The role of ferroptosis in central nervous system damage diseases

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ABSTRACT

Ferroptosis is a form of cell death, *i.e.*, programmed cell death characterized by lipid peroxidation and iron dependence, which has unique morphological and biochemical properties. This unique mode of cell death is driven by iron-dependent phospholipid peroxidation and regulated by multiple cell metabolic pathways, including redox homeostasis, iron metabolism, mitochondrial activity, and the metabolism of amino acids, lipids, and sugars. Many organ injuries and degenerative pathologies are caused by ferroptosis. Ferroptosis is closely related to central nervous system injury diseases and is currently an important topic of research globally. This research examined the relationships between ferroptosis and the occurrence and treatment of central nervous system injury diseases. Additionally, ferroptosis was assessed from the aspect of theory proposal, mechanism of action, and related signaling pathways per recent research. This review provides a relevant theoretical basis for further research on this theory, the prospect of its development, and the prevention and treatment of such diseases.

Subjects Biochemistry, Cell Biology, Neurology
Keywords Ferroptosis, Nerve damage, Redox, GPX4

INTRODUCTION

At present, programmed cell death (PCD) is regarded as the most important type of cell death (*Bedoui, Herold & Strasser, 2020*; *Tower, 2015*). Furthermore, PCD is a self-directed and ordered process that is crucial for the growth and maintenance of organisms (*Kopeina & Zhivotovsky, 2022*). PCD plays a crucial role in maintaining tissue and organ homeostasis by regulating the activation and expression of various fate-determining genes through complex and distinct signaling pathways (*Lockshin, 2016*). Moreover, recent genetic and biochemical studies have unveiled the remarkable flexibility and molecular plasticity within these PCD pathways, emphasizing their ability to adapt and maintain organismal

homeostasis (*Maniam & Maniam, 2021*; *Samir, Malireddi & Kanneganti, 2020*). Besides the well-known apoptosis, PCD also includes autophagy, necroptosis, pyroptosis, ferroptosis, and other processes. They are morphologically similar to apoptosis, can also induce severe inflammatory responses, and significantly affect the homeostasis of the body (*Li et al., 2023*; *Tong et al., 2022*).

Among these PCDs, ferroptosis is a unique form of programmed cell death that is iron-dependent and characterized by the accumulation of lipid peroxides (reactive oxygen species (ROS). It is distinct from other types of cell death and is regulated by various factors including amino acids, lipids, redox, and iron metabolism (*Dixon et al., 2012*). The primary mechanism involves the catalysis of the highly expressed unsaturated fatty acids on the cell membrane to undergo lipid peroxidation under the action of divalent iron or ester oxygenase, thereby inducing cell death (*Cao & Dixon, 2016*). The decrease in the regulatory core enzyme (Glutathione peroxidase 4 (GPX4)) of the antioxidant system (glutathione system) is also associated with ferroptosis. The process is described as complex, but specific details of its intricacies remain unexplored (*Dixon et al., 2014*). Research has shown that ferroptosis is closely associated with the occurrence of a variety of diseases which also include central nervous system (CNS) injury diseases. The relationship between ferroptosis and the occurrence and treatment of such diseases, along with the research on ferroptosis in recent years, was analyzed based on theory proposal, mechanism of action, and related signaling pathways. Furthermore, growing research has increasingly demonstrated the significant regulatory roles of ferroptosis in the progression of CNS damage diseases (*David et al., 2022*; *Jhelum et al., 2020*; *Xie et al., 2019*; *Zhu et al., 2022*). Gaining a deeper understanding of the mechanism of ferroptosis may effectively improve the diagnosis and treatment of CNS diseases. Therefore, the aim of the review is to provide a relevant theoretical basis for further research on this theory, the likelihood of its development, and the prevention and treatment of CNS injury diseases.

SURVEY METHODOLOGY

We searched related literature by pubmed using the key words (ferroptosis) AND (central nervous system damage)/(ferroptosis) AND (central nervous system disease)/(ferroptosis) AND (central nervous system injury). However, the papers which were not research articles or reviews were excluded.

The concept of ferroptosis

Cell death is a key driver factor of degenerative diseases and also a fundamental characteristic of multicellular organism development. Many diseases can affect the rate of metabolism, which can lead to a reduction in the normal production of energy and biomolecules. For the normal development of multicellular organisms, cell death is very important, and in many diseases, it is abnormally initiated or inhibited. Up until the mid-20th century, cell death was believed to be uncontrollable before the idea of programmed cell death was introduced. The following decades led to the discovery of a type of programmed cell death called apoptosis. For the next few years, apoptosis was used interchangeably with programmed cell death; before the concept of programmed necrosis emerged in the early

21st century. This led to the discovery of a type of cell death that is regulated by their molecules, *i.e.,* "regulated cell death," this term encompasses other types of cell death, such as necrosis and pyroptosis (*Dixon et al., 2012*; *Santagostino et al., 2021*; *Tang et al., 2019*).

In 2003, Erastin, a small molecule, was discovered to selectively attack tumor cells through a non-apoptotic mechanism (*Dolma et al., 2003*). In the following years, it was discovered that Erastin and several other compounds could activate a distinct form of cell death that relied on iron, and differed from apoptosis and other types of necrosis like pyroptosis (*Yang & Stockwell, 2008*). This iron-dependent cell death was termed "ferroptosis" in 2012 and is characterized by unique morphological, biochemical, and genetic features that set it apart from apoptosis, necrosis, and autophagy. Ferroptosis is closely associated with iron metabolism, lipids, and redox processes. Morphologically, it is characterized by mitochondrial atrophy, reduction or disappearance of mitochondrial cristae, increased density of mitochondrial membranes, and rupture of outer mitochondrial membranes. Biochemically, ferroptosis is marked by the accumulation of iron ions, aggregation of ROS, and lipid peroxidation (*Dixon et al., 2012*). Scientific literature has established a correlation between ferroptosis and various pathological features associated with tissue injury, as well as its physiological role in immune surveillance. Consequently, targeting ferroptosis inhibition holds promise as a potential therapeutic strategy for ferroptosis-related diseases. Notably, studies and reports have elucidated the induction of ferroptosis through catalyzing the elevated expression of unsaturated fatty acids on cell membranes, leading to lipid peroxidation under the influence of divalent iron or ester oxygenase. Additionally, investigations have explored alternative mechanisms, apart from GPX4 and glutathione (GSH) (*Yang et al., 2014*), employed by cells to counteract ferroptosis. Nonetheless, a comprehensive understanding of the intricate molecular pathways governing ferroptosis induction necessitates further research and analysis.

Mechanism of ferroptosis
Relationships between ferroptosis and regulation of GPX4 and GSH lipid peroxidation

Ferroptosis is a form of cell death that was first reported in 2012 (*Dixon et al., 2012*). Initially, it was believed that the specific mechanism through which ferroptosis occurs was related to the metabolism of cysteine and glutathione and the peroxidation of phospholipids. Notably, ferroptosis was found to be characterized by the accumulation of lipid peroxides within certain cells. Inhibiting the defense system responsible for removing these lipid peroxides results in their accumulation to lethal levels. This can be achieved, for example, by inhibiting the cystine-glutamate reverse transporter protein, depleting the cellular antioxidant glutathione, reducing the glutathione-dependent GPX4 and ultimately leading to the accumulation of increased levels of lipid peroxides (*Hirschhorn & Stockwell, 2019*; *Yang et al., 2014*). Furthermore, the connection between ferroptosis and the role of GPX4 is evident in studies involving mice with a knockout *GPX4* gene. These mice exhibited neurodegenerative changes and cognitive impairment that were related to the activation of extracellular signal-regulated kinases, lipid peroxidation, and a significant

increase in neuroinflammation (*Dugger & Dickson, 2017*). The research noted that the impact of the absence of GPX4 was quite severe.

Various studies noted that reduced glutathione, selenium, and GPX4 contribute to the cellular antioxidant defense system and help regulate iron-dependent cell death. The most abundant reductant in mammalian cells, reduced GSH, functions as a cofactor for a variety of enzymes, including glutathione-s-transferases and glutathione peroxidases (GPXs). An important regulator of the occurrence of iron death is the trace element selenium, which is an essential for the biosynthesis of selenoproteins that clears the ROS. This also included GPX4 (*Yang et al., 2014*). It was noted that the oxidized form of cysteine (Cystine) also counteracts ferroptosis by promoting the activity of GPXs (*Banjac et al., 2008*; *Mandal et al., 2010*; *Seiler et al., 2008*; *Shi et al., 2000*; *Yant et al., 2003*), when absorbed by the cystine-glutamate reverse transporter (*Bannai & Kitamura, 1980*; *Sato et al., 1999*). Furthermore, ferroptosis can be influenced by environmental stress and intracellular and intercellular signal transport events which impact ROS levels and cellular metabolism. In-depth studies have revealed that the deficiency of GPX4 can lead to lipid peroxidation dependence. This in turn affects the neurodegeneration of hippocampal and cortical regions within the brain (*Jia et al., 2020*). Furthermore, the interplay of oxidative stress between cells can also affect ferroptosis, ultimately leading to nerve injury. The above process is also summarized in Fig. 1.

Hippo-YAP signaling pathway

The functional performance of GPX4 is closely linked to the regulation of the Hippo-YAP signaling pathway (*Wu et al., 2019*; *Zhang et al., 2022*). The effect of the Hippo-YAP pathway on ferroptosis in epithelial cells is regulated by calmodulin-mediated cell–cell contact. This contact inhibits the expression of melin, leading to the activation of the Hippo signaling pathway through the Neurofibromatosis type 2 (NF2) gene. Consequently, the YAP activity, which is co-regulated by nuclear translocation and transcription, is suppressed. The Hippo-YAP pathway encompasses Acyl-CoA Synthetase Long Chain Family Member 4 (ACSL4), the transferrin receptor protein 1 (TFR1), and other possible genes that act as regulatory factors for ferroptosis. Notably, ACSL4 has been implicated as a transferrin receptor involved in sperm development. Furthermore, ASCL4 can further contribute to the activation of polyunsaturated fatty acid phospholipids (PUFA-PLs) and phospholipid hydroperoxides (PLOOH) (*Schneider et al., 2009*; *Ufer et al., 2008*). The activity of the Hippo pathway performs a crucial function in the occurrence of ferroptosis, and heightened susceptibility to Hippo will increase the sensitivity of ferroptosis (Fig. 2) (*Wu et al., 2019*). The data acquired indicated that the Hippo-YAP signaling pathway is intricately intertwined with ferroptosis and diseases caused by neurological damage. It was noted that this pathway is significantly upregulated and activated in the astrocytes of the optic nerve of mice with encephalomyelitis. This activation also resulted in activating both astrocytes and microglia, leading to the suppression of neuroinflammatory infiltration and the prevention of optic nerve demyelination (*Wu et al., 2021*). The involvement of the Hippo-YAP pathway in these processes highlights its potential in the modulation of ferroptosis-related pathways in the context of neurological damage.
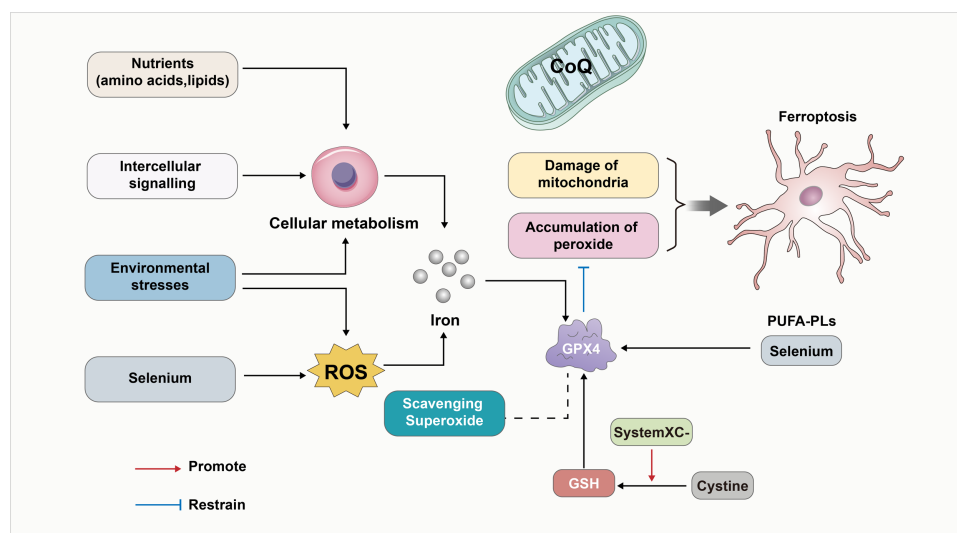
Figure 1 **GPX4 as a key linker in the development of ferroptosis.** GPX4 has been a key linker in the development of ferroptosis. First, GPX4 is an essential inhibitor of phospholipid peroxidation, together with the damage of mitochondria to contribute to the development of ferroptosis. In addition, the oxidized form of cysteine (Cystine) also counteracts ferroptosis by promoting the activity of GSH/GPX4. Furthermore, GPX4 induced ferroptosis can be influenced by environmental stress and intracellular and intercellular signal transport events which impact ROS levels, cellular metabolism and the level of Iron. In-depth studies have revealed that the deficiency of GPX4 can affect lipid peroxidation dependence. Also, Selenium/PUFA-PLs and scavenging superoxide affect the GPX4 induced ferroptosis. In addition, CoQ10 serves as a vital component of mitochondria and also inhibits lipid peroxidation outside the mitochondria. Consequently, the depletion of CoQ10 renders cells more susceptible to ferroptosis.

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Ferroptosis-related inducers

Erastin and RSL3. Erastin and RSL3 compounds were discovered initially as inducers for the occurrence of ferroptosis. The mechanism of both compounds for inducing ferroptosis involves targeting GPX4. Erastin and RSL3 can both directly lead to the inactivation of GPX4. In the case of Erastin, it can also indirectly lead to the inactivation of GPX4 by inhibiting the conversion of cystine, an essential component of glutathione synthesis. Consequently, lipid peroxidation is catalyzed, ultimately resulting not only in ferroptosis but also in neurodegenerative processes (*Conteh et al., 2019*).

FIN56. The FIN56 compound is a novel chemical inducer of ferroptosis (*Cao et al., 2019*). It functions by a dual mechanism involving the depletion of mevalonate and GPX4 protein, as well as Coenzyme Q10 (CoQ10). CoQ10 serves as a vital component of mitochondria and also inhibits lipid peroxidation outside the mitochondria. Consequently, the depletion of CoQ10 renders cells more susceptible to ferroptosis. In addition, prevention of the activity of the HMG coenzyme A reductase further heightens the vulnerability of cells to ferroptosis (*Cao et al., 2019*; *Shimada et al., 2016*). This context was also presented in Fig. 1.

Lipoxygenases (LOXs). Some studies have now found that LOXs compounds may also be inducers of ferroptosis (*Chen et al., 2021*; *Yang et al., 2016*). Ferroptosis can be inhibited
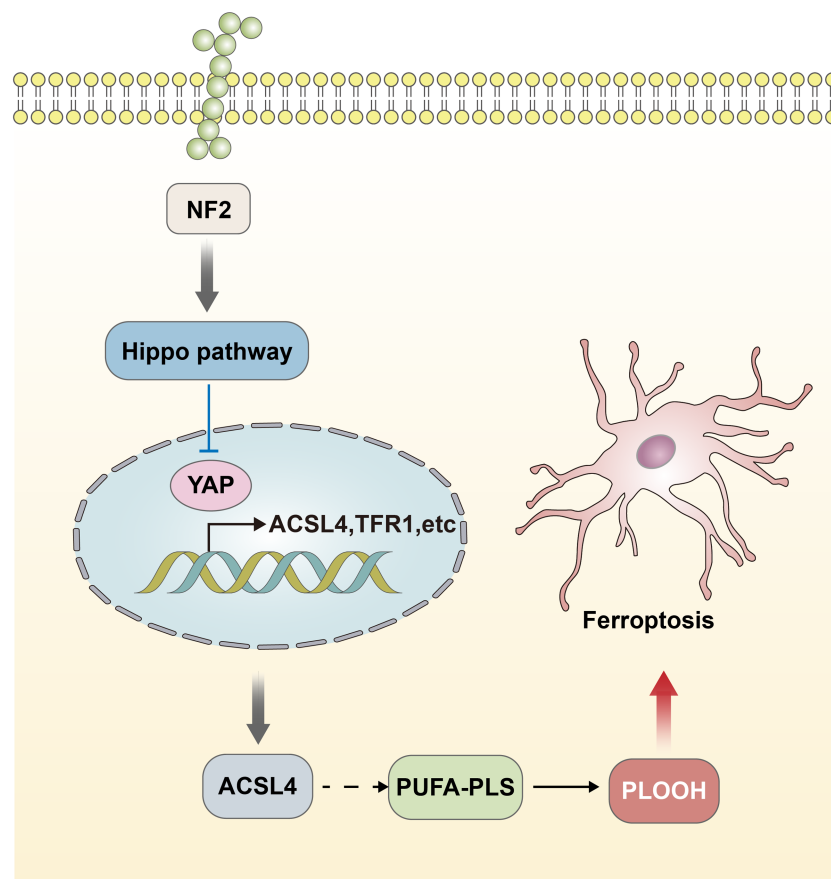
Figure 2 Hippo-YAP signaling pathway contributes to the occurrence of ferroptosis. The effect of the Hippo-YAP pathway on ferroptosis in epithelial cells is regulated by e-calmodulin-mediated cell–cell contact. This contact inhibits the expression of melin, leading to the activation of the Hippo signaling pathway through the *NF2* gene. Consequently, the YAP activity is suppressed. The Hippo-YAP pathway encompasses ACSL4, TFR1, and other possible genes that act as regulatory factors for ferroptosis. Notably, ASCL4 can further contribute to the activation of PUFA-PLs and PLOOH. The activity of the Hippo pathway performs a crucial function in the occurrence of ferroptosis, and heightened susceptibility to Hippo will increase the sensitivity of ferroptosis.

Full-size 🖾 DOI: 10.7717/peerj.16741/fig-2

by some LOXs pharmacological inhibitors (*Li, Maher & Schubert, 1997*), and baicalin can protect mice from an ischemic brain injury when *Alox15* is knocked out or when LOXs inhibitors are applied (*van Leyen et al., 2006*). However, some reports do not support this view. In the context of GPX4 knockout, further removal of the Alox15 gene did not prevent ferroptosis of fibroblasts in mice, nor did it prevent acute ischemic kidney injury and was linked to *in vivo* lethality (*Friedmann Angeli et al., 2014*). However, it is noteworthy that LOXs are primarily implicated in ferroptosis triggered by cysteine deficiency, as opposed to ferroptosis triggered by GPX4 deficiency. This observation suggests the necessity of a distinct model to further analyze the role of LOXs in diseases related to ferroptosis. The data indicates the possibility of an alternate mechanism compensating for the absence of ALOX15 activity and suggests that LOXs may be involved in certain

Table 1 A summary of the inducers of ferroptosis.

Name	Function	Molecular mechanism
Erastin	Inducer of ferroptosis	Directly lead to the inactivation of GPX4; indirectly lead to the inactivation of GPX4 by inhibiting the conversion of cystine
RSL3	Inducer of ferroptosis	Directly lead to the inactivation of GPX4
FIN56	A novel chemical inducer of ferroptosis	Depletion of mevalonate and GPX4 protein, as well as Coenzyme Q10
LOXs	Inducer of ferroptosis	Deficiency of cysteine

cases of ferroptosis-related diseases. It is also worth considering that the inhibitor typically employed to specifically LOXs may possess additional properties beyond their intended specificity. These might exhibit non-specific activity as free radical trapping antioxidants, leading to their inhibitory effects on ferroptosis through this mechanism (*Zilka et al., 2017*). Certainly, the predominantly used LOX inhibitors exhibit antioxidant activity, enabling them to capture free radicals. This poses a challenge to the conventional understanding of the role of LOXs in diseases associated with ferroptosis. Furthermore, it was noted that the occurrence of RSL3-induced ferroptosis was not prevented by the combined downregulation of all LOX isozymes. Interestingly, this downregulation had a significant rescuing effect on ferroptosis induced by Erastin, as it is possible that Erastin treatment is associated with the activation of LOX enzymes (*Shah, Shchepinov & Pratt, 2018*; *Yang et al., 2016*). These findings suggest that while oxidation may not be the primary factor driving ferroptosis in most cases, it could still contribute to the initiation and progression of injury under certain circumstances. Accordingly, in specific mouse models of cancer inhibition or neurodegeneration, the deficiency of Alox12 or Alox15 showed a positive effect (*Chu et al., 2019*). A summary of the inducers of ferroptosis is shown in Table 1.

Iron metabolism is involved in the regulation of ferroptosis

The role and regulation of iron in ferroptosis have recently been reported in studies despite the inclusion of "ferro" (meaning iron) in the name of this form of cell death. At the outset, understanding the precise cause of lipid peroxidation, a critical characteristic of ferroptosis, presented a challenge. It remained uncertain whether the transfer of an unstable iron pool within the cell membrane and its subsequent reaction with lipid peroxides was the primary trigger, or if the peroxidation process was predominantly driven by the activity of iron-dependent enzymes alone. Recent studies have shown that iron death is triggered by iron-dependent lipoxygenases by generating lipid peroxides. Additionally, it has been observed that unstable iron, which is not bound to these enzymes, further facilitates the catalysis of these peroxides, resulting in increased lipid peroxidation (*Shah, Shchepinov & Pratt, 2018*; *Wenzel et al., 2017*). In ferroptosis, cytochrome P450 oxidoreductase, an iron-dependent enzyme has been implicated in the process of lipid peroxidation, potentially playing a significant role (*Zou et al., 2020*). A critical determinant of ferroptosis progression is the abundance of ferritin, a protein involved in iron storage. Higher levels of ferritin confer resistance against ferroptosis, as they sequester iron and limit the availability of unstable iron pools. Conversely, the depletion of ferritin may result in the release of

iron into these unstable iron pool, leading to greater sensitivity against ferroptosis. Prior experiments have demonstrated that ferritin-targeted autophagy, known as ferritinophagy, triggers the breakdown of ferritin within lysosomes and releases iron into unstable iron pools, thereby increasing the sensitivity to ferroptosis (*Gao et al., 2016*; *Hou et al., 2016*). Furthermore, Prominin2 (PROM2) inhibits ferroptosis by promoting iron transport out of the cell by multivesicular bodies and exosomes containing ferritin (*Brown et al., 2019*).

The role of mitochondria in ferroptosis

Mitochondria generates key senescence metabolites during cellular metabolism and alters the sensitivity of cells to the tricarboxylic acid (TCA) cycle. Thereby increasing ferroptosis by altering the unstable iron content of cells. Mitochondria play a crucial role in regulating the respiration rate, and an increase in their activity can lead to enhanced production of ROS by automatically increasing the availability of cellular iron (*Gao et al., 2015*). Therefore, the normal degradation of ferritin within mitochondria along with its metabolic function appears to promote ferroptosis (*Gao et al., 2016*; *Hou et al., 2016*). Similarly, transferrin and its receptor play a collaborative role in iron homeostasis, facilitating the import of iron into cells. Moreover, it has been established that they actively participate in enhancing the export of iron from cells to promote oxidation (*Hou et al., 2016*; *Tuo et al., 2017*), thus promoting the formation ferroptosis. Additionally, recent studies have proposed a connection between the RSL3 induced-inhibition of O-GlcNAcylation modification and the increased autophagy of both iron and mitochondria. This enhanced autophagy regulation influences the sensitivity to ferroptosis, leading to the accumulation of unstable iron and facilitating the progression of ferroptosis (*Yu et al., 2022*). In nerve cells, the contraction of mitochondria and the accumulation of iron increase the occurrence of ferroptosis and lead to increased nerve injury, such as lumbosacral nerve root avulsion injuries (*Zhou et al., 2022*).

The relationship between ferroptosis and central nervous system injury diseases

Many studies have reported that ferroptosis plays an important role in the progression of central nervous system injury disorders. These include stroke (*Cui et al., 2021*; *Liu et al., 2020*), Parkinson's disease (*Mahoney-Sanchez et al., 2021*), Alzheimer's disease (AD) (*Yan & Zhang, 2019*), and Huntington's traumatic brain injury (TBI) (*Geng et al., 2021*; *Mi et al., 2019*). A growing number of studies have shown that ferroptosis plays a crucial role in neurodegenerative diseases, which are characterized by the accumulation of Fe^{2+}, lipid peroxidation, and alterations of mitochondrial structure.

Stroke

Current studies suggest that ferroptosis is an important causative element of cerebral ischemia/reperfusion (I/R) injury. Research indicates that spermidine/spermine n1-acetyltransferase 1 (SSAT1) activates the upregulation of arachidonic acid 15-lipoxygenase (ALOX15). Consequently, the upregulation of ALOX15 resulted in the triggering of ferroptosis in brain neurons, thereby exacerbating brain ischemia/reperfusion injury (*Zhao et al., 2022*). This form of cell death has also been implicated in the pathophysiological

process of TBI. Furthermore, studies have shown that melatonin can inhibit ferroptosis in the brain neurons after TBI and thus have a neuroprotective effect on the brain (*Rui et al., 2021*).

AD

AD is characterized by the progressive occurrence of cortical and hippocampal neuronal dysfunction and death. Its main pathological changes include neuronal degeneration and synaptic loss (*Hansson, 2021*), with neuronal death as a potential cause of AD (*Hambright et al., 2017*). Ferroptosis is characterized by increased iron content and altered lipid peroxidation in AD along with cognitive impairment (*Chen et al., 2015*; *Hambright et al., 2017*). Increased intracellular iron content directly induces oxidation-related neuronal damage (*Thirupathi & Chang, 2019*; *Yoo et al., 2010*). Thereby, the oxidation-related neuronal damage further promoted the generation and increase of ROS (*Derry et al., 2020*), which may be involved in the ferroptosis pathway (*Li et al., 2019*). The occurrence of mitochondrial oxidative dysfunction, reduced DNA repair, apoptosis, and increased autophagy associated with this leads to neuronal loss and an increased risk of AD (*Brickman et al., 2021*; *Goel et al., 2022*).

Parkinson's disease

Parkinson's disease is characterized by accumulation of misfolded alpha synuclein and loss of neurons in several brain regions, particularly dopaminergic neurons in the substantia nigra (*Guiney et al., 2017*). The key therapeutic goal is to improve dopamine levels in the brain and prevent neuronal degeneration. Notably, dopaminergic neurons in Parkinson's pathology are enriched in iron, which plays a role in both enzymatic and non-enzymatic aspects of dopamine metabolism (*Moreau et al., 2018*). Ferroptosis associated with iron content is a key cell death pathway in dopaminergic neurons (*Do Van et al., 2016*). Iron induces the oxidation of dopamine and the aggregation of a-synuclein. Moreover, excess free iron can reduce the activity of GPX4, leading to the depletion of GSH (*Duce et al., 2017*). Subsequently, the reduced ability of cells to scavenge ROS leads to an excess of ROS and induces the accumulation of lipid peroxidation and iron-dependent free radicals on neuronal and astrocyte membranes (*Angelova et al., 2015*). This ultimately results in ferroptosis, which in turn leads to increased loss of dopaminergic neurons in Parkinson's disease, and is a possible potential pathogenic mechanism (*Imai et al., 2017*; *Stockwell et al., 2017*).

Neuropathic pain due to spinal cord injury

In chronic neuropathic pain (NP), the level of Acyl CoA synthetase long-chain family member 4 (ACSl4) increased due to reduced levels of GPX4 (*Guo et al., 2021*; *Wang et al., 2021*). This led to an increase in the number of mitochondria and a decrease in the average mitochondrial area, along with elevated iron ion levels in the spinal cord of rats. The increase in ACS14 induces ferroptosis and further activates neurons in the dorsal horn of the spinal cord and astrocytes involved in the maintenance of chronic pain.

Experimental studies have shown that the spinal cord segments of rats can upregulate the expression of GPX4 and downregulate the expression of ACSL4 when treated with the

ferroptosis inhibitor ferritin. Nonetheless, the opposite effect is achieved when treated with the ferroptosis inducer Erastin (10 mg/kg). Iron ion levels are elevated in the spinal cord during NP and can be modulated by interventions such as Cci-induced iron statin-1 and Erastin; decreased by the former and increased by the latter. Ferroptosis plays a role in the development of NP in rats following peripheral nerve injury by impairing the activation of neurons and astrocytes in the spinal dorsal horn. Inhibition of ferroptosis with lipostatin-1 significantly alleviates mechanical and thermal hypersensitivity associated with NP (*Guo et al., 2021*).

Summary and outlook

Since the term ferroptosis was coined in 2012, the study of ferroptosis has exploded over the past few years. It is a regulated iron-dependent programmed cell death form characterized by the accumulation of lipid peroxidation. It has also been linked with ROS, mitochondrial metabolism, and iron metabolism; however, the exact molecular mechanism remains unelucidated. Current studies have found that the process may be correlated with the Hippo-YAP signaling pathway, but the exact mechanisms and the possible molecular mechanism markers are still being explored. *Tan, Fang & Gu (2021)* summarized a review about the role of ferroptosis in central nervous system diseases. Their review primarily dealt with lipid metabolism, iron metabolism, the GSH-dependent pathway and the CoQ10-dependent pathway. However, in our review, we mainly summarized and discussed GPX4 and GSH lipid peroxidation, the Hippo-YAP signaling pathway, ferroptosis-related inducers, and mitochondria in the process of ferroptosis. Notably, the role of ferroptosis-related inducers was explored concerning the regulation of ferroptosis. These points are the main differences between these two reviews, and we believe our review is more accessible to a different audience compared with the review of *Tan, Fang & Gu (2021)*.

Furthermore, during the development of nerve injury diseases, nerve cell oxidative stress, mitochondrial damage, and lipid oxidation are closely related to the occurrence of ferroptosis in nerve cells (*Yang & Stockwell, 2016*). Studies related to central nerve injury diseases have implicated ferroptosis in the development of ischemic brain nerve injury, traumatic brain nerve injury and neurodegenerative brain diseases. In the context of peripheral nerve injury disease, ferroptosis plays an important role in neuropathic pain linked with nerve injury, which is closely related to pain sensitization. The use of ferroptosis inhibitors has shown promise for providing a neuroprotective effect by reducing the onset of neuropathic pain.

It has been established that oxidative stress and mitochondrial dysfunction are involved in the occurrence and development of many neurodegenerative diseases, such as AD and Parkinson's disease (*Dell'Orco et al., 2016*; *Jackson, 2009*). GSH, an important antioxidant in the body, can scavenge ROS, reduce hydrogen peroxide to H_2O, repair biofilms and resist ferroptosis. In addition, the depletion of GSH can also induce a decrease in the activity of GPX4, which is a central regulatory factor of ferroptosis and antioxidant reactions. GPX4 abnormalities are thought to be a necessary precondition for cell ferroptosis (*Jia et al., 2020*), and can contribute to neurodegeneration (*Cao et al., 2019*).

Under oxidative stress conditions, the level of ROS in nerve cells increases, and promotes the peroxidation of intracellular membrane lipids and proteins, which in turn leads to neuronal oxidative injury (*Dixon & Stockwell, 2014*). Furthermore, it has been documented that excessive oxidative stress is one of the main predispositions for neurological impairment. Ferroptosis inhibitors, including some ROS scavengers, can effectively block the generation of iron-catalyzed ROS, resist oxidative stress reaction, clear intracellular accumulation of ROS, and prevent ferroptosis in cells. ROS scavengers are also commonly used as anti-nerve injury drugs. However, further investigation is needed to determine the precise mechanisms underlying their neuroprotective effects, whether it be through scavenging antioxidant stress or by blocking ferroptosis.

Several types of ferroptosis inhibitors have been found, and preclinical trials have exhibited their efficacy in reducing the occurrence of ferroptosis in neuronal cells, which may mitigate the associated nerve injury diseases in a variety of central nervous system diseases consequently. Clinical trials are underway for the treatment of Parkinson's disease by using related inhibitors. Following the dose of 15 mg/Kg body weight, patients with Parkinson's disease received oral deferiprone (DFP) for 36 weeks. As a result, the nigrostriatal iron context significantly decreased in the DFP group. Although other results were not very promising (*Devos et al., 2022*). However, the clinical application of ferroptosis inhibitors for other diseases are yet to be explored. In conclusion, further research is needed to investigate the mechanisms of ferroptosis associated with nerve injury. It is essential to explore drugs and new drug targets for the prevention and treatment of ferroptosis associated with nerve injury.

ADDITIONAL INFORMATION AND DECLARATIONS

Competing Interests

The authors declare there are no competing interests.

Author Contributions

- Mingzhu Li conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Shengbo Jin performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Xudong Zhu performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Jian Xu performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Yang Cao performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Haozhe Piao conceived and designed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.

Data Availability

The following information was supplied regarding data availability:

This is a literature review.

REFERENCES

Angelova PR, Horrocks MH, Klenerman D, Gandhi S, Abramov AY, Shchepinov MS. 2015. Lipid peroxidation is essential for alpha-synuclein-induced cell death. *Journal of Neurochemistry* **133**:582–589 DOI 10.1111/jnc.13024.

Banjac A, Perisic T, Sato H, Seiler A, Bannai S, Weiss N, Kolle P, Tschoep K, Issels RD, Daniel PT, Conrad M, Bornkamm GW. 2008. The cystine/cysteine cycle: a redox cycle regulating susceptibility versus resistance to cell death. *Oncogene* **27**:1618–1628 DOI 10.1038/sj.onc.1210796.

Bannai S, Kitamura E. 1980. Transport interaction of L-cystine and L-glutamate in human diploid fibroblasts in culture. *Journal of Biological Chemistry* **255**:2372–2376 DOI 10.1016/S0021-9258(19)85901-X.

Bedoui S, Herold MJ, Strasser A. 2020. Emerging connectivity of programmed cell death pathways and its physiological implications. *Nature Reviews Molecular Cell Biology* **21**:678–695 DOI 10.1038/s41580-020-0270-8.

Brickman AM, Manly JJ, Honig LS, Sanchez D, Reyes-Dumeyer D, Lantigua RA, Lao PJ, Stern Y, Vonsattel JP, Teich AF, Airey DC, Proctor NK, Dage JL, Mayeux R. 2021. Plasma p-tau181, p-tau217, and other blood-based Alzheimer's disease biomarkers in a multi-ethnic, community study. *Alzheimer's & Dementia* **17**:1353–1364 DOI 10.1002/alz.12301.

Brown CW, Amante JJ, Chhoy P, Elaimy AL, Liu H, Zhu LJ, Baer CE, Dixon SJ, Mercurio AM. 2019. Prominin2 drives ferroptosis resistance by stimulating iron export. *Developmental Cell* **51**:575–586 DOI 10.1016/j.devcel.2019.10.007.

Cao JY, Dixon SJ. 2016. Mechanisms of ferroptosis. *Cellular and Molecular Life Science* **73**:2195–2209 DOI 10.1007/s00018-016-2194-1.

Cao JY, Poddar A, Magtanong L, Lumb JH, Mileur TR, Reid MA, Dovey CM, Wang J, Locasale JW, Stone E, Cole SPC, Carette JE, Dixon SJ. 2019. A genome-wide haploid genetic screen identifies regulators of glutathione abundance and ferroptosis sensitivity. *Cell Reports* **26**:1544–1556 DOI 10.1016/j.celrep.2019.01.043.

Chen L, Hambright WS, Na R, Ran Q. 2015. Ablation of the ferroptosis inhibitor glutathione peroxidase 4 in neurons results in rapid motor neuron degeneration and paralysis. *Journal of Biological Chemistry* **290**:28097–28106 DOI 10.1074/jbc.M115.680090.

Chen X, Li J, Kang R, Klionsky DJ, Tang D. 2021. Ferroptosis: machinery and regulation. *Autophagy* **17**:2054–2081 DOI 10.1080/15548627.2020.1810918.

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. *Nature Cell Biology* **21**:579–591 DOI 10.1038/s41556-019-0305-6.

Conteh AM, Reissaus CA, Hernandez-Perez M, Nakshatri S, Anderson RM, Mirmira RG, Tersey SA, Linnemann AK. 2019. Platelet-type 12-lipoxygenase deletion provokes a compensatory 12/15-lipoxygenase increase that exacerbates oxidative stress in mouse islet beta cells. *Journal of Biological Chemistry* **294**:6612–6620 DOI 10.1074/jbc.RA118.007102.

Cui Y, Zhang Y, Zhao X, Shao L, Liu G, Sun C, Xu R, Zhang Z. 2021. ACSL4 exacerbates ischemic stroke by promoting ferroptosis-induced brain injury and neuroinflammation. *Brain, Behavior, and Immunity* **93**:312–321 DOI 10.1016/j.bbi.2021.01.003.

David S, Jhelum P, Ryan F, Jeong SY, Kroner A. 2022. Dysregulation of iron homeostasis in the central nervous system and the role of ferroptosis in neurodegenerative disorders. *Antioxidants & Redox Signaling* **37**:150–170 DOI 10.1089/ars.2021.0218.

Dell'Orco M, Milani P, Arrigoni L, Pansarasa O, Sardone V, Maffioli E, Polveraccio F, Bordoni M, Diamanti L, Ceroni M, Peverali FA, Tedeschi G, Cereda C. 2016. Hydrogen peroxide-mediated induction of SOD1 gene transcription is independent from Nrf2 in a cellular model of neurodegeneration. *Biochimica et Biophysica Acta/General Subjects* **1859**:315–323 DOI 10.1016/j.bbagrm.2015.11.009.

Derry PJ, Hegde ML, Jackson GR, Kayed R, Tour JM, Tsai AL, Kent TA. 2020. Revisiting the intersection of amyloid, pathologically modified tau and iron in Alzheimer's disease from a ferroptosis perspective. *Progress in Neurobiology* **184**:101716 DOI 10.1016/j.pneurobio.2019.101716.

Devos D, Labreuche J, Rascol O, Corvol JC, Duhamel A, Guyon Delannoy P, Poewe W, Compta Y, Pavese N, Ruzicka E, Dusek P, Post B, Bloem BR, Berg D, Maetzler W, Otto M, Habert MO, Lehericy S, Ferreira J, Dodel R, Tranchant C, Eusebio A, Thobois S, Marques AR, Meissner WG, Ory-Magne F, Walter U, De Bie RMA, Gago M, Vilas D, Kulisevsky J, Januario C, Coelho MVS, Behnke S, Worth P, Seppi K, Ouk T, Potey C, Leclercq C, Viard R, Kuchcinski G, Lopes R, Pruvo JP, Pigny P, Garcon G, Simonin O, Carpentier J, Rolland AS, Nyholm D, Scherfler C, Mangin JF, Chupin M, Bordet R, Dexter DT, Fradette C, Spino M, Tricta F, Ayton S, Bush

AI, Devedjian JC, Duce JA, Cabantchik I, Defebvre L, Deplanque D, Moreau C, Group F-IS. 2022. Trial of deferiprone in Parkinson's disease. *New England Journal of Medicine* **387**:2045–2055 DOI 10.1056/NEJMoa2209254.

Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, Morrison B, Stockwell 3rd BR. 2012. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell* **149**:1060–1072 DOI 10.1016/j.cell.2012.03.042.

Dixon SJ, Patel DN, Welsch M, Skouta R, Lee ED, Hayano M, Thomas AG, Gleason CE, Tatonetti NP, Slusher BS, Stockwell BR. 2014. Pharmacological inhibition of cystine-glutamate exchange induces endoplasmic reticulum stress and ferroptosis. *Elife* **3**:e02523 DOI 10.7554/eLife.02523.

Dixon SJ, Stockwell BR. 2014. The role of iron and reactive oxygen species in cell death. *Nature Chemical Biology* **10**:9–17 DOI 10.1038/nchembio.1416.

Do Van B, Gouel F, Jonneaux A, Timmerman K, Gele P, Petrault M, Bastide M, Laloux C, Moreau C, Bordet R, Devos D, Devedjian JC. 2016. Ferroptosis, a newly characterized form of cell death in Parkinson's disease that is regulated by PKC. *Neurobiology of Disease* **94**:169–178 DOI 10.1016/j.nbd.2016.05.011.

Dolma S, Lessnick SL, Hahn WC, Stockwell BR. 2003. Identification of genotype-selective antitumor agents using synthetic lethal chemical screening in engineered human tumor cells. *Cancer Cell* **3**:285–296 DOI 10.1016/s1535-6108(03)00050-3.

Duce JA, Wong BX, Durham H, Devedjian JC, Smith DP, Devos D. 2017. Post translational changes to alpha-synuclein control iron and dopamine trafficking; a concept for neuron vulnerability in Parkinson's disease. *Molecular Neurodegeneration* **12**:45 DOI 10.1186/s13024-017-0186-8.

Dugger BN, Dickson DW. 2017. Pathology of neurodegenerative diseases. *Cold Spring Harbor Perspectives in Biology* **9**(7):a028035 DOI 10.1101/cshperspect.a028035.

Friedmann Angeli JP, Schneider M, Proneth B, Tyurina YY, Tyurin VA, Hammond VJ, Herbach N, Aichler M, Walch A, Eggenhofer E, Basavarajappa D, Radmark O, Kobayashi S, Seibt T, Beck H, Neff F, Esposito I, Wanke R, Forster H, Yefremova O, Heinrichmeyer M, Bornkamm GW, Geissler EK, Thomas SB, Stockwell BR, O'Donnell VB, Kagan VE, Schick JA, Conrad M. 2014. Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice. *Nature Cell Biology* **16**:1180–1191 DOI 10.1038/ncb3064.

Gao M, Monian P, Pan Q, Zhang W, Xiang J, Jiang X. 2016. Ferroptosis is an autophagic cell death process. *Cell Research* **26**:1021–1032 DOI 10.1038/cr.2016.95.

Gao M, Monian P, Quadri N, Ramasamy R, Jiang X. 2015. Glutaminolysis and transferrin regulate ferroptosis. *Molecular Cell* **59**:298–308 DOI 10.1016/j.molcel.2015.06.011.

Geng Z, Guo Z, Guo R, Ye R, Zhu W, Yan B. 2021. Ferroptosis and traumatic brain injury. *Brain Research Bulletin* **172**:212–219 DOI 10.1016/j.brainresbull.2021.04.023.

Goel P, Chakrabarti S, Goel K, Bhutani K, Chopra T, Bali S. 2022. Neuronal cell death mechanisms in Alzheimer's disease: an insight. *Frontiers in Molecular Neuroscience* **15**:937133 DOI 10.3389/fnmol.2022.937133.

Guiney SJ, Adlard PA, Bush AI, Finkelstein DI, Ayton S. 2017. Ferroptosis and cell death mechanisms in Parkinson's disease. *Neurochemistry International* **104**:34–48 DOI 10.1016/j.neuint.2017.01.004.

Guo Y, Du J, Xiao C, Xiang P, Deng Y, Hei Z, Li X. 2021. Inhibition of ferroptosis-like cell death attenuates neuropathic pain reactions induced by peripheral nerve injury in rats. *European Journal of Pain* **25**:1227–1240 DOI 10.1002/ejp.1737.

Hambright WS, Fonseca RS, Chen L, Na R, Ran Q. 2017. Ablation of ferroptosis regulator glutathione peroxidase 4 in forebrain neurons promotes cognitive impairment and neurodegeneration. *Redox Biology* **12**:8–17 DOI 10.1016/j.redox.2017.01.021.

Hansson O. 2021. Biomarkers for neurodegenerative diseases. *Nature Medicine* **27**:954–963 DOI 10.1038/s41591-021-01382-x.

Hirschhorn T, Stockwell BR. 2019. The development of the concept of ferroptosis. *Free Radical Biology and Medicine* **133**:130–143 DOI 10.1016/j.freeradbiomed.2018.09.043.

Hou W, Xie Y, Song X, Sun X, Lotze MT, Zeh 3rd HJ, Kang R, Tang D. 2016. Autophagy promotes ferroptosis by degradation of ferritin. *Autophagy* **12**:1425–1428 DOI 10.1080/15548627.2016.1187366.

Imai H, Matsuoka M, Kumagai T, Sakamoto T, Koumura T. 2017. Lipid peroxidation-dependent cell death regulated by GPx4 and ferroptosis. *Current Topics in Microbiology and Immunology* **403**:143–170 DOI 10.1007/82_2016_508.

Jackson SP. 2009. The DNA-damage response: new molecular insights and new approaches to cancer therapy. *Biochemical Society Transactions* **37**:483–494 DOI 10.1042/BST0370483.

Jhelum P, Santos-Nogueira E, Teo W, Haumont A, Lenoel I, Stys PK, David S. 2020. Ferroptosis mediates cuprizone-induced loss of oligodendrocytes and demyelination. *Journal of Neuroscience* **40**:9327–9341 DOI 10.1523/JNEUROSCI.1749-20.2020.

Jia M, Qin D, Zhao C, Chai L, Yu Z, Wang W, Tong L, Lv L, Wang Y, Rehwinkel J, Yu J, Zhao W. 2020. Redox homeostasis maintained by GPX4 facilitates STING activation. *Nature Immunology* **21**:727–735 DOI 10.1038/s41590-020-0699-0.

Kopeina GS, Zhivotovsky B. 2022. Programmed cell death: past, present and future. *Biochemical and Biophysical Research Communications* **633**:55–58 DOI 10.1016/j.bbrc.2022.09.022.

Li LB, Chai R, Zhang S, Xu SF, Zhang YH, Li HL, Fan YG, Guo C. 2019. Iron exposure and the cellular mechanisms linked to neuron degeneration in adult mice. *Cell* **8** DOI 10.3390/cells8020198.

Li Z, Li D, Chen R, Gao S, Xu Z, Li N. 2023. Cell death regulation: a new way for natural products to treat osteoporosis. *Pharmacological Research* **187**:106635 DOI 10.1016/j.phrs.2022.106635.

Li Y, Maher P, Schubert D. 1997. A role for 12-lipoxygenase in nerve cell death caused by glutathione depletion. *Neuron* **19**:453–463 DOI 10.1016/s0896-6273(00)80953-8.

Liu J, Guo ZN, Yan XL, Huang S, Ren JX, Luo Y, Yang Y. 2020. Crosstalk between autophagy and ferroptosis and its putative role in ischemic stroke. *Frontiers in Cellular Neuroscience* **14**:577403 DOI 10.3389/fncel.2020.577403.

Lockshin RA. 2016. Programmed cell death 50 (and beyond). *Cell Death and Differentiation* **23**:10–17 DOI 10.1038/cdd.2015.126.

Mahoney-Sanchez L, Bouchaoui H, Ayton S, Devos D, Duce JA, Devedjian JC. 2021. Ferroptosis and its potential role in the physiopathology of Parkinson's disease. *Progress in Neurobiology* **196**:101890 DOI 10.1016/j.pneurobio.2020.101890.

Mandal PK, Seiler A, Perisic T, Kolle P, Banjac Canak A, Forster H, Weiss N, Kremmer E, Lieberman MW, Bannai S, Kuhlencordt P, Sato H, Bornkamm GW, Conrad M. 2010. System x(c)- and thioredoxin reductase 1 cooperatively rescue glutathione deficiency. *Journal of Biological Chemistry* **285**:22244–22253 DOI 10.1074/jbc.M110.121327.

Maniam S, Maniam S. 2021. Small molecules targeting programmed cell death in breast cancer cells. *International Journal of Molecular Sciences* **22(18)**:9722 DOI 10.3390/ijms22189722.

Mi Y, Gao X, Xu H, Cui Y, Zhang Y, Gou X. 2019. The emerging roles of ferroptosis in Huntington's disease. *NeuroMolecular Medicine* **21**:110–119 DOI 10.1007/s12017-018-8518-6.

Moreau C, Duce JA, Rascol O, Devedjian JC, Berg D, Dexter D, Cabantchik ZI, Bush AI, Devos D, Group F-Is. 2018. Iron as a therapeutic target for Parkinson's disease. *Movement Disorders* **33**:568–574 DOI 10.1002/mds.27275.

Rui T, Wang H, Li Q, Cheng Y, Gao Y, Fang X, Ma X, Chen G, Gao C, Gu Z, Song S, Zhang J, Wang C, Wang Z, Wang T, Zhang M, Min J, Chen X, Tao L, Wang F, Luo C. 2021. Deletion of ferritin H in neurons counteracts the protective effect of melatonin against traumatic brain injury-induced ferroptosis. *Journal of Pineal Research* **70**:e12704 DOI 10.1111/jpi.12704.

Samir P, Malireddi RKS, Kanneganti TD. 2020. The PANoptosome: a deadly protein complex driving pyroptosis, apoptosis, and necroptosis (PANoptosis). *Frontiers in Cellular and Infection Microbiology* **10**:238 DOI 10.3389/fcimb.2020.00238.

Santagostino SF, Assenmacher CA, Tarrant JC, Adedeji AO, Radaelli E. 2021. Mechanisms of regulated cell death: current perspectives. *Veterinary Pathology* **58**:596–623 DOI 10.1177/03009858211005537.

Sato H, Tamba M, Ishii T, Bannai S. 1999. Cloning and expression of a plasma membrane cystine/glutamate exchange transporter composed of two distinct proteins. *Journal of Biological Chemistry* **274**:11455–11458 DOI 10.1074/jbc.274.17.11455.

Schneider M, Forster H, Boersma A, Seiler A, Wehnes H, Sinowatz F, Neumuller C, Deutsch MJ, Walch A, Hrabe de Angelis M, Wurst W, Ursini F, Roveri A, Maleszewski M, Maiorino M, Conrad M. 2009. Mitochondrial glutathione peroxidase 4 disruption causes male infertility. *FASEB Journal* **23**:3233–3242 DOI 10.1096/fj.09-132795.

Seiler A, Schneider M, Forster H, Roth S, Wirth EK, Culmsee C, Plesnila N, Kremmer E, Radmark O, Wurst W, Bornkamm GW, Schweizer U, Conrad M. 2008. Glutathione peroxidase 4 senses and translates oxidative stress into 12/15-lipoxygenase dependent- and AIF-mediated cell death. *Cell Metabolism* **8**:237–248 DOI 10.1016/j.cmet.2008.07.005.

Shah R, Shchepinov MS, Pratt DA. 2018. Resolving the role of lipoxygenases in the initiation and execution of ferroptosis. *ACS Central Science* **4**:387–396 DOI 10.1021/acscentsci.7b00589.

Shi ZZ, Osei-Frimpong J, Kala G, Kala SV, Barrios RJ, Habib GM, Lukin DJ, Danney CM, Matzuk MM, Lieberman MW. 2000. Glutathione synthesis is essential for mouse development but not for cell growth in culture. *Proceedings of the National Academy of Sciences of the United States of America* **97**:5101–5106 DOI 10.1073/pnas.97.10.5101.

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. *Nature Chemical Biology* **12**:497–503 DOI 10.1038/nchembio.2079.

Stockwell BR, Friedmann Angeli JP, Bayir H, Bush AI, Conrad M, Dixon SJ, Fulda S, Gascon 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, Salnikow K, Tang D, Torti FM, Torti SV, Toyokuni S, Woerpel KA, Zhang DD. 2017. Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. *Cell* **171**:273–285 DOI 10.1016/j.cell.2017.09.021.

Tan Q, Fang Y, Gu Q. 2021. Mechanisms of modulation of ferroptosis and its role in central nervous system diseases. *Frontiers in Pharmacology* **12**:657033 DOI 10.3389/fphar.2021.657033.

Tang D, Kang R, Berghe TV, Vandenabeele P, Kroemer G. 2019. The molecular machinery of regulated cell death. *Cell Research* **29**:347–364 DOI 10.1038/s41422-019-0164-5.

Thirupathi A, Chang YZ. 2019. Brain iron metabolism and CNS diseases. *Advances in Experimental Medicine and Biology* **1173**:1–19 DOI 10.1007/978-981-13-9589-5_1.

Tong X, Tang R, Xiao M, Xu J, Wang W, Zhang B, Liu J, Yu X, Shi S. 2022. Targeting cell death pathways for cancer therapy: recent developments in necroptosis, pyroptosis, ferroptosis, and cuproptosis research. *Journal of Hematology & Oncology* **15**:174 DOI 10.1186/s13045-022-01392-3.

Tower J. 2015. Programmed cell death in aging. *Ageing Research Reviews* **23**:90–100 DOI 10.1016/j.arr.2015.04.002.

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. *Molecular Psychiatry* **22**:1520–1530 DOI 10.1038/mp.2017.171.

Ufer C, Wang CC, Fahling M, Schiebel H, Thiele BJ, Billett EE, Kuhn H, Borchert A. 2008. Translational regulation of glutathione peroxidase 4 expression through guanine-rich sequence-binding factor 1 is essential for embryonic brain development. *Genes and Development* **22**:1838–1850 DOI 10.1101/gad.466308.

van Leyen K, Kim HY, Lee SR, Jin G, Arai K, Lo EH. 2006. Baicalein and 12/15-lipoxygenase in the ischemic brain. *Stroke* **37**:3014–3018 DOI 10.1161/01.STR.0000249004.25444.a5.

Wang H, Huo X, Han C, Ning J, Chen H, Li B, Liu J, Ma W, Li Q, Yu Y, Shi K. 2021. Ferroptosis is involved in the development of neuropathic pain and allodynia. *Molecular and Cellular Biochemistry* **476**:3149–3161 DOI 10.1007/s11010-021-04138-w.

Wenzel SE, Tyurina YY, Zhao J, St Croix CM, Dar HH, Mao G, Tyurin VA, Anthonymuthu TS, Kapralov AA, Amoscato AA, Mikulska-Ruminska K, Shrivastava IH, Kenny EM, Yang Q, Rosenbaum JC, Sparvero LJ, Emlet DR, Wen X, Minami Y, Qu F, Watkins SC, Holman TR, Van Demark AP, Kellum JA, Bahar I, Bayir H, Kagan VE. 2017. PEBP1 wardens ferroptosis by enabling lipoxygenase generation of lipid death signals. *Cell* **171**:628–641 DOI 10.1016/j.cell.2017.09.044.

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 DOI 10.1038/s41586-019-1426-6.

Wu Q, Miao X, Zhang J, Xiang L, Li X, Bao X, Du S, Wang M, Miao S, Fan Y, Wang W, Xu X, Shen X, Yang D, Wang X, Fang Y, Hu L, Pan X, Dong H, Wang H, Wang Y, Li J, Huang Z. 2021. Astrocytic YAP protects the optic nerve and retina in an experimental autoimmune encephalomyelitis model through TGF-beta signaling. *Theranostics* **11**:8480–8499 DOI 10.7150/thno.60031.

Xie BS, Wang YQ, Lin Y, Mao Q, Feng JF, Gao GY, Jiang JY. 2019. Inhibition of ferroptosis attenuates tissue damage and improves long-term outcomes after traumatic brain injury in mice. *CNS Neuroscience & Therapeutics* **25**:465–475 DOI 10.1111/cns.13069.

Yan N, Zhang J. 2019. Iron metabolism, ferroptosis, and the links with Alzheimer's disease. *Frontiers in Neuroscience* **13**:1443 DOI 10.3389/fnins.2019.01443.

Yang WS, Kim KJ, Gaschler MM, Patel M, Shchepinov MS, Stockwell BR. 2016. Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis. *Proceedings of the National Academy of Sciences of the United States of America* **113**:E4966–E4975 DOI 10.1073/pnas.1603244113.

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 DOI 10.1016/j.cell.2013.12.010.

Yang WS, Stockwell BR. 2008. Synthetic lethal screening identifies compounds activating iron-dependent, nonapoptotic cell death in oncogenic-RAS-harboring cancer cells. *Chemistry and Biology* **15**:234–245 DOI 10.1016/j.chembiol.2008.02.010.

Yang WS, Stockwell BR. 2016. Ferroptosis: death by lipid peroxidation. *Trends in Cell Biology* **26**:165–176 DOI 10.1016/j.tcb.2015.10.014.

Yant LJ, Ran Q, Rao L, Van Remmen H, Shibatani T, Belter JG, Motta L, Richardson A, Prolla TA. 2003. The selenoprotein GPX4 is essential for mouse development and protects from radiation and oxidative damage insults. *Free Radical Biology and Medicine* **34**:496–502 DOI 10.1016/s0891-5849(02)01360-6.

Yoo MH, Gu X, Xu XM, Kim JY, Carlson BA, Patterson AD, Cai H, Gladyshev VN, Hatfield DL. 2010. Delineating the role of glutathione peroxidase 4 in protecting

cells against lipid hydroperoxide damage and in Alzheimer's disease. *Antioxidants & Redox Signaling* **12**:819–827 DOI 10.1089/ars.2009.2891.

Yu F, Zhang Q, Liu H, Liu J, Yang S, Luo X, Liu W, Zheng H, Liu Q, Cui Y, Chen G, Li Y, Huang X, Yan X, Zhou J, Chen Q. 2022. Dynamic O-GlcNAcylation coordinates ferritinophagy and mitophagy to activate ferroptosis. *Cell Discovery* **8**:40 DOI 10.1038/s41421-022-00390-6.

Zhang J, Zheng Y, Wang Y, Wang J, Sang A, Song X, Li X. 2022. YAP1 alleviates sepsis-induced acute lung injury via inhibiting ferritinophagy-mediated ferroptosis. *Frontiers in Immunology* **13**:884362 DOI 10.3389/fimmu.2022.884362.

Zhou Z, Lu J, Ma J, Zhu L. 2022. Identification of potential ferroptosis key genes in the pathogenesis of lumbosacral spinal root avulsion by RNA sequencing and bioinformatics analysis. *Frontiers in Molecular Biosciences* **9**:902607 DOI 10.3389/fmolb.2022.902607.

Zhao J, Wu Y, Liang S, Piao X. 2022. Activation of SSAT1/ALOX15 axis aggravates cerebral ischemia/reperfusion injury via triggering neuronal ferroptosis. *Neuroscience* **485**:78–90 DOI 10.1016/j.neuroscience.2022.01.017.

Zhu K, Zhu X, Liu S, Yu J, Wu S, Hei M. 2022. Glycyrrhizin attenuates hypoxic-ischemic brain damage by inhibiting ferroptosis and neuroinflammation in neonatal rats via the HMGB1/GPX4 pathway. *Oxidative Medicine and Cellular Longevity* **2022**:8438528 DOI 10.1155/2022/8438528.

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 peroxidation in ferroptotic cell death. *ACS Central Science* **3**:232–243 DOI 10.1021/acscentsci.7b00028.

Zou Y, Li H, Graham ET, Deik AA, Eaton JK, Wang W, Sandoval-Gomez G, Clish CB, Doench JG, Schreiber SL. 2020. Cytochrome P450 oxidoreductase contributes to phospholipid peroxidation in ferroptosis. *Nature Chemical Biology* **16**:302–309 DOI 10.1038/s41589-020-0472-6.