Ferroptosis: a critical player and potential therapeutic target in traumatic brain injury and spinal cord injury

Qing-Sheng Li1,2, Yan-Jie Jia1,*

https://doi.org/10.4103/1673-5374.350187

Date of submission: January 27, 2022
Date of decision: April 22, 2022
Date of acceptance: May 31, 2022
Date of web publication: August 2, 2022

From the Contents

Introduction .............................................. 506
Retrieval Strategy ....................................... 506
Mechanisms for Ferroptosis ......................... 506
Ferroptosis Plays a Crucial Role following Central Nervous System Trauma ......................... 508
Treatments for Ferroptosis following Central Nervous System Trauma ............................... 509
Conclusion ................................................ 510

Introduction

Traumatic brain injury (TBI) and spinal cord injury (SCI) are the primary causes of traumatic injuries to the central nervous system (CNS). From 1990 to 2016, the total global incidence of TBI and SCI increased significantly because of increased falls and road-related injuries (GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators, 2019). Moreover, the increased incidence of TBI and SCI seems to continue over time, given the growing and aging population. Unfortunately, SCI is currently incurable. Patients with TBI and SCI require a prolonged and high level of specialized nursing. Treatments only maximize residual functional abilities by rehabilitating and minimizing secondary complications (Ahuja et al., 2017; Ismael et al., 2021). Similarly, despite promising laboratory results, many multicenter, clinical, randomized controlled trials of medical and surgical interventions for TBI did not have beneficial effects (Maas et al., 2017). Therefore, the long-term burdens of CNS trauma for patients, caregivers, healthcare systems, and the economy are a considerable part of the global diseases burden (Badiwala et al., 2019).

The primary SCI and the direct physical injury to neurons and axons results in a secondary injury cascade characterized by edema and inflammation that contributes to progressive neuronal and glial cell death that spreads beyond the initial impact site. Cystic cavities form a chronic, physical, and chemical barrier surrounding the glial/fibrotic scar and remodel the lesion, to potently stabilize the spread of inflammation and lesion volume, but inhibit axonal regeneration (Tran et al., 2018). The secondary injury also plays a marked role in TBI. For example, neuroinflammation and swelling can cause an increase in intracranial pressure, which blocks blood flow or damages brain tissues. The procedures for secondary injury include glutamate excitotoxicity, calcium overload, mitochondrial dysfunction, and free radical-induced oxidative damage. These are closely related to chronic traumatic encephalopathy (CTE) (Simon et al., 2017) and ferroptosis (Gleitze et al., 2021; Li et al., 2021; Zhang et al., 2021c).

Programmed cell death (PCD) includes apoptosis, necroptosis, autophagy, ferroptosis, pyroptosis, and paraptosis and is known to play a crucial role in eliminating unnecessary and damaged cells in the progress of neurogenesis and neurodegeneration after CNS trauma (Green, 2019; Zhu et al., 2021b). Ferroptosis, a unique iron-dependent form of non-apoptotic PCD, was discovered and named by Dixon et al. (2012). It genetically, biochemically, and morphologically differs from other PCDs. Recent evidence has suggested that ferroptosis is crucial for secondary injuries following both SCI and TBI, but currently, there are few studies. Researching the mechanisms of ferroptosis can enhance understanding of the pathophysiological mechanisms of SCI and TBI and help guide strategies to improve neuron regeneration and recovery of function at acute and chronic phases. This review describes the most recent understanding of ferroptosis and its crucial role following SCI and TBI. Last, we list the latest inhibitors of ferroptosis used in CNS traumatic injuries.

Mechanisms for Ferroptosis

Phospholipid peroxidation

Unrestrained accumulation of phospholipid hydroperoxides (PLOOHs) is currently the most downstream step of ferroptosis. It may damage membrane integrity, other macromolecules, and cellular structures and cause inflammation or immune response (Jiang et al., 2021). Plasma membrane damage in ferroptosis is related to the formation of membrane nanoscale. During this process, an accumulation of cellular Ca2+ induces activation of the endosomal sorting complexes required for transport-III-dependent membrane repair machinery (Pedrera et al., 2021). Therefore, Ca2+ fluxes before plasma membrane rupture may be a general feature of PCD, and local endosomal sorting complexes are likely required for transport-III activation as a universal protective mechanism.

Doll et al. (2017) found acyl-coenzyme A (CoA) synthetase long-chain family member 4 (ACSL4) as an essential propellant of ferroptosis. ACSL4 preferentially acylates long-chain polyunsaturated fatty acids (PUFAs), and lysophosphatidylcholine acyltransferase 3 catalyzes acylated long-chain PUFAs inserted into cellular membrane phospholipids (PL). Inhibition of ACSL4 enables cells’ resistance to ferroptosis. This effect may result from a conversion from easily oxidized PUFA to monounsaturated fatty acid (MUFFA) in membrane PL (Doll et al., 2017). Therefore, exogenous MUFAs can potentially inhibit ferroptosis, and this reaction requires acyl-CoA synthetase long-chain

1Department of Neurology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province, China; 2Academy of Medical Sciences, Zhengzhou University, Zhengzhou, Henan Province, China
*Correspondence to: Yan-Jie Jia, MD, PhD, jiayanjie1971@zzu.edu.cn.
https://orcid.org/0000-0002-2220-9257 (Yan-Jie Jia)

Funding: The work was supported by the National Natural Science Foundation of China, No. U1604170 (to YJJ).

How to cite this article: 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(3): 506-512.
family member 3 acylating MUFA's (Magenta et al., 2019). Lipoleases with conjugated double bonds insert into cellular lipids via acyl-CoA synthetase long-chain family member 1 and induce ferroptosis in diverse cancer cell types (Beatty, 2021).

PL contains PUFAs inserted on cellular membranes—the primary targets for iron-catalyzed lipid peroxidation. This process includes lipid peroxidation, iron-dependent generation of reactive oxygen species (ROS), and oxidative stress pathways in the absence of iron overload, and dietary antioxidant therapy and iron restriction can prevent this process. Therefore, polyC binding protein 1 is crucial for preventing cellular iron toxicity (Protkenko et al., 2021).

Ferritin and ferritinophagy are key regulators of cellular iron metabolism. Ferritinophagy is regulated by the iron regulatory protein (IRP) 1 and 2, which bind to iron response elements (IREs) in the 5′-untranslated region of ferritin mRNA. The IRPs play a crucial role in maintaining iron homeostasis by regulating ferritin expression and degradation.

Lipoxigenases (LOXs) are the central players in cell death induced by the knockdown of glutathione (GSH) peroxidase type 4 (GPX4) (Seiler et al., 2018). However, Friedemann Angeli et al. (2014) proved that the knockdown of arachidonate 5-lipoxygenase (ALOX) 5 and ALOX15—two crucial LOXs—did not impact cell death and Pratt, 2019). SecohLXs and P450 oxidoreductase require iron for catalyzing lipid oxidation (Yosca et al., 2013; Dufrusine et al., 2019). In acidic cancer cells, omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) undergo lipid peroxidation, leading to the formation of reactive oxygen species (ROS) (Dixon and Stockwell, 2014). The transferrin receptor (TFR) regulates cellular iron uptake through endocytosis of iron-loaded transferrin. The lipogenesis regulator steryl regulatory element-binding transcription factor 2 (SREB2) directly mediates the expression of the lipogenic enzyme ACAT, increasing the synthesis of triglycerides and cholesterol.

The transferin receptor (TFR) regulates cellular iron uptake through endocytosis of iron-loaded transferrin. The lipogenesis regulator steryl regulatory element-binding transcription factor 2 (SREB2) directly mediates the expression of the lipogenic enzyme ACAT, increasing the synthesis of triglycerides and cholesterol. In the membrane, FSP1 suppresses ferroptosis by either reducing ubiquinone concentration or as a synergist of this inhibitor in high GPX4 expression. FSP1 is used to synthesize dehydrogenase (DHODH) to ferroptosis. DHODH is a flavin-dependent enzyme containing iron, which plays an essential role in the de novo synthesis of pyrimidines. It alleviates lipid peroxides accumulated via redox cycle, which suppresses ferroptosis of cancer cells. In non-small cell lung cancer cells, deprivation of cyst(e)ine prevents this process. Therefore, poly(rC) binding protein 1 is crucial for preventing cellular iron toxicity (Protkenko et al., 2021).

Figure 1

Iron metabolism
Ferroptosis is dependent on intracellular iron. First, iron is the necessary reactant of the non-enzymatic Fenton chain reaction, critical for lipid peroxidation. Peroxidation in the cell death results in autophagy activation and degradation of ferritin and ferritinophagy cargo receptor nuclear receptor coactivator 4 (NCOA4). Inhibiting ferritinophagy by blocking autophagy or NCOA4 can inhibit iron overload, lipid oxidation, and eventual ferroptosis (Ajoalbabyd et al., 2021). Fang et al. (2021) identified a new ferroptosis inhibitor 9a, which targets NCOA4 and reduces the intracellular ferrous iron by breaking the NCOA4-ferritin H (Fth) interaction. It can ameliorate ischemia/reperfusion injury in a rat model (Fang et al., 2021). Zhang et al. (2021b) found that coatomer complex subunit delta 2 knockout makes mice more sensitive to fenton death. In imaging, the mycoyte enhancer factor 2C promotes the expression of NF2 and E-cadherin, and silencing mycoyten factor 2C can enhance ferroptosis which can be limited by forcing expression of the myocyte enhancer factor 2C (Bao et al., 2021a). G-linked β-(N-acetylglucosaminyl) enhances and stabilizes the expression of YAP, which is capable of promoting HCC cells to ferroptosis (Zhu et al., 2021a). This modification is dependent on the hexosamine biosynthesis pathway, for which glutamine-fructose-6-phosphate transaminase is the rate-limiting enzyme. Thus, in lung adenocarcinoma
Figure 1 | Mechanism of ferroptosis. Ferroptosis is executed by iron-dependent phospholipid peroxidation. It needs processes including iron metabolism, lipogenesis, and finally lipid peroxidation. Iron metabolism relies on the transport, translation, and storage of metal iron. Iron transport into cells is through transferrin receptor (TFR), which can promote ferroptosis, and transport out of cells is via ferroportin (FPN) and transferrin (TF), inhibiting ferroptosis. Ferritin stores Fe\(^{3+}\), and its autophagy can release Fe\(^{2+}\) and aggravate ferroptosis. Lipogenesis mainly involves producing phospholipids containing polyunsaturated fatty acids (PLA\(_2\)) mediated by acetyl-coenzyme A (CoA) synthetase long-chain family member 4 (ACSL4). Multiple other enzymes are required for phospholipid (PL) peroxidation and ferroptosis. Phospholipid peroxidation can be initiated by physical and chemical reagents, enzymes including lipoxygenases (LOXs), cytochrome P450 oxidoreductase (POR), and reactive oxygen species (ROS). Once the initial phospholipid hyperoxides (PLOOHs) are produced and not cleared by suppressors, activating propagation reacts with cellular labile iron to accumulate PLOOH. YAP is the crucial modulator in catalyzing ferroptosis. It is regulated by E-cadherin–merlin (NE2)–Hippo–yes associated proteins (YAP) pathway and promotes iron accumulation, PUFAPL synthesis, and phospholipid peroxidation for ferroptosis via increasing the expression of TFR, LOX, ACSL4, and others. ACSL3: Acyl-CoA Synthetase Long-Chain Family Member 3; ADH: alcohol dehydrogenase; COX2: cyclooxygenase 2; COX1: cyclooxygenase 1; ALDH: aldehyde dehydrogenase; SLC7A11: solute carrier family 7 member 11; USP11: ubiquitin-specific-processing protease 11; PL: phospholipid radical; PLO•: phospholipid alkoxyl; PLOO•: phospholipid peroxyl radical; SREBP2: sterol regulatory element-binding transcription factor 2; USP35: ubiquitin-specific protease 35.

Figure 2 | Suppressors of ferroptosis. Glutathione peroxidase type 4 (GPX4), the canonical and most studied ferroptosis-controlling suppressor, entails reducing with glutathione (GSH) generating oxidized glutathione (GSSG), which can be recycled via glutathione-disulphide reductase (GSR) electrons from nicotinamide adenine dinucleotide phosphate (NADPH). Ferroptosis suppressor protein 1 (FSP1) and dihydrooarote dehydrogenase (DHDH) can prevent lipid peroxidation by reducing ubiquinone (CoQ) to ubiquinol (CoQH\(_2\)). Response for FSP1 needs electrons from NADPH and is found in the membranes of cells, Golgi complex, the nucleus. DHDH is found in the inner membrane of the mitochondria, which entails reduced flavin mononucleotide (FMNH\(_2\)) to contribute electrons. Nuclear factor erythroid 2-related factor 2 (NRF2) is the core regulator of antioxidation and restrains ferroptosis. It can inhibit ferroptosis by increasing iron storage and transfer via ferritin, ferroportin (FPN), and others; GSH synthesis by increasing the expression of glutamate-cysteine ligase catalytic subunit (GCLC), GPX4, and others; and inhibiting lipid oxidation. 4E8P: Eukaryotic translation initiation factor 4E binding protein 1; A: ARE, antioxidant response element; AMPK: AMP-activated protein kinase; CAMKK2: calcium/calmodulin-dependent protein kinase 2; EGFR: epidermal growth factor receptor; FMN: Flavin mononucleotide; Glu: glutamate; GSS: glutathione synthase; GSTZ1: glutathione S-transferase zeta 1; LOX: lipoxygenase; MGGT1: microsomal glutathione-S-transferase 1; mTOR: mechanistic target of rapamycin 1; JNK: c-Jun N-terminal kinase; JUN: Jun N-terminal kinase; OGL: O-linked β-N-acetylglucosamine transferase; NFE2L2: NFE2-like 2; ORF15: open reading frame 15; ORF44: open reading frame 44; PPIA: peptidylprolyl isomerase A; PON1: paraoxonase 1; PON2: paraoxonase 2; PON3: paraoxonase 3; PPARα: peroxisome proliferator-activated receptor alpha; PKC: protein kinase C; PKCε: protein kinase C epsilon; PKCθ: protein kinase C theta; PI3K: phosphatidylinositol 3-kinase; PIK3R1: phosphatidylinositol 3-kinase regulatory subunit 1; PIK3R2: phosphatidylinositol 3-kinase regulatory subunit 2; STAT3: signal transducer and activator of transcription 3; TSG101: tumor protein 53KDa; USP35: ubiquitin-specific-processing protease 35; WNK1: with no lysine (K)-protein kinase 1; WNK4: with no lysine (K)-protein kinase 4; γGC: γ-glutamyl-cysteine; γGP: γ-glutamyl-peptides. 4E8P: Eukaryotic translation initiation factor 4E binding protein 1; A: ARE, antioxidant response element; AMPK: AMP-activated protein kinase; CAMKK2: calcium/calmodulin-dependent protein kinase 2; EGFR: epidermal growth factor receptor; FMN: Flavin mononucleotide; Glu: glutamate; GSS: glutathione synthase; GSTZ1: glutathione S-transferase zeta 1; LOX: lipoxygenase; MGGT1: microsomal glutathione-S-transferase 1; mTOR: mechanistic target of rapamycin 1; JNK: c-Jun N-terminal kinase; JUN: Jun N-terminal kinase; OGL: O-linked β-N-acetylglucosamine transferase; NFE2L2: NFE2-like 2; ORF15: open reading frame 15; ORF44: open reading frame 44; PPIA: peptidylprolyl isomerase A; PON1: paraoxonase 1; PON2: paraoxonase 2; PON3: paraoxonase 3; PPARα: peroxisome proliferator-activated receptor alpha; PKC: protein kinase C; PKCε: protein kinase C epsilon; PKCθ: protein kinase C theta; PI3K: phosphatidylinositol 3-kinase; PIK3R1: phosphatidylinositol 3-kinase regulatory subunit 1; PIK3R2: phosphatidylinositol 3-kinase regulatory subunit 2; STAT3: signal transducer and activator of transcription 3; TSG101: tumor protein 53KDa; USP35: ubiquitin-specific-processing protease 35; WNK1: with no lysine (K)-protein kinase 1; WNK4: with no lysine (K)-protein kinase 4; γGC: γ-glutamyl-cysteine; γGP: γ-glutamyl-peptides.
Ferroptosis-related changes and symptoms after SCI and TBI. The inhibition of AOX15 protects the brain against ferroptosis (Kenny et al., 2019). AOXSL4 promotes neuronal ferroptosis via mediating lipid peroxidation. In acute cerebral infarction, the expression of AOXSL4 is suppressed via hypoxia-inducible factor 1α subunit signaling. Knockdown of AOXSL4 can inhibit miR21 activation and, afterward, proinflammatory cytokine production (Cui et al., 2021). The p53 protein is a critical regulator of ferroptosis. Sirtuin 2 is an NAD-dependent deacetylase that could mitigate TBI by regulating ferroptosis via p53. Inhibition of sirtuin 2 increases the expression and acetylation of p53, aggravating ferroptosis following TBI, which was significantly blocked by the knockdown of p53 (Gao et al., 2021; Figure 3).

Immune polarization in the CNS post-TBI. After SCI and TBI, multiple changes associated with ferroptosis appear, including iron homeostasis dysfunction, GSH synthesis disruption, and increased phospholipid oxidation. Inflammation plays a critical role in this phase. Microglia and macrophages are recruited into the M1 state under the condition of lipid peroxidation and iron accumulation. Inflammation results in ferroptosis in local lesions and damages distant brain tissue after SCI. Similar changes occur following brain injuries. These include acute and chronic iron homeostasis dysfunction, lipid oxidation, inflammation, and tau and amyloid β (Ab) proteins deposition. These changes are associated with acute and chronic symptoms, such as central pain (CP) and chronic traumatic encephalopathy (CTE). AOXSL4: Acyl-coenzyme A synthetase long-chain family member 4; BBB: blood-brain barrier; FlowJo®: Flow cytometry software; FPN: ferroportin; GPX4: glutathione peroxidase type 4; GSH: glutathione; HIF-1α: hypoxia-inducible factor 1α; IRE: iron-responsive-element binding protein; LOX: lipoxygenases; NF-κB: nuclear factor-κB; NOX2: nicotinamide adenine dinucleotide phosphate oxidase 2; P2X: phospholipids; Prkx: prokinetin-2; PTGS: prostaglandin-endoperoxide synthase; SCI: spinal cord injury; SLCA7A1: solute carrier family 7 member 1; sirt2: sirtuin 2; TFR1: transferrin receptor; TNR: tumor necrosis factor.

Immunization related to ferroptosis following CNS trauma. Neuronal and microglial ferroptosis is associated with chronic inflammation, neurodegeneration, and cognitive deficits. For example, increased brain iron accumulation following TBI, which was significantly blocked by the knockdown of p53 (Gao et al., 2021), and the upregulation of CD44 in microglia/macrophages, which can drive the switch from M2 to M1 polarization, is associated with the increase of NOX2 post-TBI reduced ROS in myeloid cells. Genetic knockout or inhibition of NOX2 suppressed the proinflammatory M1 microglia/macrophages while increasing the anti-inflammatory M2 subtype in the lesion. These alterations are linked to down-regulation of the nuclear factor-κB pathway in microglia/macrophages, which can decrease proinflammatory cytokines after TBI (Wang et al., 2017). Following blast-induced TBI, expression of NOX2 subtypes are differently increased in various regions: It can increase NOX1 in the hippocampus and thalamus, and NOX2 in the frontal cortex. In neurons, the increase of NOX1 and NOX2 levels is higher than those in astrocytes and microglia, which indicates that neurons are more sensitive to oxidative damage than glial cells (Rama Rao et al., 2018; Figure 3).

The symptoms associated with ferroptosis. Increased iron levels occur in some brain areas after SCI through the nitric oxide synthase-iron regulatory protein 1 pathway. This intracranial iron change can activate central pain (Meng et al., 2017). Peripheral injury can generate iron-mediated metabolic disorders of the spinal cord and adolodina. Spinal cord injury-relevant depressive behavior and posttraumatic memory deficits (Lopez-Caperuchipi et al., 2021). Iron and lipid accumulation and chronic iron homeostasis dysfunction, lipid oxidation, inflammation, and tau and amyloid β (Ab) proteins deposition. These changes are associated with acute and chronic symptoms, such as central pain (CP) and chronic traumatic encephalopathy (CTE). Iron accumulation modulated by spinal cord N-methyl-D-aspartate modulating IRE-DMT1 plays an essential role in central pain. Acute post-TBI headache is associated with iron accumulation in multiple brain regions, proven by magnetic resonance transverse relaxation rates (T2*) (Nikolova et al., 2022; Figure 3).

CET. Tau and amyloid precursor protein are related to cellular iron retention in the brain associated with ferroptosis. Tau-mediated elimination of iron overload following ischemic stroke may prevent ferroptosis in adult mice (Tuo et al., 2017). Amyloid precursor protein can lower neuronal iron and confer neuroprotection in TBI (Aytong et al., 2014). Functional failures of these two proteins contribute to age-related, iron-modulated neurotoxicity and iron accumulation in TBI tissue. This functional deficiency may exaggerate secondary injuries after TBI. Iron accumulation and chronic iron homeostasis dysfunction supposedly play a central role in mild TBI pathophysiology and its related long-term cognitive dysfunction. The prolonged cognitive impairment seems to be mediated via three pathways: iron accumulation mediates tau phosphorylation, forming neurofibrillary tangles; neuronal death; and iron accumulation in damage of neural networks via axonal damage caused by the iron sensitivity of oligodendrocytes (Huang et al., 2021b). In a study on the relationship between neocrosis and CET, chronic brain damage could be detected almost exclusively in iron-accumulated areas and was significantly reduced in mice deleted receptor-interacting protein kinase 1 or 3 (Wehn et al., 2021).

Additionally, recent research on a large postmortem cohort proved that iron, via activating ferroptosis, may play an additional downstream role in neurodegeneration, acting independently of tau or amyloid (Aytong et al., 2014). Magnetic resonance imaging has demonstrated that regional brain iron quantification is associated with neurophysiological test scores in mild TBI: iron overload in deep gray matter—like the globus pallidus, thalamus, and hippocampus—may contribute to the pathology of TBI, eventually leading to neurological decline and cognitive impairments (Raz et al., 2011; Lu et al., 2012). Consistent with the above notion following TBI, iron-related proteins may contribute to long-term cellular iron pool overload, leading to ferroptosis. Glasgow coma scale scores at clinical admission and fatal outcomes after severe TBI correlate with increased serum ferritin levels (Simon et al., 2015). Iron overload may be a major contributor to the long-term cognitive impairment following TBI. Iron overload following TBI, iron-related proteins may contribute to long-term cellular iron pool overload, leading to ferroptosis. Functional failures of these two proteins contribute to age-related, iron-modulated neurotoxicity and iron accumulation in TBI tissue. This functional deficiency may exaggerate secondary injuries after TBI. Iron accumulation and chronic iron homeostasis dysfunction supposedly play a central role in mild TBI pathophysiology and its related long-term cognitive dysfunction. The prolonged cognitive impairment seems to be mediated via three pathways: iron accumulation mediates tau phosphorylation, forming neurofibrillary tangles; neuronal death; and iron accumulation in damage of neural networks via axonal damage caused by the iron sensitivity of oligodendrocytes (Huang et al., 2021b). In a study on the relationship between neocrosis and CET, chronic brain damage could be detected almost exclusively in iron-accumulated areas and was significantly reduced in mice deleted receptor-interacting protein kinase 1 or 3 (Wehn et al., 2021).

Treatments for Ferroptosis following Central Nervous System Trauma. Recent reviews have listed some medicines for inhibiting ferroptosis after...
CNS traumatic injuries (Shen et al., 2020; Hu et al., 2021). In this section, we update some new studies on ferroptosis suppression and the prevention used as medicines (Additional Table 1).

Spinal cord injuries

Deferoxamine, an iron chelator, can increase the expression of GPX4, system Xc-, and GSH, inhibit glrosis, and eventually recover the long-term motor function (Huang et al., 2021). Furthermore, it can reduce motor cortex iron overload and neuronal ferroptosis following SCI and contribute to motor function recovery (Feng et al., 2021). SRS 16–86, a novel ferroptosis inhibitor with high stability in the plasma and liver, was shown to elevate GPX4, GSH, and protect against lipid peroxidation, and neuronal death in an SCI model (Zhang et al., 2019). Pancreatin, a potent free radical scavenger commonly found in grape seeds, can decrease the levels of iron and thiobarbituric acid-reactive substances and diminish the expression of ALOX5. Allopurinol, a xanthine oxidase inhibitor and blocker of endogenous lipid peroxidation (ho-1), NRF2, GSH, and GPX4; consequently, it can rescue functionality after SCI (Zhou et al., 2020).

In one study, Fer-1, an inhibitor for ferroptosis, decreased iron ROS deposition and downregulated the ferroptotic genes, iREB2 and PTGS2, to inhibit ferroptosis in oligodendrocytes, finally alleviating white matter injury and improving functional recovery in an SCI rat model. In addition, Fer-1 could inhibit the activation of reactive astrocytes and microglia (Ge et al., 2021). It was found that Zinc gluconate can increase GSH, superoxide dismutase, and GPX4 and decrease ROS, malondialdehyde, and lipid peroxides via increasing NRF2/HO-1 signaling pathway expression and attenuating ferroptosis in spinal cord contusion. Zinc gluconate also cured injured mitochondria and inflammation, although the NRF2 inhibitor Brusatol could reverse the effects of Fer-1 (Li et al., 2021). Eventually, zinc gluconate may promote behavioral and structural recovery after SCI. Lipoxin A4, an anti-inflammatory mediator, can induce neuroprotective and function improvements after SCI by regulating the PI3K/Akt signaling (Lu et al., 2018). Subsequently, in primary spinal cord neurons via the same signaling pathway, lipoxin A4 can also inhibit erastin-induced ferroptosis (Wei et al., 2021).

TBI

In one study, Fer-1-decreased intracellular iron accumulation and the number of degenerating neurons diminished the volume of damaged lesions and ameliorated prolonged motor and cognitive prognosis after TBI in mice (Xie et al., 2018). Liproxstatin-1 (Lip-1), as a positive control of melatonin in a study by Rui et al. (2021), prevented the expression and transcription of ferroptosis-related proteins, including system Xc-, Fth, Tfr1, Fpn, ferritin L, Fth, and 4-hydroxy-2-nonalen following TBI. Both Lip-1 and melanotin prevented TBI-induced neuroglialis, decreased pyknotic and necrotic neurons and neurons' ferroptosis product and iron deposition. Lip-1 and melanotin treatment attenuated neuronal death and ameliorated the motor performance (Rui et al., 2021).

In oligodendrocytes, Lip-1 was shown to inhibit lipid peroxidation and restore the levels of FSP1, GPX4, and GSH, thereby ameliorating ferroptosis induced by inhibition of GPX4 which could alleviate spinal cord and brain demyelination (Fan et al., 2021).

Melatonin (N-acyethyl-5-methoxytryptamine), a hormone secreted by the pineal gland and other organs, can improve TBI-induced damages and alleviate functional deficits. As mentioned above, obtaining similar effects with Lip-1, Fth-knockout mice were found to be more sensitive to ferroptosis following trauma, and the neuroprotection by melatonin was essentially canceled in Fth-knockout mice, which demonstrated neuroprotection of melanotin partly via regulating the expression of ferroptosis-related proteins and iron deposition. Lip-1 and melanotin treatment attenuated neuronal death after TBI partly by targeting PTGS2 (Xie et al., 2018). Based on RNA sequencing, Wu et al. (2022) identified the expression of different circular RNAs after melanotin treatment for TBI and found that melanotin could exert anti-endoplasmic reticulum stress and anti-ferroptosis effect in vitro. It was shown that the microRNA let-7c, an essential component of black mamilla venum and frog skin, and a member of the prokineticin family, has been shown to upregulate F-box protein 10 expression and promote ACSL4 ubiquitination and degradation. Intracerebral injection of Adenovirus-associated virus-protinin-2 increased Gpx4 expression, decreased the level of ACSL4 and the lesion volume, and then improved motor ability-learning performance following TBI. This prokineticin-2-driven cascade elevates ferroptosis and protects mice from injury following trauma. A positive effect on TBI-injured mice (Bao et al., 2021c) Polyclatin, a compound extracted from Polygonum, exhibited potent neuroprotective effects in TBI via protecting against ferroptosis. It can reverse TBI-induced iron deposition, lipid peroxidation, and expression of genes correlating with neurodegeneration, brain edema, motor dysfunction, memory deficits, and anxiety behavior post-TBI (Chen et al., 2021).

Certain other drugs may also protect against neuronal death via inhibiting ferroptosis following TBI, but the evidence is insufficient. Tannic acid can reverse lipid peroxidation, decrease GSH level, activities of antioxidant enzymes and the expression of 4-hydroxy-2-nonalen, and neurodegeneration after SCI. Ferrostatin-1 (Fer-1) can effectively ameliorate the behavioral alterations, oxidative damage, mitochondrial impairment, and inflammation, which may be attributed to activation of the peroxisome proliferator-activated receptor gamma coactivator 1-q/NRF2/HO-1 signaling pathway (Salman et al., 2009). There is no evidence that it inhibits iron accumulation, but the above text has mentioned that NRF2 pathway could impact iron homeostasis and ferroptosis. Allopurinol, a xanthine oxidase inhibitor, can protect against ferroptosis via increasing GSH and GPR17. They are effective against erastin- and Ras-selective lethal small molecule 3-induced ferroptosis in vitro. In the cerebral ischemia-reperfusion injury mouse model, pretreatment with methyl selenocysteine or selenoproteins prevented the injury caused by ischemia-reperfusion (Rui et al., 2021). N,N-di(2-hydroxy benzyl) ethylenediamine-N,N’-diacetate acid monohydrichloride, a unique iron chelator with the ability to penetrate the intact blood-brain barrier, has a higher affinity to iron and a longer half-life than most common chelators. It can significantly reduce TBI-induced cortical iron injury volume, hippocampal swelling, and total hemispheric volume (Khalaf et al., 2018).

Conclusion

Ferroptosis plays a crucial role in secondary injuries after CNS traumatic injuries, including free iron overload, lipid peroxidation, and ferroptosis-related protein overexpression. These injuries can induce subsequent activation of neuroglia, immunoreaction, and inflammation, which need inhibition of treatment of ferroptosis. Researchers and clinicians have demonstrated the importance of iron deposition, lipid accumulation, oxidation, and their related systematic changes for a period. Ferroptosis is a crucial point that connects all such secondary injuries. The new strategies for CNS treatment can reduce ferroptosis and induce cascade reactions, thus finally reaching neuron reconnection and functional reestablishment. Furthermore, many other related drugs may be used for inhibited ferroptosis, influencing iron metabolism and lipid oxidation, thereby providing the potential to find new clinical indications for central nervous system, from neurogenesis to degeneration and from acute injury to chronic prognosis. A limitation of this review is that it did not include clinical studies. Currently, there are few clinical studies that have investigated ferroptosis. To our knowledge, the only clinical studies in this field primarily focused on biomarker identification. However, inhibition of ferroptosis has shown significant potency in protecting neurotraumatic injury in basic experiments. Further study of ferroptosis in nerve trauma will provide new avenues to clinical treatment in the future.

Author contributions: Review conception: YJJ; literature collection and manuscript draft: QLS. Both authors contributed to manuscript revision, read, and approved the final version of the manuscript for publication.

Conflict of interest: The authors declare that there is no potential conflict of interest.

Availability of data and materials: All data generated or analyzed during this study are included in this published article and its supplementary information files.

Open access statement: This is an open access journal, and articles are distributed under the terms of the Creative Commons AttributionNonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Open peer reviewers: Sagar Gaikwad, The University of Texas, Brain Branch at UT Southwestern, USA; Yuri Matteo Falzone, San Raffaele Scientific Institute, Italy.

Additional files: Additional Table 1: Effects of ferroptosis inhibitors on central nervous system injuries.

Additional references: Additional Table 1: open peer review report 1.

References

Arhupu CS, Wilson JR, Nori S, Kotter MRN, Druschel C, Curt A, Fehlings MG (2017) Traumatic spinal cord injury. Nat Rev Dis Primers 3:17018.

Apolabady A, Alikhadapashandokhmal B, Libby F, Tuomilehto J, Lip GYH, Penninger J, Libby P, Richardsson D, Tang D, Zhou H, Wang S, Klonowska DK, Kroemer G, Renaud D (2019) Ferroptophagy and ferroptosis in the management of metabolic diseases. Trends Endocrinol Metab 32:442-462.

Alim I, Caulfield JT, Chen Y, Sarwar P, Geschwind DH, Ivanova E, Seravalli J, I, A, Sainsing 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.
Review

Antonnyzhutsu TS, Tsurina YY, Sun WX, Mikulska-Ruminska K, Shrivastava HT, Tsurina VA, Cinembe FB, Dar HH, VanDenmark AP, Holman TR, Sadowsky Y, Stockwell BR, He RR, Bahar J, Bayer H, Kagan VE (2021) Resolving the paradox of ferroptotic cell death: Ferrostatin-1 binds to SOLSD/PERP1 complex, suppresses generation of peroxidized ETE-PE, and protects against ferroptosis. Redox Biol 38:101744.

Aspetti M, Bellini S, Grilli E, Gyzik M, Cantamessa L, Ronca R, Maccarini F, Salvi A, De Petro G, Arosio P, Mitola S, Poli M (2021) H-ferritin suppression and pronounced mitochondrial respiration make hepatocellular carcinoma cells sensitive to RSL3-induced ferroptosis. Autophagy 2019:3:299-316.

Aytos S, Zhang M, Roberts BR, Lam LG, Lind M, McLean C, Bush AI, Frugter T, Crack P, Duca JA (2014) Ceruloplasmin and β-amyloid precursor protein confer neuroprotection in traumatic brain injury and lower neuronal iron. Free Radic Biol Med 62:1-11.

Aytos S, Portbury S, Kalinowski P, Agarwal P, Diouf I, Schneider JA, Morris AI, Bush AI (2021) Regional brain iron associated with deterioration in Alzheimer’s disease: A large cohort study and theoretical significance. Alzheimers Dement 17:1244-1256.

Badgley MA, Kremen DM, Maurer HC, DelGiorno KE, Lee HJ, Purohit V, Sagalowsky IR, Ma A, Kominami E, Lake CL, Decker AB, Sattar SA, Atkinson DE, Li Z, Toglia MP, Zisch JS, Cheng Q, Gao F, Yu Y, Song Z, Wu Q, An P, Huang S, Dixon SJ, Stockwell BR (2014) The role of iron and reactive oxygen species in cell death. Cancer Discov 11:678-695.

Cui Y, Zhang Y, Zhao X, Shao L, Liu G, Sun C, Xu R, Zhang Z (2021) ACSL4 exacerbates pancreatic tumor ferroptosis in mice. Science 368:85-89.

Badhwala JH, Wilson JR, Fehlings MG (2019) Global burden of traumatic brain and spinal cord injury. Lancet Neurol 18:24-35.

Bao WD, Zhou XT, Zhou TF, Wang L, Yin X, Liu Y, Zhu Q, Liu D (2020) Targeting miR-124/ferroptokin signaling ameliorates neural insults to mouse brain through the activation of autophagy and the suppression of ferroptosis. J Neurochem 157:331-343.

Bao WD, Zhou XT, Kalinowski P, Agarwal P, Diouf I, Schneider JA, Morris AI, Bush AI (2021) Regional brain iron associated with deterioration in Alzheimer’s disease: A large cohort study and theoretical significance. Alzheimers Dement 17:1244-1256.

Badgley MA, Kremen DM, Maurer HC, DelGiorno KE, Lee HJ, Purohit V, Sagalowsky IR, Ma A, Kominami E, Lake CL, Decker AB, Sattar SA, Atkinson DE, Li Z, Toglia MP, Zisch JS, Cheng Q, Gao F, Yu Y, Song Z, Wu Q, An P, Huang S, Dixon SJ, Stockwell BR (2014) The role of iron and reactive oxygen species in cell death. Cancer Discov 11:678-695.

Cui Y, Zhang Y, Zhao X, Shao L, Liu G, Sun C, Xu R, Zhang Z (2021) ACSL4 exacerbates pancreatic tumor ferroptosis in mice. Science 368:85-89.

Badhwala JH, Wilson JR, Fehlings MG (2019) Global burden of traumatic brain and spinal cord injury. Lancet Neurol 18:24-35.

Bao WD, Zhou XT, Zhou TF, Wang L, Yin X, Liu Y, Zhu Q, Liu D (2020) Targeting miR-124/ ferroptokin signaling ameliorates neural insults to mouse brain through the activation of autophagy and the suppression of ferroptosis. J Neurochem 157:331-343.

Bao WD, Zhou XT, Kalinowski P, Agarwal P, Diouf I, Schneider JA, Morris AI, Bush AI (2021) Regional brain iron associated with deterioration in Alzheimer’s disease: A large cohort study and theoretical significance. Alzheimers Dement 17:1244-1256.

Badgley MA, Kremen DM, Maurer HC, DelGiorno KE, Lee HJ, Purohit V, Sagalowsky IR, Ma A, Kominami E, Lake CL, Decker AB, Sattar SA, Atkinson DE, Li Z, Toglia MP, Zisch JS, Cheng Q, Gao F, Yu Y, Song Z, Wu Q, An P, Huang S, Dixon SJ, Stockwell BR (2014) The role of iron and reactive oxygen species in cell death. Cancer Discov 11:678-695.

Cui Y, Zhang Y, Zhao X, Shao L, Liu G, Sun C, Xu R, Zhang Z (2021) ACSL4 exacerbates pancreatic tumor ferroptosis in mice. Science 368:85-89.

Badhwala JH, Wilson JR, Fehlings MG (2019) Global burden of traumatic brain and spinal cord injury. Lancet Neurol 18:24-35.

Bao WD, Zhou XT, Zhou TF, Wang L, Yin X, Liu Y, Zhu Q, Liu D (2020) Targeting miR-124/ferroptokin signaling ameliorates neural insults to mouse brain through the activation of autophagy and the suppression of ferroptosis. J Neurochem 157:331-343.

Bao WD, Zhou XT, Kalinowski P, Agarwal P, Diouf I, Schneider JA, Morris AI, Bush AI (2021) Regional brain iron associated with deterioration in Alzheimer’s disease: A large cohort study and theoretical significance. Alzheimers Dement 17:1244-1256.

Badgley MA, Kremen DM, Maurer HC, DelGiorno KE, Lee HJ, Purohit V, Sagalowsky IR, Ma A, Kominami E, Lake CL, Decker AB, Sattar SA, Atkinson DE, Li Z, Toglia MP, Zisch JS, Cheng Q, Gao F, Yu Y, Song Z, Wu Q, An P, Huang S, Dixon SJ, Stockwell BR (2014) The role of iron and reactive oxygen species in cell death. Cancer Discov 11:678-695.

Cui Y, Zhang Y, Zhao X, Shao L, Liu G, Sun C, Xu R, Zhang Z (2021) ACSL4 exacerbates pancreatic tumor ferroptosis in mice. Science 368:85-89.

Badhwala JH, Wilson JR, Fehlings MG (2019) Global burden of traumatic brain and spinal cord injury. Lancet Neurol 18:24-35.

Bao WD, Zhou XT, Zhou TF, Wang L, Yin X, Liu Y, Zhu Q, Liu D (2020) Targeting miR-124/ ferroptokin signaling ameliorates neural insults to mouse brain through the activation of autophagy and the suppression of ferroptosis. J Neurochem 157:331-343.
Tuo QZ, Masaldan S, Southon A, Mawal C, Ayton S, Bush AI, Lei P, Belaidi AA (2021) Ferroptosis and necroinflammation, a yet poorly explored mechanism of cytoprotection by ferrostatin-1 and liproxstatin-1 and the role of lipid phosphorylation at Tyr1472 regulates IRE(-)DMT1-mediated iron accumulation and import in glioblastoma cell lines. Oncogene 38:356-369.e10.

Shen L, Lin D, Li X, Wu H, Lenahan C, Pan Y, Xu W, Chen Y, Shao A, Zhang J (2020) Endothelial iron homeostasis regulates blood brain barrier integrity via the HIF-2α-ve-cadherin pathway. Pharmaceuticals 13:311.

Zilka O, Shah R, Li B, Friedmann Angeli JP, Griesser M, Conrad M, Pratt DA (2017) On the mechanism of cytoprotection by ferrostatin-1 and liproxstatin-1 and the role of lipid phosphorylation at Tyr1472 regulates IRE(-)DMT1-mediated iron accumulation and import in glioblastoma cell lines. Oncogene 38:356-369.e10.

Zhang JY, Swanda RV, Nie L, Liu X, Wang C, Lee H, Lei G, Mao C, Koppula P, Cheng W, Zhang YQ (2021a) O-GlcNAcylation enhances sensitivity to RSL3-induced ferroptosis via the NCOA4 mediated autophagy and ferroptosis in glioblastoma cell lines. Oncogene 40:1706-1720.

Wu C, Du M, Yu R, Cheng Y, Wu B, Fu J, Tan W, Zhou Q, Balawi E, Liao ZB (2022) A novel mechanism linking ferroptosis and endoplasmic reticulum stress via the cimirp14t/miR-351-5p/Sqox signaling in melanoma-mediated treatment of traumatic brain injury. Front Cell Dev Biol 10:614396.

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.

Wang X, Yang WH, Lin CC, Wu J, Chao PY, Chen K, Chen PH, Chi JT (2021) The Hippo pathway effector YAP promotes ferroptosis by activating the E3 ligase SKP2. Mol Cancer Res 19:1014-1024.

Wang Z, Xue Y, Song J, Wang H, Wu J, Liu Y, Wu J, Wu W, Gao Y, Cao D, Jiang H, Zhan J, Li Y (2021) MiR-351-5p/5-LOX signaling in melatonin-mediated treatment of traumatic brain injury in mice. CNS Neurosci Ther 25:465-475.

Wang YJ, Lin CC, Wu J, Chao PY, Chen K, Chen PH, Ji JT (2021) The Hippo pathway effector YAP promotes ferroptosis by activating the E3 ligase SKP2. Mol Cancer Res 19:1014-1024.

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.

Van Broeckhoven J, Sommer D, Dooley D, Hendrisch K, Franssen A (2021) Macrophage phagocytosis after spinal cord injury: when friends become foes. Brain 144:2933-2945.

Wang J, Ma JW, Dhandapani KM, Brain DW (2017) Regulatory role of NADPH oxidase 2 in the polarization dynamics and neurotoxicity of microglia/macrophages after traumatic brain injury. Free Radic Biol Med 113:119-131.

Wang Q, lin C, Xue Q, Gao Q, Huang A, Wang K, Tang N (2021) GSTT1 sensitizes human breast cancer cells to sorafenib-induced ferroptosis via inhibition of NRF2/GPX4 axis. Cell Death Dis 12:426.

Wang S, Yi X, Wu Z, Guo S, Dai W, Wang H, Shi Q, Zeng K, Guo W, Li C (2022) CAMKK2 defines ferroptosis sensitivity of melanoma cells by regulating AMPK-NRF2 pathway. J Invest Dermatol 142:189-200.

Wehns AC, Khaliq I, Duering M, Helfal F, Culmsee C, Vandenabeele P, Plesnila N, Terzilli NA (2021) RIPK1 or RIPK3 deletion prevents progressive neuronal cell death and improves memory function after traumatic brain injury. Acta Neurologica Compreh 91:330-340.

Wen N, Lu T, Yang L, Dong Y, Liu X (2021) Lipoxin A4 protects primary spinal cord neurons from erastin-induced ferroptosis by activating the Akt/Nrf2/HO-1 signaling pathway. FEBS Open Bio 11:2118-2126.

Wenzel SE, Tyurina YY, Zhao S, Croix CM, Dar HH, Mao G, Tyurin VA, Anthonymuth N, Tsaparov AA, Amosco AA, Mikulinska-Ruminska K, Shivasritva IH, Kenny EM, Yang Q, Rosenbaum JC, Sparvero LJ, Emlet DR, Wen X, Minami Y, Qu F, et al. (2017) PEBP1 wards ferroptosis by enabling lipoxigenase generation of lipid death signals. Cell 171:628-641.e26.

Wright PS, Xie X, Wolkenstein P, Tian G, Zhou W, Zhang Q, Wang W, Liu L, Song J, Wang P, he X (2019) Membrane damage during ferroptosis is caused by oxidation of phospholipids catalyzed by the oxoeductases POR and CYB5R1. Mol Cell 81:356-369.e10.

Xie BS, Wang YD, Lin Y, Mao Q, Feng J, Gao GY, Jiang YJ (2019) Inhibition of ferroptosis attenuates tissue damage and improves neurological outcomes after traumatic brain injury in mice. CNS Neurosci Ther 25:465-475.

Xiao X, Yang J, Liang W, Yang C, Yao S, Han L, Zhang Z (2019) miR-211-5p attenuates ferroptotic neuronal death after traumatic brain injury by targeting Ptg2. Mol Brain 12:78.

Xiong H, Li XL, Liuyang ZY, Roisman L, Zhang ST, Ayton S, Tran AP, Warren PM, Silver J (2018) A single primary blast-induced traumatic brain injury in a rodent model causes progressive neuronal cell death and modulates spinal iron accumulation via activating DMT1(-)IRE in remifentanil-induced spinal analgesia. Brain Res 1719:177-187.

Xu W, Chen Y, Cao C, Li P, Wang J, Li Y, Gao Z, Wang J, Shi Q, Zeng K, Guo W, Li C (2022) Ferroptosis and necroinflammation, a yet poorly explored mechanism of cytoprotection by ferrostatin-1 and liproxstatin-1 and the role of lipid phosphorylation at Tyr1472 regulates IRE(-)DMT1-mediated iron accumulation and import in glioblastoma cell lines. Oncogene 38:356-369.e10.

Xu X, Wang Y, Li Q, Cheng Y, Gao Y, Yang F, Fan H, Xu X, Bai L, Wang K, Xu W, Xu Y, Hu Y, Liu C, Kong XH, Feng SQ (2019) Deterferoxone promotes panoramic treatment of traumatic spinal cord injury by inhibiting ferroptosis. Neuroregen Res 14:532-541.

Yasuhisa TH, Rittie JL, Kress CM, Onderko EL, Silakov A, Calisto JC, Behan RK, Green MT (2013) iron(V)/hydroxide p(k) and the role of thiolate ligand in C-H bond activation by cytochrome P450. Science 342:825-829.

Yang WH, Lin CC, Wu J, Chao PY, Chen K, Chen PH, Ji JT (2021) The Hippo pathway effector YAP promotes ferroptosis by activating the E3 ligase SKP2. Mol Cancer Res 19:1005-1014.

Yang Z, Zhang Y, hao J, Duan HQ, Zhao C, Sun C, li B, Fan BY, Wang J, Xu WK, Fu HY, Xu Y, Liu C, Kong XH, Feng SQ (2019) Deterferoxone promotes panoramic treatment of traumatic spinal cord injury by inhibiting ferroptosis. Neuroregen Res 14:532-541.

Yang Z, Xu Y, Huang Z, Cao C, Wu Z, Wang Z, Wang J, Wang B, Wang J (2022) Macrophage phagocytosis after spinal cord injury is regulated by ALOXE3-mediated lipid peroxidation accumulation. Front Cell Dev Biol 10:614396.
**Additional Table 1 Effects of ferroptosis inhibitors on central nervous system injuries**

| Disease | Medicines                        | Classification                  | Model of CNS                               | Route of administration | Effectiveness                                                                                                                                                                                                 | References                  |
|---------|----------------------------------|---------------------------------|--------------------------------------------|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| SCI     | Deferoxamine                     | Iron chelator                   | Impact SCI model of female Wistar rats     | Intraperitoneal          | Increase GPX4, SLC7A11, and GSH; inhibit gliosis; recover the neuronal function.                                                                                                                        | Yao et al., 2019             |
|         |                                  |                                 | Clip-compression SCI model of female       | Intracerebroventricular  | Reduce motor cortex iron overload and neurons death; recover motor function.                                                                                                                             | Feng et al., 2021            |
|         |                                  |                                 | Sprague-Dawley rats                        |                         | Reduce iron and ROS accumulation; downregulate the expression of IREB2 and PTGS2; inhibit ferroptosis in oligodendrocytes; alleviate white matter injury; promote functional recovery. | Ge et al., 2022              |
|         | Ferrostatin-1                    | Lipid peroxidation inhibitor    | Impact SCI model of female Wistar rats     | Microinjection into the spinal cord |                                                                                                                                                                                                            |                              |
|         |                                   |                                 | Clip-compression SCI model of female       | Intraperitoneal          | Decrease the levels of iron, the expression of TBARS, ACSL4, and ALOX15; elevate the concentration of GSH, GPX4, NRF2, and HO-1; rescue the function of the spinal cord. | Zhou et al., 2020            |
|         | Proanthocyanidin                 | Free radical scavenger          | Clip-compression SCI model of female       | Intraperitoneal          | Increase GPX4, SOD, and GSH; decrease lipid peroxides, MDA, and ROS; cure injured mitochondria and inflammation; promote behavioral and structural recovery.                                                | Ge et al., 2021              |
|         |                                   |                                 | C57BL/6 mice                               |                         |                                                                                                                                                                                                            |                              |
|         | Zinc gluconate                   | Metal salt                      | Impact SCI model of female C57BL/6 mice    | Intraperitoneal          | Attenuate allodynia and hyperalgesia; reduce lesions; inhibit apoptotic signaling; and improve functional recovery.                                                                                      | Ge et al., 2021              |
|         |                                   |                                 |                                             |                         | Upregulate PTGS2 and ACSL4; rescue inhibition of GSH and cysteine levels; break down-regulation of GPX4; reduce ROS levels. Reduce cell viability of primary spinal cord neurons.                                    | Lu et al., 2018              |
|         | Lipoxin A4                       | Anti-inflammatory mediator      | Impact SCI model of pregnant C57BL/6 mice  | Intrathecal              |                                                                                                                                                                                                            | Wei et al., 2021             |
|         |                                   |                                 |                                             |                         | Erastin-induced ferroptosis in primary spinal cord neurons from pregnant C57BL/6 mice(in vitro)                                                                                                           |                              |
| Condition     | Treatment         | Model                          | Route                          | Effects                                                                 | References   |
|---------------|-------------------|-------------------------------|--------------------------------|-------------------------------------------------------------------------|--------------|
| TBI           | Ferrostatin-1     | Impact CCI model of male C57BL/6 mice | Intracerebroventricular       | Rescue iron deposition; degenerate neurons; attenuate the volume of injury lesions; ameliorate long-term motor and cognitive prognosis. | Xie et al., 2019 |
|               | Liproxstatin-1    | Impact CCI model of male C57BL/6J mice | Intraperitoneal               | Increase GSH; inhibit system xc-, Fth, TFR1, FPN, Ftl, Fth, and 4HNE; decrease iron and lipid oxidation; attenuate the degenerating neurons and the motor performance. | Rui et al., 2021 |
|               |                   |                               |                               | RSL3-induced ferroptosis in oligodendrocyte (in vitro) | Not applicable |
| Melatonin     |                   | Impact CCI model of male C57BL/7J mice | Intraperitoneal               | Upregulate GSH; inhibit system xc-, Fth, Tfr1, Fpn, Ftl, Fth, and 4HNE; reduce iron and lipid oxidation; improve the neuron's survival and motor performance. | Rui et al., 2021 |
| MiR-212       | MicroRNA          | Impact CCI model of male C57BL/6J mice | Intracerebroventricular       | Improved memory and learning performance.                             | Xiao et al., 2019 |
| Baicalein     | Lipooxygenase inhibitor | Impact CCI model of male C57BL/6 mice | Intraperitoneal               | Attenuate phosphatidylethanolamine oxidation and improve function.     | Kenny et al., 2019 |
|               |                   | FeCl3-induced PTE model of male C57/B6 mice | Intraperitoneal               | Attenuate epileptic seizure behavior.                                  | Li et al., 2019 |
| Adeno-associated virus-prokineticin-2 | Chemokine | Impact CCI model of male C57BL/6 mice | Intracerebroventricular       | Increase Gpx4; decrease ACSL4; preserve mitochondrial function; protect neurons; reduce the lesion volume; improve motor ability and learning performance. | Bao et al., 2021c |
| Polydatin     | Plant extract     | Impact CCI model of male C57BL/6 mice | Intraperitoneal               | Reverse increase of iron and MDA; increase the activity of GPX4; attenuate cell death and tissues loss. | Huang et al., 2021a |
| Ruxolitinib | Inhibitor of Janus kinase | Impact CCI model of male C57BL/6J mice | Intraperitoneal | Ameliorate iron deposition and tissue loss; reverse the lower expression of GPX4; inhibit the expressions of COX2 and TFR1; alleviate the brain edema and degree of neurodegeneration. | Chen et al., 2021 |

4HNE: 4-hydroxy-2-nonenal; ACSL4: acyl-coenzyme A synthetase long-chain family member 4; ALOX15: Arachidonate 15-lipoxygenase; COX2: Cyclooxygenase 2; FPN: Ferroprotein; FSP1: ferroptosis suppressor protein 1; Fth: ferritin H; GPX4: glutathione peroxidase type 4; GSH: glutathione; HO-1: heme oxygenase-1; IREB2: iron-responsive-element binding protein 2; MDA: malondialdehyde; Nrf2: nuclear factor erythroid 2-related factor 2; PTGS2: prostaglandin-endoperoxide synthase 2; ROS: reactive oxygen species; SCI: spinal cord injury; SLC7A11: solute carrier family 7 member 11; SOD: superoxide dismutase; TBARS: thiobarbituric acid reactive substances; TFR1: transferrin receptor 1.