NEURAL REGENERATION RESEARCH
www.nrronline.org

Review

Ferroptosis: a potential therapeutic target for stroke

Chengli Liu[#], Guijun Wang[#], Wenrui Han, Qi Tian, Mingchang Li[*]

https://doi.org/10.4103/1673-5374.385284

Date of submission: May 4, 2023

Date of decision: July 5, 2023

Date of acceptance: August 3, 2023

Date of web publication: September 22, 2023

Abstract

Ferroptosis is a form of regulated cell death characterized by massive iron accumulation and iron-dependent lipid peroxidation, differing from apoptosis, necroptosis, and autophagy in several aspects. Ferroptosis is regarded as a critical mechanism of a series of pathophysiological reactions after stroke because of iron overload caused by hemoglobin degradation and iron metabolism imbalance. In this review, we discuss ferroptosis-related metabolisms, important molecules directly or indirectly targeting iron metabolism and lipid peroxidation, and transcriptional regulation of ferroptosis, revealing the role of ferroptosis in the progression of stroke. We present updated progress in the intervention of ferroptosis as therapeutic strategies for stroke *in vivo* and *in vitro* and summarize the effects of ferroptosis inhibitors on stroke. Our review facilitates further understanding of ferroptosis pathogenesis in stroke, proposes new targets for the treatment of stroke, and suggests that more efforts should be made to investigate the mechanism of ferroptosis in stroke.

Key Words: cell death; ferroptosis; oxidative stress; stroke; treatment

From the Contents

Introduction	988
Retrieval Strategy	988
Ferroptosis and Metabolism	988
Regulatory Pathway of Ferroptosis in Stroke	990
The Transcriptional Regulation of Ferroptosis	990
Ferroptosis Inducers	991
Potential Therapy Targeting Ferroptosis in Stroke	991
Ferroptosis and Stroke	993
Limitations	994
Conclusions and Perspectives	994

Introduction

Stroke is a very common cerebrovascular disease in older individuals, and has various forms, such as ischemic stroke (IS), intracerebral hemorrhage (ICH), and spontaneous subarachnoid hemorrhage (SAH). Stroke is a major cause of death worldwide, with high morbidity and disability rates, ultimately causing great harm to human health and posing a heavy burden on patients' families and society. Ischemic stroke results from insufficiency or interruption of the cerebral blood supply, while hemorrhagic stroke occurs when endovascular blood enters into the intracranial and subarachnoid space caused by an abnormal vascular structure or cerebrovascular rupture (Hegazy et al., 2021). If effective measures are not taken in time, rapid progression of stroke can seriously endanger a patient's life, and survivors may face long-term cognitive and emotional impairments, loss of sensation and mobility, and significantly reduced quality of life (Rabinstein, 2017). Therefore, developing effective neuroprotective strategies for stroke patients will have a profound impact on global health.

The mechanisms underlying the pathology of strokes are extremely complex, including oxidative stress, excitotoxicity, neuroinflammation, apoptosis, and autophagy. In ischemic stroke, some pathological changes are closely associated to ferroptosis, involving lipid peroxidation, excitatory neurotoxicity, and iron metabolism disorder (Wei et al., 2022a). An increase in iron deposition aggravates oxidative stress, increases reactive oxygen species (ROS), and inflammatory response, ultimately resulting in cell death (Guo et al., 2023; Zheng et al., 2023). In hemorrhagic stroke, after SAH/ICH-induced blood-brain barrier (BBB) breakdown, a large number of red blood cells (RBCs) are released into the intracranial space (Halder et al., 2023). RBCs are rapidly lysed, and hemoglobin and its decomposition products play neurotoxic roles through various pathways (Chen et al., 2014). Studies continue to explore the molecular mechanisms of post-stroke brain injury, and some researchers are committed to developing anti-vasospasm, anti-apoptosis, and anti-inflammation drugs (Chen et al., 2022; Kawakita et al., 2023). However, most drugs have been shown to have a limited effect on the prognosis of stroke patients (Macdonald, 2014). Hence, it is necessary to explore a new pathogenesis of stroke. A large number of studies on ferroptosis support a close relationship between stroke and ferroptosis (Wang et al., 2023a; Zheng et al., 2023). In this review, we summarize the most recent advances in the mechanisms and regulatory pathways of ferroptosis, focusing on updated progress in therapeutic strategies for stroke.

Retrieval Strategy

An electronic literature review was performed using the PubMed database. The following combinations of key words were used to initially select the articles to be evaluated: ferroptosis and subarachnoid hemorrhage, oxidative stress and subarachnoid hemorrhage, cell death and subarachnoid hemorrhage, ferroptosis and stroke, oxidative stress and stroke, cell death and stroke, neuroprotection and subarachnoid hemorrhage, therapy and subarachnoid hemorrhage, neuroprotection and stroke, and therapy and stroke. Most of the selected studies (80% of all references) were published from 2013 to 2023.

Ferroptosis and Metabolism

Ferroptosis is defined as an iron-dependent form of regulatory cell death characterized by oxidative damage to cells caused by large accumulation of lipid hydroperoxides (Jhelum and David, 2022; Li and Jia, 2023). It is distinct from apoptosis, autophagy, and pyroptosis in some respects (Wu et al., 2021). Morphologically, cells undergoing ferroptosis exhibit distinct morphological changes different from other death types at the cellular and subcellular levels. At the cellular level, ferroptotic cells are typically isolated and rounded up. Under electron microscope, the mitochondria of ferroptotic cells are smaller than normal, the mitochondria cristae are narrowed or absent, and the outer mitochondria membrane is disrupted with electron-dense characteristics (Dixon et al., 2012). However, nuclei of ferroptotic cells remain structurally intact without chromatin condensation (Xie et al., 2016). In the process of apoptosis, cells show shrinkage and blebbing. At the ultrastructural level, it is usually manifested by nuclear membrane breakdown, chromatin fragmentation, and the formation of apoptotic bodies at the edge of the cell surface (Fricker et al., 2018). Autophagic cells accumulate double-membraned autophagic vacuoles in cytoplasm (Li et al., 2020). Cells undergoing pyroptosis exhibit dense blebbing and loss of plasma membrane integrity (Liang et al., 2019). Generally, these morphological changes are not found in ferroptotic cells. However, recent studies have shown that excessive autophagy and impaired lysosomal activity may promote ferroptosis (Liu et al., 2020a). The mechanism of autophagy-dependent ferroptosis still remains largely unclear.

In recent years, studies on the mechanism of ferroptosis have made rapid progress, involving various metabolic pathways and signaling molecules.

Department of Neurosurgery, Renmin Hospital of Wuhan University, Wuhan, Hubei Province, China
*__Correspondence to:__ Mingchang Li, MD, PhD, mingcli@whu.edu.cn.
https://orcid.org/0000-0003-4019-8886 (Mingchang Li)
#These authors contribute equally to this study.

Funding: *This work was supported by the National Natural Science Foundation of China, Nos. 81971870 and 82172173 (to ML).*
How to cite this article: *Liu C, Wang G, Han W, Tian Q, Li M (2024) Ferroptosis: a potential therapeutic target for stroke. Neural Regen Res 19(5):988-997.*

In addition to the preliminary discovery of the role of the glutathione-glutathione peroxidase 4 (GSH-GPX4) pathway, new GPX4-independent ferroptosis pathways are constantly being discovered. Furthermore, more targets are proposed to regulate these signaling pathways and have been extensively studied in the process of ferroptosis. Notably, these studies have focused on cellular metabolism, revealing a close relationship between ferroptosis and metabolic pathways (**Figure 1**).

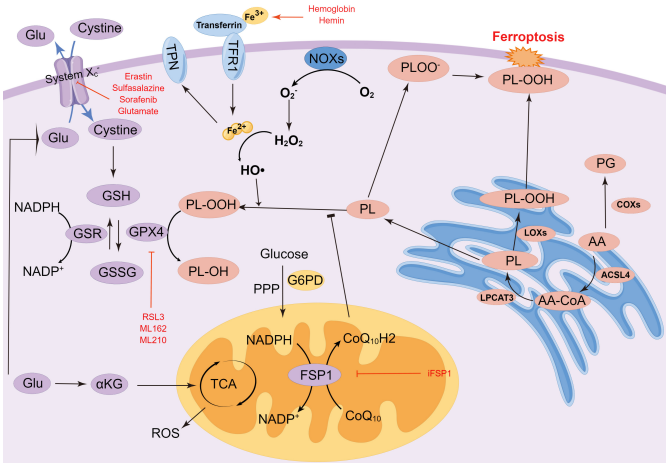

Figure 1 | **Mechanism of ferroptosis.**
Extracellular iron enters cells primarily through the TF-TFR complex, with TPN mediating iron export. When excessive intracellular iron accumulates, hydroxyl free radicals can be produced by the Fenton reaction in the presence of H_2O_2 and Fe^{2+}. System xc^- mediated cystine uptake, and subsequent GSH production and GPX4 activation, play essential roles in reducing PLOOH levels. NAPDH is produced by glucose through the PPP and is involved in various physiological functions. FSP1 suppresses ferroptosis by catalyzing the formation of CoQ10H2 from CoQ10. Lipid peroxidation is accompanied by ACSL4-catalyzed AA-CoA formation mainly present in the endoplasmic reticulum, followed by esterification of AA-CoA to PL mediated by LPCAT3. Several ROS-producing enzymes, such as LOXs, COXs, and NOXs, also participate in the production of lipid peroxidation. The red text depicts ferroptosis inducers. AA: Arachidonic acid; ACLS4: acyl-CoA synthetase long-chain family member 4; CoA: coenzyme A; CoQ10: coenzyme Q10; CoQ10H2: ubiquinol; COXs: cyclooxygenases; FPN: ferroportin; FSP1: ferroptosis suppressor protein 1; G6PD: glucose-6-phosphate dehydrogenase; Glu: glutamate; GPX4: glutathione peroxidase 4; GSH: glutathione; GSR: glutathione-disulfide reductase; GSSG: oxidized glutathione; H_2O_2: hydrogen peroxide; HO•: hydroxyl radical; LOXs: lipoxygenases; LPCAT3: lysophosphatidylcholine acyltransferase 3; NOXs: NADPH oxidases; PG: prostaglandin; PL: phospholipid; PLOOH: phospholipid hydroperoxides; PPP: pentose phosphate pathway; Se: selenium; TCA: tricarboxylic acid cycle; TFR: transferrin receptor; αKG: α-ketoglutarate.

Iron metabolism

The adult human body has the highest concentration of heavy metals, containing as much as 2.5–4.0 g of iron, which is widely considered a medium for electron flow in cellular activity (Ganz, 2019). Abnormal iron content and distribution can change the physiological activities of the body. In mammals, iron is absorbed by the gastrointestinal system, especially through duodenal mucosal cells that carry divalent metal transporter 1 (DMT1) (Yanatori and Kishi, 2019). Iron is taken into cells from the extracellular environment via the transferrin (TF) system, with TF and its associated receptor considered essential for iron accumulation. Fe^{2+} formed by erythrocyte degradation and intestinal absorption can be oxidized to Fe^{3+} by ceruloplasmin. Circulating iron enters into cells by binding to TF in the form of Fe^{3+}, which is a complex recognized by membrane protein TF receptor 1 (TFR1) and endocytosed (Li et al., 2020). Subsequently, the complex is reduced to Fe^{2+} by ferric reductases in the endosome and transported to the cytoplasm by DMT, and this Fe^{2+} is stored in the unstable iron pool and ferritin (Frazer and Anderson, 2014). Ferroportin (FPN) is the main channel protein to export intracellular iron in iron metabolism (Ganz, 2005). Iron export is accomplished by FPN through the oxidation of Fe^{2+} to Fe^{3+}, helping to maintain iron balance in the body. This FPN related circulation of internal iron strictly regulates iron homeostasis in cells (Bogdan et al., 2016). In fact, iron homeostasis is severely unbalanced in FPN-deficient mice (Drakesmith et al., 2015). Mitochondria are both the main component of ROS production and the main functional site of iron regulation. Intracellular Fe^{2+} flows into the mitochondria through the iron-sulfur cluster (Fe-S) system, which plays an important role in the mitochondrial electron transport chain (ETC) and vitamin synthesis (Doll and Conrad, 2017). When intracellular Fe^{2+} increases, hydroxyl free radicals can be generated by the Fenton reaction in the presence of H_2O_2 and Fe^{2+}, which can induce lipid peroxidation in the plasma membrane, resulting in ferroptosis (Takashi et al., 2020). Iron is a double-edged sword in the human body. A lack of iron causes iron-deficiency anemia, whereas excessive iron produces ROS via the Fenton reaction, causing ferroptosis (Toyokuni et al., 2020). Ferroptotic cells show iron metabolism disorder caused by imbalance between iron import, storage, and export, accompanied by increased expression of TFR and DMT1, as well as a reduction of FPN (Zhang et al., 2019a; Huang et al., 2022a). Deferoxamine, ciclopirox, and deferiprone can inhibit ferroptosis through the regulation of iron levels (Dixon et al., 2012).

Lipid peroxidation

Excessive lipid peroxidation and ROS accumulation are involved in all ferroptosis pathways (Dixon et al., 2012). ROS are a series of molecules containing reduced oxygen, such as superoxide, peroxides, singlet oxygen, and free radicals, which can lead to cell death by damaging biomolecules, such as DNA/RNA, lipids, and proteins (Dickinson and Chang, 2011). Lipid peroxidation can occur through different pathways, which can be divided into non-enzyme- and enzyme-dependent reactions. The main substrates of lipid peroxidation are polyunsaturated lipids containing carbon-carbon double bonds, which are sensitive to ROS, such as the hydroxyl radical (HO•) (Clemente et al., 2020).

In non-enzymatic reactions, Fenton and Haber-Weiss reaction mediated HO• production depends on Fe to initiate radical chain reactions for lipid peroxidation (Koppenol, 1993). The formation of complexes between iron and lipids is necessary for the initiation of lipid peroxidation (Clemente et al., 2020). The initiation reaction begins when hydrogen atoms are extracted from lipids to form alkyl radicals; then, chain-carrying carbon radicals react with oxygen, causing alkyl peroxy radical formation. This radical can obtain hydrogen from an organic substrate to form hydroperoxide and organic radicals, or bind to alkenes, such as the fatty acyl chains of polyunsaturated fatty acids (PUFA) found in phospholipids (Pratt et al., 2011). PUFAs are sensitive to lipid peroxidation, which initiates the Fenton reaction, making them vital elements in ferroptosis (Yang and Stockwell, 2016). Intracellular free PUFAs are considered the primary substrate of synthetic lipid signal transduction mediators; however, they need to be esterified into membrane phospholipids and oxidized to transmit ferroptosis signals (Kerr et al., 1972).

Enzyme-dependent reactions are performed by multiple peroxidases. When redox homeostasis is disrupted, cell death occurs due to the activation of many enzymes, involving lipoxygenases (LOXs), cyclooxygenases (COXs), and NADPH oxidases (NOXs) (Moloney and Cotter, 2018). Coordinated iron is the key to these enzymes' catalytic center. Certain LOXs, as non-heme iron-dependent dioxygenases, can oxygenate PUFAs of biological membranes (Kuhn et al., 2015), promoting the prospect that LOXs may mediate ferroptosis. A few studies have observed that some inhibitors of LOXs can inhibit ferroptosis (Li et al., 1997). Furthermore, 12/15-LOX knockout or LOX inhibition is associated with reduced ischemic brain injury in mice (Jin et al., 2008). NOXs are NADPH-dependent membrane-spanning enzymes, including superoxide (NOX1-3, NOX5) and hydrogen peroxide (NOX4, DUOX1-2) (Magnani and Mattevi, 2019). As the final product of $NADP^+$ after receiving electrons, NADPH is involved in various physiological activities as a hydrogen transmitter in cells (Wang et al., 2022a). In fact, NOXs have been found to be related to oxidative stress and ROS accumulation in brain injury (Ma et al., 2018). COXs are the key enzyme that catalyzes the rate-limiting reaction of the arachidonic cascade to convert free arachidonic acid (AA) into prostaglandin (PG) H2 (Uchida, 2017). AA is a 20-carbon fatty acid produced by phospholipids in the nuclear membrane, and exhibits phospholipase A2 (PLA2) activity, which can be further metabolized by LOXs or COXs (Çolakoğlu et al., 2018). Taking this into account, inhibition of COX-2 could ameliorate neuronal ferroptosis in traumatic brain injury and cerebral ischemic reperfusion (Liang et al., 2022; Xu et al., 2022).

Specific lipids, including free fatty acids and cis-unsaturated fatty acids, can regulate both apoptotic and nonapoptotic cell death pathways (Magtanong et al., 2016). Phosphatidylethanolamine (PE) containing AA or its derivative, has been reported to be the key phospholipid necessary for the induction of ferroptosis in cells (Kagan et al., 2017). Acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) were found to be involved in the biosynthesis of PE. ACSL4 can catalyze AA and AdA to acyl-CoA derivatives. These derivatives were then esterified by LPCAT3 into phosphatidylethanolamines (AA-PE and AdA-PE). Ultimately, 15-LOX (ALOX15) can directly oxidize AA-PE and AdA-PE to lipid hydroperoxides, participating in ferroptosis signals (Doll et al., 2017). Studies have shown that 12-LOX also mediates ACSL4-independent ferroptosis in p53-dependent tumor suppression (Chu et al., 2019). In addition, LOXs have been shown to catalyze PUFA peroxidation, affecting the transmembrane properties of PUFAs (Yang et al., 2016). Hence, suppressing the expression of LPCAT3 and ACSL4 to reduce the production of lipid peroxide substrates is a potential mechanism to inhibit ferroptosis. Moreover, monounsaturated fatty acids (MUFAs), including exogenous oleic acid (OA) and palmitoleic acid (POA), may suppress ferroptosis induced by RSL3 (Magtanong et al., 2019). This inhibition requires ACSL3 to activate exogenous MUFA and is independent of LD formation. Activated MUFAs were shown to replace PUFAs in phospholipids and decrease the sensitivity of plasma membrane lipids to oxidation (Magtanong et al., 2019).

Amino acid metabolism

Amino acid metabolism imbalance promotes ferroptosis. The alteration of glutamine metabolism is important in the process of ferroptosis. In glutamine catabolism, glutamine, the production of glutamate and ammonia catalyzed by GLUL/glutamine synthetase, can be catalyzed by glutaminase (GLS/GLS1) and glutaminase 2 (GLS2) to glutamate in cells, which regulates extracellular glutamate concentrations (Altman et al., 2016). Then, glutamate is converted into α-ketoglutarate (α-KG) in mitochondria, which is a significant substrate for the tricarboxylic acid (TCA) cycle to generate ATP and is sensitive to ROS (Hansen and Gibson, 2022). When glutamine and a-KG are depleted, which is caused by cystine deficiency, ferroptosis will occur due to the accumulation

of lipid peroxides and ROS (Gao et al., 2015). Abnormal glutamolysis and glutamine-fueled metabolism were noted to cause cysteine depletion and increased glutamate levels, which were shown to activate NMDA receptors and accelerate neuronal iron uptake (Shu et al., 2021). GSL1 inhibition protected against ferroptosis in the early stage by ablating glutaminolysis (Rodríguez-Graciani et al., 2022). However, some studies have indicated that GLS2, but not GLS1, increases ROS production, thereby promoting ferroptosis (Suzuki et al., 2022). The upregulation of GSL2, as the p53 target gene, mediates p53-dependent ferroptosis (Jennis et al., 2016). Cysteine is the limiting factor in GSH biosynthesis. With the exception of the system xc^- pathway, some cells are tolerant to ferroptosis induced by system xc^- inhibitors through the conversion of methionine to cysteine via the transsulfuration pathway (Stockwell et al., 2017).

Glucose metabolism

Glucose provides the main energy source for maintaining bioenergetic, biosynthetic, and redox homeostasis in most cells (Boroughs and DeBerardinis, 2015). Glucose-dependent mitochondrial catabolic processes involve the transfer of electrons from Complex I and Complex III in the electron transport chain to molecular oxygen, resulting in the production of ROS in these metabolic reactions. ROS can be used as signaling molecules to regulate cell proliferation (Corbet et al., 2016). Upon glucose deprivation, cells trigger the energy deficiency censoring adenosine monophosphate-activated protein kinase (AMPK) to promote ATP generation and inhibit its degradation (Lee et al., 2020). AMPK-mediated phosphorylation of acetyl-CoA carboxylase (ACC) restrains the biosynthesis of PUFAs and other fatty acids, and subsequent ferroptosis. The energy stress-mediated activation of AMPK also compensates for the pentose phosphate pathway (PPP)-inhibitory reduction of cellular NADPH, enhancing their resistance to ferroptosis (Lee et al., 2020). However, other studies have reported that AMPK-induced BECN1 phosphorylation promoted lipid peroxidation and ferroptosis via suppressing SLC7A11-mediated cystine transport (Song et al., 2018). The role of AMPK in ferroptosis relies on its substrate, which needs further investigation.

The primary function of the PPP is to mediate the synthesis of glucose 6-phosphate into ribose 5-phosphate, erythrose 4-phosphate, and NADPH (Jiang et al., 2011). NADPH can regulate ferroptosis in several ways. NAPDH, as a ligand of oxidoreductases on the endoplasmic reticulum, including NADH-cytochrome b5 reductase and NADPH-cytochrome P450 reductase (POR), may participate in the catalysis of lipid peroxidation in ferroptosis (Yan et al., 2021). The NOX family consists of seven members, which are pivotal in mediating the generation of membrane-associated ROS by forming different protein complexes (Bedard and Krause, 2007). NOX1, NOX2, and NOX4 have been shown to induce ferroptosis in cancer via different regulatory mechanisms (Chen et al., 2019a; Yang et al., 2020a). NOXs act as transmembrane enzymes that participate in ferroptosis by mediating electron transfer from NADPH to form O_2^- (Dixon et al., 2012). In contrast, NADPH can support SLC7A11-mediated cystine intake, and act as electron carriers, providing electrons for the reduction of glutathione disulthione (GSSG) mediated by glutathione reductase to GSH, eventually mediating the reduction of lipid ROS to suppress ferroptosis (Liu et al., 2020b). NADPH is also involved in thioredoxin (Trx) regeneration mediated by thioredoxin reductase (TR) and the formation of the reduced protein-disulfides system for ferroptosis regulation.

Regulatory Pathway of Ferroptosis in Stroke

System xc^--GSH-GPX4 pathway

System xc^-, as part of the necessary antioxidant system, is a widely distributed amino acid transporter in phospholipid bilayers, which is also a heterodimer composed of SLC3A2 and SLC7A11. Glutamate and cystine are transported inside and outside the cell by the xc^- system in equal proportions (Dixon et al., 2012). However, the flow direction of the bidirectional transporter is regulated by substrate concentration, with the concentration difference between intracellular and extracellular cystine and glutamate driving the flux (Lewerenz et al., 2013). GSH, as the reducing substrate of GPX4 activity, is essential in the prevention of ferroptosis. Furthermore, inhibition of γ-Glu-Cys ligase (GCL), as the rate-limiting enzyme of GSH synthesis, could be fatal (Ursini and Maiorino, 2020). Intracellular GSH concentration is regulated by a homeostatic mechanism, wherein steady concentration is subject to the kinetics of a specific enzymatic reaction (Ursini and Maiorino, 2020). The absorbed cystine is converted to cysteine in the cytoplasm, which participates in GSH synthesis (Tarangelo et al., 2018). GSH decreases the concentration of ROS and reactive nitrogen under the activity of GPXs. Restricting the function of system xc^- influences GSH synthesis by suppressing the uptake of cystine, resulting in decreased GPX activity, the accumulation of ROS, and finally, the occurrence of ferroptosis (Dixon et al., 2012). BRCA1-associated protein 1 (BAP1) and p53 can also suppress cystine absorption and the level of GSH by inhibiting the expression of SLC7A11, leading to ROS accumulation and ferroptosis (Jiang et al., 2015a; Zhang et al., 2018a). Moreover, ATF4 can upregulate the expression level of SLC7A11 to increase GSH biosynthesis and inhibit ferroptosis (Bai et al., 2021).

GPX4, a selenoprotein discovered via biochemical purification, is the primary enzyme that catalyzes the reduction of phospholipid hydroperoxide (PLOOH) in mammalian cells (Ursini et al., 1985). GPX4 activity is obviously controlled by selenium utilization. However, cultured cells are often a deficient source of selenium, and providing nanomolar amounts of $NaSeO_3$ to the culture medium can significantly promote GPX4 expression and activity (Maiorino et al., 1991; Lewerenz et al., 2013). Catalytic residue of GPX4 and electrons supplied mainly by GSH can reduce cholesterol hydroperoxides and phospholipids to their corresponding alcohols (Maiorino et al., 2018). Simultaneously, GPX4 reduces cytotoxic lipid peroxides (L-OOH) to the corresponding alcohols (L-OH), accompanied by the conversion of GSH to glutathione oxide (GSSG) for reducing lipid peroxidation (Yang et al., 2014). Inhibiting activity of GPX4 can contribute to the accumulation of lipid peroxides, thereby inducing ferroptosis (Yang and Stockwell, 2008). Some studies have found that the SLC7A11-GSH-GPX4 pathway plays an important role in neuronal injury, and that the inhibition of the cystine/glutamate transporter gene (SLC7A11)-GSH-GPX4 signal pathway aggravates neuronal ferroptosis and BBB disruption after stroke (Li et al., 2023; Xu et al., 2023a).

Nuclear factor erythroid 2-related factor 2-antioxidant response element (NRF2-ARE) pathway

NRF2, as a stress-inducible transcription factor, is recognized to be a major regulator of antioxidant response, because many of its downstream target genes participate in regulating redox balance in cells, such as SLC7A11 and GPX4 (Dodson et al., 2019). Under normal circumstances, the transcriptional activity of NRF2 is inhibited, because it is still bound through three distinct E3-ubiquitin ligase complexes: SCF/β-TrCP, KEAP1-CUL3-RBX1, and synoviolin/Hrd1 (Maeda et al., 2016; Sun et al., 2016; Yang et al., 2020b). When endogenous stress-induced modifications, competitive binding, or exogenous pharmacological inhibition occur in these complexes, activated NRF2 dissociates from KEAP1 and then translocates to the nucleus to bind ARE for triggering the transcription of downstream genes (Buendia et al., 2016). A variety of enzymes and proteins responsible for inhibiting lipid peroxidation, are the target genes of NRF2 (Dodson et al., 2019). NRF2 plays a vital role in the transcriptional regulation of ferroptosis-related genes, involved in iron metabolism (FTH1, FTL, SLC40A1, NQO1, and HMOX1) (Kerins and Ooi, 2018) and GSH synthesis (SLC7A11, GPX4, GCLM, CBS, CHAC1, GCLC, and GSS) (Dodson et al., 2019; Anandhan et al., 2020). Some studies have shown that the activation of the NRF2-ARE pathway can attenuate neuronal ferroptosis after IS (Wang et al., 2023b; Xu et al., 2023b). Moreover, NRF2 has been reported to be involved in the production of NAPDH. NAPDH oxidative (NOX1 and NOX2) and aldo-keto reductases (AKRs), including AKR1C1/2/3, are also potential NRF2 target genes to prevent lipid peroxidation (Almanza et al., 2019; Yang et al., 2020a). Notably, heme-oxygenase 1 (HO-1) regulated by NRF2, as an enzyme catalyzing heme into biliverdin, can be activated by stress signals, such as inflammatory mediators and ROS (Kassovska-Bratinova et al., 2009). Nevertheless, the effect of HO-1 on ferroptosis remains controversial. Studies have shown that the upregulation of HO-1 can reduce oxidative stress, and HO-1 is regarded as an antioxidative and cytoprotective enzyme (Ma et al., 2020). However, other studies have found that HO-1 overexpression induces the ferroptotic process by increasing ferrous iron levels, and HO-1 enters into the nucleus and mitochondria, leading to mitochondrial dysfunction and intracellular accumulation of ROS and lipid peroxides (Yang et al., 2022a). Therefore, considering the significant increase of HO-1 caused by severe brain injury after stroke and the release of massive heme after hemorrhagic stroke, it is of great significance to determine whether HO-1 promotes or inhibits ferroptosis after stroke. Accordingly, further investigation on this topic is needed.

FSP1-CoQ10-NADPH pathway

Ferroptosis suppressor protein 1 (FSP1), renamed from apoptosis-inducing factor mitochondria-associated 2 (AIFM2), is a flavoprotein that was initially considered to be a pro-apoptotic protein (Wu et al., 2002). FSP1 overexpression has robustly protective effects against pharmacological and genetic inducers of ferroptosis in cells. It was found that the anti-ferroptosis function of FSP1 was independent of cellular GSH levels, ACSL4 expression, and GPX4 activity (Doll et al., 2019). Coenzyme Q10 (CoQ10), as an endogenous isoprenyl benzoquinone compound, plays an essential role in the mitochondrial electron transport chain by carrying electrons from complexes I and II to complexes III (Shimada et al., 2016). The reduced form of CoQ10 (CoQ10-H2) has been found to be an effective radical-trapping antioxidant in lipoproteins and phospholipids (Frei et al., 1990). CoQ10 regulated by FSP1 contributes to the shuttling of reduction equivalents from NADPH to lipid bilayer to inhibit the propagation of lipid peroxidation, while FSP1 catalyzes CoQ10 regeneration via NADPH (Doll et al., 2019). The protective effects of Netrin-1 on neuronal ferroptosis after SAH are dependent on the CoQ10-FSP1 pathway (Chen et al., 2023). NADPH plays a crucial role in ferroptosis, and its level is considered to be a biomarker of ferroptosis sensitivity (Lin et al., 2021). The NOX family mediates oxidation reactions by transferring electrons via biological membranes. NOX4 has been found to be the main source of ROS through impaired mitochondrial metabolism, oxidative stress-induced lipid peroxidation leading to brain damage, and promotion of ferroptosis in astrocytes (Park et al., 2021). Different from the GSH-GPX4 pathway, the FSP1-CoQ10-NADPH pathway is a potential suppressor of phospholipid peroxidation and ferroptosis.

The Transcriptional Regulation of Ferroptosis

Mounting evidence suggests that transcription factors are critical in the regulation of ferroptosis, and these factors act as blockers or promoters by mediating the expression of downstream genes in metabolic and signaling pathways (Dai et al., 2020). Several genes related to ferroptosis may also be simultaneously controlled by multiple transcription factors. Understanding the regulatory role of these transcription factors is of great significance for the study of the underlying mechanism responsible for ferroptosis. The functions of some ferroptosis-related transcription factors, including tumor suppressor protein p53 (TP53), BAP1, HIFs, and YAP/YAP1, are summarized in **Figure 2**.

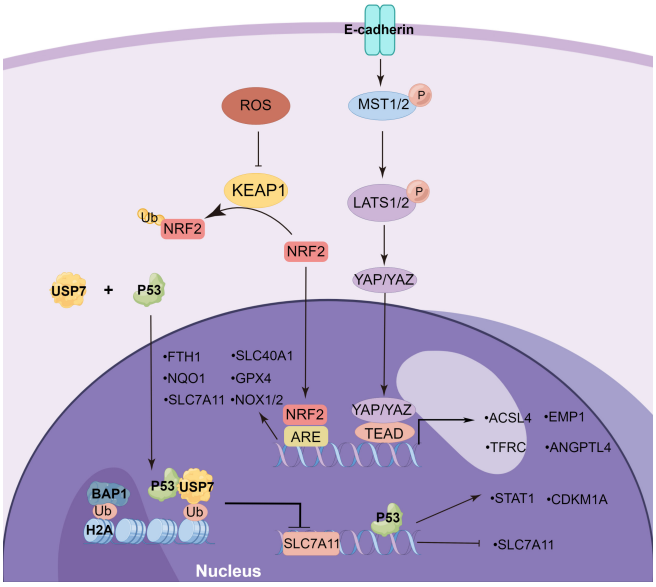

Figure 2 | **The transcriptional regulation of ferroptosis**
BAP1 can directly bind histones and p53 promotes nuclear transfer of USP7; both regulate H2Aub levels and inhibit transcription of SLC7A11. In addition, p53 can directly bind promoters to promote STAT1 transcription and inhibit SLC7A11 transcription to promote ferroptosis. P53 also promotes the transcription of CDKM1A to enhance the anti-ferroptosis effect. YAP/TAZ can promote ferroptosis by regulating multiple gene transcription through TEAD in the Hippo pathway. NRF2 regulated by KEAP1 can combine with ARE to regulate the expression of some ferroptosis-related genes. ANGPTL4: Angiopoietin-like protein 4; ARE: antioxidant response element; ASCL4: acyl-CoA synthetase long-chain family member 4; BAP1: BRCA1-associated protein 1; CDKN1A: cyclin dependent kinase inhibitor 1A; EMP1: epithelial membrane protein 1; FTH1: ferritin heavy polypeptide 1; H2A: histones H2A; KEAP1: Kelch-like ECH-associated protein 1; LATS1/2: large tumor suppressor 1/2; MST1/2: mammalian sterile20-like kinase 1/2; NOX1/2: NADPH oxidase 1/2; NQO1: NADH dehydrogenase, quinone 1; NRF2: nuclear factor erythroid 2-related factor 2; P53: tumor protein P53; SAT1: spermidine/spermine N1-acetyltransferase 1; SLC40A1: solute carrier family 40 member 1; SLC7A11: solute carrier family 7 member 11; TAZ: PDZ-binding motif; TEAD: TEA domain family member; TFRC: transferrin receptor protein 1; Ub: ubiquitin; USP7: ubiquitin-specific protease 7; YAP1: Yes-associated protein 1.

P53

P53 is a known tumor suppressor protein that is involved in a variety of cellular stresses, such as oncogene activation, hypoxia, DNA damage, nutrition starvation, and ribosomal stress (Kastenhuber and Lowe, 2017). Low levels of cell stress activate p53, which induces DNA repair, cell cycle arrest, and survival. Conversely, high levels of stress lead to p53 activation, thus inducing cell death (Kang et al., 2019). TP53 bi-directionally regulates its susceptibility to ferroptosis via both transcription-dependent and transcription-independent mechanisms. P53 can promote ferroptosis through regulation of SLC7A11, SAT1, and GLS2 expression. Studies have shown that p53 can inhibit cystine uptake and sensitize cells to ferroptosis by suppressing SLC7A11 expression, and chromatin immunoprecipitation (ChIP) results in U2OS cells, showing that p53 polypeptides combine the promoter region of the *SLC7A11* gene (Jiang et al., 2015b). The knockout of TP53 (3KR), an acetylation-defective mutant at three lysine residues, results in the loss of p53's role in regulating pro-apoptotic genes and transcriptionally inhibits SLC711A expression in H1299 cells (Jiang et al., 2015b). In contrast, p53 (4KR), an acetylation-defective mutant at lysine K98, fails to reduce SLC711A expression (Wang et al., 2016). P53 can inhibit the levels of H2Bub1 by regulating the nuclear translocation of the deubiquitinase USP7, suppressing the transcription levels of SLC7A11 (Wang et al., 2019). These results indicate the critical impact of p53 acetylation on SLC7A11 expression during ferroptotic responses. Spermidine/Spermine N1-acetyltransferase 1 (SAT1) can acetylate spermidine and spermine by acetyl-CoA, which is an important regulatory factor of polyamine metabolism, and can participate in the regulation of cell growth, differentiation, and proliferation (Casero et al., 2018). SAT1, as the transcription target of TP53, increases the expression of ALOX15 to promote lipid peroxidation, while an ALOX15 inhibitor can reverse SAT1-induced ferroptosis (Ou et al., 2016). P53 acetylation-mutant ($Trp53^{3KR}$) mice were reported to induce SAT1 transcription as well as the wild-type p53 (Casero et al., 2018). GSL2, which promotes the conversion of glutamate to α-ketoglutarate, has been found to be a transcriptional target of p53 and its expression is involved in mitochondrial respiration and the production of ATP (Hu et al., 2010).

P53 also exerts an anti-ferroptosis effect through the regulation of dipeptidyl peptidase-4 (DPP4) localization and activity, as well as through the promotion of cyclin-dependent kinase inhibitor 1A (CDKN1A/p21) expression (Kang et al., 2019). TP53 directly blocks DPP4 activity in the nucleus, with the loss of p53 facilitating DDP4 relocation in the plasma membrane. DDP4 facilitates plasma-membrane-associated lipid peroxidation and ferroptosis by increasing NOX1 activity (Xie et al., 2017). P53 also inhibits erastin2-induced ferroptosis by transcriptionally inducing CDKN1A expression in HT1080 cells (Tarangelo et al., 2018), but the protective role of the p53-CDKN1A axis remains unclear.

BAP1

BAP1, as a nuclear deubiquitinating (DUB) enzyme, can interact with some histones and transcriptional factors, including ASXL1/2, FOXK1/2, HCF1, OGT, KDM1B, and H2A, and is involved in the regulation of gene transcription (Carbone et al., 2020). BAP1 and its related proteins constitute the DUB complex, whose primary function is to remove monoubiquitin from ubiquitinated H2A at lysine 119 (Scheuermann et al., 2010) and ubiquitinated H2B (Lee et al., 2013). BAP1 inhibits the expression of SLC7A11 by BAP1-mediated H2Aub deubiquitination on the promoter of SLC7A11, resulting in elevated lipid peroxidation and ferroptosis (Zhang et al., 2018a).

YAP1 and TAZ

The Hippo pathway interacts with and attaches to neighboring cells to affect ferroptosis in cancer by regulating E-cadherin-mediated cellular adhesion (Yang et al., 2019a). The Hippo pathway comprises the kinase cascade, such as LATS1/2 and MST1/2, and downstream effectors, for instance, PDZ-binding motif (TAZ) and Yes-associated protein 1 (YAP1) (Sun and Chi, 2021). LATS1 and LATS2 can regulate the phosphorylation of YAP1, thereby promoting ferroptosis by increasing the nuclear retention of YAP1. Neurofibromin 2 (NF2) is required for the activation of LATS1 and LATS2 (Wu et al., 2019). After nuclear translocation, activated YAP can upregulate multiple ferroptosis-related transcriptional target genes, such as ACSL4, TFRC, and E3 ligase SKP2 (Yang et al., 2021a). The inhibition of YAP can reduce BBB damage and endothelial cell injury after I/R injury (Gong et al., 2021). Moreover, an integrative genomic analysis confirmed that ANGPTL4 is a direct target gene controlled by TAZ, which sensitizes ferroptosis by activating NOX2 in ovarian tumors (Yang et al., 2020a). Epithelial membrane protein 1 is also a target gene of TAZ in renal cancer, and induces the expression of NOX4 (Yang et al., 2019a).

HIFs

Hypoxia-inducible factors (HIFs) are heterodimers consisting of an α-subunit (HIF-1α, HIF-2α, and HIF-3α) and a β-subunit (HIF-β), which are widely involved in hypoxic responses (Su et al., 2022). HIF1α plays an essential role in changes in oxygen availability at the transcriptional level, including migration, immunity, metabolism, and survival (Kaplan et al., 2018). In HT1080 and Calu-1 cells, HIF1α was found to reduce erastin-induced ferroptosis, the anti-ferroptosis effect of which was associated with the activation of clockophagy, a selective form of autophagy for degrading ARNTL (Liu et al., 2019). ARNTL, as a core component of the molecular clock, was reported to regulate gene transcription levels by combining with E-box elements. ARNTL knockdown upregulates the transcription level of Egl-9 family hypoxia-inducible factor 2 (EGLN2), which is a positive regulator involved in HIF1α degradation in proteasoma-dependent pathways (Yang et al., 2019b). ARNTL inhibition or EGLN2 overexpression reduces HIF1α expression, thereby triggering ferroptosis, while HIF1α upregulation obviously inhibits ferroptosis (Yang et al., 2019b). This manifestation is dependent on HIF1α-induced upregulation of FABP3 and FABP7, which facilitates fatty-acid intake and lipid storage, leading to the reduction of ferroptosis (Dai et al., 2020). Deferoxamine protects against cerebral ischemia by promoting HIF-1α expression (Li et al., 2008). A previous study showed that HIF-1α can transcriptionally suppress ACSL4 expression in the early phase of IS, and attenuate lipid metabolism to inhibit ferroptosis (Cui et al., 2021a). Moreover, It has been suggested that roxadustat induces ferroptosis via HIF-2α activation, which is the primary cause of lipid peroxidation accumulation in ferroptosis (Su et al., 2022). HIF-2α can inactivate hepcidin and upregulate ferroportin, TF, and DMT1 to facilitate iron absorption and transportation, thereby promoting ferroptosis (Kaplan et al., 2018). The opposite effect of HIF1α and HIF2α on ferroptosis warrants further investigation.

Ferroptosis Inducers

Ferroptosis can be mediated by small-molecule drugs or compounds, directly or indirectly, through alteration of a variety of ferroptosis-related metabolism or regulatory pathways, including GSH depletion, GPX4 inhibition, iron overload, and organic peroxides (**Table 1**). These drugs primarily act on tumor cells; although a few have been shown to act on neurons or glial cells. Among these, heme and hemoglobin, as natural products of hemorrhagic stroke, are also important inducers of ferroptosis and are involved in various disease processes, further explaining the important role of ferroptosis in stroke.

Potential Therapy Targeting Ferroptosis in Stroke

Given that ferroptosis may be an important pathogenesis of stroke, its therapeutic potential should be considered (Shen et al., 2020). The occurrence of ferroptosis increases brain damage after stroke (**Figure 3**). Here, we summarize published compounds that have therapeutic effects on ferroptosis processes *in vivo* or *in vitro* after stroke (**Table 2**), so as to provide as much theoretical support as possible for the treatment of stroke in the future. Various inhibitors (including iron chelators, antioxidants, and enzyme inhibitors) may restrict iron overload or lipid peroxidation accumulation, providing a potential therapeutic strategy for the treatment of brain injury after stroke. Interestingly, some animal experiments and clinical trials have

Table 1 | **Summary of ferroptosis inducers**

Compounds	Mechanisms	Effects	References
Erastin	System xc^- inhibitor	Inhibit cystine import and induce GSH depletion	Duan et al., 2021
Piperazine erastin			Yang et al., 2014
Imidazole ketone erastin			Zhang et al., 2019b
Glutamate			Jiang et al., 2020a; Lachowicz et al., 2022
Sulfasalazine			You et al., 2021
Sorafenib			Sun et al., 2021
RSL3	GPX4 inhibitor	Inhibit GPX4 activity and lipid peroxidation	Cui et al., 2021b
Artemisinin			Ye et al., 2021
ML162			Shin et al., 2018
ML210			You et al., 2021
Withaferin A			Zhang et al., 2023
JKE-1674			Eaton et al., 2019
JKE-1716			Eaton et al., 2019
Acetaminophen	GSH depletion	Increase 4-HNE levels and lipid peroxidation	Niu et al., 2022
Trigonelline	NRF2 inhibitor	GPX4 inhibition and lipid peroxidation	Roh et al., 2017
Pseudolaric acid B	Activate NOX4, and downregulate SLC7A11	Increase intracellular iron and lipid peroxidation	Wu et al., 2022
IFNγ	Inhibit MEK/ERK phosphorylation	Inhibition of SLC7A11 and GPX4, and lipid peroxidation	Yang et al., 2022b
$FeCl_2$	Iron overload	ROS accumulation and lipid peroxidation	Li et al., 2017
Ferrous ammonium sulfate			Hayashima et al., 2021
Ferric ammonium citrate			Liu et al., 2021; Lu et al., 2021
Hemin			Xiao et al., 2022
Hemoglobin			Fan et al., 2022
Siramesine and lapatinib	Increase iron level by upregulation of transferrin and down regulation of ferroportin-1	Increase intracellular iron, ROS accumulation, and lipid peroxidation	Villalpando-Rodriguez et al., 2019
Doxorubicin	Inhibit ALAS1 levels	Increase intracellular iron and lipid peroxidation	Abe et al., 2022
Dihydroartemisinin	induce degradation of ferritin	Increase intracellular iron and lipid peroxidation	Su et al., 2021
Salinomycin	Block iron translocation and deplete ferritin	Lipid peroxidation	Antoszczak et al., 2022
Artesunate	Organic peroxides	Lipid peroxidation	Roh et al., 2017
Hydrogen peroxide	Organic peroxides	GPX4 inhibition and lipid peroxidation	Jiang et al., 2020b
Piperlongumine	Inhibit the thioredoxin reductase	ROS accumulation and lipid peroxidation	Yang et al., 2022c
Zalcitabine	Activation of STING1-mediated autophagy	Lipid peroxidation	Li et al., 2021a
BAY 11-7085	IκBα inhibitor	ROS accumulation and lipid peroxidation	Chang et al., 2018
Concanavalin A	Lectin	Increase RNS	Zeng et al., 2020
CH004	CBS inhibitor	ROS accumulation and lipid peroxidation	Wang et al., 2018
Buthionine sulfoximine	γ-glutamylcysteine synthetase inhibitor	Induces GSH depletion	Luo et al., 2021
Brefeldin A	Golgi-dispersing compounds	Induces Golgi stress and GPX4 inhibition	Alborzinia et al., 2018
iFSP1	FSP1 inhibitor	Lipid peroxidation	Jo et al., 2022
Statins	HMG-CoA inhibitor	Block biosynthesis of CoQ10 and decrease GPX4 levels	Zhang et al., 2022
BAY 87–2243	Mitochondrial complex I inhibition	Depolarized the mitochondrial membrane potential, increased lipid peroxidation and ROS levels	Basit et al., 2017
Arsenite	Toxicant	Reduce the mitochondrial membrane potential, increased ROS levels	Wei et al., 2020

CBS: Cystathionine βsynthase; CoQ10: Coenzyme Q10; ERK: extracellular regulated protein kinases; FSP1: ferroptosis suppressor protein 1; GPX4: glutathione peroxidase 4; GSH: glutathione; HMG-CoA: 3-hydroxy-3-methyl glutaryl coenzyme A; IFNγ: Interferon gamma; IκBα: NF-kappa-B inhibitor alpha; MEK: mitogen-activated protein; NOX4: NADPH oxidase 4; NRF2: nuclear factor erythroid 2-related factor 2; ROS: reactive oxygen species; SLC7A11: solute carrier family 7 member 11.

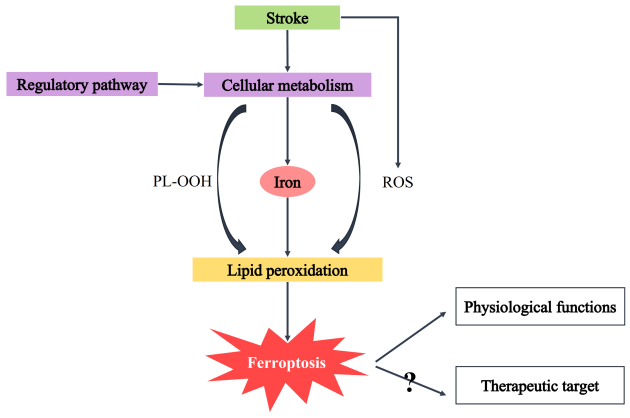

Figure 3 | **Molecular mechanism of ferroptosis and therapeutic targets in stroke.**
DFO: Deferoxamine; Fer-1: ferrostatin-1; Lip-1: Liproxstatin-1; NAC: N-acetylcysteine; PIH: Pyridoxal isonicotinoyl hydrazine; PLOOH: phospholipid hydroperoxides; ROS: reactive oxygen species.

also reported the protective effect of these ferroptosis inhibitors on stroke, and the effective use of these ferroptosis inhibitors has in turn demonstrated the important role of ferroptosis in brain injury after stroke.

Iron chelators

Iron overload caused by iron metabolism imbalance or heme degradation after stroke, is an essential factor in the occurrence of ferroptosis. Excess iron accumulation can induce a non-enzymatic iron-induced Fenton reaction and iron-involved lipid peroxidation, eventually leading to mitochondrial destruction and cell death. Hence, the use of iron chelating agents at 6 hours after ICH to reduce intracellular and extracellular iron content is an important treatment for ferroptosis (Zhang et al., 2021). Clinical trials have further demonstrated the therapeutic effect and safety of DFO, which reduces iron saturation of blood TF over 1–3 days, and may provide long term benefit (i.e., 3 months) for patients with IS (Millán et al., 2021). A study suggested that mitochondrial ferritin can attenuate neuronal ferroptosis by suppressing inflammation-regulated iron deposition in MCAO mice (Wang et al., 2022c). Furthermore, pyridoxal isonicotinoyl hydrazine, a lipophilic iron-chelating agent, has been found to attenuate lipid peroxidation and iron accumulation in ICH mice (Zhang et al., 2021). Therefore, reducing the intracellular iron pool is important to reduce ferroptosis after stroke.

Antioxidants

Phenols and aromatic amines, as the most common chain-breaking antioxidants, carry relatively weak N-H and O-H bonds, respectively, which can remove chain-carrying radicals to terminate the autoxidation chain reaction (Conrad and Pratt, 2019). Ferrostatin-1 and lipstatin-1, as aromatic amines, have been recognized as classic ferroptosis inhibitors both *in vitro* and *in vivo*, which can significantly reduce brain injury after stroke (Chen et al., 2021a; Li et al., 2021b; Wei et al., 2022b). As phenolic compounds, curcumin, puerarin, and edaravone are potential antioxidant agents for the treatment of ferroptosis after stroke. Edaravone and its derivatives have been reported to effectively improve the prognosis of SAH and IS in clinical studies (Xu et al.,

Table 2 | Treatment strategy of ferroptosis in stroke

Reagents	Types	Functional mechanisms	Diseases	References
Deferoxamine	Iron chelating agent	Prevent lipid peroxidation	IS, HT, ICH	Gu et al., 2009; Hatakeyama et al., 2013; Xie et al., 2014; Abdul et al., 2021
Pyridoxal isonicotinoyl hydrazine	Lipophilic iron-chelating agent	Increase GPX4 level and inhibit COX2 level	ICH	Zhang et al., 2021
Ferrostatin-1	Antioxidant agent	Prevent lipid peroxidation	IS, ICH, SAH	Chen et al., 2019b; Li et al., 2021b; Xu et al., 2022
Liproxstatin-1	Antioxidant agent	Increase GPX4 expression and suppress COX2 expression	I/R, SAH	Cao et al., 2021; Chen et al., 2021a; Wei et al., 2022b
Curcumin	Antioxidant agent	Increase GPX4 expression	ICH	Yang et al., 2021b
Edaravone	Antioxidant agent	Increase NRF2 and FPN expression	I/R	Liu et al., 2022a
Puerarin	Antioxidant agent	Activation of the AMPK/PGC1α/Nrf2-signaling pathway	SAH	Huang et al., 2022b
N-acetylcysteine	GSH precursor	Increase GSH level and inhibit ALOX5	IS, HT, ICH	Guo et al., 2016; Krzyżanowska et al., 2017; Karuppagounder et al., 2018; Uemura et al., 2018; Hong et al., 2020
Dihydromyricetin	Flavonoid compound	Inhibit SPHK1/mTOR signaling	IS	Xie et al., 2022
Selenium	Microelement	Increase GPX4 expression	IS, ICH	Alim et al., 2019; Tuo et al., 2021; Shi et al., 2022
UBIAD1	Antioxidant enzyme	Catalyze coenzyme Q10 biosynthesis	IS	Huang et al., 2022c
Dexpramipexole	Antiparkinson drug	Increase GPX4 and ferroptosis suppressor protein 1 level	ICH	Wang et al., 2022b
Epicatechin	COX inhibitor	Diminished heme-oxygenase 1 expression and brain iron deposition	ICH	Chang et al., 2014
Baicalein	ALOX inhibitor	Increase GSH, ACSL4, and ACSL3 level	IS	Li et al., 2022
Rosiglitazone	ACSL4 inhibitor	Inhibit ACSL4 expression	IS	Chen et al., 2021a
Pioglitazone	PPARγ agonist	Promote NRF2 and GPX4 expression	ICH	Duan et al., 2022
U0126	MEK inhibitor	Inhibit ERK1/2 signaling	ICH	Zille et al., 2022

ACSL: Acyl-CoA synthetase long-chain family member; ALOX5: arachidonate 5-lipoxygenase; AMPK: adenosine monophosphate-activated protein kinase; ASCL4: Achaete-scute-like protein 4; COX: cyclooxygenase; ERK1/2: extracellular regulated protein kinases; FPN: ferroportin; GPX4: glutathione peroxidase 4; HT: hemorrhagic transformation; ICH: intracranial hemorrhage; IS: ischemic stroke; MEK: mitogen-activated protein; mTOR: mammalian target of rapamycin; NOX4: NADPH oxidase 4; NRF2: nuclear factor erythroid 2-related factor 2; PGC1α: peroxisome proliferators-activated receptor γ coactivator l alpha; PPARγ: peroxisome proliferator activated receptor γ; ROS: reactive oxygen species; SAH: subarachnoid hemorrhage; SPHK1: sphingosine kinase 1.

2021). However, liproxstatin-1 may be a more potent drug than edaravone or deferoxamine for the treatment of central nervous system diseases (Fan et al., 2021). In addition, some important antioxidants, such as vitamin E (Hu et al., 2021), have been shown to reduce ferroptosis in other diseases. A meta-analysis has shown that a higher dietary vitamin E intake is associated with lower stroke risk (Cheng et al., 2018). However, other studies have reported that excessive α-tocopherol, which belongs to the vitamin E family, aggravates neuroinflammatory responses and brain injury after IS (Khanna et al., 2015). Vitamin E can inhibit platelet aggregation and thrombus formation in patients with stroke (Kobzar, 2020), which may increase bleeding risk. The role of vitamin E in stroke deserves further experimental investigation.

Enzyme inhibitors

Some reviews have shown that multiple enzyme inhibitors are involved in ferroptosis protection (Chen et al., 2021b). ACSL4 inhibitors (e.g., rosiglitazone), ALOX inhibitors (e.g., baicalein), and COX inhibitors (e.g., epicatechin) have been reported to suppress ferroptosis through the prevention of lipid peroxidation. Moreover, baicalein may suppress ferroptosis via its off-target antioxidant activity (Conrad and Pratt, 2019). The role of enzyme inhibitors in stroke is worthy of further discussion.

Other ferroptosis inhibitors

N-acetylcysteine (NAC), approved by the America Food and Drug Administration, is a GSH precursor (Karuppagounder et al., 2018). NAC is believed to have a variety of beneficial effects in multiple animal models because of its ability to influence diverse targets. NAC can increase cellular GSH levels and drive the activity of the xc- transporter (Krzyżanowska et al., 2017). A study found that NAC, given via intraperitoneal injection 2 hours after collagenase infusion, prevents ferroptosis *in vivo* and *in vitro* and improves outcomes after hemorrhagic stroke in rats (Karuppagounder et al., 2018). Selenium, an essential element in humans, acts as an activator of GPX, which mediates the antioxidant effect to reduce oxidative damage (Shi et al., 2022). CoQ10 is one of the pivotal parts of the mitochondrial electron transport chain and plays an important role outside the mitochondria to suppress lipid peroxidation by trapping radicals (Stockwell et al., 2020). Statins suppress mevalonate-derived CoQ10 by restricting HMG-CoA reductase, which sensitizes cells to ferroptosis (Zhang et al., 2022). UBIAD1 regulates ischemia/reperfusion (I/R)-mediated ferroptosis by catalyzing CoQ10 biosynthesis and restoring mitochondrial dysfunction in injured neurons (Huang et al., 2022c).

Ferroptosis and Stroke

Ferroptosis in IS and hemorrhagic transformation

IS cases account for 70–80% of total stroke patients worldwide; survivors frequently have sequelae of sensorimotor impairment in one or more body parts (Barthels and Das, 2020). Ischemia occurs when the blood supply to brain tissues is interrupted, contributing to a cascade of pathophysiological reactions (Davidson et al., 2020). It has been reported that ferroptosis mediates and aggravates brain tissue injury during the occurrence and development of cerebral I/R (Alim et al., 2019; She et al., 2020). Transient I/R injury increases brain iron levels in mice, and iron-targeted interventions can suppress MCAO-induced I/R injury (Tuo et al., 2017).

Tissue plasminogen activator (t-PA) is an approved-thrombolytic drug that works by activating proteolytic enzymes to dissolve blood clots, which is beneficial to the rehabilitation and prognosis of patients with AIS (Liu et al., 2022c). Nevertheless, it has been reported that the therapeutic window of t-PA is only 4.5 hours, and the risk of HT gradually increases after appropriate time window is missed (Liu et al., 2022b). Moreover, one study found that delayed administration of tissue plasminogen activator resulted in a poor prognosis in mice (El Amki et al., 2018). Therefore, the clinical use of thrombolytic drugs should be carefully considered. The occurrence of HT is accompanied by the diffusion of more RBCs into the brain tissue. Heme degradation and iron accumulation after HT further promote ferroptosis and deteriorate brain tissue damage after stroke. The mechanism of injury may be similar to that of hemorrhagic stroke (Liu et al., 2023). Recent studies have shown that ferroptosis is involved in HT after I/R, which may be associated with ferroptosis of cerebral vascular endothelial cells (Abdul et al., 2021; Liu et al., 2023). Clinical trials have also shown that when edaravone dexborneol was administered within 48 hours after IS, brain injury and clinical outcomes were improved in IS patients (Xu et al., 2021). Additionally, DFO followed by 72 hours of continuous infusion initiated during tPA infusion also resulted in improved outcomes for IS patients (Millán et al., 2021).

Ferroptosis in ICH

ICH patients account for approximately 15% of all stroke patients, causing high mortality and morbidity; however, there are currently few effective therapies for ICH (Donnan et al., 2010). ICH occurs when a fragile vessel bursts and bleeds into the brain tissue (Wang, 2010). Primary brain injury occurs in the first few hours after ICH, because the formation and expansion of hematoma or edema mediate mass effects and increase intracranial pressure, which can cause cerebral herniation and even death. Subsequently, the enlarged hematoma compresses the brain tissue, leading to neuroinflammation, neuronal death, and secondary tissue damage (Wu et al., 2010). Preclinical studies have suggested that iron released from hematomas might result in brain damage after ICH (Xiong et al., 2014). Hemoglobin (Hb)/heme is a putative neurotoxin. Hb released from lysed RBCs can be phagocytic by macrophages and microglia in the perihematomal zone, and metabolized into Fe^{2+}, which mediates the production of ROS and lipid peroxidation (Wu et al., 2012; Li et al., 2017). Then, excess Fe^{2+} is transported out of microglia and accumulates in neurons by the Tf–Tf receptor system, where it forms highly toxic radicals by the Fenton reaction. These radicals attack lipid membranes, proteins, and DNA, thus damaging cellular function and promoting ferroptosis (Salvador, 2010). GPX4 expression is significantly decreased after ICH, while GPX4 overexpression was shown to reduce neuronal ferroptosis and improve prognosis in rats (Zhang et al., 2018b). Furthermore, treatment with Fer-1 after ICH improved neurological function, attenuated lipid ROS generation, and decreased the expression level of PTGS2 and COX-2 in OHSCs and *in vivo* (Wan et al., 2019).

Ferroptosis in SAH

SAH is caused by blood flow into the subarachnoid space following cerebrovascular rupture, and accounts for approximately 10% of all strokes (Schatlo et al., 2021). Similar to ICH, Hb degradation products in the subarachnoid space can also activate oxidation stress and iron accumulation, which results in ferroptosis after SAH (Li et al., 2021b). Despite advances in research of the clinical diagnosis and underlying mechanism of SAH, there is still a lack of effective drug therapies to improve poor outcomes in patients. Fer-1, lip-1, and puerarin have been reported to attenuate EBI after SAH through the inhibition of ferroptosis. Additionally, treatment with edaravone has been shown to improve the prognosis of patients with aneurysmal SAH (Munakata et al., 2009). Another study found drug candidates that were found to reduce ferroptosis, preventing SAH damage, but more clinical application studies are needed (Gao et al., 2022; Huang et al., 2022b).

Limitations

While the current review tried to elaborate on the mechanism of ferroptosis in stroke, it has several limitations to note. First, since the studies of ferroptosis in tumors are abundant, this review refers to some mechanisms and pathways that have been demonstrated in tumors; yet whether some of the discussed molecules have similar effects in stroke pathology requires further study. Second, in this paper, we try to summarize the existing studies as much as possible to illustrate the mechanism of ferroptosis in stroke and its therapeutic potential, so as to provide as much theoretical support as possible for the treatment of stroke in the future. However, the fast pace of published literature on ferroptosis in stroke means that research findings and recommendations are constantly developing as new evidence arises. Third, our review introduces some drugs for the treatment of ferroptosis after stroke and their possible mechanisms of action, but the details of drug action are not specific enough.

Conclusions and Perspectives

In recent years, owing to iron accumulation caused by hemoglobin degradation, hypoxia, and iron metabolism imbalance, ferroptosis has been found to play an important role in the pathological process of brain injury after stroke. In this review, we summarized ferroptosis-related metabolism, important regulatory pathways targeting iron metabolism and lipid peroxidation, transcriptional regulation of ferroptosis, and therapeutic strategies of stroke. We discussed the recent advances of some drugs with anti-ferroptosis effects *in vitro* and *in vivo* after IS, ICH, and SAH. However, several anti-ferroptosis drugs have shown significant side effects during the process of clinical research transformation, which deserve further study. Hence, elucidating the molecular mechanism of ferroptosis will not only facilitate understanding of the relative mechanism of cell death, but can also contribute to an increased drive in the discovery of new pharmacotherapeutic strategies for stroke in the future.

Author contributions: *CL, GW, WH, and QT collected the data and wrote the manuscript. ML reviewed and revised the manuscript. All authors approved the final version of the manuscript.*

Conflicts of interest: *The authors declare that there is no conflict of interest for the publication of this article.*

Data availability statement: *Not applicable.*

References

Abdul Y, Li W, Ward R, Abdelsaid M, Hafez S, Dong G, Jamil S, Wolf V, Johnson MH, Fagan SC, Ergul A (2021) Deferoxamine treatment prevents post-stroke vasoregression and neurovascular unit remodeling leading to improved functional outcomes in type 2 male diabetic rats: role of endothelial ferroptosis. Transl Stroke Res 12:615-630.

Abe K, Ikeda M, Ide T, Tadokoro T, Miyamoto HD, Furusawa S, Tsutsui Y, Miyake R, Ishimaru K, Watanabe M, Matsushima S, Koumura T, Yamada KI, Imai H, Tsutsui H (2022) Doxorubicin causes ferroptosis and cardiotoxicity by intercalating into mitochondrial DNA and disrupting Alas1-dependent heme synthesis. Sci Signal 15:eabn8017.

Alborzinia H, Ignashkova TI, Dejure FR, Gendarme M, Theobald J, Wölfl S, Lindemann RK, Reiling JH (2018) Golgi stress mediates redox imbalance and ferroptosis in human cells. Commun Biol 1:210.

Alim I, Caulfield JT, Chen Y, Swarup V, Geschwind DH, Ivanova E, Seravalli J, Ai Y, Sansing LH, Ste Marie EJ, Hondal RJ, Mukherjee S, Cave JW, Sagdullaev BT, Karuppagounder SS, Ratan RR (2019) Selenium drives a transcriptional adaptive program to block ferroptosis and treat stroke. Cell 177:1262-1279.e25.

Almanza A, Carlesso A, Chintha C, Creedican S, Doultsinos D, Leuzzi B, Luís A, McCarthy N, Montibeller L, More S, Papaioannou A, Püschel F, Sassano ML, Skoko J, Agostinis P, de Belleroche J, Eriksson LA, Fulda S, Gorman AM, Healy S, Kozlov A, Muñoz-Pinedo C, Rehm M, Chevet E, Samali A (2019) Endoplasmic reticulum stress signalling- from basic mechanisms to clinical applications. FEBS J 286:241-278.

Altman BJ, Stine ZE, Dang CV (2016) From Krebs to clinic: glutamine metabolism to cancer therapy. Nat Rev Cancer 16:619-634.

Anandhan A, Dodson M, Schmidlin CJ, Liu P, Zhang DD (2020) Breakdown of an ironclad defense system: the critical role of NRF2 in mediating ferroptosis. Cell Chem Biol 27:436-447.

Antoszczak M, Müller S, Cañeque T, Colombeau L, Dusetti N, Santofimia-Castaño P, Gaillet C, Puisieux A, Iovanna JL, Rodriguez R (2022) Iron-sensitive prodrugs that trigger active ferroptosis in drug-tolerant pancreatic cancer cells. J Am Chem Soc 144:11536-11545.

Bai X, Ni J, Beretov J, Wasinger VC, Wang S, Zhu Y, Graham P, Li Y (2021) Activation of the eIF2α/ATF4 axis drives triple-negative breast cancer radioresistance by promoting glutathione biosynthesis. Redox Biol 43:101993.

Barthels D, Das H (2020) Current advances in ischemic stroke research and therapies. Biochim Biophys Acta Mol Basis Dis 1866:165260.

Basit F, van Oppen LM, Schöckel L, Bossenbroek HM, van Emst-de Vries SE, Hermeling JC, Grefte S, Kopitz C, Heroult M, Hgm Willems P, Koopman WJ (2017) Mitochondrial complex I inhibition triggers a mitophagy-dependent ROS increase leading to necroptosis and ferroptosis in melanoma cells. Cell Death Dis 8:e2716.

Bedard K, Krause KH (2007) The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. Physiol Rev 87:245-313.

Bogdan AR, Miyazawa M, Hashimoto K, Tsuji Y (2016) Regulators of iron homeostasis: new players in metabolism, cell death, and disease. Trends Biochem Sci 41:274-286.

Boroughs LK, DeBerardinis RJ (2015) Metabolic pathways promoting cancer cell survival and growth. Nat Cell Biol 17:351-359.

Buendia I, Michalska P, Navarro E, Gameiro I, Egea J, León R (2016) Nrf2-ARE pathway: An emerging target against oxidative stress and neuroinflammation in neurodegenerative diseases. Pharmacol Ther 157:84-104.

Cao Y, Li Y, He C, Yan F, Li JR, Xu HZ, Zhuang JF, Zhou H, Peng YC, Fu XJ, Lu XY, Yao Y, Wei YY, Tong Y, Zhou YF, Wang L (2021) Selective ferroptosis inhibitor liproxstatin-1 attenuates neurological deficits and neuroinflammation after subarachnoid hemorrhage. Neurosci Bull 37:535-549.

Carbone M, Harbour JW, Brugarolas J, Bononi A, Pagano I, Dey A, Krausz T, Pass HI, Yang H, Gaudino G (2020) Biological mechanisms and clinical significance of BAP1 mutations in human cancer. Cancer Discov 10:1103-1120.

Casero RA Jr, Murray Stewart T, Pegg AE (2018) Polyamine metabolism and cancer: treatments, challenges and opportunities. Nat Rev Cancer 18:681-695.

Chang CF, Cho S, Wang J (2014) (-)-Epicatechin protects hemorrhagic brain via synergistic Nrf2 pathways. Ann Clin Transl Neurol 1:258-271.

Chang LC, Chiang SK, Chen SE, Yu YL, Chou RH, Chang WC (2018) Heme oxygenase-1 mediates BAY 11-7085 induced ferroptosis. Cancer Lett 416:124-137.

Chen B, Cao P, Guo X, Yin M, Li X, Jiang L, Shao J, Chen X, Jiang C, Tao L, Zhou L, Yu H (2022) Maraviroc, an inhibitor of chemokine receptor type 5, alleviates neuroinflammatory response after cerebral Ischemia/reperfusion injury via regulating MAPK/NF-κB signaling. Int Immunopharmacol 108:108755.

Chen B, Chen Z, Liu M, Gao X, Cheng Y, Wei Y, Wu Z, Cui D, Shang H (2019b) Inhibition of neuronal ferroptosis in the acute phase of intracerebral hemorrhage shows long-term cerebroprotective effects. Brain Res Bull 153:122-132.

Chen J, Yang L, Geng L, He J, Chen L, Sun Q, Zhao J, Wang X (2021a) Inhibition of Acyl-CoA synthetase long-chain family member 4 facilitates neurological recovery after stroke by regulation ferroptosis. Front Cell Neurosci 15:632354.

Chen J, Wang Y, Li M, Zhu X, Liu Z, Chen Q, Xiong K (2023) Netrin-1 alleviates early brain injury by regulating ferroptosis via the PPARγ/Nrf2/GPX4 signaling pathway following subarachnoid hemorrhage. Transl Stroke Res doi: 10.1007/s12975-022-01122-4.

Chen S, Feng H, Sherchan P, Klebe D, Zhao G, Sun X, Zhang J, Tang J, Zhang JH (2014) Controversies and evolving new mechanisms in subarachnoid hemorrhage. Prog Neurobiol 115:64-91.

Chen X, Li J, Kang R, Klionsky DJ, Tang D (2021b) Ferroptosis: machinery and regulation. Autophagy 17:2054-2081.

Chen X, Xu S, Zhao C, Liu B (2019a) Role of TLR4/NADPH oxidase 4 pathway in promoting cell death through autophagy and ferroptosis during heart failure. Biochem Biophys Res Commun 516:37-43.

Cheng P, Wang L, Ning S, Liu Z, Lin H, Chen S, Zhu J (2018) Vitamin E intake and risk of stroke: a meta-analysis. Br J Nutr 120:1181-1188.

Chu B, Kon N, Chen D, Li T, Liu T, Jiang L, Song S, Tavana O, Gu W (2019) ALOX12 is required for p53-mediated tumour suppression through a distinct ferroptosis pathway. Nat Cell Biol 21:579-591.

Clemente SM, Martínez-Costa OH, Monsalve M, Samhan-Arias AK (2020) Targeting lipid peroxidation for cancer treatment. Molecules 25:5144.

Çolakoğlu M, Tunçer S, Banerjee S (2018) Emerging cellular functions of the lipid metabolizing enzyme 15-Lipoxygenase-1. Cell Prolif 51:e12472.

Conrad M, Pratt DA (2019) The chemical basis of ferroptosis. Nat Chem Biol 15:1137-1147.

Corbet C, Pinto A, Martherus R, Santiago de Jesus JP, Polet F, Feron O (2016) Acidosis drives the reprogramming of fatty acid metabolism in cancer cells through changes in mitochondrial and histone acetylation. Cell Metab 24:311-323.

Cui Y, Zhang Y, Zhao X, Shao L, Liu G, Sun C, Xu R, Zhang Z (2021a) ACSL4 exacerbates ischemic stroke by promoting ferroptosis-induced brain injury and neuroinflammation. Brain Behav Immun 93:312-321.

Cui Y, Zhang Z, Zhou X, Zhao Z, Zhao R, Xu X, Kong X, Ren J, Yao X, Wen Q, Guo F, Gao S, Sun J, Wan Q (2021b) Microglia and macrophage exhibit attenuated inflammatory response and ferroptosis resistance after RSL3 stimulation via increasing Nrf2 expression. J Neuroinflammation 18:249.

Dai C, Chen X, Li J, Comish P, Kang R, Tang D (2020) Transcription factors in ferroptotic cell death. Cancer Gene Ther 27:645-656.

Davidson SM, Adameová A, Barile L, Cabrera-Fuentes HA, Lazou A, Pagliaro P, Stensløkken KO, Garcia-Dorado D; EU-CARDIOPROTECTION COST Action (CA16225) (2020) Mitochondrial and mitochondrial-independent pathways of myocardial cell death during ischaemia and reperfusion injury. J Cell Mol Med 24:3795-3806.

Dickinson BC, Chang CJ (2011) Chemistry and biology of reactive oxygen species in signaling or stress responses. Nat Chem Biol 7:504-511.

Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, Morrison B 3rd, Stockwell BR (2012) Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell 149:1060-1072.
Dodson M, Castro-Portuguez R, Zhang DD (2019) NRF2 plays a critical role in mitigating lipid peroxidation and ferroptosis. Redox Biol 23:101107.
Doll S, Conrad M (2017) Iron and ferroptosis: A still ill-defined liaison. IUBMB Life 69:423-434.
Doll S, Proneth B, Tyurina YY, Panzilius E, Kobayashi S, Ingold I, Irmler M, Beckers J, Aichler M, Walch A, Prokisch H, Trümbach D, Mao G, Qu F, Bayir H, Füllekrug J, Scheel CH, Wurst W, Schick JA, Kagan VE, et al. (2017) ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. Nat Chem Biol 13:91-98.
Doll S, Freitas FP, Shah R, Aldrovandi M, da Silva MC, Ingold I, Goya Grocin A, Xavier da Silva TN, Panzilius E, Scheel CH, Mourão A, Buday K, Sato M, Wanninger J, Vignane T, Mohana V, Rehberg M, Flatley A, Schepers A, Kurz A, et al. (2019) FSP1 is a glutathione-independent ferroptosis suppressor. Nature 575:693-698.
Donnan GA, Hankey GJ, Davis SM (2010) Intracerebral haemorrhage: a need for more data and new research directions. Lancet Neurol 9:133-134.
Drakesmith H, Nemeth E, Ganz T (2015) Ironing out ferroportin. Cell Metab 22:777-787.
Duan C, Jiao D, Wang H, Wu Q, Men W, Yan H, Li C (2022) Activation of the PPARγ prevents ferroptosis-induced neuronal loss in response to intracerebral hemorrhage through synergistic actions with the Nrf2. Front Pharmacol 13:869300.
Duan L, Zhang Y, Yang Y, Su S, Zhou L, Lo PC, Cai J, Qiao Y, Li M, Huang S, Wang H, Mo Y, Wang Q (2021) Baicalin inhibits ferroptosis in intracerebral hemorrhage. Front Pharmacol 12:629379.
Eaton JK, Ruberto RA, Kramm A, Viswanathan VS, Schreiber SL (2019) Diacylfuroxans are masked nitrile oxides that inhibit GPX4 covalently. J Am Chem Soc 141:20407-20415.
El Amki M, Lerouet D, Garraud M, Teng F, Beray-Berthat V, Coqueran B, Barsacq B, Abbou C, Palmier B, Marchand-Leroux C, Margaill I (2018) Improved reperfusion and vasculoprotection by the poly(ADP-ribose)polymerase inhibitor PJ34 after stroke and thrombolysis in mice. Mol Neurobiol 55:9156-9168.
Fan BY, Pang YL, Li WX, Zhao CX, Zhang Y, Wang X, Ning GZ, Kong XH, Liu C, Yao X, Feng SQ (2021) Liproxstatin-1 is an effective inhibitor of oligodendrocyte ferroptosis induced by inhibition of glutathione peroxidase 4. Neural Regen Res 16:561-566.
Fan X, Zhang X, Liu LC, Zhang S, Pelger CB, Lughmani HY, Haller ST, Gunning WT 3rd, Cooper CJ, Gong R, Dworkin LD, Gupta R (2022) Hemopexin accumulates in kidneys and worsens acute kidney injury by causing hemoglobin deposition and exacerbation of iron toxicity in proximal tubules. Kidney Int 102:1320-1330.
Frazer DM, Anderson GJ (2014) The regulation of iron transport. Biofactors 40:206-214.
Frei B, Kim MC, Ames BN (1990) Ubiquinol-10 is an effective lipid-soluble antioxidant at physiological concentrations. Proc Natl Acad Sci U S A 87:4879-4883.
Fricker M, Tolkovsky AM, Borutaite V, Coleman M, Brown GC (2018) Neuronal cell death. Physiol Rev 98:813-880.
Ganz T (2005) Cellular iron: ferroportin is the only way out. Cell Metab 1:155-157.
Ganz T (2019) Erythropoietic regulators of iron metabolism. Free Radic Biol Med 133:69-74.
Gao M, Monian P, Quadri N, Ramasamy R, Jiang X (2015) Glutaminolysis and transferrin regulate ferroptosis. Mol Cell 59:298-308.
Gao S, Zhou L, Lu J, Fang Y, Wu H, Xu W, Pan Y, Wang J, Wang X, Zhang J, Shao A (2022) Cepharanthine attenuates early brain injury after subarachnoid hemorrhage in mice via inhibiting 15-lipoxygenase-1-mediated microglia and endothelial cell ferroptosis. Oxid Med Cell Longev 2022:4295208.
Gong S, Ma H, Zheng F, Huang J, Zhang Y, Yu B, Li F, Kou J (2021) Inhibiting YAP in endothelial cells from entering the nucleus attenuates blood-brain barrier damage during ischemia-reperfusion injury. Front Pharmacol 12:777680.
Gu Y, Hua Y, Keep RF, Morgenstern LB, Xi G (2009) Deferoxamine reduces intracerebral hematoma-induced iron accumulation and neuronal death in piglets. Stroke 40:2241-2243.
Guo J, Tuo QZ, Lei P (2023) Iron, ferroptosis, and ischemic stroke. J Neurochem 165:487-520.
Guo ZN, Xu L, Hu Q, Matei N, Yang P, Tong LS, He Y, Guo Z, Tang J, Yang Y, Zhang JH (2016) Hyperbaric oxygen preconditioning attenuates hemorrhagic transformation through reactive oxygen species/thioredoxin-interacting protein/Nod-like receptor protein 3 pathway in hyperglycemic middle cerebral artery occlusion rats. Crit Care Med 44:e403-411.
Halder SK, Sapkota A, Milner R (2023) The importance of laminin at the blood-brain barrier. Neural Regen Res 18:2557-2563.
Hansen GE, Gibson GE (2022) The α-ketoglutarate dehydrogenase complex as a hub of plasticity in neurodegeneration and regeneration. Int J Mol Sci 23:12403.
Hatakeyama T, Okauchi M, Hua Y, Keep RF, Xi G (2013) Deferoxamine reduces neuronal death and hematoma lysis after intracerebral hemorrhage in aged rats. Transl Stroke Res 4:546-553.
Hayashima K, Kimura I, Katoh H (2021) Role of ferritinophagy in cystine deprivation-induced cell death in glioblastoma cells. Biochem Biophys Res Commun 539:56-63.
Hegazy MI, Malik AA, Shannawaz M (2021) Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol 20:795-820.
Hong DK, Kho AR, Lee SH, Jeong JH, Kang BS, Kang DH, Park MK, Park KH, Lim MS, Choi BY, Suh SW (2020) Transient receptor potential melastatin 2 (TRPM2) inhibition by antioxidant, N-acetyl-l-cysteine, reduces global cerebral ischemia-induced neuronal death. Int J Mol Sci 21:6026.
Hu Q, Zhang Y, Lou H, Ou Z, Liu J, Duan W, Wang H, Ge Y, Min J, Wang F, Ju Z (2021) GPX4 and vitamin E cooperatively protect hematopoietic stem and progenitor cells from lipid peroxidation and ferroptosis. Cell Death Dis 12:706.
Hu W, Zhang C, Wu R, Sun Y, Levine A, Feng Z (2010) Glutaminase 2, a novel p53 target gene regulating energy metabolism and antioxidant function. Proc Natl Acad Sci U S A 107:7455-7460.
Huang S, Wang Y, Xie S, Lai Y, Mo C, Zeng T, Kuang S, Zhou C, Zeng Z, Chen Y, Huang S, Gao L, Lv Z (2022a) Isoliquiritigenin alleviates liver fibrosis through caveolin-1-mediated hepatic stellate cells ferroptosis in zebrafish and mice. Phytomedicine 101:154117.
Huang Y, Liu J, He J, Hu Z, Tan F, Zhu X, Yuan F, Jiang Z (2022c) UBIAD1 alleviates ferroptotic neuronal death by enhancing antioxidative capacity by cooperatively restoring impaired mitochondria and Golgi apparatus upon cerebral ischemic/reperfusion insult. Cell Biosci 12:42.
Huang Y, Wu H, Hu Y, Zhou C, Wu J, Wu Y, Wang H, Lenahan C, Huang L, Nie S, Gao X, Sun J (2022b) Puerarin attenuates oxidative stress and ferroptosis via AMPK/PGC1α/Nrf2 pathway after subarachnoid hemorrhage in rats. Antioxidants (Basel) 11:1259.
Jennis M, Kung CP, Basu S, Budina-Kolomets A, Leu JI, Khaku S, Scott JP, Cai KQ, Campbell MR, Porter DK, Wang X, Bell DA, Li X, Garlick DS, Liu Q, Hollstein M, George DL, Murphy ME (2016) An African-specific polymorphism in the TP53 gene impairs p53 tumor suppressor function in a mouse model. Genes Dev 30:918-930.
Jhelum P, David S (2022) Ferroptosis: copper-iron connection in cuprizone-induced demyelination. Neural Regen Res 17:89-90.
Jiang L, Hickman JH, Wang SJ, Gu W (2015a) Dynamic roles of p53-mediated metabolic activities in ROS-induced stress responses. Cell Cycle 14:2881-2885.
Jiang L, Kon N, Li T, Wang SJ, Su T, Hibshoosh H, Baer R, Gu W (2015b) Ferroptosis as a p53-mediated activity during tumour suppression. Nature 520:57-62.
Jiang P, Du W, Wang X, Mancuso A, Gao X, Wu M, Yang X (2011) p53 regulates biosynthesis through direct inactivation of glucose-6-phosphate dehydrogenase. Nat Cell Biol 13:310-316.
Jiang T, Cheng H, Su J, Wang X, Wang Q, Chu J, Li Q (2020a) Gastrodin protects against glutamate-induced ferroptosis in HT-22 cells through Nrf2/HO-1 signaling pathway. Toxicol In Vitro 62:104715.
Jiang T, Chu J, Chen H, Cheng H, Su J, Wang X, Cao Y, Tian S, Li Q (2020b) Gastrodin inhibits H2O2-induced ferroptosis through its antioxidative effect in rat glioma cell line C6. Biol Pharm Bull 43:480-487.
Jin G, Arai K, Murata Y, Wang S, Stins MF, Lo EH, van Leyen K (2008) Protecting against cerebrovascular injury: contributions of 12/15-lipoxygenase to edema formation after transient focal ischemia. Stroke 39:2538-2543.
Jo A, Bae JH, Yoon YJ, Chung TH, Lee EW, Kim YH, Joh HM, Chung JW (2022) Plasma-activated medium induces ferroptosis by depleting FSP1 in human lung cancer cells. Cell Death Dis 13:212.
Kagan VE, Mao G, Qu F, Angeli JP, Doll S, Croix CS, Dar HH, Liu B, Tyurin VA, Ritov VB, Kapralov AA, Amoscato AA, Jiang J, Anthonymuthu T, Mohammadyani D, Yang Q, Proneth B, Klein-Seetharaman J, Watkins S, Bahar I, et al. (2017) Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. Nat Chem Biol 13:81-90.
Kang R, Kroemer G, Tang D (2019) The tumor suppressor protein p53 and the ferroptosis network. Free Radic Biol Med 133:162-168.
Kaplan JM, Sharma N, Dikdan S (2018) Hypoxia-inducible factor and its role in the management of anemia in chronic kidney disease. Int J Mol Sci 19:389.
Karuppagounder SS, Alin L, Chen Y, Brand D, Bourassa MW, Dietrich K, Wilkinson CM, Nadeau CA, Kumar A, Perry S, Pinto JT, Darley-Usmar V, Sanchez S, Milne GL, Pratico D, Holman TR, Carmichael ST, Coppola G, Colbourne F, Ratan RR (2018) N-acetylcysteine targets 5 lipoxygenase-derived, toxic lipids and can synergize with prostaglandin E(2) to inhibit ferroptosis and improve outcomes following hemorrhagic stroke in mice. Ann Neurol 84:854-872.
Kassovska-Bratinova S, Yang G, Igarashi K, Dennery PA (2009) Bach1 modulates heme oxygenase-1 expression in the neonatal mouse lung. Pediatr Res 65:145-149.
Kastenhuber ER, Lowe SW (2017) Putting p53 in Context. Cell 170:1062-1078.
Kawakita F, Nakano F, Kanamaru H, Asada R, Suzuki H (2023) Anti-apoptotic effects of AMPA receptor antagonist perampanel in early brain injury after subarachnoid hemorrhage in mice. Transl Stroke Res doi: 10.1007/s12975-023-01138-4.
Kerins MJ, Ooi A (2018) The roles of NRF2 in modulating cellular iron homeostasis. Antioxid Redox Signal 29:1756-1773.
Kerr JF, Wyllie AH, Currie AR (1972) Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 26:239-257.
Khanna S, Heigel M, Weist J, Gnyawali S, Teplitsky S, Roy S, Sen CK, Rink C (2015) Excessive α-tocopherol exacerbates microglial activation and brain injury caused by acute ischemic stroke. FASEB J 29:828-836.
Kobzar G (2020) Inhibition of platelet activation using vitamins. Platelets 31:157-166.
Koppenol WH (1993) The centennial of the Fenton reaction. Free Radic Biol Med 15:645-651.
Krzyżanowska W, Pomierny B, Bystrowska B, Pomierny-Chamioło L, Filip M, Budziszewska B, Pera J (2017) Ceftriaxone- and N-acetylcysteine-induced brain tolerance to ischemia: Influence on glutamate levels in focal cerebral ischemia. PLoS One 12:e0186243.
Kuhn H, Banthiya S, van Leyen K (2015) Mammalian lipoxygenases and their biological relevance. Biochim Biophys Acta 1851:308-330.
Lachowicz JI, Pichiri G, Piludu M, Fais S, Orrù G, Congiu T, Piras M, Faa G, Fanni D, Dalla Torre G, Lopez X, Chandra K, Szczepski K, Jaremko L, Ghosh M, Emwas AH, Castagnola M, Jaremko M, Hannappel E, Coni P (2022) Thymosin β4 Is an Endogenous Iron Chelator and Molecular Switcher of Ferroptosis. Int J Mol Sci 23:551.
Lee H, Zandkarimi F, Zhang Y, Meena JK, Kim J, Zhuang L, Tyagi S, Ma L, Westbrook TF, Steinberg GR, Nakada D, Stockwell BR, Gan B (2020) Energy-stress-mediated AMPK activation inhibits ferroptosis. Nat Cell Biol 22:225-234.
Lee SW, Youn H, Kim EJ, Um SJ (2013) Retracted: Histone H2B ubquitination regulates retinoic acid signaling through the cooperation of ASXL1 and BAP1. Mol Cell 51:200-210.
Lewerenz J, Hewett SJ, Huang Y, Lambros M, Gout PW, Kalivas PW, Massie A, Smolders I, Methner A, Pergande M, Smith SB, Ganapathy V, Maher P (2013) The cystine/glutamate antiporter system x(c)(-) in health and disease: from molecular mechanisms to novel therapeutic opportunities. Antioxid Redox Signal 18:522-555.
Li C, Zhang Y, Liu J, Kang R, Klionsky DJ, Tang D (2021a) Mitochondrial DNA stress triggers autophagy-dependent ferroptotic death. Autophagy 17:948-960.
Li J, Cao F, Yin HL, Huang ZJ, Lin ZT, Mao N, Sun B, Wang G (2020) Ferroptosis: past, present and future. Cell Death Dis 11:88.
Li M, Meng Z, Yu S, Li J, Wang Y, Yang W, Wu H (2022) Baicalein ameliorates cerebral ischemia-reperfusion injury by inhibiting ferroptosis via regulating GPX4/ACSL4/ACSL3 axis. Chem Biol Interact 366:110137.

Li Q, Han X, Lan X, Gao Y, Wan J, Durham F, Cheng T, Yang J, Wang Z, Jiang C, Ying M, Koehler RC, Stockwell BR, Wang J (2017) Inhibition of neuronal ferroptosis protects hemorrhagic brain. JCI Insight 2:e90777.

Li Q, Peng F, Yan X, Chen Y, Zhou J, Wu S, Jiang W, Jin X, Liang J, Peng C, Pan X (2023) Inhibition of SLC7A11-GPX4 signal pathway is involved in aconitine-induced ferroptosis in vivo and in vitro. J Ethnopharmacol 303:116029.

Li QS, Jia YJ (2023) Ferroptosis: a critical player and potential therapeutic target in traumatic brain injury and spinal cord injury. Neural Regen Res 18:506-512.

Li Y, Maher P, Schubert D (1997) A role for 12-lipoxygenase in nerve cell death caused by glutathione depletion. Neuron 19:453-463.

Li Y, Liu Y, Wu P, Tian Y, Liu B, Wang J, Bihl J, Shi H (2021b) Inhibition of ferroptosis alleviates early brain injury after subarachnoid hemorrhage in vitro and in vivo via reduction of lipid peroxidation. Cell Mol Neurobiol 41:263-278.

Li YX, Ding SJ, Xiao L, Guo W, Zhan Q (2008) Desferoxamine preconditioning protects against cerebral ischemia in rats by inducing expressions of hypoxia inducible factor 1 alpha and erythropoietin. Neurosci Bull 24:89-95.

Liang C, Zhang X, Yang M, Dong X (2019) Recent progress in ferroptosis inducers for cancer therapy. Adv Mater 31:e1904197.

Liang H, Tang T, Huang H, Li T, Gao C, Han Y, Yuan B, Gao S, Wang H, Zhou ML (2022) Peroxisome proliferator-activated receptor-γ ameliorates neuronal ferroptosis after traumatic brain injury in mice by inhibiting cyclooxygenase-2. Exp Neurol 354:114100.

Lin CC, Ding CC, Sun T, Wu J, Chen KY, Zhou P, Chi JT (2021) The regulation of ferroptosis by MESH1 through the activation of the integrative stress response. Cell Death Dis 12:727.

Liu C, Sun S, Xie J, Li H, Li T, Wu Q, Zhang Y, Bai X, Wang J, Wang X, Li Z, Wang W (2022b) GLP-1R agonist exendin-4 protects against hemorrhagic transformation induced by rtPA after ischemic stroke via the Wnt/β-catenin signaling pathway. Mol Neurobiol 59:3649-3664.

Liu C, Tian Q, Wang J, He P, Han S, Guo Y, Yang C, Wang G, Wei H, Li M (2023) Blocking P2RX7 attenuates ferroptosis in endothelium and reduces HG-induced hemorrhagic transformation after MCAO by inhibiting ERK1/2 and P53 signaling pathways. Mol Neurobiol 60:460-479.

Liu C, Xie J, Sun S, Li H, Li T, Jiang C, Chen X, Wang J, Le A, Wang J, Li Z, Wang J, Wang W (2022c) Hemorrhagic transformation after tissue plasminogen activator treatment in acute ischemic stroke. Cell Mol Neurobiol 42:621-646.

Liu J, Yang M, Kang R, Klionsky DJ, Tang D (2019) Autophagic degradation of the circadian clock regulator promotes ferroptosis. Autophagy 15:2033-2035.

Liu J, Kuang F, Kroemer G, Klionsky DJ, Kang R, Tang D (2020a) Autophagy-dependent ferroptosis: machinery and regulation. Cell Chem Biol 27:420-435.

Liu W, Wang L, Liu C, Dai Z, Li T, Tang B (2022a) Edaravone ameliorates cerebral ischemia-reperfusion injury by downregulating ferroptosis via the Nrf2/FPN pathway in rats. Biol Pharm Bull 45:1269-1275.

Liu X, Olszewski K, Zhang Y, Lim EW, Shi J, Zhang X, Zhang J, Lee H, Koppula P, Lei G, Zhuang L, You MJ, Fang B, Li W, Metallo CM, Poyurovsky MV, Gan B (2020b) Cystine transporter regulation of pentose phosphate pathway dependency and disulfide stress exposes a targetable metabolic vulnerability in cancer. Nat Cell Biol 22:476-486.

Liu Y, Bell BA, Song Y, Kim HJ, Sterling JK, Kim BJ, Poli M, Guo M, Zhang K, Rao A, Sparrow JR, Su G, Dunaief JL (2021) Intraocular iron injection induces oxidative stress followed by elements of geographic atrophy and sympathetic ophthalmia. Aging Cell 20:e13490.

Lu S, Wang XZ, He C, Wang L, Liang SP, Wang CC, Li C, Luo TF, Feng CS, Wang ZC, Chi GF, Ge PF (2021) ATF3 contributes to brucine-triggered glioma cell ferroptosis via promotion of hydrogen peroxide and iron. Acta Pharmacol Sin 42:1690-1702.

Luo Y, Yan P, Li X, Hou J, Wang Y, Zhou S (2021) pH-sensitive polymeric vesicles for GOx/BSO delivery and synergetic starvation-ferroptosis therapy of tumor. Biomacromolecules 22:4383-4394.

Ma H, Wang X, Zhang W, Li H, Zhao W, Sun J, Yang M (2020) Melatonin suppresses ferroptosis induced by high glucose via activation of the Nrf2/HO-1 signaling pathway in type 2 diabetic osteoporosis. Oxid Med Cell Longev 2020:9067610.

Ma MW, Wang J, Dhandapani KM, Brann DW (2018) Deletion of NADPH oxidase 4 reduces severity of traumatic brain injury. Free Radic Biol Med 117:66-75.

Macdonald RL (2014) Delayed neurological deterioration after subarachnoid haemorrhage. Nat Rev Neurol 10:44-58.

Maeda T, Tanabe-Fujimura C, Fujita Y, Abe C, Nanakida Y, Zou K, Liu J, Liu S, Nakajima T, Komano H (2016) NAD(P)H quinone oxidoreductase 1 inhibits the proteasomal degradation of homocysteine-induced endoplasmic reticulum protein. Biochem Biophys Res Commun 473:1276-1280.

Magnani F, Mattevi A (2019) Structure and mechanisms of ROS generation by NADPH oxidases. Curr Opin Struct Biol 59:91-97.

Magtanong L, Ko PJ, Dixon SJ (2016) Emerging roles for lipids in non-apoptotic cell death. Cell Death Differ 23:1099-1109.

Magtanong L, Ko PJ, To M, Cao JY, Forcina GC, Tarangelo A, Ward CC, Cho K, Patti GJ, Nomura DK, Olzmann JA, Dixon SJ (2019) Exogenous monounsaturated fatty acids promote a ferroptosis-resistant cell state. Cell Chem Biol 26:420-432.e9.

Maiorino M, Chu FF, Ursini F, Davies KJ, Doroshow JH, Esworthy RS (1991) Phospholipid hydroperoxide glutathione peroxidase is the 18-kDa selenoprotein expressed in human tumor cell lines. J Biol Chem 266:7728-7732.

Maiorino M, Conrad M, Ursini F (2018) GPx4, lipid peroxidation, and cell death: discoveries, rediscoveries, and open issues. Antioxid Redox Signal 29:61-74.

Millán M, DeGregorio-Rocasolano N, Pérez de la Ossa N, Reverté S, Costa J, Giner P, Silva Y, Sobrino T, Rodríguez-Yáñez M, Nombela F, Campos F, Serena J, Vivancos J, Martí-Sistac O, Cortés J, Dávalos A, Gasull T (2021) Targeting pro-oxidant iron with deferoxamine as a treatment for ischemic stroke: safety and optimal dose selection in a randomized clinical trial. Antioxidants (Basel) 10:1270.

Moloney JN, Cotter TG (2018) ROS signalling in the biology of cancer. Semin Cell Dev Biol 80:50-64.

Munakata A, Ohkuma H, Nakano T, Shimamura N, Asano K, Naraoka M (2009) Effect of a free radical scavenger, edaravone, in the treatment of patients with aneurysmal subarachnoid hemorrhage. Neurosurgery 64:423-429.

Niu B, Lei X, Xu Q, Ju Y, Xu D, Mao L, Li J, Zheng Y, Sun N, Zhang X, Mao Y, Li X (2022) Protecting mitochondria via inhibiting VDAC1 oligomerization alleviates ferroptosis in acetaminophen-induced acute liver injury. Cell Biol Toxicol 38:505-530.

Ou Y, Wang SJ, Li D, Chu B, Gu W (2016) Activation of SAT1 engages polyamine metabolism with p53-mediated ferroptotic responses. Proc Natl Acad Sci U S A 113:E6806-6812.

Park MW, Cha HW, Kim J, Kim JH, Yang H, Yoon S, Boonpraman N, Yi SS, Yoo ID, Moon JS (2021) NOX4 promotes ferroptosis of astrocytes by oxidative stress-induced lipid peroxidation via the impairment of mitochondrial metabolism in Alzheimer's diseases. Redox Biol 41:101947.

Pratt DA, Tallman KA, Porter NA (2011) Free radical oxidation of polyunsaturated lipids: New mechanistic insights and the development of peroxyl radical clocks. Acc Chem Res 44:458-467.

Rabinstein AA (2017) Intracerebral haemorrhage: no good treatment but treatment helps. Lancet 389:575-576.

Rodríguez-Graciani KM, Chapa-Dubocq XR, Ayala-Arroyo EJ, Chaves-Negrón I, Jang S, Chorna N, S Maskrey T, Wipf P, Javadov S (2022) Effects of ferroptosis on the metabolome in cardiac cells: the role of glutaminolysis. Antioxidants (Basel) 11:278.

Roh JL, Kim EH, Jang H, Shin D (2017) Nrf2 inhibition reverses the resistance of cisplatin-resistant head and neck cancer cells to artesunate-induced ferroptosis. Redox Biol 11:254-262.

Salvador GA (2010) Iron in neuronal function and dysfunction. Biofactors 36:103-110.

Schatlo B, Fung C, Stienen MN, Fathi AR, Fandino J, Smoll NR, Zumofen D, Daniel RT, Burkhardt JK, Bervini D, Marbacher S, Reinert M, D Alonzo D, Ahlborn P, Mendes Pereira V, Roethlisberger M, Seule M, Kerkeni H, Remonda L, Weyerbrock A, et al. (2021) Incidence and outcome of aneurysmal subarachnoid hemorrhage: The Swiss study on subarachnoid hemorrhage (Swiss SOS). Stroke 52:344-347.

Scheuermann JC, de Ayala Alonso AG, Oktaba K, Ly-Hartig N, McGinty RK, Fraterman S, Wilm M, Muir TW, Müller J (2010) Histone H2A deubiquitinase activity of the Polycomb repressive complex PR-DUB. Nature 465:243-247.

She X, Lan B, Tian H, Tang B (2020) Cross talk between ferroptosis and cerebral ischemia. Front Neurosci 14:776.

Shen L, Lin D, Li X, Wu H, Lenahan C, Pan Y, Xu W, Chen Y, Shao A, Zhang J (2020) Ferroptosis in acute central nervous system injuries: the future direction. Front Cell Dev Biol 8:594.

Shi Y, Han L, Zhang X, Xie L, Pan P, Chen F (2022) Selenium alleviates cerebral ischemia/reperfusion injury by regulating oxidative stress, mitochondrial fusion and ferroptosis. Neurochem Res 47:2992-3002.

Shimada K, Skouta R, Kaplan A, Yang WS, Hayano M, Dixon SJ, Brown LM, Valenzuela CA, Wolpaw AJ, Stockwell BR (2016) Global survey of cell death mechanisms reveals metabolic regulation of ferroptosis. Nat Chem Biol 12:497-503.

Shin D, Kim EH, Lee J, Roh JL (2018) Nrf2 inhibition reverses resistance to GPX4 inhibitor-induced ferroptosis in head and neck cancer. Free Radic Biol Med 129:454-462.

Shu R, Zhang L, Zhang H, Li Y, Wang C, Su L, Zhao H, Wang G (2021) NMDA receptor modulates spinal iron accumulation via activating DMT1(-)IRE in remifentanil-induced hyperalgesia. J Pain 22:32-47.

Song X, Zhu S, Chen P, Hou W, Wen Q, Liu J, Xie Y, Liu J, Klionsky DJ, Kroemer G, Lotze MT, Zeh HJ, Kang R, Tang D (2018) AMPK-mediated BECN1 phosphorylation promotes ferroptosis by directly blocking system X(c)(-) activity. Curr Biol 28:2388-2399.e5.

Stockwell BR, Friedmann Angeli JP, Bayir H, Bush AI, Conrad M, Dixon SJ, Fulda S, Gascón S, Hatzios SK, Kagan VE, Noel K, Jiang X, Linkermann A, Murphy ME, Overholtzer M, Oyagi A, Pagnussat GC, Park J, Ran Q, Rosenfeld CS, et al. (2017) Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. Cell 171:273-285.

Stockwell BR, Jiang X, Gu W (2020) Emerging mechanisms and disease relevance of ferroptosis. Trends Cell Biol 30:478-490.

Su X, Xie Y, Zhang J, Li M, Zhang Q, Jin G, Liu F (2022) HIF-α activation by the prolyl hydroxylase inhibitor roxadustat suppresses chemoresistant glioblastoma growth by inducing ferroptosis. Cell Death Dis 13:861.

Su Y, Zhao D, Jin C, Li Z, Sun S, Xia S, Zhang Y, Zhang Z, Zhang F, Xu X, Shao J, Zhang B, Zheng S (2021) Dihydroartemisinin induces ferroptosis in HCC by promoting the formation of PEBP1/15-LO. Oxid Med Cell Longev 2021:3456725.

Sun J, Zhou C, Zhao Y, Zhang X, Chen W, Zhou Q, Hu B, Gao D, Raatz L, Wang Z, Nelson PJ, Jiang Y, Ren N, Bruns CJ, Zhou H (2021) Quiescin sulfhydryl oxidase 1 promotes sorafenib-induced ferroptosis in hepatocellular carcinoma by driving EGFR endosomal trafficking and inhibiting NRF2 activation. Redox Biol 41:101942.

Sun T, Chi JT (2021) Regulation of ferroptosis in cancer cells by YAP/TAZ and Hippo pathways: The therapeutic implications. Genes Dis 8:241-249.

Sun X, Ou Z, Chen R, Niu X, Chen D, Kang R, Tang D (2016) Activation of the p62-Keap1-NRF2 pathway protects against ferroptosis in hepatocellular carcinoma cells. Hepatology 63:173-184.

Suzuki S, Venkatesh D, Kanda H, Nakayama A, Hosokawa H, Lee E, Miki T, Stockwell BR, Yokote K, Tanaka T, Prives C (2022) GLS2 is a tumor suppressor and a regulator of ferroptosis in hepatocellular carcinoma. Cancer Res 82:3209-3222.

Takashi Y, Tomita K, Kuwahara Y, Roudkenar MH, Roushandeh AM, Igarashi K, Nagasawa T, Nishitani Y, Sato T (2020) Mitochondrial dysfunction promotes aquaporin expression that controls hydrogen peroxide permeability and ferroptosis. Free Radic Biol Med 161:60-70.

Tarangelo A, Magtanong L, Bieging-Rolett KT, Li Y, Ye J, Attardi LD, Dixon SJ (2018) p53 suppresses metabolic stress-induced ferroptosis in cancer cells. Cell Rep 22:569-575.

Toyokuni S, Yanatori I, Kong Y, Zheng H, Motooka Y, Jiang L (2020) Ferroptosis at the crossroads of infection, aging and cancer. Cancer Sci 111:2665-2671.

Tuo QZ, Lei P, Jackman KA, Li XL, Xiong H, Li XL, Liuyang ZY, Roisman L, Zhang ST, Ayton S, Wang Q, Crouch PJ, Ganio K, Wang XC, Pei L, Adlard PA, Lu YM, Cappai R, Wang JZ, Liu R, Bush AI (2017) Tau-mediated iron export prevents ferroptotic damage after ischemic stroke. Mol Psychiatry 22:1520-1530.

Tuo QZ, Masaldan S, Southon A, Mawal C, Ayton S, Bush AI, Lei P, Belaidi AA (2021) Characterization of selenium compounds for anti-ferroptotic activity in neuronal cells and after cerebral ischemia-reperfusion injury. Neurotherapeutics 18:2682-2691.

Uchida K (2017) HNE as an inducer of COX-2. Free Radic Biol Med 111:169-172.
Uemura T, Watanabe K, Ko K, Higashi K, Kogure N, Kitajima M, Takayama H, Takao K, Sugita Y, Sakamoto A, Terui Y, Toida T, Kashiwagi K, Igarashi K (2018) Protective effects of brain infarction by N-acetylcysteine derivatives. Stroke 49:1727-1733.
Ursini F, Maiorino M, Gregolin C (1985) The selenoenzyme phospholipid hydroperoxide glutathione peroxidase. Biochim Biophys Acta 839:62-70.
Ursini F, Maiorino M (2020) Lipid peroxidation and ferroptosis: The role of GSH and GPx4. Free Radic Biol Med 152:175-185.
Villalpando-Rodriguez GE, Blankstein AR, Konzelman C, Gibson SB (2019) Lysosomal destabilizing drug siramesine and the dual tyrosine kinase inhibitor lapatinib induce a synergistic ferroptosis through reduced heme oxygenase-1 (HO-1) levels. Oxid Med Cell Longev 2019:9561281.
Wan J, Ren H, Wang J (2019) Iron toxicity, lipid peroxidation and ferroptosis after intracerebral haemorrhage. Stroke Vasc Neurol 4:93-95.
Wang B, Zhang X, Zhong J, Wang S, Zhang C, Li M, Hu Q, Wang S, Chen L, Chen W, Ge H, Feng H (2022b) Dexpramipexole attenuates white matter injury to facilitate locomotion and motor coordination recovery via reducing ferroptosis after intracerebral hemorrhage. Oxid Med Cell Longev 2022:6160701.
Wang J (2010) Preclinical and clinical research on inflammation after intracerebral hemorrhage. Prog Neurobiol 92:463-477.
Wang L, Cai H, Hu Y, Liu F, Huang S, Zhou Y, Yu J, Xu J, Wu F (2018) A pharmacological probe identifies cystathionine β-synthase as a new negative regulator for ferroptosis. Cell Death Dis 9:1005.
Wang L, Liu C, Wang L, Tang B (2023b) Astragaloside IV mitigates cerebral ischaemia-reperfusion injury via inhibition of P62/Keap1/Nrf2 pathway-mediated ferroptosis. Eur J Pharmacol 944:175516.
Wang P, Ren Q, Shi M, Liu Y, Bai H, Chang YZ (2022c) Overexpression of mitochondrial ferritin enhances blood-brain barrier integrity following ischemic stroke in mice by maintaining iron homeostasis in endothelial cells. Antioxidants (Basel) 11:1257.
Wang SJ, Li D, Ou Y, Jiang L, Chen Y, Zhao Y, Gu W (2016) Acetylation is crucial for p53-mediated ferroptosis and tumor suppression. Cell Rep 17:366-373.
Wang XX, Wang F, Mao GH, Wu JC, Li M, Han R, She J, Zhang R, Sheng R, Chen Z, Qin ZH (2022a) NADPH is superior to NADH or edaravone in ameliorating metabolic disturbance and brain injury in ischemic stroke. Acta Pharmacol Sin 43:529-540.
Wang Y, Niu H, Li L, Han J, Liu Z, Chu M, Sha X, Zhao J (2023a) Anti-CHAC1 exosomes for nose-to-brain delivery of miR-760-3p in cerebral ischemia/reperfusion injury mice inhibiting neuron ferroptosis. J Nanobiotechnology 21:109.
Wang Y, Yang L, Zhang X, Cui W, Liu Y, Sun QR, He Q, Zhao S, Zhang GA, Wang Y, Chen S (2019) Epigenetic regulation of ferroptosis by H2B monoubiquitination and p53. EMBO Rep 20:e47563.
Wei H, Peng Z, Chen Y, Guo J, Chen L, Shao K (2022b) cPKCγ ameliorates ischemic injury in cultured neurons exposed to oxygen glucose deprivation/reoxygenation by inhibiting ferroptosis. Neurosci Res 181:95-104.
Wei S, Qiu T, Yao X, Wang N, Jiang L, Jia X, Tao Y, Wang Z, Pei P, Zhang J, Zhu Y, Yang G, Liu X, Liu S, Sun X (2020) Arsenic induces pancreatic dysfunction and ferroptosis via mitochondrial ROS-autophagy-lysosomal pathway. J Hazard Mater 384:121390.
Wei Z, Xie Y, Wei M, Zhao H, Ren K, Feng Q, Xu Y (2022a) New insights in ferroptosis: Potential therapeutic targets for the treatment of ischemic stroke. Front Pharmacol 13:1020918.
Wu H, Zhang Z, Hu X, Zhao R, Song Y, Ban X, Qi J, Wang J (2010) Dynamic changes of inflammatory markers in brain after hemorrhagic stroke in humans: a postmortem study. Brain Res 1342:111-117.
Wu H, Wu T, Li M, Wang J (2012) Efficacy of the lipid-soluble iron chelator 2,2'-dipyridyl against hemorrhagic brain injury. Neurobiol Dis 45:388-394.
Wu J, Minikes AM, Gao M, Bian H, Li Y, Stockwell BR, Chen ZN, Jiang X (2019) Intercellular interaction dictates cancer cell ferroptosis via NF2-YAP signalling. Nature 572:402-406.
Wu M, Xu LG, Li X, Zhai Z, Shu HB (2002) AMID, an apoptosis-inducing factor-homologous mitochondrion-associated protein, induces caspase-independent apoptosis. J Biol Chem 277:25617-25623.
Wu X, Li Y, Zhang S, Zhou X (2021) Ferroptosis as a novel therapeutic target for cardiovascular disease. Theranostics 11:3052-3059.
Wu X, Sheng H, Zhao L, Jiang M, Lou H, Miao Y, Cheng N, Zhang W, Ding D, Li W (2022) Co-loaded lapatinib/PAB by ferritin nanoparticles eliminated ECM-detached cluster cells via modulating EGFR in triple-negative breast cancer. Cell Death Dis 13:557.
Xiao X, Chen M, Zhang Y, Li L, Peng Y, Zhou W, Li J (2022) Hemin-incorporating DNA nanozyme enabling catalytic oxygenation and GSH depletion for enhanced photodynamic therapy and synergistic tumor ferroptosis. J Nanobiotechnology 20:410.
Xie J, Zhang T, Li P, Wang D, Liu T, Xu S (2022) Dihydromyricetin attenuates cerebral ischemia reperfusion injury by inhibiting SPHK1/mTOR signaling and targeting ferroptosis. Drug Des Devel Ther 16:3071-3085.
Xie Q, Gu Y, Hua Y, Liu W, Keep RF, Xi G (2014) Deferoxamine attenuates white matter injury in a piglet intracerebral hemorrhage model. Stroke 45:290-292.
Xie Y, Hou W, Song X, Yu Y, Huang J, Sun X, Kang R, Tang D (2016) Ferroptosis: process and function. Cell Death Differ 23:369-379.
Xie Y, Zhu S, Song X, Sun X, Fan Y, Liu J, Zhong M, Yuan H, Zhang L, Billiar TR, Lotze MT, Zeh HJ 3rd, Kang R, Kroemer G, Tang D (2017) The tumor suppressor p53 limits ferroptosis by blocking DPP4 activity. Cell Rep 20:1692-1704.
Xiong XY, Wang J, Qian ZM, Yang QW (2014) Iron and intracerebral hemorrhage: from mechanism to translation. Transl Stroke Res 5:429-441.
Xu J, Wang A, Meng X, Yalkun G, Xu A, Gao Z, Chen H, Ji Y, Xu J, Geng D, Zhu R, Liu B, Dong A, Mu H, Lu Z, Li S, Zheng H, Chen X, Wang Y, Zhao X, Wang Y (2021) Edaravone dexborneol versus edaravone alone for the treatment of acute ischemic stroke: a phase iii, randomized, double-blind, comparative trial. Stroke 52:772-780.
Xu P, Kong L, Tao C, Zhu Y, Cheng J, Li W, Shen N, Li R, Zhang C, Wang L, Zhang Y, Wang G, Liu X, Sun W, Hu W (2023b) Elabela-APJ axis attenuates cerebral ischemia/reperfusion injury by inhibiting neuronal ferroptosis. Free Radic Biol Med 196:171-186.
Xu S, Li X, Li Y, Li X, Lv E, Zhang X, Shi Y, Wang Y (2023a) Neuroprotective effect of Dl-3-n-butylphthalide against ischemia-reperfusion injury is mediated by ferroptosis regulation via the SLC7A11/GSH/GPX4 pathway and the attenuation of blood-brain barrier disruption. Front Aging Neurosci 15:1028178.
Xu Y, Liu Y, Li K, Yuan D, Yang S, Zhou L, Zhao Y, Miao S, Lv C, Zhao J (2022) COX-2/PGE2 pathway inhibits the ferroptosis induced by cerebral ischemia reperfusion. Mol Neurobiol 59:1619-1631.
Yan B, Ai Y, Sun Q, Ma Y, Cao Y, Wang J, Zhang Z, Wang X (2021) Membrane damage during ferroptosis is caused by oxidation of phospholipids catalyzed by the oxidoreductases POR and CYB5R1. Mol Cell 81:355-369.e10.
Yanatori I, Kishi F (2019) DMT1 and iron transport. Free Radic Biol Med 133:55-63.
Yang C, Han M, Li R, Zhou L, Zhang Y, Duan L, Su S, Li M, Wang Q, Chen T, Mo Y (2021b) Curcumin nanoparticles inhibiting ferroptosis for the enhanced treatment of intracerebral hemorrhage. Int J Nanomedicine 16:8049-8065.
Yang M, Chen P, Liu J, Zhu S, Kroemer G, Klionsky DJ, Lotze MT, Zeh HJ, Kang R, Tang D (2019b) Clockophagy is a novel selective autophagy process favoring ferroptosis. Sci Adv 5:eaaw2238.
Yang Q, Li K, Huang X, Zhao C, Mei Y, Li X, Jiao L, Yang H (2020b) lncRNA SLC7A11-AS1 promotes chemoresistance by blocking SCF(β-TRCP)-mediated degradation of NRF2 in pancreatic cancer. Mol Ther Nucleic Acids 19:974-985.
Yang S, Ouyang J, Lu Y, Harypursat V, Chen Y (2022a) A dual role of heme oxygenase-1 in tuberculosis. Front Immunol 13:842858.
Yang WH, Ding CC, Sun T, Rupprecht G, Lin CC, Hsu D, Chi JT (2019a) The Hippo pathway effector TAZ regulates ferroptosis in renal cell carcinoma. Cell Rep 28:2501-2508.e4.
Yang WH, Huang Z, Wu J, Ding CC, Murphy SK, Chi JT (2020a) A TAZ-ANGPTL4-NOX2 axis regulates ferroptotic cell death and chemoresistance in epithelial ovarian cancer. Mol Cancer Res 18:79-90.
Yang WH, Lin CC, Wu J, Chao PY, Chen K, Chen PH, Chi JT (2021a) The Hippo pathway effector YAP promotes ferroptosis via the E3 ligase SKP2. Mol Cancer Res 19:1005-1014.
Yang WS, SriRamaratnam R, Welsch ME, Shimada K, Skouta R, Viswanathan VS, Cheah JH, Clemons PA, Shamji AF, Clish CB, Brown LM, Girotti AW, Cornish VW, Schreiber SL, Stockwell BR (2014) Regulation of ferroptotic cancer cell death by GPX4. Cell 156:317-331.
Yang WS, Kim KJ, Gaschler MM, Patel M, Shchepinov MS, Stockwell BR (2016) Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis. Proc Natl Acad Sci U S A 113:E4966-4975.
Yang WS, Stockwell BR (2016) Ferroptosis: death by lipid peroxidation. Trends Cell Biol 26:165-176.
Yang WS, Stockwell BR (2008) Synthetic lethal screening identifies compounds activating iron-dependent, nonapoptotic cell death in oncogenic-RAS-harboring cancer cells. Chem Biol 15:234-245.
Yang Y, Ma Y, Yu S, Lin Z, Yan C, Wang Y, Yuan Q, Meng Z, Yan G, Wu Z, Tang H, Peng Z, Huang J, Zhuang G (2022b) TIPE2 knockout reduces myocardial cell damage by inhibiting IFN-γ-mediated ferroptosis. Biochim Biophys Acta Mol Basis Dis 166566.
Yang Y, Sun S, Xu W, Zhang Y, Yang R, Ma K, Zhang J, Xu J (2022c) Piperlongumine inhibits thioredoxin reductase 1 by targeting selenocysteine residues and sensitizes cancer cells to erastin. Antioxidants (Basel) 11:710.
Ye L, Jin F, Kumar SK, Dai Y (2021) The mechanisms and therapeutic targets of ferroptosis in cancer. Expert Opin Ther Targets 25:965-986.
You JH, Lee J, Roh JL (2021) Mitochondrial pyruvate carrier 1 regulates ferroptosis in drug-tolerant persister head and neck cancer cells via epithelial-mesenchymal transition. Cancer Lett 507:40-54.
Zeng T, Deng G, Zhong W, Gao Z, Ma S, Mo C, Li Y, Huang S, Zhou C, Lai Y, Xie S, Xie Z, Chen Y, He S, Lv Z, Gao L (2020) Indoleamine 2,3-dioxygenase 1enhanceshepatocytes ferroptosis in acute immune hepatitis associated with excess nitrative stress. Free Radic Biol Med 152:668-679.
Zhang H, Wen M, Chen J, Yao C, Lin X, Lin Z, Ru J, Zhuge Q, Yang S (2021) Pyridoxal isonicotinoyl hydrazone improves neurological recovery by attenuating ferroptosis and inflammation in cerebral hemorrhagic mice. Biomed Res Int 2021:9916328.
Zhang Q, Qu H, Chen Y, Luo X, Chen C, Xiao B, Ding X, Zhao P, Lu Y, Chen AF, Yu Y (2022) Atorvastatin induces mitochondria-dependent ferroptosis via the modulation of Nrf2-xCT/GPx4 axis. Front Cell Dev Biol 10:806081.
Zhang Q, Wu H, Zou M, Li L, Li Q, Sun C, Xia W, Cao Y, Wu L (2019a) Folic acid improves abnormal behavior via mitigation of oxidative stress, inflammation, and ferroptosis in the BTBR T+ tf/J mouse model of autism. J Nutr Biochem 71:98-109.
Zhang Y, Shi J, Liu X, Feng L, Gong Z, Koppula P, Sirohi K, Li X, Wei Y, Lee H, Zhuang L, Chen G, Xiao ZD, Hung MC, Chen J, Huang P, Li W, Gan B (2018a) BAP1 links metabolic regulation of ferroptosis to tumour suppression. Nat Cell Biol 20:1181-1192.
Zhang Y, Tan H, Daniels JD, Zandkarimi F, Liu H, Brown LM, Uchida K, O'Connor OA, Stockwell BR (2019b) Imidazole ketone erastin induces ferroptosis and slows tumor growth in a mouse lymphoma model. Cell Chem Biol 26:623-633.e9.
Zhang Y, Tan Y, Liu S, Yin H, Duan J, Fan L, Zhao X, Jiang B (2023) Implications of Withaferin A for the metastatic potential and drug resistance in hepatocellular carcinoma cells via Nrf2-mediated EMT and ferroptosis. Toxicol Mech Methods 33:47-55.
Zhang Z, Wu Y, Yuan S, Zhang P, Zhang J, Li H, Li X, Shen H, Wang Z, Chen G (2018b) Glutathione peroxidase 4 participates in secondary brain injury through mediating ferroptosis in a rat model of intracerebral hemorrhage. Brain Res 1701:112-125.
Zheng H, Guo X, Kang S, Li Z, Tian T, Li J, Wang F, Yu P, Chang S, Chang YZ (2023) Cdh5-mediated Fpn1 deletion exerts neuroprotective effects during the acute phase and inhibitory effects during the recovery phase of ischemic stroke. Cell Death Dis 14:161.
Zille M, Oses-Prieto JA, Savage SR, Karuppagounder SS, Chen Y, Kumar A, Morris JH, Scheidt KA, Burlingame AL, Ratan RR (2022) Hemin-induced death models hemorrhagic stroke and is a variant of classical neuronal ferroptosis. J Neurosci 42:2065-2079.

C-Editors: Wang J, Zhao M; S-Editor: Li CH; L-Editors: Li CH, Song LP; T-Editor: Jia Y