Comorbid mechanisms of neuroinflammation and astrocytic ferroptosis in neurological disorders: A vicious cycle (Review)

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Abstract. Neuroinflammation and astrocytic ferroptosis form a self-reinforcing vicious cycle across multiple neurological disorders, constituting a core pathological mechanism driving the progression of neurodegeneration, stroke, epilepsy, autoimmune encephalopathy. Initial neuroinflammation activates microglia to release pro-inflammatory factors such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α, inducing the transformation of astrocytes into a neurotoxic A1 phenotype, disrupting iron homeostasis, inhibiting the glutathione (GSH)-glutathione peroxidase 4 (GPX4) antioxidant system, activating the NADPH oxidase 4 (NOX4) and acyl-CoA synthetase long-chain family member 4 (ACSL4) pathways, and triggering ferroptosis. Damage-associated molecular patterns, [including high mobility group box 1 (HMGB1), adenosine triphosphate (ATP), and mitochondrial DNA] and pro-inflammatory mediators (including reactive oxygen species and lipid peroxidation products) released by ferroptotic cells further activate glial cells and amplify inflammation, establishing a positive feedback loop. Key regulatory nodes include forkhead box (Fox)O1a, nuclear factor (NF)-κB, nuclear factor erythroid 2-related factor 2 (Nrf2), and sirtuin 1 (SIRT1), while mitochondria-endoplasmic reticulum interactions participate in subcellular regulation. Current intervention strategies encompass iron chelation combined with antioxidants, NOX4 inhibition, blockade of A1 phenotype transformation, targeted activation of receptor tyrosine kinases, and blood-brain barrier-targeted drug delivery. However, challenges remain in cell-specific targeting, spatiotemporal dynamic monitoring, and clinical translation. Breaking this vicious cycle may offer a novel neuroprotective therapeutic direction for neurological disorders.

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Abbreviations: 4-HNE, 4-hydroxynonenal; ACSL4, acyl-CoA synthetase long-chain family member 4; ALS, amyotrophic lateral sclerosis; Aβ, amyloid-β; BBB, blood-brain barrier; CRISPR/Cas9, clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9; cPLA2, cytosolic phospholipase a2; CXCL10, C-X-C Motif Chemokine Ligand 10; CXCR3, C-X-C motif chemokine receptor 3; DAMPs, damage-associated molecular patterns; DFO, deferoxamine; ErbB4, ErbB-b2 receptor tyrosine kinase 4; FoxO1a, forkhead box O1a; GFAP, glial fibrillary acidic protein; GPX4, glutathione peroxidase 4; GSH, glutathione; HMGB1, high mobility group box 1; HO-1, heme oxygenase 1; IL-1β, interleukin-1β; Lcn2, lipocalin 2; LDH, lactate dehydrogenase; MAPK, mitogen-activated protein kinase; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MDA, malondialdehyde; NF-κB, nuclear factor-κB; NLRP3, NOD-like receptor family pyrin domain containing 3; NOX4, NADPH oxidase 4; NMOSD, neuromyelitis optica spectrum disorders; Nrf2, nuclear factor erythroid 2-related factor 2; PCBP1, poly(rC)-binding protein 1; ROS, reactive oxygen species; siRNA, small interfering RNA; STAT3, signal transducer and activator of transcription 3; SLC7A11, solute carrier family 7 member 11; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-α

Key words: neuroinflammation, astrocytes, ferroptosis, A1 astrocytes, vicious cycle, lipid peroxidation, signaling pathways

Contents

1. Introduction

Neuroinflammation and ferroptosis, as two critical pathological processes, exhibit significant clinical relevance across multiple neurological disorders. Neuroinflammation is typically initiated by the activation of microglia and astrocytes, accompanied by the release of pro-inflammatory factors including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, cyclooxygenase-2 (COX2), and Toll-like receptor 4 (TLR4), and contribute to the progression of Alzheimer's disease (AD) (1), Parkinson's disease (PD) (2), Huntington's disease (HD), stroke, epilepsy, amyotrophic lateral sclerosis (ALS), and neuromyelitis optica spectrum disorders (NMOSD) (3). Concurrently, ferroptosis, an iron-dependent lipid peroxidative programmed cell death, is characterized by disrupted iron homeostasis, glutathione (GSH) depletion, glutathione peroxidase 4 (GPX4) inactivation, and accumulated lipid reactive oxygen species (ROS), which are widely observed in the aforementioned disorders (4).

Notably, neuronal ferroptosis plays a particularly prominent role in neurodegenerative diseases (5), often preceding overt neuronal loss and contributing directly to disease progression. As comprehensively reviewed by Wang *et al* (6), ferroptosis constitutes a convergent pathological endpoint in AD, PD, HD, and ALS, where iron accumulation, lipid peroxidation, and antioxidant system failure collectively drive neuronal death. In AD, iron deposition in the hippocampus and cortex is associated with cognitive decline, and ferroptosis-related genes including GPX4 and solute carrier family 7 member 11 (SLC7A11) have been shown to be significantly downregulated in affected brain regions. In PD, ferroptosis contributes to the selective vulnerability of dopaminergic neurons in the substantia nigra, where iron overload and mitochondrial dysfunction create a microenvironment conducive to lipid peroxidation (7). The therapeutic potential of targeting ferroptosis in neurodegenerative diseases has been demonstrated by the neuroprotective effects of ferroptosis inhibitors such as ferrostatin-1 (Fer-1) and liproxstatin-1, as well as iron chelators such as deferiprone, which has entered Phase II clinical trials for PD (6). These findings underscore that neuronal ferroptosis is not merely a downstream consequence of neuroinflammation but represents an independent and equally critical pathological driver in neurodegeneration.

For instance, in a spontaneous subarachnoid hemorrhage (SAH) model, hydrogen was shown to exert neuroprotective effects by activating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway to upregulate GPX4 and inhibit TLR4, effectively alleviating oxidative stress, neuroinflammation, and neuronal ferroptosis, thereby improving cognitive and motor functions (8). In an intracerebral hemorrhage (ICH) model, mesenchymal stem cell-derived extracellular vesicles were found to regulate ferroptosis-related genes via mcroRNA (miR)-214-3p, significantly reducing cortical neuronal damage (9). Furthermore, clinical studies demonstrated that plasma levels of glial fibrillary acidic protein (GFAP) and YKL-40 are significantly elevated in patients with AD and increase further with disease progression, indicating a close association between neuroinflammation and glial activation (10,11). Notably, damage-associated molecular patterns (DAMPs), large endogenous molecules such as high mobility group box 1 (HMGB1), adenosine triphosphate (ATP), and mitochondrial DNA (mtDNA) released upon cell rupture during ferroptosis, along with small-molecule oxidative mediators including ROS and lipid peroxidation products, can further activate neuroimmune pathways, promote glial activation, and amplify inflammatory responses, forming a vicious cycle (3,12,13). Notably, while ROS and lipid peroxides serve as potent pro-inflammatory triggers, they do not fall within the classical category of DAMPs, which are defined as large endogenous molecules released from damaged cells (14). Thus, neuroinflammation and ferroptosis not only independently contribute to neural injury but also act synergistically to form a collaborative pathogenic network, representing a key therapeutic target for neurological disorders.

The bidirectional interaction between neuroinflammation and ferroptosis operates through distinct but interconnected cellular pathways. On the one hand, neuroinflammation promotes astrocytic lipid peroxidation and ferroptosis by disrupting iron homeostasis, inhibiting the System Xc^--GSH-GPX4 antioxidant axis, and activating oxidases such as NADPH oxidase 4 (NOX4) (12,15). On the other hand, neuronal ferroptosis itself can trigger neuroinflammation by releasing intracellular contents and danger signals that activate microglia, which in turn release pro-inflammatory cytokines (such as IL-1β and TNF-α) that further propagate astrocytic ferroptosis (3,12,16,17). This dual-directional relationship, operating across both neuronal and glial compartments, constitutes the core of the 'vicious cycle' theory.

Astrocytes play a pivotal role in maintaining central nervous system (CNS) homeostasis; however, under pathological conditions, they undergo reactive transformation, particularly toward a pro-inflammatory A1 phenotype, a process central to the pathogenesis of multiple neurological disorders. A1 astrocytes highly express chemokines including C-X-C motif chemokine ligand (CXCL)10, C-C motif chemokine ligand (CCL)5, CXCL9, and receptors such as C-C motif chemokine receptor 7 (CCR7) and IL7R, and secrete abundant neurotoxic substances that directly impair neuronal function (18). For example, in an epilepsy model, A1 astrocytes were shown to promote neuronal ferroptosis in a GPX4-dependent manner by secreting CXCL10 to activate neuronal signal transducer and activator of transcription 3 (STAT3) signaling and inhibit SLC7A11 expression, and ferroptosis inhibitors significantly attenuated neurotoxicity (19). In an NMOSD model, aquaporin-4 (AQP4)-IgG induced upregulation of acyl-CoA synthetase long-chain family member 4 (ACSL4) in astrocytes, promoting ferroptosis and exacerbating demyelination, while ACSL4 inhibition improved outcomes (20,21). Additionally, astrocytic dysfunction is characterized by reduced GSG synthesis, decreased glutamine synthetase and connexin 43 levels, and enhanced glutamate excitotoxicity, a phenomenon validated by arundic acid (ONO-2506) intervention in a status epilepticus model (22). Single-cell RNA sequencing (scRNA-seq) has further revealed the heterogeneity of astrocytes during chronic neuroinflammation, with the lipocalin-2-Cre recombinase estrogen receptor T2-positive ($Lcn2CreERT2^+$) subpopulation specifically involved in immune regulation, and another transthyretin (Ttr)-high subpopulation potentially influencing angiogenesis and metabolic reprogramming (18). In a PD model, astrocytes were shown to exhibit enhanced mitochondrial oxidative phosphorylation and activated ferroptosis due to impaired crosstalk with oligodendrocytes, accompanied

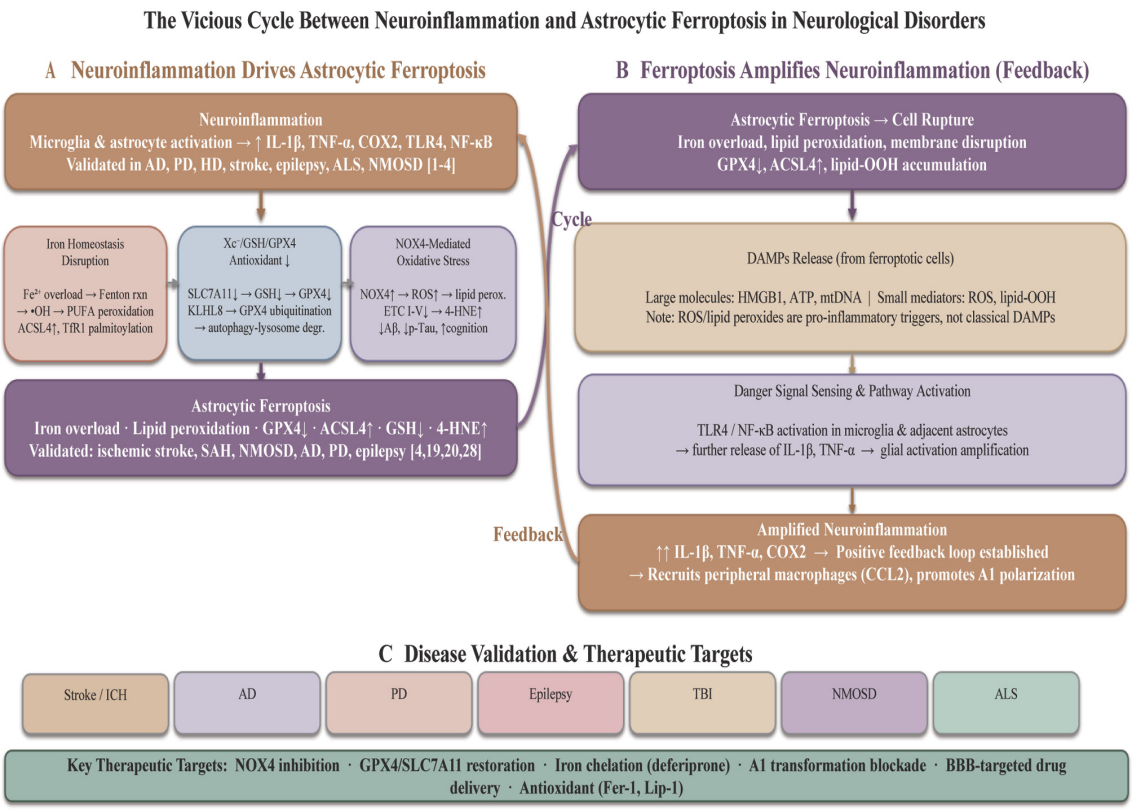

Figure 1. Vicious cycle between neuroinflammation and astrocytic ferroptosis in neurological disorders. (A) The left panel illustrates how neuroinflammation drives astrocytic ferroptosis through three interconnected mechanisms: Iron homeostasis disruption (Fe^{2+} overload, Fenton reaction, and ACSL4 upregulation), system Xc^-/GSH/GPX4 antioxidant axis inhibition (SLC7A11 downregulation, and GPX4 degradation via KLHL8-mediated ubiquitination), and NOX4-mediated oxidative stress amplification (ROS production, mitochondrial ETC impairment, and 4-HNE accumulation). (B) The right panel depicts the feedback pathway in which ferroptotic astrocytes release DAMPs (HMGB1, ATP, and mtDNA) and pro-inflammatory mediators (ROS, and lipid peroxidation products), activating TLR4/NF-κB signaling in microglia and adjacent astrocytes, thereby amplifying neuroinflammation. Curved arrows connecting the two panels represent the self-reinforcing cycle. (C) The bottom section summarizes disease models validating this mechanism (stroke, AD, PD, epilepsy, TBI, NMOSD, and ALS) and key therapeutic targets. ACSL4, acyl-CoA synthetase long-chain family member 4; GSH, glutathione; GPX4, glutathione peroxidase 4; SLC7A11, solute carrier family 7 member 11; KLHL8, Kelch-like ECH-associated protein 8; NOX4, NADPH oxidase 4; ROS, reactive oxygen species; ETC, electron transport chain; 4-HNE, 4-hydroxynonenal; DAMPs, damage-associated molecular patterns; HMGB1, high mobility group box 1; ATP, adenosine triphosphate; mtDNA, mitochondrial DNA; TLR4, Toll-like receptor 4; NF-κB, nuclear factor-κB; AD, Alzheimer's disease; PD, Parkinson's disease; TBI, traumatic brain injury; NMOSD, neuromyelitis optica spectrum disorder; ALS, amyotrophic lateral sclerosis.

by significant downregulation of the Nrf2/SLC7A11/GPX4 antioxidant pathway (23). Collectively, these findings indicate that astrocytes act not only as effectors of neuroinflammation but also as executors and amplifiers of ferroptosis, with their phenotypic transformation serving as a critical hub linking inflammation and ferroptosis.

Based on existing evidence, a bidirectional interaction exists between neuroinflammation and astrocytic ferroptosis, giving rise to the 'vicious cycle' theory. This theory posits that neuroinflammation promotes astrocytic lipid peroxidation and ferroptosis by disrupting iron homeostasis, inhibiting the System Xc^--GSH-GPX4 antioxidant axis, and activating oxidases such as NOX4 (6,12). Conversely, DAMPs (such as HMGB1 and mtDNA) released in response to ferroptosis, along with pro-inflammatory mediators including lipid peroxidation products and ROS, act as endogenous danger signals to activate inflammatory pathways including TLR4 and nuclear factor (NF)-κB in microglia and adjacent astrocytes, further amplifying the release of pro-inflammatory factors (such as IL-1β and TNF-α) and exacerbating neuroinflammation (3,12,16). This positive feedback mechanism has been validated in multiple disease models. For example, in cerebral ischemia-reperfusion injury, inflammation was found to induce ferroptosis, and ferroptotic products in turn promoted inflammation, collectively exacerbating neuronal damage (12,24). In a traumatic brain injury (TBI) model, ferroptotic neurons recruited peripheral macrophages by secreting CCL2, aggravating local inflammatory infiltration, while adeno-associated virus-mediated GPX4 overexpression simultaneously inhibited ferroptosis and neuroinflammation, improving cognitive function (25). Furthermore, quercetin has been shown to reduce brain iron deposition and lipid peroxidation in an atherosclerosis-associated neuroinflammation model by promoting microglial M2 polarization, while inhibiting neuronal pyroptosis and ferroptosis, further supporting the existence of this cycle (26). Accordingly, the scientific hypothesis is proposed that, during the progression of neurological disorders, neuroinflammation drives the transformation of astrocytes into the A1 phenotype and induces ferroptosis, and DAMPs released in response to ferroptosis in turn reinforce neuroinflammation, forming a self-amplifying vicious cycle that continuously drives neurodegeneration and dysfunction (Fig. 1). Targeting key nodes of this cycle (such as NOX4, GPX4, or the A1 transformation pathway) may represent a core strategy for novel therapeutic approaches.

Although the conceptual framework of a 'vicious cycle between neuroinflammation and ferroptosis' was previously discussed by Cheng *et al* (3), the present review extends this framework with unique and distinct contributions. Specifically, this review, to the best of our knowledge, is the first to systematically position the A1 reactive astrocyte as the structural and functional hub connecting neuroinflammation and ferroptosis, rather than treating these processes as general phenomena across all cell types. It is delineated how astrocyte-specific molecules, including ACSL4 and poly(rC)-binding protein 1 (PCBP1), serve as critical nodes that link inflammatory signaling to ferroptotic execution within astrocytes, and how these molecules may represent therapeutic targets to break the cycle without broadly affecting neuronal ferroptosis. This astrocyte-centric perspective offers a refined framework for understanding cell-type-specific vulnerabilities and for developing targeted interventions that preserve neuronal function while selectively modulating astrocytic pathology. Furthermore, emerging evidence on regulatory networks [forkhead box (Fox)O1a, NF-κB, Nrf2, sirtuin 1 (SIRT1)], spatiotemporal dynamics, and translational biomarkers that have not been previously synthesized in the context of astrocyte-specific ferroptosis are integrated, thereby providing an updated and actionable roadmap for future research.

2. Literature search strategy

A comprehensive literature search was conducted using PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com/), Scopus (https://www.scopus.com/), and Google Scholar (https://scholar.google.com/) databases, covering publications from inception through June 2026. The search strategy employed the following key terms and combinations: ('ferroptosis' OR 'iron-dependent cell death') AND ('neuroinflammation' OR 'astrocyte' OR 'A1 astrocyte' OR 'microglia') AND ('neurodegenerative diseases' OR 'Alzheimer's disease' OR 'Parkinson's disease' OR 'stroke' OR 'epilepsy' OR 'NMOSD' OR 'ALS'). Additional searches included ('Nrf2' OR 'NF-κB' OR 'NOX4' OR 'ACSL4' OR 'PCBP1' OR 'GPX4') AND ('ferroptosis' OR 'astrocyte') AND ('brain' OR 'neurological').

The inclusion criteria were as follows: i) Original research articles or comprehensive reviews published in peer-reviewed journals; ii) studies directly investigating the mechanisms of ferroptosis, neuroinflammation, or their interplay in neurological disorders; iii) studies focusing on astrocyte-specific pathways, A1 astrocyte transformation, or astrocyte-ferroptosis interactions; iv) publications in English; and v) priority was given to high-impact studies published between 2021 and 2026.

The exclusion criteria were as follows: i) Studies not directly related to ferroptosis or neuroinflammation in the CNS; ii) conference abstracts, editorials, or non-peer-reviewed content; iii) studies lacking mechanistic insight or primarily focused on peripheral organ systems without CNS relevance; and iv) duplicate publications or overlapping datasets.

The initial search yielded ~4,832 records. After removing duplicates and screening titles and abstracts, 277 full-text articles were assessed for eligibility. A final set of 105 references was selected for inclusion in this review, prioritizing recent high-impact original research and comprehensive reviews from independent research groups to ensure a balanced and fair representation of the field. A PRISMA-style flowchart was used to transparently show the literature-selection process (Fig. 2).

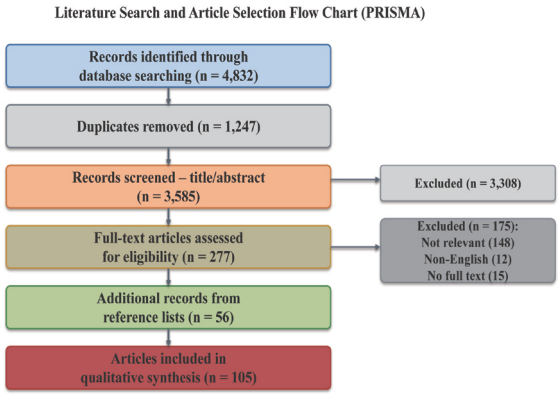

Figure 2. Literature search and study selection flow chart. The diagram illustrates the systematic literature search process across PubMed, Web of Science, Scopus, and Google Scholar databases (inception through June 2026). The initial search yielded approximately 4,832 records; after removal of duplicates and title/abstract screening, 277 full-text articles were assessed for eligibility; 105 references were ultimately included based on the predefined inclusion and exclusion criteria. Key search terms, screening stages, and exclusion reasons are indicated at each step.

3. Molecular mechanisms of astrocytic ferroptosis

This section delineates the core molecular mechanisms driving astrocytic ferroptosis, encompassing iron metabolic disturbance and lipid peroxidation initiation, NOX4-mediated oxidative stress amplification, and GSH metabolic dysfunction with GPX4 inactivation. These three interconnected pathways collectively constitute the biochemical framework underlying astrocytic susceptibility to ferroptosis and provide the mechanistic basis for understanding how neuroinflammation triggers ferroptotic cell death in astrocytes.

Iron metabolic disturbance and initiation of lipid peroxidation. The core initiating event of astrocytic ferroptosis is the lipid peroxidation cascade triggered by disrupted intracellular iron homeostasis. Significantly elevated intracellular free iron (Fe^{2+}) and iron overload have been observed in astrocytes across multiple neurological disorder models, including ischemic stroke, SAH, and NMOSD (20,27,28). This iron metabolic disturbance (29) activates the Fenton reaction, catalyzing the production of abundant hydroxyl radicals, which attack cell membrane phospholipids rich in polyunsaturated fatty acids (PUFAs), triggering uncontrolled lipid peroxidation (30-32). In an NMOSD model, AQP4-IgG stimulation was shown to upregulate ACSL4 expression, promoting PUFA incorporation into membrane phospholipids and significantly increasing cellular susceptibility to ferroptosis; early growth response 1 (Egr1) small interfering RNA (siRNA) intervention reversed ACSL4 upregulation and attenuated ferroptosis (20). Additionally, in a PD model, astrocytic iron deposition was found to be closely associated with abnormal mitochondrial oxidative phosphorylation,

further exacerbating lipid peroxidative injury (23). Notably, under ischemia/reperfusion conditions, elevated palmitic acid was revealed to promote palmitoylation of transferrin receptor 1 (TfR1), exacerbating astrocytic iron uptake and overload via clathrin-mediated endocytosis (27). Collectively, these findings demonstrated that iron metabolic disturbance constitutes the initial trigger of astrocytic ferroptosis by driving lipid peroxidation.

Critical role of NOX4-mediated oxidative stress. NOX4 serves as a key pro-oxidant mediator in astrocytic ferroptosis, with its sustained production of ROS significantly amplifying lipid peroxidative injury. In an AD model, scRNA-seq data revealed specifically high expression of NOX4 in astrocytes; pharmacological or genetic inhibition of NOX4 not only attenuated ferroptosis but also improved cognitive function, reduced Aβ and p-Tau levels, and alleviated mitochondrial structural and functional abnormalities (15). In the context of AD pathogenesis (33), amyloid-β (Aβ) peptides, generated through amyloidogenic processing of the amyloid precursor protein (APP), aggregate into extracellular plaques that disrupt synaptic function and activate microglia. Hyperphosphorylated Tau (p-Tau), in turn, forms intracellular neurofibrillary tangles that destabilize microtubules and impair axonal transport. Together, Aβ accumulation and p-Tau pathology synergistically drive neurodegeneration, and the observed reduction of both upon NOX4 inhibition underscores the functional link between ferroptosis-related oxidative stress and the core pathological hallmarks of AD (15,34). Similarly, in a rat model of collagenase-induced ICH, NOX4 expression was found to be upregulated in the perihematomal tissue, accompanied by activation of the ferritin/transferrin receptor system, collectively promoting oxidative stress and iron deposition; NOX4-siRNA intervention effectively alleviated lipid peroxidation and neuronal ferroptosis, and improved motor function (35). In patients with PD and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mouse models, a widely used chemically-induced PD model in which the neurotoxin MPTP is metabolized to MPP^+, selectively destroying dopaminergic neurons in the substantia nigra pars compacta and recapitulating key motor features of PD, NOX4 expression was shown to be elevated in hippocampal astrocytes, positively associated with myeloperoxidase (MPO) and osteopontin (OPN) levels. NOX4 directly induces ferroptosis by inhibiting the activity of mitochondrial electron transport chain complexes I-V and increasing lipid peroxidation end products such as 4-hydroxynonenal (4-HNE) (36). Although direct regulation of NOX4 by FoxO1a has not been fully elucidated in the current literature, multiple studies suggest that FoxO1a may participate in upstream regulation of the oxidative stress axis (37-39). As a key executor of oxidative stress, NOX4 expression may be indirectly regulated by FoxO family transcription factors. Furthermore, in a chronic kidney disease model, homeobox D10 (HOXD10) was shown to inhibit NOX4 transcription by directly binding to its promoter, attenuating ferroptosis (40), highlighting the importance of transcriptional regulation in NOX4 expression and providing indirect support for the potential regulation of NOX4 by FoxO1a (Fig. 3).

Abnormal GSH metabolism and GPX4 inactivation. The GSH-GPX4 axis is the core antioxidant defense system against ferroptosis, and its dysfunction is a decisive step in astrocytic ferroptosis. GPX4 relies on GSH as a reducing equivalent to convert toxic lipid hydroperoxides into harmless alcohols, thereby blocking the lipid peroxidation chain reaction. This pathway is significantly inhibited in multiple neurological disorders. For example, after ischemic stroke, astrocytes tend to upregulate SLC7A11 and GPX4 expression more than neurons, but GPX4 inactivation still occurs under severe pathological conditions (27). In an SAH model, downregulated GPX4 expression was found to directly contribute to astrocytic ferroptosis, and the ferroptosis inhibitor Fer-1 effectively alleviated oxidative stress-induced brain injury (28). Notably, GPX4 stability is also regulated by post-translational modifications: In an ischemic stroke model, oxygen-glucose deprivation/reoxygenation (OGD/R) activated autophagy, and the E3 ubiquitin ligase Kelch like E3 ubiquitin protein ligase 8 (KLHL8) ubiquitinated GPX4, promoting its binding to the selective autophagy receptor Tax1 binding protein 1 (TAX1BP1) and degradation via the autophagy-lysosome pathway; clinical sample analysis showed significant upregulation of KLHL8 and TAX1BP1 in brain tissue of stroke patients, positively correlating with ferroptosis scores (41). Additionally, in an NMOSD model, GSH levels were found to be significantly reduced in astrocytes, accompanied by increased malondialdehyde (MDA) and lactate dehydrogenase (LDH) release, further confirming the key role of GSH metabolic disturbance in ferroptosis (20). In summary, GSH depletion and GPX4 inactivation collectively constitute the terminal step whereby astrocytes lose antioxidant capacity and undergo ferroptosis.

4. Pathological characteristics of A1 astrocytes

A1 reactive astrocytes serve as the central cellular hub connecting neuroinflammation and ferroptosis in the vicious cycle. The molecular markers that define A1 phenotypic transformation, the environmental triggers that initiate this conversion, and the secretory profile through which A1 astrocytes exert their neurotoxic effects are examined in this section. Understanding these characteristics is essential for identifying therapeutic targets that can selectively block A1 transformation without disrupting the homeostatic functions of normal astrocytes.

Molecular markers of pro-inflammatory phenotypic transformation. As a pro-inflammatory subtype of reactive astrocytes, A1 astrocytes exhibit distinct molecular markers during phenotypic transformation. Multiple studies confirm that complement component C3 is the most representative and widely recognized marker of A1 astrocytes, significantly upregulated in multiple neurological disorder models including ischemic stroke, AD, epilepsy, and TBI (42-44). Additionally, major histocompatibility complex class I molecules H2-D1 and H2-T23, and the serine protease inhibitor Serping1, have been identified as key transcriptional markers of A1 transformation (45). At the functional level, A1 astrocytes exhibit downregulated expression of neuroprotection-related genes such as S100 calcium binding protein

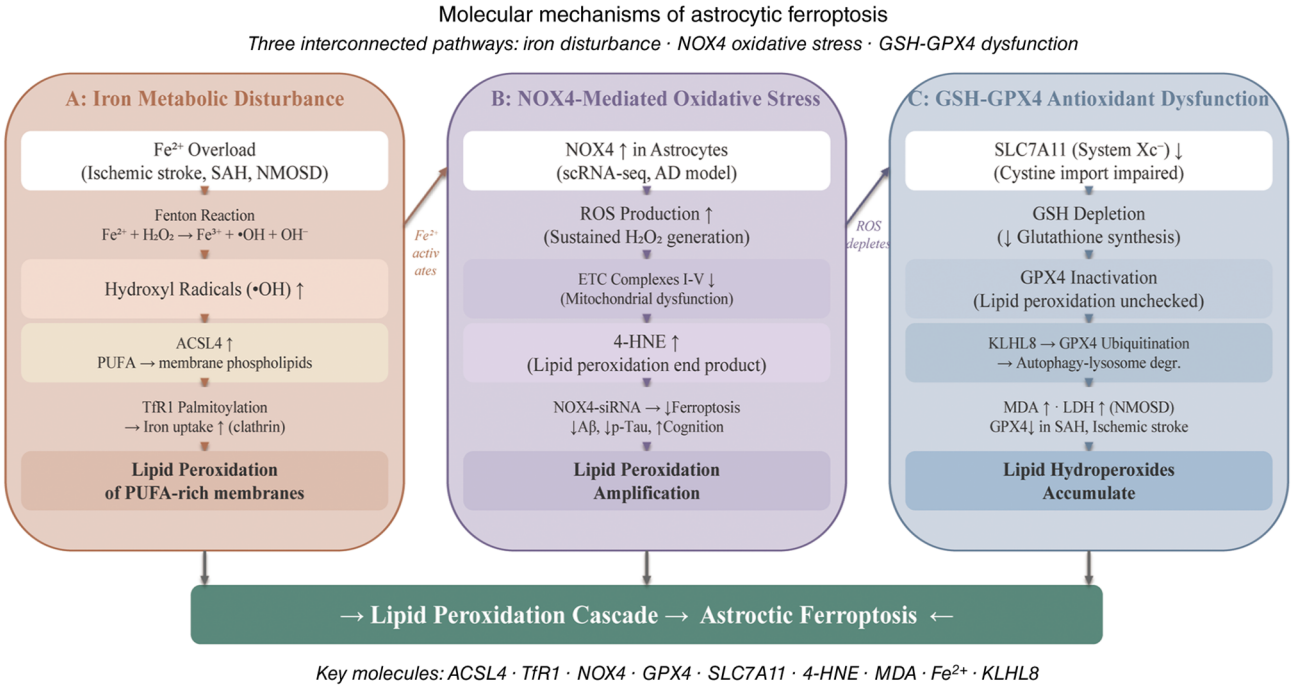

Figure 3. Schematic diagram of molecular mechanisms of astrocytic ferroptosis. Three interconnected pathways are illustrated in parallel columns: (A) Iron metabolic disturbance: Fe^{2+} overload triggers the Fenton reaction generating hydroxyl radicals (•OH), ACSL4 upregulation facilitates PUFA incorporation into phospholipids, and TfR1 palmitoylation enhances iron uptake, collectively initiating lipid peroxidation. (B) NOX4-mediated oxidative stress: NOX4 upregulation drives ROS production, impairing mitochondrial electron transport chain complexes I-V and generating 4-HNE; NOX4 silencing attenuates ferroptosis and reduces Aβ/Tau pathology. (C) GSH-GPX4 antioxidant system dysfunction: SLC7A11 (System Xc^-) downregulation depletes GSH, GPX4 inactivation impairs lipid hydroperoxide reduction, and KLHL8-mediated GPX4 ubiquitination promotes its lysosomal degradation, resulting in MDA/LDH accumulation. Cross-arrows indicate inter-pathway crosstalk (Fe^{2+} activating NOX4; ROS depleting GSH). All three pathways converge on the lipid peroxidation cascade culminating in astrocytic ferroptosis. ACSL4, acyl-CoA synthetase long-chain family member 4; PUFA, polyunsaturated fatty acid; TfR1, transferrin receptor 1; NOX4, NADPH oxidase 4; ROS, reactive oxygen species; 4-HNE, 4-hydroxynonenal; Aβ, amyloid-β; SLC7A11, solute carrier family 7 member 11; GSH, glutathione; GPX4, glutathione peroxidase 4; KLHL8, Kelch-like ECH-associated protein 1; MDA, malondialdehyde; LDH, lactate dehydrogenase.

A10 (S100A10) (26,29), and elevated expression of activation markers including GFAP and S100 calcium binding protein B (S100B) (22,46). Notably, the expression of A1 markers exhibits regional heterogeneity across different pathological contexts; for example, friend leukemia integration 1 (Fli-1) expression has been shown to be elevated and correlated with increased A1 numbers in the hippocampus of 5xFAD mice and patients with AD (42), while in an SAH model, neogenin 1 (NEO1) was revealed to drive A1 polarization via the cytosolic phospholipase A2 (cPLA2)-mitochondrial antiviral-ignaling protein (MAVS)-NF-κB pathway (47). These molecular markers not only reflect the pro-inflammatory state of A1 astrocytes but also represent potential biomarkers for targeted intervention.

Environmental triggers of A1 astrocyte transformation. The transformation of astrocytes into the A1 phenotype can be triggered by diverse stimuli beyond a single environmental factor. While this section initially focused on cadmium exposure as a specific trigger, it is important to contextualize this within the broader spectrum of known A1-inducing factors.

Environmental heavy metal exposure specifically induces the transformation of astrocytes into a pro-inflammatory A1 phenotype. Research shows that cadmium exposure triggers A1 transformation in chick striatal astrocytes, with the key mechanism involving internalization of connexin 43 (48). Connexin 43 is a critical component of astrocytic gap junctions, and its internalization not only disrupts intercellular communication homeostasis but may also trigger downstream inflammatory signaling cascades. This process is accompanied by upregulation of typical A1 markers and activation of neuroinflammation, providing novel cytological evidence for cadmium-induced neurotoxicity (48). Although this study does not fully elucidate whether cadmium mediates transformation indirectly via microglia, combined with the classical mechanism of TNF-α, IL-1α, and C1q as tripartite inducers of A1 transformation in other models (42), cadmium may promote A1 polarization by directly damaging astrocytes or activating adjacent microglia to release these cytokines. This finding emphasizes the role of environmental toxins in initiating neuroinflammation and suggests that connexin 43 may be a potential target for intervening in cadmium-related neurodegenerative diseases.

Beyond cadmium exposure, multiple other factors have been demonstrated to trigger A1 astrocyte transformation. The classical induction pathway involves activated microglia releasing the triad of TNF-α, IL-1α, and C1q, which together convert resting astrocytes into the A1 phenotype (42,49). Additional triggers include ischemic stroke-induced inflammatory cascades (44), lipopolysaccharide (LPS)-mediated TLR activation (50), human immunodeficiency virus type 1 transactivator of transcription (HIV-1 Tat) protein exposure (51), and chronic neurodegenerative protein aggregates

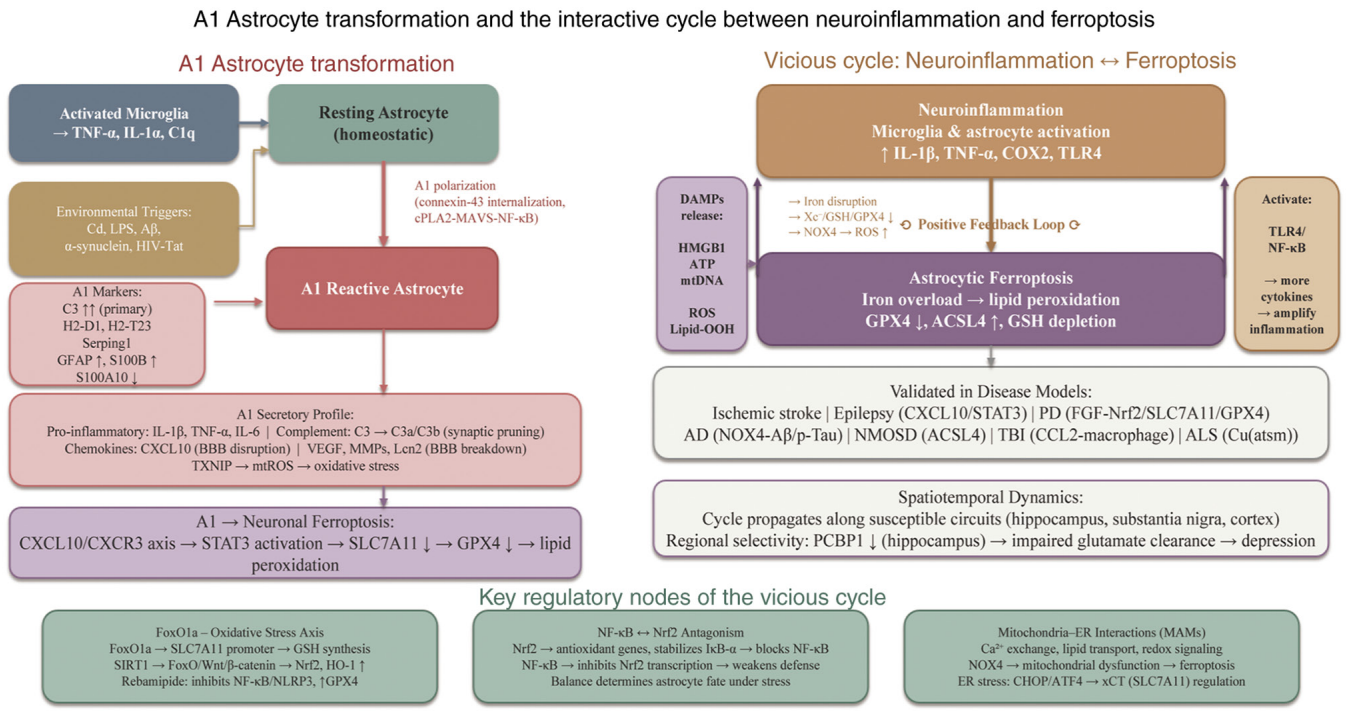

Figure 4. Schematic diagram of A1 astrocyte transformation and the interactive cycle between neuroinflammation and ferroptosis. The left panel depicts A1 astrocyte polarization: Activated microglia release TNF-α, IL-1α, and C1q, which, together with environmental triggers (Cd, LPS, Aβ, α-synuclein, and HIV-Tat), transform resting astrocytes into the A1 reactive phenotype via cPLA2-MAVS-NF-κB signaling and connexin 43 internalization. A1 astrocytes are characterized by upregulation of C3, H2-D1, H2-T23, Serping1, GFAP, and S100B, and downregulation of S100A10. Their secretory profile includes pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6), complement components (C3 → C3a/C3b for synaptic pruning), chemokines (CXCL10 for BBB disruption), and neurotoxic mediators (TXNIP → mtROS). The CXCL10/CXCR3-STAT3 axis links A1 astrocytes to neuronal ferroptosis via SLC7A11 suppression. The right panel illustrates the vicious cycle: Neuroinflammation promotes ferroptosis through iron disruption, antioxidant system inhibition, and NOX4 activation, while ferroptosis-derived DAMPs reinforce neuroinflammation via TLR4/NF-κB signaling, establishing a self-amplifying loop. TNF-α, tumor necrosis factor-α; IL-1α, interleukin-1α; C1q, complement component 1q; Cd, cadmium; LPS, lipopolysaccharide; Aβ, amyloid-β; HIV-Tat, human immunodeficiency virus transactivator of transcription; cPLA2, cytosolic phospholipase A2; MAVS, mitochondrial antiviral-signaling protein; NF-κB, nuclear factor-κB; C3, complement component 3; H2-D1, histocompatibility 2, D region locus 1; H2-T23, histocompatibility 2, T region locus 23; Serping1, serpin family G member 1; GFAP, glial fibrillary acidic protein; S100B, S100 calcium-binding protein B; S100A10, S100 calcium-binding protein A10; IL-1β, interleukin-1β; IL-6, interleukin-6; C3a, complement component 3a; C3b, complement component 3b; CXCL10, C-X-C motif chemokine ligand 10; BBB, blood-brain barrier; TXNIP, thioredoxin-interacting protein; mtROS, mitochondrial reactive oxygen species; CXCR3, C-X-C motif chemokine receptor 3; STAT3, signal transducer and activator of transcription 3; SLC7A11, solute carrier family 7 member 11; NOX4, NADPH oxidase 4; DAMPs, damage-associated molecular patterns; TLR4, Toll-like receptor 4.

such as Aβ and α-synuclein (52). Cardiac arrest has also been shown to trigger IL-17-mediated neuroinflammation and astrocyte polarization (53). Environmental factors such as chronic stress and heavy metal exposure (including lead and mercury) have also been implicated in A1 induction (48). Cadmium is highlighted in the present review because it provides a particularly well-characterized mechanistic model, demonstrating how environmental toxicants directly modulate astrocyte-specific gap junction proteins (connexin 43) to initiate A1 transformation through a pathway distinct from the canonical cytokine-mediated mechanism. This unique mode of action offers complementary insights into how non-cytokine stimuli can drive astrocyte phenotypic conversion, broadening the therapeutic target landscape beyond classical inflammatory signaling.

Secretory profile of neurotoxic substances. A1 astrocytes lose their normal neuronal support function and instead secrete diverse neurotoxic substances, forming the core of their pathogenicity. Their secretory profile mainly includes pro-inflammatory cytokines, complement system components, and chemokines. Specifically, A1 astrocytes prominently release inflammatory mediators including IL-1β, TNF-α, and IL-6 (53-55) and amplify inflammatory responses via TLR4, receptor for advanced glycation end products (RAGE), and other pathways (22,54). Complement cascade activation is another key feature, with C3 not only serving as a marker but also being cleaved into C3a and C3b to mediate synaptic elimination and neuronal injury (42). Additionally, A1 cells have been shown to highly express the chemokine CXCL10, promoting the infiltration of peripheral immune cells across the blood-brain barrier (BBB) (42). In an ischemic stroke model, A1 astrocytes were found to also secrete vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs), and Lcn2, directly disrupting BBB integrity and inhibiting axonal regeneration (56). Notably, some A1 cells exhibit aberrant metabolic activity, such as thioredoxin-interacting protein (TXNIP) overexpression, leading to excessive mitochondrial ROS (mtROS) production, further exacerbating oxidative stress and neuronal apoptosis (57). These secreted factors collectively construct a self-reinforcing neurotoxic microenvironment that drives the progression of neurological disorders (Fig. 4).

5. Interactive cycle between neuroinflammation and ferroptosis

The bidirectional promoting mechanisms that constitute the core of the vicious cycle are examined in this section. The first subsection addresses how pro-inflammatory cytokines drive ferroptosis, while the second subsection examines how DAMPs and inflammatory mediators released in response to ferroptosis reciprocally amplify neuroinflammation. The third subsection explores the spatiotemporal dynamics of this positive feedback loop across different disease contexts and brain regions. Together, these subsections provide the mechanistic foundation for understanding how the cycle self-perpetuates and propagates across neural circuits.

Promotive effect of inflammatory factors on ferroptosis. Pro-inflammatory cytokines released during neuroinflammation, particularly TNF-α, play a key role in driving astrocytic ferroptosis. In a cerebral ischemia-reperfusion injury model, the inflammatory response was shown to disrupt iron homeostasis and inhibit the antioxidant defense system, promoting lipid peroxidation and inducing ferroptosis (12). TNF-α binds to TNF receptor 1 (TNFR1)/TNF receptor 2 (TNFR2) on the surface of astrocytes, activating downstream signaling pathways, enhancing pro-inflammatory phenotypic transformation, and further reducing cellular resistance to oxidative stress. Studies have shown that in a PD model, the regulator of G Protein signaling 5 (RGS5) protein in astrocytes interacts with TNFR1 and TNFR2 to enhance TNF signaling, leading to chronic neuroinflammation and neuronal injury; inhibiting this interaction significantly reduces astrocytic cytokine release and improves neuroinflammation and neuronal survival (58). Additionally, in the early stage of TBI, the pro-inflammatory microenvironment is accompanied by downregulated GPX4 expression and elevated ACSL4 and arachinodate 15-lipoxygenase (ALOX15) levels, creating conditions conducive to ferroptosis (25). These findings indicate that pro-inflammatory cytokines such as TNF-α act not only as inflammatory mediators but also directly promote astrocytic ferroptosis by regulating iron metabolism and antioxidant pathways.

DAMPs and inflammatory mediators released in response to ferroptosis exacerbate neuroinflammation. As an iron-dependent lipid peroxidative cell death, ferroptosis triggers the release of DAMPs, including large endogenous molecules such as HMGB1, ATP, and mtDNA, as well as small-molecule pro-inflammatory mediators including ROS and lipid peroxidation products, which further activate immune cells in the CNS and exacerbate neuroinflammation. It is important to distinguish between these two categories: DAMPs are large endogenous molecules (typically >1 kDa) released upon cell rupture that activate pattern recognition receptors, while ROS and lipid peroxides are small-molecule oxidative mediators that serve as pro-inflammatory triggers but do not fall within the classical DAMP category (14,59). Existing studies demonstrate that DAMPs and pro-inflammatory mediators whose production is triggered by ferroptosis activate microglia and astrocytes, inducing them to release more pro-inflammatory factors and form a vicious cycle (12). In particular, HMGB1 released from ferroptotic cells activates TLR4/NF-κB signaling in adjacent microglia and astrocytes, triggering a cascade of pro-inflammatory cytokine release (60,61). In the spinal cord tissue of patients with ALS and superoxide dimsutase (SOD)1 transgenic mouse models, microglia were shown to undergo sublethal ferroptotic stress, triggering an inflammatory cascade, promoting the transformation of astrocytes into a neurotoxic phenotype, and causing non-cell-autonomous neuronal death; the brain-penetrant ferroptosis inhibitor Cu(atsm) was revealed to effectively alleviate ferroptosis markers and exert neuroprotective effects (62). Furthermore, in an inflammatory pain model induced by complete Freund's adjuvant, ferroptosis in spinal glial cells was found to lead to upregulation of the nuclear receptor nuclear receptor subfamily 4 group A member 1 (NR4A1), which exacerbates lipid peroxidation by promoting mitogen-activated protein kinase 3 (MAPK3) transcription, thereby amplifying neuroinflammation (63). These findings collectively support that DAMPs and pro-inflammatory mediators released in response to ferroptosis are important drivers of sustained neuroinflammation, and that the reciprocal amplification between ferroptotic cell death and inflammatory activation constitutes the self-reinforcing core of the vicious cycle.

Spatiotemporal dynamic characteristics of the positive feedback cycle. The positive feedback cycle between neuroinflammation and ferroptosis exhibits significant spatiotemporal dynamic properties, with heterogeneity across different disease stages and brain regions. After ischemic stroke, astrocytes and microglia rapidly undergo phenotypic transformation, initiating pro-inflammatory responses, accompanied by disrupted iron metabolism and inhibited antioxidant systems, creating conditions for ferroptosis; ferroptosis further triggers the release of DAMPs and pro-inflammatory mediators, reinforcing glial activation and forming a self-amplifying pathological loop (16,64). In an epilepsy model, A1 astrocytes were found to promote GPX4-dependent lipid peroxidation and neuronal ferroptosis by secreting CXCL10 to activate the STAT3 pathway and inhibit neuronal SLC7A11 expression; clinical samples also confirmed the significant co-localization of ferroptosis markers and A1 astrocytes in brain tissue of patients with epilepsy (19). Additionally, in a PD model, impaired fibroblast growth factor (FGF) signaling between oligodendrocytes and astrocytes was revealed to lead to abnormal mitochondrial oxidative phosphorylation and downregulation of the Nrf2/SLC7A11/GPX4 pathway in astrocytes, inducing regional ferroptosis that affects dopaminergic neurons (23). This spatiotemporal specificity indicates that the inflammation-ferroptosis cycle is not uniformly distributed but gradually spreads along specific neural circuits or susceptible brain regions (such as the hippocampus, substantia nigra, and cortex). In a postoperative cognitive dysfunction model, decreased PCBP1 expression in hippocampal astrocytes was shown to increase their susceptibility to ferroptosis, impairing glutamate clearance, interfering with neuronal activity, and inducing depression-like behaviors (65,66), further confirming the functional consequences of this cycle in specific brain regions. In summary, the positive feedback mechanism between neuroinflammation and ferroptosis exhibits a complex network characterized by dynamic evolution, regional selectivity, and cell-type dependence.

6. Key regulatory nodes and signaling networks

The central signaling networks that govern the balance between neuroinflammation and ferroptosis are examined in this section. The FoxO1a-oxidative stress axis, the antagonistic NF-κB/Nrf2 pathway interaction, and mitochondria-endoplasmic reticulum (ER) communication collectively form a multi-layered regulatory architecture. Understanding these nodes is critical for identifying intervention points that can disrupt the vicious cycle at specific molecular levels.

Central role of the FoxO1a-oxidative stress axis. As an important member of the transcription factor family, FoxO1a plays a key role in regulating astrocytic oxidative stress responses. Research has shown that under neuroinflammatory conditions, FoxO1a influences cellular susceptibility to lipid peroxidation and ferroptosis by regulating the expression of antioxidant genes. In a letrozole-induced depression-like behavior model in female rats, rebamipide activated SIRT1, thereby upregulating the FoxO/Wnt/β-catenin signaling pathway, enhancing the expression of Nrf2, SOD, and heme oxygenase-1 (HO-1), and inhibiting NF-κB-p65, TNF-α, and NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation, ultimately reducing iron accumulation and upregulating GPX4 and SLC7A11 levels to inhibit ferroptosis (67). This process could be reversed by the SIRT1 inhibitor nicotinamide, indicating the important role of SIRT1/FoxO signaling in regulating oxidative stress and ferroptosis. In summary, FoxO1a not only participates in regulating astrocytic antioxidant capacity but also interacts with other signaling pathways (such as SIRT1 and Nrf2) to form a critical defense line against ferroptosis.

Antagonistic interaction between NF-κB and Nrf2 pathways. The NF-κB and Nrf2 pathways exhibit a significant antagonistic relationship in the regulation of neuroinflammation and ferroptosis. Multiple studies (68,69) confirm that Nrf2 activation inhibits NF-κB signaling by enhancing antioxidant gene expression and stabilizing inhibitor of nuclear factor κB-α (IκB-α) protein, thereby blocking NF-κB nuclear translocation; conversely, NF-κB activation inhibits Nrf2 transcriptional activity and weakens cellular antioxidant defense capacity (70). In a PD mouse model, the Nrf2/SLC7A11/GPX4 pathway was significantly inhibited in astrocytes, accompanied by activated ferroptosis and loss of dopaminergic neurons (23). In a mouse cerebral ischemia and primary astrocyte OGD model, icariside II (ICS II) exerted neuroprotective effects by promoting Nrf2 nuclear translocation and effectively regulating the oxidative phosphorylation (OXPHOS)/NF-κB/ferroptosis axis, an effect significantly attenuated in Nrf2-deficient mice or siRNA-treated cells (71). Similarly, sesamin was shown to inhibit ferroptosis and improve oxidative stress and inflammatory responses by activating the Nrf2/SLC7A11/GPX4 pathway (72); *Artemisia ordosica* polysaccharide (AOP) was also found to reduce ROS, 8-hydroxy-2'-deoxyguanosine (8-OhdG), protein carbonyl (PC) levels, and IL-1β, IL-6 expression by activating Nrf2/Kelch-like ECH-associated protein 1 (Keap1) and inhibiting the TLR4/NF-κB pathway (73). Furthermore, in glioblastoma cells, RSL3-induced GPX4 inhibition triggered ferroptosis while activating NF-κB, and NF-κB inhibition attenuated ferroptosis, suggesting its pro-death role in ferroptosis (74). In ALS models, pharmacological activation of Nrf2 by RTA-408 restored the expression of SLC7A11 and GPX4 and elevated GSH levels, mitigating ferroptosis and conferring neuroprotection both *in vitro* and *in vivo* (75). Collectively, the dynamic balance between Nrf2 and NF-κB determines the fate of astrocytes under oxidative stress and inflammatory stimulation, representing a key target for intervening in the neuroinflammation-ferroptosis vicious cycle.

Mitochondria-ER interactions. Structural and functional coupling between mitochondria and the ER is increasingly recognized as critical for regulating astrocytic ferroptosis. These organelles mediate calcium exchange, lipid transport, and redox signaling via mitochondria-associated ER membranes (MAMs), collectively maintaining cellular homeostasis. In a PD model, astrocytes were shown to exhibit enhanced mitochondrial oxidative phosphorylation accompanied by inhibition of the Nrf2/SLC7A11/GPX4 pathway, indicating a close association between mitochondrial dysfunction and ferroptosis (23). Additionally, accumulated lipid peroxidation during ferroptosis has been demonstrated to disrupt mitochondrial membrane integrity, releasing pro-inflammatory mediators such as ROS, which activate neuroimmune pathways and promote glial release of IL-1β, TNF-α, and other inflammatory factors, forming a positive feedback cycle (3,76). It should be noted that ROS released from damaged mitochondria function as small-molecule oxidative stress signals rather than classical DAMPs, which are defined as large endogenous molecules released upon cell rupture. ER stress has also been found to trigger pathways such as C/EBP homologous protein (CHOP) and activating transcription factor 4 (ATF4), regulating xCT (SLC7A11) expression and affecting GSH synthesis and GPX4 activity (74). Notably, in an epilepsy model, CXCL10 secreted by A1 astrocytes mediated STAT3 phosphorylation via C-X-C motif chemokine receptor 3 (CXCR3), inhibiting neuronal SLC7A11 expression and leading to GPX4-dependent ferroptosis, a process potentially involving dysregulated mitochondria-ER communication (19). Although direct evidence for mitochondria-ER crosstalk in astrocytes remains limited, existing data strongly suggest that their interaction is a key platform integrating oxidative stress, iron metabolism, and inflammatory signals, representing a novel intervention target to break the vicious cycle (Fig. 5).

7. Advances in experimental models and detection technologies

The experimental tools and technologies that have advanced our understanding of astrocytic ferroptosis and its interplay with neuroinflammation are reviewed in this section. From genetic model organisms and single-cell sequencing to ferroptosis-specific biomarker detection, these methodological advances have been instrumental in dissecting the cell-type-specific and spatiotemporal dynamics of the vicious cycle. The following subsections highlight how each technology contributes unique insights that bridge mechanistic discovery and clinical translation.

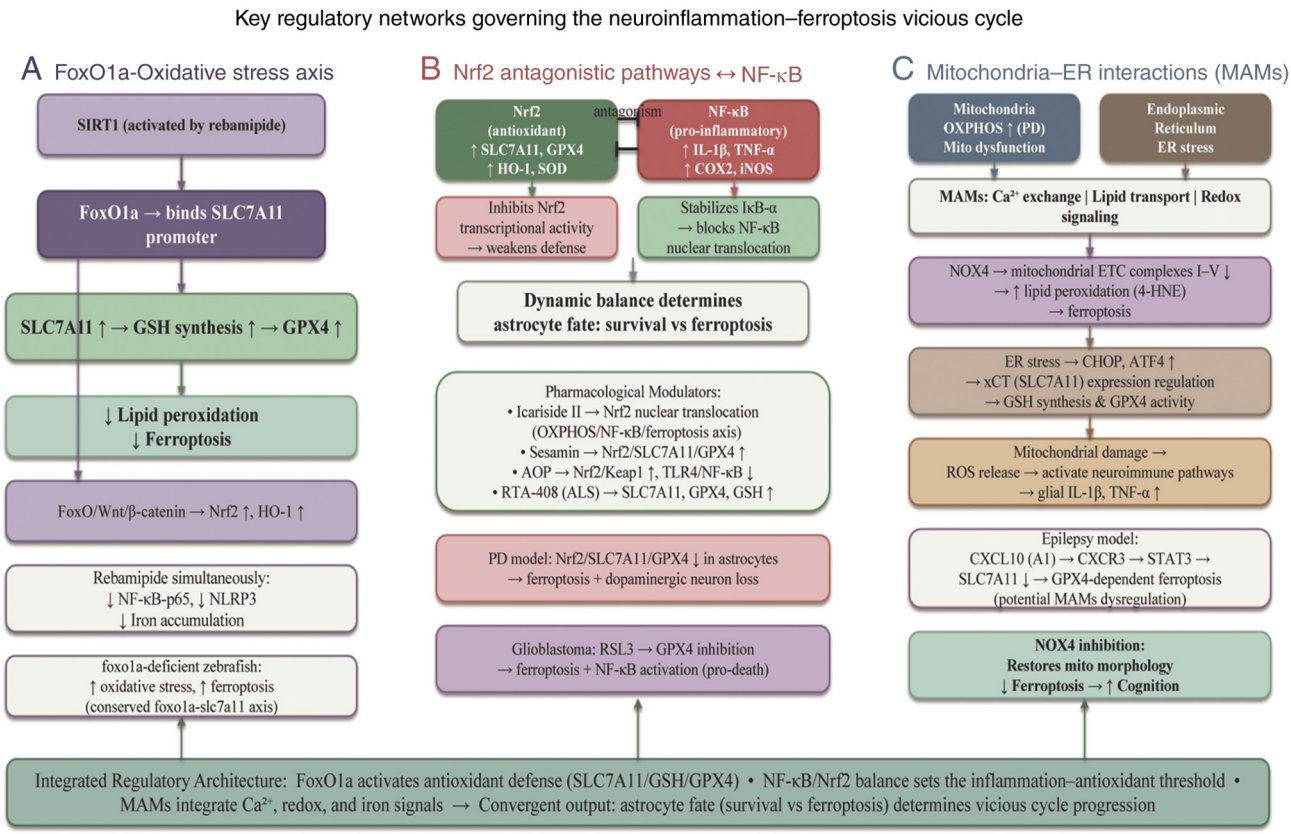

Figure 5. Schematic diagram of key regulatory networks governing the neuroinflammation-ferroptosis vicious cycle. Three regulatory layers are depicted: (A) The FoxO1a-oxidative stress axis: FoxO1a directly regulates the SLC7A11 gene promoter to maintain GSH synthesis and antioxidant capacity; SIRT1 activation upregulates FoxO/Wnt/β-catenin signaling, enhancing Nrf2, SOD, and HO-1 expression while inhibiting NF-κB/NLRP3, as validated in letrozole-induced depression models. (B) The antagonistic NF-κB/Nrf2 interaction: Nrf2 activation inhibits NF-κB by stabilizing IκB-α and enhancing antioxidant gene expression; conversely, NF-κB activation suppresses Nrf2 transcriptional activity. Pharmacological Nrf2 activators (RTA-408, icariside II, sesamin, and AOP) restore SLC7A11/GPX4 expression and attenuate ferroptosis, while NF-κB inhibition reduces inflammatory cytokine release. (C) Mitochondria-endoplasmic reticulum interactions: MAMs mediate calcium exchange, lipid transport, and redox signaling; NOX4 drives mitochondrial dysfunction and ferroptosis, while ER stress activates CHOP/ATF4 pathways regulating SLC7A11 expression. These three networks collectively determine astrocyte fate under oxidative and inflammatory stress, representing multi-level intervention targets for disrupting the vicious cycle. FoxO1a, forkhead box O1a; SLC7A11, solute carrier family 7 member 11; GSH, glutathione; SIRT1, sirtuin 1; FoxO, forkhead box O; Wnt, wingless-related integration site; Nrf2, nuclear factor erythroid 2-related factor 2; SOD, superoxide dismutase; HO-1, heme oxygenase-1; NF-κB, nuclear factor-κB; NLRP3, NOD-like receptor family pyrin domain-containing 3; IκB-α, inhibitor of nuclear factor κB-α; AOP, *Artemisia ordosica* polysaccharide; GPX4, glutathione peroxidase 4; MAMs, mitochondria-associated membranes; NOX4, NADPH oxidase 4; ER, endoplasmic reticulum; CHOP, C/EBP homologous protein; ATF4, activating transcription factor 4.

Insights from the foxo1a-deficient zebrafish model. In recent years, zebrafish, as an important model organism for studying neural development and disease mechanisms, have provided critical evidence for elucidating astrocytic ferroptosis regulatory pathways. A foxo1a-deficient zebrafish model constructed via CRISPR/Cas9 technology showed that foxo1a gene deletion not only affects hematopoietic system development but also significantly interferes with the expression of oligodendrocyte, astrocyte, and myelin-related markers in the CNS, inducing oxidative stress and ferroptosis (77). Additionally, pharmacological modulation of astrocyte phenotype polarization using rottlerin has been shown to attenuate trimethyltin-induced neurotoxicity (43). Mechanistic studies demonstrate that foxo1a maintains intracellular GSH synthesis and antioxidant capacity by directly binding to and regulating the slc7a11 gene promoter, thereby inhibiting lipid peroxidation and ferroptosis (77). Notably, the foxo1a-slc7a11 axis is highly conserved between zebrafish and human cells, indicating its evolutionary significance in neuroprotection among jawed vertebrates (77). These findings collectively indicate that the foxo1a-deficient zebrafish model provides a powerful tool for dissecting the interactive mechanisms between astrocytic ferroptosis and neuroinflammation.

Applications of organoids and single-cell sequencing technologies. With the development of high-throughput sequencing technologies, scRNA-seq and spatial transcriptomics have become key tools for dissecting cellular heterogeneity and molecular networks in neurological disorders. In AD research, scRNA-seq data revealed significant upregulation of NOX4 in ferroptotic astrocytes. Similarly, in a PD model, single-nucleus sequencing combined with spatial transcriptomic analysis revealed impaired FGF1/FGF9-FGFR signaling between oligodendrocytes and astrocytes, leading to enhanced mitochondrial oxidative phosphorylation, downregulation of the Nrf2/SLC7A11/GPX4 pathway, and preferential induction of ferroptosis in the substantia nigra, thereby driving dopaminergic neuronal injury (23). In an NMOSD model, single-nucleus RNA sequencing identified AQP4-IgG-induced ACSL4 upregulation as a key step in astrocytic ferroptosis,

which could be reversed by Egr1 siRNA (20). Furthermore, in recurrent glioblastoma, single-cell data analysis identified zinc finger protein 36 (ZFP36) as an inhibitor of astrocytic ferroptosis, which influences tumor progression by regulating MAPK and metabolic pathways (78). Recent research has also identified ferroptosis-related astrocyte subpopulations in PD through integrative scRNA-seq and bulk RNA transcriptomics, with diagnostic biomarkers including nuclear paraspeckle assembly transcript 1 (NEAT1), heat shock protein family B (small) member 1 (HSPB1), and heat shock protein family A (HSP70) member 5 (HSPA5) showing promise for non-invasive early detection (79). These studies highlight the irreplaceable value of single-cell and spatial omics technologies in accurately delineating astrocytic phenotypic transformation, ferroptosis drivers, and intercellular communication networks. Furthermore, brain organoid models are increasingly used to simulate human neuroinflammation-ferroptosis interactions, providing a platform closer to the human physiological environment for mechanistic validation and drug screening.

Detection of ferroptosis-specific biomarkers. Given that ferroptosis is an iron-dependent, lipid peroxidation-driven form of regulated cell death, the detection of ferroptosis-specific biomarkers is critical for disease diagnosis and therapeutic efficacy evaluation. Currently recognized ferroptosis markers include GSH depletion, decreased GPX4 activity or expression, accumulation of lipid peroxidation products (such as MDA and 4-HNE), and elevated iron levels (20,80). In an epilepsy model, ferroptosis was confirmed by detecting an inactivated GPX4-GSH system and downregulated SLC7A11 expression in neurons, consistent with pathological changes observed in brain tissue of clinical patients (8). In an NMOSD model, ferroptosis was confirmed by multiple indicators including elevated iron concentration, increased MDA and LDH release, decreased GSH levels, and upregulated ACSL4 expression (20). Additionally, mitochondrial shrinkage and increased membrane density observed by transmission electron microscopy are typical morphological features of ferroptosis, used for auxiliary validation in multiple models (81). In recent years, the protective effects of ferroptosis inhibitors such as Fer-1 and liproxstatin-1 have also been used as functional biomarkers, significantly alleviating neural injury and improving behavioral outcomes in animal models, indirectly reflecting ferroptosis activity (80,82). Emerging neuroimaging techniques, including quantitative susceptibility mapping and susceptibility-weighted imaging, enable non-invasive detection of brain iron accumulation in specific regions such as the substantia nigra in PD and the hippocampus in AD, although these methods cannot yet distinguish ferroptosis-specific iron from other forms of deposition (83). Biofluid biomarkers, including cerebrospinal fluid (CSF) lipid peroxide levels, serum GPX4 activity, and the ACSL4/GPX4 ratio, are being validated across multiple disease contexts and hold promise for clinical translation (84). Although fully specific and noninvasively detectable clinical biomarkers remain lacking, multidimensional detection strategies combining oxidative stress indicators, iron metabolism proteins, and lipid peroxidation end products are gradually improving the capacity for monitoring and guiding interventions of ferroptosis in neurological disorders.

8. Therapeutic intervention strategies

Current and emerging therapeutic approaches targeting the neuroinflammation-ferroptosis vicious cycle, ranging from iron chelation and antioxidant combination therapy to NOX4 inhibition, gene editing strategies for blocking A1 transformation, BBB-targeted drug delivery, and receptor tyrosine kinase activation are reviewed in this section. Each strategy targets distinct nodes of the cycle and offers complementary advantages for multi-modal intervention.

Combined application of iron chelators and antioxidants. The combined strategy of iron chelators and antioxidants aims to simultaneously block the core drivers of ferroptosis, iron overload and lipid peroxidation. This combined intervention has shown significant neuroprotective effects in multiple neurological disorder models. For example, in a mouse model of ischemic stroke, the iron chelator deferoxamine (DFO) combined with antioxidants effectively alleviated astrocytic iron accumulation and neuronal injury, with mechanisms involving inhibition of TfR1 palmitoylation-mediated iron endocytosis and restoration of GSH-dependent antioxidant defense systems (27). Additionally, in an *in vitro* model of rotenone-induced neurotoxicity, DFO and hydroxytyrosol (HT) co-delivered via a nanocarrier system exhibited synergistic neuroprotective effects, significantly reducing iron deposition and lipid peroxidation (7,85). In PD models, the oral iron chelator deferiprone, which can cross the BBB, has demonstrated safety and efficacy in Phase II clinical trials, reducing substantia nigra iron deposition and slowing motor dysfunction progression in patients with early-onset PD (86). Iron chelation combined with antioxidant supplementation thus addresses both the initiating trigger (iron overload) and the amplifying mechanism (lipid peroxidation) of the ferroptotic cascade, representing a dual-target strategy for breaking the vicious cycle.

NOX4 inhibition as a therapeutic strategy. Given the central role of NOX4 in driving astrocytic ferroptosis and neuroinflammation, NOX4 has emerged as a promising therapeutic target. Pharmacological inhibition of NOX4 using GKT137831 or specific siRNA approaches was shown to effectively reduce lipid peroxidation and neuroinflammatory cytokine release while restoring mitochondrial function (36). NOX4 inhibition was also found to alleviate autophagy-lysosome pathway impairment and reduce the degradation of GPX4, thereby restoring the cellular antioxidant defense system (15,87). Notably, neuron-specific knockdown of the NOX4 gene has been shown to alleviate cognitive decline, indicating NOX4 as a key pathogenic target for Tau-related neurodegenerative diseases (87). Therefore, developing NOX4-specific inhibitors with BBB permeability is a current research focus. Although no clinically approved NOX4-selective inhibitors for neurological disorders exist, such drugs hold therapeutic potential for established disease stages based on their key position at the intersection of ferroptosis and neuroinflammation (15,61,82). Additionally, NOX4 inhibition has been proposed as part of glioblastoma therapy to exploit tumor cell sensitivity to iron-dependent death (88).

Gene editing strategies to block A1 transformation. A1 reactive astrocytes are considered important drivers of the neuroinflammation-ferroptosis vicious cycle due to their secretion of neurotoxic factors. Research shows that A1 astrocytes induce neuronal ferroptosis by inhibiting neuronal SLC7A11 expression via the CXCL10/CXCR3 axis, thereby weakening GPX4-dependent antioxidant capacity (19). Thus, blocking A1 transformation is a key strategy for intervening in this vicious cycle. Although no gene editing therapies directly targeting A1 markers have entered the clinic, basic research provides feasible approaches. For example, in an NMOSD model, inhibiting ACSL4 expression attenuated AQP4-IgG-induced astrocytic ferroptosis and reactive hyperplasia, suggesting that targeting key lipid metabolism enzymes may indirectly inhibit the A1 phenotype (20). Furthermore, single-cell sequencing data have revealed multiple intervenable transcriptional regulatory nodes during A1 transformation, such as sustained activation of the NF-κB pathway. In the future, CRISPR/Cas9 or RNA interference technology can be used to specifically knockdown pro-inflammatory signaling molecules (such as C3, Serping1, and A1 markers) or upstream regulatory factors (such as STAT3), enabling precise blockade of A1 transformation. Combining such strategies with astrocyte-specific promoters can further enhance targeting and reduce off-target effects, providing novel gene therapy approaches for epilepsy, AD, and other diseases (19).

Design of BBB-targeted drug delivery systems. The BBB severely limits the central delivery efficiency of macromolecular or polar drugs such as iron chelators, antioxidants, and NOX4 inhibitors. Accordingly, diverse BBB-targeted delivery systems have been developed to improve the central bioavailability of therapeutic drugs. For example, molecularly imprinted nanoparticles templated with ferrous sulfate adsorb iron ions with high affinity and penetrate the BBB via circulating neutrophils as 'Trojan horses', achieving targeted iron clearance in ischemic brain regions, significantly inhibiting ferroptosis, and regulating inflammatory responses (89). Another study constructed a nanocarrier co-assembled with Pluronic F68 and dequalinium, successfully co-delivering DFO and HT to the hCMEC/D3-SH-SY5Y co-culture system, with particle size <170 nm and encapsulation efficiency of 97%, significantly enhancing neuroprotective effects (85). Additionally, peptidomimetic chelators integrating copper/zinc bimetallic chelating structures not only instantly inhibit ROS production induced by amyloid-β peptide-Cu complexes but also initially exhibit favorable BBB penetration potential (90). The common advantages of these delivery platforms are targeted delivery, high drug loading efficiency, and biocompatibility, providing technical support for dual intervention of ferroptosis and neuroinflammation. In the future, combining receptor-mediated transport (such as transferrin receptor targeting) or cell membrane biomimetic strategies may further optimize the spatiotemporal precision of delivery systems and promote the clinical translation of related therapeutic strategies (88,91).

Receptor tyrosine kinase activation as an emerging anti-ferroptosis strategy. Recent research has revealed that activation of receptor tyrosine kinases, particularly Erb-B2 receptor tyrosine kinase 4 (ErbB4), represents a novel approach to suppressing ferroptosis and alleviating neuroinflammation. Dao *et al* (13) demonstrated that targeted ErbB4 receptor activation using a small-molecule agonist (E4A) effectively prevents D-galactose-induced neuronal senescence by inhibiting the ferroptosis pathway (13). In this study, E4A administration significantly reversed the downregulation of GPX4 and SLC7A11, reduced iron accumulation and lipid peroxidation, and ameliorated cognitive dysfunction in D-galactose-treated mice. Mechanistically, ErbB4 activation attenuates ferroptosis by upregulating the Nrf2/SLC7A11/GPX4 antioxidant axis and suppressing NF-κB-mediated neuroinflammation, thereby simultaneously addressing both arms of the vicious cycle. Notably, E4A also markedly ameliorated erastin-induced ferroptosis in mouse hippocampal neuronal cells, confirming the direct anti-ferroptotic effect of ErbB4 signaling (13). These findings suggest that receptor tyrosine kinase activation may serve as a complementary therapeutic strategy to iron chelation and antioxidant approaches, offering a receptor-level intervention point that can modulate both ferroptotic and inflammatory pathways simultaneously. The combination of ErbB4 agonists with conventional ferroptosis inhibitors or nano-delivery systems may provide synergistic neuroprotection, although further studies are needed to evaluate their efficacy in astrocyte-specific contexts and their potential for clinical translation.

9. Current challenges and future directions

The key obstacles that must be overcome to translate mechanistic insights into clinical applications are addressed in this section. The challenges span three domains: Achieving cell-type-specific targeting in the heterogeneous glial landscape, developing real-time spatiotemporal monitoring tools for the dynamic vicious cycle, and constructing a systematic translational roadmap from preclinical discovery to human application.

Technical bottlenecks in cell-specific targeting. Despite significant progress in understanding astrocytic ferroptosis and its role in neuroinflammation, achieving precise cell-type-specific intervention remains a major technical obstacle. Existing ferroptosis inhibitors (such as Fer-1) or antioxidant strategies are broadly active, unable to distinguish between glial subpopulations or neuronal subtypes, leading to off-target effects and systemic side effects (92). For example, in an epilepsy model, A1 astrocytes specifically induced neuronal ferroptosis via the CXCL10/CXCR3 axis, but no delivery system currently exists that targets only this astrocytic subpopulation without affecting other neuroprotective glial cells (19). Furthermore, single-cell transcriptomic studies have revealed the high heterogeneity of reactive astrocytes; for example, astrocytes in sepsis models simultaneously express neurotoxic A1 and neuroprotective A2 gene signatures (93), dynamic changes in the Lcn2CreERT2^{+} subpopulation (18), and a specific subpopulation with low GFAP expression but high Aβ clearance capacity (94), further increasing the complexity of targeted intervention. Although gene editing tools (such as CRISPR/Cas9) and RNA interference technology have successfully inhibited ACSL4 or Egr1 to attenuate astrocytic ferroptosis in *in vitro* models (20),

achieving astrocyte-specific delivery *in vivo* without affecting microglia or other non-target cells remains an urgent bottleneck. Nanocarriers show brain-targeting potential, such as the RFP nanoplatform that co-delivers Pt-TiC nanozymes and Fer-1 to ischemic regions (95), but their selectivity for specific glial subtypes requires optimization.

Unresolved challenges in spatiotemporal dynamic monitoring. The vicious cycle formed by neuroinflammation and astrocytic ferroptosis is highly dynamic and region-specific; however, no technical means currently exist for real-time, noninvasive, *in vivo* monitoring of this interaction. Core ferroptosis markers such as lipid peroxides, GSH depletion, and decreased GPX4 activity mostly rely on post-fixation immunohistochemistry or biochemical detection, failing to reflect instantaneous changes at key nodes during disease progression (20,96). Although single-cell and single-nucleus RNA sequencing technologies have revealed the dynamic polarization and enhanced communication between astrocytes and microglia in sepsis, AD, and other models (93,94), these data are endpoint analyses and cannot capture the continuous process of cycle initiation, amplification, or regression. For example, in the hippocampal CA3 region following high-salt diet induction, the reactivity of disease-associated astocyte-like cells depends on the Lcn2/24p3R axis, but the time window of this transformation and its coupling relationship with local iron fluctuations remain unclear (97). Similarly, after TBI, activation of the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway has been shown to drive neuroinflammation and promote ferroptosis, but no dynamic imaging tools exist to define when the positive feedback between inflammatory factor release and ferroptosis-related pro-inflammatory mediators (such as ROS and MDA) reaches a critical threshold (98,99). Developing fluorescent probes or positron emission tomography tracers that penetrate the BBB and respond to lipid peroxidation or iron concentration changes will be a key direction to break through spatiotemporal monitoring bottlenecks.

Roadmap for clinical translational research. Translating intervention strategies targeting the neuroinflammation-ferroptosis vicious cycle from preclinical models to human applications requires a systematic translational roadmap. First, high-potential targets should be screened based on disease-specific mechanisms. For example, in multiple sclerosis, ACSL4 expression changes were shown to be associated with early ferroptosis in experimental autoimmune encephalomyelitis, and ACSL4 targeting improved behavioral phenotypes and alleviated neuroinflammation (100); in NMOSD, AQP4-IgG-induced astrocytic ferroptosis could be reversed by inhibiting ACSL4 or Egr1 (20), indicating ACSL4 as a biomarker and therapeutic target for specific diseases. Second, combined intervention strategies show greater promise, such as iron chelators combined with antioxidants, NOX4 inhibitors combined with anti-inflammatory drugs, or the RFP nanoplatform that simultaneously regulates oxidative stress and ferroptosis (95). Third, a standardized biomarker system should be established to support clinical trial design. Combined detection of ferroptosis-specific markers (such as plasma MDA, and GSH/GSSG ratio) and neuroinflammatory indicators (such as IL-1β and TNF-α) can help identify patient subgroups eligible for enrollment (3,12). Finally, candidate drugs with initially verified safety should be prioritized for advancement, such as Fer-1 liposomes showing favorable biocompatibility in a corneal injury model (92), or rebamipide that simultaneously inhibits neuroinflammation and ferroptosis by activating SIRT1 (67), with drug repurposing strategies considered to accelerate clinical translation. Future multicenter, longitudinal cohort studies should be conducted, combining imaging, liquid biopsy, and multi-omics analysis to construct a 'mechanism-target-efficacy' closed-loop validation system and promote the implementation of precision neuroprotective therapies.

10. Discussion and conclusions

The present review systematically elaborated the vicious cycle mechanism between neuroinflammation and astrocytic ferroptosis and its core pathological role in multiple neurological disorders. Consistent evidence from existing studies indicates that neuroinflammation significantly promotes astrocytic ferroptosis by disrupting iron homeostasis, inducing lipid peroxidation, and inhibiting antioxidant defense systems (such as GPX4 and GSH); in addition, DAMPs (including HMGB1, ATP, and mtDNA) released in response to ferroptosis, along with pro-inflammatory mediators such as lipid peroxides and ROS, further activate microglia and astrocytes, inducing them to secrete pro-inflammatory factors such as IL-1β and TNF-α, thereby exacerbating neuroinflammation (3,12). This bidirectional positive feedback mechanism has been validated in multiple disease models, including ischemic stroke, epilepsy, PD, AD, NMOSD, and diabetes-related neurological complications (21,23,64,101).

Notably, A1 reactive astrocytes play a key role in this cycle. They not only undergo pro-inflammatory phenotypic transformation but also induce neuronal ferroptosis by secreting neurotoxic factors such as CXCL10 to inhibit SLC7A11 expression in adjacent neurons and weaken GPX4-dependent antioxidant capacity (19). Additionally, in an NMOSD model, AQP4-IgG was shown to directly induce astrocytic ferroptosis accompanied by ACSL4 upregulation, and ACSL4 inhibition effectively attenuated ferroptosis and demyelination, indicating this enzyme as a key target for astrocyte-specific intervention (20). Similarly, in a depression-like behavior model, downregulated expression of the iron chaperone protein PCBP1 in astrocytes was found to increase their susceptibility to ferroptosis, and pharmacological inhibition of ferroptosis or PCBP1 overexpression restored glutamate clearance and improved behavioral phenotypes, further highlighting the pathogenic role of astrocytic ferroptosis in neuropsychiatric disorders (65).

From the perspective of regulatory networks, FoxO, NF-κB, and Nrf2 form the core signaling axis. For example, rebamipide was demonstrated to simultaneously alleviate neuroinflammation and ferroptosis by activating SIRT1, inhibiting NF-κB-p65 and NLRP3 inflammasome, and enhancing the FoxO/Wnt/β-catenin pathway to upregulate GPX4 and SLC7A11 expression (67). Hydrogen has also been shown to break the vicious cycle and improve cognitive and motor functions by activating Nrf2, upregulating GPX4, and inhibiting

the TLR4 pathway (8). Furthermore, the NR4A1-MAPK3 pathway has been revealed to drive spinal glial ferroptosis in inflammatory pain, and its inhibitor DIM-C-pPhOH significantly alleviated hyperalgesia and neuroinflammation (63), indicating common but disease-specific regulatory nodes across different pathological contexts.

In terms of therapeutic strategies, iron chelators (such as deferoxamine), ferroptosis inhibitors (such as Fer-1 and liproxstatin-1), NOX inhibitors, and gene editing methods targeting A1 transformation show promising prospects (82,102). In particular, nanotechnology-based delivery systems, such as bovine serum albumin/iron-tannic acid nanoparticles, not only penetrate the BBB but also exert multi-enzyme-like activity to clear ROS/reactive nitrogen species and regulate microglial polarization, providing a novel intervention paradigm for PD (103). Exosome therapy also exhibits neuroprotective potential by regulating the GPX4-GSH axis and iron homeostasis (4). Furthermore, emerging strategies such as ErbB4 receptor tyrosine kinase activation offer a receptor-level approach to simultaneously suppress ferroptosis and neuroinflammation (13), broadening the therapeutic landscape beyond conventional small-molecule inhibitors.

However, current research faces several challenges: First, the high heterogeneity of astrocytic subtypes makes cell-type-specific targeting a technical bottleneck; second, the spatiotemporal dynamic characteristics of the vicious cycle lack high-resolution *in vivo* monitoring tools; finally, most intervention strategies remain in animal models, requiring clarification of clinical translation pathways (82,104). Future research should combine single-cell sequencing, spatial transcriptomics, and organoid models to deeply dissect the key temporal nodes of cycle initiation and maintenance, and promote precision therapies targeting nodes such as the FoxO-Nrf2-NF-κB axis, ACSL4, or PCBP1 into clinical trials.

Several limitations should be acknowledged. First, while this review integrated evidence from multiple disease models, the heterogeneity of experimental designs, disease stages, and brain regions across studies may limit the generalizability of the proposed vicious cycle framework. Second, the majority of evidence was derived from preclinical animal and *in vitro* models, which may not fully recapitulate the complexity of human neurological disorders. Third, the review primarily focused on A1 astrocytes and may not adequately address the contributions of other reactive astrocyte subtypes (such as A2 and pan-reactive astrocytes) or the dynamic spectrum of astrocyte reactivity that has been increasingly recognized in recent single-cell studies. Fourth, while it was endeavored to provide a balanced representation of the literature, publication bias and the predominance of ferroptosis-focused research in certain disease areas (such as stroke and AD) may introduce unintended emphasis. Finally, the proposed therapeutic targets and strategies remain at preclinical stages, and their clinical feasibility, safety, and efficacy in human patients require rigorous validation through well-designed clinical trials.

In conclusion, neuroinflammation and astrocytic ferroptosis form a self-reinforcing pathological loop throughout the progression of multiple neurological disorders. Breaking this vicious cycle is not only theoretically innovative but also provides a solid foundation for developing disease-modifying therapies. Future integration of multi-omics, advanced imaging, and intelligent drug delivery systems will drive the full-chain breakthrough from mechanistic dissection to clinical application (3,12,105).

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Authors' contributions

YR and HQ designed and planned the review. DW and LZ organized the data and created the figures. JC and WW participated in data collection. YR and HQ reviewed and revised the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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