Ferroptosis in hepatic ischemia-reperfusion injury: Regulatory mechanisms and new methods for therapy (Review)

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Abstract. Ischemia-reperfusion injury (IRI), also called reoxygenation injury, is the outcome of inflammatory processes and oxidative damage through the induction of oxidative stress. In the clinical setting, IRI contributes to severe hepatic injury, including liver cell death by apoptosis and ferroptosis. Ferroptosis is a novel type of cell death in hepatic IRI that involves small molecules that inhibit glutathione biosynthesis or glutathione peroxidase 4 (GPX4), which is a glutathione-dependent antioxidant enzyme, causing mitochondrial damage. Currently, ferroptosis has been systematically described in neurological settings, kidney diseases and different types of cancer, while few studies have analysed the presence of ferroptosis and the regulatory mechanism of ferroptosis in hepatic IRI. Exploring the exact role played by ferroptosis in the liver following hepatic IRI in accordance with existing evidence and mechanisms could guide potential therapeutic interventions and provide a novel research avenue.

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Abbreviations: AA, arachidonic acid; ACSL4, acyl-CoA synthetase long-chain family 4; AdA, adrenoyl; ALA, alpha-lipoic acid; ALT, alanine aminotransferase; ASRK1, apoptosis signal-regulating kinase 1; ATP, adenosine triphosphate; BMP, bone morphogenetic protein; CAT, catalase, Ccl2, chemokine (C-C motif) ligand 2; Cxcl1, chemokine (C-X-C motif) ligand 1; Cxcl2, chemokine (C-X-C motif) ligand 2; CYP, cytochrome P450; CVF, cobra venom factor; DISC, death-inducing signalling complex; DMT1, divalent metal transporter 1; ERK, extracellular signal-regulated kinase; Fas, Fas cell surface death receptor; Fer-1, ferrostatin-1; FN, fibronectin; FINs, ferroptosis-inducing agents; GdCl3, gadolinium chloride; GP, glycogen phosphorylase; GPX4, glutathione peroxidase 4; GSH, glutathione; GSSG, oxidized glutathione; HSPB1, shock protein family B member 1; IL, interleukin; INOS, inducible nitric oxide synthase; IP, inositol phosphate; IPC, ischemic preconditioning; IRI, ischemia-reperfusion injury; JAK, Janus kinase; JNK, c-Jun N-terminal kinases; LOOH, alkyl radical; LOXs, lipoxygenases; LPCAT3, lysophosphatidylcholine acyltransferase 3; LT, leukotrienes; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase; MLKL, mixed-lineage kinase domain-like; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, transcription factors nuclear factor κB; NLRP3, pyrin domain containing 3; NOX, nitric oxide; PE-OOH, phosphatidylethanolamine-OOH; PHKG2, phosphorylase kinase G2; PMNs, polymorphonuclear neutrophils; PUFAs; polyunsaturated fatty acids; RCD; regulated cell death; RIPK1, receptor-interacting serine/threonine-protein kinase 1; ROS, reactive oxygen species; RSL3, Ras-selective lethal small molecule; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; STEAP3, six-transmembrane epithelial antigen of prostate 3; TfR, transferrin receptor; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-α; TRAF-2, TNF-receptor-associated factor 2

Key words: ferroptosis, hepatic IRI, ROS, lipid peroxidation, iron

Contents

1. Introduction

Ferroptosis has emerged as a novel type of regulated cell death (RCD) in various diseases, particularly in hepatic or renal ischemia-reperfusion injury (IRI). The occurrence of ferroptosis is based on iron overload, which generates reactive oxygen species (ROS) and lipid peroxides, primarily phosphatidylethanolamine-OOH (PE-OOH) *in vivo* (1-3). Ferroptosis was identified in 2012 and was originally reported to be associated with mutant RAS cancer cells 1 (4,5). Although the mechanism of ferroptosis has a relatively specific description, primarily including iron-dependent accumulation of lipid ROS and the consumption of plasma membrane polyunsaturated fatty acids (PUFAs) (5), the role of ferroptosis in cancer, heart, liver or

kidney injury, and neurotoxicity remains unclear (6). Severe hepatic IRI may lead to serious impairment of liver function or even acute liver failure (7,8). Therefore, it is critical to prevent hepatic IRI, especially in liver transplantation, due to the high risk of urgent re-transplantation (9). Distinct from other types of RCD (apoptosis, necroptosis and autophagy), ferroptosis is characterized by resulting oxidative damage in the mitochondria, which exerts harmful effects on hepatic ischemia-reperfusion (6,8). Furthermore, these injuries can be prevented by the ferroptosis-specific inhibitor ferrostatin-1 (Fer-1) and by iron chelators (6,8). Therefore, ferroptosis is a potential target for preventing and treating hepatic IRI. Thus, exploration of the exact mechanisms of ferroptosis in liver cell death is required.

The present review firstly introduces the types of hepatic IRI and subsequently describes the molecular mechanisms of liver IRI. Thirdly, the general mechanisms of ferroptosis and the role of ferroptosis in hepatic IRI are discussed; primarily including the inflammatory response and oxidative stress. In the final part of this review, several therapeutic strategies associated with ferroptosis are described in detail.

2. Hepatic IRI

Types of liver IRI. Hepatic IRI is still a long-standing problem in clinical conditions that occurs in hepatic resection surgery, liver transplantation and during states of shock. Two main types of hepatic IRI exist, including warm and cold IRI. Warm IRI, initiated by hepatocellular injury, occurs ischemia at routine temperature and is generally present in liver transplantation surgery or different forms of trauma or shock, and might lead to liver failure, or even bring the outcome of multiorgan failure (10). Cold IRI starts at the injury of endothelial cells in hepatic sinusoidal and microcirculation disorders with the temperature of liver decreasing rapidly and uniformly, which develops during *in vitro* preservation and is usually accompanied by warm IRI in the process of liver transplantation surgery (10,11). Although the two IRI types might possess distinct initial cellular targets, they do share similar pathophysiological processes, including local inflammatory innate immune activation (10,12,13), and expression of fibronectin (FN) in endothelial cells is a prominent feature of the liver injury response (14). At present, there is no evidence that hot or cold IRI causes different types of cell death.

In addition, IRI can be divided into two phases, ischemia and reperfusion, which are primarily the result of oxidative stress accompanied by nutritional deficiency, loss of blood flow, inflammation and other conditions (15). Such trauma primarily causes autophagy in liver cells, including apoptosis and necrosis (16). There is evidence that various markers of autophagy are elevated throughout the entire IRI process (17). Among them, iron-mediated death is primarily believed to be associated with oxidative stress from ROS, especially during blood reperfusion (18).

Ferroptosis is a type of iron-dependent oxidative cell death characterized by accumulation of intracellular ROS, which will be discussed in more detail. Furthermore, iron-mediated cell death is an important form of autophagy (19,20).

Molecular mechanisms of liver IRI. ROS (such as OH- and HOO-), chemically reactive species containing oxygen, are an important cause of initial liver injury (21) and are originally produced in Kupffer cells, which kill hepatocytes through lipid peroxidation, DNA oxidation and enzymatic degeneration (22). The pathway regulated by ROS that promotes apoptosis contains different molecules and transporters. Initially, ROS activates apoptosis signal-regulating kinase 1 (ASRK1) through TNF-receptor-associated factor 2 (TRAF-2) that leads to c-Jun-N-terminal kinase (JNK), which directly regulates the activities of pro- and anti-apoptotic mitochondrial proteins through different phosphorylation events or via upregulating pro-apoptotic genes through the trans-activation of specific transcription factors (23). In addition, tumour necrosis factor-α (TNF-α), subsequently released by ROS, can increase the damage after IRI by promoting extra release of inflammatory cytokines and creating positive feedback circuits, which leads to organ damage. Furthermore, TNF-α regulates the production of gangliochemical genes and adhesion molecules that are absorbed into the liver, and these neutrophils are eventually responsible for the subsequent stage of injury. In addition to TFN-α, other proinflammatory cytokines, such as IL-1β (24), IL-12 (25), IL-18 and IL-6 (10), are critical for the hepatic inflammatory response. Furthermore, IL-12 is indispensable for fully producing TNF-α in the liver and the ensuing inflammatory response, which was confirmed using neutralizing antibodies or IL-12 knockout mice to eliminate IL-12 (10). These injuries eventually lead to biliary microcirculatory disorders and apoptosis of biliary epithelial cells.

Relevant proinflammatory signalling pathways include nuclear factor κB (NF-κB), which is activated by proinflammatory cytokines, such as IL-1 and TNF-α.

Of note, ROS can also stimulate NF-κB to promote hepatic IRI (26,27). Hence, antioxidants decrease the expression of pro-inflammatory genes by inhibiting the activation of NF-κB (28-31). On the other hand, superoxide formation in endothelial cells (32) and hepatocytes (33) was recently shown to originate from a phagocyte-type nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Therefore, inhibiting Rac1, a member of the Rho family of small GTPases that can regulate this oxidase, attenuates intracellular oxidant stress and protects against hepatocyte injury during the early reperfusion phase (33).

3. Brief overview of ferroptosis

Ferroptosis is a form of RCD that is dependent on iron and ROS, and is initiated by the failure of glutathione biosynthesis or the inactivation of glutathione peroxidase 4 (GPX4), an antioxidant enzyme that depends on glutathione, thus resulting in lipid peroxidation, the consumption of PUFAs, and eventual cell death (4). Ferroptosis has distinct features at the morphological, biochemical, and genetic level compared with other forms of RCD, including necroptosis, apoptosis and autophagy. Small molecules, such as erastin, ras-selective lethal small molecule (RSL3), high concentrations of glutamate, and sulfasalazine are known to reduce ferroptosis, while α-tocopherol, ferrostatin-1, liproxstatin-1, glutathione, zileuton and iron chelators (such as deferasirox, deferiprone, chelation with deferoxamine and 1,10-phenanthroline) are inhibitors involved in relevant mechanisms of ferroptosis that contribute to hepatic IRI (6,34,35). However, how ferroptosis plays an

essential role in cell injury is not well understood. Moreover, the detailed signalling pathway that lie between IRI induction and ferroptosis activation remains unknown. Validation is still required to understand all the molecules on this pathway, and the known details are summarized, which is still the inevitable limitation of this review.

4. The ferroptotic signalling pathway

The activation of mitogen-activated protein kinase (MAPK), iron metabolism and lipid peroxidation signalling pathways are currently known to contribute to ferroptotic cell death (36). However, it has been reported that the MAPK pathway was associated to to cancer cell death, which inhibits ferroptosis induced by erastin by blocking the Ras/Raf/MEK/ERK pathway in Ras-mutated cancer cells (8). Hence, iron and ROS signalling pathways are primarily described in the present review.

Iron and ferroptosis. The principal role of iron is to transport oxygen in the haematological system. Iron possesses two forms in cells: Fe^{2+} and Fe^{3+}. The Fe^{2+} absorbed into the blood is oxidized to Fe^{3+} by ceruloplasmin, and Fe^{3+} is transported to the tissues after binding with transferrin or is absorbed into the cell through the membrane transferrin receptor (TfR), then localised to the internal body, and Fe^{3+} is reduced to Fe^{2+} by the ferrireductase activity of six-transmembrane epithelial antigen of prostate 3 (STEAP3). Finally, release of Fe^{2+} from the endosome to a labile iron pool is mediated by divalent metal transporter 1 (DMT1) in the cytoplasm. Excess iron is kept in the monocyte-macrophage system of the liver, spleen, bone marrow and other organs in the form of ferritin and hemosiderin. Membrane protein ferroportin, an iron efflux pump that oxidizes Fe^{2+} into Fe^{3+}, transmits signals to mediate iron output (Fig. 1). Fe^{2+} has the feature of a catalyst, which can transfer electrons and participate in various oxidation-reduction reactions, while Fe^{3+} primarily exists in the process of transportation and storage.

However, iron overload is recognized as poisonous to cells, since the transferred electrons are given to O_2 and H_2O_2 to produce superoxide anions and hydroxyl radicals, which exert harmful influences on biological macromolecules, such as nucleic acids, proteins and lipids (37). Moreover, Fe^{2+} can oxidize organics combined with H_2O_2 to generate ROS by the Fenton reaction (3,37). As Wang *et al* (38) stated, hepatocytes and macrophages are sensitive to extracellular iron levels, and a high-iron diet in mice could trigger ferroptotic cell death. Additionally, shock protein family B member 1 (HSPB1) inhibits ferroptosis through decreasing intracellular iron levels and upholding glutathione (GSH) in its reduced form. Furthermore, TfR1-mediated iron uptake is inhibited by HSPB1, which blocks the endocytosis and recycling of transferrin to decrease intracellular iron levels (39-41). These studies suggest that iron plays a critical role during ferroptosis, although the role of iron in the signalling pathway of ferroptosis remains poorly understood. To date, in addition to the Fenton reaction by Fe^{2+}, there is an additional source involved in the iron-dependent accumulation of lipid ROS in ferroptosis: Lipid peroxidation controlled by iron-containing lipoxygenases (LOXs) (Fig. 1) (42).

LOXs are a family of non-haem, iron-containing enzymes, and most of them catalyse the deoxygenation of PUFAs, such as arachidonic acid (AA) and linolenic acid, in lipids containing a *cis*, *cis*-1,4-pentadiene into cell signalling agents (43-45). As one type of PUFA, AA is converted to adrenoyl (AdA) under the action of elongase (2), and then on the endoplasmic reticulum or mitochondrial outer membrane, AA and AdA are catalysed by acyl-CoA synthetase long-chain family 4 (ACSL4) to form AdA-CoA/AA-CoA, which is next esterified to AA-PE under the action of lysophosphatidylcholine acyltransferase 3 (LPCAT3), finally forming AA-OOH-PE, a cell death signal of ferroptosis, under the oxidation of iron-containing LOXs (46,47). However, the role of iron in regulating LOXs relies on phosphorylase kinase G2 (PHKG2), which activates glycogen phosphorylase (GP) to release glucose-1-phosphate from glycogen, promoting the phosphorylation of LOXs to synthesise lipid peroxides. Furthermore, glycogen primarily exists in liver and muscle tissues; therefore, glycogen breakdown might be an important factor in ferroptosis in liver or muscle injury, although no current studies have confirmed this. In conclusion, iron-containing LOXs are required for ferroptosis in the reaction of lipid peroxidation, and inhibition of ACSL4 and LPCAT3 may decrease oxidation of some sensitive fatty acids in the membrane. However, more studies are required to further explain the detailed role of iron in mediating LOX activity.

ROS and ferroptosis. ROS are primarily located in the mitochondria during electron transport (48), and iron-dependent lipid ROS produced by the two aforementioned sources mediate lipid peroxidation that further promotes the accumulation of lipid peroxides (Fig. 1) (6). Furthermore, peroxides lead to fundamental changes in lipids, especially phospholipids, which are essential for maintaining the integrity of the mitochondrial membrane architecture. In addition, peroxides can affect the fluidity of lipids, thus blocking receptor clustering and propagating inflammatory signalling (49). The peroxidation of phospholipids also inactivates membrane-bound proteins, ultimately causing destruction of the membrane (50). In addition, the occurrence of ROS accompanies single electron leakage of oxidative phosphorylation in the mitochondria, thus decreasing the yield of ATP and inhibiting cell survival (49). Thus, increased mitochondrial ROS can destroy the integrity of the electron transport chain, causing respiratory chain dysfunction (51). Moreover, lipid peroxidation products lead to mtDNA damage, further contributing to mitochondrial mutations, whereas mutations in the mitochondria further increase levels of ROS with toxic effects (49,51), resulting in a vicious circle. On the one hand, stable aldehyde peroxidation products from PUFAs, such as 4-hydroxynonenal and malondialdehydes, are involved in mtDNA mutations or deletions (52). Although aldehydes have significant toxic effects, some enzymes *in vivo*, such as cytochrome P450 (CYP), aldehyde dehydrogenase and aldo-keto reductases, can metabolize them to less toxic compounds (53). Evidence shows that members of CYP3A and CYP4A oxidize 4-hydroxynonenal (38). However, when mitochondrial dysfunction and increased ROS occur, oxidation and antioxidant systems lose balance *in vivo*, and the mitochondrial crest decreases or disappears. The outer wall of the mitochondrial membrane ruptures, which is a typical

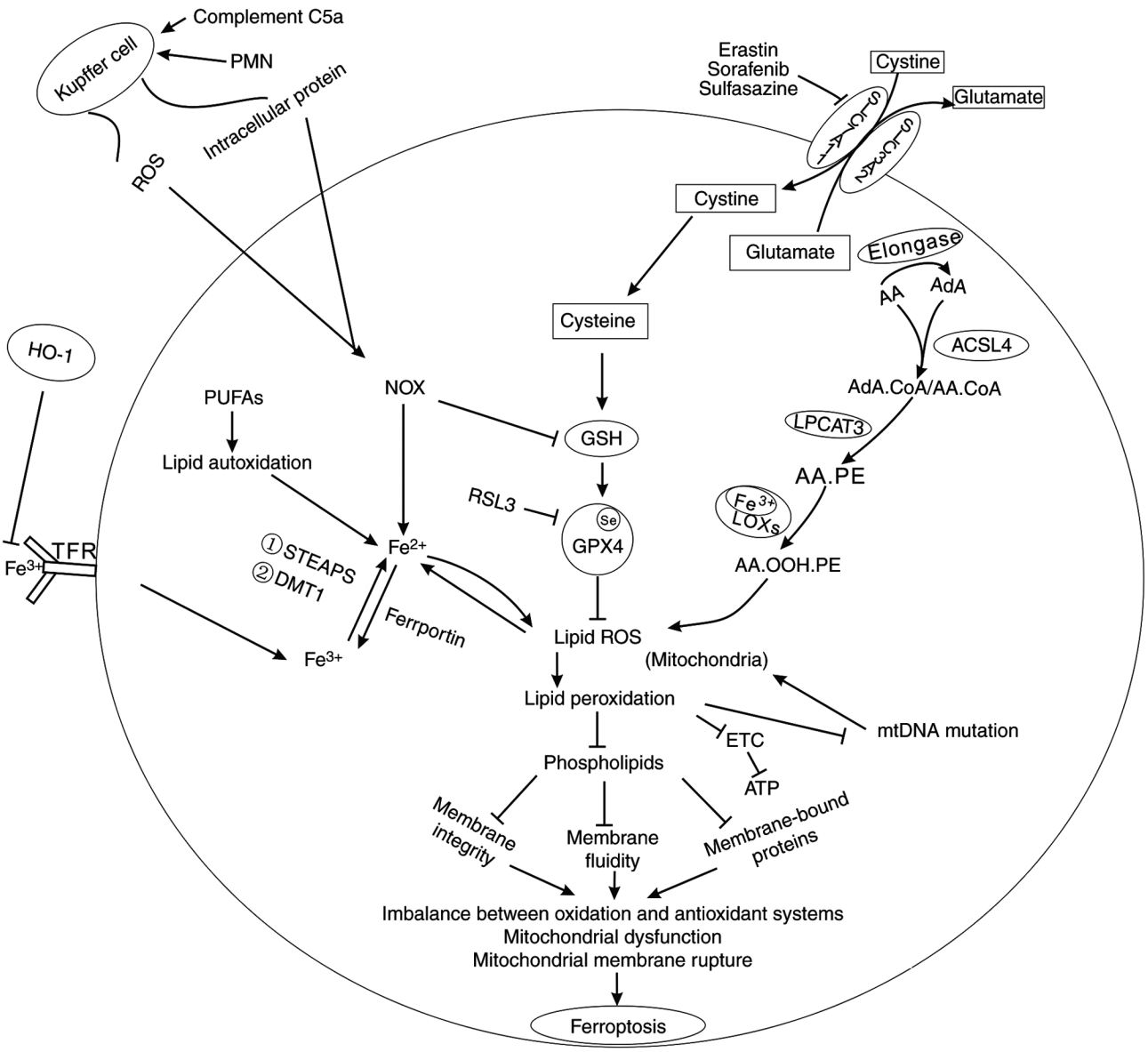

Figure 1. Iron metabolism in ferroptosis. Accumulation of lipid ROS: The Fenton reaction by Fe^{2+}; lipid peroxidation controlled by iron-containing lipoxygenases; and lipid auto-oxidation controlled by iron-catalysed enzyme. The mechanism of lipid ROS leading to ferroptosis. Complement and PMNs participate in the process of oxidant stress induced by Kupffer cells. ROS, reactive oxygen species; PMNs, polymorphonuclear neutrophils.

feature of ferroptosis that differentiates it from apoptosis, necroptosis and autophagy (6). In conclusion, it is postulated that ROS-induced ferroptosis depends on changes in the mitochondria.

5. Ferroptosis in hepatic IRI

Recent evidence has shown that ferroptosis is associated with the pathogenesis of various diseases, such as neoplastic diseases and ischemic injury to the brain, heart, liver, kidney and intestine (6-8,54-56). Furthermore, several studies have indicated that inhibitors of ferroptosis, such as ferrostatins-1 and liproxstatins-1, protect against cell death in the liver, kidney, brain and heart ischemic injury in mouse models (55-57). In a study by Yamada *et al* (8), the role of ferroptosis in hepatic IRI was explored, which established a murine model of hepatic ischemia-reperfusion injury and found that upregulation of the ferroptosis marker Ptgs2, lipid peroxidation and liver damage were induced by hepatic ischemia reperfusion. Moreover, all of these liver cell injuries can be prevented when super-inducing the ferroptosis-specific inhibitor Fer-1 and by iron chelation (8,54). Thus, it seems that iron overload is a critical factor for hepatic IRI, and the pathogenesis of hepatic IRI is partly attributed to ferroptosis (8).

Role of iron in inflammation in hepatic IRI. At present, it is widely accepted that hepatic IRI is characterized by an excessive inflammatory response, release of inflammatory cytokines and chemokines, as well as neutrophil and macrophages infiltration. In addition, IL-1β is the decisive factor that drives many sterile inflammatory diseases (58), especially in hepatic IRI (Fig. 2). However, there are two stages in the release process of IL-1β: The synthesis of pro-IL-1β and the maturation of IL-1β. Regarding the priming process, Toll-like receptor 4 (TLR4)

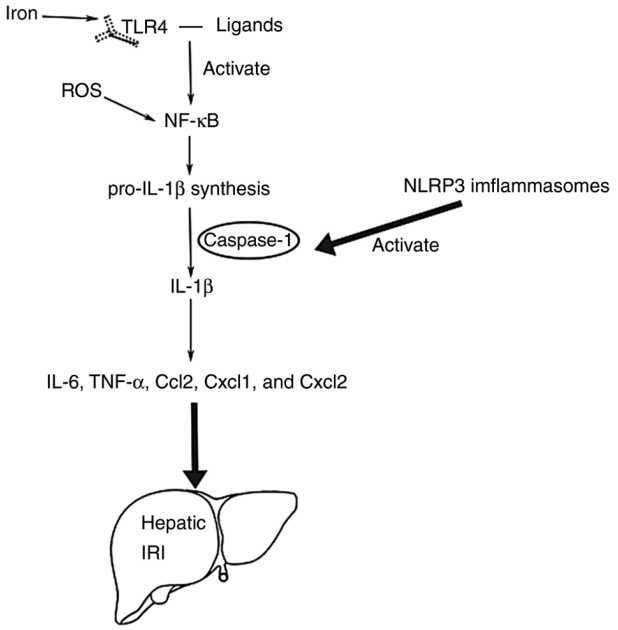

Figure 2. The role of IL-1β in hepatic IRI. Two stages in the release process of IL-1β: i) The synthesis of pro-IL-1β; and ii) the maturation of IL-1β. Finally, IL-1β induces expression of IL-6, TNF-α, Ccl2, Cxcl1, and Cxcl2, leading to tissue injury in the ischemia-reperfusion liver. IRI, ischemia-reperfusion injury; IL, interleukin; TNF-α, tumor necrosis factor-α; Ccl2, chemokine (C-C motif) ligand 2; Cxcl1, chemokine (C-X-C motif) ligand 1; Cxcl2, chemokine (C-X-C motif) ligand 2; TLR4, Toll-like receptor 4; NF-κB, transcription factors nuclear factor κB; NLRP3, pyrin domain containing 3.

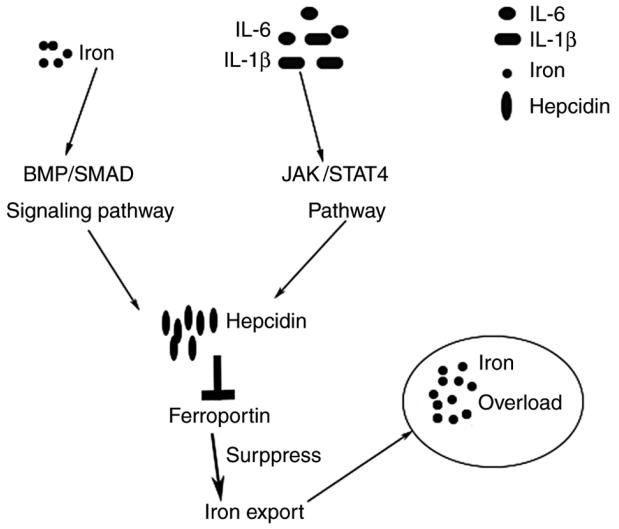

Figure 3. Regulation of iron homeostasis by increasing the expression of hepcidin at the transcriptional level. Increased hepcidin downregulates the level of ferroportin to suppress iron export. JAK, Janus kinase; BMP, bone morphogenetic protein; IL, interleukin.

binds to the ligands (such as heat shock proteins, fibronectin, fibrinogen, high mobility group box 1, hyaluronan and heparin sulphate) to produce signal transduction (59) and then through NF-κB activation, induces pro-IL-1β synthesis. Concerning the maturation of IL-1β, it is reported that receptor family pyrin domain containing 3 (NLRP3) inflammasomes play an important role (60-62). Firstly, NLRP3 inflammasomes, containing adaptor molecule apoptosis-associated speck-like protein, containing a caspase recruitment domain, cysteine protease caspase-1 and NLRP3, contribute to the activation of caspase-1. Secondly, pro-IL-1β is processed into its mature form by caspase-1 as an IL-1β converting enzyme, and caspase-1 induces the release of IL-1β. Finally, IL-1β induces expression of IL-6, TNF-α, Ccl2, Cxcl1 and Cxcl2, leading to tissue injury in the ischemia-reperfusion liver (63).

By performing real-time RT-PCR analysis, a previous investigation evaluated the expression of inflammatory cytokines and cell markers to confirm the association between iron overload and inflammatory response in the liver (8). The results showed that inflammatory cytokines and cell markers were significantly inhibited by Fer-1. Furthermore, the infiltration of neutrophils and macrophages was also apparently inhibited (8). This implies that ferroptosis in liver cell death might be closely associated with the inflammatory reaction in hepatic IRI. Further evidence demonstrated that iron is central to many aspects of the innate immune response, including ROS generation and host inflammatory regulation (1). Iron overload causes metabolic disturbance, leading to an increased susceptibility to infection and triggering the inflammatory response as the oversaturation of host transferrin leads to defective nutritional immunity (64). In a healthy individual, *in vivo* iron is a stable condition, and excess iron accumulation can lead to the production of ROS. Regarding the role of iron in inflammation in hepatic IRI, several studies have demonstrated that the TLR4-activated inflammatory response is modulated by iron, as well as increasing oxidative stress through the generation of reactive oxygen and nitrogen species (65,66). As previously stated, induction of pro-IL-1β synthesis is required for NF-κB activation, while ROS can activate the transcription factor NF-κB (67). Furthermore, systemic iron homeostasis is regulated in the liver, and the hepatic hormone hepcidin is the central regulator (68). There are two pathways to increase the expression of hepcidin at the transcriptional level, including inflammatory cytokines, such as IL-1β and IL-6 via the JAK/STAT3 pathway, and iron via the BMP/Smad signalling pathway (Fig. 3) (69). Increased hepcidin downregulates the level of ferroportin, the sole known iron exporter on the cell surface of hepatocytes, so that intracellular iron levels increase due to suppression of iron export (69). Hence, it is conjectured that the inflammatory response triggered in hepatic IRI induces iron overload in hepatocytes. In other words, ferroptosis greatly contributes to the pathogenesis of hepatic IRI.

Role of iron in oxidative damage in hepatic IRI. In order to continue exploring the role of iron in hepatic IRI, oxidative damage in liver cell injury is described in detail in the present review. In the mechanism of ferroptosis occurrence, iron-dependent accumulation of lipid ROS can be produced from GSH depletion and NADPH-dependent lipid peroxidation (5,70). Low levels of ROS, including hydrogen peroxide (H_2O_2), superoxide anions (O^{2-}) and hydroxyl radicals (-OH) (71-73), play an indispensable role in various molecular biological processes, such as intracellular messaging and molecular pathways in cellular progression (cell growth, differentiation and death) or immunity (74), the arrest of growth, and defence against microorganisms and apoptosis (75,76). In contrast, high or and/or inadequate removal of lipid ROS from Kupffer cells is the cardinal factor in vascular

and parenchymal cell oxidative damage during reperfusion, which occurs by inducing oxidant stress (77). According to current studies, there are distinct factors participating oxidant stress. First, complement and polymorphonuclear neutrophils (PMNs) participate in the process of oxidant stress induced by Kupffer cells (Fig. 1) (78). Kupffer cells release intracellular proteins and ROS during hepatic ischemia, inducing the activation of complement and leading to slight initial injury. Complement, on the one hand, activates and further stimulates Kupffer cells to produce ROS, and on the other hand, directly or indirectly causes activation and generation of PMNs in the liver through aggravating the initial injury induced by Kupffer cells. Moreover, the mechanism of complement-induced activation of neutrophils has been described in other studies, which demonstrated that complement factors, such as C5a, can recruit neutrophils into sinusoids by upregulating the Mac-1 receptor on circulating neutrophils (79,80). However, the generation of PMNs in the liver also causes hepatocyte injury, and this damage further promotes the activation of complement and PMNs, stimulating the Kupffer cells to produce reactive oxygen that contributes to the oxidative damage in hepatic IRI (81). An investigation using cobra venom factor (CVF) that effectively inhibits complement activation through the classical and alternate pathway (82,83), induced the depletion of complement and a novel soluble complement receptor type 1, significantly attenuating the increase of plasma alanine aminotransferase (ALT) activities (81). This experiment confirms that complement exerts an indispensable role in Kupffer cell-induced oxidative injury. Secondly, a current view suggested that Kupffer cells could be potentially activated during the ischemic period, resulting in the Kupffer cells generating superoxides, such as the superoxide anion radical (O^{2-}), when subjected to reoxygenation (84). This process is likely to be activated by nitric oxide (NOX), while the oxidase also stimulates the activation of ferroptosis by inhibiting glutathione biosynthesis or GPX4 (4). Moreover, NOX induces lipid peroxidation, producing many complex products, such as epoxides, hydroperoxides, and carbonyl compounds (85). Lipid peroxidation primarily targets cellular membranes, then peroxide PUFAs of membrane phospholipids, and finally causes structural and functional tissue damage due to the disintegration of the cellular membrane (86). In hepatic IRI, this mechanism exacerbates erythrocyte functions, impairing membrane integrity (87) and significantly altering erythrocyte deformability (86). Diminished erythrocyte deformability not only attenuates oxygen transport capacity of the erythrocytes but also affects the survival of circulating erythrocytes (87,88). Furthermore, another product of lipid peroxidation is malondialdehyde, which can react with DNA and as a result is toxic and mutagenic (88). Ultimately, malondialdehyde is substantially generated in the liver and results in the death of hepatic parenchyma cells. An antioxidant defence system containing glutathione peroxidase (GPX), ascorbic acid (vitamin C), superoxide dismutase (SOD), a-tocopherol (vitamin E), catalase (CAT), and GSH also exists in the body to fight against the generation of free radicals by eliminating superoxide anions and hydrogen peroxides (89-92). When the balance between oxidation and antioxidant systems is disrupted, increased lipid peroxidation can induce oxidative stress (89). As previously reported, iron promotes ferroptosis by lipid peroxidation in hepatic IRI (6,8,36). To affirm this mechanism, a mouse ischemic model was given iron chelation with deferoxamine treatment, which decreased the liver iron content and serum ferritin levels (8).

6. Other types of regulated cell death

In addition to ferroptosis, there are other types of regulated cell death, such as apoptosis, necrosis and autophagy. Apoptosis, a form of programmed cell death, leads to characteristic cell changes including blebbing, cell shrinkage, nuclear fragmentation, chromatin condensation, chromosomal DNA fragmentation, and global mRNA decay, which finally leads to the formation of apoptotic bodies and phagocytosis of the apoptotic bodies by adjacent parenchymal cells, neoplastic cells or macrophages (93). The pathways that initiate apoptosis are categorized as intrinsic or extrinsic, which are initiated by different types of stimuli, and finally through pro-apoptotic proteins to activate caspase-9 and caspase-8, respectively (94-96). Bcl-2 family members and cell death receptor/ligand (FasL/FasR and TNF-α/TNFR1) are the main molecules of the main apoptosis signal pathway (95,97,98). In contrast to apoptosis, necrosis, a passive type of RCD is initiated by external physical or chemical factors, and mainly characterized by swelling of cytoplasm and mitochondria, loss of plasma membrane integrity, resulting in the release of pro-inflammatory factors and the inflammation in the surrounding tissue (99). Similar to the extrinsic signaling pathway of apoptosis, necrosis also is initiated by cell death receptor/ligand (FasL/FasR and TNF-α/TNFR1), which forms a death-inducing signaling complex (DISC) with procaspase-8 by recruiting Fas-associated death-domain and receptor-interacting serine/threonine-protein kinase 1 (RIPK1) (94). Differentially, apoptosis originates from the activation of caspase-8 by the complex, while necrosis is caused by deubiquitinated RIPK1 recruiting RIPK3 through the RIP homotypic interaction motif interaction and phosphorylation of mixed-lineage kinase domain-like (MLKL) protein when caspase-8 activity is inhibited. The oligomerization of phosphorylated MLKL seems to bind to high-order inositol phosphate (IP), which is then transferred to the plasma membrane to induce cytolysis, resulting in the release of pro-inflammatory damage-associated molecular proteins. Besides, it also activates NLRP3, then leads to the secretion of interleukin (IL)-1β and IL-18 (100). It is common that the inflammatory responses activated by ferroptosis and necrosis both involve the participation of molecules such as IL-1β and TNF-α. However, ferroptosis accounts more for lipid peroxidation caused by iron overload, and the accumulation of ROS leads to the hepatocyte mitochondrial membrane permeability.

As aforementioned, hepatic IRI is divided into two processes: Ischemia and reperfusion. In the process of liver ischemia, it mainly causes hypoxia and energy depletion, and the reperfusion process causes oxidative stress and inflammatory reaction. Both of these processes will lead to apoptosis and necrosis, and finally result in autophagy. Autophagy is another type of RCD regarding to a process that cytoplasmic substances are transported to lysosomes, autophagy-related protein forms autophagosomes, and finally the components contained are degraded. More importantly, autophagy plays a critical role in regulating liver metabolism, energy production and quality control checkpoints as organelles such as

mitochondria (101). However, a study shows that autophagy is also associated with hepatocyte death (102). Autophagy can be divided into three types: i) autophagy-associated cell death; ii) autophagy-mediated cell death, and iii) autophagy-dependent cell death (103). For the first two types, autophagy plays a minor role in the mechanism of cell death, thus should depend on other types of cell death, such as apoptosis, necrosis and ferroptosis. The third type of autophagy can independently mediate the mechanism of cell death, so in the process of hepatocyte death, apoptosis, necrosis, autophagy and ferroptosis can be either interdependent or independently mediated. Interestingly, studies have shown that there is a link between the activation of autophagy and the development of ferroptosis, a process known as 'ferritinophagy', which is characterized by autophagy degradation of ferritin. In this process, the nuclear receptor coactivator 4, a selective cargo receptor for the turnover of ferritin, enables the maintenance of iron homeostasis, then results in iron overload and promotes the development of ferroptosis through the degradation of ferritin (104,105).

7. Current therapeutic strategies in hepatic IRI

Currently, some potential therapeutic strategies have been reported for ferroptosis regulation in liver ischemia-reperfusion, primarily including antioxidants and iron-removing molecules (such as desferoxamine, ferrostatin-1, liproxstatin-1, α-tocopherol, ascorbic acid, GSH, alpha lipoic acid, gadolinium chloride, zileuton and gadolinium chloride).

Desferoxamine. As aforementioned, iron overload promotes lipid peroxidation and is involved in the inflammatory response of hepatic IRI, leading to ferroptosis in liver cells. Desferoxamine is an iron chelator that can decrease the levels of intracellular iron. Experimental studies on hepatic ischemia models using desferoxamine pretreatment have shown beneficial effects, such as decreasing the liver iron content, decreasing serum ferritin levels, and restoring total GSH levels, in response to warm or cold hepatic ischemia (8,106,107).

Ferrostatin-1. Ferrostatin-1 is a first-generation ferrostatin that inhibits ferroptosis by interfering with ROS accumulation from lipid peroxidation (7,8). Mechanistically, to fight against ferroptosis, a previous study (108) demonstrated that anti-ferroptotic activity of fer-1 primarily depends on the scavenging of initiating alkoxyl radicals produced by ferrous iron from lipid hydroperoxides, and moreover, when fer-1 attenuates lipid peroxidation, its levels are not significantly consumed. The mechanism underlying this effect is not currently understood, and more molecular studies are needed to explain it. In addition to ferrostatin-1, there exits second- and third-generation ferrostatins that are more stable, exhibiting increased metabolic stability in the plasma. All of the third-generation ferrostatins are significantly protective against tissue injury, including acute kidney injury and IRI, *in vivo* (6).

Liproxstatin-1. Liproxstatin-1 is a potent ferroptosis inhibitor in $Gpx4^{-/-}$ cells that acts by preventing ROS accumulation. Liproxstatin-1 also inhibits ferroptosis in a mouse model of liver tissue injury induced by ischemia-reperfusion (57). A previous study reported that liproxstatin-1 decreases voltage-dependent anion channel 1 levels and restores GPX4 levels to protect against ischemia-reperfusion (109). Furthermore, post-treatment with liproxstatin-1 protects mitochondrial structural integrity (109). Although liproxstatin-1 decreases ROS levels, it does not affect Ca^{2+}-induced mitochondrial permeability transition pore opening. Moreover, compared to fer-1, liproxstatin-1 has relatively stronger potency. Liproxstatin-1 also suppresses ferroptosis-inducing agents (FINs), comprising RSL3, erastin, and BODIPY 581/591 C11 oxidation (57). Hence, liproxstatin-1 may represent an extremely promising therapeutic drug in hepatic IRI.

α-Tocopherol. α-Tocopherol is a type of membrane and extracellular antioxidant, also called vitamin E. It helps to prevent free radicals from damaging hepatic cells and serves as an inhibitor of protein kinase C and lipid peroxidation that increases GSH levels (110,111). The efficacy of protecting liver cells during ischemia-reperfusion was shown in an animal experiment, which indicated that the group treated with α-tocopherol exhibited a significantly higher survival rate (110). Another study showed that pretreatment with high doses of α-tocopherol (30 and 300 mg/kg of body weight administered intramuscularly) enhanced ATP levels, attenuated lipid peroxidation, and prevented the loss of hepatic glutathione (111-113). Furthermore, α-tocopherol has shown beneficial effects in both cold and warm IRI, decreases mitochondrial damage induced by oxidative stress (113,114). Low doses of α-tocopherol can also protect against liver cell death if combined with gadolinium chloride ($GdCl_3$) or ischemic preconditioning (IPC) (110,115).

Ascorbic acid. Ascorbic acid, also known as vitamin C, is a vital antioxidant with strong inhibition of lipid peroxidation and ROS scavenging ability (116). Ascorbic acid conveys an electron(s) to ROS, providing site-specific protection against oxidative stress (117). The clotting factors can be used to access acute liver cell damage, and after treatment with ascorbic acid, the activity of clotting factors I, II, V, VII, and X showed significant improvement (116). Furthermore, ascorbic acid avoids the oxidative degradation of vitamin E (a type of antioxidant) by reacting directly with intermediates of tocopherol oxidation, as well as free radicals (118). Another study treated rats with ascorbic acid (100 mg/kg, i.v.) 5 min before sustained ischemia, and IPC and ascorbic acid synergistically attenuated mitochondrial damage during reperfusion due to decreased oxidant stress (119). During the process of ferroptosis in hepatic IRI, iron reacts with hydrogen peroxide to form hydroxyl-like radicals, hydroxyl and ferric ions, and these products are reduced by ascorbic acid, which inhibits iron-dependent Fenton reactions (120). In accordance with another study, it was clearly demonstrated that serum aminotransferase levels, lipid peroxidation, the loss of bile flow and cholate output were inhibited by ascorbic acid doses of 30 and 100 mg/kg but were promoted by a dose of 1,000 mg/kg (120). Therefore, low doses of ascorbic acid (30 and 100 mg/kg) have antioxidant effects, while high doses (1,000 mg/kg) have pro-oxidant effects; thus, the dose should be adjusted when ascorbic acid is applied. Moreover, the therapeutic window might be appropriate over a short time prior to or just at the beginning of reperfusion (121).

GSH. GSH is a thiol-containing compound, oxidizing sulfhydryl group of cysteine that exerts antioxidant effects (122). It is a substrate of GPX4, and GSH depletion results in inactivation of GPX4, contributing to ferroptosis by accumulation of ROS from lipid peroxidation (70). Therefore, pretreatment with GSH directly scavenges ROS (123). The GSH/GSSG redox system majorly regulates intracellular redox status (112) and giving GSH in advance may promote intracellular reduction response to prevent oxidative damage. However, there exit some administrative limitations. For instance, whether intracellular GSH is simply available and its ability to decrease GSSG and to what extent are not completely understood (124). A previous analysis demonstrated significant protection for hepatocytes in both warm and cold liver ischemia by intravenous glutathione administration (doses over 100 mol/h/kg) (125). It is assumed that GSH will become an additional therapeutic approach for ferroptosis during hepatic IRI.

α lipoic acid (ALA). ALA is a natural compound that occurs *in vivo*. ALA is an antioxidant that provides protection against damage to the body's cells. Because of its antioxidant and oxidant-scavenging properties, ALA may protect the liver against oxidative injury (126), and this function has been corroborated in rat liver that underwent 90 min of warm ischemia (127). ALA was shown to significantly decrease levels of AST, increase ATP content, and lower apoptotic hepatocyte injury by improving expression of anti-apoptotic proteins to decrease hepatic injury (128). Moreover, ALA also protects against IRI caused by cirrhosis or steatosis due to improving cholinesterase activity in the serum (128). Furthermore, another study reported additional findings for ALA in the treatment of hepatic IRI, including decreasing levels of TNF-α and IL-1β, reversing myeloperoxidase activity (indicating increased neutrophil infiltration to the tissue), and maintaining regular morphology of the central vein and hepatocytes (126). As a powerful direct chain-breaking antioxidant, ALA strengthens the antioxidant potency of both ascorbate and vitamin E (129). Currently, ALA is a potential strategy to protect against hepatic IRI.

CVF. CVF has been affirmed to be beneficial for the protection of hepatocytes during ischemia-reperfusion in clinical settings (81,130). CVF is a stable complement inhibitor from cobra venom that binds to factor B as a structural and functional analogue of the complement component C3b, forming the bimolecular complex CVF/Bb through the cleavage of factor D (130). CVF/Bb is a C3/C5 convertase that simultaneously cleaves complement C3 and C5 (131-133). Thus, continuous activation of C3 and C5 leads to the depletion of complement components and inhibits their activation. In a final analysis, through subsequently suppressing the release of inflammatory mediators, such as TNF-α and IL-1β, oxidant stress induced by Kupffer cells and hepatic cell apoptosis was decreased to attenuate hepatic injury (78,130). However, the window of time available for therapeutic intervention to block complement-mediated inflammatory responses and oxidant stress in hepatic cells should be reviewed due to the recovery of complement activity and regeneration in hepatocytes (78,130). As an anticomplement protein, CVF may represent a novel therapy to improve multiple organ injury induced by ischemia-reperfusion.

Zileuton. Zileuton inhibits the biosynthesis of leukotrienes (LTB4, LTC4, LTD4 and LTE4) because it is an active inhibitor of 5-lipoxygenase. Zileuton decreases glutamate-induced ROS accumulation, significantly inhibiting glutamate- and erastin-induced ferroptosis (134).

Gadolinium chloride. $GdCl_3$, a rare earth metal, is a protective intervention in a rat hepatic reperfusion injury model that inhibits Kupffer cell activation (115,135). It has been shown that pretreatment with $GdCl_3$ for hepatic IRI enhances the survival rate (115), decreases neutrophil infiltration and myeloperoxidase activity (136), and decreases platelet aggregation in cold-perfusion liver (137). Additional experiments have concluded that $GdCl_3$ promotes recovery of hepatic function (135,138), prevents sinusoid endothelial cell apoptosis (137), inhibits the formation of free radicals, and attenuates lipid peroxidation (139,140). However, the use of $GdCl_3$ may induce side effects (115), including significant loss of bile flow, altered hepatocellular integrity (increased serum enzyme activities), and inhibition of phagocytic activity in Kupffer cells. In addition, inhibition of Kupffer cells damages host defences (141,142) because the ability to clear bacterial lipopolysaccharides from the blood is deranged. Hence, the dose of $GdCl_3$ should be kept as low as possible due to potential adverse effects, and it is necessary to monitor hepatic function when using $GdCl_3$ for treatment (115).

8. Conclusions and future perspectives

Hepatic IRI is a complex process that involves various pathways and is complicated by a range of factors. Therefore, it is important to understand the pathophysiological pathways involved in liver damage during ischemia-reperfusion. This review discussed the detailed mechanism of ferroptosis, a novel and determinant type of regulated cell death, and concluded that it involves differential activation of various signal transduction pathways. Iron primarily participates in the relevant inflammatory response, stimulating the release of inflammatory and cytokines, and induces iron-dependent lipid peroxidation that generates oxidative damage to hepatic cells. Currently, ferroptosis still comprises some challenges, including the lack of a specific marker for animal studies and clinical settings (7). Additional studies about ferroptosis in hepatic IRI are required to better understand the presence of ferroptosis in the liver. This novel type of cell death in hepatic IRI will provide more precise therapeutic targets and will be advantageous for developing new clinical therapeutic methods.

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Authors' contributions

LL, GM and DH conceived and designed the study; LL prepared the original draft of the manuscript; LL and GM reviewed and edited the manuscript; and DH supervised the study and acquired the funding. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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