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Ferroptosis and Its Role in Diverse Brain Diseases

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Abstract

Ferroptosis is a recently identified, iron-regulated, non-apoptotic form of cell death. It is characterized by cellular accumulation of lipid reactive oxygen species that ultimately leads to oxidative stress and cell death. Although first identified in cancer cells, ferroptosis has been shown to have significant implications in several neurologic diseases, such as ischemic and hemorrhagic stroke, Alzheimer's disease, and Parkinson's disease. This review summarizes current research on ferroptosis, its underlying mechanisms, and its role in the progression of different neurologic diseases. Understanding the role of ferroptosis could provide valuable information regarding treatment and prevention of these devastating diseases.

Keywords Ferroptosis · Brain disease · Stroke · Cancer

Introduction

Ferroptosis, first described by Dixon et al. in 2012, is a form of cell death characterized by accumulation of intracellular iron [1]. It is defined by depletion of plasma membrane unsaturated fatty acids and accumulation of iron-induced lipid reactive oxygen species (ROS) [2]. The over-accumulation of lipid ROS leads to an oxidative stress response in cells that causes lethal damage to proteins, nucleic acids, and lipids [3] and eventually to cell death. Thus, ferroptosis requires the coincident depletion of glutathione (GSH) or inactivation of glutathione-dependent antioxidant enzyme glutathione peroxidase 4 (GPX4) and the incorporation of oxidizable polyunsaturated fatty acids into phospholipids [4].

Ferroptosis differs from apoptosis, necrosis, and autophagy morphologically, biochemically, and genetically [1]. Under electron microscopy, ferroptotic cells exhibit shrunken mitochondria, whereas mitochondria are usually swollen in other forms of cell death [1]. Initially, Dixon et al. identified a distinct set of genes that regulate the ferroptotic mechanism, including ribosomal protein L8 (*RPL8*), iron response element binding protein 2 (*IREB2*), and ATP synthase F_0 complex subunit C3 (*ATP5G3*) [1]. Later studies showed that numerous genes/proteins participate in this unique cell death process, including cyclooxygenase-2 (*PTGS2*) [5], p53 [6], nuclear factor E2-related factor 2 (Nrf2) [7], PEBP1 [8], and more. In addition to those key regulators, ferroptosis can be induced by excessive glutamate, intracellular iron accumulation, or treatment with small molecules—for example, erastin, RSL3, and others listed in Table 1. The first ferroptosis-inducing compounds, erastin (which inhibits system x_c^-, the glutamate/cystine antiporter) and Ras selective lethal 3 (RSL3, which directly inhibits GPX4), were discovered several years before identification of the ferroptosis concept [65, 66]. Stockwell's group was surprised to find that cells treated with those compounds were neither apoptotic nor necroptotic [1, 57, 65, 66], and that cell death could be inhibited by lipophilic antioxidants (α-tocopherol, butylated hydroxytoluene, and β-carotene), indicating that lipoxygenase activity and lipophilic ROS were involved in this cell death process [61, 67, 68].

Known inducers of ferroptosis can be divided into several categories: system x_c^- inhibitors (glutamate, erastin, sulfasalazine, and sorafenib), GSH depletion compounds (buthioninesulfoximine and acetaminophen), and GPX4 direct inhibitors (RSL3 and FIN56) [1, 68, 69]. Additionally,

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Table 1 Main inducers, inhibitors, and regulators in brain diseases relevant to ferroptosis

Target	Compound name/protein/gene	Function	Brain diseases with relevance to ferroptosis
Inducers			
VDACs and system x_c^-	Erastin [1], erastin derivatives (PE [5], AE [9], IKE [9])	Reduces intracellular GSH content	Neuroblastoma [10]
System x_c^-	Sulfasalazine [11], sorafenib [12], lanperisone [13], glutamate [14]	Depletes GSH	PD [15], AD [16], HD [17], PVL [18], glioblastoma [19]
GPX4	RSL3 [1], (1S,3R)-RSL3 [5], DPI7 [5], DPI10 [5], DPI12 [5], DPI13 [5], DPI17 [5], DPI18 [5], DPI19 [5], ML162 [20], WA [21]	Directly inhibits GPX4, accumulation of lipid hydroperoxides	PD [22], AD [23], HD [24], ASL [25]
Lipid peroxidation	$FINO_2$ [26], ART [27]	$FINO_2$ indirectly inhibits GPX4 function and directly oxidizes iron, leading to accumulation of lipid hydroperoxides. ART interacts with lysosomal iron and generates ROS.	AD [28], PD [29], HD [30], ASL [31], Friedreich's ataxia [32]
Iron	t-BHP [33], ferric ammonium citrate [33], WA [21]	Increases iron abundance	Neurodegenerative diseases [33], ischemic stroke [34], ICH [35], aging [36], PD [37], neuroblastoma [21]
Inhibitors			
GSH	DPI2 [5], cisplatin [38], Ace [39], BSO [5]	Depletes GSH	PD [40], HD [41], AD [42], ALS [43], Friedreich's ataxia [44]
Iron	DFO [1], Ciclopirox olamine [45], 2,2-bipyridyl [1], deferiprone [46]	Chelates iron	Ischemic stroke [34], ICH [47], PD [47]
Lipid peroxidation	Fer-1 [1], SRS11–92 [18], SRS16–86 [48], trolox [1], liproxstatin-1 [49], vitamin E [1], CoQ_{10} [1], U0126 [50], Flt3 [51]	Inhibits lipid ROS	AD [28], PD [15], ICH [50], HD [18], PVL [18], ischemic stroke [34]
Cystine	β-mercaptoethanol [1]	Increases cystine uptake	Glioblastoma [52]
Lipoxygenase	Zileuton [53], baicalein [54], NDGA [55], PD146176 [56], CDC [57], AA861 [56]	Blocks lipoxygenase-induced lipid peroxidation	HD [57], PVL [57]
Protein synthesis	Cp [34]	Suppresses ferroptosis	Ischemic stroke [34], AD [58], PD [58]
Regulators			
	GPX4 [5]	Essential regulators	PD [22], HD [57], PVL [57]
	P53 [6], HSPB1 [59], Rb [12], SLC7a11 [60], VDACs [61], Nrf2 [62], ATF4 [11]	Cancer cell regulators	Glioblastoma [63]
	RPL13 [64], *IREB2* [1], *ATP5G3* [1], *CS* [1], *TTC35* [1], *ACSF2* [1]	Mitochondrial genes	AD [64]

ACSF2, acyl-CoA synthetase family member 2; *AD*, Alzheimer's disease; *AE*, aldehyde erastin; *ALS*, amyotrophic lateral sclerosis; *ART*, artesunate; *ATF4*, activating transcription factor 4; CoQ_{10}, coenzyme Q_{10}; *Cp*, ceruloplasmin; *CS*, citrate synthase; *DFO*, deferoxamine; *DPI*, diphenylene iodonium; *Fer-1*, ferrostatin-1; $FINO_2$, 1, 2-dioxolane; *Flt3*, FMS-like tyrosine kinase-3; *GPX4*, glutathione peroxidase 4; *GSH*, glutathione; *HD*, Huntington's disease; *HSPB1*, heat shock protein β-1; *ICH*, intracerebral hemorrhage; *IKE*, imidazole ketone erastin; *IREB2*, iron response element binding protein 2; *NDGA*, nordihydroguaiaretic acid; *Nrf2*, nuclear factor E2-related factor 2; *PD*, Parkinson's disease; *PE*, phosphatidylethanolamines; *PVL*, periventricular leukomalacia; *Rb*, retinoblastoma; *ROS*, reactive oxygen species; *RPL13*, ribosomal protein L13; *RSL3*, Ras-selective lethal 3; *t-BHP*, tert-butylhydroperoxide; *TTC35*, tetratricopeptide repeat domain 35; *VDACs*, voltage-dependent anion channels; *WA*, withaferin A

several molecules have been identified as inhibitors of ferroptosis, including ferrostatin-1 (Fer-1, which inhibits lipid ROS) [1], deferoxamine (DFO, which chelates iron) [1], zileuton (which inhibits 5-lipoxygenase) [53], and recently identified $FINO_2$ (which oxidizes iron) [70], depending on the mechanism of ferroptosis. In this review, we focus on ferroptosis in different brain diseases and summarize the primary inducers, regulators, and inhibitors of ferroptosis-associated brain disorders, as shown in Table 1.

Ferroptosis has been identified in various cancer cells, including breast [71], lung [1], lymphoma [72], kidney [73], and brain [10]. Strikingly, the inducers of ferroptosis have been shown to target and kill cancerous cells [74]. In 2015, Jiang et al. reported that ferroptosis also contributes to embryo development and that p53 plays a vital role in ferroptosis regulation [6]. More importantly, research in organotypic hippocampal slice cultures has shown that ferroptosis also contributes to neuronal death [1]. Indeed, we and others have shown a connection between ferroptosis and neurodegeneration in experimental intracerebral hemorrhage [35, 75], Parkinson's disease [15], and periventricular leukomalacia [18]. In this article, we will systematically review the role of ferroptosis in different brain diseases, discuss our current understanding of the underlying mechanism, and describe the possible therapeutic strategies (Figs. 1 and 2).

Ferroptosis in Stroke

Stroke ranks number 5 among all causes of death, behind diseases of the heart, cancer, chronic lower respiratory disease, and unintentional injuries/accidents [76]. Each year, approximately 795,000 people experience a new or recurrent stroke, 87% of which are ischemic strokes [76]. An ischemic stroke occurs when the blood supply to certain parts of the brain is restricted secondary to occlusion of the internal carotid, middle cerebral, or vertebral/basilar arteries [77]. The resulting depletion of oxygen and nutrients may cause cells to activate the ischemic cascade, which results in oxidative stress, mitochondrial impairment, and, ultimately, cell death [78]. Before ferroptosis was identified, it was already known that iron accumulation exaggerates neuronal damage during reperfusion both clinically and in animal models of ischemic stroke [79–85]. It had been shown that iron chelation reduces reperfusion damage in animals after an ischemic event [86–89]. In 2013, Speer et al. hypothesized that ferroptosis might contribute to neuronal death induced by cerebral ischemia and that hypoxia-inducible factor (HIF) prolyl hydroxylases might serve as a target for the beneficial effects of metal chelators [90]. They further postulated that the beneficial effects of iron chelators in preventing ferroptosis were due to inhibition of 2-oxoglutarate, oxygen-dependent dioxygenases, and the HIF prolyl hydroxylases, but not to direct inhibition of Fenton chemistry or ROS formation [90]. Then, in 2017, a study showed that ferroptosis inhibition protected mice against ischemia-reperfusion injury in a middle cerebral artery occlusion (MCAO) model, indicating that ferroptosis contributes to neuronal death after ischemic stroke [34]. Interestingly, the authors found that tau knockout mice were protected from ferroptotic cell death after ischemia-reperfusion injury and introduced the tau–iron interaction as a pleiotropic modulator of ferroptosis and ischemic stroke outcome [34].

Intracerebral hemorrhage (ICH) accounts for 10–30% of all stroke cases and is associated with higher rates of mortality and morbidity than is ischemic stroke [76, 91]. Until recently, apoptosis, necrosis, and autophagy were thought to be the only contributors to neuronal death after ICH [92–97]. However, solid data have shown the presence of neuronal ferroptosis after ICH in vitro and in vivo [35, 50, 98]. In 2014, we found that (−)-epicatechin, a brain-permeable flavanol, reduced early brain injury after ICH, in part by decreasing brain iron deposition and ferroptosis-related gene expression [75]. In 2017, we found that Fer-1 prevented hemoglobin-induced neuronal death and reduced GPX4 activity deficiency in brain slice cultures, and it rescued ferroptotic neurons and reduced cyclooxygenase-2 (Cox-2) expression in collagenase- and blood injection-induced ICH mouse models [35]. In addition, using transmission electron microscopy, we showed that ferroptosis co-exists with necrosis and autophagy in vivo and that using a combination of inhibitors to target these different forms of cell death rescued neurons from hemoglobin-induced toxicity better than any inhibitor alone [35, 98]. At the same time, Zille et al. found that a number of ferroptosis inhibitors, including Fer-1, DFO, N-acetylcysteine (which inhibits ROS and reactive lipid species), and Trolox (a vitamin E analog that targets reactive lipid species), were able to rescue mouse primary cortical neurons from hemin- and hemoglobin-induced death in vitro [50]. Additionally, they found that elevated phospho-ERK1/2 levels were associated with enhanced neuronal ferroptosis and that U0126, an MEK inhibitor, inhibited this cell death mechanism [50]. Notably, in erastin- or amino acid starvation-induced ferroptosis in cancer cells, the more selective and potent MEK inhibitor PD0325901 failed to block cell death [99]. The authors claimed that U0126 had off-target effects and that the MEK-ERK1/2 signaling pathway was not involved in the ferroptotic mechanism [99]. Interestingly, Zille et al. found that necroptosis inhibitor necrostatin-1 also reduced hemin-induced cell death and that the treated cells exhibited a necrotic phenotype with loss of plasma membrane integrity and disintegration of organelles in vitro, indicating that ferroptosis may be an early stage of necrosis [50]. Recently, Zhang et al. showed that GPX4 expression level was dramatically reduced during the acute phase of ICH and that increasing GPX4 level was able to rescue neurons from secondary ferroptotic death and improve ICH outcomes in rats [100].

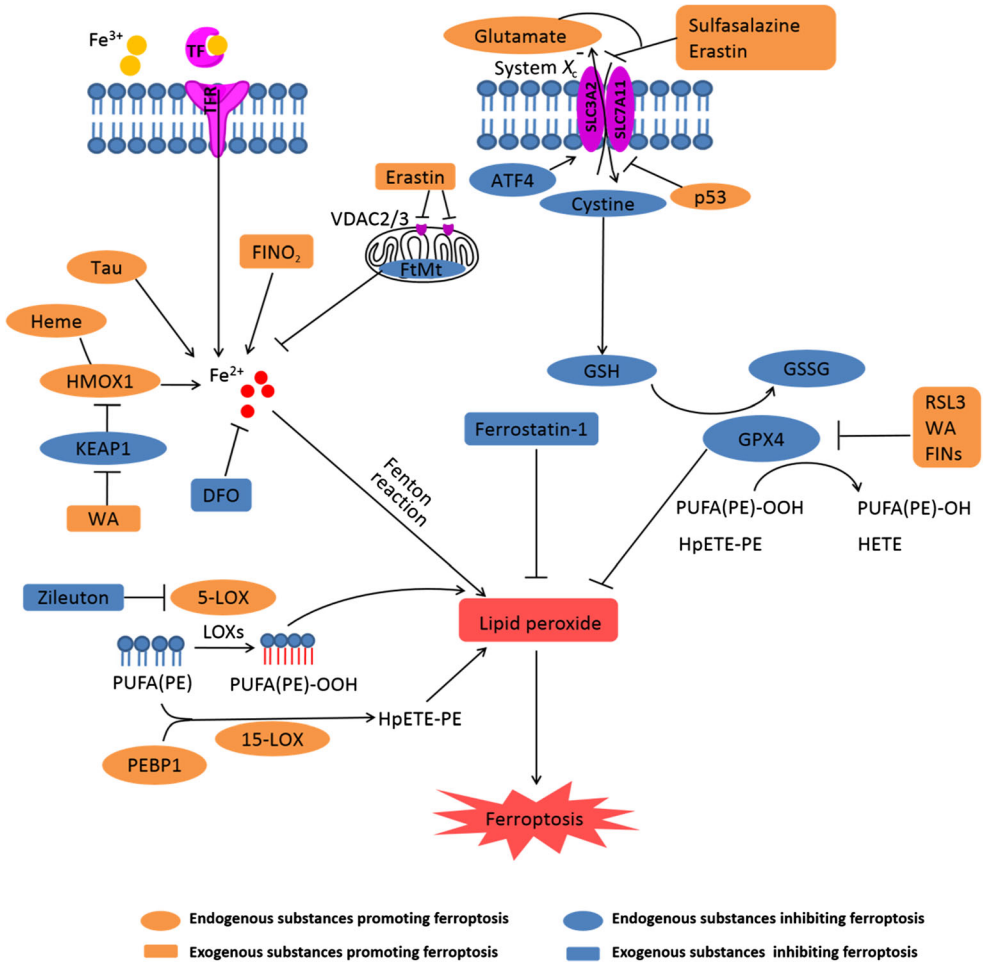

Fig. 1 Induction and inhibition of ferroptosis. Ferroptosis is induced by lethal lipid peroxidation in the central nervous system. Dysregulation of intracellular iron metabolism and/or glutathione peroxidation pathways leads to accumulation of lipid reactive oxygen species (ROS) and eventually causes cell death. Various inducers and inhibitors are shown. Arrows indicate promotion; blunt-ended lines indicate inhibition. ATF4, activating transcription factor 4; DFO, deferoxamine; $FINO_2$, 1, 2-dioxolane; FINs, ferroptosis-inducing agents; FtMt, mitochondrial ferritin; GPX4, glutathione peroxidase 4; GSH, glutathione; HMOX1, heme oxygenase-1; HpETE, hydroperoxyeicosatetraenoic acid; KEAP1, Kelch-like ECH-associated protein 1; LOX, lipoxygenase; PE, phosphatidylethanolamine; PEBP1, phosphatidylethanolamine-binding protein 1; PUFA, polyunsaturated fatty acid; RSL3, Ras-selective lethal 3; TF, transferrin; TFR, transferrin receptor; VDAC2/3, voltage-dependent anion channel 2/3; WA, withaferin A

Ferroptosis in Parkinson's Disease

Parkinson's disease (PD) is typified by death of neurons in the substantia nigra pars compacta (SNpc), which regulates motor function. PD causes rigidity, tremor, and other motor symptoms [101, 102]. Apoptosis is known to be a major contributor to cell death during the progression of the disease [103]. Evidence also has shown that iron and dopamine levels in the SNpc are elevated in patients with PD [104–106]. Notably, GSH depletion, lipid peroxidation, and elevated ROS levels, which are commonly observed in patients with PD, are also features of ferroptosis [107–109]. Consistent with these findings, Ayton et al. reported that mice with a genetic deletion for ceruloplasmin (an iron-export ferroxidase) developed parkinsonism that was rescued by iron chelation [110]. Additionally, iron chelators have been shown to improve motor symptoms in animal models [106, 110–112] and in a clinical trial [46].

Recently, ferroptosis has also been linked to PD [15]. Researchers found that ferroptosis is a key cell death pathway for dopaminergic neurons and that Fer-1 administration reduces neuronal death in vitro (SH-SY5Y cell line and differentiated Lund human mesencephalic [LUHMES] cells), ex vivo (organotypic slice cultures), and in vivo (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP] mouse model) [10, 15]. Importantly, Do Van et al. claimed that ferroptosis induced by erastin in LUHMES cells was initiated by activation of MEK in a RAS-independent manner [15]. This mechanism differed from findings in other cell lines, in which the calcium chelator BAPTA and PKC inhibitors (the bisindolylmaleimide analog Bis-III and siRNA) were very effective at counteracting erastin-induced cell death [15, 113]. The authors explained that

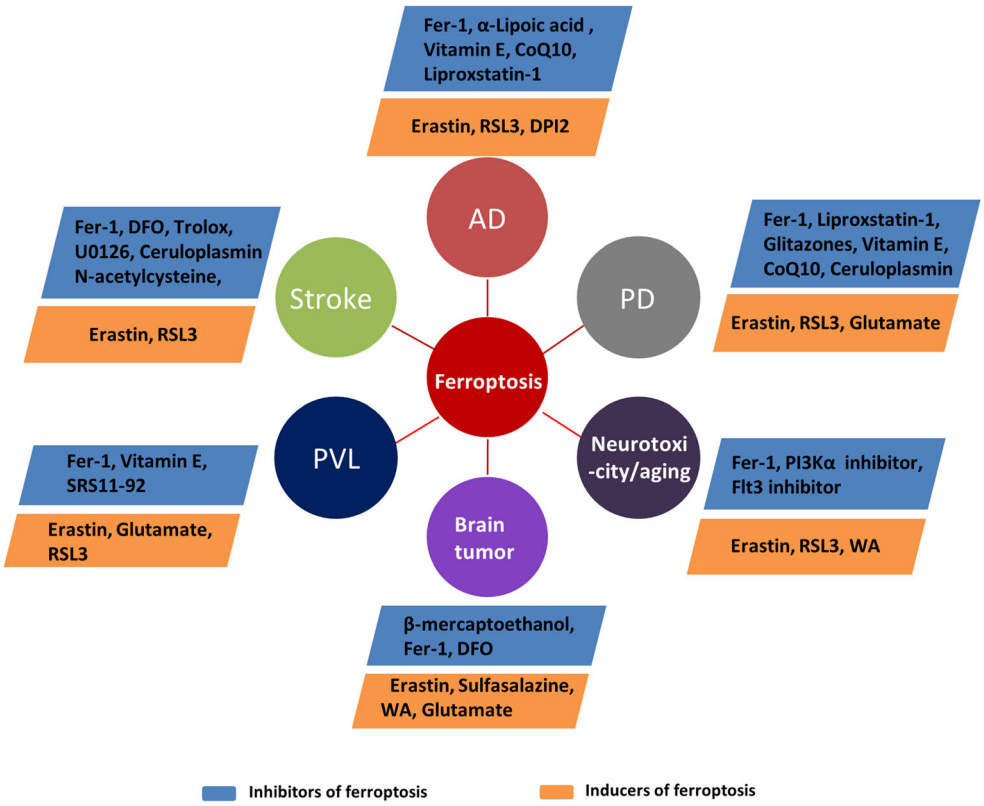

Fig. 2 The role of ferroptosis in diverse brain diseases. Various inducers and inhibitors in different brain diseases are shown. AD, Alzheimer's disease; CoQ_{10}, coenzyme Q_{10}; DFO, deferoxamine; DPI, diphenylene iodonium; Fer-1, ferrostatin-1; Flt3, FMS-like tyrosine kinase-3; PD, Parkinson's disease; PI3Kα, phosphatidylinositol 3-kinase α; PVL, periventricular leukomalacia; RSL3, Ras-selective lethal 3; WA, withaferin A

the distinctive mechanisms were due to the unique metabolic feature of dopaminergic neurons [15]. A year later, Gouel et al. found that human platelet lysates protected the LUHMES cell line from erastin-induced ferroptosis [114]. However, they found that AKT, but not MEK or RAS, participated in erastin-induced cell death when they used U0126 and manumycin A to inhibit MEK and RAS, respectively [114]. These controversial results [15, 114] in erastin-treated LUHMES cells may stem from the off-target effect of MEK inhibitor U0126. Thus, whether erastin-induced ferroptosis is RAS-dependent needs further investigation.

On the other hand, some studies have focused on how astrocytes protect against neuronal ferroptotic cell death. Astrocytes have a high capacity to store iron and prevent iron overload in neurons [115]. Astrocytes provide neurons with glutathione S-transferase Mu 2 and other antioxidants to protect them from oxidative damage. Therefore, dysregulation of astrocyte-neuron interactions and inadequate Nrf2 activation in astrocytes may lead to ferroptosis-like cell death in neurons, especially dopaminergic neurons [47, 116].

Ferroptosis in Alzheimer's Disease

Alzheimer's disease (AD) is caused by the degeneration of neurons required for learning and memory [16]. Postmortem analysis of brains from AD patients shows evidence of apoptosis, which is likely responsible for a large amount of the neurodegeneration [117, 118]. However, new forms of cell death are now considered to contribute to the neuronal destruction of AD because several of the degenerating processes cannot be explained by apoptosis alone and drugs targeting apoptosis are largely ineffective [119–122].

Lipid peroxidation and iron dysregulation, which are hallmarks of ferroptosis, have long been noted in AD brains [123, 124]. In a recent study, mice with specific cerebral cortex and hippocampal neuronal GPX4 knockout (GPX4 brain inducible knockout, Gpx4BIKO) exhibited marked cognitive impairment in a water maze test, as well as degeneration of hippocampal neurons [16]. The authors suggested that the degenerating neurons might be undergoing ferroptosis because the level of neurodegeneration was reduced when the mice were fed a high-vitamin E diet or administered the ferroptosis inhibitor liproxstatin-1 [16]. Another study published earlier this year showed that overexpression and hyperphosphorylation of Tau induced ferroptotic neuronal death and that α-lipoic acid administration rescued neurons by downregulating iron transferrin receptor, decreasing phospho-P38 level, and upregulating xCT and GPX4 expression [125]. These studies suggest that ferroptosis can potentially affect neurons important for learning and memory. As an extension, the findings also indicate that ferroptosis may play an important role in neuronal death during AD progression.

Ferroptosis in Huntington's Disease

Huntington's Disease (HD) is yet another progressive neurodegenerative disorder that leads to rapid involuntary

movements and dementia [126]. Oxidative damage [127], lipid oxidation [128], iron accumulation [17], dysregulation of GSH [41], and decreased GPX activity [24] have been noted in experimental HD animal models and in patients with HD. Delivery of iron chelators has been shown to improve cognitive function in an HD mouse [17].

To date, only one study has used a cellular model of HD (overexpression of HD-causing gene, huntingtin [htt] exon 1) to examine whether ferroptosis inhibitor Fer-1 could prevent cell death [18]. The data indicated a probable role for ferroptosis in the progressive neurodegeneration of HD. In vivo studies are needed to validate the role of ferroptosis in the progression of HD and its disease-specific pathologic mechanisms.

Ferroptosis in Periventricular Leukomalacia

Periventricular leukomalacia (PVL) is a form of cerebral white matter injury that affects premature infants. It is characterized by the death of developing oligodendrocytes [129]. Several studies have indicated an important role for iron in oligodendrocyte death, and some have found elevated levels of ROS biomarkers [130–133]. In addition, an abundance of lipid oxidation products typical of ferroptosis have been found in the cerebrospinal fluid of infants with white matter injuries [131]. Another study found that GSH depletion in rat oligodendrocytes induced cell death that could be prevented with vitamin E (known to act as a ferroptosis inhibitor) [134]. All evidence indicates that ferroptosis may play a role in PVL.

To mimic PVL in vitro, Skouta et al. cultured oligodendrocytes in cystine-free medium, which depletes GSH and causes cell death [18]. Fer-1 and SRS11-92 (15-fold more potent than the parent Fer-1) fully protected oligodendrocytes from cystine deprivation [18]. These data suggest that ferroptosis is a likely mechanism oligodendrocyte death in PVL.

Ferroptosis in General Neurotoxicity and Aging

Neurotoxicity is defined by the Environmental Protection Agency as "an adverse change in the structure or function of the central and/or peripheral nervous system following exposure to a chemical, physical, or biological agent" [135]. In their initial classification and identification of ferroptosis, Dixon and colleagues found that using Fer-1 to inhibit ferroptosis protected rat hippocampal slice cultures from glutamate-induced neurotoxicity, suggesting a role for lipid ROS-induced cell death and most likely ferroptosis in neurotoxicity [1]. One study from Sanford-Burnham Medical Research Institute identified two potential ferroptosis inhibitors with distinct molecular mechanisms: the PI3Kα inhibitor protects neuronal cells by inducing partial restoration of depleted GSH levels and accumulation of intracellular amino acids, whereas the Flt3 inhibitor prevents lipid peroxidation, a key mechanism of glutamate-mediated toxicity [51]. Another study showed that inhibition of HIF prolyl hydroxylases prevents oxidative stress-induced ferroptosis in vitro [90].

Levels of iron have long been known to increase with aging [136]. Additionally, iron and intra-cell iron retention have been associated with aging in diverse cell types, including neurons [137]. During the process of aging, the distribution of iron molecules changes between neurons and glial cells [138]. Iron accumulation in aged glial cells has been shown to damage neurons by increasing proinflammatory cytokines and establishing neuroinflammation [139, 140]. It has been reported recently that iron retention in neurons promotes premature aging via induction of DNA damage [141]. Intracellular iron retention also has been linked to damage in the epigenome through hypomethylation and transposable elements [142, 143]. The acceleration of aging via DNA damage has recently been named ferrosenescence [137].

Research into senescent cells has revealed an increase in iron accumulation, but impaired ferritinophagy, a lysosomal process that promotes ferritin degradation and ferroptosis [36]. Impaired ferritin degradation leads to a phenotype of senescent cells with elevated iron accumulation, whereby iron is effectively trapped in ferritin, creating a perceived cellular deficiency [36]. Thus, senescent cells are highly resistant to ferroptosis [36].

Ferroptosis in Brain Tumors

Ferroptosis was first identified in the non-small cell lung cancer cell line HT-1080 [1]. Although research has been conducted in relation to ferroptosis in many forms of cancer, little work has examined the role of ferroptosis in brain cancers. Nevertheless, Fer-1 recently was shown to have a neuroprotective role in the dopaminergic neuroblastoma cell line SH-SY5Y under conditions of rotenone-induced oxidative stress [10]. Fer-1 was able to decrease ROS/reactive nitrogen species generated under rotenone insult, mitigate rotenone-induced α-synuclein aggregation, and even quench the stable radical from 2,2-diphenyl-1-picrylhydrazyl (DPPH) [10]. Other investigators reported that mitochondrial ferritin (FtMt) overexpression in SH-SY5Y cells significantly inhibited erastin-induced ferroptosis [144]. They also found that FtMt inhibited ferroptosis by regulating iron homeostasis, in particular by repressing cellular labile iron pool overload and altering iron-related proteins [144].

Relatively more ferroptosis-related studies have pertained to glioblastoma than to neuroblastoma. Shortly after ferroptosis was discovered, a group in Russia transplanted glioma-35 cells into mouse and found that administering iron-containing water to tumor-bearing mice before radiation therapy reduced the supercoiled DNA index on days 1 and 21 after irradiation. Additionally, it dramatically decreased the

tumor volume compared with that of control on day 21 [19]. The same group repeated their study in a rat model and found consistent results that iron-containing water promoted radiation-induced tumor cell apoptosis and ferroptosis [145]. Injection of DFO into the tumor-bearing rats reduced the efficiency of this treatment but had no effect on the efficiency of radiotherapy alone [145].

From 2016 to 2018, the Savaskan group published five papers discussing the role of glutamate exchanger xCT (*SLC7a11* gene coding protein, a subunit of system x_c^-) in temozolomide (Temodal/Temcad®, TMZ)-treated glioma cells [60, 63, 146–148]. They reported that xCT expression correlated with the malignancy grade of brain tumor and that xCT inhibition disrupted the neurodegenerative and microenvironment-toxifying activity of gliomas [146]. TMZ efficacy can be potentiated when combined with erastin (which inhibits system x_c^-), and gliomas with high xCT expression are more vulnerable to combination treatment with erastin-TMZ [146]. In the same year, they found that high concentrations (> 200 μM) of sulfasalazine, a system x_c^- inhibitor that inhibits glioma growth [149], reduced glioma tumor volume by mechanistically inducing ferroptotic cell death in glioma cells in vitro [60]. Importantly, neurons and normal brain tissue barely responded to sulfasalazine, and isolated astrocytes were less sensitive than glioma cells to sulfasalazine toxicity [60]. Sulfasalazine treatment did not affect experimental tumor growth, but it did reduce glioma-derived edema in vivo [60]. Later, they revealed that activating transcription factor 4 (ATF4) was a vital step in elevating cellular xCT and that ATF4 knockdown rendered glioma cells susceptible to erastin, sorafenib, and RSL3-induced ferroptosis [63]. Therefore, they confirmed the previous results [150] that inhibition of ATF4 may be an option for reducing glioma tumor growth and angiogenesis [63], overcoming chemo-resistance from TMZ, and promoting drug efficacy in human gliomas [148]. Fan and colleagues found that, in addition to AFT4, Nrf2 overexpressed in glioma and negatively correlated with patient survival [147]. Consistent with studies in a lung carcinoma cell line [7], bladder carcinoma cells [151], and other cancer cell lines [152], they found that Nrf2 upregulated xCT expression and that activation of Nrf2 signaling promoted resistance to ferroptosis in glioma cell lines [147]. However, Berghe's group found that withaferin A induced ferroptotic cell death in high-risk neuroblastoma cells by binding to KEAP1 [21]. Consequently, it increased Nrf2 protein level and activated heme oxygenase-1 (HO-1). Elevated HO-1 induced accumulation of Fe^{2+} and subsequently induced lipid ROS and ferroptosis [21]. Moreover, withaferin A decreased GPX4 expression and induced ferroptosis [21]. Although most researchers believe that activation of the Nrf2 signaling pathway inhibits ferroptosis [153], these results suggest that Nrf2 may play a role in promoting ferroptosis under certain conditions.

Conclusions, Limitations, and Further Directions

The goal of this review was to discuss the role of ferroptosis, a newly identified form of cell death, in various brain disease processes, including neurologic disorders and brain tumors. Although it was first identified in cancer cells [1], ferroptosis has been shown to play an important role in the progression and toxicity of numerous neurologic diseases, including stroke, PD, and HD. As shown in Fig. 2, the common ferroptotic mechanisms in brain diseases result from system x_c^- blockade, GSH depletion, GPX4 inactivity, lipoxygenase inactivation, and/or intracellular iron accumulation. These mechanisms are consistent with those seen in other disease states (renal disease, ischemic-reperfusion-related disease, and brain tumor) that can be modified by known ferroptotic inducers (glutamate, erastin, and RSL3) and inhibitors (Fer-1, liproxstatin-1, DFO, and vitamin E). However, whether MAPK, PI3K/Akt/mTOR, or KEAP1/Nrf2/HO-1 signaling pathways are common to ferroptosis-related brain diseases, or whether these signaling pathways are disease-specific, remains an open question. In addition, neurons differ from other brain cells (microglia, astrocytes, or oligodendrocytes) and cells from other organs in their metabolism, dividing capacity, nerve impulse function, circuit formation, etc. Thus, when neurons are challenged with ferroptosis inducers, they could exhibit unique mechanisms that have not yet been fully investigated.

Ferroptosis is a unique form of regulated cell death that involves gene sets and signaling pathways distinct from those of apoptosis, necrosis, autophagy, and oxytosis [1, 154]. Apoptotic cells exhibit classic features such as mitochondrial cytochrome c release, caspase activation, and chromatin fragmentation. Additionally, apoptosis can be inhibited by caspase inhibitors, and its main regulators are Bcl-2 and caspase-3 [1, 2]. Cells undergoing necrosis exhibit plasma membrane permeabilization and swollen organelles. Phosphorylation of RIPK1 and RIPK3 play important roles in necrosis, and the necrotic process can be inhibited by necrostatins [1, 2]. Autophagy is characterized by the formation of autophagosomes and autolysosomes, and it can be inhibited by 3-MA [1, 2]. Upregulation of Atg5 and Atg6 plays a vital role in the autophagy pathway [1, 2]. Ferroptosis is induced by iron-dependent lipid ROS [1]. Cells undergoing ferroptosis exhibit shrunken mitochondria and a highly intense mitochondrial membrane [1, 2]. However, emerging evidence shows that ferroptosis might be a regulated necrotic cell death [4, 50]. In addition, studies have found that autophagy and ferroptosis share key regulators (SLC7a11, GPX4, Nrf2, p53, HSPB1, CISD1, FANCD2, and ACSL4) [155]. Some elegant studies showed that autophagy promotes ferroptosis by degradation of ferritin in cancer cells and fibroblasts [156] and that activation of BECN1 (an important regulator in autophagy) promotes ferroptosis by directly blocking system x_c^- activity in tumor cells [157].

Oxytosis, also known as oxidative glutamate toxicity, is another form of cell death that was identified 30 years ago [158]. It is frequently compared to ferroptosis because the two cell death forms have similar mechanisms of lethality [154]. Oxytosis is induced by depletion of GSH that can result from high concentrations of extracellular glutamate or other reagents that inhibit system x_c^- [2]. Mitochondrial ROS production, Ca^{2+} influx, and oxidative stress are the hallmarks of oxytosis [2]. Increasing evidence shows that oxytosis and ferroptosis share many similarities, including inducers (glutamate and RSL3), lethal mechanisms (GSH depletion and lipid ROS), a key regulator (GPX4), metal dependency (iron), and ultrastructural features (mitochondria abnormality) [1, 154, 159, 160]. Some researchers believe that these mechanisms could be one cell death form with two names [154]. The data remain controversial. Dixon et al. claimed that ferroptosis depends on iron only [1], but recent studies showed that ferroptosis may also involve copper and calcium, as oxytosis does [154, 161]. Studies have shown that most ferroptotic cells (erastin-treated MEF cells, erastin-treated BJeLR cells, and RSL3-treated MEF cells) have shrunken mitochondria with increased electron density [1, 6, 154]. In their review, Lewerenz et al. noted that both ferroptotic cells (RSL3-treated MEF cells) and oxytotic cells (glutamate-induced HT4 cells) had swollen mitochondria with outer membranes that ruptured in a time-dependent manner [154]. At this point, more studies are needed to ascertain the relationship and crosstalk between ferroptosis and other forms of cell death and to determine whether ferroptosis belongs to one of those forms of cell death.

This review is generally limited by the amount of research currently being performed on ferroptosis. Given that ferroptosis was only first identified in 2012, relatively few studies have been published on the topic. Iron accumulation that leads to cell death has been shown to contribute to many disease states, but research into the role of ferroptosis in particular is still sparse. Most of the research to date has focused on the contribution of ferroptosis to neurologic processes, but future research should also address the therapeutic benefits of inhibiting ferroptosis in brain cells that exhibit certain neurodegenerative disease characteristics and promoting ferroptosis in brain cancers. Some studies have suggested a role for GSH depletion in the progression of amyotrophic lateral sclerosis (ALS) [43], a neurodegenerative disease that causes muscular atrophy and paralysis [126]. However, conclusions have been mixed, with some researchers indicating no change in GSH levels [162, 163]. At present, the role of ferroptosis in ALS is unclear and requires further research.

Epigenetic modifications are also important regulators of cellular activity and cell death. Although several miRNAs (miR-137 and miR-9) have been linked to ferroptosis [164, 165], studies are needed to investigate how long non-coding RNA or circulating RNA regulates ferroptosis, and how methylation status of the CpG island and modifications of histone tails in the promoter regions of key regulators regulate ferroptosis. Furthermore, little is known about the relationship between ferroptotic cells and circulating immune system reaction. Future research could focus on how ferroptotic cells induce immune cell activation/infiltration or how surrounding immune cells regulate ferroptosis in brain cells.

We believe that ferroptosis is one of the most important cell death forms in brain diseases and that in-depth studies of ferroptosis will provide new opportunities for diagnosis and therapeutic intervention.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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