/GPX4 axis being a consistently observed phenomenon in IRI models of various organs. In renal IRI, this mechanism has been directly validated: the natural compound tiliroside can activate the NRF2/GPX4 pathway by hindering the NRF2-KEAP1 interaction, thereby inhibiting ferroptosis and exerting a protective effect [7].

The pathophysiological association between IRI and Ferroptosis is close. The phase of ischemia is characterized by an energy metabolism disorder which reduces antioxidant capacity, disturbances of iron metabolism promote free iron accumulation, and it induces ferroptosis. When the reperfusion phase occurs, the generation of reactive oxygen species consumes GSH, inhibits GPX4 activity and enhances lipid peroxidation which eventually induces cell death with iron involvement. The above process creates a positive feedback loop with the characteristic oxidative stress-inflammation-cell death axis of IRI, causing much more damage to the tissue [8]. Iron-dependent cell death known as ferroptosis is significant in IRI (ischemia-reperfusion injury) alongside a variety of other regulated forms of cell death such as apoptosis and necroptosis. Moreover, ferroptosis might act as a hub unifying various metabolic disruptions and oxidation damage to ultimate cell fate. Energy metabolism collapse and oxidative stress-inflammation axis activation in IRI also trigger various regulated cell deaths. For example, ATP-induced cell death and inflammatory mediators (IL-6, etc.) mediated myocardial injury play important roles in the process of heart failure due to IRI [9, 10]. According to clinical studies, the combined effect of the cell death pathways can lead to lethal disease, for example death due to ventricular septal rupture from an acute myocardial infarction. The energy metabolism disorders, oxidative stress and inflammatory process caused by IRI leads to the increasing damage that is profoundly reflected in this pathological process [11].

With the above understanding in mind, this review will systematically summarize the main pathological process of IRI, summarize the core molecular mechanism of ferroptosis, and integrate research progress from different organ models to clarify the role of ferroptosis in IRI and its possible therapeutic value. This aims to create a theoretical underpinning and translational reference for mechanistic research and intervention approaches to these diseases.

Pathophysiological mechanisms of ischemia-reperfusion (I/R) injury

Metabolism changes during an ischemic phase

Characterized by diminished blood flow, IRI is a damaging process. The ischemic phase initiates the pathology, with its pathological changes playing a most important part in disabling function and causing damage afterwards. This phase features the marked restructuring of cellular metabolic networks. Also, there is disruption of energy metabolism, oxidative stress and iron metabolism. The molecular basis of ferroptosis may stem from the overlap of these

pathological processes. Therefore, an investigation and systematic review are warranted.

Ischemia has the most important defects in the tricarboxylic acid or the tricarboxylic acid (TCA) cycle and mitochondrial electron transport chain in organs with a high oxygen requirement, such as the heart, brain, and kidney. Suppression of oxidative phosphorylation reduces ATP production in oxidative tissue. To meet minimum energy needs, cells are forced to employ anaerobic glycolysis [12, 13]. Glycolysis process may be inefficient. It may cause the buildup of lactic acid. This may lower intracellular pH. Further, this kind of acidosis does increase a sort of stress response in cells [12]. The lactate does not only act as an end product. Also, it acts as a signalling molecule. Through lactylation modification, it inhibits the degradation of pyruvate kinase M2 (PKM2), which is a key rate-limiting enzyme in glycolysis. It sets up a positive feedback loop that further disrupts mitochondrial homeostasis to aggravate endothelial dysfunction [12].

At the molecular level, regulation of ischemia-induced metabolic reprogramming is primarily under the control of hypoxia-inducible factor-1α (HIF-1α). The activity of the transcription factor promotes the expression of various metabolic enzymes that play important roles in the metabolism of glucose and lactate. These include lactate dehydrogenase A (LDHA), pyruvate dehydrogenase kinase 4 (PDK4), and monocarboxylate transporter 4 (MCT4). Collectively, these enzymes assist in enhancing uptake of glucose and efflux of lactate [13-15]. In particular, the activated ALDH3A1 is induced under hypoxia, which activates the HIF-1α/LDHA axis to enhance glycolytic activity and cellular proliferation in tumors. The process of moving is reversible by Allyl Disulfide [14]. In A549 lung cancer cells, hypoxia is associated with increased glucose uptake with reduced ATP synthesis, cell cycle arrest and increased migratory capacity, whose metabolic changes depend on p53 status [13]. Additionally, the upregulation of MCT4, cargo that is important for lactate efflux. This both reduces the intracellular acid load and enhances cellular sensitivity to glycolytic inhibitors [15].

In addition to energy metabolism disorders, ischemia also disrupts the functions of membrane ion pumps such as Na^+/K^+-ATPase and Ca^{2+}-ATPase causing cell swelling, membrane depolarization, and structural damage. More critically, hypoxia increase the expression of TfR1, which mediates iron uptake, while inhibiting GSH synthesis and activity of GPX4. The inability to clear lipid peroxides increases oxidative stress and further drives the ferroptotic pathway [16]. Damaged mitochondria release free iron, which interacts with hydrogen peroxide to generate hydroxyl radicals (•OH), triggering LPO chain reactions. This process causes mitochondria membranes to collapse and fall apart.

In the event of an energy crisis, cells can activate the 5'AMP-activated protein kinase (AMPK) signalling pathway to help restore metabolic homeostasis. The clinically used sedative dexmedetomidine may also provide metabolic protection by enhancing AMPK signalling and promoting PEX activation in alveolar macrophages. Inhibition of NLRP3 inflammasome activation may be involved in this effect [16]. This factor is responsible for the phosphorylation of NR3C1 and inhibition of the expression of PDK4, reducing lactate production, enhancing mitochondrial function and alleviating the myocardial injury induced by ferroptosis during I/R [17].

The E3 ubiquitin ligase TRIM21 has been shown to drive ferroptosis in renal ischemia models by targeting GPX4 for ubiquitination and degradation. The knockout of TRIM21, together with the JAK2 inhibitor Fedratinib, decreased iron deposition and mitochondrial injury, which improves renal function. Given its role in promoting ferroptosis, TRIM21 represents a promising therapeutic target [18].

The multiple cellular stress signalling pathways are activated besides metabolic disorder. Ischemia causes endoplasmic reticulum (ER) stress, which activates the unfolded protein response (UPR) and increases the synthesis of pro-apoptotic molecules such as CHOP. Persistent energy depletion can also induce autophagy or programmed cell death, via AMPK-mediated mechanisms [16, 19]. From an immunometabolic viewpoint, hypoxic microenvironments drive macrophages to polarize toward the pro-inflammatory M1 phenotype. It is believed that weak oxidative phosphorylation is a major regulator of metabolic programming.

Also, it is a functional fate of macrophages that worsens tissue inflammation and damage [19].

Oxidative stress during the reperfusion phase

Reperfusion is defined as the restoration of blood flow to ischemic tissues and the initiation of various detrimental mechanisms like oxidative stress, inflammatory response, programmed cell death and many others. After re-establishing blood flow oxygen delivery, oxygen radicals, reperfusion arrhythmia, and among other factors can cause tissue injury. These processes are the essential pathologic basis of I/R injury. Among other processes, reperfusion injury onset is marked by the generation of oxidative stress and an early and highly damaging event playing a central role in tissue injury. Inhibition of sodium-glucose cotransporter-2 (SGLT-2) has been demonstrated to ameliorate such damage by effectively reducing oxidative stress and suppressing inflammatory responses [20].

Despite reoxygenation promptly reactivating the mitochondrial respiratory chain, prior ischemic damage to complexes I and III results in electron leakage from these complexes, leading to the excessive generation of superoxide anions (O_2^-). At the same time, there is an upsurge in the activity of xanthine oxidase (XO), and malfunction of NADPH oxidases (NOX2/4), MPO and endothelial nitric oxide synthase (eNOS) also leads to overproduction of ROS and reactive nitrogen species (RNS). The ROS/RNS build-up overwhelms the internal antioxidant system consisting of superoxide dismutase (SOD), catalase (CAT) and GSH leading to the generation of MDA along with attendant lipid, protein and DNA damage [21-23].

Reactive oxygen species play an essential role in the injury of tissues. They achieve this through multiple pathways: inducing LPO and loss of mitochondrial membrane potential; activating the NLRP3 inflammasome and NF-κB signaling, thereby enhancing local inflammation; inducing ER stress; dysregulating calcium homeostasis; and causing mitochondrial damage. This collective damage leads to the activation of various programmed cell death pathways, including apoptosis, necroptosis, and ferroptosis. Additionally, ROS can mobilize iron stores present in cells. This gives rise to reactions such as the Fenton reaction. This leads to an intensification of the LPO cascade which eventually causes iron-dependent death of the cell [21-23].

Many studies have shown that targeting oxidative stress pathways reduces the harm of I/R injury. Ligustilide (LIG) protects against renal tubular injury by activating Sirt3 that maintains mitochondrial homeostasis as well as reduces levels of ROS and mitochondrial damage-induced abnormal energy metabolism in renal tubular epithelial cells [21]. Receptor-interacting serine/threonine-protein kinase 4 (RIPK4) is a kinase that responds to oxidative stress. RIPK4 regulates the expression of ACSM1 and ACSL4, facilitating the accumulation of PUFAs and LPO. RIPK4 knockout alleviates I/R- and cisplatin-induced AKI [22]. Longxuetongluo Capsule (LTC) shows myocardial dysfunction amelioration against I/R by inhibiting NOX2/4-mediated ROS generation and regulating mitochondrial dynamics [23].

Recent studies show transcriptional and epigenetic regulation may also play a role in oxidative injury. The inhibitor KC7F2 can abolish the effects HIF-1α stabilizing which causes oxidative damage via deSUMOylation when SENP1 is present [24]. Nrf2 pathway activation by ISL and adjusting gene expression including HO-1, SLC7A11, GPX4, ACSL4, and Drp1 to modulate LPO and restrict iron deposition showcase Nrf2 is essential to ISL's antioxidative mechanism [25]. A mitochondria-targeted nanodrug (MHT), constructed using tannic acid and melanin, scavenges ROS and inhibits the cGAS-STING pathway, thereby alleviating mitochondrial damage and neuronal apoptosis induced by cerebral I/R [26].

Besides, SETDB1 aggravates mitochondrial oxidative damage during I/R via the recruitment of HP1β to the SESN2 promoter, causing H3K9me3 modification and repressing SESN2 expression. Knockdown or pharmacological inhibition of SETDB1 significantly improves injury phenotypes [27]. Luteolin reduces myocardial infarct size by attenuating the activation of p53 signalling and subsequent production of ROS and expression of apoptotic markers [28]. Curcumin reduces the oxidative damage and mitochondrial dysfunction induced by hypoxia/reoxygenation (H/R) through upregulating the expression of HES1 and GPX4 to inhibit ferroptosis and activating AMPK to balance autopha-

gy and apoptosis. Interestingly, the protective effects of curcumin are opposed by erastin and Compound C, indicating that it uses multiple mechanisms [29].

The role of inflammatory responses in IRI

In IRI, inflammation refers to an important early host response to tissue injury. Although inflammation protects by removing danger signals and containing the affected area, it has a central pathogenic role during reperfusion that exacerbates tissue injury and initiates various types of programmed cell death, especially ferroptosis. Inflammation is one of the important parts of IRI pathophysiology.

When ischaemia occurs, injury to the cell membrane of various types causes the release of endogenous damage-associated molecular patterns (DAMPs) like ATP and HMGB1. Subsequently, damage pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), which rapidly initiate sterile inflammation. After blood flow is restored, many immune cells are attracted to the injury. Neutrophils, macrophages and T cells will appear. The pro-inflammatory cytokines (e.g. TNF-α, IL-1β, IL-6) and chemokines (e.g. MCP-1, CXCL8) are released by these cells while they induce the expression of adhesion molecules (ICAM-1, VCAM-1) on the vascular endothelial cells. These processes promote the passage of immune cells through the endothelium, further intensifying inflammation. At the same time, degranulation of neutrophil uses MPO along with huge amounts of ROS generates oxidative stress that aggravates the inflammation, ROS, mitochondrial dysfunction, ferroptosis vicious circle [30-32].

Recent studies show that inflammatory signalling and ferroptotic cell death have extensive crosstalk and synergism. The NLRP3 inflammasome, a major inflammatory platform in ischemia/reperfusion injury (IRI), can be activated by reactive oxygen species (ROS), potassium efflux, and mitochondrial damage. This activity induces the maturation and release of IL-1β and IL-18 via caspase-1, which triggers pyroptosis. Furthermore, through causing localized inflammation, it disrupts iron metabolism and it accelerates LPO, thus forming the pathological basis of ferroptosis. For example, ginsenoside Rg1 shows dose-dependent inhibition of AIM2 inflammasome activation in macrophages. In addition, it also suppresses M1 macrophage polarization and production of pro-inflammatory cytokines. Overall, it relieves post-reperfusion myocardial inflammation and alleviates infarct size [33]. Also, macrophage-specific protein SHEP1 inhibits MAPK inflammatory signalling pathway by competing with G3BP1. In doing so, it limits macrophage migration and cytokine expression. This protective mechanism has been confirmed in both SHEP1-lacking models and G3BP1 inhibitor treatments [34].

Insights from multi-organ studies have advanced our understanding of the regulatory networks between inflammation and ferroptosis. GRINA promotes ubiquitin-mediated degradation of ATF6 in hepatic IRI which attenuates inflammation and apoptosis, inhibits ER-phagy, and maintains calcium homeostasis [32]. Icariin aglycone (ICT) protects against hepatic IRI by activating the PI3K/AKT/mTOR signaling pathway, thereby suppressing excessive autophagy and inflammatory mediator release. Clinically significant levels of the lipid second messenger, PI3P, can hypothetically block a PtdIns(3)P-PH domain by competing with PtdIns(3)P for binding [35].

In liver transplantation-related IRI models, hypoxia activates YAP/TEAD1 signaling in liver endothelial cells, resulting in CXCL17 secretion. CXCL17 attaches to the GPR35 receptor on myeloid-derived suppressor cells (MDSCs), and this enables targeted recruitment to the liver. MDSCs via the STAT3 pathway inhibit the M1 macrophage polarization thus reducing inflammation and liver injury. This mechanism has been validated through single-cell sequencing and adoptive transfer experiments in mice and patient samples [36]. Human induced pluripotent stem cell (iPSC)-derived cardiac organoid model of I/R on myocardial tissue found type I interferon (IFN-I) to be a damaging factor in co-culture system with THP-1 monocytes. Application of the FDA-approved IFN-I receptor antagonist Anifrolumab significantly inhibited inflammation and oxidative stress, reducing myocardial injury and demonstrating promising translational potential [31]. In renal IRI models, DbpA, a mitochondria-located protein (coded by Ybx3), enhances mitochondrial membrane potential and oxygen consumption, increases

antioxidant capacity, and represses ferroptosis. As a result, this offers a new and promising therapeutic target for kidney IRI [30]. To further clarify the dynamic changes and specific mechanisms of cellular injury during ischemia or reperfusion, we constructed a schematic illustration (**Figure 1**).

Mechanisms of ferroptosis

Regulation of iron metabolism and cellular homeostasis

Iron is a trace element that maintains the metabolic homeostasis of the cell. Iron plays important roles in the transport of oxygen, energy production, DNA synthesis and redox reactions. However, iron overabundance stemming from unregulated iron metabolism can fuel the formation of highly reactive •OH through the Fenton reaction. Consequently, it induces LPO and oxidative stress that results in the dysregulation of ferroportin (FPN). Iron homeostasis inside the cell is maintained by balancing its uptake, storage, and export. TfR1 is responsible for taking in Fe^{3+}. Ferritin, especially the heavy chain subunit FTH1, acts as a major intracellular iron-storage protein. Ferroportin is the only known cellular iron exporter. Hepcidin, a hepatic hormone, negatively regulates ferroportin, which can efflux iron. In addition, microRNAs, long non-coding RNAs (lncRNAs) and other epigenetic modifications finely modulate the expression of iron metabolism-related proteins. The stressed cells usually uptake more iron, storage of iron is impaired, and efflux of iron is reduced under the conditions like I/R, impacting labile iron pool (LIP) significantly which provides the substrate necessary for ferroptosis induction [37, 38].

Execution of ferroptosis requires not only iron accumulation but also dysfunction of antioxidant defenses and unchecked accumulation of lipid peroxides. Recent studies indicate that NCOA4-mediated ferritinophagy plays a vital role in the development of diabetic complications [37]. Ferroptosis triggers can be divided into extrinsic pathway and intrinsic pathway. The extrinsic pathway can be triggered by the inhibition of System Xc^-, leading to GSH depletion. This triggers ferroptosis. The intrinsic pathway often involves the inactivation of GPX4. Ferroptosis can occur in acute organ injuries, infections, cancer, neurodegeneration, etc. [38]. In glioblastoma, tumor progression is promoted by E3 ubiquitin ligase TRIM7 by K48-linked ubiquitinating and degrading NCOA4, inhibition of ferritinophagy and intracellular free iron accumulation and ferroptosis blockade. Inhibition of TRIM7 augments sensitivity to temozolomide in tumors, highlighting its therapeutic potential [39]. Research suggests that hypoxia causes the activation of JNK-miR-6862-5p axis which suppresses the NCOA4 expression and increases the level of FTH and mitochondrial ferritin (FTMT). This enhances macrophage resistance to RSL3-induced ferroptosis. It is important to note that not all tumor cells have this protective mechanism, suggesting that iron regulation is cell-type specific [40]. The tumor immune microenvironment is shaped through the process of ferroptosis. In gastric cancer, the cancer-associated fibroblasts (CAFs) increase the Hephaestin and iron transporter to enhance iron release into the tumor microenvironment (TME), which is then taken up by natural killer (NK) cells. FSTL1 also promotes ferroptosis in NK cells through the DIP2A-P38-NCOA4 signaling pathway and inhibits their cytotoxicity. Treatment of DFO in conjunction with an anti-FSTL1 neutralizing antibody has been shown to restore NK cell function in a study; the findings were validated with human organoid models [41]. Cadmium (Cd) has been reported to induce ferroptosis in hepatocytes by activating the PERK-eIF2α-ATF4-CHOP pathway to trigger ER stress and upregulating NCOA4 to facilitate ferritinophagy in toxicology studies. Chloroquine, autophagy inhibitors, ferroptosis inhibitors, and iron chelators can effectively inhibit this injury process, signifying its association with environmental toxins-induced liver injury [42]. Context of antitumor therapy also clarifies how to confound the mechanism of ferroptosis. In head and neck tumor, PCBP1 intervenes in BECN1 by suppressing autophagosome formation and inhibiting LPO enzyme ALOX15 to modulate ferroptosis sensitivity. ALOX15 modulates LPO. Together, these act to reduce cellular susceptibility to ferroptosis. Animal experiments have shown that knocking down PCBP1, especially in combination with ferroptosis inducers like sulfasalazine, impedes tumor growth [43]. In neurodegenerative diseases, FTH1 overexpression inhibits ferritinophagy via the LC3-II/NCOA4 pathway and reduces Fe^{2+} release to prevent

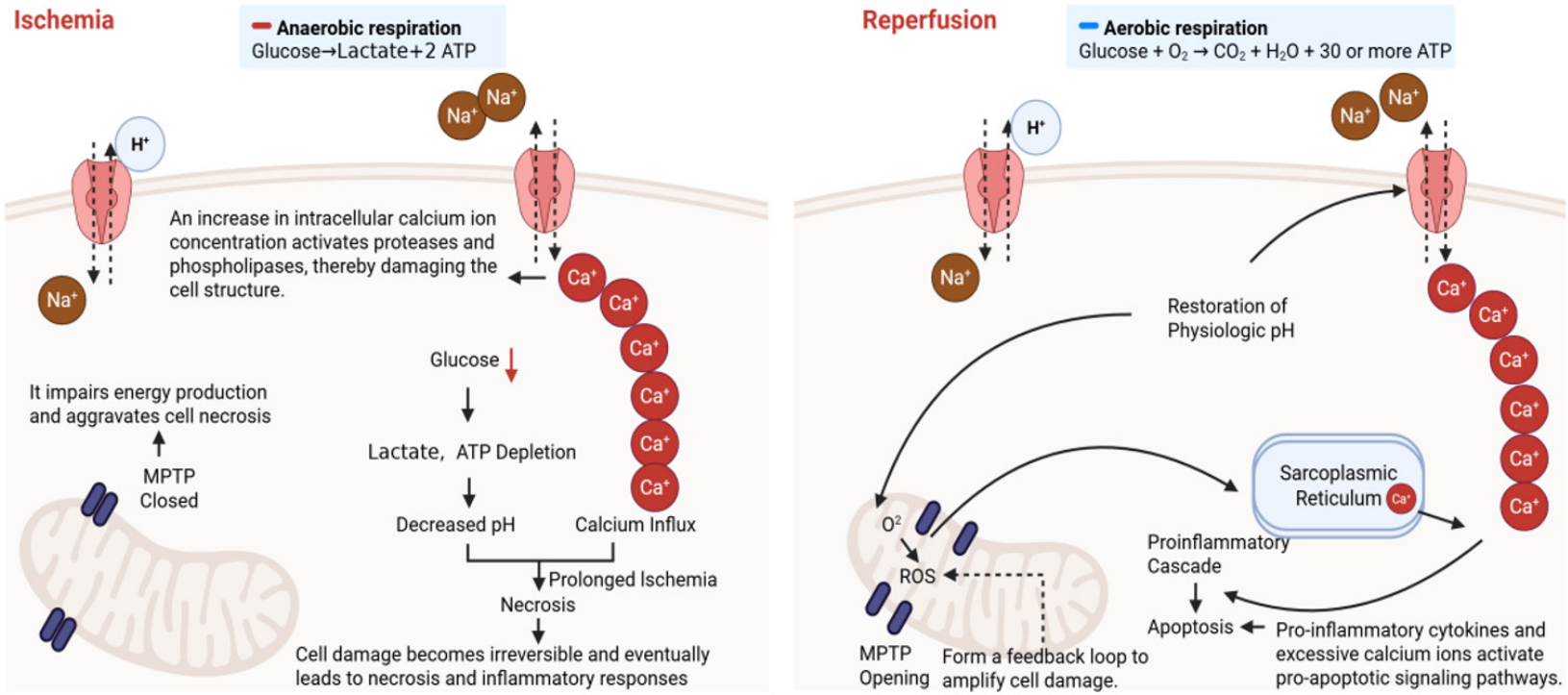

Figure 1. Schematic illustration of cellular injury mechanisms during ischemia and reperfusion. This figure illustrates the key pathological processes during ischemia and reperfusion. Ischemia causes a shift to anaerobic metabolism with ATP depletion, lactate accumulation, acidosis, and calcium overload, leading to structural damage and necrosis. Reperfusion restores aerobic metabolism but induces mitochondrial permeability transition pore (MPTP) opening, excessive ROS generation, and sustained calcium overload, which together activate inflammatory and pro-apoptotic pathways, exacerbating tissue injury.

ferroptosis in a 6-OHDA-induced Parkinson's disease (PD) model. On the contrary, knockdown of FTH1 aggravated mitochondrial dysfunction, confirming this axis as a potential therapeutic target for PD [44]. Through transcriptomic analysis of myocardial infarction datasets in the cardiovascular system like GSE116250, 10 ferroptosis/autophagy-related hub genes, including IL-6, PTGS2 and JUN, were found to be closely related to IL-17, JAK-STAT, MAPK signaling pathways. The study findings were validated by qPCR and single-cell RNA sequencing in mice, identifying potential targets for molecular subtyping and prognostic interventions of MI [45]. In metabolic-associated steatohepatitis (MASH), NOX subunit NCF1 in macrophages is activated by oxidized phospholipids, activating TLR4-dependent signaling that stimulates hepatocyte secretion of hepcidin. This cascade increases iron accumulation and ferroptosis in Kupffer cells, leading to intensified liver inflammation and immune cell infiltration. A human hypomorphic NCF1 variant (p.90H) appearing to antagonize this pathological pathway, may provide a theoretical basis for immunometabolic intervention in MASH [46].

Characteristic markers and signaling pathways of ferroptosis

Ferroptosis is a different type of regulated cell death that features iron-dependent LPO. It is not identical to conventional apoptosis or autophagy or necrosis. Ferroptosis characteristically features an increase of intracellular ferrous iron (Fe^{2+}), massive accumulation of phospholipid peroxides, depletion of GSH, and functional inactivation of GPX4. Furthermore, cells undergoing ferroptosis display ultrastructural alterations including smaller mitochondrial size, a lower number of cristae and higher membrane density [47, 48]. GPX4 is an important antioxidant enzyme that detoxifies membrane phospholipid hydroperoxides. GPX4 activity is dependent on GSH availability. Inhibition of System Xc^- - a cystine/glutamate antiporter composed of SLC7A11 and SLC3A2 - leads to depletion of GSH, which in turn inhibits GPX4 activity and induces ferroptosis. Enzymes involved in lipid metabolism, such as ACSL4 and LPCAT3, facilitate the esterification and incorporation of PUFAs into membrane phospholipids, providing substrates for LPO. Currently, their activity has been recognized as a molecular marker of ferroptosis [49].

Multiple signaling pathways regulate ferroptosis. The activity of System Xc^- is diminished upon repression of SLC7A11 via tumor suppressor p53. On the other hand, NRF2 upregulates genes such as GPX4 and FTH1 that restore iron homeostasis. The MAPK, Hippo-YAP, and HIF-1α pathways also play a critical role in the regulation of lipid metabolism and oxidative stress [49, 50]. Recent studies have uncovered certain regulatory mechanisms involved in ferroptosis. Salidroside (Sal) inhibits the PI3K/AKT/mTOR pathway to downregulate SCD1-mediated monounsaturated fatty acid synthesis and further activates NCOA4-mediated ferritinophagy. As a result of these actions, there is an accumulation of Fe^{2+} and formation of LPO, which dramatically enhances the sensitivity of triple-negative breast cancer (TNBC) cells to ferroptosis. Overexpression of GPX4 or SCD1 or knockout of NCOA4 can reverse the effect of Sal [47]. CircLRFN5 in gliomas promotes the degradation of PRRX2 protein, thus relieving its transcriptional activation of the ferroptosis suppressor GCH1. Ferroptosis caused by the drug in glioma stem-like cells inhibits their growth [48]. The expression of MTHFD2 is high and has a bad prognosis in TNBC. By silencing MTHFD2, it downregulates the SLC7A11/GPX4/NRF2 axis causing LPO and ROS accumulation, inhibiting tumor proliferation and migration [49]. In gastric cancer, high GPX4 expression coupled with low levels of 4-HNE (4-hydroxynonenal), indicates poor prognosis, while patients with low FSP1 and high 4-HNE expression have better prognosis. In vitro studies prove that co-inhibition of GPX4 and FSP1 can synergistically induce non-apoptotic ferroptosis, suggesting a new therapeutic option for treatment-refractory gastric cancer [50]. Standardization of Detection and Assessment Techniques of Ferroptosis is on the Rise as Research Advances. Pharmacological validation together with 4-HNE immunostaining and TUNEL assay with Lip-1 has been used to detect Ferroptosis in a renal I/R injury mode [51]. Transcriptomic analysis in patients with lupus nephritis (LN) identified multiple differentially expressed genes relevant to ferroptosis (e.g., CYBB up, G0S2 down). The expression of CYBB was correlated with monocyte infiltration as well as treatment response among them, suggesting its potential as a ferroptosis biomarker in LN [52].

In the I/R injury, several regulatory factors are known to be key regulators of ferroptosis. TMEM16A induces ferroptosis during liver ischemia/reperfusion injury through activating ubiquitin-dependent degradation of GPX4. The tissue injury and LPO are substantially lessened when either TMEM16A is removed from liver-specific tissue, or its interaction with GPX4 is impaired [53]. In mice with brain ischemia-reperfusion injury, THBS-1 from macrophage-derived exosomes induces ferroptosis in brain microvascular endothelial cells. Salvianolic Acid B (SAB) can reverse the changes in GPX4 expression and prevent the disruption of the blood-brain barrier [54]. In AKI, ferroptosis is increased by the F-box protein FBXW7 through the degradation of GPX4. Increased FBXW7 levels exacerbate tissue damage in the presence of erastin. Either FBXW7 knockdown or Fer-1 administration inhibit I/R-induced renal injury [55].

The role and impact of mitochondria in ferroptosis

Mitochondria are essential for energy production in the cell. They are also central to cellular iron homeostasis and play a key role in regulating lipid peroxidation and oxidative stress scavenging. Growing evidence has identified multiple mitochondrial structures and components that regulate ferroptosis. The biosynthesis of heme and iron-sulfur clusters, which are critical for oxidative phosphorylation, requires the presence of intramitochondrial iron. Nonetheless, under stressful situations, free Fe^{2+} may generate •OH via the Fenton reaction that can induce LPO of mitochondrial membrane triggering the ferroptotic cascade. According to the morphology, ferroptosis displays obvious mitochondrial changes. These changes include a reduced volume, distorted cristae and an increased density of the membrane. These changes help us to differentiate between ferroptosis and the other types of cell death like apoptosis and necrosis [56]. Mitochondrial dysfunction exacerbates ferroptosis in I/R injury. The mitochondrial protein DbpA, which is associated with Ybx3, is found in renal tubular mitochondria. Knockdown of DbpA increases the mitochondrial membrane potential and oxygen consumption rate, the antioxidant capacity develops, and I/R ferroptosis and kidney injury decrease significantly [30]. Infertility has also been caused by abnormal cellular iron. Mutations in the COX15 gene of mitochondria impair its respiratory chain function. Involved in heme A biosynthesis, this mutation leads to the accumulation of Fe^{2+} and the generation of ROS. These two factors impair oocyte maturation through ferroptosis, thus causing oocyte maturation arrest. Treatment with Fer-1 can restore this phenotype in vitro [57].

Strategies were identified by targeting sensitivity to ferroptosis in mitochondria. Through its GTPase activity, OPA1 involves the accumulation of lipid ROS and suppression of ATF4 to enhance the susceptibility to ferroptosis, while deficiency of OPA1 reverses this outcome [56]. Propafenone activates the JNK/JUN pathway to upregulate mitochondrial HMOX1 to promote Fe^{2+} accumulation and ROS production to enhance the sensitivity of melanoma cells to ferroptosis inducers and immune checkpoint inhibitors [58]. In colorectal cancer, icariin can thermodynamically induce ferroptosis by interrupting the HMGA2/STAT3/HIF-1 system. This is characterized by impaired mitochondrial activity, increased lipid ROS and down-regulated GPX4 expression, respectively, ultimately ameliorating immunotherapy efficacy [59]. In addition to that, regulation of ferroptosis requires mechanisms maintaining mitochondrial homeostasis. NUDT16L1 is a mitochondrial maintenance factor that binds NAD-capped RNAs to regulate MALAT1 expression, and thus limit mitochondrial DNA (mtDNA) leakage and ferroptosis sensitivity. Animal models and clinical tissue showed the anti-tumor effect of the inhibition [60]. Within corpus cavernosum smooth muscle cells, more mitochondria-rich microvesicles (MVs) donate functionally active mitochondria to increase antioxidants and restore membrane potential. This effect greatly reduces neural-injury-induced erectile dysfunction and is affected by mitochondrial activity [61].

In a glucocorticoid-induced model of femoral head necrosis, isovitexin was shown to activates SIRT3 and by doing so, increases the resistance of osteoblasts to ferroptosis while inhibiting the mitophagy that occurs through the use of BNIP3/NIX [62]. In hepatic I/R models under cholestatic conditions, it is microvascular impairment and delayed recovery of mitochondrial metabolism that play key roles in damage to tissues as opposed to the use of

conventional oxidative stress markers or GSH depletion [63].

Strategies targeting the mitochondria to protect the organ are being explored. The addition of trimetazidine (TMZ) to liver preservation solutions in transplantation activates the AKT/GSK3β signaling axis, stabilizes voltage-dependent anion channel (VDAC) structure, and inhibits mitochondrial apoptosis, ER stress, and oxidative damage at the same time. According to this strategy, cold I/R injury during liver transplantation is reduced [64]. It should be noted that VDACs, which are located on the outer mitochondrial membrane are important in maintaining the mitochondrial integrity. Their structural stability is crucial in modulating ferroptosis.

The role of ferroptosis in IRI

Ferroptosis in cardiac IRI

Ferroptosis is a novel regulated form of cell death that is iron ion- and lipid peroxidation-dependent. This form of cell death is implicated in cardiac IRI. Through an ischemic phase the impairment of GSH synthesis and GPX4 activity compromises the antioxidant defenses. The surge of ROS on reperfusion, along with the accumulation of intracellular iron, enhances LPO and Fenton chemistry, leading ultimately to ferroptosis. The upregulation of TfR1 with the downregulation of ferritin heavy chain (FTH1) also exacerbates overload of free iron, which enhances oxidative stress. Mitochondria play a key role in ferroptosis and undergo distinct morphological changes during this process, including a loss of membrane potential, rupture of cristae, and rupture of the outer membrane. Animal studies show that pro-ferroptotic markers like ACSL4 and COX-2 are significantly upregulated after IRI. In contrast, GPX4 expression decreases significantly. The use of iron chelator DFO and ferroptosis inhibitor Fer-1 markedly reduces myocardial injury thus implying that ferroptosis is a reversible process and provides a window for IRI treatment intervention [65]. Ferroptosis is also implicated in radiation-induced heart disease, where its inhibition represents a viable therapeutic strategy [66].

More studies have revealed many important regulators and signalling pathways in myocardial ferroptosis. Metformin (Met) is a biguanide that can protect cardiomyocytes by activating AMPKα signaling as well as suppressing NOX4 which leads to increased oxidative stress. Non-heme iron accumulation may lead to the inhibition of GPX4 activity which will finally lead to ferroptosis. Particularly, the cardioprotective effects of met were completely abolished by silencing of AMPKα, indicating that AMPKα-NOX4 axis is critical for the cardioprotective effect of met [65]. At the epigenetic level, NAT10 facilitates Mybbp1a stability via ac4C RNA acetylation, which activates the p53 pathway and downregulates SLC7A11 to impair System Xc^--mediated antioxidant defense and promote ferroptosis. Both the NAT10 knockout and pharmacological inhibition with Remodelin significantly reduces myocardial damage caused by IRI. Notably, this protective effect is even more significant than other anti-apoptotic strategies. Because of this potential, clinical translation is warranted [67]. Similarly, the deubiquitinase USP38 stabilizes p53. Consequently, SLC7A11 expression is suppressed. Furthermore, LPO and iron overload are intensified, worsening myocardial injury. In addition, this intensified LPO and iron overload makes the body more susceptible to ventricular arrhythmias. The knockout of cardiac-specific USP38 will attenuate these pathological changes; hence, the USP38-p53-SLC7A11 axis is a potential therapeutic target to regulate ferroptosis in the heart [68]. Ferroptosis Regulation is Also Achieved via Mitochondrial Mechanisms. MPV17, a downstream target of Nrf2, prevents destabilization of mitochondrial carrier SLC25A10 to maintain mitochondrial GSH. Excess iron reduces MPV17, which leads to the ubiquitination and degradation of SLC25A10 and the depletion of mitochondrial GSH (mtGSH), which can trigger ferroptosis. Adenoviral overexpression of MPV17 reverses these effects showing the cardioprotective effect of the Nrf2-MPV17-SLC25A10/mtGSH pathway [69]. Dexmedetomidine, a pharmacological agent, activates SLC7A11/GPX4 axis, inhibits ferroptosis, decreases myocardial infarct size, enhances cardiac function, and reduces mitochondrial oxidative stress, exhibiting strong cardioprotective efficacy [70]. Oxidized phosphatidylcholines (OxPCs) present in cardiomyocytes inhibit GPX4 activity directly. This causes intracellular calcium dysregulation, mitochondrial dysfunction, and cell death. Adding the

E06 monoclonal antibody or Fer-1 can successfully block these adverse effects [71]. In addition, exosomes from bone marrow mesenchymal stem cells (BMSCs-Exo) can protect from ferroptosis by delivering high levels of lncRNA Mir9-3hg, which inhibits the RNA-binding protein Pum2. PRDX6 antioxidant path is activated in which molecular ferroptosis inhibition occurs that greatly reduces IRI-induced cardiac injury [72].

Advances in research on ferroptosis in cerebral ischemia-reperfusion injury (CIRI)

CIRI is among the key mechanisms that cause secondary brain injury in stroke. The onset and progression of the disease involves episodes of ROS release, activation of inflammatory mediators, and multiple death pathways in distinct types of cells, that together contribute to brain tissue damage. In recent years, recognition of ferroptosis, a distinctive form of programmed cell death linked with iron-dependent LPO, has garnered increasing recognition, with its significant role in CIRI becoming increasingly apparent. Research suggests that the accumulation of free iron ions in brain tissues is significantly enhanced by ischemia-reperfusion, which also promotes the Fenton reaction. At the same time, it causes GSH depletion and reduced GPX4 activity, thus causing excessive accumulation of lipid peroxides, which then leads to neuronal ferroptosis.

The system Xc^-/GSH/GPX4 axis is considered the core signaling pathway regulating ferroptosis at the molecular level. Under CIRI conditions, the expression of the essential transporter SLC7A11 is downregulated. This limits cystine uptake and GSH synthesis. Thus, GPX4 cannot eliminate lipid peroxides. Nuclear factor erythroid 2-related factor 2 (Nrf2), is an antioxidant transcription factor that can increase resistance to ferroptosis. It can achieve this by inducing the expression of SLC7A11 and GPX4. N-butyl phthalide or dl-3-n-butylphthalide (NBP) is a natural compound extracted from celery. Previous studies found that NBP can activate the Nrf2/GPX4 signaling pathway and inhibit the LPO driver ACSL4 and iron transporter TfR1. This can reduce levels of LPO products like malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), leading to significant mitigation of brain injury. Nrf2 inhibitors or genetic knockout can reverse these protective effects, further confirming the crucial Nrf2 pathway that inhibits CIRI-related ferroptosis [73-76]. In addition to conventional antioxidant pathways, ferroptosis interacts with various cellular stress signaling pathways. The pathway of HSP90-GCN2-ATF4 is an important mediator between necroptosis and ferroptosis. According to studies, this compound NTF can preserve the blood-brain barrier integrity and ease neuronal damage by blocking this pathway and downregulating HSP90 expression [77]. Exosomal thrombospondin-1 (THBS1) from macrophages is able to bind to OTUD5, leading to GPX4 ubiquitination and degradation (which induces ferroptosis) in brain microvascular endothelial cells. The disturbance of this molecular interaction by SAB stabilizes the GPX4 protein and aids in the repair of blood-brain barrier injury [54]. Non-coding RNAs also play an essential role in regulating ferroptosis in CIRI. For instance, the m6A demethylase FTO can suppress primiR320 maturation to promote the decrease of miR320-3p levels, which will relieve inhibition on SLC7A11. This enhances the antioxidant capacity and mitigates ferroptosis during CIRI [78]. Another study concluded that electroacupuncture could downregulate p53 expression. It relieves the suppression of SLC7A11, restoring GPX4 levels, reducing LPO and iron deposition, and improving neurological function [79].

Many natural compounds can also prevent ferroptosis. TQHX has been shown to reduce neuronal injury by promoting the ubiquitination and degradation of ACSL4 [80], as well as enhancing the efficacy of GPX4 along with better iron sequestration via the iron-storage protein FTH1 to minimize ROS and iron accumulation [80]. Puerarin exerts neuroprotective effects similar to Ferroptosis inhibitor Fer-1 synergistically inhibiting both ferroptosis and pyroptosis (caspase-1/GSDMD-mediated) [81]. In addition, the RNA-binding protein IGF2BP1 can aggravate neuronal ferroptosis by upregulating Keap1 expression and suppressing Nrf2 signaling. Knockout of IGF2BP1 promotes GPX4 expression, drives microglial polarization toward the M2 phenotype, attenuates neuroinflammation, and improves neurological function, suggesting it as a potential therapeutic target for ferroptosis modulation [82].

The role of ferroptosis in ischemia-reperfusion injury (IRI) of other organs

Ferroptosis, a form of programmed cell death characterized by iron-dependent LPO, has been extensively demonstrated to play a key pathogenic role in IRI across multiple organs. Taking myocardial IRI as an example, disturbances in iron homeostasis synergize with oxidative stress to markedly trigger ferroptosis, typically manifested by elevated free iron concentration, downregulated GPX4 expression, and massive lipid peroxide accumulation. Research indicates that inhibitors of ferroptosis Fer-1 and Lip-1 can decrease the area of myocardial infarction and improve heart function. In addition, activating the Nrf2/GPX4 pathway or targeting ACSL4 and TfR1 has been confirmed to confer cardioprotection.

Ferroptosis primarily takes place at the onset of injury in hepatic IRI. Evidence indicates that DAMPs like high mobility group box 1 (HMGB1) and mtDNA can activate the cGAS pathway to induce hepatocyte ferroptosis. In later stages, the macrophages predominantly trigger death in the forms of pyroptosis and necroptosis. Using both ferroptosis inhibitors and pyroptosis blockers is a strategy that can help in liver IRI, which is the application of the two [83]. Besides, ticlopidine was shown to broadly inhibit ferroptosis, prevent the accumulation of hepatic iron (shown with reduction of Prussian blue staining), reduce LPO products (MDA, 4-HNE), and lower the serum liver enzyme levels (ALT, AST) with significant mitochondrial protective effect, in both in vivo and in vitro models [84]. A systematic review further summarized five categories of ferroptosis inhibitors including free radical scavengers, iron chelators and antioxidants, which have shown promising efficacy in preclinical models of hepatic, renal and intestinal IRI. While there have been clinical translations, issues to be solved include optimizing drug delivery, bioavailability and mechanisms of action, and applications to pancreatic IRI remain unfound [85].

The kidney is a very vulnerable organ that gets affected by IRI. During the reperfusion of renal tubules, picking up ferroptosis early on is a consequence of it. The reason behind cell ferroptosis is due to the increased iron-loading of cells, suppression of GPX4, and lipid peroxide accumulation. It has been mentioned that CK-666 can block ferroptosis independently of the Arp2/3 complex by removing lipid peroxides and reorganizing actin filaments and exhibits strong antioxidant capacity, as demonstrated in a DPPH assay [86]. In addition, due to their surface functional groups, carbon dot nanozymes can chelate Fe^{2+}. They also scavenge ROS and downregulate ACSL4 expression to maintain iron homeostasis and significantly alleviate oxidative stress injury in renal tissue [87]. Using a renal transplantation IRI model, we found that low dose of cyclosporine A (CsA) in combination with DFO has a synergistic effect on inhibiting ferroptosis. This synergy arises because CsA inhibits mitochondrial ROS generation, while DFO chelates free iron. In addition, our treatment lowered blood urea nitrogen (BUN) levels and reduced tubular necrosis. More importantly, we found very robust evidence of its translational potential [88]. Also, the TGF-β1/α-SMA signaling pathway causes the progression of renal IRI to chronic kidney disease is mediated by the RNA-binding protein eCIRP. The antagonist of eCIRP, C23, can cause the upregulation of GPX4, downregulation of LPO and iron accumulation significantly improving renal function and GFR [89]. The mechanism of Ferroptosis is also a major player in Lung IRI. In a lung transplantation model, four ferroptosis-related genes--TNFAIP3, CXCL2, NEDD4L, and SESN2--were identified, among which SESN2 was validated via Mendelian randomization as being significantly protective for primary graft dysfunction (PGD), thus representing a potential target for personalized immunomodulatory intervention [90]. Moreover, another mechanism has been identified wherein the up-regulation of the ALOX12-12-HETE pathway promotes ferroptosis and subsequent extracellular trap (NET) formation in lung IRI [91]. Likewise, lipoxin A4 (LxA4) acts on the FPR2 receptor on the type II epithelial cells of alveoli to activate the Nrf2 signaling pathway leading to improved synthesis of GSH. This counteracts LPO (lower MDA levels) while oxygenation effectively improves (increased PaO_2). The anti-oxidative effects were completely negated when FPR2 or Nrf2 were not present [92]. Ferroptosis in intestinal IRI contributes to the pathological process at multiple levels by perforating mucosal barriers and aggravating inflammation. Baicalin activates Nrf2-GPX4 pathway to inhibit ferroptosis and

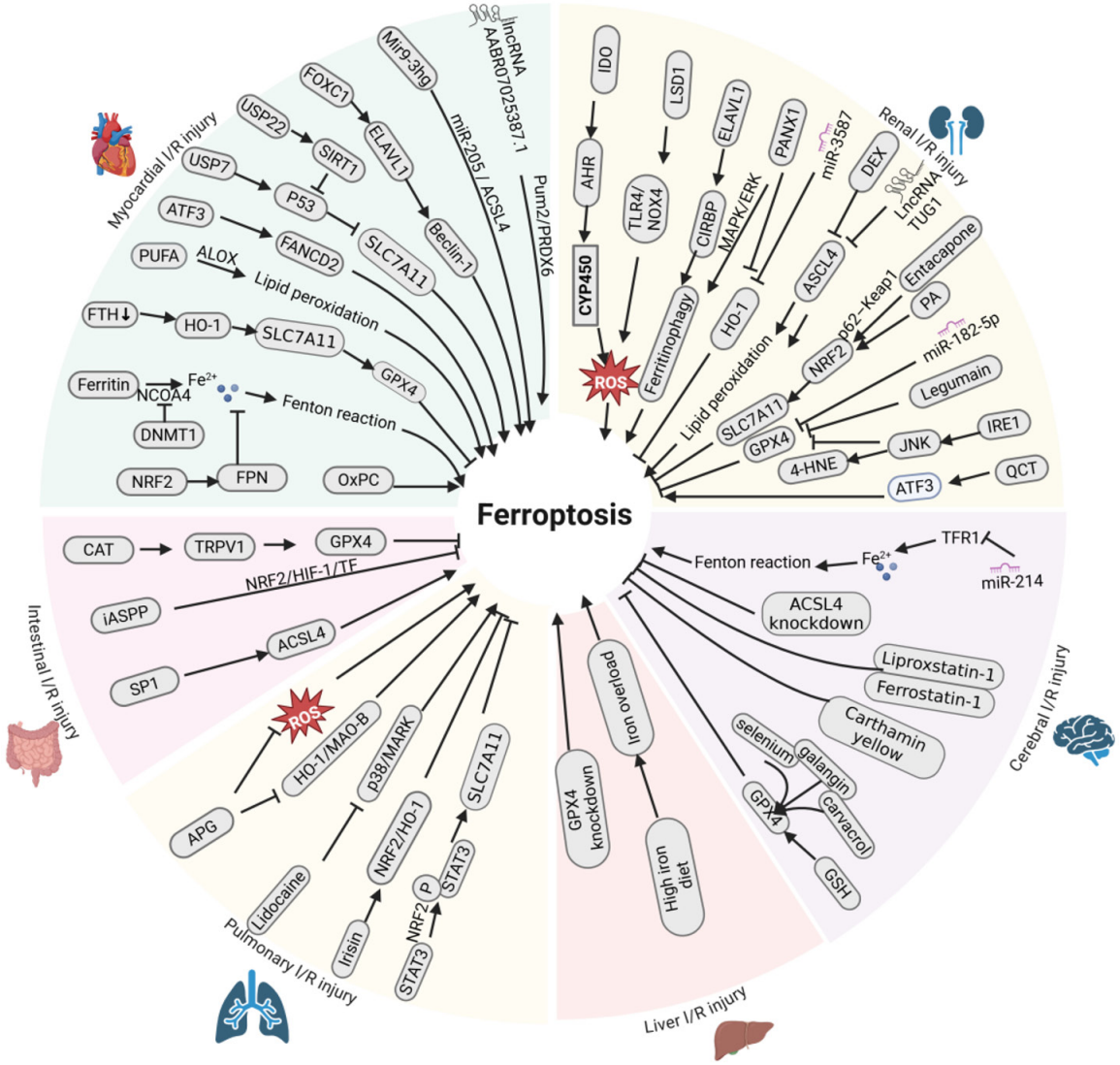

Figure 2. Molecular mechanisms and regulatory networks of ferroptosis in ischemia reperfusion injury across multiple organs. The figure depicts the major molecular pathways of ferroptosis in IRI across the heart, brain, liver, kidneys, lungs, and intestines. It highlights key events such as iron overload, the Fenton reaction, ACSL4/ALOX-mediated LPO, GPX4 inactivation, and ROS amplification, along with organ-specific regulators, non-coding RNAs, transcription factors, and pharmacological inhibitors. This schematic integrates common mechanisms with organ-specific features, indicating potential therapeutic targets.

reduce ROS levels and iron loading, and enhancing the expression of tight junction proteins ZO-1 and occludin, thereby attenuating mitochondrial damage and intestinal inflammation; its protective effects can be completely abolished by Nrf2 inhibitors [93]. Sevoflurane acts via the AMPK/Nrf2 signaling axis to upregulate iron-chelation-related protein FTL and GSH synthesis genes (SLC7A11 and GCLM), thereby lowering ferrous iron concentration, reducing LPO stress, and suppressing intestinal ferroptosis [94]. Moreover, NCOA4-mediated ferritinophagy promotes the release of free iron, induces ACSL4 expression, enhances LPO reactions, and suppresses GPX4 and GSH expression, thereby accelerating intestinal ferroptosis. The process can be efficiently blocked by either the knockdown of NCOA4 or by the application of autophagy inhibitors which highlights the therapeutic potential of targeting intestinal IRI [95]. A systematic overview of the shared and organ-specific regulatory mechanisms of ferroptosis in IRI indicates that the key molecular events, signaling pathways and therapeutic targets of various organs are illustrated in an integrative schematic (**Figure 2**).

Ferroptosis and oxidative stress interactions

Impact of oxidative stress on iron metabolism

A pathological correlation exists amongst dysregulated iron metabolism and oxidative stress in IRI that is closely interwoven. During the early reperfusion phase, ROS is produced in excess, overloading the ability of the endogenous antioxidant system to scavenge all the free radicals. Various kinds of reactive oxygen species (ROS) are continuously produced in human cells because of mitochondrial respiration. Research conducted to verify oxidative stress as a key inducer of ferroptosis has indicated that oxidative stress acts as the driving factor to cause ferroptosis. Consequently, many investigators consider it an upstream regulator of several key nodes in the iron metabolism network. A prime example is in MIRI, where oxidative stress activates, with the NLRP3 inflammasome playing a key role, the inflammatory cell death signalling pathway of pyroptosis [96]. The self-amplifying mechanism between oxidative stress and ferroptosis forms a positive feedback loop that exacerbates tissue and cellular injury.

At the molecular level, oxidative stress promotes hepcidin expression, which limits the localization of the iron export protein FPN on the cell membrane, causing intracellular iron retention. The NOX system can also be activated by ROS as well as the expression of the prooxidant enzymes inducible nitric oxide synthase (iNOS) and LOX which further drive LPO. When H_2O_2 is present, Fe^{2+} participates in the Fenton reaction to produce the highly cytotoxic •OH, which initiates chain LPO and ultimately triggers the ferroptotic program. Cellular harm can cause the autophagic degradation of ferritin (ferritinophagy), which frees up the stored iron. This can greatly increase the LIP. Further diminishment of the antioxidants can boost the risk for iron-dependent cell death [97-99]. As for iron uptake and transport, ROS can upregulate TfR1 and divalent metal transporter 1 (DMT1), which promote the uptake of external Fe^{3+} and transmembrane transport of Fe^{2+} which creates a vicious cycle that amplifies oxidative stress [74, 100]. For instance, in patients suffering from β-thalassemia, LIP levels inside erythrocytes are elevated and positively correlated with ROS levels. LIP is consequently suggested to be a biomarker of choice for monitoring iron overload and evaluating the efficacy of chelation therapy [100]. Additionally, prion infection models indicate that regulating iron homeostasis disruptions delays iron processing and maintains ROS elevation. Furthermore, increasing cellular susceptibility to iron toxicity is likely because Fe(II) drives oxidative stress at low levels (few μM range) [101].

Oxidative stress can additionally inhibit the Nrf2 signaling pathway, thereby reducing the cellular ability to maintain iron homeostasis and counteract oxidative stress. Inhibition of the Nrf2 signaling pathway is associated with reduced expression of key downstream antioxidant and iron-regulatory molecules of key downstream antioxidant and iron-regulatory molecules, such as SLC7A11, GPX4, ferritin, and FPN. Decreased antioxidant activity, coupled with impaired iron efflux, raises the susceptibility towards ferroptosis above the baseline level [25, 74]. Studies on animals confirmed Nrf2 signaling activation can inhibit ferroptotic injury. For example, isoglycyrrhizin promotes Nrf2 nuclear translocation and upregulates HO-1, SLC7A11, and GPX4, while inhibiting the expression of ACSL4 and Drp1, thereby significantly ameliorating myocardial IRI [25]. In a diabetic nephropathy model, atorvastatin has an anti-ferroptotic effect comparable to Fer-1 via upregulation of GPX4 and FTH expression and inhibition of TfR1 [74]. Furthermore, oxidative stress is closely involved in mitochondrial dysfunction. OPA1 helps produce harmful molecules in mitochondria through its GTPase activity ATF4-mediated stress responses, thereby facilitating ferroptosis; conversely, OPA1 deficiency significantly enhances cellular resistance to ferroptosis [56]. In a polycystic ovary syndrome (PCOS) model, elevated CISD2 expression inhibits mitophagy, leading to NOX2-mediated ROS accumulation and GSH depletion, which further amplifies oxidative stress injury [102]. Meanwhile, CGI1746, by targeting the σ1 receptor, regulates Ca^{2+} transfer within mitochondria-associated membranes (MAMs), reducing mitochondrial ROS production and PUFA-triglyceride (PUFA-TG) accumulation, thereby effectively alleviating cisplatin-induced AKI and offering a new avenue for targeting MAMs-associated ferroptosis [103].

How ferroptosis exacerbates oxidative damage

Ferroptosis, a form of iron-dependent, lipid peroxidation-induced cell death, represents a major manifestation of oxidative stress in IRI. In addition, it is a mechanism that mediates oxidative damage through many other processes. Ferroptosis establishes a self-amplifying positive feedback loop between iron and ROS by enhancing Fe^{2+}-mediated Fenton reactions, compromising the cellular antioxidant capacity, disrupting the homeostasis of mitochondria, and promoting the release of oxidized DAMPs. This loop significantly aggravates membrane damage and leads to inflammatory cascades. The oxidative amplification effect of ferroptosis is evident in numerous disease models. As an example, ZMYND8 could activate the NRF2 antioxidant pathway by two mechanisms: silencing its inhibitor KEAP1, and boosting NRF2 binding to antioxidant gene promoters. Ferroptosis inhibition reduces the accumulation of intracellular ROS and load of iron, while enhancing cancer stem cell properties and tumorigenic potential to form a tumor-promoting feedback loop [104]. Nanomedicine platforms have been developed to synergistically induce ferroptosis and oxidative stress in anticancer therapeutic strategies. The p53/Ce6@ZF-T nanodrug synergistically induces apoptosis and ferroptosis in tumor cells by enhancing the Fenton reaction, promoting photo-oxidative ROS production, and inactivating GPX4 via p53, thereby abolishing lipid repair capacity [105]. A folate-targeted upconversion nanosystem, which converts near-infrared light into ultraviolet radiation, is able to catalyze the reduction of Fe^{3+} to Fe^{2+} causing ferroptosis, and achieves synergistic TNBC therapy when combined with cisplatin [106]. Another intensified oxidative strategy involves HBGL nanoliposomes that co-deliver heme, β-lapachone, and glucose oxidase. This system generates endogenous H_2O_2 to drive Fenton-derived •OH, while depleting GSH and inhibiting GPX4, thereby damaging mitochondria and the ER to induce ferroptosis [107]. Likewise, ALOX15 catalyzes LPO to produce 4-HNE and ROS, impairing sperm acrosomal function and zona pellucida binding; its inhibitor PD146176 effectively mitigates such oxidative injury, providing a potential therapeutic target for male infertility [108].

Mechanistic studies on ferroptosis also benefit from advances in visualization tools. The OG-3 dual-channel fluorescent probe enables real-time imaging of •OH and GSH, revealing dynamic changes in both exogenous (SLC7A11 downregulation) and endogenous (GPX4 inactivation) ferroptosis pathways, thus offering a novel platform for mechanistic exploration and inhibitor screening [109]. In a sepsis-induced acute lung injury model, UPP1-mediated uridine metabolic dysregulation activated the Nrf2 pathway, upregulating SLC7A11, GPX4, and HO-1, suppressing LPO, and reducing expression of the ferroptosis marker ACSL4, thereby alleviating inflammation and tissue injury [110].

Another critical factor is the metabolic regulation of ferroptosis and oxidative stress, which are mutually amplified. Overexpression of SOX8 suppresses adipogenesis, glycolysis, TCA cycle, and pentose phosphate pathway (PPP), resulting in limiting the synthesis of NADPH. Additionally, it upregulates gene expression of ferroptosis-related genes, which leads to production of lethal lipid peroxides and mitochondrial damage, ultimately inhibiting the growth of hepatocellular carcinoma [111]. Gallic acid (GA) can exert a dual protective effect on exercise-induced skeletal muscle injury: scavenging mitochondrial ROS, restoring membrane potential, and replenishing ATP to relieve mitochondrial stress; and reducing Fe^{2+}, MDA, and COX2 levels while increasing GPX4 expression to inhibit ferroptosis [112]. The susceptibility to ferroptosis was influenced by glucose-6-phosphate dehydrogenase (G6PD), which controls glutathione and NADPH levels. Increasing G6PD levels produces more antioxidants in pancreatic cancer cells and suppresses ferroptosis cells. On the other hand, G6PD knockdown activates the AMPK-mTOR pathway to initiate autophagy-dependent ferroptosis. This is reversible by inhibiting AMPK. The above indicates the interplay of ferroptosis and energy metabolism signalling [113]. In addition, using Raman spectroscopy with microfluidics to monitor the lipid -specific 1436 -cm^{-1} peak in real-time unveils a mechanism through which NADPH, ferredoxin clusters, and ROS cooperatively drive LPO, DNA damage, and mitochondrial dysfunction. Quantum mechanical and molecular docking simulations have validated the above, resulting in new useful strategies for the

proper diagnosis and targeted treatment of ferroptosis [114].

Interplay between oxidative stress and iron metabolism: implications for therapeutic strategies

During IRI, a tightly coupled pathological loop forms between oxidative stress and ferroptosis whose combined effect on iron homeostasis exacerbates cellular damage significantly and is one of the top mechanisms driving IRI. Oxidative stress triggers the activation of NOX, LOX, and iNOS, causing an overproduction of ROS. Ferritin undergoes autophagic degradation (ferritinophagy), releasing stored iron which then enlarges the LIP in this process. While this is happening, oxidative stress causes an increase of TfR1 and DMT1, which increases Fe^{2+} uptake that further promotes Fenton chemistry generating very toxic •OH. This leads to a mutually reinforcing cycle involving oxidative stress and iron overload [115, 116]. As this feedback process continues, the key antioxidant regulator Nrf2 becomes functionally compromised. Therefore, cells become even more vulnerable to ferroptosis due to oxidative stress. Using ROS to upregulate miR-126-3p/5p can inhibit p85β and SETD5 to hyperactivate PPP and induce ferroptosis in NRF2-wild-type lung squamous cell carcinoma. On the other hand, cells with NRF2 mutations counter this regulatory particular, highlighting a potential molecular therapeutic strategy [115]. Additionally, the environmental pollutant 6PPD generates oxidative stress and ferroptosis and damages the intestinal villus structure of zebrafish, with the antioxidant N-acetylcysteine (NAC) effectively reversing these toxic effects, further proving both the generalizability and therapeutic manipulability of the oxidative stress-iron metabolism relationship [116].

The oxidative stress-ferroptosis axis is also promising for the treatment of neurological disease. In animal models of Alzheimer's disease, oleanolic acid (OA) has been shown to activate the Nrf2/HO-1 pathway to down-regulate the expression of amyloid precursor protein (APP), reduce the production of ROS as well as modulate autophagy, ferroptosis and the functionality of mitochondria and ER. This induces a protective effect on neurons against the Aβ-induced toxicity [117]. ISL alleviates oxidative stress and neuronal apoptosis in cerebral IRI by dissociating Keap1, promoting Nrf2 nuclear translocation, and improving mitochondrial dynamics and autophagy. The Nrf2 inhibitor brusatol completely abolishes its neuroprotective effects, indicating Nrf2-dependence [118]. In hepatic IRI models, the deubiquitinase OTUD1 stabilizes Nrf2 via the Cys320 catalytic site and the ETGE motif, significantly reducing oxidative stress, apoptosis, and inflammation. Notably, ETGE-containing short peptides can mimic OTUD1-mediated Nrf2 activation, providing a novel targeted approach for IRI therapy [119]. To facilitate a mechanistic understanding of the bidirectional amplification and evidence chain of the "oxidative stress-ferroptosis" axis in IRI, key events at the levels of molecular pathways, organelle functions, and biological effects are systematically summarized (see **Table 1**).

Potential therapeutic strategies targeting ferroptosis

Development of ferroptosis inhibitors and their clinical prospects

A contemporary cell death mechanism that is related to the iron catalyzed lipoperoxidation (LPO), ferroptosis has gained recognition for its pathogenic role in IRI and different acute organ injuries. Ferroptosis has emerged as a promising therapeutic target as its molecular basis becomes better understood. Drug development is ongoing for antioxidants, iron chelators, LPO inhibitors, and core regulators such as GPX4 and SLC7A11. Fer-1 and Lip-1 can inhibit the peroxidation of phospholipids, which can significantly reduce the neuronal apoptosis that occurs in the cerebral IRI models and tubular necrosis that occurs in the renal IRI models. DFO prevents the generation of the hydroxyl radicals by interfering in the Fenton reaction, which prevents iron overload-induced oxidative stress and provides extensive organ protection [120]. From the mechanistic perspective, PrA is a dual-target inhibitor whose first action is to bind to ACSL4 to block its phosphorylated form and thus prevent LPO. Its second action is to bind to FTH1 to inhibit ferritin degradation and release of free Fe^{2+}. These acts work together to help maintain mitochondrial function and reduce doxorubicin-induced toxicity [120]. Moreover, high-throughput screening assisted by

Table 1. Mechanistic interactions between ferroptosis and oxidative stress in IRI

Interaction level	Key Events/Molecules in Ferroptosis	Key Events/Molecules in Oxidative Stress	Mode of Interaction	Biological Effect	Experimental Evidence and Regulatory Targets	References
Molecular Pathway Level (Nrf2/xCT/GPX4 Axis)	GPX4 Downregulation, System xc^- Inhibition, and Iron Accumulation	Increased LPO and Elevated Serum Oxidative Stress Markers	NAR Activates Nrf2→Upregulates System xc^-/GPX4 →Inhibits Ferroptosis	Attenuation of Myocardial Infarction, Cell Death, and Tissue Injury	NAR Upregulates GPX4; Erastin Reverses the Protective Effect	[151]
Association Between the Ischemic Phase and Ferroptosis in Intestinal I/R Injury	ACSL4 and Lipstatin-1 Inhibit Ferroptosis	Protein and LPO Levels	Sp1 Binds to the ACSL4 Promoter to Promote Its Transcription	Inhibition of Ferroptosis and Cell Death, and Amelioration of Intestinal I/R Injury	ROSI and siRNA Inhibit ACSL4, with Sp1 as a Regulatory Factor	[152]
Association between Distal Cholesterol Biosynthesis and Ferroptosis	7-DHC and MSMO1 inhibition; DHCR7 activation	Phospholipid auto-oxidation and conjugated diene formation	7-DHC regulates ferroptosis by inhibiting phospholipid autoxidation	Inhibits tumor growth and metastasis; alleviates renal IRI	CRISPR-Cas9 screening identifies EBP and other targets involved in 7-DHC regulation	[153]
In vivo rat tMCAO/R and in vitro PC12 cell OGD/R models	ACSL4, TfR1, FTH1, GPX4, and iron accumulation	Levels of MDA and ROS, and SOD activity	Binding of formononetin to ACSL4 inhibits its activity	Ameliorates cerebral I/R injury and preserves neurological function	Fer-1 control group, with ACSL4 as a key target	[154]
Kinase signaling level (AMPK-ACC pathway)	LPO accumulation (inhibited)	LPO (a key phenotypic marker)	Energy stress → AMPK activation → ACC phosphorylation → Inhibition of PUFA synthesis	Inhibits ferroptosis and alleviates renal IRI	Loss of AMPK activity abolishes the protective effect; ACC phosphorylation serves as a critical regulatory node	[16]
Protein modification level (USP11-mediated stabilization of Beclin1)	Lipid peroxide accumulation (USP11-dependent)	Lipid peroxide accumulation (a hallmark phenotype)	USP11 stabilizes Beclin1 → activates autophagy → promotes ferroptosis	Impaired/improved motor function recovery (dependent on USP11 levels)	USP11 knockdown/knockout inhibits ferroptosis; autophagy blockade reverses the effect	[155]
Organelle level (mitochondrial membrane damage)	Hmox1↑ → free iron accumulation → mitochondrial iron overload	Mitochondrial LPO (a core execution mechanism)	Hmox1-mediated heme degradation → iron release → mitochondrial LPO	Cardiomyocyte death and worsening of heart failure	Protection by Fer-1/iron chelators; rescue by Mito-TEMPO	[156]
Cell-cell interaction level (macrophage-hepatocyte crosstalk)	Iron overload-induced ferroptosis in hepatocytes	Ferroptosis-associated LPO	METs release promotes ferroptosis in hepatocytes	Increased hepatocyte death and exacerbated IRI injury	Inhibition of METs, Fer-1, or DFO alleviates injury	[157]
Enzyme-substrate regulation level (gp78-ACSL4 pathway)	Increased ACSL4 expression and disrupted PUFA metabolism → accumulation of oxidized lipids	Accumulation of oxidized lipids (a specific phenotype)	gp78 overexpression → upregulation of ACSL4 → PUFA metabolic imbalance → ferroptosis	Aggravation/alleviation of liver injury (dependent on gp78 levels)	Inhibition of ACSL4 or ferroptosis abrogates gp78-mediated injury	[158]
Enzymatic activity inhibition level (AS directly binds to ACSL4)	Increased ACSL4 enzymatic activity (inhibited by AS)	LPO (a core execution phenotype)	AS binds to ACSL4-Gln464 → inhibits enzymatic activity → blocks LPO	Attenuates renal IRI and acute liver injury	Nanoparticle-delivered AS is effective; ACSL4 serves as a specific target	[159]
Transcriptional regulation level (HES1-GPX4 pathway)	Decreased GPX4 expression accompanied by increased iron accumulation (total iron/ferrous iron)	ROS↑, MDA↑, and GSH/GSSG imbalance	Cur ↑ HES1 → ↑ GPX4 → inhibition of ferroptosis and oxidative stress	Cell viability restoration; LDH↓, MDA↓, iron↓	HES1 shRNA blocks protection; Fer-1synergistically enhances efficacy	[29]

Signaling pathway level (Nrf2-HO-1/GPX4 axis)	GPX4↓, iron deposition↑	ROS↑, iron deposition↑, neuroinflammation↑	AA9 → Nrf2 activation → GPX4/HO-1↑ → oxidative stress & ferroptosis inhibition	Reduced cerebral infarct size; improved neurological function; decreased neuronal injury	ML385-mediated Nrf2 inhibition abolishes AA9 effect	[160]
Transcriptional regulation level (Nrf2-GPX4/FTH/xCT axis)	GPX4↓, xCT↓, iron overload↑, LPO↑	LPO(hallmark phenotype)	Gal → Nrf2 activation → ↑GPX4/FTH/xCT → ↓iron accumulation & LPO	↓Myofibril damage, ↓infarct size, ↑cardiac function	Gal loses efficacy following Nrf2 inhibition by Brusatol	[161]
Cell Death Pathways (Independent of Necroptosis)	Ferroptosis; ferrostatins (16-86, Fer-1)	Iron-dependent LPO (core execution mechanism)	Ferroptosis directly induces tubular necrosis (non-secondary event)	Acute tubular necrosis (IRI/oxalate crystal model)	Ferroptosis blockade by 16-86 provides robust protection; co-treatment yields enhanced therapeutic benefits	[162]
Protein interaction level (HSP90-GCN2-ATF4 pathway)	GPX4↓, Fe^{2+}↑, GSH↓ (direct ferroptosis markers)	Decreased GSH and increased Fe^{2+} (key evidence of redox imbalance)	HSP90↑ → GCN2-ATF4 activation → dual induction of ferroptosis and necroptosis	Exacerbated cerebral infarction, blood-brain barrier disruption, and neuronal injury	NTF confers dose-dependent protection; HSP90 overexpression abrogates the protective effect of NTF	[77]
Protein interaction level (Keap1-Nrf2 binding regulation)	GPX4↓, iron accumulation↑ (direct detection markers)	Ferroptosis-associated oxidative damage	Rg3 inhibits Keap1, activates Nrf2, upregulates GPX4, and suppresses iron deposition	Improved cardiac function and reduced myocardial infarct size	Molecular docking confirms Rg3-Keap1 binding; Nrf2 pathway plays a central regulatory role	[163]
Molecular/organelle level (mitochondrial iron transport)	GPX4 degradation and HO-1 upregulation lead to mitochondrial iron overload	Organic oxidants (tBHP/CHP) induce GSH depletion and lipid ROS accumulation	Mitochondrial translocation of HO-1 leads to iron accumulation and increased LPO	Ferroptosis in cardiomyocytes (distinct from apoptosis and necrosis)	FTMT/mCAT ↑ → ferroptosis suppression; Bach1 ↓ → HO-1 induction	[149]
Signaling pathway level (nuclear translocation of NRF2 activates HO-1 expression)	Signaling pathway level (NRF2 nuclear translocation activates HO-1)	Elevated ROS and iron accumulation (dual oxidative injury)	BCP → NRF2 nuclear localization → ↑HO-1 → inhibition of ROS and iron accumulation	Improved neurological scores, reduced cerebral infarct size, and alleviated histopathological damage	BCP loses efficacy upon NRF2 inhibition by ML385; HO-1 expression is upregulated	[164]
Membrane receptor-transcription factor level (GPR30-Nrf2 pathway)	Upregulation of GPX4, reduced iron accumulation, and decreased MDA levels	↓MDA formation (LPO marker)	GPR30 activation → Nrf2↑ → GPX4↑ → inhibition of iron overload and MDA formation	Improved neurological outcomes and reduced cerebral infarct size	Protective efficacy of G1 via GPR30 depends on Nrf2; ML385 abolishes the benefit	[75]
Dual-pathway regulatory level (independent targeting of ferroptosis and pyroptosis)	↓GPX4, ↑lipid peroxides, ↑iron accumulation	Increased lipid peroxides (key detection marker)	Raffinose → GPX4↑ → ↓LPO & ↓iron accumulation	Improved cardiac function and reduced infarct size	GPX4 upregulation confirmed; LPO and iron levels decreased	[165]
Iron transport regulatory level (transmembrane and mitochondrial iron pathways)	↑Total iron levels (↑Zip14, ↓iron efflux, ↑mitochondrial iron)	↑Oxidative stress	RRP↓Zip14 → ↑hepcidin/iron transporters → ↑Cisd1 → enhanced iron efflux	Attenuated liver injury and reduced hepatocellular death	siRNA-mediated hamp silencing enhances the effect of RRP; Cisd1 upregulation is confirmed	[166]
Organelle level (lysosome-mTOR pathway)	↑Ferritinophagy → ↑iron release and ↑LPO	Broad-spectrum ROS accumulation (key clearance target)	PMO → lysosomal enrichment → ROS clearance, iron sequestration, mTOR activation	Alleviation of drug-induced and ischemic acute liver injury	Confirmed macrophage uptake; lysosomal localization; sustained mTOR activity	[167]

Iron Metabolism/ Oxidative Damage Level (Dual-Core Regulation)	Iron accumulation ↑, LPO ↑ (MDA, 4-HNE, PTGS2)	LPO markers ↑ (MDA, 4-HNE)	Ticlopidine↓ → iron accumulation↓ → LPO↓ → ferroptosis inhibition	Hepatic necrosis/fibrosis ↓, ALT/AST ↓, inflammatory infiltration alleviated	Prussian blue staining for iron ↓; LPO markers ↓; PTGS2 ↓	[84]
Signaling/organelle level (Nrf2/SLC7A11/ GPX4 axis)	GPX4 ↓, SLC7A11 ↓, iron accumulation ↑, mitochondrial damage	LPO accumulation (hallmark of ferroptotic execution)	Lip-1 intervention during cold ischemia blocks ferroptosis pathway activation	Improved lung pathology, restored pulmonary function, and reduced inflammation	Validated in both human lung biopsies and mouse models; enhanced efficacy with cold ischemia phase intervention	[168]
Dual-pathway level (ROS scavenging + ferroptosis inhibition)	GPX4 activity ↓, GSH depletion	Increased intracellular/ mitochondrial ROS (key target)	↑HC activates Nrf2 → eliminates ROS; ↑GSH activates GPX4 → inhibits ferroptosis	Improved cardiac function, reduced fibrosis, and increased capillary density	Effective when administered prior to reperfusion; protective effect validated in erastin/RSL3 models	[169]
Transcriptional regulation level (EGR1 as a central target)	Iron overload, GSH depletion, and lipid peroxide accumulation	Lipid peroxide accumulation (no other oxidative markers mentioned)	Lip-1 ↓ EGR1 → inhibits ferroptosis	Reduced renal tubular cell death, decreased macrophage infiltration, and alleviated inflammation	EGR1 identified as a key factor; Lip-1 suppresses EGR1 expression	[170]
Preconditioning intervention level (synergistic effect of iron and IPC)	GPX4 ↓ (iron preconditioning promotes ferroptotic effect)	Iron contributes to the generation of ROS	IPC combined with iron inhibition mitigates adverse effects → confers cardioprotection	Fe-PC alone is ineffective; Fe + IPC improves LVDP recovery and provides antiarrhythmic effects	Fe-PC group: GPX4↓; Fe+IPC group: enhanced recovery of contractile function↑	[171]
Transcriptional regulation level (Nrf2 nuclear translocation and activation)	Free iron ↑, LPO ↑, GPX4 ↓	ROS ↑, LPO ↑ (dual damage)	Loureirin C → promotes Nrf2 nuclear translocation → ↑ HO-1/NQO1/GPX4	Alleviated brain injury and inhibited neuronal ferroptosis	Nrf2 knockdown attenuates protection; dose-dependent inhibition of ROS	[172]
Inflammation-iron metabolism regulation level (IL-6/hepcidin axis)	DMT1 ↑, FPN1 ↓, TfR1 ↑ → neuronal iron overload	LPO (inhibited by EE to reduce iron-induced ferroptosis)	EE↓IL-6→↓JAK2-STAT3→↓hepcidin→DMT1↓/ FPN1↑	Decreased neuronal iron levels, mitigated ferroptosis, and exerted neuroprotective effects	IEE group: hepcidin ↓; validation of altered iron transporter expression	[173]
Protein modification level (ubiquitination and methylation regulation)	GPX4 ↓, SLC7A11 ↓, iron ions ↑, oxidative stress ↑	Oxidative stress levels ↑ (general indicator)	USP7 ↓ → TBK1 ubiquitination ↓/FMR1 methylation ↓ → inhibition of ferroptosis	Cell proliferation ↑, renal function improvement, inhibition of ferroptosis	USP7 siRNA validation; TBK1/FMR1 overexpression reverses the effect	[174]

machine learning has identified a plethora of novel ALOX15 inhibitors, three FDA-approved drugs, and seven structurally different compounds with beneficial ADMET properties. This adds to the pharmacological toolbox for LPO chain targeting [121]. In addition, the necroptosis inhibitors KW-2449 and Necrostatin-1 have been shown to block ULK1-mediated autophagy, jointly suppressing both ferroptosis and necroptosis, suggesting the presence of an autophagy-centered regulatory hub between the two and providing a rationale for multi-target combination strategies [122].

The harmful involvement of ferroptosis in inflammation and tumor microenvironments should not be overlooked. For instance, when CTH is modulated positively by SENP3 it is subject to degradation owing to the removal of SUMO modification activating ferroptosis and enhancing the inflammation that drives AAA. The pathology is significantly alleviated by either SENP3 knockout or exogenous supplementation with H2S donors, e.g., ATB346 [123]. Ferroptosis activators, e.g., dihydroartemisinin and JKE1674 induced Fe^{2+} accumulation and LPO in breast cancer models resistant to FOXM1 inhibitors, leading to reversion of resistance phenotypes and inhibition of tumor cell migration and proliferation [124].

Interestingly, some clinically approved drugs have suggested new possibilities in regulating ferroptosis. The in vivo metabolism of seratrodast has led to the identification of a hydroquinone form that exhibits free radical scavenging activity. This form of seratrodast has also been shown to selectively inhibit ferroptosis without affecting apoptosis or necrosis. Notably, seratrodast has demonstrated significant renoprotective effects in murine renal IRI models. Thus, seratrodast serves as a model case for drug repurposing [125]. Ryan et al., in models of neurodegeneration, reported that microglia under iron overload displayed signs of “iron sagging” and were able to recover function by application of ferroptosis inhibitors, representing a novel target for intervention of these disorders [126]. In orthopedics, the natural substance cynarin could activate the GPX4/NRF2 signalling pathway to reduce TNF-α-induced ferroptosis in NP cells and maintain mitochondrial cristae structure and redox homeostasis, effectively slowing down intervertebral disc degeneration [127]. Ubastatin A directly inhibits the enzymatic activity of GPX4, through an HDAC6-independent mechanism, counteracts radiotherapy-induced anti-ferroptotic responses ultimately improving radiosensitivity. Favorable bioavailability and targeting potential [128]. In addition to this, the PARP inhibitor olaparib reduces SLC7A11 in a p53-dependent manner, thereby limiting GSH synthesis and inducing ferroptosis; this occurred in combination with FIN-class agents that synergistically increased the sensitivity of BRCA-wild-type ovarian cancer cells offering a potential strategy to surmount current therapeutic bottleneck [129].

Effects of novel antioxidants on IRI

Excess ROS production is considered to be an important trigger of pathological processes like LPO, mitochondrial injury, and ferroptosis during IRI. Regular antioxidants are NAC and vitamin E, which can scavenge free radicals. But unfortunately, they have low bioavailability, poor tissue penetration and lack target specificity. Thus, they are not suitable for the precision treatment of IRI. As a result, the development of structurally novel, mechanistically well-defined, and more target-specific antioxidants has gained importance in mitigating IRI damage and suppressing ferroptosis.

In recent years, natural products have proved quite effective in this area. Amphioxus polysaccharide (APS) can significantly increase the contents of GSH above the baseline. APS can also lower the level of MDA, an important structural marker in myocardial IRI-related ferroptosis, which can further inhibit ferroptosis and LPO production by upregulating GPX4 [130]. Furthermore, upregulating Nrf2 and HO-1 can reduce intracellular labile iron and improve myocardial IRI. It will involve reducing lipid peroxidation and MDA levels in the injured myocardial cells. It can also restore iron homeostasis. Either iron metabolism disorder or excess Fe^{2+} can induce lipid toxicity. It may further participate in the cell dysfunction process. Overall, APS may exert protective effects against ferroptosis via the Nrf2/GPX4 pathway, as evidenced by reduced Fe^{2+} and MDA levels. However, specific research is still necessary to confirm its validity [131]. Likewise, Eriobotrya japonica polysaccharide (EJP) at myocardial IRI model conditions significantly increased activi-

ties of SOD and glutathione peroxidase (GSH-Px), and decreased MDA, IL-6 and TNF-α levels, offered cardioprotective effects and probably renalprotective effects [132]. Of synthetic antioxidants, flavonoid derivative 13 displayed remarkable free radical scavenging activity which include higher iron-reducing capacity along with efficient scavenging of ABTS and DPPH radicals. The impact of this treatment on myocardial pathology. In particular, this treatment reduces markers of myocardial injury, LDH, CK and LPO (MDA). Furthermore, it has the effect of improving the structure and function of myocardial tissue. Overall, we see that it has high potential for clinical application [133]. Also, pre-conditioning a short-term transverse aortic constriction (TAC) can lessen myocardial IRI-induced tissue injury by promoting SIRT3-mediated deacetylation of SOD2. So, this will maintain autophagic flux and prevent the aberrant activation of autophagy. Moreover, mimicking this protective mechanism can help with SIRT3 overexpression or Beclin1 knockdown [134].

Considerable advancements have also taken place in the development of antioxidants aimed at mitochondria to combat those mitochondrial ROS. SkQ1 and MitoQ can selectively build up in the mitochondrial inner membrane, stabilize mitochondrial membrane potential, and markedly inhibit ROS generation, thereby blocking upstream ferroptosis signaling in multiple IRI animal models involving the brain, heart, and liver. The free radical scavenger edaravone, which is already in clinical use for acute cerebral infarction, has been shown to alleviate neuronal death in a cerebral ischemic model by upregulating GPX4 expression and inhibiting lipid oxidation chain reactions that are closely related to ferroptosis [120]. In addition, the creation of many nanotech-based antioxidant platforms with promising anti-ferroptosis therapeutic benefits has occurred. An example of an innovative nanomaterial with a unique design is transferrin-mineralized iridium oxide nanoaggregates (Tf-IrO_2 NAs), which exhibit dual mimicking activities of SOD, CAT, and GPX and possess the capacity to scavenge •OH. This system uses TPF-mediated targeting to pass the blood-brain barrier, eliminate ROS storms, mitigate local inflammation, and exert strong neuroprotective effects in cerebral IRI models [135].

Regulation of iron metabolism in personalized therapeutic strategies

Dysregulated iron metabolism and aberrant activation of ferroptosis are recognized as the main mechanisms underlying cellular structural damage and organ dysfunction in IRI. Studies show significant differences among individuals in their ability to regulate iron homeostasis. This variability can limit the efficacy of broad-spectrum therapeutic strategies targeting oxidation or apoptosis. As precision medicine advances, a major focus of intervention research on IRI has become the integration of iron metabolism regulation into individualized treatment systems.

The regulatory network of iron metabolism includes iron uptake (TfR1, DMT1), storage (ferritin), export (FPN), regulatory factors (hepcidin), and recycling by ferritinophagy. The expression of these molecules differs widely between individuals, tissue types and disease contexts. In MASH, a mechanism in which NOX subunit NCF1 expressed in macrophages activates hepatocyte hepcidin secretion through the oxidized phospholipid-TLR4 pathway, induces iron accumulation in Kupffer cells which in turn, leads to ferroptosis, thereby enhancing inflammation. Impact on signaling pathway by hypofunctional NCF1 p.90H. The hypofunctional NCF1 p.90H variant disrupts signaling pathway in liver. As a result, it is potential novel therapeutic target for MASH [136]. The down regulation of GPX4 expression due to combined effect of IRI and bile salt fatality through liver rather than bile duct obstruction in liver transplantation, inducing LPO and ferroptosis in cholangiocytes; administration of the ferroptosis inhibitor Lip-1 can effectively alleviate bile duct injury. In addition, bile salts have been observed to worsen iron homeostasis disturbance owing to their ferritinophagy-promoting activity in cholangiocytes, indicating that this pathway also constitutes a crucial target for postoperative intervention [137].

Iron homeostasis regulation is determined by genetic background of an organism. One example, deletion of genes such as HJV, SLC40A1 and PKLR, of pathogenic variant (not HFE) occurs in hereditary spherocytosis (HS). Iron overload is not transfusion-dependent in this case. This suggests a polygenic basis for abnor-

mal iron metabolism which also underscores the importance of larger cohorts to build improved predictions [138]. In endometriosis, studies have shown that creatine can bind to prion protein (PrP) and inhibit the conversion of Fe^{3+} to Fe^{2+}. This process then reduces iron uptake and LPO level which improve the resistance of ectopic endometrial cells to ferroptosis. The DART trial provided further support for the creatine-PrP axis as a novel target for the regulation of ferroptosis [139]. In addition, for the formation of calcium oxalate kidney stones, ER stress activates the ATF4/CHAC1 signalling pathway, leading to GSH depletion, iron accumulation, and increased LPO, driving ferroptosis. Renal injury and crystal deposition can be efficiently relieved by interventions with 4-phenylbutyric acid (4-PBA) or deletion of CHAC1, further implicating the therapeutic potential of this pathway in iron homeostasis modulation [140]. Collectively, and based on the current evidence, ferroptosis-targeted therapeutic strategies can be broadly classified into the following dimensions: inhibition of LPO/stabilization of GPX4 - iron modulation and chelation - mitochondrial and autophagy axis - inflammation/immune regulation - genetic and delivery platforms. **Table 2** presents a summary of the key targets, typical agents/approaches, types of evidence and research progress.

Discussion

Ferroptosis, a process of cell death driven by iron-dependent lipid peroxidation (LPO) that is dependent on iron, has gained more attention owing to its role in IRI. According to the evidence accumulating, with regard to IRI-induced damage in metabolically active organs like the heart, brain, liver and kidneys, the defined ferroptosis-related signalling pathways involving inhibition of GPX4, upregulation of TfR1 and activation of ACSL4 consistently show a pattern of alteration. This alteration indicates a common pathogenesis across various organs [141]. Nevertheless, despite these shared features, the regulatory mechanisms of ferroptosis exhibit marked organ-specific differences. In the myocardium, AMPK-NOX4-GPX4 axis plays a major role in governing ROS clearance as well as antioxidative regulation, brain regulation of ferroptosis relies more on Nrf2/GPX4 pathway and non-coding RNA mediated mechanisms [142]. Inflammatory microenvironment, metabolic status and cell type together determine organ-specific sensitivity to ferroptosis [143]. Clarifying these tissue-specific mechanisms is crucial for formulating more effective drug strategies. In a molecular context, oxidative stress is a main upstream trigger for ferroptosis. During the early phase of reperfusion, excessive generation of ROS results in the depolarization of mitochondrial membrane potential (MMP), LPO and ferritinophagy. The increase in the expression of TfR1/DMT1 and the downregulation of FPN result in rapid intracellular labile iron accumulation. As a result, Fenton chemistry and oxidative chain reactions intensify. The central driver of ferroptosis progression is the feedback loop involving "oxidative stress-iron metabolism dysregulation-LPO" [144], Nrf2 agonists, GPX4 stabilizers, and iron chelators have been shown to provide strong tissue-protective effects [145], suggesting that interrupting this positive feedback loop is of therapeutic value.

Notably, ferroptosis does not take place on its own but is linked to other types of programmed cell death such as apoptosis, autophagy, and pyroptosis. For instance, Gpx4 inactivation can synergistically trigger caspase-1-mediated pyroptosis, and NCOA4-mediated ferritinophagy is closely related to regulation of autophagic flux [146]. Studies have also shown that these death pathways do cross-talk and there are compensatory mechanisms, such as how inhibition of apoptosis leads to enhanced ferroptosis in some models. This shows that it could be beneficial to design interventions from a system's biology perspective that target multiple pathways.

Though many molecules involved in regulating ferroptosis have been found, targeted agents are still challenging in terms of clinical translation. The most well-known ferroptosis inhibitors, for instance Fer-1 and Lip-1 [147], have been shown to be effective in animal models; however, their stability, tissue specificity and safety still need more assessment. Additionally, a lack of highly sensitive, non-invasive biomarkers, as well as tools for real-time monitoring, limits clinical application of ferroptosis in diagnosis and therapeutic assessment. Research in the future can focus on the ongoing development of detection and drug delivery systems

Table 2. Potential therapeutic strategies for ferroptosis in IRI and research progress

Intervention category/ target	Specific drugs/ methods	Main mechanisms of action	Experimental model/ evidence source	Effect/protective effect	Research stage/remarks	References
Key proteins in the mitochondrial autophagy pathway (e.g., PINK1, PRKN, BNIP3, etc.)	Experimental inducers (e.g., CCCP) or genetic manipulation methods	Clearance of damaged mitochondria, reduction of oxidative stress, and attenuation of cell death	Various AKI models (e.g., IRI, CI-AKI, LPS, FA)	Alleviate renal injury, improve cell survival and function	In the basic research stage, with complex mechanisms and unclear interactions	[175]
OTUD5-GPX4 stabilization axis (deubiquitinase and core ferroptosis protein)	AAV-mediated OTUD5 gene delivery; OTUD5 gene knockout	OTUD5 stabilizes GPX4; mTORC1-mediated autophagic degradation of OTUD5 triggers a reduction in GPX4	Kidney I/R model; spatial transcriptomics localization; renal tubular cell study	OTUD5 deletion exacerbates ferroptosis and renal injury; AAV-OTUD5 alleviates injury and promotes recovery	Mechanistic research stage, with AAV delivery suggesting potential gene therapy approaches	[176]
Targeted inhibition of ferroptosis, involving iron metabolism and other pathways	Ferroptosis inhibitors (specific drugs not specified)	Block ferroptosis, alleviate inflammation, immune response, and neuronal damage	Mouse retinal I/R model; single-cell RNA sequencing analysis	Reduce retinal cell loss and improve retinal ganglion cell survival rate	Basic mechanistic research stage, with single-cell atlas revealing the key role of ferroptosis	[177]
IREB2 ferroptosis target and miR-29a-3p regulatory axis	HO-1/BMMSCs exosomes (containing miR-29a-3p) transplantation	Exosome delivery of miR-29a-3p targets and inhibits IREB2 to suppress ferroptosis	Fatty degeneration liver IRI model; hepatocyte H/R model; IREB2 knockdown validation	Alleviate fatty liver injury, suppress ferroptosis, and mitochondrial dysfunction	Mechanistic research stage, exosome-mediated miRNA-targeted therapy as a new strategy	[178]
Nrf2 signaling pathway (regulating TfR1/ACSL4/ antioxidant genes)	Caffeic acid (2 mg·kg^{-1}·d^{-1}, oral/injection)	Activate the Nrf2 pathway to inhibit oxidative stress/ inflammation/ferroptosis (downregulate TfR1/ACSL4)	Rat pMCAO model; SK-N-SH cell OGD/R model; ML385 reverse validation	Reduce infarct size, improve neurological function, and alleviate neuroinflammation	Preclinical research stage, with a potential therapeutic window of 2 hours after pMCAO treatment	[179]
HUWE1 ubiquitin E3 ligase and TfR1	Genetic inhibition methods such as gene knockout and chemical inhibition techniques	HUWE1 ubiquitination-mediated degradation of TfR1 regulates iron metabolism and inhibits ferroptosis	Huwe1 knockout mouse primary hepatocyte and embryonic fibroblast cell model	Alleviate liver injury, reduce ferroptosis, and protect liver function	Basic research stage with potential clinical guidance significance	[180]
Iron-dependent ferroptosis and mitochondrial permeability transition-induced necrosis	Deferoxamine and CsA, alone or in combination	Inhibit iron overload, LPO, ferroptosis, and mitochondrial necrosis	Culture of cardiomyocytes and mouse I/R injury model	Reduce infarct size and improve cardiac remodeling synergistically	Preclinical research with potential clinical application value	[181]
The Role of Actin Filaments in Ferroptosis	CK-666 and CK-636 Inhibitors	Direct Elimination of LPO to Alleviate Ferroptosis	Renal IRI Model	Improving Renal Injury and Reducing Ferroptosis	Research on Potential Therapeutic Effects	[182]
Ferroptosis, GPx4 Downregulation, and HO-1 Upregulation Targets	Targeting Ferroptosis with Drugs and Cyclosporin A Combination	GPx4 Downregulation and Iron Overload Induce Ferroptosis	In Vivo Phenotype and In Vitro Mechanism Study	Reducing Infarct Size and Improving Cardiac Remodeling	Research on Potential Therapeutic Strategies	[183]
ACSL4-Mediated Ferroptosis Pathway	Traditional Chinese Medicine Formula HJ11 Decoction	Regulating ACSL4/ Ferroptosis-Related Protein Expression	Rat Myocardial I/R Model and H9c2 Cell OGD/R Model	Improving Cardiac Function, Reducing Infarct Size, and Inhibiting Ferroptosis	Mechanism Study of Traditional Chinese Medicine in Treating Myocardial I/R Injury	[184]
Ferroptosis Pathway and LPO Targets	Natural Product Gossypol Acetate (GAA)	Chelating Iron Content, Downregulating Ptgs2, and Upregulating GPX4 Protein	Rat Myocardial I/R Model, Neonatal Rat Cardiomyocytes, and H9c2 Cells	Reducing Infarct Size, Inhibiting LPO, and Ferroptosis	Mechanism of Cellular Protection in the Preclinical Research Stage	[185]

Ferroptosis and the PKCε-Nrf2 Signaling Pathway	γ-Glutamylcysteine (γ-GC)	Activating the PKCε-Nrf2 Pathway to Increase GSH Synthesis	Rat Cerebral I/R Model	Alleviating Brain Injury Symptoms and Inhibiting LPO	Research on Potential Neuroprotective Therapies	[186]
Ferroptosis and the AMPKα2-GPX4 Pathway	Ferulic Acid (FA) Treatment	Upregulating AMPKα2 to Inhibit Ferroptosis and Improve Oxidative Stress	Rat Myocardial Ischemia/Reperfusion Injury Model	Reducing Infarct Size, Improving Cardiac Function, and Inhibiting LPO	Mechanism Study with Cardiac Protection Potential	[187]
Iron Deposition and FtMt	Gene Knockdown and Overexpression Methods	Regulating Iron Homeostasis to Reduce Iron Accumulation and Inhibit Iron Deposition	Mouse Cerebral I/R Model	Alleviating Brain Injury and Neurological Dysfunction	Providing New Potential Therapeutic Targets	[188]
Retinal Ganglion Cell Death (Ferroptosis/Apoptosis/Necroptosis)	Fer-1, z-VAD-FMK, and Necrostatin-1 Combination	Inhibiting Iron Deposition/LPO to Alleviate Programmed Cell Death	Mouse Retinal I/R Model and Primary RGC Cultures	Optimal RGC Protection by Alleviating Immune Response and ROS Accumulation	Unveiling the Death Cascade Mechanism to Guide Future Therapies	[189]
Epigenetic Regulatory Targets (PRMT1/TAF15 Axis)	PRMT1 Inhibitor or TAF15 Overexpression	Inhibiting TAF15 Methylation → Activating GPX4/NRF2 Pathway → Inhibiting Ferroptosis	Blood from AMI Patients, Mouse AMI Model, and HL-1 Cardiomyocytes	Fe^{2+}↓, MDA↓, GSH↑, Improved Cardiac Function, Reduced Infarct Size	Preclinical (Animal/Cell Validation)	[190]
Key Genes in Iron Deposition Pathway: SLC7A11, PSAT1, ASNS	No Specific Drugs Developed Yet, Providing Potential Targets	Regulating Iron-Dependent PUFA Oxidation and Degradation	GEO Database Analysis + Mouse Heart Transplantation Model of I/R	High Expression of Targets Associated with Increased Iron Deposition and I/R Injury	Mechanism Exploration and Target Discovery Stage, with Animal Model Validation	[191]
FtMt Target	FtMt Overexpression, Iron Chelator DFO	Inhibiting Iron Dysregulation and ROS Accumulation, Protecting Tight Junctions	Brain I/R Model, OGD/R Injury in bEnd.3 Cells	Alleviating Blood-Brain Barrier Disruption, Cell Apoptosis, and Tight Junction Loss	Mechanism Exploration Stage, with Animal and Cell Model Validation	[178]
OGFOD1 Gene Target	OGFOD1 Gene Knockout	Resistance to Diet-Induced Obesity and Insulin Resistance	OGFOD1 Knockout Mice Fed a High-Fat Diet	Prevention of Obesity, Insulin Resistance, and Impaired Glucose Tolerance	Mechanism Exploration Phase: Validation Using Gene Knockout Animal Models	[192]
Mitochondrial Protein mitoNEET Target	MitoNEET Ligand NL-1 (10 mg/kg Intraperitoneal Injection)	Inhibition of Hydrogen Peroxide Production and Regulation of Cellular Bioenergetics	Mouse Transient Middle Cerebral Artery Occlusion (t-MCAO) Model	Reduction of 43% in Infarct Volume and 68% in Brain Edema	Animal Model Validation Phase: Effective Only in Reperfusion Injury	[193]
CPB-Induced Ferroptosis-Related Genes	Focus on Mechanism Exploration	Regulation of Myocardial LPO Inflammatory Response and	Atrial Biopsy Before and After CPB Surgery in ToF Patients	Confirmation of CPB-Induced Cardiac Ferroptosis	Preclinical Mechanism Discovery Phase: Target Group Identification	[194]
Iron Chelation Targets/Ferroptosis Pathway	Platelet Membrane-Mimetic Liposome Platesome-DFO	Targeted Reduction of Lesional Iron Content to Inhibit Ferroptosis	Mouse Model of Cerebral I/R Injury	Reversal of Neurological Deficits; Reduction of Iron Deposition and Ferroptosis	Preclinical Study: Nanotargeted Delivery System	[195]
Circulating Endothelial Cell Ferroptosis Gene Markers	Construction of a Random Forest Diagnostic Model	Ferroptosis Genes as Diagnostic Markers for Acute Myocardial Infarction	GEO Database CECs Data and Clinical Sample Validation	The Diagnostic Model Achieved an AUC of 0.8550 (Validation Set)	Biomarker Discovery Phase: Clinical Diagnostic Application Potential	[196]

Oxidized Albumin (ox-Alb) Induces Ferroptosis	Iron Chelator DFO and Ferroptosis Inhibitor Lip-1	Triggering Downregulation of GPX4/xCT and Upregulation of ACSL4/LPO	Vitamin C/Copper Model, I/R, and Doxorubicin Nephropathy Mouse Model	ox-Alb Aggravates Renal Injury; DFO/Lip-1 Inhibit Ferroptosis	Mechanism Exploration Stage: Unveiling the Pathogenic Role of ox-Alb	[197]
Target of RNA Demethylase Alkbh5	Overexpression of Alkbh5 Gene	Reduction of m6A Methylation Promotes Fth1 Translation and Inhibits Ferroptosis	H9C2 Cell H/R Model + Rat Myocardial I/R Model	Inhibition of Ferroptosis Markers; Alleviation of Myocardial Injury	Mechanism Exploration Stage: Targeting the m6A Methylation Pathway	[198]
miRNA-541-5p Target/ Ferroptosis Pathway	Iron Chelator DFO; miRNA Inhibition	Regulation of the Expression of Ferroptosis Markers such as GPX4 and ACSL4	Rat Myocardial I/R Model + H9C2 Cell H/R Model	DFO Reverses Oxidative Stress and Ferroptosis Injury Markers	Marker Discovery Stage, miRNA-541-5p as a Diagnostic Target	[199]
Mitochondrial Fe^{2+} Chelation Detection Target	Novel Fluorescent Probe MFF (Detection Tool)	Electrophoretic Accumulation + Covalent Binding to Mitochondrial Proteins, Specific Indicator of Fe^{2+}	Hepatocyte and Multi-Cell Line ΔΨ m Model	ΔΨ m Loss Retained, Fe^{2+}-Specific Fluorescence Quenching Rate 80%	Tool Development Stage, New Technology for Live Cell Mitochondrial Iron Detection	[200]
Ferroptosis Regulation Database (FerIG) Resource Platform	Inclusion of 445 Ferroptosis-Related Drugs/Molecules	Integration of Xc-/GPX4 Axis, LPO and Iron Metabolism Data	Constructed Based on Literature Data Mining	Provides 51 Targets, 718 Regulatory Factors Disease Association Data	Database Tool Stage	[201]
Gender-Specific Targets: p53/Nrf2 Pathway	Focus on Mechanism Exploration	Psychological Stress-Induced Enhanced Cardiac Oxidative Stress and Ferroptosis in Women	Sex-specific C57BL/6 Mice Under Combined Restraint Stress and I/R	Significant Increase in Superoxide/LPO/Ptgs2 in Females	Mechanism Discovery Phase: First-time Identification of the Association Between Gender Differences and Ferroptosis	[202]
Ferroptosis-Related Subtype Markers (BECN1/ NF2 Gene Cluster)	Construction of a Six-Gene DGF Prediction Model	Metabolic Exhaustion Subtype Associated with High DGF Risk and Immune Infiltration	Clinical Dataset of Renal IRI	Prediction Model for Distinguishing DGF Risk and Guiding Patient Stratification	Clinical Prediction Model Phase: DGF Risk Assessment Based on FRGs	[203]

that will integrate nanoprobes, advanced bioimaging, and multi-omics technologies.

From a wider pathological view, ferroptosis does not only contribute to IRI, it also plays dual regulatory roles in a wide array of conditions like cancer and neurodegenerative diseases and metabolic disorders. This duality implies that ferroptosis not only executes tissue damage but also serves as a critical node in preserving cellular homeostasis, creating a good scope for therapeutics.

In the last couple of years, the strategies for suppressing and curing iron-dependent cell death (ferroptosis) that happen due to IRI have... Research has shown that antioxidant, iron homeostasis, and metabolic reprogramming have been three main strategies to inhibit ferroptosis. Nrf2/GPX4 pathway activators can greatly reduce damage caused by ischemia-reperfusion injury by increasing antioxidant ability. One natural compound whose capacity to inhibit the NRF2-KEAP1 protein interaction has been validated is tiliroside. Direct activation of the NRF2/GPX4 pathway by tiliroside effectively suppresses ferroptosis and offers renal protective effects in cisplatin and IRI-induced acute kidney injury models, providing a novel drug candidate and direct evidence for this strategy [7]. Iron chelators (deferoxamine) and blocking NCOA4-mediated ferritinophagy can effectively reduce free iron load and block the chain reaction for amplifying the Fenton reaction. This strategy has been critically validated in a human ex vivo liver IRI model; studies confirmed that the iron chelator deferoxamine reduced intrahepatic iron content and downregulated HO-1 and HIFα, thereby decreasing liver injury. At the same time, activation of energy-sensing pathways including AMPK, SIRT3, and mTOR can restore metabolic homeostasis and reduce lipid peroxidation, while interventions targeting the inflammation-ferroptosis positive feedback loop (inhibition of NLRP3 or TNF-α) can also alleviate immune cell-mediated secondary damage [148]. Future integrated strategies of nanocarrier e.g. targeted drug delivery and multi-target small molecule combination therapy together with an individualized iron metabolism profiles monitoring could lead to precise ferroptosis blockade in IRI and long-lasting functional protection. This theoretical foundation not only aids in clinical prevention and treatment but also provides a basis for future drug development along these new directions.

Informed by existing studies, we propose that ferroptosis contributing to IRI is not a simple cell death mechanism, but a hub event arising from different energy and metabolic stressors. The defining characteristic of iron homeostasis imbalance is that oxidative stress and mitochondrial dysfunction amplify each other, resulting in the establishment of a metabolism-immunity-death coupling loop. Evidence supporting this theory has emerged from studies using cardiomyocytes, showing that organic oxidant-induced oxidative stress promotes cytosolic and mitochondrial iron overload through functional activation of the Bach1/HO-1 axis, which combined with GPX4 degradation, unleashes the hallmark ferroptosis rather than other forms of cell death. Importantly, the findings revealed that moving HO-1 to the mitochondria acts as the “trigger point” for mitochondrial iron overload and lipid peroxidation, thus demonstrating that dysregulation of iron metabolism is coupled to mitochondrial dysfunction at the sub-organelle level. Additionally, in models of ischemia-reperfusion injury and doxorubicin cardiotoxicity, targeting either mitochondrial iron (driven by FTMT overexpression) or mitochondrial ROS (driven by mCAT overexpression) inhibited this process. The discovery validates mitochondria as the main executor of metabolic stress while identifying specific molecular targets to break this vicious cycle [149]. Further validation of this could pave way for the development of effective clinical strategies for the treatment of ferroptosis. Present research has lent important information in that direction. For example, in the skeletal system, spermidine (SPD) could specifically reverse excess iron-induced metabolic imbalance and differentiation inhibition in osteoblasts (MC3T3-E1) and osteoclasts (RAW264.7) via SIRT1/SOD2 activation, reducing the bone loss of aged rats. SIRT1, a pivotal metabolic sensor, plays a central nodal role in bone tissue iron metabolism disorder can be effectively intervened. Building on this, by systematically deciphering its upstream (e.g., non-coding RNAs) and downstream (immune-inflammatory factors) regulatory networks using integrated multi-omics technologies, and correlating these with individualized aging and iron overload metabolic

profiles, we can aspire to achieve precise identification and targeted intervention of ferroptosis in conditions such as senile osteoporosis. This offers a new theoretical foundation and methodological basis for clinical translation [150].

In summary, ferroptosis is an important link in the process of IRI which is regulated through oxidation stress, iron metabolism, autophagy, and immune signaling. Discovering tissue-specific signaling pathways, clarifying its crosstalk with other death pathways and formulating effective targeted interventions may open up avenues for prevention and treatment of ischemic diseases.

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Disclosure of conflict of interest

None.

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