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REVIEW

Targeting Ferroptosis for Cerebral Neuroprotection in Ischemic Stroke: Pathophysiological Insights

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Abstract: Acute ischemic stroke, a leading cause of neurological disability, stemed from cerebral hypoperfusion-induced ischemia/reperfusion (I/R) injury. Ferroptosis, an iron-dependent, lipid peroxidation-driven cell death, has emerged as a key pathological driver. Unlike apoptosis, ferroptosis involves glutathione peroxidase 4 (GPX4) inactivation, iron dysregulation, and lethal lipid peroxides. Its preclinical inhibition reduced neuronal loss, demonstrating therapeutic promise. Ischemic injury activated accidental/regulated cell death pathways, with ferroptosis, apoptosis, and pyroptosis dynamically regulated by ischemia duration/severity. Convergent mechanisms included hypoxia-induced mitochondrial dysfunction, iron/lipid peroxidation disrupting blood-brain barrier integrity, glutamate-ferroptosis oxidative crosstalk, and Ca^{2+} overload via reversed Na^{+}/Ca^{2+} exchange and NMDA hyperactivity. Clinically, cerebrospinal ferritin elevation and parenchymal iron deposition predicted poor outcomes, prioritizing iron homeostasis modulation. GPX4 activation, ACSL4/LOX inhibition, and ACSL3-mediated MUFA integration have showed efficacy in preclinical models. Translational barriers included poor blood-brain barrier permeability of inhibitors, unvalidated human pathways, and lack of relevant comorbid models. Advancing therapies required biomarker discovery, human tissue validation, and integrated models to bridge mechanisms and clinical translation. Ferroptosis inhibition emerged as a neuroprotective strategy with transformative therapeutic potential for acute ischemic stroke, offering a novel avenue to mitigate neuronal injury and improve clinical outcomes.

Keywords: ferroptosis, acute ischemic stroke, ischemia/reperfusion injury, lipid peroxidation, neuroprotection

Introduction

Acute ischemic stroke, a major contributor to global disability, primarily stemed from arterial occlusion-induced cerebral hypoperfusion.[1] Current treatments prioritize revascularization (thrombolysis/endovascular intervention) to rescue metabolically vulnerable penumbral tissue, though reperfusion frequently exacerbates injury via oxidative/inflammatory cascades.[2,3]

Ferroptosis, an iron-dependent form of regulated cell death driven by GPX4 inactivation, dysregulated iron metabolism, and lipid peroxide accumulation, constitutes a mechanistically integral component of stroke pathology. This process, distinguished from classical apoptosis, is characterized by mitochondrial shrinkage accompanied by membrane rupture and cristae loss.[4,5] The underlying pathophysiology involved synergistic iron overload, compromised antioxidant defenses, and enzymatic peroxidation of polyunsaturated fatty acids (PUFAs) phospholipids. Critically, preclinical studies have consistently demonstrated reduced cerebral infarct volumes following pharmacological inhibition of ferroptosis.[6,7] Emerging research has further expanded the understanding of ferroptosis-targeted neuroprotection, particularly in the context of subarachnoid hemorrhage (SAH), a severe stroke subtype with high mortality and limited

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therapeutic options. Oroxin A (OA) demonstrates neuroprotection in SAH by activating the Nrf2/GPX4 pathway and upregulating FSP1 to inhibit ferroptosis and reduce early brain injury. Subsequently, idebenone (IDB) is shown to mitigate SAH-induced cognitive impairment and neuronal damage by enhancing FSP1 stability through N-myristoylation, thereby suppressing ferroptosis and neuroinflammation.[8,9]

Therapeutic strategies targeting iron chelation, GPX4 activation, and lipid antioxidant pathways have shown preclinical promise but face barriers to clinical translation, including the lack of validated biomarkers, insufficient understanding of pathway crosstalk, and challenges in blood-brain barrier (BBB) penetration. Convergent cellular signaling pathways, particularly those governing survival and stress responses, also regulate ferroptosis sensitivity. The PI3K/Akt/mTOR signaling cascade, a central hub for regulating cell growth, metabolism, and survival, plays a complex role during cerebral ischemia. While transient activation of Akt can be neuroprotective, sustained or aberrant modulation of its activity has been linked to various forms of cell death, potentially intersecting with ferroptosis by modulating oxidative stress responses and metabolic adaptation.[10] Advancing neuroprotection required multi-omics-driven biomarker discovery, computationally optimized BBB-permeable agents, and preclinical models that incorporate comorbidities.

Multifaceted Regulation of Ferroptosis in Ischemic Stroke

Ischemic stroke results from cerebrovascular occlusion attributable to atherosclerosis, hypertension, diabetes, and/or dyslipidemia, which precipitates acute cerebral hypoperfusion.[11] This critical deprivation of oxygen and glucose rapidly depletes ATP reserves, inducing lactic acidosis and activating the ischemic/hypoxic cascade. Subsequently, this cascade triggers neuronal death mediated through excitotoxicity, mitochondrial dysfunction, and necrotic core formation,[12] manifesting clinically as hemiplegia, sensory deficits, and aphasia.[13]

Ischemic brain tissue differentiates into two distinct compartments based on perfusion thresholds. The ischemic core undergoes irreversible necrosis due to catastrophic ATP depletion resulting from collateral circulation failure (perfusion <20% of baseline).[14] Adjacent to the core, the penumbra maintains partial perfusion (20–40% of baseline), sustaining metabolically compromised but potentially salvageable neurons within a 4.5- to 6-hour therapeutic window.[15]

Reperfusion paradoxically amplifies ischemic injury through oxidative stress exacerbation, neuroinflammatory cytokine storms, and glutamatergic excitotoxicity mediated by intracellular Calcium overload.[16] These cascades intensify following BBB disruption, mitochondrial permeability transition pore (mPTP) activation, and ferroptosis, an iron-dependent, lipid peroxidation-driven cell death pathway initiated by GPX4 inactivation.[17] Ferroptosis mechanistically intersects with excitotoxicity and inflammation via Fe^{2+}-dependent Fenton chemistry, establishing self-amplifying cascades that propagate ischemic damage. Therapeutic targeting of ferroptosis regulators (ACSL4, SLC7A11) represents a promising strategy to stabilize the penumbra and improve neurological recovery (Figure 1).

Abnormal Glucose Metabolism and Ferroptosis in Ischemic Stroke

The brain's disproportionate metabolic demand (consuming 20% of systemic resources despite comprising only 2% of body mass) renders it exceptionally vulnerable to ischemic cascades.[18] Cerebral hypoxia induces anaerobic glycolysis in neural cells, generating graded acidosis through lactate accumulation. Moderate acidosis (pH 6.5–6.8) may attenuate excitotoxicity via NMDA receptor suppression,[19] whereas severe acidemia (pH <6.2) triggers mitochondrial permeability transition and cytotoxic edema. Paradoxically, reperfusion amplifies ischemic injury, as demonstrated in MCAO models where transient pH recovery fails to reverse sustained core acidosis.[20] Astrocyte-derived lactate demonstrates context-dependent duality: sustaining neuronal metabolism via the astrocyte, neuron lactate shuttle under normoxic conditions, yet mitigating ferroptosis through redox regulation during ischemia.[21] HIF-1α-mediated metabolic reprogramming upregulates glucose transporters and glycolytic enzymes, prioritizing ATP production over metabolic efficiency; this intersects with ferroptosis pathways via iron retention—marked by enhanced transferrin receptors and mitochondrial reactive oxygen species (ROS)-induced lipid peroxidation.[22,23] Further deepening the link between glucose metabolism and ferroptosis, molecular evidence highlights the pivotal roles of GABARAPL1(a core autophagy-related protein) and HIF-1α.[24] Under ischemia, stabilized HIF-1α orchestrates an adaptive metabolic shift by upregulating genes for glucose transporters (GLUT1/3) and glycolytic enzymes, diverting flux towards lactate production but simultaneously promoting

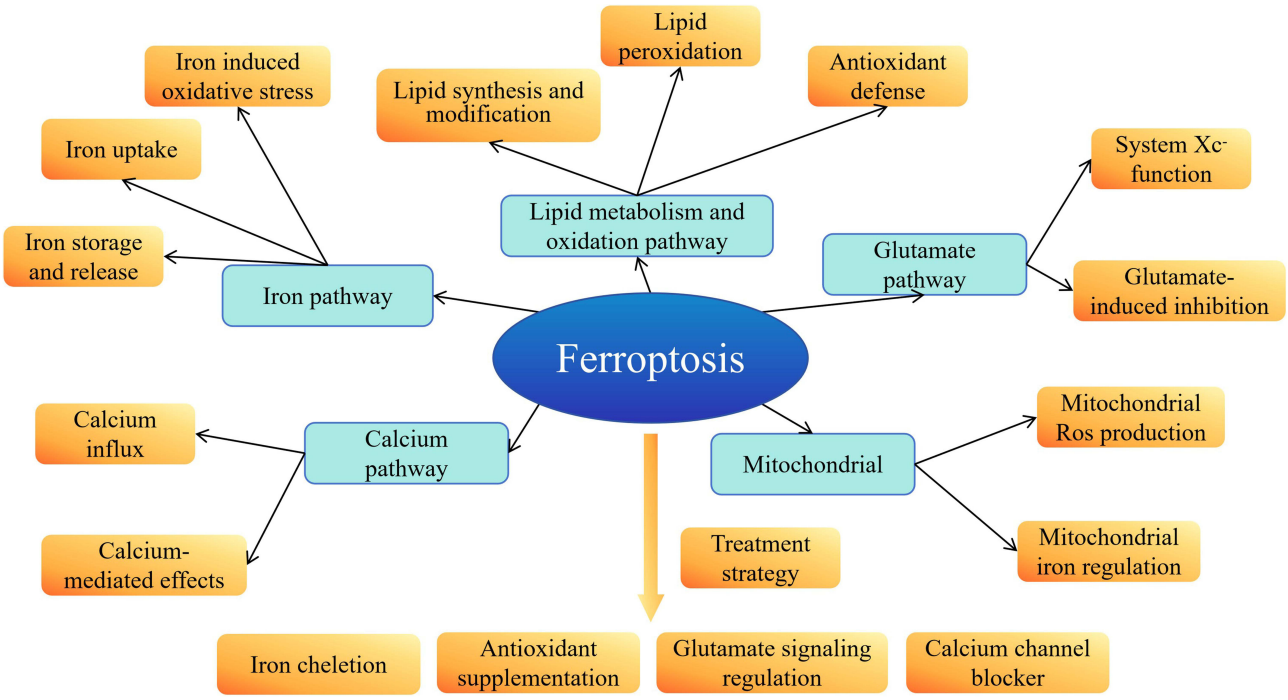

Figure 1 Ferroptosis mechanism diagram.

an "iron-sink" phenotype by increasing transferrin receptor (TfR) expression and suppressing ferritin heavy chain (FTH), thereby elevating the labile iron pool (LIP). This iron overload, coupled with HIF-1α-induced lactate production, accelerates lipid ROS generation within an environment primed for ferroptosis.[25] Conversely, GABARAPL1 regulates glucose supply by mediating glycophagy (autophagy of glycogen) within astrocytes. During reperfusion or metabolic stress, GABARAPL1 downregulation leads to impaired glycogen degradation, glycogen accumulation, and disrupted glucose-to-lactate cycling. Crucially, this impairs the generation of NADPH via the pentose phosphate pathway (PPP), a metabolic axis critical for regenerating reduced glutathione (GSH) and detoxifying lipid peroxides, consequently sensitizing neurons to ferroptosis. Thus, while HIF-1α promotes glycolysis and co-opts iron metabolism to potentiate ferroptosis, GABARAPL1 mitigates it by ensuring efficient glycogen-to-glucose conversion and NADPH availability. The dysregulation of either axis, HIF-1α's iron-retentive glycolysis or GABARAPL1's support of the PPP, compromises metabolic defenses against ferroptosis.[26] Emerging evidence establishes glycophagy as critical in cerebral I/R injury: GABARAPL1 downregulation impairs astrocytic glycogen clearance, exacerbating oxidative stress, while its overexpression preserves neuronal viability during reperfusion.[27] Cross-pathological analyses reveal conserved metabolic adaptations against ferroptosis: tumor cells leverage pentose phosphate pathway (PPP) activation to sustain NADPH-dependent antioxidant defenses,[28] while neuronal SK channel modulation shifts energy production toward glycolysis to suppress iron-mediated cell death.[29] Notably, insulin enhances hippocampal glucose utilization and PPP flux, counteracting lipid peroxidation in lipopolysaccharide (LPS)-impaired cognition.[30] Therapeutic strategies targeting nodal regulators including GABARAPL1-mediated glycophagy restoration, Hsp27-driven glycolytic enhancement, and insulin-induced PPP activation synergistically preserve metabolic homeostasis and neuronal survival in cerebral ischemia. This integrated approach concurrently addresses ischemia's mechanistic triad: pH dysregulation, bioenergetic failure, and iron overload.

Integrated Mechanisms of BBB Disruption and Ferroptosis in Ischemic Stroke

I/R induces dynamic BBB breakdown through endothelial tight junction disassembly, pericyte dysfunction, and astrocytic end-foot detachment. This structural compromise promotes vasogenic edema, hemorrhagic transformation, and leukocyte-platelet aggregation-mechanisms perpetuating the post-recanalization "no-reflow" phenomenon.[31,32] Ischemic injury

initiates a biphasic neuroinflammatory cascade wherein M1-polarized microglia and infiltrating peripheral immune cells coordinate with reactive astrocytes to release cytokines, chemokines, and matrix metalloproteinases (MMPs), collectively amplifying vascular permeability and extracellular matrix degradation. Subsequent to neuronal necrosis, damaged cells release damage-associated molecular patterns (DAMPs) in temporally segregated phases: HMGB1 (peaking within 6h post-injury) followed by peroxiredoxins (12–72h post-injury). These DAMPs activate the TLR4/NF-κB signaling pathway across diverse cell types, establishing a self-sustaining necroinflammatory loop via persistent cross-cellular activation.[33,34]

Ferroptosis bridges metabolic collapse and neuroinflammation during cerebral ischemia. Iron overload fuels Fenton reactions that generate hydroxyl radicals, which subsequently oxidize PUFAs into lipid peroxides. Concurrently, inflammatory stress depletes GPX4, disabling antioxidant defenses and accelerating ferroptosis progression. Critically, ferroptotic cells release damage-associated molecular patterns (DAMPs) that amplify TLR4/NF-κB-mediated cytokine production, establishing a self-reinforcing cycle connecting iron dysregulation, oxidative injury, and neuroinflammation.[35,36]

MMP9 exacerbates ischemic injury through dual pathological mechanisms: degradation of BBB tight junction proteins and transcriptional suppression of GPX4/FSP-1 via SP1/NRF2/ATF4 regulators, thereby directly promoting iron retention and lipid peroxidation.[26,37] Soluble epoxide hydrolase (sEH) compromises BBB integrity by catabolizing protective 14,15-EET; pharmacological inhibition of sEH attenuates pro-inflammatory cytokine release and enhances functional recovery.[38,39] Post-reperfusion endothelial lysophospholipase activity facilitates parenchymal iron influx, which activates the ACSL4-LPCAT3-LOX enzymatic axis to amplify ferroptotic cascades.[40,41] Collectively, MMP9-mediated barrier disruption, sEH-driven neuroinflammation, and lysophospholipase-induced iron dysregulation synergistically propagate oxidative injury and ferroptotic cell death.

Oxidative Stress Injury and Ferroptosis in Ischemic Stroke

Oxidative stress critically drives neuroinflammation and neuronal death in ischemic stroke through redox imbalance, damaging lipids, proteins, and nucleic acids while disrupting blood-brain barrier integrity.[42] During I/R, lactic acidosis amplifies lipid peroxidation and free radical generation including ROS and RNS overwhelming endogenous antioxidant defenses.[43,44] Mitochondrial electron transport chain leakage and enzymatic reactions (notably NADPH oxidases and xanthine oxidase) constitute primary ROS sources, though their relative contributions remain contended.[45] This oxidative surge synergizes with ferroptosis via coordinated mechanisms: depleting GPX4, impairing lipid peroxide detoxification, and accelerating iron-dependent Fenton reactions, thereby perpetuating neuronal injury.[46]

Mitochondrial Dysfunction and Ferroptosis in Ischemic Stroke

Severe hypoxia disrupts mitochondrial homeostasis by impairing ATP synthesis, reducing membrane potential, and elevating mitochondrial reactive oxygen species (mtROS), which oxidize mitochondrial DNA (mtDNA) and drive neurodegeneration.[47] Structural perturbations including cristae fragmentation and fission/fusion imbalance, further exacerbated energy metabolism collapse.[48] While compensatory mechanisms such as mitochondrial fusion (facilitating genetic mixing), fission (segregating damaged DNA), and Parkin/PKM2-mediated mitophagy sustain homeostasis during mild ischemia, prolonged hypoxia/reperfusion pathologically overactivates mitophagy, accelerating neuronal death.[49] Hypoxia-induced dysregulation of mitochondrial dynamics manifests through downregulation of fusion proteins MFN1/2, upregulation of fission factors (MFF and phosphorylated DRP1), and severe ATP depletion. Notably, adenylate kinase 4 overexpression restores cellular viability by rescuing mitophagic flux.[50] Chronic ischemia ultimately collapses mitochondrial quality control, amplifying ferroptosis via mtROS-driven lipid peroxidation and iron release.

Mitochondrial autophagy mitigates ferroptosis through CHK2-dependent clearance of ROS-generating organelles.[51] Conversely, mPTP opening induced by ROS and Ca^{2+} overload triggers bioenergetic failure, thereby bridging apoptosis, necrosis, and ferroptosis.[52] Ischemic injury disrupts oxidative phosphorylation, amplifying ROS production at electron transport chain complexes. Complex I significantly contributes to ROS via NADH-driven electron leakage and reverse electron transfer (RET) from complex II, with RET-derived ROS dominating reperfusion pathology.[53] The α-ketoglutarate dehydrogenase complex (composed of DLST/DLD/E3) regulates TCA cycle flux and ROS dynamics:

DLST haploinsufficiency reduces basal ROS, whereas DLD deficiency suppresses RET-induced ROS accumulation.[54] Necroptosis, a regulated form of necrosis triggered by TNFα and other cytokines, can share upstream signals with ferroptosis. Compound NecroX-7, a necroptosis and mPTP opening inhibitor, has demonstrated neuroprotective effects in preclinical cerebral I/R models by preserving mitochondrial membrane potential and reducing oxidative damage.[22] While its primary target is RIPK1/RIPK3/MLKL-mediated necroptosis, its potent ROS scavenging ability also mitigates lipid peroxidation, suggesting a potential role in alleviating ferroptosis-associated injury. During I/R, TIGAR-mediated inhibition of succinate dehydrogenase (SDH) attenuates RET, mitochondrial ROS (mitoROS), and subsequent lipid peroxidation.[55] Targeting regulators of RET may represent a therapeutic strategy to mitigate ferroptosis, though mechanistic validation remains imperative.

Enzyme-Driven ROS/RNS Generation in Ischemic Stroke

NADPH oxidase (NOX) and xanthine oxidase (XO) critically mediated neuronal injury and ferroptosis through ROS overproduction. Among seven NOX isoforms (NOX1-5, DUOX1-2), NOX1 knockdown reduced infarct volume and oxidative DNA damage in rodents. Microglial NOX2 activation exacerbates post-reperfusion neuroinflammation, establishing it as a therapeutic target in middle cerebral artery occlusion/reperfusion (MCAO/R) models.[56,57] Clinical evidence indicates that NOX4 upregulation correlates with stroke severity and ischemia-induced ROS generation, highlighting its translational potential.[58] Human-specific NOX5 aggravates BBB dysfunction via endothelial oxidative injury in humanized mouse models,[59] while hypoxia-inducible DUOX1/2 activation promotes ferroptosis through HIF-2α-dependent ROS overproduction.[60] Concurrently, I/R injury upregulates XO, which catalyzes xanthine oxidation to generate superoxide, hydrogen peroxide (H_2O_2), and peroxynitrite. Salivary XO activity clinically distinguishes ischemic from hemorrhagic stroke, while elevated serum XO levels predict unfavorable neurological outcomes.[61,62]

Arachidonic acid (AA) metabolites generated through cyclooxygenase (COX) and cytochrome P450 (CYP) pathways amplify ferroptosis by driving ROS-dependent lipid peroxidation. In MCAO/R models, pathological COX2 upregulation exacerbates oxidative neuronal injury, whereas its pharmacological inhibition attenuates damage.[63] During reperfusion, peroxynitrite ($ONOO^-$) formation via nitric oxide-superoxide interaction accumulates chronically through inducible nitric oxide synthase (iNOS) overactivation, overwhelming endogenous antioxidant defenses and promoting macromolecular oxidation.[64] Therapeutic strategies targeting neuronal nitric oxide synthase (nNOS) or scavenging $ONOO^-$ demonstrate significant neuroprotective efficacy in preclinical studies.[65] Preclinical evidence supports targeting NOX1/2/4 and xanthine oxidase (XO) to mitigate oxidative injury, though mechanistic roles of NOX3 and dual oxidase (DUOX) isoforms require further elucidation. While isoform-selective NOX inhibitors show therapeutic promise, interspecies variations, notably the absence of NOX5 in rodents, demand caution in clinical translation. Combinatorial antioxidant approaches simultaneously inhibiting NOX, XO, and COX/CYP pathways may synergistically suppress lipid peroxidation and ferroptosis. Nevertheless, optimal therapeutic windows and dosing regimens require refinement to maximize efficacy while minimizing off-target effects.

Antioxidant System Dysregulation and Therapeutic Implications in Ischemic Stroke

Ischemic stroke disrupts enzymatic antioxidant defenses, thereby exacerbating oxidative injury. Activity reduction of SOD in stroke patients positively correlates with impaired ROS detoxification pathways.[66] GPX4 deficiency accelerates ferroptosis, whereas activation of the Nrf2/HO-1/GPX4 axis mitigates neuronal death in I/R models.[67] The Nrf2 transcription factor coordinates antioxidant responses through transcriptional upregulation of SOD, catalase, and GPX via binding to antioxidant response elements (AREs). Ischemic conditions activate Nrf2 through Keap1 dissociation and PI3K/AKT/NF-κB signaling, enhancing ROS neutralization, mitochondrial integrity, and BBB stabilization.[68,69] Notably, natural Nrf2 activators derived from botanical sources have garnered attention for their neuroprotective potential. For instance, eriodictyol-7-O-glucoside, a flavonoid glycoside, has been shown in preclinical models to activate the Nrf2/HO-1 signaling axis, thereby suppressing oxidative stress and inflammatory cascades. By enhancing the cellular antioxidant defense system, compounds like eriodictyol-7-O-glucoside may indirectly support GPX4 activity and inhibit ferroptosis, offering a complementary therapeutic approach.[70] Despite adaptive antioxidant responses, persistent oxidative stress ultimately overwhelms cellular defense mechanisms. Nrf2-targeted therapeutics and exogenous antioxidants demonstrate

potential in restoring redox homeostasis and suppressing ferroptosis. However, precise therapeutic timing and dosage optimization are critical to prevent disruption of physiological reactive oxygen species signaling cascades.[71] These findings underscore the dual regulatory role of antioxidant modulation in both stroke pathogenesis and neuroprotective intervention strategies.

Calcium Overload and Ferroptosis in Ischemic Stroke

Ischemic stroke-induced ATP depletion impairs Na^+/K^+-ATPase and Na^+/Ca^{2+}-ATPase function, triggering pathological Ca^{2+} overload through three distinct mechanisms including (1) Reverse-mode operation of the Na^+/Ca^{2+} exchanger during reperfusion; (2) Glutamate-mediated N-methyl-D-aspartate receptor (NMDAR) activation inducing mPTP opening and subsequent bioenergetic collapse; (3) Impaired sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) activity, exacerbated by glucose-regulated protein 75 (GRP75)-dependent mitochondrial Ca^{2+} overload at endoplasmic reticulum-mitochondria contact sites, a process attenuated by GRP75 inhibition.[72–74]

Mitochondrial calpain activation destabilized mPTP, inducing cytochrome c release and apoptosis, while NOX2-driven ROS amplifies ER Ca^{2+} leakage, perpetuating Ca^{2+}-ROS cycles.[75,76] Targeting NCX modulation, SERCA activation, or mitochondria-ER crosstalk (eg, GRP75 inhibitors) may restore Ca^{2+} homeostasis, whereas ROS scavengers disrupt feedback loops.

Mitochondrial calpain activation promotes mPTP destabilization, inducing cytochrome c release and apoptotic pathways. Concurrently, NADPH oxidase 2 (NOX2)-derived reactive oxygen species amplify endoplasmic reticulum Ca^{2+} leakage, establishing self-amplifying Ca^{2+}-ROS feedforward cycles.[77] Therapeutic targeting of NCX modulation, SERCA activation, or mitochondria-endoplasmic reticulum crosstalk represents a strategic approach to restore calcium homeostasis. Conversely, ROS scavengers disrupt these pathological feedback loops.

Calcium dysregulation mechanistically intersects with ferroptosis through iron-calcium crosstalk. Influx of Ca^{2+} through voltage-gated calcium channels and N-methyl-D-aspartate receptors (NMDARs) potentiates intracellular iron accumulation, whereas endoplasmic reticulum Ca^{2+} release mediated by ryanodine receptors (RyRs) aggravates GPX4 inhibition-induced ferroptotic cell death.[77,78] Intriguingly, ferroptosis inhibitors such as ferrostatin-1 demonstrate capacity to attenuate cytoplasmic Ca^{2+} surges, indicative of a bidirectional regulatory relationship.[79] In fluoride-induced neuroinflammation models, L-type calcium channel (LTCC)-dependent iron entry initiates ferroptosis, a process pharmacologically reversible by nifedipine administration.[80] The precise role of Ca^{2+} remains controversial, as redox-sensitive ion channels may potentiate iron-mediated toxicity, whereas early calcium dyshomeostasis might directly induce oxidative collapse independent of iron pathways.[81,82] This functional duality positions Ca^{2+} as both a pathogenic mediator and regulatory modulator of ferroptosis, necessitating condition-specific mechanistic investigations.

Glutamate Homeostasis Disruption and Ferroptosis in Ischemic Stroke

Ischemic stroke disrupts glutamate homeostasis through multiple pathological mechanisms. Astrocytic excitatory amino acid transporter (EAAT) dysfunction secondary to energy failure elevates extracellular glutamate concentrations.[83] Activation of volume-regulated anion channels (SWELL1) in neurons and astrocytes amplifies cytotoxic edema and pathological glutamate release; pharmacological inhibition of SWELL1 reduces neuronal death and improves functional outcomes in MCAO models.[84] Pathological glutamate accumulation suppresses mitochondrial oxidative phosphorylation via AMP-activated protein kinase (AMPK)-mediated pathways, driving lactate accumulation and consequent tissue acidosis.[59] Excessive activation of GluN2B-containing NMDARs exacerbates calcium overload and apoptotic pathways, while selective modulation of GluN2A-containing NMDARs demonstrates neuroprotective effects.[85] Glutamate-iron interplay further drives ferroptosis. HIF-1α-dependent system xc− upregulation sustains glutamate release, while sorafenib-mediated inhibition attenuates neuronal injury.[86] Paradoxically, GCPII elevation in MCAO rats promotes ferroptosis by hydrolyzing N-acetylglucosylglutamate, suppressing system xc−, depleting GSH, and impairing GPX4.[87] Glutamate-activated acid sphingomyelinase in oligodendrocytes disrupted mitochondrial integrity via permeability transition pore opening, whereas folate supplementation mitigates injury by modulating GCPII.[88] Therapeutic strategies included SWELL1 inhibition to attenuate edema, GluN2A-selective NMDAR activation combined with

GluN2B blockade, and timed system xc− inhibition. Concurrent iron chelation or Wnt pathway activation synergistically combated ferroptosis by restoring redox balance and organelle function. These insights highlighted glutamate's dual role as excitotoxic mediator and ferroptosis amplifier, necessitating multi-target therapeutic strategies.

Iron Homeostasis Dysregulation and Ferroptosis in Ischemic Stroke

Under physiological conditions, systemic iron homeostasis is maintained through tightly regulated mechanisms. Duodenal absorption initiates via reduction of dietary iron by duodenal cytochrome B, followed by divalent metal transporter 1 (DMT1)-mediated Fe^{2+} uptake. Absorbed iron is either stored as ferritin or circulated bound to transferrin (Tf). Hepatic ferroportin (FPN) serves as the primary regulator of systemic iron export, preventing pathological overload.[89,90] Within the central nervous system, Tf-bound iron traverses the BBB through TfR1/DMT1 complexes expressed on brain microvascular endothelial cells (BMVECs), a process modulated by astrocytic ferro-modulin. Subsequent parenchymal iron release requires FPN stabilization by the cuproenzymes ceruloplasmin (Cp) and hephaestin.[91,92]

Ischemic stroke disrupts iron regulatory pathways, elevating non-transferrin-bound iron (NTBI) levels and promoting parenchymal deposition. Cerebrovascular endothelial dysfunction exacerbates iron extravasation, overwhelming astrocytic buffering capacity. Concurrent upregulation of neuronal DMT1 and impaired FPN/Cp/hephaestin (Heph) activity establish a cytotoxic intracellular iron pool that promotes ferroptosis. STEAP3-mediated ferric iron reduction and NCOA4-dependent ferritinophagy drive labile iron accumulation, while mitochondrial ferritin (FtMt) deficiency amplifies ferroptotic cascades.[93,94] Dysregulation of iron transporters (SLC39A14), heme catabolism via heme oxygenase-1 (HO-1), and mitochondrial regulators (CISD1) further potentiate oxidative injury.[95,96] Therapeutic interventions targeting ferroportin stabilization, iron regulatory protein 2 (IRP2)-mediated pathway modulation, or mitochondrial-iron crosstalk may restore cerebral iron homeostasis and mitigate ischemia-induced ferroptosis.[97,98]

Cerebral Iron Accumulation in Ischemic Stroke: Clinical and Mechanistic Insights

Clinical neuroimaging confirms pathological iron accumulation in ischemic territories. Quantitative susceptibility mapping (QSM) demonstrates significantly elevated iron deposition in acute infarcts compared to healthy controls, indicating regional regulatory failure.[99] Complementary MRI signatures, notably T1 hypointensity and T2 hyperintensity within infarct cores, further corroborate iron overload. Cortical superficial siderosis independently serves as a biomarker for recurrent stroke risk, identified in 2.2% of stroke/transient ischemic attack (TIA) patients.[100,101] Serum ferritin elevation correlates with ischemic stroke incidence in type 2 diabetes and associates causally with adverse post-stroke outcomes.[102,103] Preclinical models parallel these observations, with hypoxic-ischemia inducing dynamic iron deposition that peaks at day 3 and persists for 28 days in neonatal rats.[104] Ischemic injury disrupts iron homeostasis through three interconnected mechanisms: BBB compromise facilitating dysregulated iron influx, oxidative damage impairing ceruloplasmin Cp/hephaestin (Heph)-dependent ferroportin export complexes, and hypoxia-induced upregulation of neuronal TfR1DMT1 under bioenergetic stress. This pathogenic iron accumulation drives lethal lipid peroxidation and oxidative damage, establishing a self-perpetuating cytotoxic cascade. Pharmacological strategies targeting iron chelation, ferroportin stabilization, or key iron-trafficking proteins may disrupt this vicious cycle.

Iron Dysregulation and Ferroptosis in Ischemic Stroke

Ischemic stroke compromises BBB integrity, facilitating parenchymal iron influx through hemoglobin degradation pathways and NTBI transport. Hypoxia upregulates neuronal TfR1 and DMT1 expression via HIF-1α-mediated pathways, amplifying cellular iron uptake.[105,106] Concurrent ceruloplasmin deficiency impairs FPN1 stability while promoting DMT1 activity, thereby exacerbating intracellular iron retention.[107] Post-ischemic attenuation of ferroportin-modulatory mechanisms elevates neuronal FPN1 levels, mitigating iron overload and ferroptotic cell death.[108] Astrocytic knockdown of ferroportin-regulatory components increases neuronal FPN1 expression, revealing intercellular iron-regulatory networks.[109]

NCOA4-dependent ferritinophagy liberates stored iron, which synergizes with lipoxygenase (LOX)-driven lipid peroxidation to amplify ferroptotic cell death.[110,111] Ischemic acidosis potentiates iron toxicity through pH-sensitive upregulation of DMT1, augmenting cellular iron influx.[112] This pathological triad comprising impaired iron export

(FPN1 downregulation), enhanced import (TfR1/DMT1 upregulation), and dysregulated iron release (ferritinophagy) drives lethal accumulation of lipid ROS. Therapeutic strategies targeting ferroportin-modulatory interactions, NCOA4 inhibition, or LOX suppression may disrupt this vicious cycle, providing protection against ferroptosis.

Crosstalk Between Regulated Cell Death and Ferroptosis in Ischemic Stroke

Ischemic stroke triggers both accidental cell death (ACD) and regulated cell death (RCD), the latter encompassing multiple mechanistically distinct subtypes including apoptosis, ferroptosis, pyroptosis, cuproptosis, and immunogenic cell death (ICD). These cell death modalities exhibit dynamic spatiotemporal heterogeneity during cerebral ischemic progression, with their activation patterns tightly modulated by the duration and severity of ischemic insults.[113]

Core infarct neurons undergo necrotic cell death, whereas the penumbral region predominantly displays apoptotic features.[114] Moderate I/R injury induces autophagic cell death, while severe I/R triggers mixed apoptosis-necrosis phenotypes.[115] Dysregulation of autophagic flux exacerbates penumbral damage through impaired autophagosome clearance.[116] Apoptosis manifests characteristic chromatin condensation and membrane blebbing, though therapeutic intervention remains viable only during early phases.[117] Pyroptosis and necroptosis involve lytic plasma membrane rupture, releasing damage-associated molecular patterns (DAMPs) such as HMGB1 that amplify neuroinflammatory cascades.[118] ICD facilitates recruitment of peripheral immune cells via BBB disruption, with nine identified genetic markers (eg, CASP1, MYD88) demonstrating diagnostic potential.[119,120]

Emerging cell death pathways include cuproptosis, which is mediated through mitochondrial enzyme disruption by Cu^{+} and suppressed through copper chelation strategies.[121] Notably, retinal I/R models demonstrate sequential activation of necroptosis during early phases, followed by parthanatos, apoptosis, and ferroptosis.[122] Furthermore, cerebral I/R injury exhibits time-dependent escalation of ferroptosis and necroptosis, with ACSL4 upregulation initiating within 2 hours post-reperfusion. While GPX4 and SLC7A11 activity show partial recovery, persistent ACSL4 dysregulation underscores its particular vulnerability to ischemic conditions.[123,124]

Mechanisms of Ferroptosis

Ferroptosis in ischemic stroke develops through a tripartite pathogenesis comprising iron overload, glutathione depletion, and lipid peroxidation. Iron dysregulation arises from imbalanced TfR1/DMT1-mediated uptake, FPN/ceruloplasmin Cp/hephaestin (Heph)-dependent export failure, and nuclear receptor coactivator 4 (NCOA4)-driven ferritinophagy, with mitochondrial iron-buffering deficits via FtMt/CDGSH iron sulfur domain 1 (CISD1) dysfunction exacerbating these perturbations.[125,126] Excess Fe^{2+} catalyzes Fenton reactions that generate hydroxyl radicals, oxidizing phospholipids containing PUFAs while concurrently disabling lipid repair mechanisms.[127]

Glutathione system failure involves dual mechanisms encompassing GPX4-dependent and GPX4-independent pathways. Cysteine deprivation resulting from impaired SLC7A11 disrupts glutathione synthesis, with this impairment being exacerbated by p53/NRF2-mediated transcriptional imbalance.[128] Concurrent GPX4 inactivation, whether through selenium deficiency or pharmacological inhibition combined with FSP1-CoQ_{10}axis disruption impairs lipid hydroperoxide detoxification.[129,130]

Lipid peroxidation amplification occurs through ACSL4-LPCAT3-mediated incorporation of PUFAs coupled with POR-driven peroxide generation, concurrent with suppression of protective ACSL3-MUFA pathways.[131,132] HIF-1α-dependent upregulation of ALOX12/15 further shifts this metabolic equilibrium toward peroxidation dominance.[133] Combined therapeutic strategies concurrently targeting iron export (via ferroportin stabilization), GPX4 activation, and ALOX inhibition may restore redox homeostasis, providing multi-pathway neuroprotection.

Dual Regulatory Failures in Glutathione Metabolism and Redox Homeostasis Drive Ferroptosis in Ischemic Stroke

Ferroptosis in ischemic stroke pathogenesis stems from dual regulatory failures in glutathione metabolism and redox homeostasis. Dysfunction of the cystine/glutamate antiporter SLC7A11 disrupts GSH biosynthesis, with its expression

subject to p53-mediated repression (reversed through ubiquitination) and NRF2 transcriptional activation.[134,135] Post-transcriptional suppression by miRNA-27a and PUM2 promotes pathological iron accumulation, which can be pharmacologically countered by trifluoperazine via AMPK/FoxO3a/HIF-1α signaling.[136] Concurrently, ATF3/ATF4-mediated transcriptional divergence and glutamate-NMDAR-induced GPX4/GSH depletion establish context-dependent ferroptotic cascades in neuronal cells.[137,138]

GPX4 serves as the central ferroptosis inhibitor, utilizing GSH to catalyze the reduction of lipid peroxides into non-toxic lipid alcohols and thereby neutralizing oxidative damage. Pharmacological agents such as Ferrostatin-1 amplify GPX4 enzymatic activity while concurrently scavenging ROS,[139] with selenium supplementation sustaining GPX4 expression under ischemic stress conditions.[140] Transcriptional regulators including RXRγ and GRSF1, along with post-translational modifications mediated by TRIM26 ubiquitination and creatine kinase B (CKB) phosphorylation, stabilize GPX4 during reperfusion phases.[141] Complementary mitochondrial resilience mechanisms further fortify this system: FtMt overexpression diminishes cytosolic iron toxicity,[142] SLC25A39 supports redox-dependent oxidative phosphorylation,[143] and DHODH activation mitigates iron-driven ferroptosis.[144] Coenzyme Q10 analogs act synergistically to suppress lipid peroxidation and counteract mitochondrial dysfunction.[145]

Moreover, alterations in lipid metabolism directly influence ferroptosis susceptibility, with emerging roles for lipid chaperones like Fatty Acid-Binding Protein 5 (FABP5). FABP5 facilitates the intracellular shuttling of PUFAs to sites of peroxidation and regulates ACSL4 activity. In models of ischemic brain injury, neuronal FABP5 expression is upregulated, where it co-localizes with the ferroptosis marker 4-HNE and interacts with mitochondrial membranes, promoting lipid peroxidation and exacerbating ferroptotic neuronal death. The co-upregulation of FABP5 with related isoform FABP3 in neurons post-ischemia further underscores the critical involvement of specific lipid-binding proteins in stroke-associated ferroptosis. This positions FABP5 as a promising and specific biomarker for ferroptosis in ischemic stroke, whose detection in cerebrospinal fluid or via targeted imaging could improve disease stratification and therapeutic monitoring.[146]

Therapeutic Targeting of Iron Metabolism in Stroke

Clinical evidence confirms that elevated serum and cerebrospinal fluid ferritin correlates with post-stroke neurological decline, establishing iron overload as a validated therapeutic target.[147,148] Pharmacologically, VK-28 mitigates cerebral hemorrhage-induced white matter injury by reducing non-transferrin-bound iron, whereas deferiprone chelates labile iron in ischemia/reperfusion (I/R) models.[149,150] Natural compounds inhibit hypoxia-induced TfR1 upregulation by suppressing HIF-1α, thereby limiting neuronal iron influx.[151,152] Post-transcriptionally, iron dynamics are modulated through Roquin-mediated TfR1 mRNA stabilization, whereas FLCN deficiency impairs Rab11A-dependent TfR1 recycling via mTORC1 activation.[153,154]

Ferroptosis regulation in cytosolic iron dynamics involves STEAP3-mediated amplification, which suppresses the p53/SLC7A11 axis and is counteracted by STEAP3 inhibition during hypoxic injury.[155,156] DMT1-driven Fe^{2+} influx exacerbates ferroptotic neuronal death, as demonstrated by ebselen's neuroprotective effects through DMT1 blockade.[157] NCOA4-mediated ferritinophagy releases labile iron pools, aggravating cerebral I/R injury; conversely, NCOA4 silencing or ginkgolide B-induced disruption of NCOA4-ferritin binding reduces infarct volume.[158,159] Paradoxically, cGAS-STING pathway activation exacerbates early-phase injury via NCOA4 upregulation.[160]

FPN exhibits dual regulatory functions in ischemic stroke: its downregulation correlates with pathological iron accumulation in neurodegenerative contexts, while I/R-induced FPN upregulation alleviates neuronal Fe^{2+} overload.[161,162] Although hepatocyte growth factor (HGF) enhances FPN expression to alleviate post-ischemic iron toxicity, temporal analyses reveal conflicting therapeutic outcomes: acute FPN inhibition reduces iron burden but impairs long-term functional recovery, highlighting the need for stage-specific interventions.[163,164] Accumulating preclinical evidence implicates SLC39A14 in regulating Fe^{2+} transport dynamics.[165]

Targeting Lipid Metabolism to Counteract Stroke-Associated Ferroptosis

As the principal suppressor of ferroptosis, GPX4 requires GSH as an essential cofactor to catalyze the reduction of lipid peroxides. Pharmacological agents such as ferrostatin-1 demonstrate dual mechanisms of action by both

enhancing GPX4 activity and directly scavenging lipid ROS.[129] Selenium serves as a critical component for GPX4 functionality, with its supplementation shown to preserve mitochondrial integrity and upregulate GPX4 expression under hyperglycemic ischemic conditions.[166] Transcriptional regulation through RXRγ and GRSF1 enhances GPX4 expression, thereby ameliorating cerebral I/R injury.[167] Post-translational modifications, including TRIM26-mediated ubiquitination and CKB)-dependent phosphorylation, confer additional stabilization of GPX4 in stroke models.[168,169]

Mitochondrial pathways exhibit functional synergy with GPX4 through coordinated iron homeostasis and redox regulation. Overexpression of FtMt significantly reduces pathological cytosolic iron accumulation following ischemic insult.[168] The mitochondrial GSH transporter SLC25A39 maintains redox capacity to support oxidative phosphorylation,[161] while coenzyme Q10 (CoQ10) analogs effectively counteract both lipid peroxidation and mitochondrial dysfunction.[147] Dihydroorotate dehydrogenase (DHODH) activation demonstrates protective effects against iron-mediated toxicity, in stark contrast to the ferroptosis exacerbation observed during its deficiency.[160]

Therapeutic innovation requires the integration of GPX4-centric molecular interventions with mitochondrial-directed approaches targeting ferritin upregulation and DHODH agonism. Combining CoQ10 antioxidants with GPX4 stabilizers represents a synergistic strategy to inhibit ferroptosis execution through concomitant neutralization of lipid peroxides and restoration of iron homeostasis.

Emerging agent L-F001 shows strong brain penetration and sustained ferroptosis inhibition in preclinical mouse models. It activates/stabilizes GPX4, downregulates ACSL4 to block lipid peroxidation initiation, and exhibits delayed/reversed neuronal death potential when administered within 24 hours post I/R, indicating a broad therapeutic window.[169,170] Dimethyl fumarate, an Nrf2 activator, upregulates antioxidant genes (including GPX4) via the Nrf2/ARE pathway in CNS injury models, suppressing ferroptosis, reducing blood-brain barrier disruption and inflammation, with enhanced efficacy under continuous low-dose administration.[171] Both can be integrated into comprehensive therapies targeting lipid metabolism and oxidative stress.

Future research in the ferroptosis field is poised to deepen our understanding of this distinct form of cell death and drive the development of innovative therapeutic strategies. Significant progress has been made, yet the intricate molecular mechanisms, particularly the interactions among the iron, lipid, glutamate, calcium, and mitochondrial pathways, warrant further investigation to gain a holistic view. Key areas of focus include uncovering the roles of specific genes and proteins involved, such as ACSL4 and GPX4, to identify novel therapeutic targets (Table 1).

Discovering reliable biomarkers for ferroptosis is essential for early disease diagnosis and monitoring, necessitating research to validate these markers across diverse biological samples. Therapeutic development is another promising avenue, involving the design of targeted treatments like iron chelators and antioxidant supplements, as well as exploring combination therapies to enhance efficacy.

Tailoring therapeutic strategies to specific diseases, including neurodegenerative disorders, cancer, and cardiovascular diseases, is crucial due to the varied roles ferroptosis plays in each context. Leveraging advanced technologies such as single-cell sequencing and CRISPR-Cas9 gene editing will further elucidate ferroptosis at the molecular and cellular levels.

However, several challenges persist. The complexity of the pathways involved complicates the dissection of individual contributions and interactions, potentially hindering the identification of specific targets. Validating biomarkers across different patient populations and disease stages is a significant hurdle, requiring markers to be specific, sensitive, and reproducible. Developing therapies that specifically target ferroptosis without affecting other cellular processes is another major challenge, alongside ensuring their safety in preclinical and clinical studies.

The heterogeneity of diseases associated with ferroptosis, such as varying tumor types and stages in cancer, complicates the development of universal therapeutic strategies. Additionally, technological limitations in resolution, sensitivity, and throughput need to be addressed through continuous innovation. Overall, while future research in ferroptosis holds great promise, overcoming these challenges is essential for translating research findings into clinical applications.

Table 1 Comparative Analysis of Key Ferroptosis Regulators in Ischemic Stroke. Summary Table of Core Signaling Molecules

Molecule	Primary Function	Regulatory Mechanisms	Pathological Role	Therapeutic Targeting
GPX4	Principal ferroptosis suppressor;[7,17] Catalyzes lipid peroxide reduction using GSH; Maintains mitochondrial integrity	Selenium-dependent activation;[127–129] Post-translational modifications (TRIM26 ubiquitination, CKB phosphorylation)[139,166,167]	Inactivation leads to lipid ROS accumulation;[47,52,54] Mitochondrial membrane rupture and cristae loss;[4,5] Neuronal death execution[67,84,155]	Selenium supplementation;[138] Ferrostatin-1;[79,137] CoQ10 combination therapy;[145] GPX4 stabilizers
ACSL4	Promotes PUFA phospholipid synthesis;[6,7] Enhances lipid peroxidation sensitivity;[17,22,23,26,37] Collaborates with LPCAT3[40,41,122,123]	ALOX12/15 upregulation enhances activity;[131] HIF-1α signaling pathway regulation;[19,20,80] Suppression of protective ACSL3-MUFA pathways[129,130]	Increases membrane lipid peroxidation damage;[13,22,23] Shifts metabolic equilibrium toward peroxidation	Pharmacological inhibitor development; ACSL3-MUFA pathway activation;[129,130] ALOX inhibition strategies[121,131]
SLC7A11	System Xc^- cystine transporter subunit; Maintains glutathione synthesis;[119] Critical antioxidant defense component;[6,7,28,43,44]	p53/NRF2 transcriptional balance regulation;[126] Ischemia-induced expression suppression; Cysteine deprivation response[126]	Dysfunction causes GSH depletion;[135,136] Indirectly leads to GPX4 inactivation;[4,5,17,127,128] Disrupts redox homeostasis[21,42,70,71]	NRF2 agonists;[26,37,67] Cystine supplementation therapy;[132,133] Transcriptional modulation approaches[5,153,154]
Nrf2	Master regulator of antioxidant response;[68,69,71] Coordinates multiple ferroptosis-related genes; Maintains cellular redox balance[21,42,71,72]	Forms regulatory balance with p53;[127,132,133,153,154] Oxidative stress activation; Transcriptional control of SLC7A11 and GPX4[123,124,132,133]	Signaling imbalance exacerbates oxidative damage;[15,16,27,35,36,46,59,81,84] Affects both SLC7A11 and GPX4 expression;[123,124,132,133] Central hub in ferroptosis regulation	NRF2 pathway activators;[26,37,67] Multi-target synergistic regulation;[68,69,126,168] Redox homeostasis restoration[71]

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Nanotherapeutic Strategies: ROS Scavenging by Recombinant Human Heavy Chain Ferritin Nanoparticles

Emerging nanotherapeutic approaches are revolutionizing targeted neuroprotection in ischemic stroke by addressing the dual challenges of blood-brain barrier penetration and off-target effects. Among these, recombinant human heavy chain ferritin nanoparticles (rHFn) have demonstrated remarkable potential, particularly leveraging the role of Ferritin heavy chain (FTH1) in modulating the labile iron pool and mitigating oxidative stress.[172] FTH1 is primarily responsible for intracellular iron sequestration, thereby limiting the catalytic action of iron in Fenton reactions, a primary source of hydroxyl radicals that drive lethal lipid peroxidation characteristic of ferroptosis. Recent studies show that recombinant ferritin heavy chain nanoparticles offer a neuroprotective effect by integrating three synergistic mechanisms: (1) Inherent ROS Scavenging: rHFn directly scavenges deleterious reactive oxygen species, reducing oxidative damage to neuronal membranes and preventing the initiation of the peroxidation cascade; (2) Labile Iron Sequestration: It mimics and enhances the function of endogenous ferritin, chelating redox-active Fe^{2+} and preventing its participation in Fe^{2+}-mediated oxidation reactions; and (3) Biomimetic Nanocarrier Properties: Exhibiting BBB permeability via transferrin receptor-1 (TFR1)-mediated transcytosis, enabling it to accumulate preferentially within ischemic penumbra tissues. Preclinical findings in models of middle cerebral artery occlusion (MCAO) revealed that systemic administration of rHFn significantly attenuated infarct volume, improved motor outcomes, and curtailed neuronal apoptosis.[173,174] Moreover, the nanoparticle was found to diminish inflammatory cytokine expressions (TNF-α, IL-1β) and restored GPX4 activity, thereby protecting cells from lipid peroxidation, mediated cell death.[175,176] Unlike small-molecule ROS scavengers (eg, Edaravone), rHFn displays minimal diffusion clearance and longer circulation times, prolonging its therapeutic window after reperfusion injury. This nanoenzyme platform underscores the potential of integrating bio-inspired antioxidant and iron-chelating properties into a single multifunctional entity, establishing new paradigms for ferroptosis-specific pharmacotherapy. Future translational efforts should focus on optimizing dosing regimens, elucidating rHFn's long-term immunogenicity profile, and testing its efficacy in comorbid preclinical stroke models that mimic the clinical complexity of stroke patients. These advances highlight rHFn as a promising candidate for advancing ischemic stroke therapeutics into clinical trials.

Core Pathogenic Mechanisms

Ferroptosis in ischemic stroke develops through three synergistic pathways: iron dysregulation (TfR1/DMT1-mediated uptake, FPN/Cp/Heph export failure, NCOA4-driven ferritinophagy), glutathione depletion (system Xc^- dysfunction, GPX4/FSP1-CoQ_{10}axis disruption), and lipid peroxidation (ACSL4-LPCAT3-POR axis with suppressed ACSL3-MUFA pathway).

Therapeutic Strategies

Multitarget interventions include iron chelators, GPX4 activation (selenium/ferrostatin-1), RXRγ/GRSF1-mediated transcription, TRIM26/CKB-regulated stabilization, ACSL4/LOX inhibition, ACSL3 activation, and mitochondrial support (SLC25A39, CoQ10, DHODH). Combining GPX4 stabilizers with CoQ10 antioxidants provides synergistic protection by neutralizing peroxides and restoring iron homeostasis.

Future Directions

Key priorities involve: multi-omics to resolve cell death crosstalk; BBB-optimized inhibitor design; biomarker development; comorbidity-integrated animal models; multi-target cocktails and nanocarriers; integration with thrombolytic therapies.

Conclusion

The core contribution of this review lies in the systematic and multi-dimensional integration of the complex pathophysiological mechanisms of ferroptosis in acute ischemic stroke, establishing a clear framework that spans from fundamental mechanisms to clinical translation, and accordingly proposing a future research roadmap with a clear direction and a focus on clinical translation.

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.

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