

Ferroptosis in Cerebral Ischemia/Reperfusion Injury: Mechanistic Drivers and Therapeutic Frontiers

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Abstract: Ferroptosis, an iron-dependent cell death pathway driven by lipid peroxidation, critically contributes to cerebral ischemia/reperfusion (I/R) injury. In ischemic stroke, neuronal ferroptosis arises from iron overload and antioxidant system failure. Excessive Fe²⁺ fuels hydroxyl radical production via the Fenton reaction, accelerating lipid peroxidation in PUFA-rich membranes. Concurrently, cysteine depletion and GPX4 inactivation disrupt the GPX4-glutathione antioxidant axis, allowing toxic lipid peroxide accumulation. Enzymes like ACSL4 and LPCAT3 esterify PUFAs into phospholipids, enabling lipoxygenases (LOXs) to generate peroxides, while impaired repair pathways (eg, FSP1-CoQ10) exacerbate damage. Therapeutic strategies target iron chelators (eg, deferoxamine), lipid peroxidation inhibitors (liproxstatin-1), and GPX4 activators to restore redox balance. Targeting propagation mediators (eg, Galectin-13, which reduces SLC7A11 membrane localization) may limit damage spread. Combinatorial therapies addressing iron regulation and lipid peroxidation pathways offer promising neuroprotection against I/R-related neurodegeneration, positioning ferroptosis as a key druggable target.

Keywords: ferroptosis, cerebral ischemia/reperfusion injury, glutathione peroxidase 4, lysophosphatidylcholine acyltransferase 3

Introduction

Acute ischemic stroke (AIS) accounts for approximately 70% of all stroke cases worldwide, ranking as a leading cause of mortality and long-term disability.¹ Despite significant advancements in acute-phase reperfusion therapies, including intra-venous thrombolysis and endovascular thrombectomy, the timely restoration of cerebral blood flow often fails to fully mitigate secondary neuronal injury. Ischemia-reperfusion (I/R) injury, triggered by the reintroduction of oxygen after prolonged hypoxia, initiates a cascade of pathological events encompassing oxidative stress, mitochondrial dysfunction, and neuroinflammation. These processes collectively exacerbate neuronal loss beyond the initial ischemic core, underscoring the critical need for adjunctive neuroprotective strategies. Emerging evidence highlights ferroptosis as a central mechanism underpinning cerebral I/R injury. First formally delineated by Dixon et al in 2012, ferroptosis is an iron-dependent, non-apoptotic form of regulated cell death characterized by the lethal accumulation of lipid peroxides.^{2,3} Unlike apoptosis, which manifests as nuclear condensation and membrane blebbing, ferroptotic cells exhibit distinct morphological features, including marked cytoplasmic swelling, mitochondrial shrinkage with cristae disruption, and preserved nuclear architecture. The biochemical hallmark of ferroptosis is the inactivation of glutathione peroxidase 4 (GPX4), a pivotal enzyme that normally suppresses lipid peroxidation by reducing phospholipid hydroperoxides using glutathione as a cofactor. The loss of GPX4 function precipitates unchecked peroxidation of polyunsaturated fatty acids in cellular membranes, culminating in membrane rupture and irreversible cell death. Preclinical studies provide compelling evidence that targeting ferroptosis pathways offers a promising therapeutic avenue for AIS.^{4,5} Specifically, iron chelators (eg, deferoxamine) and selective ferroptosis inhibitors (eg, ferrostatin-1, liproxstatin-1) have demonstrated efficacy in reducing infarct volume and improving neurological outcomes in rodent models of middle cerebral artery occlusion/reperfusion.^{6,7} These neuroprotective effects are mechanistically linked

to the preservation of mitochondrial integrity and attenuation of oxidative stress. Notably, the role of GPX4 in ferroptosis regulation transcends mere correlation. Conditional knockout of GPX4 in neurons exacerbates I/R injury, whereas its pharmacological stabilization confers robust neuroprotection.^{8–11} These findings underscore the potential of GPX4-centric interventions as a novel strategy to address the unmet clinical need for adjunctive therapies in AIS management.

Biological Functions of Iron

Iron Protein in Brain Metabolism

The storage and release of intracellular iron are subject to complex intricate control mechanisms. The metabolic pathway of iron ions is strictly regulated to ensure iron homeostasis. Disruption of this homeostatic balance can result in the aberrant accumulation of iron ions within cells, ultimately leading to ferroptosis. In mammalian systemic iron metabolism, ferrous ions (Fe^{2+}) undergo oxidation to ferric state (Fe^{3+}) within the bloodstream prior to chelation by transferrin (Tf). The resultant iron-loaded Tf subsequently engages with transferrin receptor 1 (TfR1) on cellular membranes, initiating clathrin-mediated endocytosis. Within the acidic endosomal compartment, Fe^{3+} is enzymatically reduced to its bioactive Fe^{2+} form through the ferric reductase activity of six-transmembrane epithelial antigen of prostate 3 (STEAP3), a critical rate-limiting step for intracellular iron bioavailability.¹² Following cytoplasmic entry via Divalent Metal Transporter 1 (DMT1),¹³ ferrous ions (Fe^{2+}) are sequestered within the ferritin heteropolymer - a spherical nanocage comprising 24 subunits of ferritin heavy chain (FTH1) and light chain (FTL).¹⁴ This metallochaperone system oxidizes Fe^{2+} to Fe^{3+} through its ferroxidase center, mineralizes iron as hydrous ferric oxide in the protein cavity, and thus preserves cellular free iron pool homeostasis. The autophagic degradation of ferritin (ferritinophagy), mediated by nuclear receptor coactivator 4 (NCOA4), constitutes a pivotal regulatory axis. During this process, cytoplasmic ferritin-H/ferritin-L complexes are selectively incorporated into autophagosomes through NCOA4-dependent cargo recognition, ultimately delivering ferritin to lysosomal compartments.^{15–17}

Heme oxygenase-1 (HO-1) catalyzes heme degradation, releasing iron as a byproduct during this process.¹⁸ Cellular iron influx is critically mediated by SLC39A14, a solute carrier family member responsible for iron uptake,¹⁹ while ferroportin (SLC40A1), the sole known iron exporter, regulates intracellular iron efflux.²⁰ Mitochondria serve as central hubs for iron metabolism in ferroptosis, coordinating the biosynthesis of heme and iron-sulfur clusters.²¹ Iron homeostasis within mitochondria is maintained by membrane transporters such as SLC25A37 and SLC25A28, which facilitate mitochondrial iron import.^{22,23} Elevated intracellular Fe^{2+} levels drive Fenton reactions, generating hydroxyl radicals ($\bullet\text{OH}$) that interact with polyunsaturated fatty acids (PUFAs) to initiate lipid peroxidation. Concurrently, arachidonate lipoxygenases (ALOXs) oxidize PUFAs into lipid hydroperoxides (LOOH), which are further converted into lipid radicals via Fe^{2+} -dependent reactions.^{24,25} Additionally, iron potentiates the activity of ALOXs and cytochrome P450 oxidoreductases, enzymes that directly catalyze phospholipid peroxidation.²⁶

In cerebral I/R injury, distinct cell death pathways including ferroptosis, apoptosis, necroptosis, pyroptosis, and autophagy contribute to neuronal damage through unique mechanisms. Ferroptosis, an iron-dependent process, involves lipid peroxidation, mitochondrial shrinkage, and membrane damage without nuclear fragmentation. Apoptosis, characterized by caspase activation, chromatin condensation, and nuclear fragmentation, is minimal in inflammation. Necroptosis, triggered by RIPK1/RIPK3-MLKL signaling, causes cellular swelling, membrane rupture, and DAMP release, provoking inflammation. Pyroptosis, mediated by gasdermin D (GSDMD) cleavage, features cell swelling, membrane bubbling, and cytokine release, intensifying inflammation. Autophagy, primarily protective, can transition to autophagic cell death under stress. In vivo, ferroptosis is distinguished by elevated iron levels, lipid peroxidation products, and shrunken mitochondria, while apoptosis is confirmed by Annexin V/PI staining and caspase activity. Necroptosis is identified by MLKL phosphorylation and RIPK3 activation, pyroptosis by GSDMD cleavage, and autophagy by LC3-II conversion and p62 degradation. Ferroptosis-specific inhibitors like ferrostatin-1 reduce neuronal loss, highlighting its therapeutic potential in I/R injury.

During the acute reperfusion period, neurons experience rapid influx of oxygen and glucose, triggering oxidative stress, mitochondrial dysfunction, and iron accumulation. Ferroptosis is initiated by iron-dependent lipid peroxidation, characterized by mitochondrial shrinkage and membrane damage, while apoptosis is activated by caspase-3/7 cleavage,

marked by chromatin condensation and nuclear fragmentation. Microglia and astrocytes respond by phagocytosing necrotic debris and releasing pro-inflammatory cytokines, with necroptosis triggered by MLKL activation and pyroptosis mediated by GSDMD cleavage, causing DAMP release and cytokine production. Endothelial cells disrupt the blood-brain barrier (BBB) due to oxidative stress, with necroptosis activated by RIPK1/RIPK3-MLKL signaling and autophagy serving as a protective mechanism that can transition to autophagic cell death under severe stress. Oligodendrocytes sustain myelin sheath damage due to oxidative stress and calcium influx, with apoptosis activated by Bcl-2 family proteins and caspase-8, and ferroptosis initiated by iron-dependent lipid peroxidation, leading to myelin lysis. In the delayed secondary injury phase, neurons continue to experience persistent oxidative stress and inflammation, with ferroptosis sustained by iron accumulation and GSH depletion, and apoptosis activated by caspase-3/7 cleavage. Microglia and astrocytes exhibit chronic inflammation and phagocytosis of necrotic debris, with necroptosis and pyroptosis persisting and cytokine production upregulated. Endothelial cells maintain persistent BBB disruption, with necroptosis and autophagy continuing, and oligodendrocytes sustain myelin damage, with apoptosis and ferroptosis contributing to axonal degeneration. This timeline model underscores the critical role of ferroptosis in the acute reperfusion phase and its persistence in the delayed secondary injury phase, highlighting the need for targeted therapies to address iron-dependent oxidative stress and inflammation in cerebral I/R injury.

TfR1

Targeting Non-Transferrin-Bound Iron to Mitigate I/R Injury

Emerging therapeutic strategies focus on reducing NTBI overload, a critical driver of oxidative damage in I/R injury. Preclinical evidence demonstrates that the brain-penetrant iron chelator VK-28 induces microglial polarization toward the neuroprotective M2 phenotype, attenuates white matter injury, and improves survival rates in intracerebral hemorrhage (ICH) models. These models replicate clinical hallmarks of early neurological deterioration, hematoma expansion, and elevated intracranial pressure observed in ICH patients. Parallel studies in a porcine model of cardiac I/R injury (closely mimicking human cardiac pathophysiology) revealed that deferoxamine, a clinically approved iron chelator, suppresses ventricular remodeling and pathological myocardial hypertrophy while enhancing contractile function.²⁷ Collectively, the results demonstrate that iron chelation-induced NTBI depletion restores iron balance, effectively reducing ferroptosis-linked oxidative stress and cellular injury in various I/R injury paradigms.

Regulation of TfR1 in Iron Homeostasis and Cerebral I/R Injury

TfR1 is indispensable for cellular iron uptake and systemic iron metabolism. Genetic studies reveal that TfR1-knockout mice exhibit embryonic lethality, while heterozygous mutants display reduced organ iron content, underscoring TfR1's essential role in iron acquisition.²⁸ In cerebral I/R injury, therapeutic interventions, including astragalus, dexmedetomidine, hyperbaric oxygen, and electroacupuncture, downregulate TfR1 expression, reduce iron accumulation, and suppress ferroptosis in preclinical models.^{29–32} These findings suggest that TfR1-mediated iron overload is a hallmark of cerebral I/R pathology.³³

TfR1 expression is post-transcriptionally regulated by iron regulatory proteins (IRPs). IRPs bind to the iron-responsive element (IRE) in the 3' untranslated region (3'UTR) of TfR1 mRNA, stabilizing it to enhance iron import. Simultaneously, IRPs bind to the 5'UTR of ferritin mRNA to inhibit iron storage. Under iron-deficient conditions, cytoplasmic aconitase converts to IRP1, whereas IRP2 (lacking aconitase activity) is regulated via iron-dependent degradation. Conversely, high iron levels promote IRP1's reversion to aconitase and IRP2 degradation, favoring iron sequestration and limiting uptake.³⁴

Dysregulation of TfR1 is implicated in neurodegenerative disorders. For example, in neurodegeneration with brain iron accumulation, artemisinin enhances TfR1 palmitoylation in patient-derived fibroblasts, reducing ferritin levels and total cellular iron.³⁵ Additionally, the RNA-binding protein Roquin destabilizes TfR1 mRNA by targeting three conserved hairpin loops in its 3'UTR, a mechanism critical for iron homeostasis.³⁶

TfR1 trafficking also depends on Rab11A, which interacts with folliculin (FLCN) to mediate receptor recycling. Loss of FLCN function impairs Rab11A-mediated recycling of TfR1, resulting in delayed receptor trafficking, cellular iron deficiency, and compensatory activation of hypoxia-inducible factor (HIF) signaling, all of which are rescued by exogenous iron supplementation.³⁷

Collectively, TfR1 modulation through transcriptional regulation, mRNA stabilization, post-translational modifications (eg, palmitoylation), and Rab11A-mediated transport represents a multi-layered strategy to restore iron homeostasis during cerebral I/R injury. Targeting these pathways may mitigate ferroptosis and improve outcomes in iron-associated neurological disorders.

Iron Transporter Protein (FPN)

Role of FPN in Cerebral I/R Injury and Ferroptosis Regulation

Ferroportin (FPN/SLC40A1), the sole iron efflux transporter in mammals, plays a pivotal role in maintaining cellular iron homeostasis by mediating iron release from neurons and glial cells. During cerebral I/R injury, iron regulatory factors such as hepcidin bind to FPN, inducing its internalization and subsequent degradation. This process suppresses iron export from cells, exacerbating intracellular iron overload.³⁸ Experimental studies demonstrate that knockdown of hepcidin prevents FPN downregulation under cerebral I/R conditions, preserving neuronal iron efflux capacity. Therapeutic interventions targeting FPN expression showed neuroprotective effects. For instance, by upregulating FPN and GPX4 and suppressing ferritin expression, Naotaifang administration protects oxygen-glucose deprivation/reoxygenation (OGD/R)-injured microglia against ferroptosis.³⁹ Similarly, edaravone administration in middle cerebral artery occlusion/reperfusion rats reduces Fe^{2+} , MDA, and LPO levels while elevating GSH content, correlating with enhanced FPN expression and attenuated ferroptosis.⁴⁰ These findings collectively indicate that augmenting FPN activity during cerebral I/R promotes iron clearance from neural cells, offering a promising strategy to inhibit ferroptosis-driven neuronal damage.

STEAP3

Mechanisms of Iron Metabolism Dysregulation and Ferroptosis

Iron ions imported into cells are reduced to Fe^{2+} by STEAP3, a metalloreductase essential for iron metabolism. In cerebral I/R injury, STEAP3 expression is upregulated in hippocampal tissues of gerbil models, correlating with elevated Fe^{2+} levels and activation of ferroptosis. Inhibition of STEAP3 mitigates neuronal iron overload and alleviates brain I/R damage, underscoring its pathogenic role in ferroptosis-driven injury.⁴¹ Beyond the brain, STEAP3 exacerbates liver I/R injury by driving inflammation and apoptosis through the TAK1-dependent JNK/p38 MAPK pathway, positioning it as a promising therapeutic target for multi-organ I/R protection.⁴²

Ferrous iron is transported into the cytoplasm via DMT1. In preclinical SAH models, ibuprofen, a DMT1 inhibitor, attenuates iron accumulation and lipid peroxidation, leading to inhibition of ferroptosis.⁴³ Conversely, FPN modulation through DMT1 signaling promotes ferroptosis in SAH, underscoring the duality of iron transporters in disease progression.⁴⁴

NCOA4-mediated ferritinophagy, a selective autophagy pathway, plays a pivotal role in regulating intracellular iron homeostasis. This process liberates Fe^{2+} from ferritin storage, directly linking iron autophagy to ferroptosis. In cerebral I/R injury models, silencing NCOA4 reduces infarct volume, decreases free iron levels, and inhibits ferroptosis, demonstrating that blocking ferritinophagy alleviates iron overload.⁴⁵ The cGAS-STING pathway further exacerbates cerebral I/R injury by amplifying NCOA4-dependent ferritinophagy. Notably, the compound GB (eg, Ginkgo biloba extract) mitigates ferroptosis in OGD/R-injured neurons by suppressing autophagy and disrupting interactions between NCOA4 and ferritin heavy chain.⁴⁶ Collectively, cerebral I/R injury initiates a cascade of iron dysregulation involving STEAP3-mediated Fe^{2+} generation, DMT1-dependent iron import, and NCOA4-driven ferritinophagy, highlighting interconnected pathways in ferroptotic injury. By targeting these pathways through iron chelation, transporter inhibition, or autophagy modulation, cytoplasmic iron levels are reduced, leading to ferroptosis suppression and mitigation of I/R injury.⁴⁷

System Xc⁻

Ferroptosis is driven by cysteine deprivation, GSH depletion, and inactivation of GPX4, which collectively impair cellular antioxidant defenses.⁴⁸ GSH, a tripeptide composed of cysteine, glutamate, and glycine, relies on cysteine as its rate-limiting precursor, which is primarily acquired via the cystine/glutamate antiporter system xCT, a heterodimeric complex comprising SLC7A11 and its chaperone subunit SLC3A2 that mediates the 1:1 exchange of extracellular cystine

for intracellular glutamate.⁴⁹ Upon uptake, cystine undergoes NADPH-dependent reduction to cysteine in the cytosol, a critical step for sustaining GSH biosynthesis, with GSH serving as an essential cofactor for GPX4 to facilitate the reduction of lipid peroxides to non-toxic lipid alcohols, thereby preventing ferroptosis.^{50,51} The balance of ferroptosis susceptibility is tightly regulated by transcriptional control of SLC7A11, where p53 enhances cellular susceptibility to ferroptosis through transcriptional repression of SLC7A11, leading to reduced cystine uptake, while nuclear factor erythroid 2-related factor 2 (NRF2) enhances ferroptosis resistance by upregulating SLC7A11 expression, ensuring robust cystine import and GSH synthesis, underscoring the dynamic regulation of redox homeostasis.^{52,53} In cerebral I/R injury, the cystine/glutamate antiporter system Xc⁻ is a critical regulator of ferroptosis, with p53 driving ferroptosis by transcriptionally repressing SLC7A11, while *Rehmannia* Decoction reduces ferroptosis by enhancing p53 ubiquitination, suggesting a context-dependent regulatory mechanism.⁵⁴ MicroRNA-27a exacerbates cerebral I/R injury by directly targeting SLC7A11 mRNA, suppressing its expression and accelerating ferroptosis, while post-transcriptional regulation further modulates ferroptosis sensitivity through RNA-binding proteins, with SIRT1 normally inhibiting ferroptosis by stabilizing SLC7A11, but its impaired activity in I/R injury disrupting this protective mechanism.^{55,56} The Keap1/Nrf2 pathway is a key upstream regulator of SLC7A11, where activation of Nrf2 upregulates both SLC7A11 and GPX4, bolstering antioxidant defenses, with Rhein exerting protective effects by activating the NRF2/SLC7A11/GPX4 signaling axis, and in NLRP3-knockout mice, inhibition of the NLRP3 inflammasome via the Keap1/Nrf2 pathway reducing iron overload and lowering MDA levels while elevating GSH, highlighting the interplay between inflammasome signaling and ferroptosis.^{57,58} Additionally, excessive extracellular glutamate directly inhibits the cystine/glutamate antiporter system Xc⁻, and studies reveal multifaceted mechanisms linking system Xc⁻ dysfunction to ferroptosis and glutamate excitotoxicity in cerebral I/R injury, with trifluoperazine attenuating ferroptosis by activating the AMPK/FoxO3a/HIF-1 α signaling axis, where FoxO3a interacts with the SLC7A11 promoter region, resulting in transcriptional suppression of SLC7A11 and diminished cystine uptake, mitigating both glutathione depletion and glutamate excitotoxicity,⁵⁹ while glutamate excitotoxicity further exacerbates ferroptosis via NMDA receptor activation through the NMDA-NO-Dexras1-PAP7-DMT1 signaling cascade that promotes neuronal iron overload by upregulating DMT1, directly linking glutamate receptor hyperactivity to iron-dependent lipid peroxidation,⁶⁰ and HIF-1 α modulating system Xc⁻ activity by binding to the SLC7A11 promoter, sustaining system Xc⁻-dependent glutamate efflux under ischemic conditions, amplifying excitotoxic damage while simultaneously depleting antioxidant defenses.⁶¹ Therapeutic targeting of system Xc⁻ exerts neuroprotection through two synergistic pathways via downregulating SLC7A11 (reducing intracellular glutathione consumption, inhibiting ferroptosis, and alleviating oxidative stress) and mitigating glutamate efflux (attenuating NMDA receptor hyperactivation and iron overload, breaking the cycle of excitotoxicity and lipid peroxidation). Collectively, these findings position system Xc⁻ as a pivotal node for intervention in cerebral I/R injury, offering a dual strategy to counteract both ferroptosis and glutamate-driven neuronal damage.

GPX4

GPX4, a selenium-dependent enzyme, plays a crucial role in protecting cells from iron-mediated lipid peroxidation by detoxifying peroxidation products, thereby maintaining cellular membrane integrity and suppressing ferroptosis.⁶² Its inhibition through compounds such as RSL3, ML162, and ML210 induces ferroptosis across various cell types by depleting GPX4 activity, leading to unchecked lipid peroxidation.^{63–66} The interplay between system Xc⁻, glutathione, and GPX4 is essential, as dysregulation of system Xc⁻ reduces intracellular GSH levels, impairing GPX4's ability to reduce lipid peroxides; although GSH does not directly neutralize peroxides, it maintains the redox-active selenocysteine residue in GPX4's catalytic site, which is vital for its enzymatic function.⁶⁷ Selenium supplementation enhances GPX4 expression, offering neuroprotection by protecting against mitochondrial structural damage during cerebral I/R through stimulation of mitochondrial biogenesis via the Hippo signaling pathway.⁶⁸ GPX4 expression and activity are regulated at both transcriptional and post-translational levels, with GRSF1, an anti-aging factor, upregulating GPX4 to counter oxidative stress-mediated ferroptosis, RXR γ promoting GPX4 transcription to inhibit ferroptosis in cerebral I/R models, and TRIM26, an E3 ubiquitin ligase, stabilizing GPX4 through K63-linked polyubiquitination at specific lysine residues, enhancing its anti-ferroptotic activity and implicated in glioma resistance.^{69–71} Therapeutic strategies targeting GPX4 in cerebral I/R injury focus on upregulating GPX4 transcription via factors like RXR γ or GRSF1, enhancing GPX4 stability

through post-translational modifications such as TRIM26-mediated ubiquitination, and preserving enzymatic activity by maintaining selenium availability and GSH redox balance, positioning GPX4 as a pivotal therapeutic target with multifaceted approaches to combat ferroptosis in cerebral I/R pathology.

ACSL

Dual roles of ACSL4 and ACSL3 in ferroptosis regulation during cerebral I/R injury are well established, with ACSL4 driving ferroptosis via polyunsaturated fatty acid (PUFA) metabolism. Acyl-coenzyme A (CoA) synthetase long-chain family member 4 (ACSL4) catalyzes the esterification of PUFAs with CoA, forming PUFA-CoA derivatives that integrate into membrane phospholipids, thereby priming lipid membranes for peroxidation, a hallmark of ferroptosis.⁷² Pharmacological targeting of ACSL4 mitigates neuronal ferroptosis, as demonstrated by poplar extract that suppresses ferroptosis during cerebral IRI by downregulating ACSL4 expression, consequently reducing lipid peroxidation and protecting against neuronal damage.⁷³ Furthermore, baicalin, a flavonoid, exhibits neuroprotective effects in transient middle cerebral artery occlusion models by coordinately downregulating ACSL4 and upregulating anti-ferroptotic markers including GPX4, ACSL3, and xCT, thus restoring redox balance and attenuating I/R injury.⁷³ In contrast to ACSL4, ACSL3 confers resistance to ferroptosis by promoting the incorporation of monounsaturated fatty acids into phospholipids, stabilizing cellular membranes and thereby conferring resistance to lipid peroxidation.⁷⁴ Therapeutic strategies aimed at inhibiting ferroptosis in CIRI often involve upregulating ACSL3 to counteract ACSL4-driven peroxidation, highlighting the antagonistic roles of ACSL4 (pro-ferroptotic) and ACSL3 (anti-ferroptotic) as critical regulators of neuronal survival in CIRI, with targeting this axis representing a promising strategy to mitigate ferroptosis-associated brain injury.

LPCAT3

LPCAT3, a key member of the lysophosphatidylcholine acyltransferase family, maintains phosphatidylcholine (PC) homeostasis by catalyzing the esterification of PUFAs into phospholipids (PUFAs PL), a critical step in lipid remodeling.⁷⁵ This enzymatic activity not only supplies substrates for lipid peroxidation but also directly activates ferroptosis through the production of oxidized lysophosphatidylcholine derivatives.⁷⁶ Experimental evidence demonstrates that hyperbaric oxygen (HBO) therapy alleviates cerebral ischemia-reperfusion injury in rats by suppressing ferroptosis, with concomitant downregulation of LPCAT3 expression in neural tissues.²⁹ Conversely, hypoxic conditions markedly upregulate LPCAT3 activity in microvascular endothelial cells, and pharmacological inhibition of ferroptosis effectively mitigates hypoxia-induced blood-brain barrier dysfunction. Liver-specific overexpression studies further reveal that LPCAT3 modulates postprandial lipoprotein metabolism and glucose homeostasis, highlighting its systemic regulatory role in lipid-glucose crosstalk. Collectively, these findings position LPCAT3 as a molecular nexus linking phospholipid metabolism to ferroptosis execution. Therapeutic targeting of LPCAT3 may offer dual benefits: (1) reducing lipid peroxidation substrates by limiting PUFA incorporation into membranes; (2) interrupting oxidative stress signaling cascades that drive iron-dependent cell death.⁷⁷ This strategy holds promise for treating ferroptosis-associated pathologies, including ischemic stroke and metabolic disorders.

The Pathophysiological Role of Ferroptosis in Cerebral I/R Injury Iron Metabolism

Accumulating evidence indicates that systemic iron overload positively correlates with the severity of stroke-induced brain injury, as elevated iron reserves amplify oxidative stress cascades and exacerbate cerebral damage in both clinical observations and experimental I/R models.^{78,79} A prospective cohort study demonstrated a dose-dependent relationship between serum ferritin levels at admission and modified Rankin Scale (mRS) scores, with patients exhibiting hyperferritinemia showing significantly poorer functional recovery than those with normal iron profiles.⁸⁰ Mechanistically, I/R injury disrupts blood-brain barrier integrity, enabling excessive iron influx into brain parenchyma. Concurrently, oxygen-glucose deprivation triggers metabolic dysfunction in neurons, promoting iron ion liberation from intracellular storage pools and subsequent pathological iron accumulation. This iron dyshomeostasis creates a permissive microenvironment

for ferroptosis execution through two synergistic pathways: Lipid peroxidation potentiation: Unbound iron catalyzes Fenton reactions, generating hydroxyl radicals that initiate membrane lipid oxidation.⁸¹ Ferroptosis pathway activation: Iron overload upregulates ACSL4-mediated polyunsaturated fatty acid incorporation into phospholipids, amplifying lipid peroxide production.^{82,83} These findings highlight iron chelation therapy and ferroptosis inhibition as promising strategies to mitigate secondary neuronal death in stroke management.

Cerebral I/R Injury and Ferroptosis

GSH, a tripeptide thiol with diverse biological functions, serves as a critical regulator in cerebral I/R injury by maintaining redox balance and modulating neurotransmitter systems.⁸⁴ Experimental evidence indicates that neonatal rats with pharmacologically induced GSH deficiency show a 62% reduction in cortical GSH levels, accompanied by mitochondrial ultrastructural damage such as fragmented cristae and matrix swelling.⁸⁵ The relationship between GSH metabolism and glutamatergic neurotransmission is bidirectional: inhibiting the γ -glutamyl cycle pharmacologically lowers cytoplasmic glutamate by 38%, which in turn reduces the frequency of miniature excitatory postsynaptic potentials in hippocampal neurons,⁸⁶ whereas genetic disruption of GSH biosynthesis elevates cytosolic glutamate concentrations by 2.1-fold, enhancing synaptic excitability.⁸⁷

Therapeutic strategies targeting GSH's neuroprotective properties have demonstrated efficacy in preclinical models. In middle cerebral artery occlusion models, exogenous GSH administration mitigates striatal ischemic damage via dopamine receptor co-activation, leading to a 41% reduction in infarct volume compared to controls.⁸⁸ Additionally, post-spinal cord injury studies reveal a strong positive correlation between pontine GSH metabolite levels and locomotor recovery, highlighting its potential role in neuroplasticity during rehabilitation.⁸⁹ Collectively, these findings underscore GSH's multifaceted role as a molecular regulator integrating antioxidant defense, synaptic transmission, and neural repair in cerebrovascular disorders (Table 1).

Lipid peroxidation proceeds through both enzymatic and non-enzymatic pathways, both of which are intricately connected to ferroptosis. Non-enzymatic peroxidation is mediated by hydroxyl radicals ($\bullet$ OH) produced through Fe^{2+} -catalyzed Fenton reactions, leading to the indiscriminate oxidation of polyunsaturated fatty acids (PUFAs).⁹⁰ In contrast, enzymatic peroxidation is orchestrated by a coordinated cascade involving ACSL4, which activates phospholipids containing PUFAs, LPCAT3, which facilitates the incorporation of PUFAs into membrane phospholipids; and LOXs, which directly oxidize PUFA-phospholipids to form hydroperoxides.⁹¹ These reactions generate reactive aldehydes, such as 4-hydroxynonenal and malondialdehyde, which not only serve as biomarkers of oxidative stress but also amplify ferroptotic processes.

The brain's elevated PUFA content renders it highly susceptible to lipid peroxidation during I/R injury. Recent therapeutic approaches have focused on modulating this critical pathway. Pharmacological interventions, such as theobromine administration, have demonstrated efficacy in suppressing hippocampal lipid peroxidation post-I/R through a 35% increase in GSH levels and a 42% reduction in 4-hydroxynonenal (4-HNE).⁹² Concurrently, dietary strategies incorporating ryegrass oil (abundant in ω -3 PUFAs) and thymoquinone (a lipoxygenase inhibitor) have shown promise in attenuating lipid peroxidation within rat hippocampal I/R models, resulting in a 28% improvement in neuronal survival.⁹³ Interestingly, metabolic modulators like branched-chain amino acids exhibit a paradoxical effect by promoting ferroptosis through the

Table 1 Mechanisms of Herbal Interventions on Diverse Models

Experimental Model	Herbal Interventions	Mechanisms	Reference
OGD/R	Naotafang formula; Ginkgo biloba extract	Regulation of microglial M1/M2; Suppress of autophagy and disruption of interaction between NCOA4 and ferritin heavy chain	[39, 47]
MCAO/R	Edaravone	Downregulation Ferroptosis	[40]
I/R	Ginkgolide B; Rhein; Chrysin; Baicalein; Rehmannioside A	Inhibition of ferroptosis	[48, 58, 73, 74, 76, 90]
Cell type (SH-SY5Y cells)	Rehmannioside A	Inhibition of ferroptosis and activation of PI3K/AKT/Nrf2 and SLC7A11/GPX4 signaling pathway	[90]

disruption of mitochondrial β -oxidation and glutathione recycling, leading to a 1.7-fold increase in lipid peroxide accumulation.^{94,95} Collectively, these findings emphasize the druggable nature of lipid peroxidation as a regulatory checkpoint in ferroptosis, highlighting its significant therapeutic potential for mitigating I/R-induced brain injury.

Conclusions

Ferroptosis contributes substantially to cerebral I/R injury through its hallmark features of iron-dependent lipid peroxidation, coupled with glutathione depletion, mitochondrial dysfunction, and metabolic/epigenetic dysregulation. Therapeutic strategies targeting these pathways, such as iron chelators, GPX4 activators, or lipid peroxidation inhibitors, exhibit significant promise. However, current evidence is predominantly derived from preclinical models, and clinical translation remains constrained by the absence of specific biomarkers and approved therapies. To advance treatment strategies, prioritizing clinical trials to validate ferroptosis inhibitors and establish reliable diagnostic tools is imperative.

Data Sharing Statement

The data used to support the findings are available from the corresponding author Yongpan Huang upon request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by Hunan Natural Science Foundation (2023JJ60263, 2026JJ80933) and Natural Science Foundation of Changsha (kq2502202).

Disclosure

The authors report no conflicts of interest in this work.

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