Histol Histopathol (2025) 40: 813-823

Histology and Histopathology
From Cell Biology to Tissue Engineering

REVIEW Open Access

Ferroptosis: A key regulator and potential target for tissue injury

Ruihan Liu, Qing Luo and Guanbin Song

College of Bioengineering, Chongqing University, Key Laboratory of Biorheological Science and Technology, Ministry of Education, Chongqing, PR China

Summary. The maintenance of iron homeostasis is essential for proper body function. A growing body of evidence suggests that iron imbalance is the common denominator in many tissue injuries, including acute, chronic, and reperfusion injuries. Ferroptosis, a novel form of programmed cell death due to metabolic abnormalities, has become increasingly recognized as an important process mediating the pathogenesis and progression of numerous tissue injuries, including cerebral, myocardial, lung, liver, kidney, and intestinal injuries. Therefore, a thorough understanding of the mechanisms involved in the regulation of ferroptosis might contribute to improvements in disease management. In this review, we summarize the importance of ferroptosis in various tissue injuries, discuss the potential targets of ferroptosis in the treatment of tissue injuries, and describe the current limitations and future directions of these novel treatment targets.

Key words: Ferroptosis, Tissue injury, Tissue repair, Therapeutic strategy

Introduction

Ferroptosis is an iron-dependent, non-apoptotic cell death process that has gained significant attention since 2012, particularly regarding its mechanisms (Li and Huang, 2022). It involves disruptions in redox homeostasis and increased lipid free radicals, linking to lipid and iron metabolism as well as oxidative stress. Key biomarkers include compromised antioxidant defenses like the cystine/glutamate anti-transporter (system Xc-), glutathione (GSH), glutathione peroxidase 4 (GPX4), and ferroptosis suppressor protein 1 (FSP1) (Dixon and Olzmann, 2024). The depletion of these defenses triggers a Fenton reaction with free iron, producing toxic phospholipids that destabilize membranes. Lipid peroxidation reduces membrane integrity and fluidity, affecting membrane protein activities and allowing harmful compounds to infiltrate (Qiu et al., 2024). Ultimately, increased reactive oxygen species (ROS) and redox imbalance lead to ruptured nuclear and plasma membranes, resulting in cell death.

The inflammatory surge and alterations in the intracellular redox environment associated with ferroptosis can result in severe tissue injury. According to reports, signals of ferroptosis propagating in a wave-like manner among cells lead to extensive tissue damage (Stockwell, 2022). Research suggests that in the event of drug-induced or environmental stress-related tissue injuries, such as ischemia-reperfusion (I/R) injuries, cells tend to opt for the ferroptosis pathway to die (Fujiki et al., 2019). Consequently, the inhibition of ferroptosis may represent a potential treatment strategy for the

Corresponding Author: Guanbin Song, College of Bioengineering, Chongqing University. Key Laboratory of Biorheological Science and Technology, Ministry of Education, Chongqing 400030, PR China. e-mail: song@cqu.edu.cn

www.hh.um.es. DOI: 10.14670/HH-18-838

Abbreviations. AA, arachidonic acid; ACSL4, acyl-CoA synthetase long-chain family member 4; AdA, adrenergic acid; ALI, acute lung injury; ALR, augmenter of liver regeneration; AKI, acute kidney injury; CIRI, cerebral I/R injury; CoQ10, coenzyme Q10; CNS, central nervous system; DEX, dexmedetomidine; DFO, deferoxamine; DFR, deferasirox; FSP1, ferroptosis suppressor protein 1; GAA, gossypol acetic acid; GCS, glutamate-cysteine synthase; GPX4, glutathione peroxidase 4; GS, glutathione synthetase; GSH, glutathione; GSSG, oxidized glutathione; Hb, hemoglobin; HC, histochrome; HIRI, hepatic I/R injury; iASPP, inhibitor of apoptosis-stimulating protein of p53; IBD, inflammatory bowel disease; IIRI, intestinal I/R injury; IRE1, inositol-requiring enzyme 1; JNK, c-Jun NH2-terminal kinase; I/R, ischemia-reperfusion; LPS, lipopolysaccharide; MIRI, myocardial I/R injury; -OH, hydroxyl radicals; PIH, pyridoxal isonicotinoyl hydrazide; PTGS2, prostaglandin-endoperoxide synthase 2; PUFAs, polyunsaturated fatty acids; QCT, quercetin; ROS, reactive oxygen species; ROSI, rosiglitazone; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; STAT6, signal transducers and activators of transduction 6; System Xc-, cystine/glutamate anti-transporter; Tf, transferrin; TNF-α, Tumor necrosis factor-α; USP7, ubiquitin-specific protease 7; XN, xanthohumol.

prevention and intervention of tissue injury-related diseases.

Previous research on ferroptosis has been concentrated on oncology, aiming to eradicate tumor cells by triggering ferroptosis. However, recent findings have revealed that it is prevalent in various cell types and organs, including cerebral tissue, myocardium, lungs, liver, kidneys, and intestine. Ferroptosis has been linked to numerous diseases related to tissue damage, particularly ischemic conditions (Pan et al., 2022). This article compiles the advancements in understanding the connection between ferroptosis and tissue injury.

Ferroptosis in various tissue injuries

Ferroptosis and cerebral injury

Cerebral hemorrhage, a severe form of stroke, poses high risks of mortality and morbidity (Wan et al., 2019). Research has highlighted that post-hemorrhage secondary injuries primarily arise from inflammation-driven neurological injury and cell death triggered by free radicals, closely linked to ferroptosis (Cao et al., 2023). Following cerebral hemorrhage, hemoglobin (Hb) is released from lysed red blood cells. Microglia phagocytose Hb, leading to its metabolism into iron ions, and triggering the accumulation of ROS and lipid peroxidation. Subsequently, the excess iron ion is expelled from microglia, accumulates in neurons via the transferrin (Tf)-Tf receptor system, and reacts with hydrogen peroxide to generate highly toxic hydroxyl radicals (-OH) through the Fenton reaction. These radicals damage DNA, proteins, and lipid membranes, disrupting cell functionality (Wan et al., 2019). Furthermore, following hemorrhage, there is a significant increase in extracellular glutamate levels in neurons, disruption of the system Xc- glutamate transport balance, reduced glutamate uptake, inhibited GSH synthesis, and weakened cellular antioxidant defenses, leading to the accumulation of lipid ROS and triggering ferroptosis (Lu et al., 2022). Bioinformatics analyses have also pinpointed potential crucial genes implicated in ferroptosis during cerebral hemorrhage pathogenesis (Liu et al., 2021).

In addition to bleeding, the ischemic state also causes serious cerebral injury. Cerebral I/R injury (CIRI) represents a sequence of pathophysiological episodes occurring when blood flow is reestablished and reoxygenated. This not only directly damages cerebral tissue but also instigates a chain of pathological signaling pathways leading to inflammation and escalating cerebral tissue injury. During cerebral ischemia, oxygen scarcity in mitochondria restricts the oxidative phosphorylation process, severely diminishing the energy supply. The structure of the mitochondrial inner membrane and cristae becomes disrupted due to excessive oxygen radicals and Ca^{2+} load, leading mitochondria to produce substantial ROS and accumulate Ca^{2+}. During reperfusion, after the oxygen supply is restored, the excess ROS overwhelm the cellular antioxidant defense mechanisms, preventing the scavenging free radicals and disrupting neuronal homeostasis, which leads to inflammatory responses, oxidative stress, apoptosis, necrosis, and other pathological processes, ultimately leading to cell death (She et al., 2023). There is considerable evidence that ferroptosis plays an important role in the pathogenesis of CIRI (Liu et al., 2022; Xu et al., 2023a). It has been shown that ferroptosis occurs mainly in neurons and that oxidative stress induces neuronal ferroptosis and hyperactivation of glial cells and exacerbates CIRI (Li et al., 2023b). The pathogenesis of CIRI leads to an increased vulnerability to oxidative stress and ATP production, which impedes the maintenance of metabolic activity and system Xc- activity. Meanwhile, neuronal membranes are rich in polyunsaturated fatty acids (PUFAs), which readily lipidate hydroperoxides and induce ferroptosis (Conrad and Pratt, 2019).

These findings support that, after cerebral hemorrhage, blood accumulates and compresses the surrounding cerebral tissues, causing tissue injury, inflammation, and neuronal death, and the metabolism of released Hb forms excessive iron, causing ferroptosis. Furthermore, ischemia disrupts the redox balance in cerebral tissue, triggering ferroptosis in neuronal cells. In turn, oxidative stress, inflammation, and ferroptosis aggravate cerebral injury. Thus, the relationship between cerebral injury and ferroptosis is mutual influence and reinforcement.

Ferroptosis and myocardial injury

Myocardial infarction results from localized myocardial necrosis due to severe and persistent ischemia and hypoxia following coronary artery occlusion, leading to extensive tissue injury, heart failure, and other complications (Wang and Kang, 2021). Myocardial injury can lead to the release and accumulation of iron in the injured tissue. This accumulated iron generates ROS in cardiac tissues, triggering pathological events such as ferroptosis and inflammation (Sawicki et al., 2023). Depletion of iron transporter proteins in mouse cardiomyocytes has been reported to increase iron accumulation in the heart, resulting in heart failure (Lakhal-Littleton et al., 2015). Proteomic analysis of a mouse model of myocardial infarction revealed a significant reduction in GPX4 levels during myocardial infarction. Additionally, it has also been shown that the blockage of ferroptosis mitigates myocardial injury by reducing ROS production (Baba et al., 2018). Increased iron transporters have been found to decrease the concentration of unstable iron in cells, thus protecting the heart from oxidative stress by inhibiting ferroptosis (Nishizawa et al., 2020).

Among all types of I/R injury, ferroptosis in myocardial I/R injury (MIRI) is the most widely studied. With the development of reperfusion injury caused by hemodialysis after coronary artery occlusion,

cardiomyocytes undergo ferroptosis and release inflammatory mediators, exacerbating myocardial injury (Tang et al., 2021). Studies show that increased oxidized phosphatidylcholine leads to mitochondrial dysfunction, disrupts calcium transients, and results in extensive cardiomyocyte death via ferroptosis during MIRI (Stamenkovic et al., 2021).

These findings support that ferroptosis is associated with the onset and progression of myocardial injury (Guo et al., 2022). Inhibition of ferroptosis provides a new strategy for precision treatment of myocardial infarction. Since iron transporter proteins affect intracellular iron homeostasis, finding ways to increase their expression or transport may be a potential therapeutic target for diseases associated with cardiac ferroptosis.

Ferroptosis and lung injury

Acute lung injury (ALI) represents a condition where alveolar epithelial and capillary endothelial cells are subjected to damage due to diverse intrapulmonary and extrapulmonary causative elements, thereby prompting a spread of interstitial and alveolar edema, which subsequently leads to acute hypoxic respiratory failure. Numerous contributors, including severe pulmonary infection, pulmonary contusion, non-thoracic traumatic injury, and severe acute pancreatitis, among other direct or indirect factors, can precipitate ALI (Bos and Ware, 2022). Currently, there is no specific clinical treatment for this disease. During the pathological progression of ALI, the discharge of varied ROS coupled with free radical production can harm alveolar epithelial cells. Iron overload can enhance the conversion of hydrogen peroxide into free radicals via the Fenton reaction, consequently facilitating the progression of ALI (Yin et al., 2021). Ferroptosis has been demonstrated to be present in several animal or cellular models of ALI. It has been shown that after lipopolysaccharide (LPS) intervention in the bronchial epithelial cell line BEAS-2B, there is down-regulation of ferroptosis-associated protein solute carrier family 7 member 11 (SLC7A11) and GPX4, whereas the levels of malondialdehyde and total iron are significantly increased in a dose-dependent manner (Liu et al., 2020). Similar conclusions were reached in an ALI model established by intratracheal or intravenous injection of LPS (Dong et al., 2023).

The lung, a highly susceptible organ, is frequently impacted by I/R injury. Existing evidence demonstrates that inhibiting acyl-CoA synthetase long-chain family member 4 (ACSL4), a ferroptosis marker, attenuates ferroptosis after pulmonary I/R (Chen et al., 2017; Xu et al., 2020a). A recent study demonstrated that suppressing ferroptosis can diminish lung I/R injury by activating the Nrf2/HO-1 signaling axis (Wang et al., 2022). These findings endorse the potential of ferroptosis as a therapeutic target for lung injury, thereby asserting the therapeutic promise of ferroptosis inhibitors.

Ferroptosis and liver injury

Liver iron overload has long been recognized as a significant instigator of liver injury across diverse diseases. One investigation employed transmission electron microscopy to scrutinize mitochondrial morphology in hepatocytes and identified the presence of ferroptosis within a mouse model of liver injury (Li et al., 2020b). Evidence revealed that the activation of the Nrf2 signaling pathway fostering autophagy can oppose ferroptosis, thereby mitigating liver injury (Liu et al., 2023). Additionally, bolstering macrophage resistance to ferroptosis by inhibiting ferritin autophagy and suppressing autophagosome-lysosome fusion can alleviate acute liver injury (Li et al., 2023a). Furthermore, the suppression of ferroptosis via the inhibition of oxidative stress-induced autophagy may alleviate liver injury (Huang et al., 2023).

Hepatic I/R injury (HIRI), a special liver injury, is characterized by a complex cascade of events, including mitochondrial de-energization, depletion of adenosine-2'-triphosphate, alterations in electrolyte homeostasis, Kupffer cell activation, changes in oxidative stress, and the upregulation of inflammatory cytokine signaling. It was discovered that iron overload is concurrent with HIRI and produces ROS and lipid peroxides in the body (Luo et al., 2021). Initially, ROS is produced in Kupffer cells, executing hepatocytes via lipid peroxidation, DNA oxidation, and enzymatic denaturation (Papadopoulos et al., 2013). Additionally, the subsequent discharge of tumor necrosis factor-α (TNF-α) from ROS can intensify injury following I/R by stimulating the further release of inflammatory cytokines. Notably, ROS can also stimulate the NF-κB signaling pathway to promote HIRI (Hu et al., 2023). Therefore, it can be inferred that the inhibition of ferroptosis may potentially provide a therapeutic avenue for the treatment of liver injury.

Ferroptosis and kidney injury

Acute kidney injury (AKI) is a critical disease with high morbidity and mortality rates. Commonly recognized pathogenic mechanisms underpinning AKI encompass vasoconstriction, oxidative stress, apoptosis, and inflammation (Hu et al., 2019). Apart from blood purification, few treatments have exhibited substantial progress in thwarting AKI. Consequently, an urgent requirement persists for novel targets or improved regimens to treat AKI. Multiple molecular mechanisms have been speculated to incite or exacerbate AKI. ROS is considered one of the pivotal mediators. Numerous investigations have proposed ferroptosis as a promising therapeutic target, notably within diseases governed by tubular necrosis (Sanz et al., 2023). Recently, in a study utilizing inducible GPX4-deficient mice, massive tubular cell death and acute renal failure were observed following GPX4 deficiency. However, the survival of GPX4-deficient mice was extended by approximately 35% through the *in vivo* elimination of lipid peroxides

(Friedmann Angeli et al., 2014), further suggesting the significant influence of ferroptosis on kidney injury.

The pathophysiology of renal I/R injury includes inflammation, oxidative stress, lipid peroxidation, mitochondrial dysfunction, renin-angiotensin system activation, and accumulation of nitrite and nitric oxide (Li et al., 2022). Studies have reported that renal I/R injury-induced ferroptosis is mediated by augmenter of liver regeneration (ALR), which is associated with the GPX4 system. Silencing of the ALR gene resulted in increased mitochondrial injury, decreased GPX4 activity, and promoted ferroptosis (Huang et al., 2022). Another study also showed that ferroptosis plays an important role in renal I/R injury and can be prevented through the inhibition of the inositol-requiring enzyme 1 (IRE1)/c-Jun NH2-terminal kinase (JNK) pathway (Liang et al., 2022). Single-cell RNA sequencing showed predominant expression of ferroptosis-associated genes in renal tubular epithelium post I/R injury. In stark contrast, a scarcity of expression was observed for genes related to necroptosis and apoptosis (Zhao et al., 2020). Thus, ferroptosis introduces a fresh therapeutic perspective for kidney injury. Ferroptosis inhibition offers potential benefits in preventing or ameliorating renal injury triggered by diverse factors.

Ferroptosis and intestinal injury

Inflammatory bowel disease (IBD) is a non-specific and chronic inflammatory disease of the gastrointestinal tract of unknown factors, characterized by cytopenia, villous atrophy, and inflammation of the intestinal mucosa. The aberrant death of small intestinal epithelial cells compromises the intestinal barrier and exacerbates the inflammatory response. Besides apoptosis, necroptotic apoptosis, and pyroptosis, ferroptosis has been observed in small intestinal epithelial cells from inflamed sites in patients diagnosed with ulcerative colitis (Xu et al., 2020b). Crucial events of ferroptosis, such as iron accumulation, lipid peroxidation, and GPX4 inactivation, have been implicated in the pathogenesis of IBD (Wang et al., 2020). Small intestinal epithelial cells, isolated from ulcerative colitis patients and mice with colitis, exhibit an increase in Prostaglandin endo-peroxide synthase 2 (PTGS2) and a decrease in GPX4, which are recognized as biomarkers of ferroptosis. Similarly, ferroptosis occurrence in small intestinal epithelial cells has been linked to dextran sodium sulfate-induced colitis in mice (Zhang et al., 2022).

Intestinal I/R injury (IIRI) can be caused by severe trauma, extensive burns, severe infections, shock, intestinal obstruction, and cardiac surgery. Such an injury triggers the destruction of the intestinal mucosal barrier, translocation of intestinal bacteria and toxins, and subsequent release of numerous cytokines and inflammatory mediators into the bloodstream, inducing systemic inflammatory response and distant organ injury. Ischemia-caused ACSL4 activation has been manifested to instigate ferroptosis-mediated tissue damage in intestinal I/R (Li et al., 2019). To enhance the clinical relevance of the results, transcriptome sequencing from patients with IIRI was used for validation. These results indicated a strong link between ferroptosis and IIRI (Zhu et al., 2022). Taken together, the pathological evidence of ferroptosis in small intestinal epithelial cells signifies its potential as a therapeutic target for various intestinal injuries.

Therapeutic strategies targeting ferroptosis-mediated tissue injury

Based on the aforementioned studies, ferroptosis plays a vital role in the progression of tissue injury. In different organs and tissues, cell death leads to the destruction of parenchymal cells, which is a key step in the process of tissue injury. Lipid peroxidation, GPX4 inhibition, and iron accumulation accompanied by ferroptosis will destroy cell homeostasis, leading to the abnormal accumulation of inflammatory factors in tissues and promoting the injury of tissues and organs. Inflammation, excessive oxidation, and iron overload link ferroptosis with tissue injury, indicating that ferroptosis may be one of the important mechanisms regulating diseases associated with tissue injury. In different tissues and organs, ferroptosis affects tissue injury through various mechanisms. It has been reported that ferroptosis and its regulatory factors are effective strategies for treating various tissue injuries (Table 1).

Targeting iron metabolism

Iron is crucial for cell survival, participating in vital biological functions like electron transfer, cellular respiration, DNA synthesis, cell growth, differentiation, and gene regulation. The processes of maintaining and regulating iron homeostasis are complex. Excess accumulation of iron ions increases ROS levels through the Fenton reaction, in which Fe^{2+} and hydrogen peroxide form Fe^{3+} and hydroxyl radicals in a non-enzymatic process, which affects iron stability and promotes iron deposition in vital organs, leading to severe organ injury (Djulbegovic and Uversky, 2019). In the presence of iron overload, iron chelators have demonstrated efficacy in preventing and reversing ferroptosis-mediated tissue injuries.

Deferoxamine (DFO) attenuates ferroptosis and neuroinflammation by reducing iron accumulation as a way to reduce cerebral hemorrhage-induced cerebral injury (Imai et al., 2021), including edema formation (Jia et al., 2023), neuronal death, cerebral atrophy (Hatakeyama et al., 2013), and neurological deficit (Li et al., 2017). It has been shown that iron chelation therapy improves cardiac contractile function, increases cell viability, inhibits myocardial remodeling, and reduces infarct size after I/R injury (Parra-Flores et al., 2019). In a model of LPS-induced ALI, DFO removes excess iron from lung tissue to maintain iron homeostasis in cells and inhibit ferroptosis (Ritter et al., 2006). Furthermore,

hepatic I/R injury was attenuated by DFO (Yamada et al., 2020). Deferasirox (DFR) is a newer trivalent ferroptosis chelator than DFO, and it significantly inhibits intracellular Fe^{2+} accumulation and cell death induced by hemoglobin exposure. It has been demonstrated that DFR can inhibit iron-catalyzed oxygen radical formation and alleviate acute liver injury (Cerna et al., 2011). Additionally, pyridoxal isonicotinoyl hydrazide (PIH), a lipophilic iron chelator, reduced excess iron-induced cytotoxicity. PIH has a preventive effect in a mouse model of cerebral hemorrhage (Zhang et al., 2021c). The interaction between Tau and iron can inhibit iron overload and suppress I/R-related toxicity (Tuo et al., 2017). Moreover, quercetin (QCT) specifically interacts with the autophagy cargo receptor NCOA4, blocking the degradation of the iron storage protein FTH1, thereby downregulating intracellular iron levels and ferroptosis, and ultimately alleviating dopaminergic neuronal death (Lin et al., 2022a). Lastly, histochrome (HC) is a water-

Table 1. Therapeutic strategies targeting ferroptosis in tissue injury.

Therapeutic Drugs	Diseases	Key Mechanism	References
Deferoxamine (DFO)	Cerebral, Myocardial, Liver, and Lung Injury	Inhibit iron overload	Ritter et al., 2006; Hatakeyama et al., 2013; Li et al., 2017; Parra-Flores et al., 2019; Yamada et al., 2020; Imai et al., 2021; Jia et al., 2023
Liproxstatin-1 (Lip-1)	Myocardial, Lung, Liver, Kidney, and Intestinal Injury	Reduce lipid peroxidation and upregulate the GPX4 expression	Friedmann Angeli et al., 2014; Li et al., 2019; Xu et al., 2020a,b; Li et al., 2021; Zhang et al., 2021b
Ferroinhibitor-1 (Fer-1)	Cerebral, Myocardial, Liver, Lung, and Kidney Injury	Reduce lipid peroxidation and upregulate the GPX4 expression	Xie et al., 2019; Liu et al., 2020; Yamada et al., 2020; Luo et al., 2022; Xie et al., 2022
Gossypol acetic acid (GAA)	Myocardial, Liver Injury	Reduce lipid peroxidation and decrease the ACSL4 expression	El-Sharaky et al., 2009; Lin et al., 2021
Rosiglitazone (ROSI)	Lung, Intestinal Injury	Reduce lipid peroxidation	Li et al., 2019; Xu et al., 2020a
Pyridoxal isonicotinoyl hydrazide (PIH)	Cerebral Injury	Reduce iron accumulation	Zhang et al., 2021c
Tau	Cerebral Injury	Inhibit iron overload	Tuo et al., 2017
Quercetin (QCT)	Cerebral Injury	Downregulate iron levels and upregulate FTH1 expression	Lin et al., 2022a
Selenium	Cerebral Injury	Upregulate the GPX4 expression	Alim et al., 2019
Bioflavonoids	Cerebral Injury	Upregulate the GPX4 expression and inhibit the ACSL4 expression.	Pan et al., 2022
Histochrome (HC)	Myocardial Injury	Downregulate iron levels	Hwang et al., 2021
Xanthohumol (XN)	Myocardial Injury	Inhibit lipid peroxidation and upregulate the GPX4 expression	Lin et al., 2022
Dexmedetomidine (DEX)	Myocardial Injury	Regulate SLC7A11/GPX4 pathway	Yu et al., 2022
Hydroxy saffron yellow A	Myocardial Injury	Regulate HIF-1α/SLC7A11/GPX4 pathway	Ge et al., 2023
Ginsenosides	Myocardial Injury	Regulate miR-144-3p/SLC7A11 pathway	Ye et al., 2023
Ubiquitin-specific protease 7 (USP7)	Myocardial Injury	Upregulate p53/TfR1 pathway	Tang et al., 2021
Deferasirox (DFR)	Liver Injury	Inhibit iron overload	Cerna et al., 2011
α-tocopherol	Liver Injury	Reduce lipid peroxidation	Yamada et al., 2020
Irisin	Kidney Injury	Upregulate the GPX4 expression	Zhang et al., 2021a
Entacapone	Kidney Injury	Upregulate the SLC7A11 expression	Yang et al., 2022b
Ginsenoside Rg1	Kidney Injury	Regulate FSP1-CoQ10-NAD(P)H pathway	Guo et al., 2024
Andrographolide	Kidney Injury	Regulate Nrf2/FSP1 pathway	Zhang et al., 2024
Inhibitor of apoptosis-stimulating protein of p53 (iASPP)	Lung Injury	Regulate Nrf2/HIF-1/TF pathway	Li et al., 2020a
Nobiletin/Signal transducer and activators of transduction 6 (STAT6)	Lung Injury	Regulate p53/SLC7A11 pathway	Yang et al., 2022a; Chen et al., 2024

soluble form of echinodermal pigment A with strong ferroptosis-chelating and antioxidant properties. Hwang et al. recently found that the administration of HC inhibited ferroptosis, thereby protecting the myocardium (Hwang et al., 2021).

These findings underscore the prospective advantages of addressing iron homeostasis for therapeutic intervention in ferroptosis-associated conditions. Iron chelation therapy, aiming to limit free iron availability, has shown promise. However, it is not without its limitations. For instance, although DFO can chelate excess iron, its poor cell membrane permeability hinders its effectiveness in accessing intracellular sites where iron might promote ferroptosis. Additionally, its short half-life makes drug delivery difficult, particularly for conditions impacting the neurological system, along with the inherent challenges posed by the blood-brain barrier (Hamilton et al., 2016; Chen et al., 2020). Hence, there is a pressing need for more targeted and effective therapeutic agents.

Targeting lipid metabolism

Lipids are vital components of cell membranes, especially in the central nervous system (CNS), which is particularly vulnerable to lipid peroxidation (Anthonymuthu et al., 2016). This process occurs when oxygen or hydrogen peroxide reacts with lipids, leading to the formation of free PUFAs, notably arachidonic acid (AA) and adrenergic acid (AdA). Enzymes like ACSL4 and lysophosphatidylcholine acyl-transferase 3 (LPCAT3) convert these PUFAs into toxic lipid peroxides (Gaschler and Stockwell, 2017). These lipid peroxides decompose into toxic aldehydes, which impair the fluidity and permeability of cell membranes (Geng et al., 2021). GPX4 is a GSH-dependent enzyme that reduces lipid peroxides, maintaining membrane fluidity and protecting cells from lipid ROS. It converts GSH to oxidized glutathione (GSSG) and reduces lipid peroxides to alcohols, linking it to tissue injury and ferroptosis regulation.

Alim et al. showed that selenium enhances GPX4 expression, providing neuroprotection (Alim et al., 2019). Rehmannioside A, bioflavonoids including galangin, carthamin yellow, and kaempferol, have been shown to ameliorate I/R-induced neuronal ferroptosis by upregulating the GPX4 axis or inhibiting ACSL4 expression (Pan et al., 2022). Lip-1, a ferroptosis inhibitor, reduces ischemic cardiomyocyte death and alleviates lung injury by enhancing GPX4 levels and reducing ROS (Xu et al., 2020a; Li et al., 2021). It also protects against liver and intestinal injuries and prevents acute renal failure from kidney I/R injury (Friedmann Angeli et al., 2014; Li et al., 2019; Zhang et al., 2021b). Studies have shown that Fer-1, another specific ferroptosis inhibitor, effectively inhibits lipid peroxidation and significantly prevents ferroptosis-mediated tissue injury (Xie et al., 2019; Liu et al., 2020; Yamada et al., 2020; Luo et al., 2022; Xie et al., 2022). Additionally, α-tocopherol has been demonstrated to alleviate HIRI by inhibiting lipid peroxidation (Yamada et al., 2020). Xanthohumol (XN), an isoprenylated flavonoid derived from Humulus lupulus, exhibits various pharmacological effects, including inhibition of lipid peroxidation. Recent evidence suggests that XN protects cardiomyocytes from ferroptosis by inhibiting lipid peroxidation and ROS production, chelating iron, and modulating Nrf2 and GPX4 (Lin et al., 2022b). Administration of the ACSL4 inhibitor rosiglitazone (ROSI) suppressed ACSL4 expression and reduced lung injury (Xu et al., 2020a). Pretreatment with ROSI also ameliorated intestinal injury by modulating GPX4 and PTGS2 expression (Li et al., 2019). Gossypol acetic acid (GAA), a natural compound extracted from cotton seeds, has been shown to inhibit oxidation and lipid peroxidation in rat liver tissue (El-Sharaky et al., 2009), reducing ferroptosis-induced cardiomyocyte death (Lin et al., 2021). Irisin treatment has been found to attenuate kidney injury in mice by upregulating GPX4 expression (Zhang et al., 2021a).

The above research shows that lipid metabolism plays widespread roles in the pathophysiological processes of tissue injury and holds immense research potential. Decreased GPX4 activity is often positively correlated with oxidative stress and the increase of ferroptosis processes in tissue injury. Targeting GPX4 activity could serve as an important and promising therapeutic approach to inhibit ferroptosis. However, the lipid mechanisms underlying ferroptosis are complex and not fully understood, warranting further research and exploration. In addition, the therapeutic effects of some plant metabolites are also worth further exploration.

Targeting glutathione metabolism

GSH plays an important role in cellular redox balance. The synthesis of GSH occurs in two steps: the first is facilitated by γ-glutamate-cysteine synthase (γ-GCS), which catalyzes the linkage of glutamate and cysteine. The second step consists of the addition of glycine by glutathione synthetase (GS) (Averill-Bates, 2023). System Xc- is a heterodimeric transmembrane complex consisting of the light-chain SLC7A11 and the heavy-chain solute carrier family 3 member 2 (SLC3A2). This system exchanges extracellular cystine (oxidized cysteine, a precursor for GSH synthesis) for intracellular glutamate at a 1:1 ratio (Li et al., 2023c). Once inside the cell, cystine is reduced to cysteine by GSH or thioredoxin 1, preparing it for the subsequent synthesis of GSH through the aforementioned two steps. Inhibition of system Xc- affects cystine uptake, thereby limiting GSH biosynthesis and ultimately leading to GSH depletion.

Studies have shown that hydroxy saffron yellow A inhibits ferroptosis and attenuates MIRI in mice via activation of the HIF1α/SLC7A11/GPX4 signaling pathway (Ge et al., 2023). Similarly, ginsenosides reduce MIRI-induced ferroptosis through the miR-144-3p/

SLC7A11 pathway (Ye et al., 2023). Dexmedetomidine (DEX), a selective α2-adrenergic receptor, alleviates myocardial injury by inhibiting ferroptosis through the promotion of the SLC7A11/GPX4 axis (Yu et al., 2022). Furthermore, recent studies have found that entacapone reverses ferroptosis and alleviates AKI by upregulating SLC7A11 to enhance antioxidant capacity (Yang et al., 2022b).

As mentioned above, SLC7A11-mediated cystine uptake is critical for cells to suppress ferroptosis and to maintain redox homeostasis and biomass incorporation. Therefore, SLC7A11 has emerged as a promising therapeutic target in tissue injury therapy. Moreover, ferroptosis inhibitors, targeting other molecules in GSH metabolism, remain to be discovered.

Other pathways

Coenzyme Q10 (CoQ10) and NAD(P)H are crucial for reduction reactions and have significant roles in ferroptosis. CoQ10, a fat-soluble antioxidant, protects proteins, lipids, and DNA from oxidative damage (Pallotti et al., 2021). NADPH is an important intracellular reducing agent. Recent studies have found that FSP1 utilizes NAD(P)H to regenerate CoQ10 and inhibit ferroptosis (Bersuker et al., 2019). It has been shown that Ginsenoside Rg1 and Andrographolide attenuated sepsis-induced AKI by inhibiting ferroptosis through the FSP1 pathway (Guo et al., 2024; Zhang et al., 2024).

Furthermore, the protein p53, known for its roles in tumor suppression, cell cycle inhibition, senescence, and apoptosis, is also implicated in ferroptosis. The *SLC7A11* gene is a potential target of p53 (Xu et al., 2023b). Tang et al. proposed that the upregulation of ubiquitin-specific protease 7 (USP7) activates the p53/TfR1 pathway to promote ferroptosis in a rat model of MIRI (Tang et al., 2021). Li et al. found that the inhibitor of apoptosis-stimulating protein of p53 (iASPP) mediated ferroptosis through the Nrf2/HIF-1/TF pathway, exerting a protective effect and reducing lung tissue edema, atelectasis, necrosis, and inflammation in ALI (Li et al., 2020a). Nobiletin ameliorates heatstroke-induced ALI by inhibiting ferroptosis through the p53/SLC7A11 pathway (Chen et al., 2024). Furthermore, signal transducers and activators of transduction 6 (STAT6) inhibit ferroptosis and alleviate ALI by regulating the p53/SLC7A11 pathway (Yang et al., 2022a).

Together, although preclinical studies have established the proof of concept to inhibit ferroptosis in tissue injury therapy, there is still a significant need to further identify potent and specific inhibitors, study their mechanisms of action, test them in rigorous preclinical models, and eventually apply them to clinical care.

Conclusions and Prospectives

Ferroptosis is a novel type of cell death that has

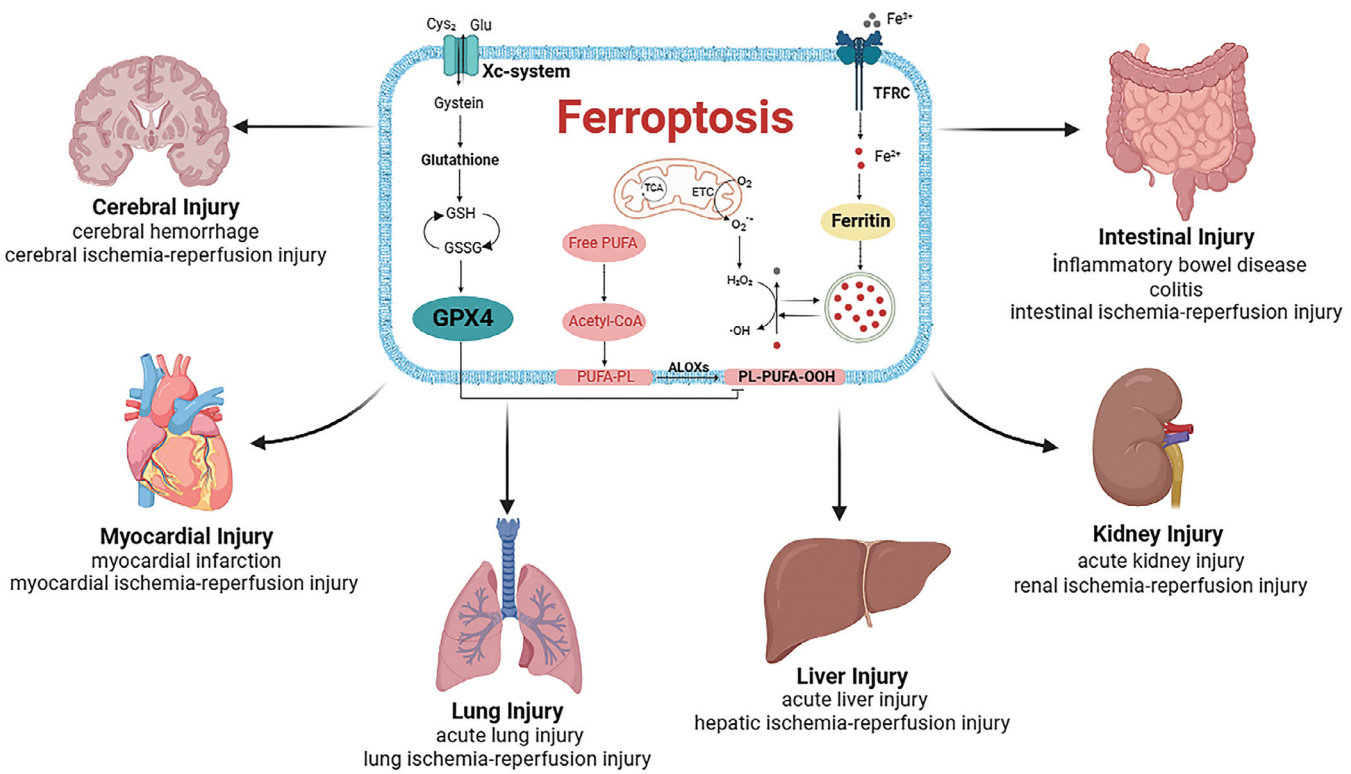

Fig. 1. Ferroptosis has been linked to a variety of tissue injuries, including cerebral, myocardial, lung, liver, kidney, and intestinal. Glutathione metabolism, lipid metabolism, and iron metabolism are the primary pathways influencing ferroptosis.

received much attention in recent years. In this review, we summarized the role of ferroptosis in various tissue injuries, including cerebral, myocardial, lung, liver, kidney, and intestinal injuries (Fig. 1). Research indicates that targeting ferroptosis could be a promising therapeutic strategy, with a focus on inhibiting iron metabolism and lipid peroxidation. Recent studies have shown that ferroptosis modulators can have therapeutic effects; however, most studies have been limited to cellular and animal models, lacking clinical evidence and an incomplete understanding of the specific mechanisms involved. Thus, clinical studies are essential to translate these findings into therapeutic applications. Currently, the use of ferroptosis inhibitors in humans is hampered by issues such as toxicity, instability, and short half-lives, underscoring the need to develop non-toxic and long-acting inhibitors. Additionally, the development of assays for the routine clinical diagnosis of ferroptosis is important. Identifying biomarkers of ferroptosis could assist in the early detection and diagnosis of tissue injury diseases.

In summary, ferroptosis undoubtedly plays a crucial role in the progression of tissue injuries. However, the impact of ferroptosis on diseases exacerbated by tissue injuries requires further investigation. Comprehensive and in-depth research is pivotal to better understanding the relationship between ferroptosis-regulating molecules and tissue injury, thereby providing a theoretical foundation for future treatment.

Acknowledgements. This work was supported by the Fundamental Research Funds for the Central Universities (2020CDJ-LHZZ-029). We thank Ms. Chunxia Zhang (Sichuan International Studies University, China) for the linguistic review of the manuscript.

Conflict of Interest. The authors declare no conflict of Interest.

Author Contributions. Conceptualization, R.L. and G.S; investigation and literature review., R.L. and Q.L.; writing-original draft preparation, R.L.; writing-review and editing, G.S.; All authors have read and agreed to the version of the manuscript.

References

Alim I., Caulfield J.T., Chen Y., Swarup V., Geschwind D.H., Ivanova E., Seravalli J., Ai Y., Sansing L.H., Ste Marie E.J., Hondal R.J., Mukherjee S., Cave J.W., Sagdullaev B.T., Karuppagounder S.S. and Ratan R.R. (2019). Selenium drives a transcriptional adaptive program to block ferroptosis and treat stroke. Cell 177, 1262-1279.

Anthonymuthu T.S., Kenny E.M. and Bayir H. (2016). Therapies targeting lipid peroxidation in traumatic brain injury. Brain Res. 1640, 57-76.

Averill-Bates D.A. (2023). The antioxidant glutathione. Vitam. Horm. 121, 109-141.

Baba Y., Higa J.K., Shimada B.K., Horiuchi K.M., Suhara T., Kobayashi M., Woo J.D., Aoyagi H., Marh K.S., Kitaoka H. and Matsui T. (2018). Protective effects of the mechanistic target of rapamycin against excess iron and ferroptosis in cardiomyocytes. Am. J. Physiol. Heart Circ. Physiol. 314, H659-H668.

Bersuker K., Hendricks J.M., Li Z., Magtanong L., Ford B., Tang P.H., Roberts M.A., Tong B., Maimone T.J., Zoncu R., Bassik M.C., Nomura D.K., Dixon S.J. and Olzmann J.A. (2019). The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis. Nature 575, 688-692.

Bos L.D.J. and Ware L.B. (2022). Acute respiratory distress syndrome: Causes, pathophysiology, and phenotypes. Lancet 400, 1145-1156.

Cao Y., Xiao W., Liu S. and Zeng Y. (2023). Ferroptosis: Underlying mechanism and the crosstalk with other modes of neuronal death after intracerebral hemorrhage. Front. Cell. Neurosci. 17, 1080344.

Cerna P., Kotyzova D. and Eybl V. (2011). The effect of the oral iron chelator deferiprone on the liver damage induced by tamoxifen in female rats. Hemoglobin 35, 255-261.

Chen K., Xu Z., Liu Y., Wang Z., Li Y., Xu X., Chen C., Xia T., Liao Q., Yao Y., Zeng C., He D., Yang Y., Tan T., Yi J., Zhou J., Zhu H., Ma J. and Zeng C. (2017). Irisin protects mitochondria function during pulmonary ischemia/reperfusion injury. Sci. Transl. Med. 9, eaao6298.

Chen X., Yu C., Kang R. and Tang D. (2020). Iron metabolism in ferroptosis. Front. Cell Dev. Biol. 8, 590226.

Chen H., Xie W., Peng Z., Liu Y., Li H. and Huang W. (2024). Nobiletin ameliorates heatstroke-induced acute lung injury by inhibiting ferroptosis via p53/slc7a11 pathway. Shock 61, 105-111.

Conrad M. and Pratt D.A. (2019). The chemical basis of ferroptosis. Nat. Chem. Biol. 15, 1137-1147.

Dixon S.J. and Olzmann J.A. (2024). The cell biology of ferroptosis. Nat. Rev. Mol. Cell Biol. 25, 424-442.

Djulbegovic M.B. and Uversky V.N. (2019). Ferroptosis - an iron- and disorder-dependent programmed cell death. Int. J. Biol. Macromol. 135, 1052-1069.

Dong X., Li D., Fang Z., Zhang C., Wang J. and Wan X. (2023). Astaxanthin alleviates lipopolysaccharide-induced acute lung injury by suppressing ferroptosis. Food Funct. 14, 6115-6127.

El-Sharaky A.S., Wahby M.M., Bader El-Dein M.M., Fawzy R.A. and El-Shahawy I.N. (2009). Mutual anti-oxidative effect of gossypol acetic acid and gossypol-iron complex on hepatic lipid peroxidation in male rats. Food Chem. Toxicol. 47, 2735-2741.

Friedmann Angeli J.P., Schneider M., Proneth B., Tyurina Y.Y., Tyurin V.A., Hammond V.J., Herbach N., Aichler M., Walch A., Eggenhofer E., Basavarajappa D., Radmark O., Kobayashi S., Seibt T., Beck H., Neff F., Esposito I., Wanke R., Forster H., Yefremova O., Heinrichmeyer M., Bornkamm G.W., Geissler E.K., Thomas S.B., Stockwell B.R., O'Donnell V.B., Kagan V.E., Schick J.A. and Conrad M. (2014). Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice. Nat. Cell Biol. 16, 1180-1191.

Fujiki K., Inamura H., Sugaya T. and Matsuoka M. (2019). Blockade of ALK4/5 signaling suppresses cadmium- and erastin-induced cell death in renal proximal tubular epithelial cells via distinct signaling mechanisms. Cell Death Differ. 26, 2371-2385.

Gaschler M.M. and Stockwell B.R. (2017). Lipid peroxidation in cell death. Biochem. Biophys. Res. Commun. 482, 419-425.

Ge C., Peng Y., Li J., Wang L., Zhu X., Wang N., Yang D., Zhou X. and Chang D. (2023). Hydroxysafflor yellow a alleviates acute myocardial ischemia/reperfusion injury in mice by inhibiting ferroptosis via the activation of the HIF-1α/SLC7A11/GPX4 signaling pathway. Nutrients 15, 3411.

Geng Z., Guo Z., Guo R., Ye R., Zhu W. and Yan B. (2021). Ferroptosis and traumatic brain injury. Brain Res. Bull. 172, 212-219.

Guo Y., Zhang W., Zhou X., Zhao S., Wang J., Guo Y., Liao Y., Lu H., Liu J., Cai Y., Wu J. and Shen M. (2022). Roles of ferroptosis in

cardiovascular diseases. Front. Cardiovasc. Med. 9, 911564.

Guo J., Chen L. and Ma M. (2024). Ginsenoside Rg1 suppresses ferroptosis of renal tubular epithelial cells in sepsis-induced acute kidney injury via the FSP1-CoQ10- NAD(P)H pathway. Curr. Med. Chem. 31, 2119-2132.

Hamilton J.L., Imran Ul-Haq M., Abbina S., Kalathottukaren M.T., Lai B.F., Hatef A., Unniappan S. and Kizhakkedathu J.N. (2016). *In vivo* efficacy, toxicity and biodistribution of ultra-long circulating desferrioxamine based polymeric iron chelator. Biomaterials 102, 58-71.

Hatakeyama T., Okauchi M., Hua Y., Keep R.F. and Xi G. (2013). Deferoxamine reduces neuronal death and hematoma lysis after intracerebral hemorrhage in aged rats. Transl. Stroke Res. 4, 546-553.

Hu Z., Zhang H., Yang S.K., Wu X., He D., Cao K. and Zhang W. (2019). Emerging role of ferroptosis in acute kidney injury. Oxid. Med. Cell. Longev. 2019, 8010614.

Hu Q.Z., Cao Z.R., Zheng W.X., Zhao M.J., Gong J.H., Chen C., Wu Z.J. and Tao R. (2023). HSP110 aggravates ischemia-reperfusion injury after liver transplantation by promoting NF-κB pathway. Hepatobiliary Pancreat. Dis. Int. 23, 344-352.

Huang Y.B., Jiang L., Liu X.Q., Wang X., Gao L., Zeng H.X., Zhu W., Hu X.R. and Wu Y.G. (2022). Melatonin alleviates acute kidney injury by inhibiting NRF2/Slc7a11 axis-mediated ferroptosis. Oxid. Med. Cell. Longev. 2022, 4776243.

Huang T., Zhang K., Wang J., He K., Zhou X. and Nie S. (2023). Quercetin alleviates acrylamide-induced liver injury by inhibiting autophagy-dependent ferroptosis. J. Agric. Food Chem. 71, 7427-7439.

Hwang J.W., Park J.H., Park B.W., Kim H., Kim J.J., Sim W.S., Mishchenko N.P., Fedoreyev S.A., Vasileva E.A., Ban K., Park H.J. and Baek S.H. (2021). Histochrome attenuates myocardial ischemia-reperfusion injury by inhibiting ferroptosis-induced cardiomyocyte death. Antioxidants 10, 1624.

Imai T., Tsuji S., Matsubara H., Ohba T., Sugiyama T., Nakamura S., Hara H. and Shimazawa M. (2021). Deferasirox, a trivalent iron chelator, ameliorates neuronal damage in hemorrhagic stroke models. Naunyn Schmiedebergs Arch. Pharmacol. 394, 73-84.

Jia H., Liu X., Cao Y., Niu H., Lan Z., Li R., Li F., Sun D., Shi M., Wa L., Liu X., Yang G., Chen F., Zhang S. and Zhang J. (2023). Deferoxamine ameliorates neurological dysfunction by inhibiting ferroptosis and neuroinflammation after traumatic brain injury. Brain Res. 1812, 148383.

Lakhal-Littleton S., Wolna M., Carr C.A., Miller J.J., Christian H.C., Ball V., Santos A., Diaz R., Biggs D., Stillion R., Holdship P., Larner F., Tyler D.J., Clarke K., Davies B. and Robbins P.A. (2015). Cardiac ferroportin regulates cellular iron homeostasis and is important for cardiac function. Proc. Natl. Acad. Sci. USA 112, 3164-3169.

Li S. and Huang Y. (2022). Ferroptosis: An iron-dependent cell death form linking metabolism, diseases, immune cell and targeted therapy. Clin. Transl. Oncol. 24, 1-12.

Li Q., Wan J., Lan X., Han X., Wang Z. and Wang J. (2017). Neuroprotection of brain-permeable iron chelator VK-28 against intracerebral hemorrhage in mice. J. Cereb. Blood Flow Metab. 37, 3110-3123.

Li Y., Feng D., Wang Z., Zhao Y., Sun R., Tian D., Liu D., Zhang F., Ning S., Yao J. and Tian X. (2019). Ischemia-induced ACSL4 activation contributes to ferroptosis-mediated tissue injury in intestinal ischemia/reperfusion. Cell Death Differ. 26, 2284-2299.

Li Y., Cao Y., Xiao J., Shang J., Tan Q., Ping F., Huang W., Wu F., Zhang H. and Zhang X. (2020a). Inhibitor of apoptosis-stimulating protein of p53 inhibits ferroptosis and alleviates intestinal ischemia/reperfusion-induced acute lung injury. Cell Death Differ. 27, 2635-2650.

Li X., Wang T.X., Huang X., Li Y., Sun T., Zang S., Guan K.L., Xiong Y., Liu J. and Yuan H.X. (2020b). Targeting ferroptosis alleviates methionine-choline deficient (MCD)-diet induced NASH by suppressing liver lipotoxicity. Liver Int. 40, 1378-1394.

Li J.Y., Liu S.Q., Yao R.Q., Tian Y.P. and Yao Y.M. (2021). A novel insight into the fate of cardiomyocytes in ischemia-reperfusion injury: From iron metabolism to ferroptosis. Front. Cell Dev. Biol. 9, 799499.

Li S., Wang R., Wang Y., Liu Y., Qiao Y., Li P., Chen J., Pan S., Feng Q., Liu Z. and Liu D. (2022). Ferroptosis: A new insight for treatment of acute kidney injury. Front. Pharmacol. 13, 1065867.

Li J., Huang Q., Lv M., Ma W., Sun J., Zhong X., Hu R., Ma M., Han Z., Zhang W., Feng W., Sun X. and Zhou X. (2023a). Role of liensinine in sensitivity of activated macrophages to ferroptosis and in acute liver injury. Cell Death Discov. 9, 189.

Li C., Wu Y., Chen Q., Luo Y., Liu P., Zhou Z., Zhao Z., Zhang T., Su B., Sun T. and Jiang C. (2023b). Pleiotropic microenvironment remodeling micelles for cerebral ischemia-reperfusion injury therapy by inhibiting neuronal ferroptosis and glial overactivation. ACS Nano 17, 18164-18177.

Li P., Yu J., Huang F., Zhu Y.Y., Chen D.D., Zhang Z.X., Xie Z.C., Liu Z.Y., Hou Q., Xie N., Peng T.H., Chen X., Li L. and Xie W. (2023c). SLC7A11-associated ferroptosis in acute injury diseases: Mechanisms and strategies. Eur. Rev. Med. Pharmacol. Sci. 27, 4386-4398.

Liang Y., Liu Z., Qu L., Wang Y., Zhou Y., Liang L., Guo Y. and Tang L. (2022). Inhibition of the IRE1/JNK pathway in renal tubular epithelial cells attenuates ferroptosis in acute kidney injury. Front. Pharmacol. 13, 927641.

Lin J.H., Yang K.T., Ting P.C., Luo Y.P., Lin D.J., Wang Y.S. and Chang J.C. (2021). Gossypol acetic acid attenuates cardiac ischemia/reperfusion injury in rats via an antiferroptotic mechanism. Biomolecules 11, 1667.

Lin Z.H., Liu Y., Xue N.J., Zheng R., Yan Y.Q., Wang Z.X., Li Y.L., Ying C.Z., Song Z., Tian J., Pu J.L. and Zhang B.R. (2022a). Quercetin protects against MPP+/MPTP-induced dopaminergic neuron death in parkinson's disease by inhibiting ferroptosis. Oxid. Med. Cell. Longev. 2022, 7769355.

Lin J.H., Yang K.T., Lee W.S., Ting P.C., Luo Y.P., Lin D.J., Wang Y.S. and Chang J.C. (2022b). Xanthohumol protects the rat myocardium against ischemia/reperfusion injury-induced ferroptosis. Oxid. Med. Cell. Longev. 2022, 9523491.

Liu P., Feng Y., Li H., Chen X., Wang G., Xu S., Li Y. and Zhao L. (2020). Ferrostatin-1 alleviates lipopolysaccharide-induced acute lung injury via inhibiting ferroptosis. Cell. Mol. Biol. Lett. 25, 10.

Liu T., Li X., Cui Y., Meng P., Zeng G., Wang Y. and Wang Q. (2021). Bioinformatics analysis identifies potential ferroptosis key genes in the pathogenesis of intracerebral hemorrhage. Front. Neurosci. 15, 661663.

Liu W., Wang L., Liu C., Dai Z., Li T. and Tang B. (2022). Edaravone ameliorates cerebral ischemia-reperfusion injury by downregulating ferroptosis via the Nrf2/FPN pathway in rats. Biol. Pharm. Bull. 45, 1269-1275.

Liu J., Huang C., Liu J., Meng C., Gu Q., Du X., Yan M., Yu Y., Liu F.

and Xia C. (2023). Nrf2 and its dependent autophagy activation cooperatively counteract ferroptosis to alleviate acute liver injury. Pharmacol. Res. 187, 106563.

Lu C., Tan C., Ouyang H., Chen Z., Yan Z. and Zhang M. (2022). Ferroptosis in intracerebral hemorrhage: A panoramic perspective of the metabolism, mechanism and theranostics. Aging Dis. 13, 1348-1364.

Luo L., Mo G. and Huang D. (2021). Ferroptosis in hepatic ischemia-reperfusion injury: Regulatory mechanisms and new methods for therapy (review). Mol. Med. Rep. 23, 225.

Luo Y., Apaijai N., Liao S., Maneechote C., Chunchai T., Arunsak B., Benjanuwattra J., Yanpiset P., Chattipakorn S.C. and Chattipakorn N. (2022). Therapeutic potentials of cell death inhibitors in rats with cardiac ischaemia/reperfusion injury. J. Cell. Mol. Med. 26, 2462-2476.

Nishizawa H., Matsumoto M., Shindo T., Saigusa D., Kato H., Suzuki K., Sato M., Ishii Y., Shimokawa H. and Igarashi K. (2020). Ferroptosis is controlled by the coordinated transcriptional regulation of glutathione and labile iron metabolism by the transcription factor BACH1. J. Biol. Chem. 295, 69-82.

Pallotti F., Bergamini C., Lamperti C. and Fato R. (2021). The roles of coenzyme q in disease: Direct and indirect involvement in cellular functions. Int. J. Mol. Sci. 23, 128.

Pan Y., Wang X., Liu X., Shen L., Chen Q. and Shu Q. (2022). Targeting ferroptosis as a promising therapeutic strategy for ischemia-reperfusion injury. Antioxidants 11, 2196.

Papadopoulos D., Siempis T., Theodorakou E. and Tsoulfas G. (2013). Hepatic ischemia and reperfusion injury and trauma: Current concepts. Arch. Trauma Res. 2, 63-70.

Parra-Flores P., Riquelme J.A., Valenzuela-Bustamante P., Leiva-Navarrete S., Vivar R., Cayupi-Vivanco J., Castro E., Espinoza-Perez C., Ruz-Cortes F., Pedrozo Z., Lavandero S., Rodrigo R. and Diaz-Araya G. (2019). The association of ascorbic acid, deferoxamine and n-acetylcysteine improves cardiac fibroblast viability and cellular function associated with tissue repair damaged by simulated ischemia/reperfusion. Antioxidants 8, 614.

Qiu B., Zandkarimi F., Bezjian C.T., Reznik E., Soni R.K., Gu W., Jiang X. and Stockwell B.R. (2024). Phospholipids with two polyunsaturated fatty acyl tails promote ferroptosis. Cell 187, 1177-1190.e18.

Ritter C., da Cunha A.A., Echer I.C., Andrades M., Reinke A., Lucchiari N., Rocha J., Streck E.L., Menna-Barreto S., Moreira J.C. and Dal-Pizzol F. (2006). Effects of N-acetylcysteine plus deferoxamine in lipopolysaccharide-induced acute lung injury in the rat. Crit. Care Med. 34, 471-477.

Sanz A.B., Sanchez-Nino M.D., Ramos A.M. and Ortiz A. (2023). Regulated cell death pathways in kidney disease. Nat. Rev. Nephrol. 19, 281-299.

Sawicki K.T., De Jesus A. and Ardehali H. (2023). Iron metabolism in cardiovascular disease: Physiology, mechanisms, and therapeutic targets. Circ. Res. 132, 379-396.

She R., Liu D., Liao J., Wang G., Ge J. and Mei Z. (2023). Mitochondrial dysfunctions induce PANoptosis and ferroptosis in cerebral ischemia/reperfusion injury: From pathology to therapeutic potential. Front. Cell. Neurosci. 17, 1191629.

Stamenkovic A., O'Hara K.A., Nelson D.C., Maddaford T.G., Edel A.L., Maddaford G., Dibrov E., Aghanoori M., Kirshenbaum L.A., Fernyhough P., Aliani M., Pierce G.N. and Ravandi A. (2021). Oxidized phosphatidylcholines trigger ferroptosis in cardiomyocytes during ischemia-reperfusion injury. Am. J. Physiol. Heart Circ. Physiol. 320, H1170-H1184.

Stockwell B.R. (2022). Ferroptosis turns 10: Emerging mechanisms, physiological functions, and therapeutic applications. Cell 185, 2401-2421.

Tang L.J., Zhou Y.J., Xiong X.M., Li N.S., Zhang J.J., Luo X.J. and Peng J. (2021). Ubiquitin-specific protease 7 promotes ferroptosis via activation of the p53/TfR1 pathway in the rat hearts after ischemia/reperfusion. Free Radic. Biol. Med. 162, 339-352.

Tuo Q.Z., Lei P., Jackman K.A., Li X.L., Xiong H., Li X.L., Liuyang Z.Y., Roisman L., Zhang S.T., Ayton S., Wang Q., Crouch P.J., Ganio K., Wang X.C., Pei L., Adlard P.A., Lu Y.M., Cappai R., Wang J.Z., Liu R. and Bush A.I. (2017). Tau-mediated iron export prevents ferroptotic damage after ischemic stroke. Mol. Psychiatry 22, 1520-1530.

Wang X.D. and Kang S. (2021). Ferroptosis in myocardial infarction: Not a marker but a maker. Open Biol. 11, 200367.

Wan J., Ren H. and Wang J. (2019). Iron toxicity, lipid peroxidation and ferroptosis after intracerebral haemorrhage. Stroke Vasc. Neurol. 4, 93-95.

Wang S., Liu W., Wang J. and Bai X. (2020). Curculigoside inhibits ferroptosis in ulcerative colitis through the induction of GPX4. Life Sci. 259, 118356.

Wang Y., Dong Z., Zhang Z., Wang Y., Yang K. and Li X. (2022). Postconditioning with irisin attenuates lung ischemia/reperfusion injury by suppressing ferroptosis via induction of the Nrf2/HO-1 signal axis. Oxid. Med. Cell. Longev. 2022, 9911167.

Xie B.S., Wang Y.Q., Lin Y., Mao Q., Feng J.F., Gao G.Y. and Jiang J.Y. (2019). Inhibition of ferroptosis attenuates tissue damage and improves long-term outcomes after traumatic brain injury in mice. CNS Neurosci. Ther. 25, 465-475.

Xie J., Ye Z., Li L., Xia Y., Yuan R., Ruan Y. and Zhou X. (2022). Ferrostatin-1 alleviates oxalate-induced renal tubular epithelial cell injury, fibrosis and calcium oxalate stone formation by inhibiting ferroptosis. Mol. Med. Rep. 26, 256.

Xu Y., Li X., Cheng Y., Yang M. and Wang R. (2020a). Inhibition of ACSL4 attenuates ferroptotic damage after pulmonary ischemia-reperfusion. FASEB. J. 34, 16262-16275.

Xu M., Tao J., Yang Y., Tan S., Liu H., Jiang J., Zheng F. and Wu B. (2020b). Ferroptosis involves in intestinal epithelial cell death in ulcerative colitis. Cell Death Dis. 11, 86.

Xu P., Kong L., Tao C., Zhu Y., Cheng J., Li W., Shen N., Li R., Zhang C., Wang L., Zhang Y., Wang G., Liu X., Sun W. and Hu W. (2023a). Elabela-APJ axis attenuates cerebral ischemia/reperfusion injury by inhibiting neuronal ferroptosis. Free Radic. Biol. Med. 196, 171-186.

Xu R., Wang W. and Zhang W. (2023b). Ferroptosis and the bidirectional regulatory factor p53. Cell Death Discov. 9, 197.

Yamada N., Karasawa T., Wakiya T., Sadatomo A., Ito H., Kamata R., Watanabe S., Komada T., Kimura H., Sanada Y., Sakuma Y., Mizuta K., Ohno N., Sata N. and Takahashi M. (2020). Iron overload as a risk factor for hepatic ischemia-reperfusion injury in liver transplantation: Potential role of ferroptosis. Am. J. Transplant. 20, 1606-1618.

Yang Y., Ma Y., Li Q., Ling Y., Zhou Y., Chu K., Xue L. and Tao S. (2022a). STAT6 inhibits ferroptosis and alleviates acute lung injury via regulating P53/SLC7A11 pathway. Cell Death Dis. 13, 530.

Yang J., Sun X., Huang N., Li P., He J., Jiang L., Zhang X., Han S. and Xin H. (2022b). Entacapone alleviates acute kidney injury by

inhibiting ferroptosis. FASEB J. 36, e22399.
Ye J., Lyu T.J., Li L.Y., Liu Y., Zhang H., Wang X., Xi X., Liu Z.J. and Gao J.Q. (2023). Ginsenoside Re attenuates myocardial ischemia/reperfusion induced ferroptosis via miR-144-3p/SLC7A11. Phytomedicine 113, 154681.
Yin X., Zhu G., Wang Q., Fu Y.D., Wang J. and Xu B. (2021). Ferroptosis, a new insight into acute lung injury. Front. Pharmacol. 12, 709538.
Yu P., Zhang J., Ding Y., Chen D., Sun H., Yuan F., Li S., Li X., Yang P., Fu L., Yu S. and Zhang J. (2022). Dexmedetomidine post-conditioning alleviates myocardial ischemia-reperfusion injury in rats by ferroptosis inhibition via SLC7A11/GPX4 axis activation. Hum. Cell 35, 836-848.
Zhang J., Bi J., Ren Y., Du Z., Li T., Wang T., Zhang L., Wang M., Wei S., Lv Y. and Wu R. (2021a). Involvement of GPX4 in irisin's protection against ischemia reperfusion-induced acute kidney injury. J. Cell. Physiol. 236, 931-945.
Zhang B., Chen X., Ru F., Gan Y., Li B., Xia W., Dai G., He Y. and Chen Z. (2021b). Liproxstatin-1 attenuates unilateral ureteral obstruction-induced renal fibrosis by inhibiting renal tubular epithelial cells ferroptosis. Cell Death Dis. 12, 843.
Zhang H., Wen M., Chen J., Yao C., Lin X., Lin Z., Ru J., Zhuge Q. and Yang S. (2021c). Pyridoxal isonicotinoyl hydrazone improves neurological recovery by attenuating ferroptosis and inflammation in cerebral hemorrhagic mice. Biomed Res. Int. 2021, 9916328.
Zhang X., Ma Y., Ji J., Zhao X., Yuan J., Wang H. and Lv G. (2022). High-fat diet alleviates colitis by inhibiting ferroptosis via solute carrier family seven member 11. J. Nutr. Biochem. 109, 109106.
Zhang Y., Zeng Y., Huang M., Cao G., Lin L., Wang X. and Cheng Q. (2024). Andrographolide attenuates sepsis-induced acute kidney injury by inhibiting ferroptosis through the Nrf2/FSP1 pathway. Free Radic. Res. 58, 156-169.
Zhao Z., Wu J., Xu H., Zhou C., Han B., Zhu H., Hu Z., Ma Z., Ming Z., Yao Y., Zeng R. and Xu G. (2020). XJB-5131 inhibited ferroptosis in tubular epithelial cells after ischemia-reperfusion injury. Cell Death Dis. 11, 629.
Zhu L., Lian W., Yao Z., Yang X., Wang Z., Lai Y., Xu S., Zhao B. and Liu K. (2022). Integrated analysis of ferroptosis and immunity-related genes associated with intestinal ischemia/reperfusion injury. J. Inflamm. Res. 15, 2397-2411.

Accepted October 28, 2024