The pathological role of ferroptosis in ischemia/reperfusion-related injury

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ABSTRACT

Ischemia/reperfusion (I/R) is a pathological process that occurs in numerous organs throughout the human body, and it is frequently associated with severe cellular damage and death. Recently it has emerged that ferroptosis, a new form of regulated cell death that is caused by iron-dependent lipid peroxidation, plays a significantly detrimental role in many I/R models. In this review, we aim to revise the pathological process of I/R and then explore the molecular pathogenesis of ferroptosis. Furthermore, we aim to evaluate the role that ferroptosis plays in I/R, providing evidence to support the targeting of ferroptosis in the I/R pathway may present as a therapeutic intervention to alleviate ischemia/reperfusion injury (IRI) associated cell damage and death.

Keywords: Ischemia/reperfusion; Ferroptosis; Reactive oxygen species; Lipid peroxidation; Iron

INTRODUCTION

Ischemia/reperfusion (I/R) is a pathological event that occurs in numerous disease states. As the name implies, I/R consists of two significant events, the results of which can cause detrimental cellular damage. Ischemia, the first significant event, refers to the restriction of blood supply to an organ, usually as a result of a blockage within the arterial blood supply by an embolus. Ischemic events are almost always associated with cellular metabolic imbalances and deleterious hypoxia. The second significant event is the reperfusion, or restoration of blood flow and reoxygenation to the affected ischemic area, which can further cause excessive tissue deterioration, initiating destructive inflammatory responses (Eltzschig & Eckle, 2011; Yellon & Hausenloy, 2007).

Ischemia/reperfusion injury (IRI) is a significant contributor to the pathology of numerous disease states, particularly post-cardiac trauma. Moreover, IRI can delay the recovery of organ transplantation and can impede patient recovery undergoing treatments. The role of IRI has been investigated in many organs. However, most research has focused on the heart (Yellon & Hausenloy, 2007), brain (Hanson et al., 2009), and kidney (Friedmann Angeli et al., 2014). The precise molecular mechanism and pathways associated with IRI is not well understood and is heavily debated. As such, the implementation of pharmaceutical strategies has been hampered. Cellular death, however, is a steadfast pathological indicator of IRI. Accordingly, it seems likely that efforts to prevent or arrest the cell death cascade associated with IRI might present as a new and currently unmet therapeutic strategy (Eltzschig & Eckle, 2011; Gudipaty et al., 2018).

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Linkermann et al., 2013; Sun et al., 2018). Indeed, the investigation and the requirement of a thorough understanding of I/R-related cell death have already been proposed, and likely will be a critical step to develop useful treatment paradigms for IRI (Yeo et al., 2013; Yu et al., 2017).

Ferroptosis is a recently recognized novel form of cell death and is a potential therapeutic target with an application for many disease states (Stockwell et al., 2017). In this review, we intend to discuss the ferroptosis cell death pathway, and how it may negatively impact outcomes of I/R-related cell death in different organs and diseases.

**THE CURRENT UNDERSTANDING OF THE PATHOMECHANISM OF ISCHEMIA/REPERFUSION-RELATED CELL DEATH**

The sudden reduction of available tissue oxygen and nutrients is the critical event initiating cellular injury in ischemic tissue. Under ischemic conditions, mitochondria switch from aerobic to anaerobic metabolism, subsequently leading to a reduction in ATP with associated tissue acidification (Gores et al., 1988; Raat et al., 2009). The inhibition of ATP generation initiates a rise in intracellular sodium and extracellular potassium levels, thus depolarizing the cell (Kimura et al., 1986), and leading to a compensatory transient calcium influx. Concomitantly, calcium-dependent proteolytic enzymes are activated, resulting in apoptosis and necrosis (Halestrap, 2006; Nayler, 1981). Furthermore, during this cellular cascade, other essential ATP-dependent cell functions, such as phosphorylation and enzymatic activity, are also suppressed (Granger et al., 2001), contributing to the cell stress and cell death cascades. Under normal, non-ischemic physiological conditions, several endogenous mechanisms are responsible for reactive oxygen species (ROS) scavenging. However, these mechanisms, and their capacity to effectively scavenge for ROS, is severely negated after I/R (Weisfeldt et al., 1988; Zweier et al., 1987). It has been demonstrated that reperfusion of ischemic tissue can lead to a "burst" of ROS, and this oxidative burst can mediate IRI (Becker & Ambrosio, 1987; Hess & Manson, 1984). The mitochondrial respiratory chain and NADPH oxidases of the NADPH oxidase (NOX) family are believed to be significant sources of ROS (Cadenas, 2018). Antioxidants, endogenous or exogenous, have been shown to protect from IRI in the liver, kidney, heart, and brain (Dare et al., 2015; Jiang et al., 2015; Ni et al., 2019; Zhou et al., 2018).

In Figure 1, we describe the current knowledge of IRI. I/R leads to the activation of cell death pathways, where necrosis, apoptosis, and autophagy-associated cell death are suggested to be the key contributors responsible for the pathology of I/R (Eltzschig & Eckle, 2011; Linkermann et al., 2013; Sun et al., 2018). Furthermore, IRI is punctuated by several cellular events such as the reperfusion associated with an increase in the generation of ROS.

Figure 1 Changes in the cytoplasmic environment during ischemia

After ischemia, the amount of ATP in cells decreased with the lack of tissue energy supply. The resting potential maintained by active transport breaks down with the large outflow of calcium. Compensatory calcium influx activates downstream calcium-dependent signaling pathways. During this process, the mitochondria produce excess ROS.
oxidation burst accompanied by lipid peroxidation (Farmer & Mueller, 2013), and elevated intracellular iron levels (Scindia et al., 2019; Zhao et al., 2018).

These cellular events, which are consistent with the presentation of iron-dependent non-apoptotic ferroptosis, are preventable by iron chelation and antioxidants. Indeed, iron chelation has been reported to be beneficial in some animal models of IRI (Galaris et al., 2006; Scindia et al., 2015). Furthermore, the observation that iron and ferroptosis mediate cellular damage to organs, and cell death has been frequently documented in recent literature (Friedmann Angeli et al., 2014; Gao et al., 2015; Linkermann et al., 2014; Skouta et al., 2014; Tuo et al., 2017).

REGULATION OF FERROPTOSIS

Ferroptosis is a non-apoptotic form of cell death that is characterized by the accumulation of iron-dependent lipid hydroperoxides to lethal levels (Stockwell et al., 2017). Ferroptosis was clearly defined in 2012, when a small chemical screened from a large library, namely erastin, was shown to inhibit antioxidant glutathione synthesis, and subsequently initiate ferroptosis-related cell death, a cell death pathway that could not be rescued by inhibitors of other known cell death forms (Dixon et al., 2012). Therefore, ferroptosis was determined to be morphologically, biochemically, and genetically distinct from other forms of cell death, and may also be involved in various diseases (Stockwell et al., 2017; Wu et al., 2018). In Figure 2, we summarize the mechanism and key regulators of ferroptosis from the perspectives of oxidation and antioxidation. Hyperactivity of the oxidation mechanism and weakening of the antioxidant mechanism will both result in ferroptosis via the accumulation of toxic lipid peroxidation.

Figure 2 The indicated pathways control the sensitivity of ferroptosis

Lipid ROS accumulation is achieved through following major pathways: (1) iron promotes lipid oxidation by Fenton reaction; (2) the arachidonic acid (AA)-containing phosphatidylethanolamine (PE) (AA-PE)/adrenoyl (AdA)-PE is generated by acyl-CoA synthetase long-chain family member 4 (ACSL4) and lyso phosphatidylcholine acyltransferase 3 (LPCAT3) and oxidized by lipooxygenases (LOXs). (3) POR can also control lipid peroxidation in ferroptosis by distinct mechanisms. Glutathione (GSH)-dependent glutathione peroxidase 4 (GPX4) and ferroptosis suppressor protein 1 (FSP1)-dependent coenzyme Q10 (CoQ10), as two parallel pathways, control generation of lipid ROS. The accumulation of lipid ROS leads to ferroptosis. PE: Phosphatidylethanolamine; LIP: Labile iron pool; NADPH: Nicotinamide adenine dinucleotide phosphate; Gln: Glutamine; Met: Methionine; Glu: Glutamate; Cys: Cysteine; Gly: Glycine; GSSG: Oxidized GSH; GCL: Glutamate-cysteine ligase; GSS: Glutathione synthetase; IREB2: Iron-responsive element binding protein 2; NCOA4: Nuclear receptor coactivator 4; NFS1: Cysteine desulfurase; HO-1: Heme oxygenase-1; POR: Cytochrome P450 oxidoreductase.
Antioxidant mechanism
Glutathione peroxidase 4 (GPx4) is a selenium-dependent enzyme, which primarily functions as an endogenous antioxidant (Cardoso et al., 2017). The catalytic center of GPx4 is a tetrad, comprising of hydrogen bonds between a redox-active cysteine or selenocysteine (Sec), coupled with the nitrogen atoms from the surrounding asparagine (Asn), glutamine (Gln) and tryptophan (Trp) residues. This structure is the key to the extraordinary catalytic efficiency of GPx4, whereby the exposure of surface positive charges account for rapid and selective oxidation of mainly cysteine residues (Tosatto et al., 2008). GPx4 has a unique ability as a cytosolic "antioxidant enzyme", whereby it can modulate substrates including H₂O₂, small hydroperoxides, hydroperoxides in complex lipids such as phospholipid, cholesterol, and cholesterol ester hydroperoxides, even when inserted into biomembranes or lipoproteins (Brigelius-Flohé & Maiorino, 2013, Thomas et al., 1990). The chemical properties of GPx4 enable it to act as the central regulator of anti-lipid peroxidation and ferroptosis resistance. Ferroptosis agonists act directly (RSL3) or indirectly (Erastin or Fin56) on GPx4 by attenuating its activity (Ke et al., 2016). Glutathione (GSH) and selenium are necessary for the maintenance of GPx4 function and activity (Ingold et al., 2018; Stockwell et al., 2017).

Erastin and RSL3 were found to trigger RAS mutation-dependent cytotoxicity in 2003 (Dolma et al., 2003), and several proteins involved in glutathione metabolism have been implicated in ferroptosis (Yagoda et al., 2007). It is now understood that glutamine-induced neuronal death shares the characteristics of ferroptosis (Choi, 1988; Murphy et al., 1989), which indirectly highlights the role of glutathione synthesis in the process. GSH is also an important endogenous antioxidant (Meister & Anderson, 1983) and is involved in the regeneration of GPx4 (Maiorino et al., 2018). GSH is synthesized from glutamate, cysteine, and glycine in two-steps, under the catalysis of cystolic enzymes, glutamate-cysteine ligase (GCL), and glutathione synthetase (GSS) (Liang et al., 2019). Numerous studies indicate that cysteine is essential for cell survival. Human fibroblasts cultured in the cysteine-free medium cannot survive without it, and the cysteine deprived cell death is caused by glutathione depletion, which in turn can be arrested by the lipophilic antioxidant atocopherol (Bannai et al., 1977). Cystine is a disulfide formed between two cysteine molecules and is the predominant form of cysteine in the extracellular space (Conrad & Sato, 2012). The exchange of cystine and glutamate across the plasma membrane is facilitated by a cystine/glutamate antiporter system (Xct), which is a disulfide-linked heterodimer composed of two subunits. The first subunit is solute carrier family 3 member 2 (SLC3A2), and the second is the catalytic subunit solute carrier family 7 member 11 (SLC7A11) (Liang et al., 2019). Once cystine is imported into the cell, it is quickly reduced to cysteine. The exchange of cystine/cystathionine with glutamate is the most important event of ferroptosis and is the main target of erastin (Dixon et al., 2012). Interestingly, cysteine may be synthesized from methionine by the transsulfuration pathway in certain types of cells (McBean, 2012), and this pathway may be resistant to erastin.

When intracellular selenium is deficient, cysteine replaces selenocysteine in the GPx4 active center (Xu et al., 2010). This recombinant Cys mutant GPx4 expressed in Escherichia coli exhibits a significant reduction in catalytic efficiency and a 1 000-fold lower activity (Yu et al., 2014) when compared with the natural selenoenzyme. However, sodium selenite (Na₂SeO₃) supplementation can restore GPx4 activity in methamphetamine-treated SH-SY5Y cells (Barayuga et al., 2013). Selenium is required by GPx4 to prevent ferroptosis from utilizing Sec deprotonation to suppress irreversible hyper-oxidation (Brigelius-Flohé & Maiorino, 2013; Ingold et al., 2018). In the central nervous system, Sec is preferred over Cys with its thiol groups, since Sec can deprotonate rapidly under acidic conditions seen in the brain (Cardoso et al., 2017; Song et al., 2014).

It was previously believed that ferroptosis was regulated exclusively by GPx4 (Friedmann Angeli et al., 2014; Yang et al., 2014). However, inhibition of GPx4 fails to trigger ferroptosis regardless of acyl-CoA synthetase long-chain family member 4 (ACSL4) expression, a pro-ferroptosis gene (Doll et al., 2017). This suggests that alternative resistance mechanisms may exist. Recent evidence indicates that the ferroptosis suppressor protein 1 (FSP1)-coenzyme Q10 (CoQ10)-(nicotinamide adenine dinucleotide phosphate)NAD(P)H pathway co-operates with GPx4 and glutathione to suppress phospholipid peroxidation and ferroptosis, as a stand-alone parallel system (Bersuker et al., 2019; Doll et al., 2019). FSP1, previously called apoptosis-inducing factor mitochondrial 2 (AIFM2), was predicted to induce apoptosis by a caspase-1 independent pathway, due to its biochemical similarities to a previously known AIFM1 (Wu et al., 2002). Instead of inducing apoptosis, however, FSP1 is recruited to the plasma membrane by myristoylation, where it functions as an oxidoreductase that catalyzes the regeneration coenzyme Q10 (CoQ10) using NAD(P)H (Bersuker et al., 2019; Doll et al., 2019). Ubiquinol, the reduced form of CoQ10, is a lipophilic radical-trapping antioxidant (RTA) (Frei et al., 1990), that regulates ferroptosis by halting the propagation of lipid peroxides. Ubiquinol is generated by the mevalonate pathway, which is an essential anabolic pathway using acetyl-CoA (Mullen et al., 2016). Small molecules have been shown to initiate ferroptosis by blocking this pathway. For example, FIN56 binds to, and activates, the enzyme squalene synthase, resulting in the depletion of endogenous CoQ10 (Shimada et al., 2016).

Oxidation mechanisms
Lipid metabolism plays an indispensable role in physiological and pathological functions in the human body. For example, fatty acids are essential building blocks of cellular membranes and are the mediator of signaling and energy metabolism in cells (Oizmann & Carvalho, 2019). Long-chain fatty acids containing two or more double bonds are called polyunsaturated fatty acids (PUFAs), and they are involved in
plasma membrane generation and maintenance (Gill & Valivety, 1997a, 1997b). However, the cis double bonds of the methylene groups of PUFAs, are easily oxidized, and the more methylene groups present, the more susceptible the fatty acid is to autoxidation (Conrad & Pratt, 2019; Rouzer & Marnett, 2003). Ultimately, the accumulation of lipid hydroperoxides is a crucial factor that triggers ferroptosis (Dixon et al., 2012; Stockwell et al., 2017). Oxidized arachidonic acid (AA)-containing phosphatidylethanolamine (PE) (AA-PE) is a ferroptosis cell death signal. AA is a type of PUFA that can be elongated into arachidonyl (AdA) by elongase (Kagan et al., 2017). A recent study indicated that AA-OOH-PE, rather than other types of phospholipids [(PL)-OOH, induced ferroptosis (Kagan et al., 2017). In this process, the acyl-CoA synthetase long-chain family 4 (ACSL4) catalyzed the formation of AA-CoA (Doll et al., 2017), which esterified into AA-PE by lysophosphatidylcholine acyltransferase 3 (LPCAT3) (Dixon et al., 2015). Indeed, AA-PE can be oxidized to AA-OOH-PE by lipoxigenases (LOXs) and reactive oxygen radicals (Forcina & Dixon, 2019; Yang et al., 2016).

Additionally, cytochrome P450 oxidoreductase (POR) facilitates lipid peroxidation via the donation of electrons to downstream effectors in cells undergoing ferroptosis inducing stress (Zou et al., 2020). When the level of AA-OOH-PE exceeds the capacity of the reduction system (GPX4 et al.), ferroptosis occurs (Doll et al., 2017; Lagarde et al., 2015; Liang et al., 2019). Iron is a redox-active metal that can be involved in lipid peroxidation (Hassannia et al., 2019), of which there are two contributory pathways. Firstly, iron can be released from the labile iron pool (LIP), subsequently promoting ROS accumulation by the Fenton reaction (Kakhlon & Cabantchik, 2002; Kruszewski, 2003). Secondly, iron acts as an essential reactive element in many enzymes such as lipoxigenases (LOXs), and NADPH oxidases, is directly involved in lipid peroxidation (Grivennikova & Vinogradov, 2006; Halliwell & Cross, 1994). These results strongly indicate that proteins associated with iron homeostasis can also regulate ferroptosis. Moreover, the silencing of the iron response element binding protein 2 (IREB2) by sh-RNA has been shown to reduce sensitivity to ferroptosis (Dixon et al., 2012). Cysteine desulfurase (NFS1), the iron-sulfur cluster biosynthetic enzyme in eukaryotes, has also been found to inhibit ferroptosis in lung cancer (Álvarez et al., 2017). And promin2, a ferroptosis stress response protein, increases the resistance to ferroptosis via stimulating iron export (Brown et al., 2019). Autophagy of ferritin in lysosomes can also increase the content of the reduced form of iron (Terman & Kurz, 2013), thus facilitating ferroptosis. Meanwhile, ferritinophagy cargo receptor nuclear receptor coactivator 4 (NCOA4), can mediate the autophagic degradation of ferritin, and its subsequent inhibition is protective to cells from ferroptosis damage (Gao et al., 2016; Hou et al., 2016). Heme oxygenase-1 (HO-1) can catalyze heme degradation to release ferrous iron, and early research indicates that oxidative stress can induce HO-1 expression via the activation of the p62-Keap1-NRF2 pathway, to antagonize ferroptosis (Sun et al., 2016). However, overexpression of HO-1 may accelerate ferroptosis in cancer cells (Chang et al., 2018; Hassannia et al., 2018).

**Ferroptosis as the Major Form of Cell Death Occurred during Ischemia-Reperfusion**

In a variety of human conditions, I/R events cause extensive tissue damage, heightened inflammatory responses, and is a major cause of morbidity and mortality. Furthermore, there is evidence suggesting that the reduction of IRI may increase organ transplantation success rates (Raat et al., 2009). It is, therefore, important to determine and understand the type of cell death in I/R events, to identify appropriate therapeutic target opportunities. As noted above, recent investigations have provided strong evidence demonstrating how ferroptosis can participate in IRI, and how targeting ferroptosis might be beneficial for I/R conditions.

**Brain I/R events**

According to the data released by the World Health Organization (WHO), a stroke occurs on average every 5 seconds affecting 15 million people annually, and it is the leading cause of brain injury and subsequent permanent disability. The majority of strokes are caused by the occlusion of a cerebral artery (ischemic stroke) (Iadecola & Anrather, 2011). To date, no significant effective therapeutic interventions have been developed to counter the deleterious effects of cerebral I/R (Krishnamurthi et al., 2013; Yeo et al., 2013).

The physiological functions of the brain post-stroke result in increased vulnerability to oxidative stress. The brain requires a constant production of high levels of ATP to maintain metabolic activity and neuronal homeostasis (Bélanger et al., 2011), and ATP production is impeded in I/R. Additionally, the brain also accumulates more deleterious byproducts of mitochondrial metabolism under ischemic conditions when compared to other organs (Cardoso et al., 2017). Further, neuronal membranes are rich in PUFAs, which are easily oxidized (Conrad & Pratt, 2019). Accordingly, antioxidant production in the brain is tightly regulated and balanced. Under I/R conditions, iron accumulation in affected brain areas has been observed in both patients, and experimental animal models of cerebral ischemia (Ding et al., 2011; Park et al., 2011) (Dietrich & Bradley, 1988; Fang et al., 2013), and has been proposed as the key mediator of neuronal damage and death (Castellanos et al., 2002; Kondo et al., 1995, 1997). Consistently, iron chelation therapy has been shown to attenuate the cellular damage observed in the brains of experimental IRI rodent animal models (Hanson et al., 2009; Patt et al., 1990).

Tuo et al. (2017) have recently shown that ischemic stroke can cause pro-ferroptotic iron accumulation via the acute suppression of tau, an Alzheimer’s disease protein that can facilitate iron export (Lei et al., 2012, 2017), leading to worsening of IRI-related cellular damage and death (Bi et al., 2017).
Kidney I/R events

Renal IRI, a common cause of acute renal failure, has been widely observed in a variety of clinical events, including renal transplantation, embolic or thrombotic events, and surgical interventions, thus playing a significant role on the morbidity and mortality of patients (Pefanis et al., 2019; Zhang et al., 2014). Similar to other I/R events summarized above, reperfusion in the kidney generates an increase in reactive oxygen species that can induce cell death (Castaneda et al., 2003; Perico et al., 2004). For some time now, iron has been suggested to play an important role in renal IRI, and iron chelators have been shown to inhibit renal tubular cell death (Linkermann 2016; Sogabe et al., 1996). Due to its specific ability to reduce lipid peroxides, the role of GPx4 in renal IRI has recently been investigated. Knockout of GPx4 induces kidney failure in mice, which presents with molecular features of ferroptosis and can be inhibited by the application of ferroptosis inhibitors (Friedmann Angeli et al., 2014). Moreover, subsequent studies have also shown that ferroptosis inhibitors can attenuate renal IRI (Friedmann Angeli et al., 2014; Linkermann et al., 2014). The ubiquitous multi-functional protein, augmenter of liver regeneration (ALR), can alleviate IRI, and the silencing of ALR aggravates ferroptosis and is intricately linked to the glutathione–glutathione peroxidase system (Huang et al., 2019). However, the targeting of ferroptosis alone may not be an optimal therapeutic strategy, as two recent studies of renal IRI demonstrate the coexistence of both necrosis and ferroptosis pathways (Pefanis et al., 2019), indicating that necrosis and ferroptosis may play a synergistic role in renal IRI (Müller et al., 2017). By using CRISPR/Cas9 technology, Müller et al. (2017) found that the pseudokinase mixed lineage kinase domain-like protein (MLKL), a molecular switch to induce necroptotic cell death, drives basal resistance to ferroptosis via the depletion PUFAs, while ACSL4 drives basal resistance to necroptosis rendering the cell membrane less amenable to MLKL-driven membrane permeabilization in renal IRI. These observations suggest that combined therapy should be considered for the treatment of renal IRI. Interestingly, the activin receptor-like kinase (ALK4/5), also known as activin-transforming growth factor (TGF) β receptor, is involved in the stress-induced renal injury, and can suppress cadmium and erastin-induced renal tubular cell death (Fujiki et al., 2019), indicating that the renal IRI model may be useful for studying the relationship of ferroptosis and other forms of cell death.

I/R events of other organs

The role of ferroptosis has been investigated in other organs that can undergo I/R events. For example, testicular IRI induces cell death of germ cells and Sertoli cells, and the death of Sertoli cells is explicitly associated with ferroptosis, as indicated by the fact that ferroptosis inhibitors only, and not inhibitors of apoptosis, necrosis or autophagy, protect Sertoli cell from oxygen-glucose deprivation/reoxygenation (Li et al., 2018). Also, ACSL4 was shown to play a critical role in intestinal IRI, which can be protected by ACSL4 inhibition and ferroptosis inhibitors (Li et al., 2019).

CONCLUDING REMARKS

Elevated iron and oxidative stress exist in many organs or tissues after I/R, and iron chelating agents have been tested for and indeed demonstrated efficacy in the improvement of outcomes in a variety of symptoms associated with I/R. (Davis et al., 1997; Patt et al., 1990; Prass et al., 2002). However, the
use of iron chelators in the clinical setting is hampered by the potential negative impact on blood physiology, and by an inability to target the specific organs requiring therapeutic intervention effectively.

Over the last ten years, clinical trials for iron chelators in IRI have shown limited success (Chan et al., 2012; Drossos et al., 1995; Lesnefsky et al., 1990). The limitations are likely due to a variety of reasons, including chelating efficiency in iron affected areas, the specific timing of use, heterogeneity among patients, and other adverse off-target side effects, suggesting that by itself iron may not be an optimal target.

A growing number of recent studies link ferroptosis with IRI, and this should not be surprising, given the fact IRI is essentially related to oxidative damage, which is one of the main causes of ferroptosis. These observations should also provide a window for intervention, whereby instead of targeting the initial cause of the disease, it may be possible to target the pathways of cell death initiated by IRI directly. Multiple studies in numerous organs demonstrate that inhibition of ferroptosis, either by chemical inhibitors or genetic ablation of key genes involved in ferroptosis, can protect cells during IRI, strongly suggesting that ferroptosis can serve as a target for drug development. It is therefore imperative that research efforts are undertaken to screen new drug-like compounds for preclinical and clinical tests of ferroptosis inhibitors to treat IRI in the future.

COMPETING INTERESTS
The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS
H.Y. and P.L. conceived the review and prepared the draft. All authors contributed to the discussions. All authors read and approved the final version of the manuscript.

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