Review Article

Advancements in understanding the role of ferroptosis in hypoxia-associated brain injury: a narrative review

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Background and Objective: Ferroptosis, a form of programmed cell death driven by lipid peroxidation and dependent on iron ions, unfolds through a sophisticated interplay of multiple biological processes. These include perturbations in iron metabolism, lipid peroxidation, aberrant amino acid metabolism, disruptions in hypoxia-inducible factor-prolyl hydroxylase (HIF-PHD) axis, and endoplasmic reticulum (ER) stress. Recent studies indicate that ferroptosis may serve as a promising therapeutic target for hypoxia-associated brain injury such as hypoxic-ischemic brain damage (HIBD) and cerebral ischemia-reperfusion injury (CIRI). HIBD is a neonatal disease that can be fatal, causing death or mental retardation in newborns. HIBD is a kind of diffuse brain injury, which is characterized by apoptosis of nerve cells and abnormal function and structure of neurons after cerebral hypoxia and ischemia. At present, there are no fundamental prevention and treatment measures for HIBD. The brain is the most sensitive organ of the human body to hypoxia. Cerebral ischemia will lead to the damage of local brain tissue and its function, and CIRI will lead to a series of serious consequences. We hope to clarify the mechanism of ferroptosis in hypoxia-associated brain injury, inhibit the relevant targets of ferroptosis in hypoxia-associated brain injury to guide clinical treatment, and provide guidance for the subsequent treatment of disease-related drugs.

Methods: Our research incorporated data on "ferroptosis", "neonatal hypoxic ischemia", "hypoxic ischemic brain injury", "hypoxic ischemic encephalopathy", "brain ischemia-reperfusion injury", and "therapeutics", which were sourced from Web of Science, PubMed, and comprehensive reviews and articles written in English.

Key Content and Findings: This review delineates the underlying mechanisms of ferroptosis and the significance of these pathways in hypoxia-associated brain injury, offering an overview of therapeutic strategies for mitigating ferroptosis.

Conclusions: Ferroptosis involves dysregulation of iron metabolism, lipid peroxidation, amino acid metabolism, dysregulation of HIF-PHD axis and endoplasmic reticulum stress (ERS). By reviewing the literature, we identified the involvement of the above processes in HIBD and CIRI, and summarized a series of therapeutic measures for HIBD and CIRI by inhibiting ferroptosis. We hope this study would provide guidance for the clinical treatment of HIBD and CIRI in the future.

Keywords: Ferroptosis; hypoxic-ischemic brain damage (HIBD); ischemia-reperfusion injury (IRI); therapeutics

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Introduction

Hypoxia in the neonatal brain can lead to a spectrum of outcomes, ranging from reduced cognitive processing and reflex responses to irreversible neurological damage. The most common hypoxia-associated brain injuries include hypoxic-ischemic brain damage (HIBD) and cerebral ischemia-reperfusion injury (CIRI) (1,2). Ferroptosis, a newly recognized form of programmed cell death, is iron-dependent and characterized by the accumulation of lipid peroxidation products and cytotoxic reactive oxygen species (ROS) (3). Distinct from apoptosis and autophagy, ferroptosis exhibits unique cellular morphologies—there is an absence of cell shrinkage, chromatin condensation, or autophagic vacuole formation (4). The ferroptotic process is catalyzed by ferrous ions or lipoxygenases, which initiate lipid peroxidation in polyunsaturated fatty acids, abundant in cell membranes, leading to cell death (5). The principal mechanisms involved in ferroptosis encompass dysregulated iron metabolism, oxidative stress, and impaired glutathione (GSH) metabolism (6,7).

Evidence suggests that ferroptosis plays a significant role in hypoxia-associated brain injury (8,9), and given that the main pathways of ferroptosis are implicated in these conditions, this review explores the association between ferroptosis and hypoxia-associated brain injury. We present this article in accordance with the Narrative Review reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-47/rc).

Methods

Our research incorporated data on "ferroptosis", "neonatal hypoxic ischemia", "hypoxic ischemic brain injury", "hypoxic ischemic encephalopathy", "brain ischemia-reperfusion injury", and "therapeutics", which were sourced from Web of Science, PubMed, and comprehensive reviews and articles written in English. The detailed search strategy is shown in *Table 1*. Upon thorough examination of the mentioned literature and subsequent comprehensive discussions, we synthesized the insights on the role of ferroptosis in hypoxia-associated brain diseases, aiming to provide perspectives on enhancing the treatment of these conditions through the pathway of ferroptosis.

Mechanisms of ferroptosis

Ferroptosis is a form of programmed cell death dependent on iron ions, characterized by lipid peroxidation, GSH depletion, and glutathione peroxidase 4 (GPX4) inactivation (10). It involves a multifaceted mechanism encompassing iron metabolism, lipid peroxidation, amino acid metabolism, alterations in the hypoxia-inducible factor-prolyl hydroxylase (HIF-PHD) axis, and endoplasmic reticulum stress (ERS). This review focuses on these biological processes that underpin ferroptosis initiation and progression.

Iron metabolism abnormalities

Iron metabolism comprises three key phases: uptake, storage, and release (11). In the dietary uptake phase, non-heme iron is primarily absorbed in the duodenum and proximal small intestine via divalent metal ion transporter 1 (DMT-1). Duodenal cytochrome b (Dcytb) and other reductants convert dietary Fe^{3+} to Fe^{2+}, which is then internalized by DMT-1 (12). During the storage phase, ferroportin 1 (FPN1) translocates Fe^{2+} from intestinal epithelial cells to the extracellular space, where multicopper oxidase facilitates its oxidation to Fe^{3+}, which subsequently complexes with transferrin (TF) as the TF-Fe^{3+} complex (13). In the release phase, Fe^{3+} transported by FPN1 enters the cell; intracellularly, it is reduced back to Fe^{2+} by ferric reductases and released to the cellular iron pool (14,15). Excess free Fe^{2+} can catalyze the formation of ROS via the Fenton reaction, promoting the onset of ferroptosis (16).

Iron homeostasis is regulated by key proteins, such as iron regulatory protein 1 (IRP1), which modulates iron transport and storage in response to intracellular iron levels. When intracellular iron is scarce, IRP1 associates with the iron-responsive element (IRE) situated at the 3' terminus of the gene, elevating the transcription of DMT1 and transferrin receptor (TFR), and thus enhancing iron absorption (17,18). Conversely, IRP1 can attach to the IRE of the ferritin (*FTN*) gene at its 5' terminus and suppress FTN synthesis,

Table 1 The search strategy summary

Items	Specification
Date of search	September 1st, 2023 to January 2nd, 2024
Databases and other sources searched	PubMed, Web of Science
Search terms used	"ferroptosis", "neonatal hypoxic ischemia", "hypoxic ischemic brain injury", "hypoxic ischemic encephalopathy", "brain ischemia-reperfusion injury", and "therapeutics"
Timeframe	1948–2023
Inclusion criteria	English language studies were included
Selection process	Independently selected by authors

curtailing iron storage. On the other hand, in the presence of abundant cellular iron, IRP1 binds to iron-sulfur clusters, adopting a role as a cis-aconitase. This switch results in augmented FTN levels and reduced TFR and DMT1 expression, consequently diminishing iron concentrations within the cell. Research has revealed that a marked reduction in IRP1 significantly impedes ferroptosis (19). IRP1 deficiency has been observed to significantly inhibit ferroptosis. Moreover, hepcidin, a cysteine-rich antimicrobial peptide produced by the liver, maintains iron homeostasis by binding to FPN1, accelerating its degradation and lowering iron release. Hepcidin has demonstrated a protective role against ferroptosis (20).

Lipid peroxidation

Lipid peroxidation is a pivotal process in the dysregulated mechanism leading to ferroptosis, a form of cell death characterized by iron dependency. This oxidative process involves the reaction of lipids with oxygen, resulting in the production of reactive oxygen species (ROS) and lipid peroxides (LPOs) (21). Iron plays a crucial role by serving as a cofactor for the enzyme oxidase that catalyzes lipid peroxidation. Moreover, enzymes like lipoxygenases can facilitate ferroptosis by promoting lipid peroxidation (22).

Polypeptide unsaturated fat (PUFA), located on cell membranes, are instrumental in preserving membrane fluidity and reducing blood cholesterol levels (23). The accumulation of lipid peroxidation products due to PUFA oxidation at the cell membrane serves as a significant initiator of ferroptosis. PUFAs with multiple unsaturated bonds are particularly vulnerable to ROS, leading to increased lipid peroxidation production (24). There are three primary mechanisms of lipid peroxidation: enzyme-catalyzed reactions, non-enzymatic autoxidation mediated by iron, and iron-induced lipid ROS generation via the Fenton reaction (25). It is well known that hydrogen peroxide plays an important role in the occurrence of Fenton reaction. The presence of hydrogen peroxide with ferrous iron generates hydroxyl radicals that oxidize PUFA to alkyl radicals (L•). L• reacts with oxygen molecules to produce lipid peroxyl radical (LOO•), which results in the accumulation of lipid hydroperoxides (LOOH) (26), phospholipid hydroperoxide (P-LOOH) production can lead to structural damage of cell membrane. Specifically, the lipid peroxidation pathway involving PUFAs entails the enzyme long-chain acyl-CoA synthetase-4 (ACSL4), which converts PUFAs into peroxidation-susceptible acyl-coenzyme A derivatives. Subsequently, lysophosphatidylcholine acyltransferase 3 (LPCAT3) incorporates these derivatives into membrane phospholipids, producing PUFA-phospholipid peroxides upon oxidation by lipoxygenase family (LOXs), thus contributing to ferroptosis (27,28). Inhibition of ACSL4, LPCAT3, or LOXs has been shown to significantly curb the ferroptosis process (29).

Amino acid metabolism abnormalities

Abnormalities in amino acid metabolism are closely associated with the dysregulation of the System Xc^-/GSH/GPX4 axis (30), a key mechanism underlying ferroptosis. GSH, a tripeptide composed of glutamic acid, cysteine, and glycine, features a γ-amide bond and sulfhydryl groups and is synthesized at a rate limited predominantly by cysteine availability (31). As a critical component of the body's antioxidant system, GSH exists in both reduced (GSH) and oxidized [glutathione disulfide (GSSG)] forms

and performs multiple functions including antioxidant protection, immune system support, and detoxification (32). It is the most prevalent intracellular antioxidant, safeguarding cells against ROS-induced damage (33). GSH facilitates the transport of glutamate out of the cell and the import of cystine for its subsequent reduction to cysteine, which is crucial for GSH synthesis. This transporter is constituted by the light chain solute carrier family 7, member 11 (SLC7A11) and the heavy chain solute carrier family 3, member 2 (SLC3A2) (34,35). On the other hand, GPX4 catalyzes the conversion of GSH to GSSG while concurrently reducing harmful phospholipid hydroperoxides to non-toxic hydroxyl PEG-modified liposomes (PL-OH) (36). Recent studies highlight the role of GPX4 as an essential inhibitor of ferroptosis, unique in its capacity to directy reduce phospholipid hydroperoxides in membranes and lipoproteins and prevent lipid peroxidation, aided by α-tocopherol (vitamin E) (37). The necessity of GPX4 is underscored by the embryonic lethality of GPX4-null mice and the survival challenges exhibited by neural-specific GPX4 knockout neonatal pups (38,39). Given that GPX4 enzymatic activity requires GSH, ferroptosis susceptibility is influenced by GSH levels (39). System Xc^-/GSH/GPX4 axis dysfunction significantly contributes to ferroptosis, with System Xc^- inhibition impairing GSH synthesis and triggering ferroptosis (40). Altering GPX4 expression modulates cellular vulnerability to ferroptosis, where diminished GPX4 expression increases susceptibility, whereas increased levels confer resistance (41). The P53 oncogene can suppress System Xc^- activity by SLC7A11 expression (42). Moreover, impeding System Xc^- function elevates the transcription of cation transport regulator-like protein 1 (*CHAC1*), a gene implicated in ERS responses, thus linking amino acid metabolism abnormalities with ER stress and subsequent ferroptosis (40).

HIF-PHD axis

HIFs are transcriptional activators induced by hypoxic stress, comprising two subunits: α and β. While HIF-β serves a structural purpose, HIF-α acts as the functional subunit and binds to the hypoxia-responsive element (HRE) promoter regions, modulating gene expression (43,44). PHDs are a family of non-heme, iron-dependent dioxygenases that require oxygen, α-ketoglutarate, and divalent iron ions for catalytic activity (45). PHDs facilitate the degradation of HIF by hydroxylating specific proline residues on HIF-α under normoxic conditions, a modification that targets HIF-α for recognition by the von Hippel-Lindau protein (pVHL) and subsequent ubiquitin proteasome-mediated degradation. During hypoxia, however, PHD activity diminishes, resulting in the stabilization and accumulation of HIF (46). Iron ions are crucial for the PHD-mediated hydroxylation of HIF, and their abnormal accumulation can enhance PHD activity, leading to increased HIF degradation—a process that is associated with ferroptosis (47). Furthermore, the HIF-PHD axis influences the expression of key players in iron metabolism, such as TF and divalent metal transporter 1 (DMT1), as well as the PUFA content in lipid metabolism, all of which are implicated in ferroptosis (28,48). These findings suggest that the HIF-PHD pathway may be intricately connected with the ferroptosis pathway.

ERS and ferroptosis

The endoplasmic reticulum (ER) is pivotal in sustaining cellular homeostasis, overseeing protein synthesis, folding, maturation, quality control, and trafficking. Disturbances to the structural and functional equilibrium of the ER—whether induced by internal or external stimuli—trigger molecular alterations, culminating in the obstruction of protein processing and transfer. This leads to considerable accumulation of unfolded or misfolded proteins within the ER, a condition termed ERS (49). In response, the unfolded protein response (UPR) is initiated as a protective mechanism against ERS, halting protein synthesis to mitigate the stress, promoting the degradation of misfolded proteins, and activating signaling pathways that recruit additional molecular chaperones for protein refolding (50). Severe ERS can compromise ER physiological functions and instigate cell death. Excessive ERS overwhelms the UPR, resulting in heightened autophagy and subsequent cellular degradation, which in turn may trigger ferroptosis (51). The ERS marker Atf4 modulates various UPR target genes, while Atf3 bolsters the expression of transcription activator Ddit43, which is implicated in apoptosis post-cerebral hemorrhage, thereby diminishing neuronal survival (52). Bioinformatic analysis has revealed upregulation of Atf3 in HIBD, reinforcing the association between ERS and ferroptosis (53).

As previously addressed, ferroptosis involves disturbances in iron metabolism, dysregulation of lipid peroxidation, impairment of the System Xc^-/GSH/GPX4 axis, and

accumulation of iron ions that contribute to the dysfunction of the HIF-PHD axis and ERS. Consequently, targeting these pathways presents a clinical opportunity to prevent ferroptosis and thereby treat neonatal hypoxia-ischemic encephalopathy. The subsequent section will explore the contribution of ferroptosis to hypoxia-associated brain injury and prospective therapeutic interventions in depth.

The impact of ferroptosis on HIBD

HIBD originates from perinatal ischemia and hypoxia, posing significant risk factors for central nervous system (CNS) injury and neonatal mortality. Clinically, HIBD is characterized by symptoms such as lethargy, convulsions, and coma, with the potential for life-threatening synchronized limb flexion during myoclonic episodes in acute cases (1). The pathophysiology of HIBD is intricate, with apoptosis and ferroptosis implicated in its progression (54,55). Moreover, the neonatal brain's susceptibility to oxidative damage is heightened due to an elevated metabolic demand for oxygen, a rich presence of unsaturated fatty acids, and a paucity of antioxidants. Subsequent analysis will elaborate on the relationship between HIBD and ferroptosis, focusing on dysregulated iron metabolism, lipid peroxidation, imbalances in amino acid metabolism, the HIF-PHD pathway, and ERS.

Association between abnormal iron metabolism and HIBD

Following hypoxia-ischemia, the body's iron cycle undergoes significant alterations, precipitating iron metabolism dysregulation in the brain as the disease progresses. This dysregulation manifests as an appreciable elevation in brain tissue iron levels. Iron ions exacerbate HIBD by facilitating ROS production. The neonatal brain, which is characteristically rich in iron yet has comparatively weak antioxidant defenses, is particularly vulnerable to iron metabolism perturbations when contrasted with the adult brain. During the initial stages of HIBD, a low intracellular pH contributes to the liberation of iron from proteins, leading to its rapid accumulation within damaged neurons and the periventricular white matter of neonates (56). Studies have identified significant iron buildup in the periventricular white matter and basal ganglia of neonates with HIBD (57). Moreover, analyses have revealed anomalies in serum iron metabolism within the peripheral blood of affected children (58), implying a contributory role of iron metabolism disorders in the pathogenesis of HIBD. With advancements in perinatal medicine, the incidence of HIBD in term infants has significantly decreased, making HIBD in preterm infants a major clinical issue (59). Preterm delivery interrupts intrauterine extramedullary hematopoiesis prematurely; concurrently, bone marrow hematopoiesis in these infants is underdeveloped compared to that in term infants, rendering them less capable of adapting to rapid postnatal growth and development. Additionally, maternal iron acquisition is limited before the eighth month of gestation but increases thereafter; premature birth, therefore, reduces the neonate's iron reserves. Consequently, blood transfusions and iron supplementation are considered necessary to manage anemia in preterm infants (60). However, frequent transfusions and excessive iron supplementation can lead to iron overload, surpassing the body's TF binding capacity and resulting in an excess of non-TF-bound iron. This excess iron then participates in the Fenton-Haber-Weiss reaction with hydrogen peroxide, produced through superoxide anion disproportionation, as previously described (61).

Research in animal models has further substantiated the involvement of iron metabolism abnormalities in HIBD. Palmer *et al.* induced hypoxic-ischemic injuries in the right cerebral hemispheres of 7-day-old rats. Enhanced Perls' stain for iron detection in cryosections from rat brains showed an escalation in iron levels, inciting oxidative stress in the neonatal rat brain post hypoxia-ischemia (62). Hu *et al.* conducted a comprehensive examination of iron distribution, content, and malondialdehyde (MDA) levels across various brain regions—including the parietal cortex, corpus callosum, and hippocampus—in neonatal rats over an 84-day period following hypoxic ischemia. The findings revealed disparate degrees of cerebral iron deposition within the initial 28 days, with peak iron staining of hypoxic-ischemic brain injury on the third day. The trajectory of MDA closely mirrored the iron content, lending further credence to the critical role of iron metabolism disruption in HIBD progression (63). Neuroprotective effects have been observed through the administration of deferoxamine, an iron ion chelator, in neonatal rodent models of brain injury, with outcomes surpassing those of control subjects (64). Additionally, intracerebroventricular injections of iron death inhibitors, such as ferrostatin-1 or resveratrol, ameliorated CIRIs in neonates (65). Collectively, these studies underscore the therapeutic promise of interventions targeting irregular iron

metabolism in HIBD patients.

Links between lipid peroxidation and HIBD

Preterm brains are particularly vulnerable to ROS attack because they are rich in polyunsaturated fatty acids but low in antioxidants (66). Newborns are in a state of high oxidative stress during pregnancy, delivery and postpartum, and they experience an environmental transition from intrauterine hypoxia to postnatal hyperoxia (during the process from intrauterine environment to extrauterine environment, the fetus changes from intrauterine environment of 20–25 to 100 mmHg PO_2), resulting in increased ROS production (67). During HIBD, the body generates an abundance of free radicals, which react with unsaturated fatty acids to form neurotoxic LPOs. This reaction is evidenced by a marked increase in plasma LPO levels in HIBD patients, leading to further neuronal cell damage (67). Free radicals initiate lipid peroxidation, producing MDA—a cytotoxic compound that can induce cross-linking and polymerization of vital macromolecules such as proteins and nucleic acids. MDA is considered a key indicator of pronounced perinatal asphyxia in newborns, with its elevated levels in patients correlating with the severity of HIBD (68). These findings imply a substantial link between lipid peroxidation and HIBD. Studies show that 17β-estradiol can mitigate brain MDA levels. In a particular study involving a rat model of hypoxic-ischemic brain injury, treatment with 17β-estradiol resulted in reduced lipid peroxidation by diminishing the expression of nitric oxide synthase and nitric oxide, thereby offering protection against brain injury post hypoxia-ischemia (69).

Association between abnormal amino acid metabolism and HIBD

An abnormal rise in glutamate levels is a critical precursor to ferroptosis. This anomalous glutamate accumulation disrupts GSH metabolism, resulting in excessive LPO and consequent cellular ferroptosis. HIBD is associated with disturbances in the System Xc^-/GSH/GPX4 axis. Notably, glutamate levels are found to be elevated in the basal ganglia, central semiovale, thalamus, and regions adjacent to the lateral and third ventricles during HIBD (70). These observations point to a strong correlation between HIBD and disruptions in amino acid metabolism. Research has revealed that melatonin mitigates the pathological alterations induced by HIBD, hinders neuronal ferroptosis, and enhances the survival of hippocampal neurons through the downregulation of GPX4 expression (70).

Association between the HIF-PHD axis and HIBD

HIF-1α holds a pivotal position in neonatal HIBD, serving dual roles: it endows neuroprotection and, paradoxically, incites neurotoxic effects. From a protective standpoint, during HIBD, HIF-1α triggers the transcriptional activation of various genes that promote erythropoiesis, confer apoptosis resistance, and stabilize neuronal structures (71). Li *et al.* explored postnatal day 10 Sprague-Dawley (SD) rats, analyzing the protein levels of HIF-1α and activated caspase-3 following hypoxia exposure. Their findings indicated an inverse relationship between HIF-1α expression and activated caspase-3, with HIF-1α levels inversely correlated with the extent of histopathological damage in HIBD, implying a protective influence on neurons post hypoxia (72). Conversely, HIF-1α has also been implicated in contributing to cell necrosis through its interaction with calcium and calpain, as well as exacerbating cerebral edema by amplifying blood-brain barrier (BBB) permeability (73). Furthermore, conditions such as hypoxia inhibit PHD expression, leading to upregulated HIF levels (46). Consequently, the interplay between HIF and the PHD axis may significantly influence the regulation of HIBD.

Association between ERS and HIBD

Apoptosis represents a key mechanism in HIBD, with ERS being a vital pathway that mediates this process. Accumulation of excessive unfolded proteins within the ER triggers a chain reaction culminating in apoptosis, which significantly impacts HIBD (74). Caspase-12, specific to ERS, has been found to increase notably after 72 hours of hypoxic-ischemic exposure in neonatal rats, alongside a significant rise in neuronal apoptosis, pointing to the activation of ERS. The administration of caspase-12 inhibitors resulted in reduced caspase-12 protein expression and enhanced neuronal survival, highlighting the significance of ERS in HIBD development (75).

Although the intricacies of ferroptosis in the neonatal brain remain to be fully elucidated, especially in the context of HIBD, vital mechanisms implicated in its process, such as abnormal iron metabolism, lipid peroxidation, amino acid metabolism disorders, the HIF-PHD axis, and ERS,

are intricately linked with the onset of HIBD. As such, it is hypothesized that ferroptosis substantially contributes to the promotion of HIBD through these mechanisms during its progression.

The role of ferroptosis in brain ischemia-reperfusion

Ischemia-reperfusion injury (IRI) is a phenomenon wherein tissue damage escalates, potentially to irreversible levels, upon the restoration of blood flow after an ischemic event, representing a primary cause of organ failure (76). Ferroptosis plays a significant role in the pathogenesis of CIRI and consequent neuronal demise. In the context of CIRI, the processes of iron accumulation and redistribution, glutamate build-up, oxidative stress, lipid peroxidation, and epigenetic modification are all implicated in the advancement of ferroptosis (77).

Role of abnormal iron metabolism in cerebral ischemia-reperfusion

As mentioned above, FTN is an essential regulator of iron homeostasis. Recent research has identified substantial downregulation of FTN in a cerebral arterial occlusion rat model. This decrease in FTN levels is vital in mediating p53 and SLC7A11-dependent ferroptosis in hippocampal neurons following cerebral ischemia. Furthermore, FTN markedly reduces both hyperphosphorylation of tau protein and oxidative stress (78). IRI further leads to FTN degradation through autophagic pathways, increasing neuronal free iron in a process known as ferritinophagy. Studies suggest that nuclear receptor coactivator 4 (NCOA4) regulates ferritinophagy in specific cell lines, and its absence significantly impedes ferritinophagy, thereby safeguarding neurons against ferroptosis (79). Additionally, iron ion concentrations are closely linked with ferroptosis; in models of CIRI, intranasal delivery of the iron chelator deferoxamine substantially minimizes brain injury, offering notable neuroprotection (80).

Role of lipid peroxidation in CIRI

Oxidative stress has been acknowledged as a ubiquitous mediator of post-ischemic injury by various inflammatory cells (81). Ischemia can result in iron accumulation and subsequent toxicity within the CNS, triggering a cascade of free radicals that lead to neuronal damage and irreversible brain injury. It has been demonstrated that PTRF expression is elevated in neuronal cells both *in vitro* and *in vivo* following brain IRI. This upregulation boosts the activity of PLA2G4A, which alters lipid metabolism and accelerates lipid peroxidation and ferroptosis (82). The newly identified antioxidant enzyme UBIAD1, which catalyzes the biosynthesis of CoQ10 in the Golgi membrane, plays a role analogous to GPX4 in the mechanism of ferroptosis. It is involved in lipid peroxidation regulation within the non-mitochondrial CoQ10 system. UBIAD1 may influence ischemia-reperfusion-induced ferroptosis by restoring mitochondrial and Golgi functions in afflicted brain tissue and neurons (83,84).

Role of abnormal amino acid metabolism in CIRI

The brain experiences a cascade of cellular, biochemical, and metabolic disruptions during ischemia-reperfusion, such as oxidative stress, intracellular calcium overload, glutamate-induced neurotoxicity, inflammation, and apoptosis (70). The inactivation of GPX4 has been tightly linked to CIRI. Baicalein has demonstrated the ability to decrease brain iron levels, reduce lipid peroxidation, and mitigate ferroptosis in murine models both *ex vivo* and *in vivo* by modulating the GPX4/ACSL4/ACSL3 axis (85). Inhibitors like calyxin exert neuroprotective effects by adjusting iron content, various iron-related proteins, and redox systems, offering therapeutic benefits comparable to ferrostatin-1 (86). Additionally, natural compounds such as galangin (87), chamomile (88), and astragaloside IV (89) have been indicated to influence the GPX4 pathway in reducing ferroptosis, with the potential for clinical application.

The role of ERS in CIRI

CIRI can precipitate depolarization of neuronal membranes and activation of voltage-gated calcium channels, resulting in substantial calcium influx into the ER and initiating ERS. C/EBP homologous protein (CHOP), a key marker of apoptosis, is upregulated when PERK proteins in the ER membranes are activated, enhancing ATF4 translation and leading to apoptosis (90). Apoptosis triggered by the ERS pathway is a significant route to neuronal death in CIRI. Cerebral ischemic preconditioning has been shown to

offer neuroprotection against IRI by mitigating ER stress-induced apoptosis through the classical PERK pathway (91). Additionally, Panax notoginseng saponin R1 diminishes ER stress-induced apoptosis via the estrogen receptor pathway, conferring protection against neuronal apoptosis and brain damage, thus representing a promising therapy for hypoxic-ischemic encephalopathy (HIE) (92). Compound Tongluo Tang facilitates angiogenesis and suppresses ER stress-induced ferroptosis by activating the SHH pathway in cerebral infarction (93). Moreover, a combination therapy comprising Rhizoma Ligustici Chuanxiong and Paeonia Lactiflora surpasses monotherapy in protecting the BBB through the ER stress-dependent apoptotic signaling pathway, improving outcomes in middle cerebral artery occlusion (MCAO)-induced focal cerebral ischemia (94). Lastly, progranulin (PGRN) has been found to alleviate CIRI by reducing ER stress and dampening the NF-κB signaling pathway (95).

Role of the HIF-PHD axis in CIRI

Transcriptional control of gene expression is significantly altered during cerebral ischemia. In this condition, there is a metabolic shift from fatty acid oxidation to more efficient glucose glycolysis, which sustains cellular vitality under ischemic stress (96). HIF-1, a key transcription factor, serves as the principal regulator of oxygen equilibrium. This metabolic shift is governed by HIF, with its stability under low oxygen conditions being managed by PHD enzymes, particularly three isoforms (PHD1–3) (97). The adaptive responses to hypoxia prompted by these enzymes support the development of novel therapeutic interventions for ischemia and reperfusion, including PHD inhibitors.

Furin, recognized as the first mammalian proprotein convertase, facilitates the proteolytic maturation of proprotein substrates in the secretory pathway (98). Furin is a connecting factor between iron overload and cognitive impairment and is upregulated in response to iron deficiency and hypoxia, influencing HIF-1α stability (99,100). Iron excess suppresses furin levels, but treatment with iron chelators can restore furin, mitigating iron-mediated synaptic harm and memory loss in mice (101). Moreover, cardamonin has been found to reduce brain injury in MCAO models and activate the HIF-1α pathway, offering protection from CIRI (102).

Conclusions

The activation of ferroptosis is multifaceted, playing a significant role in HIBD and CIRI (103,104). The susceptibility of neonates to ferroptosis and the mechanisms of ferroptosis occurrence in neonatal hypoxia-related encephalopathy is shown in *Figure 1*. Consequently, future clinical interventions for HIBD and CIRI may focus on inhibiting ferroptosis. In this review, we begin by outlining the primary mechanisms that instigate ferroptosis, followed by an examination of why neonates are particularly susceptible to this form of cell death. We then establish the strong correlation between ferroptosis mechanisms and the pathogenesis of HIBD and CIRI and underscore the intimate link between ferroptosis and these conditions. Furthermore, we review therapeutics that target ferroptosis for HIBD and CIRI treatment, we conclude that deferoxamine could provide neuroprotection by chelating iron ions and maintaining iron homeostasis; 17β-estradiol can treat HIBD by reducing lipid peroxidation, and the neuroprotective agent UBIAD1 can also reduce lipid peroxidation and protect the nerve. As for amino acid metabolism disorders, treatment with baicalein, galangin, chamomile and melatonin reduced GPX4 expression and inhibited neuronal ferroptosis; The modulators of HIF-PHD axis represented by cardamonin can protect the nerves through HIF-PHD. Panax notoginsenoside R1, caspase-12 inhibitor and other drugs can reduce neuronal ferroptosis by inhibiting ERS. Taken together, these results suggest that iron homeostasis, reducing lipid peroxidation, amino acid metabolism disorders, reducing ERS and regulating HIF-PHD axis can reduce neuronal ferroptosis. Thus, we

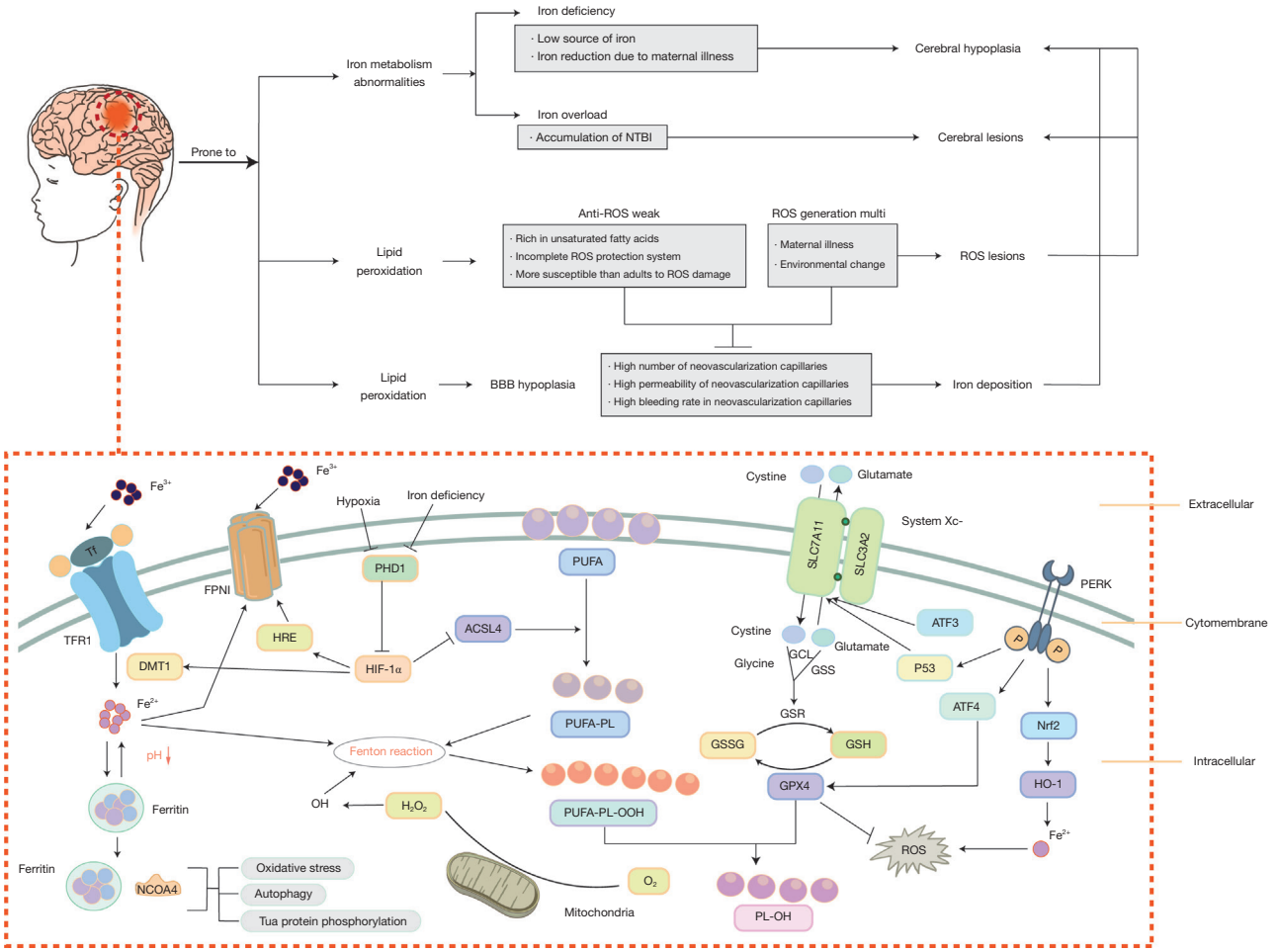

Figure 1 The susceptibility of neonates to ferroptosis and the mechanisms of ferroptosis occurrence in neonatal hypoxia-related encephalopathy. NTBI, non-transferrin bound iron; ROS, reactive oxygen species; BBB, blood-brain barrier; HIF-1, hypoxia inducible factor-1; PHD1, prolyl hydroxylase domain 1; TFR1, transferrin receptor 1; FPN1, ferroportin 1; DMT-1, divalent metal transporter 1; NCOA4, nuclear receptor coactivator 4; PUFA, polyunsaturated fatty acids; GSSG, glutathione disulfide; GSH, glutathione; GPX4, glutathione peroxidase 4; GSR, glutathione-disulfide reductase; GCL, glutamate cysteine ligase; GSS, glutathione synthetase; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; ACSL4, acyl-CoA synthetase long chain family member 4; ATF, activating transcription factor; SLC7A11, solute carrier 7A11; PERK, protein kinase R-like ER kinase; P, phosphate group.

hope to provide ideas for the clinical treatment of hypoxia-associated brain injury. Thus, we hope to provide ideas for the clinical treatment of hypoxia-associated brain injury.

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Footnote

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References

1. Yang L, Zhao H, Cui H. Treatment and new progress of neonatal hypoxic-ischemic brain damage. Histol Histopathol 2020;35:929-36.
2. Tierradentro-García LO, Saade-Lemus S, Freeman C, et al. Cerebral Blood Flow of the Neonatal Brain after Hypoxic-Ischemic Injury. Am J Perinatol 2023;40:475-88.
3. Chen X, Li J, Kang R, et al. Ferroptosis: machinery and regulation. Autophagy 2021;17:2054-81.
4. Yang WS, Stockwell BR. Ferroptosis: Death by Lipid Peroxidation. Trends Cell Biol 2016;26:165-76.
5. Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. Nat Rev Mol Cell Biol 2021;22:266-82.
6. Zheng J, Conrad M. The Metabolic Underpinnings of Ferroptosis. Cell Metab 2020;32:920-37.
7. Stockwell BR, Jiang X, Gu W. Emerging Mechanisms and Disease Relevance of Ferroptosis. Trends Cell Biol 2020;30:478-90.
8. Zhang Q, Jia M, Wang Y, et al. Cell Death Mechanisms in Cerebral Ischemia-Reperfusion Injury. Neurochem Res 2022;47:3525-42.
9. Zhu KY, Hei MY. Research advances in the role of ferroptosis in neonatal hypoxic-ischemic brain damage. Zhongguo Dang Dai Er Ke Za Zhi 2021;23:536-41.
10. Wang N, Tan HY, Chan YT, et al. Identification of WT1 as determinant of heptatocellular carcinoma and its inhibition by Chinese herbal medicine Salvia chinensis Benth and its active ingredient protocatechualdehyde. Oncotarget 2017;8:105848-59.
11. Papanikolaou G, Pantopoulos K. Iron metabolism and toxicity. Toxicol Appl Pharmacol 2005;202:199-211.
12. Fuqua BK, Vulpe CD, Anderson GJ. Intestinal iron absorption. J Trace Elem Med Biol 2012;26:115-9.
13. Gao G, Li J, Zhang Y, et al. Cellular Iron Metabolism and Regulation. Adv Exp Med Biol 2019;1173:21-32.
14. Zhou B, Liu J, Kang R, et al. Ferroptosis is a type of autophagy-dependent cell death. Semin Cancer Biol 2020;66:89-100.
15. Zhang H, Ostrowski R, Jiang D, et al. Hepcidin Promoted Ferroptosis through Iron Metabolism which Is Associated with DMT1 Signaling Activation in Early Brain Injury following Subarachnoid Hemorrhage. Oxid Med Cell Longev 2021;2021:9800794.
16. Liu J, Kang R, Tang D. Signaling pathways and defense mechanisms of ferroptosis. FEBS J 2022;289:7038-50.
17. Wang J, Chen G, Filebeen C, et al. Insights on regulation and function of the iron regulatory protein 1 (IRP1). Hemoglobin 2008;32:109-15.
18. Lan Y, Yang T, Yue Q, et al. IRP1 mediated ferroptosis reverses temozolomide resistance in glioblastoma via affecting LCN2/FPN1 signaling axis depended on NFKB2. iScience 2023;26:107377.
19. Yao F, Cui X, Zhang Y, et al. Iron regulatory protein 1 promotes ferroptosis by sustaining cellular iron homeostasis in melanoma. Oncol Lett 2021;22:657.
20. Jiao Y, Yong C, Zhang R, et al. Hepcidin Alleviates LPS-Induced ARDS by Regulating the Ferritin-Mediated Suppression of Ferroptosis. Shock 2022;57:274-81.
21. Stockwell BR. Ferroptosis turns 10: Emerging mechanisms, physiological functions, and therapeutic applications. Cell 2022;185:2401-21.
22. Xie LH, Fefelova N, Pamarthi SH, et al. Molecular Mechanisms of Ferroptosis and Relevance to Cardiovascular Disease. Cells 2022;11:2726.
23. Wiktorowska-Owczarek A, Berezińska M, Nowak JZ. PUFAs: Structures, Metabolism and Functions. Adv Clin Exp Med 2015;24:931-41.
24. Lee JY, Kim WK, Bae KH, et al. Lipid Metabolism and Ferroptosis. Biology (Basel) 2021;10:184.
25. Lei P, Bai T, Sun Y. Mechanisms of Ferroptosis and Relations With Regulated Cell Death: A Review. Front

Physiol 2019;10:139.
26. Fujii J, Yamada KI. Defense systems to avoid ferroptosis caused by lipid peroxidation-mediated membrane damage. Free Radic Res 2023;57:353-72.
27. Maheshwari S. Ferroptosis Signaling Pathways: Alzheimer's Disease. Horm Metab Res 2023;55:819-26.
28. Cui Y, Zhang Y, Zhao X, et al. ACSL4 exacerbates ischemic stroke by promoting ferroptosis-induced brain injury and neuroinflammation. Brain Behav Immun 2021;93:312-21.
29. Lv Y, Wu M, Wang Z, et al. Ferroptosis: From regulation of lipid peroxidation to the treatment of diseases. Cell Biol Toxicol 2023;39:827-51.
30. Li FJ, Long HZ, Zhou ZW, et al. System X(c) (-)/GSH/GPX4 axis: An important antioxidant system for the ferroptosis in drug-resistant solid tumor therapy. Front Pharmacol 2022;13:910292.
31. Asantewaa G, Harris IS. Glutathione and its precursors in cancer. Curr Opin Biotechnol 2021;68:292-9.
32. Owen JB, Butterfield DA. Measurement of oxidized/reduced glutathione ratio. Methods Mol Biol 2010;648:269-77.
33. Niu B, Liao K, Zhou Y, et al. Application of glutathione depletion in cancer therapy: Enhanced ROS-based therapy, ferroptosis, and chemotherapy. Biomaterials 2021;277:121110.
34. Tu H, Tang LJ, Luo XJ, et al. Insights into the novel function of system Xc- in regulated cell death. Eur Rev Med Pharmacol Sci 2021;25:1650-62.
35. Dixon SJ, Lemberg KM, Lamprecht MR, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell 2012;149:1060-72.
36. Forcina GC, Dixon SJ. GPX4 at the Crossroads of Lipid Homeostasis and Ferroptosis. Proteomics 2019;19:e1800311.
37. Ursini F, Bindoli A. The role of selenium peroxidases in the protection against oxidative damage of membranes. Chem Phys Lipids 1987;44:255-76.
38. Imai H, Hirao F, Sakamoto T, et al. Early embryonic lethality caused by targeted disruption of the mouse PHGPx gene. Biochem Biophys Res Commun 2003;305:278-86.
39. Seiler A, Schneider M, Förster H, et al. Glutathione peroxidase 4 senses and translates oxidative stress into 12/15-lipoxygenase dependent- and AIF-mediated cell death. Cell Metab 2008;8:237-48.
40. Dixon SJ, Patel DN, Welsch M, et al. Pharmacological inhibition of cystine-glutamate exchange induces endoplasmic reticulum stress and ferroptosis. Elife 2014;3:e02523.
41. Imai H, Matsuoka M, Kumagai T, et al. Lipid Peroxidation-Dependent Cell Death Regulated by GPx4 and Ferroptosis. Curr Top Microbiol Immunol 2017;403:143-70.
42. Jiang L, Kon N, Li T, et al. Ferroptosis as a p53-mediated activity during tumour suppression. Nature 2015;520:57-62.
43. Piel FB, Weatherall DJ. The α-thalassemias. N Engl J Med 2014;371:1908-16.
44. Cabaj A, Moszyńska A, Charzyńska A, et al. Functional and HRE motifs count analysis of induction of selected hypoxia-responsive genes by HIF-1 and HIF-2 in human umbilical endothelial cells. Cell Signal 2022;90:110209.
45. Smith TG, Talbot NP. Prolyl hydroxylases and therapeutics. Antioxid Redox Signal 2010;12:431-3.
46. Sen Banerjee S, Thirunavukkarasu M, Tipu Rishi M, et al. HIF-prolyl hydroxylases and cardiovascular diseases. Toxicol Mech Methods 2012;22:347-58.
47. Wu Y, Zhang S, Gong X, et al. The epigenetic regulators and metabolic changes in ferroptosis-associated cancer progression. Mol Cancer 2020;19:39.
48. Yang L, Wang D, Wang XT, et al. The roles of hypoxia-inducible Factor-1 and iron regulatory protein 1 in iron uptake induced by acute hypoxia. Biochem Biophys Res Commun 2018;507:128-35.
49. Oakes SA, Papa FR. The role of endoplasmic reticulum stress in human pathology. Annu Rev Pathol 2015;10:173-94.
50. Hetz C, Zhang K, Kaufman RJ. Mechanisms, regulation and functions of the unfolded protein response. Nat Rev Mol Cell Biol 2020;21:421-38.
51. Zhang J, Guo J, Yang N, et al. Endoplasmic reticulum stress-mediated cell death in liver injury. Cell Death Dis 2022;13:1051.
52. Wu X, Luo J, Liu H, et al. Recombinant adiponectin peptide promotes neuronal survival after intracerebral haemorrhage by suppressing mitochondrial and ATF4-CHOP apoptosis pathways in diabetic mice via Smad3 signalling inhibition. Cell Prolif 2020;53:e12759.
53. Li S, Wan L, Sun J, et al. New Insights into Mechanisms of Ferroptosis Associated with Immune Infiltration in Neonatal Hypoxic-Ischemic Brain Damage. Cells 2022;11:3778.
54. Lin W, Zhang T, Zheng J, et al. Ferroptosis is Involved in Hypoxic-ischemic Brain Damage in Neonatal Rats. Neuroscience 2022;487:131-42.
55. Yu L, Liu S, Zhou R, et al. Atorvastatin inhibits neuronal apoptosis via activating cAMP/PKA/p-CREB/BDNF

pathway in hypoxic-ischemic neonatal rats. FASEB J 2022;36:e22263.
56. Xu KY, Li F. Iron metabolism and neonatal hypoxic ischemic brain damage. Sheng Li Xue Bao 2017;69:218-24.
57. Meoded A, Poretti A, Northington FJ, et al. Susceptibility weighted imaging of the neonatal brain. Clin Radiol 2012;67:793-801.
58. Shouman BO, Mesbah A, Aly H. Iron metabolism and lipid peroxidation products in infants with hypoxic ischemic encephalopathy. J Perinatol 2008;28:487-91.
59. Chang LW, Liu J, Li WB. A preliminary study on diagnosis and grading of hypoxic-ischemic brain damage of premature infants. Zhongguo Dang Dai Er Ke Za Zhi 2007;9:293-6.
60. Saito-Benz M, Flanagan P, Berry MJ. Management of anaemia in pre-term infants. Br J Haematol 2020;188:354-66.
61. Ozment CP, Turi JL. Iron overload following red blood cell transfusion and its impact on disease severity. Biochim Biophys Acta 2009;1790:694-701.
62. Palmer C, Menzies SL, Roberts RL, et al. Changes in iron histochemistry after hypoxic-ischemic brain injury in the neonatal rat. J Neurosci Res 1999;56:60-71.
63. Hu DW, Zhang G, Lin L, et al. Dynamic Changes in Brain Iron Metabolism in Neonatal Rats after Hypoxia-Ischemia. J Stroke Cerebrovasc Dis 2022;31:106352.
64. Sarco DP, Becker J, Palmer C, et al. The neuroprotective effect of deferoxamine in the hypoxic-ischemic immature mouse brain. Neurosci Lett 2000;282:113-6.
65. Li C, Wu Z, Xue H, et al. Ferroptosis contributes to hypoxic-ischemic brain injury in neonatal rats: Role of the SIRT1/Nrf2/GPx4 signaling pathway. CNS Neurosci Ther 2022;28:2268-80.
66. Negro S, Benders MJNL, Tataranno ML, et al. Early Prediction of Hypoxic-Ischemic Brain Injury by a New Panel of Biomarkers in a Population of Term Newborns. Oxid Med Cell Longev 2018;2018:7608108.
67. D'Angelo G, Chimenz R, Reiter RJ, et al. Use of Melatonin in Oxidative Stress Related Neonatal Diseases. Antioxidants (Basel) 2020;9:477.
68. Banupriya C, Ratnakar, Doureradjou P, et al. Can urinary excretion rate of malondialdehyde, uric acid and protein predict the severity and impending death in perinatal asphyxia? Clin Biochem 2008;41:968-73.
69. Zhu H, Han X, Ji D, et al. Estrogen inhibits lipid peroxidation after hypoxic-ischemic brain damage in neonatal rats. Neural Regen Res 2012;7:2424-31.
70. Gou Z, Su X, Hu X, et al. Melatonin improves hypoxic-ischemic brain damage through the Akt/Nrf2/Gpx4 signaling pathway. Brain Res Bull 2020;163:40-8.
71. Bergeron M, Gidday JM, Yu AY, et al. Role of hypoxia-inducible factor-1 in hypoxia-induced ischemic tolerance in neonatal rat brain. Ann Neurol 2000;48:285-96.
72. Li LH, Qu Y, Zhang L, et al. The role of HIF-1alpha in neuronal apoptosis after hypoxia/hypoxia ischemia brain damage in neonatal rats. Sichuan Da Xue Xue Bao Yi Xue Ban 2008;39:912-5.
73. Fan X, Heijnen CJ, van der Kooij MA, et al. The role and regulation of hypoxia-inducible factor-1alpha expression in brain development and neonatal hypoxic-ischemic brain injury. Brain Res Rev 2009;62:99-108.
74. Hitomi J, Katayama T, Taniguchi M, et al. Apoptosis induced by endoplasmic reticulum stress depends on activation of caspase-3 via caspase-12. Neurosci Lett 2004;357:127-30.
75. Unlu MD, Asci H, Yusuf Tepebasi M, et al. The ameliorative effects of cannabidiol on methotrexate-induced neuroinflammation and neuronal apoptosis via inhibiting endoplasmic reticulum and mitochondrial stress. J Biochem Mol Toxicol 2024;38:e23571.
76. Eltzschig HK, Eckle T. Ischemia and reperfusion--from mechanism to translation. Nat Med 2011;17:1391-401.
77. Bu ZQ, Yu HY, Wang J, et al. Emerging Role of Ferroptosis in the Pathogenesis of Ischemic Stroke: A New Therapeutic Target? ASN Neuro 2021;13:17590914211037505.
78. Chen W, Jiang L, Hu Y, et al. Ferritin reduction is essential for cerebral ischemia-induced hippocampal neuronal death through p53/SLC7A11-mediated ferroptosis. Brain Res 2021;1752:147216.
79. Li C, Sun G, Chen B, et al. Nuclear receptor coactivator 4-mediated ferritinophagy contributes to cerebral ischemia-induced ferroptosis in ischemic stroke. Pharmacol Res 2021;174:105933.
80. Hanson LR, Roeytenberg A, Martinez PM, et al. Intranasal deferoxamine provides increased brain exposure and significant protection in rat ischemic stroke. J Pharmacol Exp Ther 2009;330:679-86.
81. Jin R, Yang G, Li G. Inflammatory mechanisms in ischemic stroke: role of inflammatory cells. J Leukoc Biol 2010;87:779-89.
82. Jin W, Zhao J, Yang E, et al. Neuronal STAT3/HIF-1α/PTRF axis-mediated bioenergetic disturbance exacerbates cerebral ischemia-reperfusion injury via PLA2G4A. Theranostics 2022;12:3196-216.
83. Mugoni V, Postel R, Catanzaro V, et al. Ubiad1 is an

antioxidant enzyme that regulates eNOS activity by CoQ10 synthesis. Cell 2013;152:504-18.
84. Huang Y, Liu J, He J, et al. UBIAD1 alleviates ferroptotic neuronal death by enhancing antioxidative capacity by cooperatively restoring impaired mitochondria and Golgi apparatus upon cerebral ischemic/reperfusion insult. Cell Biosci 2022;12:42.
85. Li M, Meng Z, Yu S, et al. Baicalein ameliorates cerebral ischemia-reperfusion injury by inhibiting ferroptosis via regulating GPX4/ACSL4/ACSL3 axis. Chem Biol Interact 2022;366:110137.
86. Liu H, Zhao Z, Yan M, et al. Calycosin decreases cerebral ischemia/reperfusion injury by suppressing ACSL4-dependent ferroptosis. Arch Biochem Biophys 2023;734:109488.
87. Guan X, Li Z, Zhu S, et al. Galangin attenuated cerebral ischemia-reperfusion injury by inhibition of ferroptosis through activating the SLC7A11/GPX4 axis in gerbils. Life Sci 2021;264:118660.
88. Wang M, Liu M, Tang L, et al. RETRACTED ARTICLE: Liquiritin reduces ferroptosis in doxorubicin-induced cardiotoxicity through targeting SLC7A11/GPX4 pathway. Naunyn Schmiedebergs Arch Pharmacol 2024;397:627.
89. Wang X, Wang Y, Huang D, et al. Astragaloside IV regulates the ferroptosis signaling pathway via the Nrf2/SLC7A11/GPX4 axis to inhibit PM2.5-mediated lung injury in mice. Int Immunopharmacol 2022;112:109186.
90. Yang Y, Liu Y, Zhang Y, et al. Periplogenin Activates ROS-ER Stress Pathway to Trigger Apoptosis via BIP-eIF2α- CHOP and IRE1α-ASK1-JNK Signaling Routes. Anticancer Agents Med Chem 2021;21:61-70.
91. Hu YQ, Chen W, Yan MH, et al. Ischemic preconditioning protects brain from ischemia/reperfusion injury by attenuating endoplasmic reticulum stress-induced apoptosis through PERK pathway. Eur Rev Med Pharmacol Sci 2017;21:5736-44.
92. Wang Y, Tu L, Li Y, et al. Notoginsenoside R1 Protects against Neonatal Cerebral Hypoxic-Ischemic Injury through Estrogen Receptor-Dependent Activation of Endoplasmic Reticulum Stress Pathways. J Pharmacol Exp Ther 2016;357:591-605.
93. Hui Z, Wang S, Li J, et al. Compound Tongluo Decoction inhibits endoplasmic reticulum stress-induced ferroptosis and promoted angiogenesis by activating the Sonic Hedgehog pathway in cerebral infarction. J Ethnopharmacol 2022;283:114634.
94. Gu J, Chen J, Yang N, et al. Combination of Ligusticum chuanxiong and Radix Paeoniae ameliorate focal cerebral ischemic in MCAO rats via endoplasmic reticulum stress-dependent apoptotic signaling pathway. J Ethnopharmacol 2016;187:313-24.
95. Purrahman D, Shojaeian A, Poniatowski ŁA, et al. The Role of Progranulin (PGRN) in the Pathogenesis of Ischemic Stroke. Cell Mol Neurobiol 2023;43:3435-47.
96. Eltzschig HK, Carmeliet P. Hypoxia and inflammation. N Engl J Med 2011;364:656-65.
97. Bruick RK, McKnight SL. A conserved family of prolyl-4-hydroxylases that modify HIF. Science 2001;294:1337-40.
98. Thomas G. Furin at the cutting edge: from protein traffic to embryogenesis and disease. Nat Rev Mol Cell Biol 2002;3:753-66.
99. Zhang Y, Bai X, Zhang Y, et al. Hippocampal Iron Accumulation Impairs Synapses and Memory via Suppressing Furin Expression and Downregulating BDNF Maturation. Mol Neurobiol 2022;59:5574-90.
100. Silvestri L, Pagani A, Camaschella C. Furin-mediated release of soluble hemojuvelin: a new link between hypoxia and iron homeostasis. Blood 2008;111:924-31.
101. Liu JL, Fan YG, Yang ZS, et al. Iron and Alzheimer's Disease: From Pathogenesis to Therapeutic Implications. Front Neurosci 2018;12:632.
102. Ni H, Li J, Zheng J, et al. Cardamonin attenuates cerebral ischemia/reperfusion injury by activating the HIF-1α/VEGFA pathway. Phytother Res 2022;36:1736-47.
103. Peeples ES, Genaro-Mattos TC. Ferroptosis: A Promising Therapeutic Target for Neonatal Hypoxic-Ischemic Brain Injury. Int J Mol Sci 2022;23:7420.
104. Pan Y, Wang X, Liu X, et al. Targeting Ferroptosis as a Promising Therapeutic Strategy for Ischemia-Reperfusion Injury. Antioxidants (Basel) 2022;11:2196.

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