Mitochondrial dysfunction-driven ferroptosis in cerebral ischemia-reperfusion injury: Mechanisms and therapeutic strategies (Review)

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Abstract. Ischemic stroke remains a leading cause of mortality and disability worldwide. Although vascular recanalization is essential for salvaging the ischemic penumbra, subsequent reperfusion may initiate a cascade of secondary brain injury, a pathological process referred to as cerebral ischemia-reperfusion injury (CIRI). Ferroptosis, an iron-dependent form of programmed cell death characterized by the excessive accumulation of lipid peroxides and membrane damage, has emerged as a critical driver of neuronal death in CIRI. Growing evidence supports mitochondrial dysfunction as not only a downstream outcome of bioenergetic failure, but also a central regulatory node within the ferroptotic cascade. The present review systematically summarizes how mitochondrial dysfunction increases neuronal susceptibility to ferroptosis across the pathophysiological progression of CIRI, with a particular focus on the underlying mechanisms. Specifically, a multidimensional pathological network composed of multiple mitochondrial abnormalities, including mitochondrial reactive oxygen species bursts, Ca^{2+} overload and disruption of the mitochondrial quality control system, encompassing mitochondrial biogenesis, mitochondrial dynamics and mitophagy, synergistically amplifies lipid peroxidation and drives neuronal ferroptosis. Finally, advances and future perspectives regarding mitochondria-centered therapeutic strategies are highlighted, offering novel insights into the development of targeted neuroprotective interventions against CIRI-induced ferroptosis.

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Contents

1. Introduction

Stroke represents an acute cerebrovascular event characterized by a high incidence and rates of disability and mortality (1). It is the second leading cause of death among non-communicable diseases globally (2). In 2021, ~93.8 million people were living with stroke worldwide, with 11.9 million incident strokes, while the absolute number of prevalent stroke cases increased by 86% from 1990 to 2021 (2). Based on the underlying pathology, stroke is classified into ischemic stroke (IS) and hemorrhagic stroke, with IS accounting for ~85% of all cases (3). Major risk factors for IS include smoking, alcohol consumption, obesity, hypertension, diabetes mellitus and dyslipidemia (4). Projections indicate that IS-related deaths may increase from 2.03 million in 2019 to 4.90 million by 2030 (5). IS typically arises from a sudden interruption of cerebral blood flow, leading to focal ischemia and hypoxia, which ultimately result in cerebral tissue necrosis or softening (6). Despite accounting for only 2% of the total body weight, the brain consumes ~20% of the body's oxygen and glucose, making it particularly susceptible to energy deprivation (7). Consequently, early vascular recanalization and restoration of perfusion to the ischemic region are critical for salvaging the ischemic penumbra and reducing neurological deficits (8). However, prolonged ischemia may lead to irreversible neuronal damage (9), while reperfusion following successful recanalization can paradoxically exacerbate injury through a process known as cerebral ischemia-reperfusion injury (CIRI) (10).

Mitochondria, as central organelles for energy production and metabolic regulation, serve as the primary energy source for the brain (11). Increasing evidence highlights the pivotal role of mitochondria in neuronal repair and neurological recovery following CIRI (12-14). Mitochondrial dysfunction

is a hallmark feature of CIRI, encompassing oxidative stress, Ca^{2+} overload and impaired mitochondrial quality control (MQC) (15). These mitochondrial abnormalities contribute to neuronal damage and activate regulated cell death pathways, including ferroptosis, pyroptosis and necroptosis (16). Among these, ferroptosis has emerged as a key driver of brain injury within the pathological cascade of CIRI. This distinct form of regulated cell death is characterized by iron-dependent lipid peroxidation, and is marked by dysregulated intracellular iron metabolism, excessive labile iron accumulation, overproduction of reactive oxygen species (ROS) and peroxidative damage to membrane phospholipids (17). In reperfused brain tissue, mitochondrial dysfunction exacerbates vulnerability to ferroptosis by amplifying oxidative stress, disrupting iron homeostasis, impairing antioxidant defenses and promoting lipid peroxidation (18,19).

Despite experimental progress in neuroprotective research, the translation of these findings into clinical practice remains a persistent challenge (20). A number of promising neuroprotective candidates have failed to demonstrate consistent efficacy in clinical trials due to poor blood-brain barrier (BBB) penetration, limited therapeutic effectiveness and substantial systemic toxicity (21). Identifying more disease-specific pathological drivers of CIRI is therefore critical for the development of safer and more precise targeted therapies. Within this context, the mitochondrial dysfunction-ferroptosis axis has emerged as a key pathological network that integrates cellular bioenergetics with lipid metabolism, representing a promising therapeutic target for CIRI (22). Mechanistically, mitochondrial dysfunction regulates ferroptosis through four interconnected pathways: Mitochondrial ROS (mtROS) production, remodeling of iron metabolism, lipid-peroxidation cascades and disruption of antioxidant defense systems. The significance of this axis lies in the multifaceted roles of mitochondria, which extend beyond energy production to include functioning as local hubs to coordinate labile iron utilization, redox signaling and the propagation of lipid peroxides (LPOs) (23).

While previous reviews have independently explored mitochondrial dysfunction-related regulated cell death and the mechanisms of ferroptosis in ischemic brain injury (17,24), the present review focuses on the interplay between mitochondrial dysfunction and ferroptosis susceptibility during CIRI. Specifically, the present review critically examines the mechanisms by which mtROS production, Ca^{2+} signaling and MQC modulate ferroptosis (15,25). By integrating these interconnected processes, the present review aims to provide a comprehensive framework for understanding the pathogenesis of CIRI and to offer novel insights into the development of precise, mechanism-driven therapeutic strategies for patients with CIRI. Mitochondrial dysfunction during CIRI may increase ferroptosis susceptibility through ROS burst, Ca^{2+} overload and mPTP opening, impaired mitochondrial biogenesis, disrupted mitochondrial fission-fusion homeostasis, and altered mitophagy (Fig. 1) (15,26,27).

2. Ferroptosis in CIRI

Definition and molecular features of ferroptosis. Ferroptosis is a novel form of programmed cell death first proposed by Dixon *et al* in 2012 (28). Its hallmark feature is extensive LPO accumulation, which distinguishes it morphologically, biochemically and genetically from other forms of cell death. Morphologically, ferroptosis is mainly characterized by mitochondrial shrinkage or swelling, increased density of the mitochondrial double membrane, reduction or loss of mitochondrial cristae, loss of plasma membrane integrity, cytoplasmic swelling and moderate chromatin condensation (29). Ferroptotic execution can also include detachment and cell rounding, accompanied by increased numbers of autophagosomes (30). Biochemically, ferroptosis is driven by depletion of intracellular glutathione (GSH), which reduces the activity of GSH peroxidase 4 (GPX4) and prevents LPOs from being reduced, thereby leading to their marked accumulation. Additionally, excessive Fe^{2+} accumulation promotes lipid oxidation via the Fenton reaction, generating excessive ROS, augmenting oxidative damage and driving ferroptosis (31). At the genetic level, ferroptosis is regulated by multiple genes implicated in iron homeostasis and lipid peroxidation metabolism, although the precise regulatory mechanisms remain to be further elucidated (29).

Previous findings have indicated that ferroptosis susceptibility is further modulated by several GPX4-independent or parallel defense systems, including the ferroptosis suppressor protein 1 (FSP1)-coenzyme Q_{10} (CoQ_{10})-NAD(P)H axis, the GTP cyclohydrolase 1 (GCH1)-tetrahydrobiopterin (BH4) pathway and the mitochondrial dihydroorotate dehydrogenase (DHODH)-ubiquinol ($CoQH_2$) system (32-35). In addition, acyl-CoA synthetase long chain family member 4 (ACSL4) is not universally required for ferroptosis. However, ACSL4 is not essential for all forms of ferroptosis. For example, ALOX12-mediated lipid peroxidation and ferroptotic cell death occur independently of ACSL4 (36). Such mechanisms may be relevant to CIRI, as ischemia and subsequent reperfusion collectively disrupt mitochondrial metabolism, lipid oxidation and the cellular antioxidant capacity (37); nevertheless, to the best of our knowledge, their precise roles in CIRI have not yet been directly established.

Core mechanisms of ferroptosis in CIRI. CIRI denotes secondary brain injury that develops during restoration of blood flow to previously ischemic brain tissue. Reperfusion rapidly increases oxygen availability, and induces mtROS production, inflammatory signaling, ionic imbalance and mitochondrial stress (38). Evidence suggests that ferroptosis in CIRI is mainly governed by three canonical processes: Dysregulated iron metabolism, lipid peroxidation and antioxidant system failure (39). Concurrently, emerging defense pathways, including the FSP1, GCH1 and DHODH pathways, may mitigate ferroptosis by restricting LPO accumulation (32-35) (Fig. 2).

Dysregulated iron metabolism. Iron is an essential trace element in the human body, predominantly existing in ferrous (Fe^{2+}) and ferric (Fe^{3+}) forms (40,41). Iron metabolism is tightly regulated through absorption, activation, storage, transport and utilization. Under physiological conditions, cells maintain iron homeostasis via a complex transport system, including transferrin receptor 1 for uptake and ferroportin-1 for efflux (42,43). In the pathological context of CIRI, this balance is severely disrupted, leading to abnormal accumulation of the

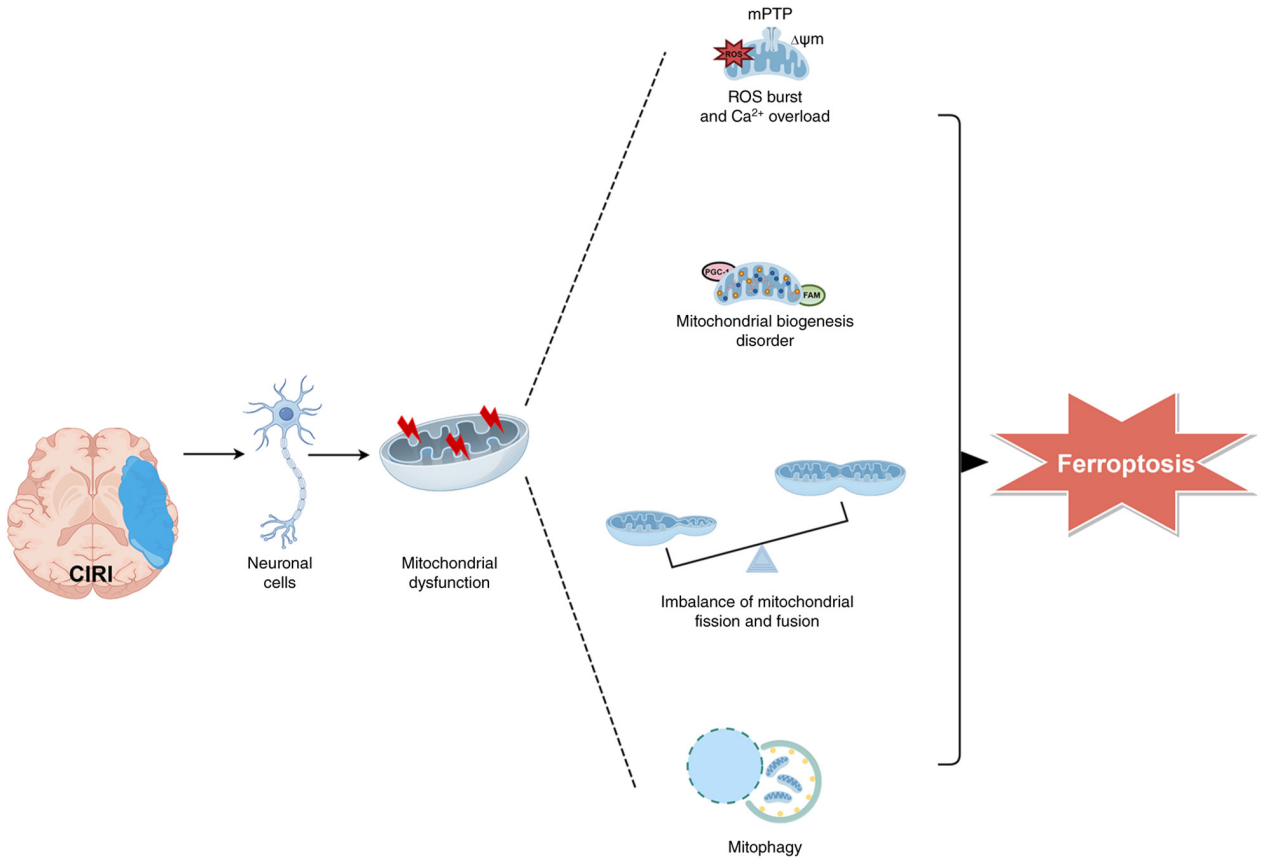

Figure 1. Mitochondrial dysfunction-driven ferroptosis in CIRI. CIRI induces mitochondrial damage in neuronal cells, leading to ROS burst and Ca^{2+} overload, impaired mitochondrial biogenesis, an imbalance between mitochondrial fission and fusion, and dysregulated mitophagy. Collectively, these mitochondrial abnormalities promote ferroptosis. CIRI, cerebral ischemia-reperfusion injury; ROS, reactive oxygen species; mPTP, mitochondrial permeability transition pore; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; TFAM, mitochondrial transcription factor A; ΔΨm, mitochondrial membrane potential.

intracellular labile iron pool (LIP), which subsequently triggers ferroptosis (44).

Ischemic and hypoxic conditions create an acidic tissue microenvironment that inhibits ceruloplasmin activity, thereby impairing the oxidation of Fe^{2+} to Fe^{3+} and binding of Fe^{3+} to transferrin, while increasing the availability and neuronal uptake of free Fe^{2+}. Concurrently, BBB disruption allows a significant influx of peripheral iron into the brain parenchyma (45-47). CIRI also induces microglial activation and triggers an inflammatory cascade, where inflammatory mediators upregulate hepcidin, disrupting cerebral iron homeostasis and exacerbating Fe^{2+} accumulation (48). Under stress conditions, intracellular iron storage proteins, such as ferritin, may be degraded through ferritinophagy, releasing substantial amounts of free iron into the LIP (49). This intracellular iron overload provides abundant catalytic substrates for lipid peroxidation (44).

Iron chelators markedly reduce infarct volume and ameliorate neurological deficits in animal models of IS; clinical observations further suggest these agents exert antioxidant and neuroprotective effects in stroke patients (50). These findings highlight the pivotal role of dysregulated iron metabolism in driving neuronal ferroptosis during CIRI, highlighting a promising therapeutic target for CIRI management.

Abnormal lipid peroxidation pathways. Lipid peroxidation constitutes the core execution mechanism of ferroptosis. The brain is highly enriched in polyunsaturated fatty acids (PUFAs), particularly arachidonic acid (AA) and adrenic acid (AdA), which function as the key substrates for the lipid peroxidation cascade during ferroptosis (29,51).

During CIRI, the upregulated expression of ACSL4 and lysophosphatidylcholine acyltransferase 3 (LPCAT3) promotes the incorporation of oxidizable PUFAs into membrane phospholipids, thereby increasing cell susceptibility to ferroptosis (52-54). Mechanistically, ACSL4 catalyzes the conversion of free AA and AdA into corresponding acyl-CoA derivatives, which are then incorporated into membrane phospholipids by LPCAT3 to generate highly oxidizable AA/AdA-containing phosphatidylethanolamines (52,55,56). Ischemia-induced energy metabolism failure and reperfusion-triggered massive oxidative stress act synergistically to intensify this lipid peroxidation cascade, resulting in substantial cytotoxic LPOs and, ultimately, impaired membrane integrity (57,58). However, ACSL4 should not be considered the exclusive mediator of ferroptotic lipid damage. Wang *et al* (36) demonstrated that ALOX12-dependent ferroptosis could proceed independently of ACSL4, indicating that requirements for lipid substrates and enzymatic machinery vary with the inducing stimulus and cell type. Whether analogous ACSL4-independent mechanisms occur in neurons during CIRI remains uncertain.

Suppression of lipid peroxidation has strong neuroprotective effects in IS. Tuo *et al* (59) reported that liproxstatin-1

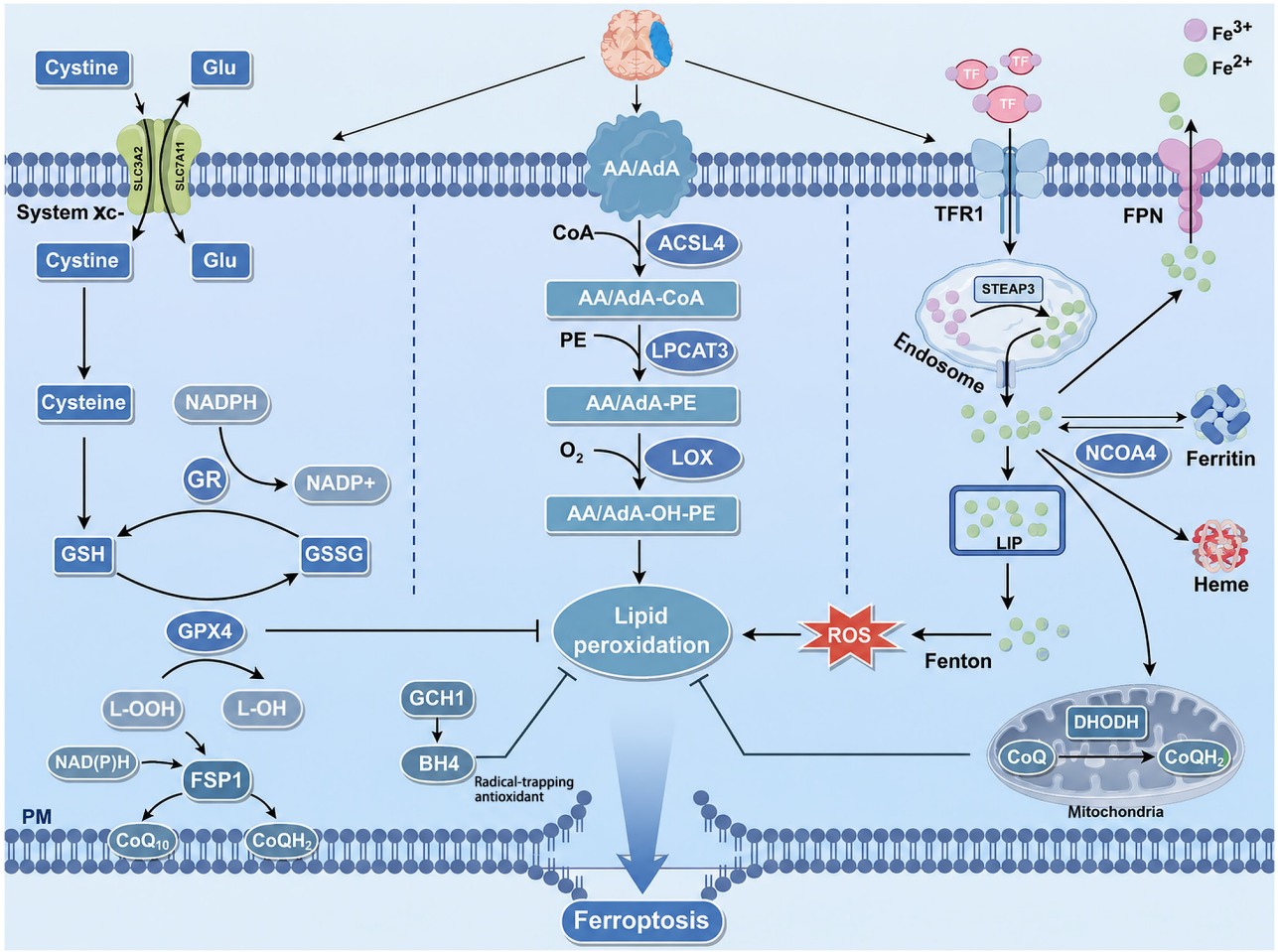

Figure 2. Core mechanisms of ferroptosis in CIRI. The diagram illustrates canonical ferroptosis pathways during CIRI: i) Iron metabolism dysregulation, in which increased transferrin receptor-mediated iron uptake, enhanced ferritinophagy, and impaired iron export lead to excessive intracellular Fe^{2+} accumulation and promote Fenton chemistry; ii) lipid peroxidation, in which polyunsaturated fatty acids in cellular membranes are oxidized via ROS-dependent and enzyme-dependent mechanisms; and iii) antioxidant system failure, including depletion of GSH, functional decline of GPX4 and System Xc^-, and insufficient compensatory defenses such as FSP1-CoQ_{10}, GCH1-BH4 and DHODH-$CoQH_2$. Together, these disruptions promote membrane lipid peroxide accumulation and ferroptotic cell death. AA, arachidonic acid; ACSL4, acyl-CoA synthetase long chain family member 4; AdA, adrenic acid; BH4, tetrahydrobiopterin; CIRI, cerebral ischemia-reperfusion injury; CoQ, coenzyme Q; CoQ_{10}, coenzyme Q_{10}; $CoQH_2$, ubiquinol; DHODH, dihydroorotate dehydrogenase; FPN, ferroportin; FSP1, ferroptosis suppressor protein 1; GCH1, GTP cyclohydrolase 1; GPX4, glutathione peroxidase 4; GSH, glutathione; GSSG, glutathione disulfide; L-OOH, lipid hydroperoxide; LIP, labile iron pool; LOX, lysyl oxidase; LPCAT3, lysophosphatidylcholine acyltransferase 3; NCOA4, nuclear receptor coactivator 4; ROS, reactive oxygen species; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; TFR1, transferrin receptor 1; GR, glutathione reductase; L-OH, lipid alcohol; PE, phosphatidylethanolamine; PM, plasma membrane; TF, transferrin.

ameliorated neurological deficits after CIRI by blocking lipid peroxidation. By contrast, ACSL4 overexpression accelerates LPO generation and worsens neuronal injury (52). Consequently, therapeutic strategies that target key lipid-metabolizing enzymes, such as ACSL4, or directly scavenge LPOs may be feasible for CIRI. Further elucidation of ALOX-associated lipid peroxidation pathways may also expand the potential therapeutic options in this area.

Amino acid metabolism and antioxidant system failure. Amino acid metabolism, especially the functional status of the cystine/glutamate antiporter, System Xc^-, directly determines how well neurons can resist ferroptosis (60). System Xc^- imports cystine and exports glutamate at a 1:1 ratio; the imported cystine is the rate-limiting substrate for synthesis of GSH, the core intracellular antioxidant (61).

During the early phase of CIRI, ischemia and hypoxia cause marked accumulation of glutamate in the synaptic cleft, leading to excitotoxicity (62). The accumulation of extracellular glutamate may competitively inhibit cystine uptake via System Xc^-, thereby contributing to intracellular GSH depletion. As GSH is an essential cofactor for GPX4, reduced GSH levels directly result in loss of GPX4 activity. GPX4 is required to detoxify membrane LPOs. When GPX4 function is impaired, lipid hydroperoxides (L-OOHs) cannot be efficiently reduced to non-toxic lipid alcohols, resulting in irreversible oxidative damage to cellular membranes (29,63).

Consistent with this mechanism, studies have reported that solute carrier family 7 member 11 (the light-chain subunit of System Xc^-) and GPX4 were downregulated in CIRI models, and LPO levels were increased (64,65). Conversely, restoring cystine uptake, increasing GSH levels or overexpressing GPX4 can suppress neuronal ferroptosis and reduce brain injury (59,66). Beyond the canonical System Xc^-/GSH/GPX4 axis, multiple parallel antioxidant pathways can counteract ferroptosis: FSP1 can regenerate reduced CoQ_{10} at the plasma membrane, GCH1-derived BH4 can act as a radical-trapping

antioxidant and DHODH couples the oxidation of dihydroorotate to orotate with the reduction of CoQ to $CoQH_2$. $CoQH_2$ traps lipid peroxyl radicals, thereby limiting the propagation of mitochondrial lipid peroxidation (32-35). Together, these findings suggest that antioxidant failure in CIRI may reflect the collapse of an integrated antioxidant network rather than a single GPX4-dependent event.

3. Association between mitochondrial dysfunction and ferroptosis in CIRI

Mitochondria, as multifunctional organelles, serve essential roles in bioenergetics, biosynthesis and regulatory processes (67). Ferroptosis, characterized by iron metabolism dysfunction, LPO accumulation and the collapse of antioxidant defenses, is intricately linked to mitochondrial dysfunction, with these pathological events being closely intertwined rather than occurring independently (68-70). During the progression of CIRI, mitochondria act not only as the central site of bioenergetic failure but also as a pivotal hub driving ferroptotic mechanisms. This process is mediated through three distinct pathways. First, mitochondria serve as the primary intracellular sites for iron utilization (71), where mitochondrial ferritin (FtMt) regulates iron homeostasis (67). In CIRI, nuclear receptor coactivator 4-mediated cytosolic ferritinophagy releases substantial amounts of iron, facilitating its transport into mitochondria and leading to iron overload (72,73). Second, dysfunction in the mitochondrial electron transport chain (ETC) results in electron leakage, which becomes a major source of ROS (74). These ROS drive the peroxidation of PUFAs within membrane lipids, further contributing to ferroptosis (75). Third, ATP depletion caused by impaired mitochondrial oxidative phosphorylation (OXPHOS) disrupts the membrane potential and ion gradients, indirectly inhibiting System Xc^- transport activity and weakening antioxidant defenses (76). These mechanisms highlight the intimate relationship between mitochondria and ferroptosis, particularly in the context of CIRI.

mtROS burst. Mitochondria are a significant source of intracellular ROS (77). Under physiological conditions, low levels of ROS act as signaling molecules involved in cellular metabolism and adaptive stress responses (78). However, under pathological stress, ETC dysfunction leads to excessive mtROS production, which promotes the accumulation of L-OOHs and heightens cellular susceptibility to ferroptosis (69). Experimental evidence reinforces the link between mitochondrial oxidative damage and ferroptosis, as mitochondria-targeted ROS scavengers, such as XJB-5-131, have been shown to inhibit ferroptosis induced by erastin and RAS-selective lethal 3 (RSL3) (79).

In CIRI, mtROS bursts caused by mitochondrial dysfunction act as amplifiers that connect ischemia-induced bioenergetic failure to lipid damage associated with ferroptosis. During ischemia, oxygen deprivation suppresses OXPHOS and ATP production, leading to the accumulation of ETC substrates and increased electron leakage. Reperfusion reintroduces oxygen abruptly, triggering a significant mtROS burst characterized by the generation of superoxide anion and hydroxyl radicals, while also promoting the production of nitric oxide and reactive nitrogen species (80,81). These reactive species synergistically drive the peroxidation of PUFA-containing membrane phospholipids, and impair mitochondrial and cellular antioxidant systems, thereby increasing neuronal vulnerability to ferroptosis (82).

Calcium ion overload. Mitochondrial calcium (Ca^{2+}) homeostasis serves a critical role in sustaining cellular energy metabolism and survival, with its disruption serving as a key mechanism by which mitochondrial dysfunction contributes to cellular injury (83). Under physiological conditions, Ca^{2+} uptake and release within mitochondria are tightly regulated to maintain proper function. Mitochondrial Ca^{2+} uptake is primarily facilitated by the coordinated actions of the voltage-dependent anion channel (VDAC) and the mitochondrial calcium uniporter (MCU) complex (84). VDAC, located in the outer mitochondrial membrane (OMM), provides a major pathway for Ca^{2+} entry into the intermembrane space and serves an essential role in transferring Ca^{2+} released from the endoplasmic reticulum (ER) into mitochondria at ER-mitochondria contact sites (85). The MCU complex consists of four principal components: The pore-forming protein MCU, the regulatory subunits mitochondrial calcium uptake protein 1 and mitochondrial calcium uptake protein 2, and the essential MCU regulator (86). This complex harnesses the electrochemical gradient generated by the mitochondrial membrane potential ($\Delta\Psi m$) to drive Ca^{2+} entry into the mitochondrial matrix (87).

Ca^{2+} release from the mitochondrial matrix is primarily mediated by three major mitochondrial Ca^{2+} efflux routes: The $Na^+/Ca^{2+}/Li^+$ exchanger (NCLX), the Ca^{2+}/H^+ exchanger (CHX) and the mitochondrial permeability transition pore (mPTP) (88). NCLX utilizes the Na^+ electrochemical gradient across the inner mitochondrial membrane (IMM) to enable electrogenic Ca^{2+} efflux from the matrix, with a stoichiometry of three Na^+ ions exchanged for one Ca^{2+} ion (89-92). By contrast, CHX relies on the inwardly directed proton gradient to extrude Ca^{2+}, with a proposed stoichiometry of two H^+ ions per Ca^{2+} ion (93). Additionally, transient openings of the mPTP may facilitate Ca^{2+} release under specific conditions, although its role as a conventional physiological efflux mechanism remains a subject of debate (94,95). The dynamic equilibrium between mitochondrial Ca^{2+} uptake and release is essential for enabling Ca^{2+} to stimulate the tricarboxylic acid cycle and OXPHOS, while preventing mitochondrial dysfunction and cellular injury caused by Ca^{2+} overload (96,97) (Fig. 3).

Excessive accumulation of Ca^{2+} in the mitochondrial matrix enhances respiratory chain-associated ROS production, promoting oxidative stress and lipid peroxidation (98). Pharmacological studies have indicated that ruthenium red, an inhibitor of mitochondrial Ca^{2+} uptake, markedly suppressed intracellular ROS-associated ferroptosis (99), while the Ca^{2+} chelator BAPTA effectively blocked erastin-induced ferroptosis (100). These findings imply that Ca^{2+} signaling may act as an upstream regulatory node within the mtROS-ferroptosis axis.

During cerebral CIRI, ischemia-induced ATP depletion impairs ATP-dependent ion pumps, leading to cytosolic Ca^{2+} accumulation (101). Reperfusion can further increase the mitochondrial Ca^{2+} load, destabilize the $\Delta\Psi m$ and promote

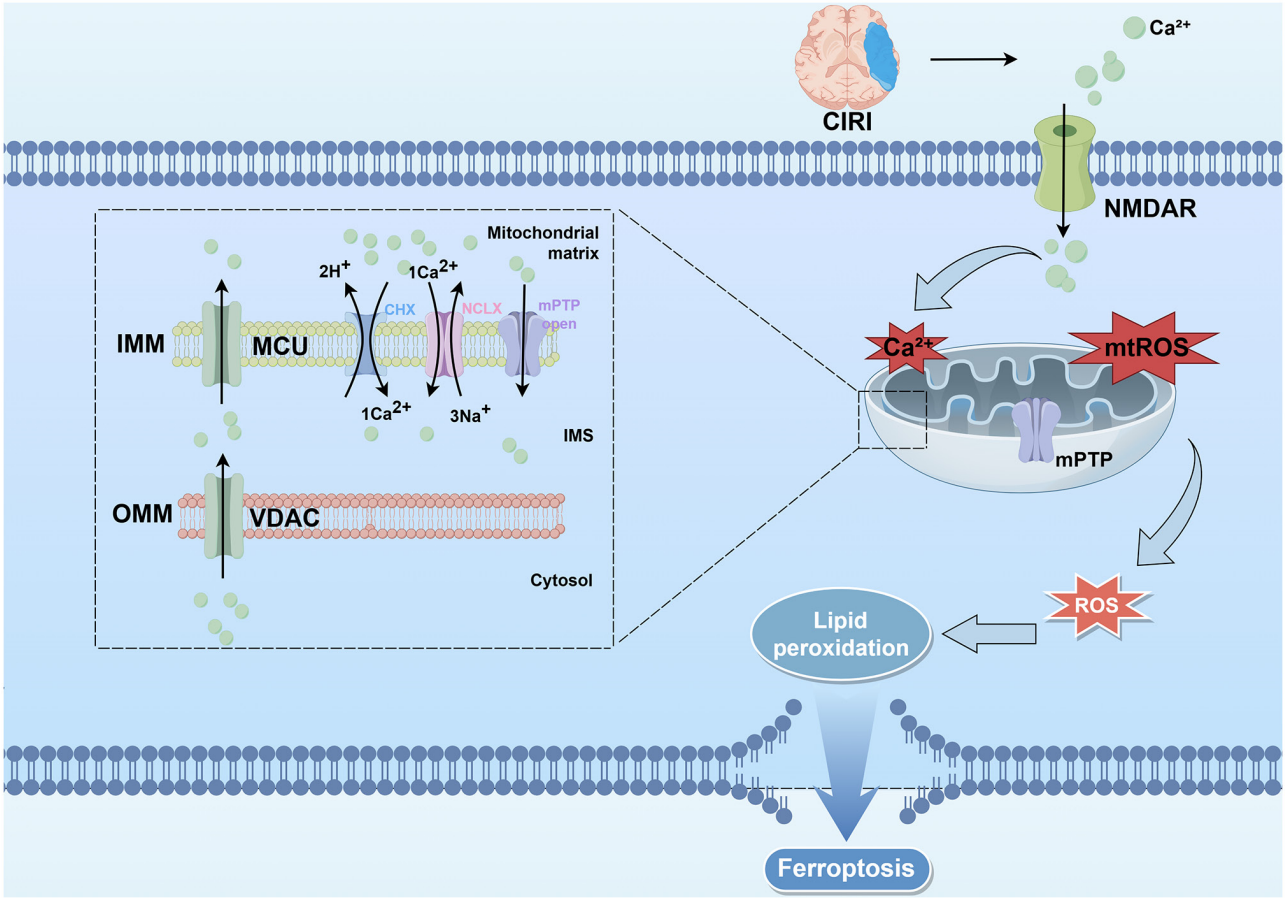

Figure 3. Interplay between mitochondrial Ca^{2+} overload and ferroptosis in CIRI. Under ischemic and reperfusion stress, excessive cytosolic Ca^{2+} enters mitochondria via the MCU complex. Pathological Ca^{2+} overload can increase mtROS generation and promote mPTP opening. CIRI, cerebral ischemia-reperfusion injury; MCU, mitochondrial calcium uniporter; mtROS, mitochondrial reactive oxygen species; mPTP, mitochondrial permeability transition pore; ROS, reactive oxygen species; IMM, inner mitochondrial membrane; OMM, outer mitochondrial membrane; VDAC, voltage-dependent anion channel; IMS, mitochondrial intermembrane space; NMDAR, N-methyl-D-aspartate receptor; CHX, Ca^{2+}/H^{+} exchanger; NCLX, mitochondrial $Na^{+}/Ca^{2+}Li^{+}$ exchanger.

mPTP opening (102,103). However, the direct causal relationship between mPTP opening and ferroptosis is not yet fully defined. Sustained mPTP opening is generally associated with mitochondrial permeability transition, bioenergetic collapse, necrotic cell death and apoptosis-related signaling (104), whereas ferroptosis is characterized by iron-dependent phospholipid peroxidation (105). Thus, mPTP opening may indirectly heighten neuronal susceptibility to ferroptosis by enhancing mtROS production, disrupting mitochondrial metabolism and weakening antioxidant defenses (106).

MQC disruption. In CIRI, MQC serves a pivotal role in maintaining mitochondrial integrity. Disruptions in key MQC-regulated processes, including mitochondrial biogenesis, dynamics and selective autophagy, can precipitate ferroptosis (107-109). Since mitochondria are the primary site of cellular energy production, mitochondrial dysfunction not only compromises cellular metabolism but also intensifies neuronal injury by disrupting iron homeostasis and promoting lipid peroxidation, ultimately driving ferroptosis (110) (Fig. 4).

Mitochondrial biogenesis disorder. Mitochondrial biogenesis constitutes a core mechanism within the MQC system, generating functional mitochondria by facilitating the growth and division of existing organelles. This process replaces damaged mitochondria and preserves cellular bioenergetic homeostasis (111). Coordinated communication between nuclear and mitochondrial genomes is essential, involving mitochondrial DNA (mtDNA) replication and transcription alongside the synthesis, import and assembly of nuclear-encoded mitochondrial proteins (112-114). Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) serves as the central transcriptional coactivator governing mitochondrial biogenesis. Upon activation by AMP-activated protein kinase (AMPK) or sirtuin 1 (16), PGC-1α interacts with nuclear respiratory factor (NRF)1 and 2. Together with mitochondrial transcription factor A (TFAM), this regulatory network coordinates the expression of respiratory-chain complexes encoded by nuclear and mtDNA, thereby driving mitochondrial biogenesis (115,116).

Neurons possess exceptionally high energy demands, making the maintenance of mitochondrial abundance and functionality critical for normal neuronal activity. CIRI induces a burst of ROS, calcium dyshomeostasis and inflammatory cascades, which collectively impair mitochondrial function. Damaged mitochondria subsequently release excessive ROS and pro-apoptotic factors, establishing a positive feedback loop that progressively exacerbates neuronal injury (117). Mitochondrial biogenesis is activated as an adaptive response

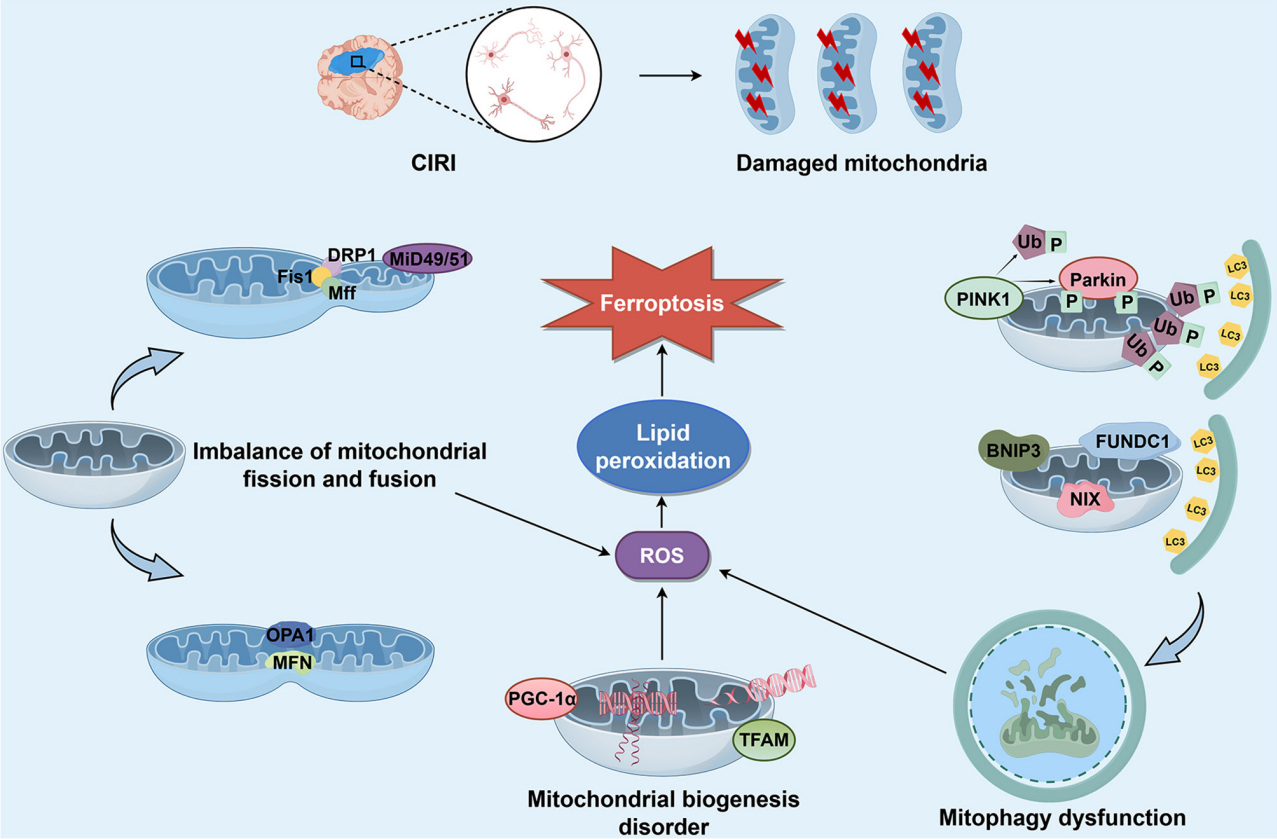

Figure 4. Disruption of the MQC system and its role in mediating ferroptosis during CIRI. The schematic highlights how the failure of individual MQC components synergistically exacerbates neuronal damage: i) Impaired mitochondrial biogenesis fails to replenish the pool of functional mitochondria; ii) dysregulated mitochondrial dynamics, characterized by an imbalance between fission and fusion, result in extensive mitochondrial fragmentation; and iii) defective mitophagy prevents the timely removal of damaged and depolarized mitochondria. The accumulation of dysfunctional mitochondria serves as a major source of excessive mitochondrial ROS and altered iron handling, creating a self-reinforcing cycle that amplifies lipid peroxidation and culminates in ferroptosis. MQC, mitochondrial quality control; CIRI, cerebral ischemia-reperfusion injury; ROS, reactive oxygen species; DRP1, dynamin-related protein 1; PINK1, PTEN-induced kinase 1; Ub, ubiquitin; P, phosphorylation; BNIP3, BCL2-interacting protein 3; FUNDC1, FUN14 domain-containing protein 1; NIX, NIP3-like protein X; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator 1α; TFAM, mitochondrial transcription factor A; OPA1, optic atrophy 1; MFN, mitofusin; Fis1, mitochondrial fission 1 protein; DRP1, dynamin-related protein 1; Mff, mitochondrial fission factor.

to hypoxic-ischemic brain injury. Enhancement of PGC-1α signaling can restore mitochondrial content and mitigate ischemic neuronal damage (38,118). Additionally, PGC-1α promotes the expression of mitochondrial antioxidant proteins, such as uncoupling protein 2 (UCP2) and superoxide dismutase 2, thereby limiting mtROS accumulation (119). In microglia, PGC-1α further suppresses post-stroke neuroinflammation (120). Collectively, these findings establish PGC-1α-mediated mitochondrial biogenesis as a protective mechanism against cerebral ischemic injury.

The link between defective mitochondrial biogenesis and ferroptosis appears to be primarily mediated by mitochondrial oxidative stress rather than ATP depletion alone. Insufficient mitochondrial renewal allows damaged mitochondria and respiratory-chain components to accumulate, perpetuating mtROS production (121). In the reperfused brain, increased labile iron availability, coupled with impaired antioxidant defenses, establishes conditions that enable mtROS to drive the initiation and propagation of polyunsaturated phospholipid peroxidation, thereby heightening susceptibility to ferroptosis (19,122). In rat middle cerebral artery occlusion/reperfusion and neuronal oxygen-glucose deprivation/reoxygenation models, reductions in mitochondrial abundance and UCP2 expression were observed, alongside increased mitochondrial oxidative stress and ferroptotic injury (68). Pharmacological activation of PGC-1α using ZLN005, a small-molecule PGC-1α transcriptional activator, enhanced mitochondrial biogenesis, restored UCP2 expression, reduced mitochondrial oxidative stress, suppressed neuronal ferroptosis and improved neurological outcomes (68). Similarly, Mito-TEMPO, a mitochondria-targeted antioxidant, replicated the anti-ferroptotic effects of ZLN005, whereas UCP2 knockdown diminished the protective effects conferred by PGC-1α activation (68). Consistent with these findings, activin A was shown to activate the PGC-1α-NRF1-TFAM pathway in CIRI, thereby increasing mtDNA content, reducing Fe^{2+} accumulation and lowering lipid ROS levels. PGC-1α knockdown abolished the enhancement of mitochondrial biogenesis and attenuated the anti-ferroptotic effects of activin A (107). Collectively, these studies suggest that impaired mitochondrial biogenesis exacerbates ferroptotic vulnerability by sustaining mitochondrial oxidative stress and promoting lipid peroxidation.

Mitochondrial dynamics (MD) imbalance. Mitochondria are highly dynamic organelles, exhibiting diverse shapes, sizes and lengths. They continuously undergo cycles of

fission and fusion, processes collectively termed MD. The balance between mitochondrial fission and fusion is essential for preserving mitochondrial function and quality, thereby supporting proper cellular activities (123).

i) Mitochondrial fission. Mitochondrial fission refers to the division of a mitochondrion into two or more daughter mitochondria with distinct ΔΨm, a process mediated by membrane constriction driven by the GTPase dynamin-related protein 1 (DRP1) (124). This process serves dual physiological roles. On one hand, DRP1 is recruited to the OMM, where it interacts with mitochondrial fission factor (Mff), mitochondrial fission 1 protein (Fis1) and mitochondrial dynamics protein 49/51 (MiD49/51) to assemble a constriction ring that facilitates membrane scission. This division maintains mitochondrial quantity and morphology homeostasis (125-128). On the other hand, fission selectively segregates mitochondria with low ΔΨm or irreparable mtDNA damage, targeting them for autophagic degradation (129,130). This mechanism prevents the accumulation of damaged mitochondria, thereby reducing mtROS release and mitigating the risk of ferroptosis (130,131).

Under conditions of iron stress, mitochondrial fission becomes dysregulated and emerges as a critical driver of ferroptosis (132). As the core trigger of ferroptosis, iron also supports mitochondrial iron-sulfur (Fe-S) cluster biogenesis and sustains ETC function (133). Under physiological conditions, mitochondria internalize iron via VDAC and mitoferrin-1, whereas excess iron is sequestered by FtMt (134). When Fe^{2+} overload occurs in the LIP or Fe-S cluster synthesis is compromised, AMPK phosphorylates Mff, promoting the recruitment of DRP1 and leading to hyperactivation of fission (135). In parallel, iron overload accelerates cellular iron accumulation through a positive feedback loop, thereby increasing susceptibility to ferroptosis (136). Liu *et al* (137) reported that cisplatin-induced intestinal injury was accompanied by synchronous upregulation of DRP1 and Fis1, consistent with pathological mitochondrial fission as a concomitant feature of ferroptosis. Furthermore, quercetin, functioning as a ferroptosis inducer, can trigger DRP1-mediated mitochondrial fission by remodeling iron homeostasis, directly driving ferroptosis (138). Collectively, these findings indicate that aberrant mitochondrial fission worsens ferroptosis progression.

During CIRI, dysregulated mitochondrial fission constitutes a critical link between ischemic injury and neuronal ferroptosis. Ischemia-reperfusion induces ROS bursts and ΔΨm depolarization, which facilitate DRP1 anchoring to the OMM through Fis1, Mff and MiD49/51, thereby promoting GTP hydrolysis-dependent hyperactivation of fission (139,140). Furthermore, both *in vitro* and *in vivo* studies consistently demonstrate that DRP1 inhibitors or targeted small interfering RNAs block aberrant mitochondrial fission, markedly alleviating CIRI and improving neurological deficits (108,141-143). Therefore, targeting DRP1-mediated aberrant mitochondrial fission is a promising therapeutic strategy for anti-ferroptotic protection following CIRI.

ii) Mitochondrial fusion. Mitochondrial fusion proceeds through two distinct stages: OMM fusion and IMM fusion, with OMM fusion occurring upstream and being governed by different mechanisms (144). OMM fusion is mediated by mitofusin 1/2 (MFN1/2), which form transmembrane *trans*-complexes through GTPase-driven homo- or hetero-oligomerization to tether adjacent OMMs in close proximity, thereby executing OMM fusion (124,145). By contrast, IMM fusion is carried out by oligomerization of optic atrophy 1 (OPA1). Additionally, OPA1 maintains mitochondrial cristae architecture and cooperates with the mitochondrial contact site and cristae organizing system to regulate and shape IMM morphology (146). Unlike the 'segregation and clearance' function of mitochondrial fission, mitochondrial fusion promotes the merging of healthy and damaged mitochondria through functional complementation, enabling the exchange of metabolites, mtDNA and ΔΨm, and ultimately restoring the functionality of impaired components (147).

Increasing numbers of studies have begun to clarify the molecular mechanisms linking mitochondrial fusion to ferroptosis (148,149). Under physiological conditions, mitochondrial fission and fusion are maintained in a dynamic equilibrium; disruption of this balance results in mitochondrial dysfunction (150). As a core regulator of ferroptosis, NRF2 can directly and transcriptionally activate MFN2 to promote mitochondrial fusion, highlighting a close relationship between mitochondrial fusion and ferroptosis (151). In addition, during oxidative stress, NRF2 activation upregulates MFN1/2, promotes mitochondrial fusion, alleviates oxidative stress and suppresses cellular ferroptosis (152). Consistently, Guo *et al* (153) reported that MFN1-mediated mitochondrial fusion effectively blocks RSL3-induced ferroptosis.

During CIRI, hypoxia promotes MFN2 depletion, which markedly weakens mitochondrial fusion, disrupts intracellular homeostasis and ultimately contributes to neuronal death (154,155). Furthermore, MFN2 downregulation not only impairs MD but also worsens CIRI by preventing autophagosome formation and their subsequent fusion with lysosomes (154). These findings suggest that enhancing mitochondrial fusion may inhibit ferroptosis during CIRI; defining the underlying molecular mechanisms represents an important direction for future research.

Mitophagy dysfunction. Mitophagy is the terminal clearance process of the MQC system and was first proposed by Lemasters (156) in 2005. When mitochondria are exposed to insults such as ROS stress, nutrient deprivation or ischemia/hypoxia, the IMM depolarizes. Cells then selectively engulf and degrade damaged mitochondria, thereby preserving mitochondrial quality and maintaining intracellular homeostasis (157,158). This process mainly consists of four key steps: i) After injury, mitochondria lose ΔΨm and undergo depolarization; ii) damaged mitochondria are sequestered into autophagosomes to form mitophagosomes; iii) mitophagosomes fuse with lysosomes; and iv) lysosomal acidic hydrolases are released to degrade the damaged mitochondria (159). In CIRI, mitophagy has dual pathological roles: Moderate mitophagy removes dysfunctional mitochondria to inhibit ferroptosis, whereas either blockade or excessive activation of mitophagy exacerbates the ferroptotic cascade triggered by mitochondrial dysfunction (160,161).

Mechanistically, mitophagy is primarily mediated by two pathways: The ubiquitin (Ub)-dependent and the Ub-independent pathways (162). The Ub-dependent pathway initiates mitophagy via ubiquitination of proteins on damaged mitochondrial surfaces, with the PTEN induced kinase 1 (PINK1)/Parkin axis serving a central role in clearing

impaired mitochondria (163). By contrast, the Ub-independent pathway does not require ubiquitination; instead, multiple OMM proteins contain LC3-interaction regions that directly bind microtubule-associated protein 1A/LC3, thereby initiating mitophagy (159).

During the cerebral ischemic phase, the interruption of oxygen, glucose and energy supply prevents neuronal ATP synthesis, resulting in mitochondrial damage (16). Upon reperfusion, the reestablishment of blood flow alleviates hypoxia but induces an explosive generation of ROS by mitochondria, thereby disrupting redox homeostasis and further damaging mitochondria and activating mitophagy (164,165). Under normal conditions, mitophagy inhibits ferroptosis by clearing damaged mitochondria (131). During CIRI, however, mitophagy may be suppressed, allowing substantial amounts of Fe^{2+} released from damaged mitochondria to accumulate in the cytoplasm, where iron-dependent lipid peroxidation catalyzes and exacerbates ferroptosis (166,167). Accordingly, regulation of mitophagy is key at this stage. Mitophagic activity can be modulated and contributes to the restoration of damaged mitochondria after CIRI (168-170). Mao *et al* (109) demonstrated that ligustilide activated PINK1/Parkin-mediated mitophagy to clear damaged mitochondria in a rat model of CIRI, thereby alleviating neuronal injury.

NRF2 not only activates mitophagy via the PINK1/Parkin pathway to improve mitochondrial function, but also modulates oxidative stress responses to inhibit ferroptosis. In addition, in a mouse model of CIRI, treatment with isoliquiritigenin (a flavonoid constituent of licorice) markedly upregulated NRF2, PINK1 and Parkin protein expression in ischemic brain tissues, thereby enhancing mitophagic activity and subsequently mitigating CIRI-induced damage (171). By contrast, in hepatic ischemia/reperfusion injury, NRF2 knockdown suppresses tangeretin-mediated mitophagy, thereby aggravating ferroptosis (172). Collectively, mitophagy and ferroptosis can be bidirectionally regulated through shared therapeutic targets. Future research should therefore emphasize the roles and mechanisms of NRF2 in these two forms of cell death.

Despite the critical involvement of mitophagy in ferroptosis after CIRI, its hyperactivation disrupts the homeostatic balance among mitochondrial functions, paradoxically exacerbating ferroptosis (173). Studies on the association between mitophagy and ferroptosis have mainly focused on cancer and cardiovascular diseases, whereas systematic investigations of their interplay in CIRI remain limited (67,174,175). Therefore, elucidation of their interactive mechanisms and identification of interventional targets require further in-depth research.

4. Therapeutic strategies targeting mitochondrial dysfunction in CIRI-induced ferroptosis

Growing evidence highlights the potential of mitochondria-centered interventions to mitigate ferroptosis during CIRI, although the translational readiness of these strategies varies markedly (16,37,148). Small-molecule agents that enhance antioxidant signaling or reduce mtROS benefit from relatively well-established pharmacological development pathways (70,176). By contrast, nanomedicines, gene-delivery systems and exosome-based therapies require more extensive validation regarding safety, targeting specificity and delivery efficiency (177). Consequently, therapeutic strategies should not be assessed solely based on their target class. Instead, evaluations must incorporate the robustness of supporting evidence, inherent limitations, unresolved controversies and clinical feasibility.

Scavenging ROS. The surge of mtROS during CIRI, driven by ETC dysfunction and depleted antioxidant defenses, serves a critical role in lipid peroxidation and neuronal ferroptosis (16). Therefore, targeted restoration of intracellular redox homeostasis represents a viable approach to suppress ferroptosis in this context. NRF2-centered antioxidant strategies have shown the ability to simultaneously attenuate oxidative stress, lipid peroxidation and iron accumulation (178). For example, Compound 8a, developed by combining N-butylphthalide (NBP) and tetramethylpyrazine, disrupts the kelch-like ECH associated protein 1-NRF2 interaction to activate NRF2 signaling. This activation enhances antioxidant defenses in brain tissue, markedly reduces intracellular ROS levels and lipid peroxidation, stabilizes the $\Delta\Psi m$, increases ATP levels and ultimately suppresses neuronal ferroptosis (179). Similarly, butylphthalide activates NRF2/heme oxygenase 1 signaling, reducing mtROS and malondialdehyde levels in a rat model of CIRI, thereby interrupting the oxidative stress-ferroptosis axis and improving neurological outcomes (180). Additionally, trifluoperazine modulates AMPK/FoxO3a signaling to reduce mtROS production and lipid peroxidation, restoring redox homeostasis and suppressing neuronal ferroptosis after CIRI (181).

A potentially more direct approach to limiting ROS involves targeting their source within the mitochondrial ETC rather than scavenging downstream ROS. UbiA prenyltransferase domain-containing protein 1 (UBIAD1), a mitochondrial antioxidant enzyme, has been shown to preserve mitochondrial electron transport and limit ROS production at their origin. Adeno-associated virus-mediated UBIAD1 overexpression enhanced the neuronal antioxidant capacity during CIRI, thereby suppressing the ferroptotic cascade (37). This strategy offers a key advantage, as redox imbalance serves as a convergent mechanism underlying various pathological processes in CIRI (182). However, challenges remain, including the lack of cell type specificity in broad antioxidant activation, as well as unresolved issues regarding the optimal dose, therapeutic window and effective delivery across the BBB (Table I).

Preserving Ca^{2+} homeostasis. Intracellular Ca^{2+} overload not only disrupts mitochondrial architecture and induces oxidative stress but also acts as a second messenger, over-activating downstream kinases and ultimately leading to neuronal ferroptosis in CIRI (182-186). Thus, maintaining Ca^{2+} homeostasis and blocking aberrant Ca^{2+} -dependent signaling have emerged as promising strategies for intervening in ferroptosis during CIRI.

Direct antagonism of calcium overload is critical for protecting mitochondrial function and preventing ferroptosis. Xiong *et al* (187) developed a Sr-substituted Prussian blue-like nanodrug (SrHCF) that simultaneously scavenges ROS, captures free Fe^{2+} and releases Sr^{2+} to antagonize Ca^{2+} overload. Through these coordinated actions, SrHCF alleviates mitochondrial dysfunction and suppresses neuronal

Table I. Comparative summary of mitochondria-centered therapeutic strategies for ferroptosis in cerebral ischemia-reperfusion injury.

First author/s, year	Strategy category	Interventions	Ferroptosis indicators	Mechanism of ferroptosis inhibition	(Refs.)
Li *et al*, 2025	ROS scavenging	Compound 8a	↑ GPX4, GSH; ↓ MDA, Fe^{2+}	Disrupts KEAP1-NRF2 interaction, activates NRF2, and reduces mtROS, lipid peroxidation and iron accumulation.	(179)
Sun *et al*, 2024		Butylphthalide	↑ GPX4, GSH; ↓ MDA, Fe^{2+}, TFR1	Activates NRF2/HO-1 signaling, strengthens endogenous antioxidant defenses and limits iron-associated lipid peroxidation.	(180)
Zhong *et al*, 2023		Trifluoperazine	↑ GPX4; ↓ MDA, Fe^{2+}, Glu, SLC7A11	Activates AMPK/FoxO3a signaling under energy stress and reduces mitochondria-associated lipid peroxidation.	(181)
Huang *et al*, 2022		AAV-mediated UBIAD1 overexpression	↑ GPX4, GSH; ↓ MDA, Fe^{2+}, FTH1	Restores mitochondrial/Golgi antioxidant capacity and supports vitamin K2/CoQ-linked electron transfer to reduce ROS generation.	(37)
Xiong *et al*, 2025	Ca^{2+} homeostasis	SrHCF	↑ GPX4, GSH; ↓ Fe^{2+}	Combines ferrous chelation, antioxidation and Ca^{2+} antagonism to reduce Fenton chemistry and mitochondrial Ca^{2+} stress.	(187)
Du *et al*, 2025		CAMK2B knockdown	↑ GPX4, GSH, MDA, SLC7A11; ↓ Fe^{2+}	Blocks Ca^{2+}-sensor CAMK2B and the AREG/JUN/ELAVL1 axis, reducing autophagy- dependent ferroptosis.	(186)
Yang *et al*, 2025	MQC regulation	ZLN005	↑ GPX4, FTH1; ↓ MDA, ACSL4, Fe^{2+}, TFR1, DMT1	Activates PGC-1α/NRF1/TFAM-mediated mitochondrial biogenesis and UCP2-dependent antioxidant protection.	(68)
Wang *et al*, 2025		Semaglutide	↑ GPX4; ↓ MDA, ACSL4, Fe^{2+}	Suppresses FoxO1/DRP1-associated excessive fission and restores mitochondrial dynamics to reduce ROS levels and lipid peroxidation.	(191)
Shi *et al*, 2022		Se	↑ GPX4, GSH, SOD; ↓ MDA, iron, FTH1	Promotes MFN1-dependent mitochondrial fusion, supports antioxidant defense and reduces iron-associated lipid peroxidation.	(148)
Li *et al*, 2025		M2-exos	↑ GPX4, GSH, SLC7A11; ↓ MDA, iron, NCOA4	Activates AMPK/ULK1/FUNDC1-mediated mitophagy and limits NCOA4-mediated ferritinophagy and iron overload.	(193)

ACSL4, acyl-CoA synthetase long chain family member 4; AMPK, AMP-activated protein kinase; CAMK2B, calcium/calmodulin-dependent protein kinase IIβ; CoQ, coenzyme Q; DRP1, dynamin-related protein 1; FUNDC1, FUN14 domain-containing 1; GPX4, glutathione peroxidase 4; GSH, glutathione; MFN1, mitofusin 1; MQC, mitochondrial quality control; mtROS, mitochondrial reactive oxygen species; NCOA4, nuclear receptor coactivator 4; NRF, nuclear respiratory factor; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11; TFAM, mitochondrial transcription factor A; TFR1, transferrin receptor 1; UBIAD1, UbiA prenyltransferase domain-containing protein 1; UCP2, uncoupling protein 2; ULK1, unc-51 like autophagy activating kinase 1. AREG, amphiregulin; DMT1, divalent metal transporter 1; ELAVL1, ELAV-like RNA-binding protein 1; FTH1, ferritin heavy chain 1; HO-1, heme oxygenase 1; M2-exos, M2 macrophage-derived exosomes; MDA, malondialdehyde; Se, selenium; SOD, superoxide dismutase; SrHCF, strontium hexacyanoferrate nanomedicine; ZLN005, 2-[4-(tert-butyl)phenyl]-1H-benzimidazole.

ferroptosis during CIRI. Equally important is blocking the downstream lethal signaling cascade triggered by calcium overload. Du *et al* (186) demonstrated that CIRI-induced calcium homeostasis imbalance markedly upregulates calcium/calmodulin-dependent protein kinase IIβ (CAMK2B), a core neuronal calcium sensor. High CAMK2B expression activates the amphiregulin/JUN/ELAV like RNA binding protein 1 signaling axis, inducing 'autophagy-dependent ferroptosis' in neurons. Targeted knockdown of CAMK2B disrupts this abnormal calcium signaling, restores

the GPX4/GSH antioxidant system, and inhibits iron and LPO accumulation, thereby reducing infarct volume and providing neuroprotective effects. These approaches illustrate two complementary strategies: Direct buffering of Ca^{2+}/iron stress and interruption of Ca^{2+}-dependent signaling. Their main limitation lies in translational complexity: Nanodrug biodistribution, long-term safety and genetic knockdown delivery require further validation before clinical application (186-188) (Table I).

Regulating MQC. The MQC system encompasses mitochondrial biogenesis, dynamics (fusion and fission) and mitophagy (189). During CIRI, restoring the dynamic equilibrium of the MQC network not only segregates and clears damaged mitochondria but also replenishes the healthy mitochondrial pool, serving as a systemic endogenous protective mechanism against neuronal ferroptosis (16).

Promoting mitochondrial biogenesis is pivotal for restoring energy metabolism in ischemic brain tissue. In CIRI models, treatment with the PGC-1α-specific agonist ZLN005 robustly induces mitochondrial biogenesis by activating the canonical PGC-1α/NRF1/TFAM pathway. Concurrently, it upregulates the antioxidant protein UCP2 to attenuate mitochondrial oxidative stress, ultimately inhibiting neuronal ferroptosis and improving neurological function (68). The dynamic nature of mitochondria, governed by the processes of fusion and fission, is essential for maintaining ultrastructural integrity and cellular energy metabolism (190). Research has indicated that the clinical antidiabetic drug semaglutide (a glucagon-like peptide-1 receptor agonist) can block DRP1-mediated aberrant mitochondrial fission and enhance mitochondrial fusion by downregulating FoxO1 expression. This restores ATP production and suppresses ROS generation, thereby alleviating ferroptosis following CIRI (191). Similarly, Shi *et al* (148) found that selenium supplementation in a mouse model of CIRI promoted OMM fusion by upregulating MFN1 expression. This maintained ΔΨm stability and effectively alleviated intracellular oxidative stress, thereby markedly inhibiting the neuronal ferroptotic cascade. Timely clearance of damaged mitochondria via mitophagy is a core component of maintaining MQC homeostasis (192). Recent findings have revealed that M2 microglia-derived exosomes can specifically promote FUN14 domain-containing 1-mediated mitophagy in recipient cells by activating the AMPK/unc-51 like autophagy activating kinase 1 signaling axis, thereby effectively mitigating CIRI-induced neuronal ferroptosis (193). The comparative advantage of MQC regulation is that it targets the health of the entire mitochondrial network rather than a single terminal event such as ROS production (194). However, its primary weaknesses include the fact that optimal intervention windows, cell type specificity, and the functional boundary between protective and maladaptive mitophagy remain incompletely defined (195) (Table I).

5. Conclusions and future perspectives

Ferroptosis represents an important form of regulated cell death in CIRI and mitochondria appear to be central determinants of cellular susceptibility to ferroptosis. Mitochondrial dysfunction during CIRI does not originate from a single linear pathway, but instead reflects a multidimensional pathological network. Excessive mtROS production, Ca^{2+} overload, mPTP opening and disrupted MQC collectively comprise this network (196). These processes perturb iron homeostasis, promote lipid peroxidation and weaken antioxidant defenses, thereby increasing neuronal vulnerability to ischemia-reperfusion injury.

Multiple therapeutic approaches are under development to target this regulatory network. Small molecule agents, including NBP, trifluoperazine and semaglutide, have demonstrated therapeutic potential in experimental models. Additional promising strategies include gene- or protein-based interventions targeting UBIAD1, PGC-1α or CAMK2B, nanomedicines such as SrHCF, and exosome-mediated modulation of mitophagy. However, the strength of supporting evidence varies substantially among these interventions. Antioxidants and MQC-modulating agents have relatively well-defined pharmacological development trajectories. By contrast, nanomedicines and exosome-based delivery systems require systematic assessment of safety, biodistribution and reproducibility.

Despite advances in understanding how mitochondrial dysfunction regulates ferroptosis in CIRI and developing pharmacological, genetic, nanomedicine-based and exosome-mediated interventions, several critical challenges remain. First, CIRI involves multiple cell death modalities, including apoptosis, necroptosis, pyroptosis and ferroptosis (197,198). Shared upstream signals include ROS accumulation, loss of ΔΨm and mitochondrial damage (16). Therefore, more specific biomarkers and genetic tools are needed to quantify the relative contribution of ferroptosis to tissue injury *in vivo*. Second, a number of proposed links between mitochondria and ferroptosis are inferred primarily from pharmacological inhibition, gene overexpression or evidence from non-CIRI (35,44,67). Third, certain mechanisms, particularly mPTP opening, are biologically plausible, direct evidence that mPTP opening regulates ferroptosis during CIRI remains limited (22,199,200).

Future studies should prioritize integrated experimental models that combine ferroptosis-specific lipid peroxidation markers, mitochondrial function assays and cell type-resolved analyses. Mechanistic investigations should clarify how mtROS, Ca^{2+} flux, MD and mitophagy interact with the FSP1-CoQ_{10}, GCH1-BH4 and DHODH-$CoQH_2$ ferroptosis-defense systems. For clinical translation, candidate therapies require systematic evaluation of therapeutic windows, BBB permeability, long-term safety and effects on neurological recovery. These evaluations may determine whether therapeutic strategies targeting mitochondrial dysfunction and ferroptosis can be translated from experimental CIRI models into clinically applicable neuroprotective treatments.

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Authors' contributions

JL conceived and designed the study, performed the literature review, wrote the manuscript and constructed figures. AL and LX performed the literature review. WG and PD performed the literature review and revised the manuscript. HL conceived the study and edited the manuscript. Data authentication is not applicable. 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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