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REVIEW

Targeting ferroptosis in ischemia/reperfusion renal injury

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Abstract
Renal I/R injury is a severe medical condition contributing to acute kidney injury (AKI), leading to rapid kidney dysfunction and high mortality rates. It is generally observed during renal transplantation, shock, trauma, and urologic and cardiovascular surgery, for which there is no effective treatment. Cell death and damage are commonly linked to I/R. Cell death triggered by iron-dependent lipid peroxidation, such as ferroptosis, has been demonstrated to have a significant detrimental effect in renal IRI models, making it a new type of cell death currently being researched. Ferroptosis is a nonapoptotic type of cell death that occurs when free iron enters the cell and is a critical component of many biological processes. In ferroptosis-induced renal I/R injury, iron chelators such as Deferasirox, Deferiprone, and lipophilic antioxidants are currently suppressed lipid peroxidation Liproxstatin-1 (Lip-1), Ferrostatin-1 along with antioxidants like vitamin and quercetin. Ferroptosis has been considered a potential target for pharmaceutical intervention to alleviate renal IRI-associated cell damage. Thus, this review emphasized the role of ferroptosis and its inhibition in renal IRI. Also, Pharmacological modulation of ferroptosis mechanism in renal I/R injury has been conferred.

Keywords Renal I/R injury · Mechanism of ferroptosis · Ferroptosis inhibitors · Therapeutic targets · Pannexin signaling · Heme oxygenase-1 · miRNAs

Introduction

Acute ischemic renal damage is a prevalent complication caused by various diseases that decrease the kidneys' ability to receive adequate arterial blood flow. Ischemic renal damage is exacerbated by restoring blood flow (Linkermann et al. 2014a, b; Wang and Bellomo 2017). Apoptosis and necrosis are the only two cell death processes previously recognized to have a role in renal ischemia AKI pathogenesis (Thapa et al. 2022). In renal I/R models, ferroptosis emerged as a newly identified regulated mechanism of cell death with deleterious effects (Yan et al. 2020). Although cell death is a vital clinical sign of IRI, preventing cell death caused by IRI could be a new therapeutic strategy. However, it has previously been suggested that a comprehensive understanding of I/R-related cell death is essential in creating effective therapy options for IRI (Yarishkin et al. 2018; Sarkar et al. 2019). Oxidative stress-induced due to lipid peroxidation and elevated intracellular iron levels are hallmarks of IRI (Saklani et al. 2022a). In the most recent literature, iron-dependent ferroptosis has been found to cause cell damage and death (Thévenod and Lee 2013; Sharma et al. 2021). The cellular activity of iron-dependent ferroptosis can be blocked by iron chelation and antioxidants. In animal models of IRI, iron chelation is therapeutic (Rodríguez-Vargas et al. 2019; Jiang et al. 2021). Thus, ferroptosis has been recently found as a therapeutic target for renal I/R damage, according to recent findings.

Ferroptosis mechanism of cell death

Antioxidant mechanism

Selenium is an endogenous antioxidant required for the activity of glutathione peroxidase 4 (GPx4) (Ighodaro and Akinloye 2018). Asparagine, glutamine, tryptophan, and selenocysteine (Sec) or cysteine form hydrogen bonds with nitrogen atoms in GPx4's catalytic core, forming a tetrad

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(Asn). One of GPx4's unique properties is its structure, which makes it an excellent catalyst for cysteine residues' rapid and specific oxidation (Tosatto et al. 2008). A wide range of substrates, comprising H_2O_2, tiny hydroperoxides, lipopeptides, and complex molecular lipids, such as phospholipid and cholesterol ester hydroperoxides, can be modified by GPx4 when injected into biomembranes or lipoproteins (Casañas-Sánchez et al. 2015; Saklani et al. 2022a, b). GPx4 is a crucial regulator of anti-lipid peroxidation and provides resistance to ferroptosis. Inhibition of GPx4 activity by ferroptosis agonists is accomplished through either direct (RSL3) or indirect (Erastin or Fin56) inhibition (Jiang et al. 2021). For GPx4 to work correctly, it needs GSH and selenium (Ursini and Maiorino 2020). It had been reported in 2003 that Erastin and RSL3 cause RAS mutation-dependent cytotoxicity, and ferroptosis had been linked to glutathione-metabolizing proteins (Zhou et al. 2020a, b). Neuronal death caused by glutamine has features comparable to ferroptosis, which implies that glutathione synthesis is involved in the method (Hayashima et al. 2021). Enzymatically generated glutathione (GSH) is an essential antioxidant involved in GPx4 renewal (Nehring et al. 2020; He et al. 2021; Tang et al.2021). The cytosolic enzymes glutathione synthetase (GSS) and glutamate-cysteine ligase (GCL) catalyze the GSH synthesis in two steps using glutamate, cysteine, and glycine (Aoyama et al. 2008; Franklin et al. 2009). Cysteine is required for cell survival, according to several studies. Due to low glutathione levels, human fibroblasts cannot be cultured in cystine-free media (Conrad and Sato 2012; Scindia et al. 2015). Disulfide-linked heterodimers of cystine/glutamate antiporter systems (Xct) are two subunits linked with the disulfide bond that allows glutamate and cysteine exchange across plasma membranes (Lewerenz et al. 2013; Liang et al. 2019). Solute carrier 3 member 2 (SLC3A2) is the first of these components, and then comes solute carrier 7 member 11 (SLC7A11). Cystine is quickly converted to cysteine when injected into the cell. Cystine/cystathionine and glutamate are the primary targets of erastin in ferroptosis, which is why this exchange is critical. Cysteine can be synthesized from methionine via the transsulfuration pathway in some cell types, and this mechanism may be resistant to erastin (Dixon et al. 2012). When selenium levels within cells are low, cysteine is positioned in the GPx4 active site (Ingold et al. 2018). For example, the enzyme's activity is 1000 times lower than that of the naturally occurring GPx4 recombinant Cys mutant (Ingold et al. 2018). Na_2SeO_3 supplementation restored GPx4 function in SH-SY5Y cells exposed to methamphetamine (Yu et al. 2017). To prevent irreversible hyperoxidation suppression by Sec deprotonation, GPx4 requires selenium. Sec has an advantage over Cys in the central nervous system with its thiol groups because Sec can deprotonate fast (Barayuga et al. 2013; Brigelius-Flohé and Maiorino 2013; Song et al. 2014; Cardoso et al. 2017; Doll et al. 2017). GPx4 was assumed to be the only regulator of ferroptosis until now. No matter whether acyl-CoA synthetase long-chain family member 4 (ACSL4) is expressed or not, blocking GPx4 does not cause ferroptosis, contrary to the common belief (Wu et al. 2018; Doll et al. 2019; Bersuker et al. 2019). This demonstrates the possibility of other mechanisms of resistance. GPx4 and glutathione may work together with ferroptosis suppressor protein 1 (FSP1) and coenzyme Q10 (CoQ10) to reduce phospholipid peroxidation and ferroptosis (Wu et al. 2002; Han et al. 2020). Because of its molecular similarities to AIFM1, the apoptosis-inducing factor mitochondrial 2 (AIFM2) was anticipated to initiate apoptosis via a caspase-1-independent pathway (Chen et al. 2020a, b; Khan et al. 2022b). FSP1 functions as an oxidoreductase after being drawn to the cellular membranes by myristoylation to promote the regeneration of coenzyme Q10 (CoQ10) utilizing NADPH. Ubiquinol, a lipophilic radical-trapping antioxidant (RTA) (Frei et al.1990; Ng et al. 2019; Kalra et al. 2022), is a reduced form of CoQ10 that inhibits the formation of lipid peroxides, hence regulating ferroptosis. The mevalonate process uses acetyl-CoA to create ubiquinol. The mechanism of ferroptosis has been reported to be blocked by small molecules. Endogenous CoQ10 levels are depleted when FIN56 attaches to and activates squalene synthase (Mullen et al. 2016; Shimada et al. 2016) (Fig. 1).

Oxidation mechanisms

Lipid metabolism is essential for both pathological and physiological processes in the human body. For example, in cell signaling and energy metabolism, fatty acids are a critical component of membranes in biology (Olzmann and Carvalho 2019). Polyunsaturated fatty acids (PUFAs) contain two or more double bonds and are crucial for plasma and membrane formation (Kihara 2012; Zárate et al. 2017). Whereas cis-double bonds of methylene groups of fatty acids are quickly oxidized, making fatty acids more susceptible to autoxidation (Carvalho et al. 2010; Dixon and Stockwell 2019). Lipid hydroperoxides are a significant element in ferroptosis. A ferroptosis cell death signal is PE (phosphatidylethanolamine) that contains arachidonic acid (AA) (AA-PE). It is possible to lengthen adrenoyl (AdA) using an enzyme called elongase (Yang and Stockwell 2016; Chen et al. 2021). It has recently been discovered that AA-OOHPE is the most potent inducer of iron apoptotic phenotype in comparison to other phospholipids (PL)-OOH forms, and it catalyzes the conversion of acyl-CoA to acyl-PE via the acyl-CoA synthetase family 4 (ACSL4) (Müller et al. 2017; Lin et al. 2021). LPCAT3 is required to complete the esterification process, whereas LOXs and reactive oxidizing radicals accelerate the transformation of AA-PE to AA-OOH-PE (Hirschhorn and

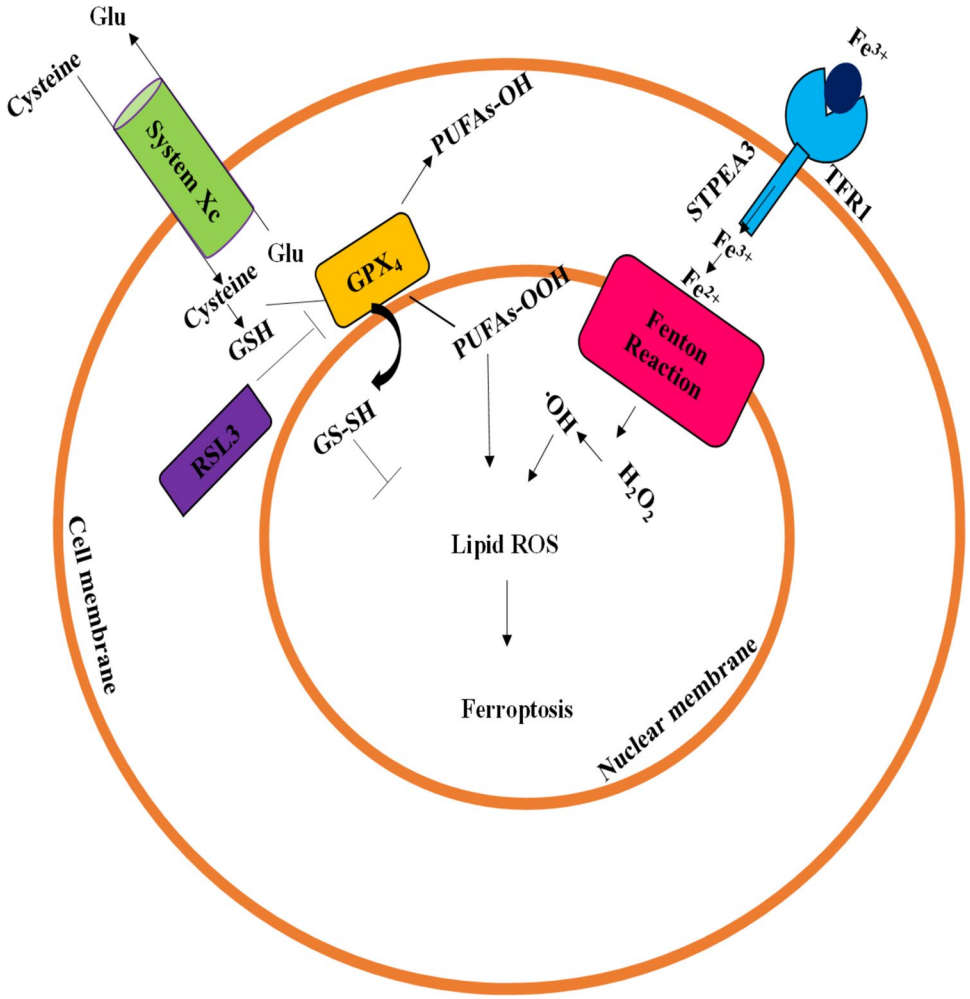

Fig. 1 Pathogenic factors trigger a Fenton reaction that oxidizes membrane lipids to lipid peroxides and regulates ferroptosis by increasing H_2O_2 or Fe^{2+} abnormally

Stockwell 2019; Capelletti et al. 2020; Wang et al. 2020). Cytochrome P450 oxidoreductase (POR), a stress-induced enzyme, increases lipid peroxidation by providing electrons to downstream effectors. Ferroptosis occurs when AA-OOH-PE exceeds the reduction mechanism's competence (Zou et al. 2020; Bagayoko and Meunier 2021). Lipid peroxidation can be caused by iron because of its ability of redox activation. The first step in the process is to release iron bound for Fenton reaction products from the labile iron pool (LIP), promoting ROS buildup (Jomova and Valko, 2011; Bertrand 2017; Li et al. 2020; Fujii et al. 2020). For example, iron's role in enzyme reactions, such as lipoxygenases (LOXs) and NADPH oxidases, directly impacts the rate and extent of lipid peroxidation. According to these studies, iron homeostasis proteins also can regulate a condition known as ferroptosis. It has also been shown that silencing the iron response element-binding protein 2 (IREB2) via sh-RNA can reduce ferroptosis sensitivity (Tao et al. 2020; Chen et al. 2020a, b). One of the iron-sulfur cluster production enzymes, NFS1 (cysteine desulfurase) and Prominin2, a ferroptosis stress response protein, have also been discovered to suppress the formation of ferroptosis in lung cancer (Adam et al. 2006). In addition, ferroptosis can be triggered by ferritin autophagy in the lysosomes, which increases the decreased iron content (Hou et al. 2016; Liu et al. 2020a, b). To prevent cellular harm from iron-mediated degradation, cells undergo ferritinophagy, a mechanism regulated by the nuclear receptor coactivator 4 (NCOA4) cargo receptor (Cicenas et al. 2017; Gryzik et al. 2021) (Fig. 1).

Targeting ferroptosis in renal I/R injury

Thrombotic or embolic events, surgical procedures, and renal transplantation have been associated with acute kidney failure induced by IRI and have played a substantial role in patient morbidity and mortality (Malek and Nematbakhsh 2015). Necrosis and ferroptosis pathways exist simultaneously in renal IRI, suggesting a "synergistic effect" in recent studies on renal I/R (Haase et al. 2010; Linkermann et al. 2014a, b; Ni et al. 2019). Mixed lineage kinase domain-like

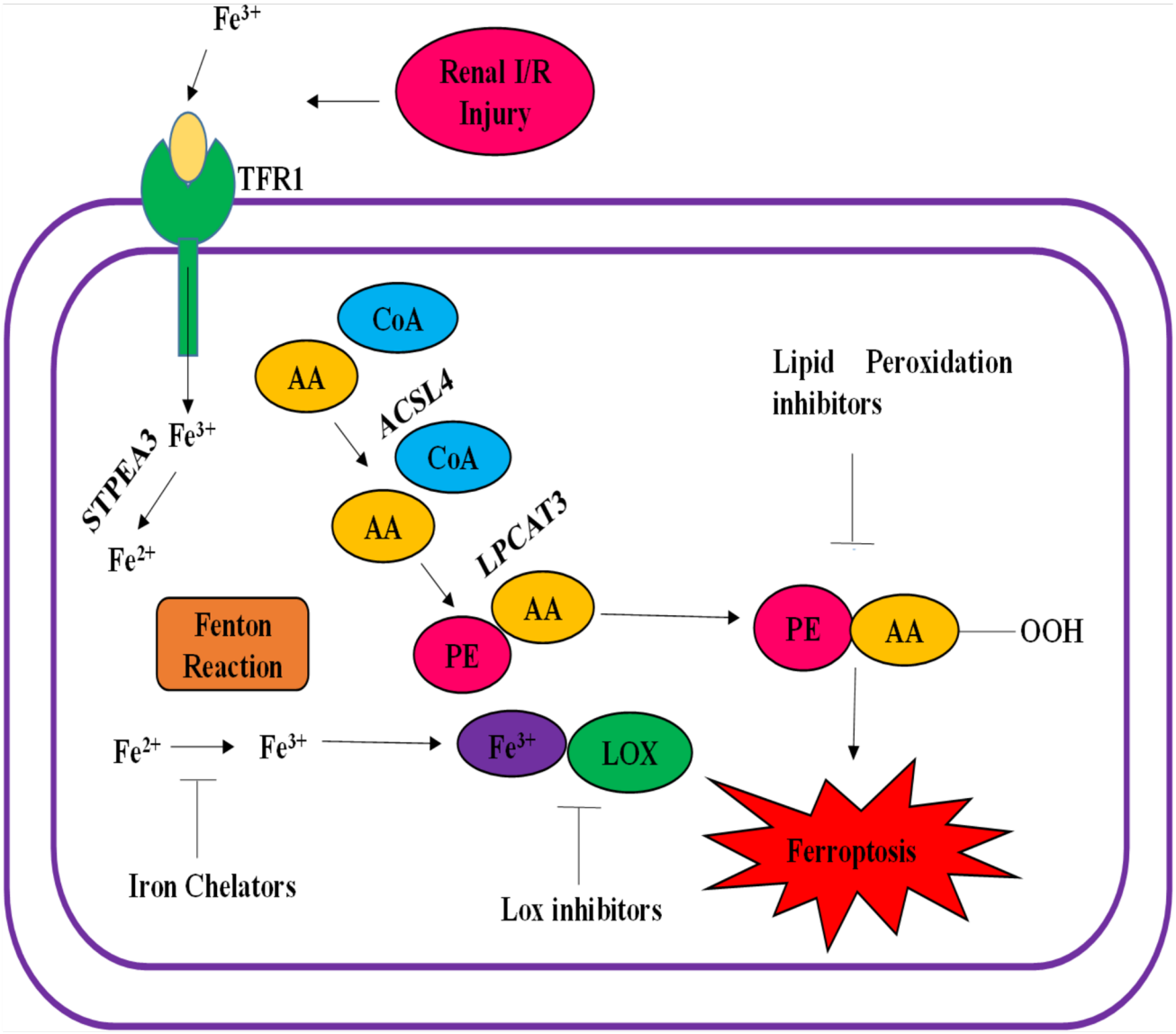

Fig. 2 Esterification of arachidonic acid (AA) by lipoxygenase (LOX) produces phosphatidylethanolamine-AA species, which is then oxidized by ferroptosis-inducing mechanisms. Ferroptosis is initiated by ACSL4 and LPCAT3, which make it easier to generate AA-PE species. This is in contrast to GPX4, which adversely regulates ferroptosis by reducing the formation of lipid hydroperoxides (L-OOH). Lipid peroxidation inhibitors, iron chelators, antioxidants, and LOX inhibitors can be used to prevent ferroptosis

protein (MLKL), a molecular switch in renal IRI, is activated by PUFA depletion and activates necroptosis. In contrast, ACSL4 is activated by necroptosis and makes the biomembrane less susceptible to MLKL-induced membrane permeabilization (Casserly and Dember 2003; Choi et al. 2019; Li et al. 2020). Iron chelators have already been reported to prevent renal tubular cell mortality in several studies of renal IRI, suggesting the significant role of iron in renal IRI (Paller and Hedlund 1994). Renal tubular cell death can be prevented by active in-transforming growth factor (TGF) receptor ALK4/5, which has been related to stress-induced renal injury (Sharma and Leaf 2019). There may be a correlation between ferroptosis and different cell death systems in the renal IRI model. Ferroptosis inhibitors are effective in a few preclinical studies for renal IRI, although discovering specific pathways regulating ferroptosis may yield better outcomes. As a result, future research efforts must focus on identifying novel mechanisms or pathways for preclinical and clinical evaluation of ferroptosis inhibitors to treat IRI (Fig. 2).

Lipid peroxidation inhibitors

Ferrostatin-1 (Fer-1) decreases membrane lipid breakdown and cell death via a reductive mechanism (Skouta et al. 2014). Lipid peroxides can be converted to alcohols (R-OOHR-OH), or lipid groups can be intercepted and scavenged by direct reduction (R-OR-OH) or hydrogen atom transfer (Hu et al. 2019; Gupta et al. 2021). SRS16-86 (a third-generation ferrostatin) was tested on an in vitro model of renal IRI, which offered better plasma, metabolic stability, improved kidney function, and prolonged life (Pefanis et al. 2019). In fact, ferrostatin 16–86, a more stable homolog, was more successful in experimental kidney IRI than Fer-1 (Angeli et al. 2014). The ferroptosis inhibitor Liproxstatin-1 was also found to be effective in inhibiting human proximal tubule epithelium, Gpx4/kidney, and a model of IRI-induced tissue injury (Angeli et al. 2014; Ran et al. 2015; Kajarabille and Latunde-Dada 2019). Ferroptosis in RSL3-stimulated mouse striatal cells was suppressed by vitamin E and its metabolites, such as quinone/hydroquinone, even though this research was conducted before ferroptosis was defined. Still, the influence on ferroptosis was not examined (Zhou et al. 2020a, b). Vitamin E also significantly reduced lipid peroxidation of renal cells induced by renal I/R in rats (Hinman et al. 2018). I/R-induced tubular epithelial cell injury and inflammation were also decreased by XJB-5–131 in mice by particularly inhibiting ferroptosis (Zhao et al. 2020). Quercetin (QCT) is a natural flavonoid-containing compound that has been proven to reduce ferroptosis in acute renal injury in patients with IRI via reducing levels of malondialdehyde (MDA) and ROS in renal proximal tubular epithelial cells while raising levels of glutathione (GSH) (Hatcher et al. 2009; Wang et al. 2021a, b, c, d, e).

Ferroptosis can also be prevented by lipid peroxidase inhibitors, such as lipoxygenase (LOX) inhibitors. Humans have several lipoxygenase isoforms (12/15-LOX, 5-LOX) isoform, and 5-LOX is the only human lipoxygenase with 3D structural data that exacerbates the ferroptosis process (Yang et al. 2016). Despite this, scientists have worked hard to identify inhibitors that specifically target particular isoforms of the protein. A definitive association between ferroptosis and a specific lipoxygenase isoform has yet to be established. For example, 15-LOX, which encodes lipoxygenase, can oxidize esterified FA and is assumed to be responsible for cell death, did not repair Gpx4 loss in genetic tests (Mao et al. 2019). Although ablation of 15-LOX in heterozygous Gpx4 mice can treat male subfertility, this suggests that Gpx4 and lipoxygenase have a complicated tissue-specific interplay (Friedmann Angeli et al. 2014). As it turns out, blocking more than one lipoxygenase had a more significant protective effect (Wang et al. 2021a, b, c, d, e) than inhibiting just one. As a result, it is necessary to determine whether a particular lipoxygenase or pan-lipoxygenase inhibitor may be used to develop new therapies that can successfully reduce ferroptosis in renal I/R injury. Cell death in human fibrosarcoma cells and GPX/mouse embryonic fibroblasts exposed to erastin was reduced by PD146176, a 15-LOX inhibitor (Doll et al. 2017).

Iron chelators

Experimental AKI has been effectively treated with iron chelation, preventing ferroptosis (Paller et al. 1998). Iron deficiency can lead to cell death in the proximal tubular cells; hence, none of these are currently used in clinical practice. However, the effect of Deferoxamine was evaluated on iron-mediated postischemic renal injury in rats; Deferoxamine infused during the first 60 min of reperfusion resulted in a marked improvement in renal function and reduction in lipid peroxidation (Paller et al. 1998). A dose-adapted form of Deferiprone can, on the other hand, be put to the test (Finazzi and Arosio 2014). H-ferritin (FtH) is expressed in the kidney's proximal tubules to sequester iron and decrease free iron-mediated toxicity efficiently. The ferritin-H (FTH) component's ferroxidase activity transforms Fe^{2+} to Fe^{3+}, which is then stored in the ferritin mineral core by ferroxidase activity. As an iron chelator, FtH is vital since each molecule can bind to up to 4500 Fe^{2+} ions. HO-1 increases the expression of FtH to store the ferrous iron produced throughout the process (Matzanke et al. 1997). This protection is also dependent on FtH being upregulated by HO-1. In addition, HO-1 must increase the expression of FtH for it to be preserved. A study used proximal tubule-specific FtH mutant mice to evaluate the role of FtH in rhabdomyolysis and cisplatin-induced AKI. The removal of FtH from proximal renal tubules exacerbated kidney injury and increased mortality, despite HO-1 expression being considerably higher (Swaminathan 2018). In AKI, Hepcidin induces H-ferritin and sequesters iron from macrophages to prevent ferroptosis (Ho et al. 2011). The iron chelators Deferasirox and Hepcidin must be studied in a preclinical model of renal I/R damage to establish their iron-chelating capacities and impact on ferroptosis inhibition (Table 1).

Table 1 Ferroptosis inhibitors against renal I/R injury

Drug	Target	Effect	Reference
Ferr-1; SRS16-86 (a third generation ferrostatin)	Lipid peroxidation	Improved renal function, decreased tubular injury, and cell death	Pefanis et al. (2019)
Liproxstatin	Lipid peroxidation	Decreased lipid peroxidation and improved tubular injury	Angeli et al. (2014); Ran et al. (2015); Kajarabille and Latunde-Dada (2019)
16–86	Lipid peroxidation	Increased survival and tubular cell death	Angeli et al. (2014)
Deferoxamine	Iron chelation	Impoved renal function and reduced lipid peroxidation	Paller et al. (1998)
PD146176	15-LOX inhibitor	Not tested in IRI but tested in human fibrosarcoma cells and GPX/mouse embryonic fibroblasts	Doll et al. (2017)
Vitamin E	Antioxidant defence system	Impoved renal function and tissue damage	Hinman et al. (2018)
Quercetin	Antioxidant defence system	Reduced ROS in renal proximal tubular epithelial cells and increased glutathione (GSH) levels	Hatcher et al. (2009); Wang et al. (2021a, b, c, d, e)

Emerging mechanism of ferroptosis in renal I/R injury

Pannexin signalling

An ATP-releasing pathway protein, pannexin, is found in every cell type. Pannexin is a membrane channel composed of three proteins (Panx1, Panx2, and Panx3). Panx1 regulates ATP release as a damage-associated molecular pattern (DAMP) molecule that activates autophagy signaling or apoptosis under oxidative conditions (Penuela and Gehi 2013). Pannexin has been reported to exhibit pro-apoptotic effects, inflammation, oxidative stress, and cell death during kidney injury. The mechanism of ferroptosis in Parkinson's disease was triggered by ATP binding to the P2Y7 receptor, activating signaling pathways such as PKC and MAPK (Karatas et al. 2013). In particular, a decrease in ATP release-dependent signaling has been found to lower oxidative stress and protect kidneys during IRI (Xu et al. 2018). P2Y7R-binding Panx 1 stimulates cell death that can be reversed by inhibiting ferroptosis, according to studies (Xu et al. 2018). A recent study found that silencing *Panx1* expression in cultured HK-2 cells treated with erastin significantly attenuated ferroptotic lipid peroxidation and iron accumulation.

Further, *Panx1* knockout mice subjected to renal IRI displayed reduced malondialdehyde (MDA), plasma creatinine levels, and tubular cell death compared to wild-type mice. Moreover, knockdown of *Panx1* in mice offered protection against renal IRI by inducing expression of heme oxygenase (HO-1) and attenuating ferroptinophagy via MAPK/ERK activation (Su et al. 2019). Therefore, *Panx1* could be a potential therapeutic target for managing acute kidney injury (AKI) due to IRI.

miRNAs

Various genes regulate the state of lipid peroxidation and iron concentrations in cells. SLC7A11 decreases ferroptosis by transferring cystine moiety into the cytosol to enhance GSH production, while GPX4 reduces lipid peroxidation in cells (Ghini et al. 2018). To affect gene transcription, microRNAs (miRNAs) target the 3′UTR of mRNA22 (Diallo et al. 2021). Many biological processes rely on miRNA-mRNA interaction, including immune responses, cell growth, autophagy, and death. A growing number of research suggest that miRNAs may play functional roles by cooperating with other noncoding RNAs (Xia et al. 2008). For example, in pediatric T-ALL cells, the expression of tumor suppressor genes PTEN and BIM was regulated by miRNAs hsa-20b-5p and hsa-363-3p and modulated survival of T-ALL cells (Drobna et al. 2020). In I/R-induced renal damage, miRNAs can slow its progression by modifying the expression of genes associated with the injury (Zager et al. 2009). Dysregulation of miR-182-5p and miR-378a-3p resulted in ferroptosis in I/R-induced kidney damage due to reduced GPX4 and SLC7A11 expression (Zager et al. 2009). As GPX4 and HMOX-1 are the essential regulatory genes in the ferroptosis form of programmed cell death and also cause injury to renal epithelial cells during IR. A recent study investigated the miRNA-mRNA regulatory system involved in ferroptosis following renal IR in which the bioinformatics analysis revealed a significant upregulation of *HMOX1* in the early stages of renal IR injury, and miRNA-3587 was found to be a regulator of *HMOX-1*. Inhibition of miR-3587 in tubular epithelial cells of hypoxia reoxygenation (HR) model system showed a significant increase in HO-1 protein (encoded by HMOX1) compared to the HR group, resulting in a simultaneous increase in GPX4 protein levels, decreased

Fe^{2+} and malondialdehyde level, and restored standard mitochondrial membrane potential. Therefore, the results indicated that miR-3587 suppression promoted HO-1 upregulation and protected renal tissues from IR-induced ferroptosis (Tao et al. 2021).

Heme oxygenase-1

Heme oxygenase is a well-known ubiquitous enzyme with a wide range of potential therapeutic applications in various disorders. Three different isoforms of the enzyme heme oxygenase 1 (HO-1) have been acknowledged: HO-1, HO-2, and HO-3, with the latter being a splice variation of HO-2. Inflammation and oxidative stress cause cell damage, which can be reduced by regulating iron metabolism (Khan et al. 2022a). Intracellular iron absorption and heme breakdown are facilitated by heme oxygenase-1 (HO-1) (Khan et al. 2022a, b, c; Khan et al. 2020). The intracellular ferrous iron level decreases when HO-1 expression or enzymatic activity is decreased. Thus, HO-1 is usually regarded as an essential regulator of iron metabolism. Gene deletion and transgenic techniques have established that HO-1 protects against AKI. It has been found that selective overexpression of HO-1 mice in the proximal tubule level is protective, whereas HO-1 deletion results in ferroptosis (Schipper et al. 2009; Liu et al. 2020a, b). However, toxin-induced HO-1 overexpression damages the kidneys and results in mitochondrial dysfunction (Wang et al. 2021a, b, c, d, e). Iron levels in the blood are maintained by FPN, the only iron export protein in mammals. In AKI mice, the FPN gene was knocked out, and renal function improved, possibly due to reduced ferroptosis and FtH chelation of ferrous iron (Shiraishi et al. 2000; Nath 2014; Wang et al. 2018; Fang et al. 2020). It has been found that HO-1 regulates oxidative stress and autophagy in a range of animal models of kidney injury, including ischemia–reperfusion, lipopolysaccharide, and cisplatin. Inflammation is regulated by HO-1, a critical contributor in this process (Adedoyin et al. 2018; Khan et al. 2020). Global HO-1 deficit in renal IRI mice model has shown to promote myeloid cell trafficking and monocyte chemoattraction through increased MCP-1 and MCP-1 trafficking (Pittock et al. 2005).

On the other hand, macrophage's overexpression with HO-1 in patients with renal IRI has shown anti-inflammatory properties and contributed to renal recovery (Zarjou et al. 2013). Other systems, such as proximal tubular ferritin, are required to protect cells against iron-induced damage and death. For example, iron generated by HO-1-catalytic activity can be stored more effectively when the heavy chain of ferritin is upregulated. The ability of HO-1 to upregulate H-ferritin is essential for protection (Zarjou et al. 2013). Researchers have studied the role of FtH in rhabdomyolysis and cisplatin-induced AKI in proximal tubule-specific mutant mice (Zarjou et al. 2013). Removing FtH from renal tubules has been shown to aggravate kidney damage and increase mortality, even though HO-1 expression is significantly higher in these tubules (Mohammad et al. 2021). Hepcidin has also modulated iron metabolism via FPN in AKI by restoring iron homeostasis and lowering inflammation. As the primary regulator of ferroportin-mediated iron export and intracellular H-ferritin levels, Hepcidin is essential for iron homeostasis. Hepcidin, a protective molecule, protects against acute kidney injury. Promising agents targeting Hepcidin, H-ferritin, and ferroptosis pathways could be an effective treatment strategy to prevent renal IRI (Mohammad et al. 2021). NRF2 activation is influenced by metabolic proteins, including ferritin and heme oxygenase 1 (HO-1), that control iron availability and ferroptosis (Nie et al. 2018). Current research revealed that HO-1 deletion in hepatocellular carcinoma and kidney cells enhanced erastin-induced ferroptosis (Nie et al. 2018; Kim et al. 2021). At the same time, NRF2 activation by ulinastatin upregulated HO-1 expression and reduced acetaminophen-induced liver I/R injury via alleviating ferroptosis, suggesting that acetaminophen induced ferroptosis via downregulation of the NRF2/HO-1 signaling pathway (Wang et al. 2021a, b, c, d, e). Therefore, NRF2 function needs to be evaluated for its beneficial effects against renal I/R damage via targeting ferroptosis.

Conclusion and perspective

Ferroptosis has emerged as a possible target for designing a novel treatment regimen for a wide range of disorders. Dysregulation in iron metabolism and ROS generation are the primary causes of ferroptosis. Several studies have shown that ferroptosis has a significant function in renal I/R models. Lipid peroxidase inhibitors and iron chelators have been shown to inhibit renal I/R damage ferroptosis. However, further therapeutic options for preventing ferroptosis in renal I/R conditions need to be developed. Renal ischemia/reperfusion (I/R) models have shown many ferroptosis regulators' expressions, comprising LOX, SLC7A11, and FTH1. Preventing ferroptosis in renal I/R injury may be possible by using pharmaceutical drugs to alter these parameters. Humans have several lipoxygenase isoforms (12/15-LOX, 5-LOX), and blocking one of these enzymes may prevent ferroptosis. Therefore, lipid peroxidase inhibitors may be evaluated in renal I/R models that may successfully reduce ferroptosis. PD146176, a 15 LOX inhibitor, had reduced cell death in GPX/mouse embryonic fibroblasts and human fibrosarcoma cells exposed to erastin. Hence, preclinical evaluation of these inhibitors in the renal I/R model should also be done. More understanding and identification of molecular mechanisms of ferroptosis in renal I/R models is required to assess the effect of modulating these mechanisms with the

desired therapeutic agent. In renal I/R models, specific indicators for ferroptosis, such as caspase activation in the event of apoptosis and the development of autophagy lysosomes in the case of autophagy, have yet to be developed. Therefore, ferroptosis inhibition could be a promising strategy to reduce renal I/R damage and should be evaluated in preclinical and clinical platforms.

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Author contribution Conceptualization: conceived and designed the experiments: Thakur Gurjeet Singh. Analyzed the data: Amarjot Kaur. Wrote the manuscript: Komal Thapa. Visualization: Amarjot Kaur. Editing of the manuscript: Komal Thapa, Amarjot Kaur, and Thakur Gurjeet Singh. Critically reviewed the article: Thakur Gurjeet Singh. Supervision: Thakur Gurjeet Singh. All authors read and approved the final manuscript.

Data availability Not applicable.

Declarations

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Consent to participate Not applicable.

Conflict of interest The authors declare no competing interests.

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