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# Research Progress on Ferroptosis in Subarachnoid Hemorrhage

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**Abstract:** Early brain injury (EBI) following subarachnoid hemorrhage (SAH) remains a pivotal determinant of patient prognosis. Emerging evidence identifies ferroptosis as a central mechanism driving neuronal damage post-SAH. The breakdown of hemoglobin/heme precipitates intracerebral labile iron overload, while the hypoxic microenvironment triggers ferritinophagy, further destabilizing iron homeostasis. This iron metabolic derangement, coupled with phospholipid remodeling mediated by enzymes such as ACSL4 and LPCAT3, leads to the accumulation of peroxidation-prone polyunsaturated fatty acids within neuronal membranes. Oxidative stress induced by SAH compromises the critical System $Xc^-$/GSH/GPX4 axis and the parallel FSP1/CoQ10 pathway, culminating in unchecked lipid peroxidation. Moreover, ferroptosis not only precipitates direct neuronal death but also releases damage-associated molecular patterns (DAMPs) that activate microglia, establishing a "ferroptosis-neuroinflammation" positive feedback loop that exacerbates cerebral injury. In response to this pathology, ferroptosis inhibitors such as ferrostatin-1 and liproxstatin-1, alongside natural agents like puerarin and melatonin, have demonstrated neuroprotective efficacy. Circulating ferroptosis markers (ACSL4, SLC7A11, GPX4) also show promise for prognostic evaluation. In summary, targeting the ferroptosis pathway offers novel therapeutic avenues for managing EBI after SAH.

**Keywords:** Subarachnoid Hemorrhage; Ferroptosis; Early Brain Injury; Neuroinflammation; Therapeutic Targets.

## 1. Introduction

Subarachnoid hemorrhage (SAH) is a severe type of hemorrhagic stroke that often results in high mortality and substantial long-term disability. Even among survivors, cognitive impairment and reduced quality of life are common. Beyond the initial insult, a cascade of secondary events—especially early brain injury (EBI) within the first 72 h—drives cerebral edema, blood–brain barrier disruption, oxidative stress, mitochondrial dysfunction, and neuroinflammation. [1]

Ferroptosis has emerged as a key component of regulated cell death in SAH-related brain injury. It is triggered by iron-dependent lipid peroxidation and failure of cellular antioxidant defenses, and it differs from apoptosis and necroptosis in both morphology and biochemistry [2]. An increasing number of studies have demonstrated that ferroptosis is one of the key mechanisms of regulated cell death in subarachnoid hemorrhage (SAH)-related brain injury. Ferroptosis, a iron-dependent, oxidative, and non-apoptotic cell death pathway, exhibits unique morphological, biochemical, and immunological characteristics. Increased lipid peroxidation, intracellular iron accumulation, glutathione (GSH) depletion, and glutathione peroxidase 4 (GPX4) inactivation are the primary causes of ferroptosis. Experimental SAH models have shown that ferroptosis-related markers are altered early after hemorrhage, and pharmacological inhibition of ferroptosis improves neurological functional outcomes [3]. This indicates that ferroptosis is not merely a superficial phenomenon but a modifiable biological process in EBI.

## 2. Mechanistic Basis of Iron Homeostasis and Ferroptosis

### 2.1. Definition and Hallmarks of Ferroptosis

Ferroptosis was first described as an iron-dependent, non-apoptotic form of regulated cell death driven by the accumulation of lipid peroxides. This unique cell death modality was identified in the context of pharmacological screenings that revealed certain compounds could trigger a lethal form of cell death that was not prevented by inhibitors of apoptosis, necroptosis, or autophagy. The defining characteristic of ferroptosis is its absolute reliance on iron, which acts as a catalyst in the Fenton reaction and other redox processes, leading to the generation of highly reactive lipid peroxyl radicals that damage cellular membranes [4].

Morphologically, ferroptotic cells typically exhibit shrunken mitochondria with increased membrane density and reduced or absent cristae, while the nucleus remains largely intact. This distinct mitochondrial phenotype, often referred to as "mitochondrial condensation," includes a reduction in mitochondrial size and a loss of the typical inner membrane folding (cristae), which is not observed in apoptosis or necrosis. In contrast to apoptotic cells, which display nuclear fragmentation and the formation of apoptotic bodies, ferroptotic cells retain an intact nuclear envelope and chromatin structure, indicating that the cell death process is primarily driven by oxidative damage to the cytoplasmic components rather than nuclear disassembly [5].

Biochemically, ferroptosis is characterized by redox imbalance, depletion of glutathione (GSH), inactivation of glutathione peroxidase 4 (GPX4), and a rise in labile iron and lipid reactive oxygen species (ROS). The biochemical cascade leading to ferroptosis is typically initiated by either

an overload of intracellular iron or a disruption in the cellular antioxidant defenses. The depletion of GSH, a crucial intracellular antioxidant, directly impairs the activity of GPX4—a selenoenzyme that reduces lipid hydroperoxides to non-toxic lipid alcohols. Once GPX4 is inactivated, lipid peroxides accumulate unchecked. Concurrently, an increase in labile iron, often released from iron-sulfur clusters or ferritin degradation, fuels further Fenton chemistry, exacerbating oxidative stress [6]. This leads to a vicious cycle where rising lipid ROS further oxidize membrane phospholipids, culminating in catastrophic membrane damage and cell death.

### 2.2. Ferroptosis Sensitivity is Primarily Governed by Three Interconnected Biological Networks.

Ferroptosis sensitivity is primarily determined by three interconnected networks. First, one of the core drivers of ferroptosis is the production of reactive oxygen species (ROS) resulting from iron metabolism imbalance. Cells acquire iron through transferrin receptor (TfR1)-mediated endocytosis, store excess iron via ferritin, and release free iron through ferritinophagy mediated by NCOA4, thereby increasing the intracellular available iron pool to promote the Fenton reaction, which directly disrupts the phospholipid bilayer in cell membranes [7, 8]. Recent studies have demonstrated that, in addition to the classical Fenton reaction, the lipoxygenase (LOX) family can also catalyze the oxidation of polyunsaturated fatty acids (PUFAs), with its activity regulated by iron ion levels [9].

Second, lipid metabolism affects the availability of polyunsaturated fatty acids (PUFAs) prone to peroxidation in membrane phospholipids, and the presence of PUFAs in membrane phospholipids is one of the essential conditions for ferroptosis. Lipid peroxidation is primarily mediated through free radical chain reactions or enzymatic reactions (e.g., LOX). The oxidation of PUFAs (particularly arachidonic acid (AA) and eicosapentaenoic acid (AdA)) in phosphatidylethanolamine (PE) is a critical execution step in ferroptosis [10, 11]. ACSL4 converts PUFAs into their acyl-CoA derivatives (PUFA-CoA), while LPCAT3 reinserts them into the phospholipid membrane. PE enriched with PUFAs is more susceptible to oxidation, leading to membrane integrity disruption [12]. Recent studies have revealed that ferroptosis suppressor protein 1 (FSP1) provides another GPX4-independent lipid antioxidant defense system by reducing coenzyme Q10 (CoQ10) on the outer membrane, further enriching our understanding of lipid metabolism regulation [13].

Third, the antioxidant system counteracts lipid peroxidation. The Xc− system (cystine/glutamate reverse transporter) supports GSH synthesis, while GPX4 detoxifies lipid hydroperoxides and serves as a core inhibitor of ferroptosis [14, 15]. Additionally, the FSP1/CoQ10 axis provides a GPX4-independent protective pathway [16].

### 2.3. Relevance to the Central Nervous System

Brain tissue exhibits a heightened sensitivity to ferroptosis, a vulnerability intrinsically linked to its distinctive physiological architecture and metabolic profile. As one of the body's most oxygen-demanding organs, the brain's cellular membranes are densely packed with polyunsaturated fatty acids (PUFAs), particularly the acyl chains within phosphatidylcholine (PC). The double bonds in these PUFA structures are exceptionally prone to attack by reactive oxygen species (ROS), triggering lipid peroxidation. This "fuel-like" configuration renders the brain highly susceptible to oxidative stress-induced lipid peroxidation chain reactions, a core hallmark of ferroptosis [17, 18]. Despite possessing antioxidant systems such as glutathione and glutathione peroxidase 4 (GPX4), the brain's overall antioxidant reserves are relatively limited and fragile against sudden oxidative challenges. During ferroptosis, the activity of the critical antioxidant enzyme GPX4 is inhibited, leading to an inability to effectively clear peroxidized lipids from the cell membrane, culminating in cell death [17].

Additionally, due to its unique metabolic environment and SAH-induced iron metabolism disorders, brain tissue is particularly prone to ferroptosis. This not only leads to neuronal apoptosis but also damages vascular endothelial cells, creating a vicious cycle of neurovascular inflammation—a key pathogenic mechanism in early brain injury (EBI) following SAH [19, 20, 21]

## 3. Molecular Mechanisms of Ferroptosis in EBI after SAH

### 3.1. Iron Overload and Ferritinophagy

Following SAH, erythrocyte lysis releases hemoglobin and heme into the subarachnoid space. Heme degradation and iron liberation increase the labile iron pool, which accelerates lipid peroxidation and mitochondrial injury. Ferritinophagy, a selective autophagy process that degrades ferritin, can further amplify iron toxicity by releasing stored iron. Hypoxia has been shown to aggravate neuronal ferroptosis during EBI by promoting NCOA4-mediated ferritinophagy; inhibiting hypoxia signaling reduced ferritinophagy markers, restored GPX4, lowered lipid peroxidation, and improved neurological function [22].

### 3.2. Lipid Metabolic Reprogramming and Lipid Peroxidation

**ACSL4**: Acyl-CoA synthetase long-chain family member 4 (ACSL4) preferentially activates PUFAs and promotes their incorporation into membrane phospholipids, thereby increasing susceptibility to lipid peroxidation. ACSL4 is upregulated in experimental SAH, and interventions that suppress ferroptosis are often accompanied by reduced ACSL4 expression and lipid ROS accumulation [23,24].

**LPCAT3**: Lysophosphatidylcholine acyltransferase 3 (LPCAT3) participates in phospholipid remodeling and facilitates the enrichment of phosphatidylethanolamines (PE) containing PUFAs. In vivo SAH studies have reported that LPCAT3 exacerbates early brain injury (EBI) and ferroptosis, suggesting that excessive phospholipid remodeling may provide an overabundance of substrates for lipid peroxidation and cell death [25].

**p53 and Stress Signaling**: p53 may promote ferroptosis by suppressing SLC7A11 and limiting cystine uptake. In rat SAH models, inhibition of p53-induced ferroptosis alleviated EBI and improved neurological outcomes, supporting a functional link between stress signaling pathways and ferroptosis in the context of SAH [26].

**PKR**: Protein kinase R (PKR) is a stress-activated kinase that can influence translational and inflammatory programs. Evidence from SAH models indicates that PKR inhibition

attenuates neuronal ferroptosis and reduces brain injury, although the upstream triggers and downstream effectors in the SAH context still require further clarification [27].

### 3.3. Failure of Antioxidant Defense Systems

In the pathological progression of SAH, oxidative stress and iron overload converge to precipitate the failure of antioxidant defense systems. The decline in System Xc− activity limits the availability of cystine, thereby impeding glutathione (GSH) synthesis; simultaneously, dysfunction of glutathione peroxidase 4 (GPX4) hampers the clearance of lipid hydroperoxides. Restoring antioxidant capacity—whether through enhancing Nrf2-dependent transcription or activating parallel defense pathways such as FSP1/CoQ10—therefore represents a rational anti-ferroptotic strategy [28].

## 4. Ferroptosis, Neuroinflammation, and Prognosis

Ferroptosis and neuroinflammation reinforce each other after SAH. Lipid peroxidation products and damage-associated signals released from ferroptotic cells can activate microglia and amplify cytokine production, while inflammatory signaling can further disrupt iron metabolism and antioxidant defenses. Microglia-derived iron-overloaded exosomes can transfer iron to neurons and trigger ferroptosis via a complement C3/C5/NF-κB pathway, thereby aggravating long-term neurological impairment [29]. In addition, S100A8 has been reported to regulate autophagy-dependent ferroptosis in microglia after experimental SAH, highlighting that ferroptosis is not restricted to neurons and may involve cell-type-specific regulatory programs [30].

Circulating ferroptosis-related markers are also being explored for prognostication. In a prospective cohort of aneurysmal SAH patients treated with clipping surgery, higher serum ACSL4 and lower SLC7A11/GPX4 levels were associated with poorer short-term functional outcome, and ACSL4 showed the highest predictive value among the tested markers [31]. Validation in larger, multi-center cohorts is still needed.

## 5. Potential Therapeutic Strategies Targeting Ferroptosis

### 5.1. Direct Ferroptosis Inhibitors

Small-molecule inhibitors that directly suppress lipid peroxidation represent the most straightforward approach. Ferrostatin-1 and liproxstatin-1 are widely used experimental inhibitors; in SAH models, liproxstatin-1 reduced neurological deficits, decreased lipid peroxidation, and attenuated neuroinflammation [23]. However, the optimal therapeutic window, dosing, and long-term safety of such agents remain to be defined.

### 5.2. Pathway Modulators with Anti-ferroptotic Effects

Several compounds confer anti-ferroptotic protection by modulating upstream metabolic and antioxidant pathways. Puerarin alleviated oxidative stress and ferroptosis through an AMPK/PGC1α/Nrf2 pathway in an experimental SAH model [32]. Melatonin reduced EBI by limiting NRF2-mediated ferroptosis and improving mitochondrial function [33]. Resveratrol was reported to mitigate ferroptosis-driven EBI via the Nrf2–GPX4 axis [28]. Astragaloside IV also showed protective effects, at least in part by suppressing ferroptosis-related injury [34].

Baicalein, a natural flavonoid with iron-chelating and lipid peroxidation-inhibiting properties, has also been reported to attenuate neuronal ferroptosis after SAH and improve neurological deficits [35]. These findings broaden the pharmacological landscape, but rigorous replication and standardized outcome assessment are essential.

### 5.3. Multi-target Protection: PPARγ/Nrf2/GPX4 and FSP1/CoQ10

Because ferroptosis is governed by multiple parallel defense systems, multi-target interventions may be advantageous. Netrin-1 was shown to protect against EBI after SAH by activating PPARγ and enhancing the Nrf2/GPX4 anti-ferroptosis program [36]. Oroxin A improved survival and neurological function after SAH and suppressed both ferroptosis and neuroinflammation, with evidence pointing to activation of Nrf2/GPX4 and FSP1/CoQ10 pathways [37]. These studies align with the concept that the FSP1/CoQ10 system acts in parallel to GPX4 and can serve as an additional therapeutic entry point [38].

### 5.4. Adjunct and Emerging Approaches

Beyond pharmacological agents, manipulating upstream triggers may also curb ferroptosis. Targeting hypoxia signaling reduced NCOA4-mediated ferritinophagy and neuronal ferroptosis in SAH models [22]. PKR inhibition has also been linked to reduced ferroptotic injury [27]. In addition, acupuncture has been suggested to influence ferroptosis- and ferritinophagy-related pathways in a cerebral ischemia–reperfusion model, but direct evidence in SAH is still lacking [40].

## 6. Clinical Translation and Future Directions

Despite rapid progress, several gaps hinder translation. First, the temporal profile and cell-type specificity of ferroptosis after SAH are incompletely mapped; neurons, microglia, astrocytes, and vascular cells may differ in susceptibility and regulatory mechanisms. Second, many interventions converge on Nrf2 signaling, yet Nrf2 target genes can both protect against oxidative injury and influence iron handling, which may complicate dosing and timing. Third, most evidence comes from rodent models, and standardized endpoints that reflect human SAH trajectories are needed. Future work should integrate multi-omics, advanced imaging of iron and lipid peroxidation, and clinically relevant biomarkers (e.g., serum ACSL4, SLC7A11, GPX4) to define therapeutic windows and stratify patients [31].

## 7. Conclusion

Ferroptosis is increasingly recognized as a central and druggable mechanism in SAH-related early brain injury. Iron overload, phospholipid remodeling, and antioxidant defense failure jointly drive lipid peroxidation and cell death, while reciprocal interactions with neuroinflammation may amplify damage. Although multiple anti-ferroptotic strategies have shown promise in experimental models, careful validation and translational design are required before clinical implementation. A clearer understanding of timing, cell specificity, and biomarker-guided intervention will be critical

for future progress.

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