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Review

Origins of nervous tissue susceptibility to ferroptosis

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ABSTRACT

Ferroptosis is a newly defined form of programmed cell death. It possesses unique processes of cell demise, cytopathological changes, and independent signal regulation pathways. Ferroptosis is considered to be deeply involved in the development of many diseases, including cancer, cardiovascular diseases, and neurodegeneration. Intriguingly, why cells in certain tissues and organs (such as the central nervous system, CNS) are more sensitive to changes in ferroptosis remains a question that has not been carefully discussed. In this Holmesian review, we discuss lipid composition as a potential but often overlooked determining factor in ferroptosis sensitivity and the role of polyunsaturated fatty acids (PUFAs) in the pathogenesis of several common human neurodegenerative diseases. In subsequent studies of ferroptosis, lipid composition needs to be given special attention, as it may significantly affect the susceptibility of the cell model used (or the tissue studied).

1. An overview of ferroptosis

Ferroptosis is an iron-dependent programmed cell death, characterized by cytosolic iron accumulation, exhaustion of antioxidant defenses and lipid peroxidation at the plasma membrane (Dixon et al., 2012). Ferroptosis is distinct from other forms of cell death in that it lacks the cell membrane blebbing, apoptotic bodies, and chromatin condensation seen in apoptosis, the cell rupture and mitochondrial swelling seen in necroptosis/necrosis, and the accumulation of autophagosomes characteristic of autophagic cell death (Lee et al., 2021). In fact, ferroptosis results in unique organelle morphological changes, namely mitochondrial shrinkage, increased mitochondrial membrane density, and loss of cristae (Dixon et al., 2012). First named in 2012 by Dixon et al., ferroptosis was discovered when researching compounds lethal to rat sarcoma virus (RAS)-mutant tumor cells. Specifically, the RAS-selective lethal (RSL) compounds (erastin and RSL3) induced an iron-dependent form of cell death in oncogenic RAS-mutant cell lines (Dixon et al., 2012). Recently, ferroptosis has been linked to several prominent diseases. In cancer, induction of ferroptosis has shown to be a promising tumor regression therapy (Chen et al., 2020; Wei et al., 2021; Yang et al., 2021). However, ferroptotic cell death causes significant tissue damage in ischemia-reperfusion and neurodegenerative diseases (Yan et al., 2021). This review aims to outline the elements and pathways involved in ferroptosis, and provide a possible explanation for the neuronal sensitivity seen in various human neurological disorders, especially neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), etc.

2. Core elements of ferroptosis: biological and inorganic factors

The mechanistic origins of ferroptosis ultimately center on GPX4 inactivation. Glutathione peroxidase 4 (GPX4) is an antioxidant selenoprotein that catalyzes the reduction of hydrogen peroxides and lipid peroxides into lipid alcohols using reduced glutathione (GSH) as a cofactor. GSH is synthesized from cysteine, which is formed from cystine that is transported into the cell through the system X_c^- (a cystine/glutamate antiporter) and then reduced to cysteine. Cysteine can also be synthesized from methionine via the transsulfuration pathway. Given the characteristic accumulation of lipid peroxide species in the plasma membrane, GPX4 acts as an inhibitor of ferroptosis. GPX4 can be inactivated through several ferroptosis inducers (FINs), such as erastin-induced inactivation of SLC7AII (a component of the X_c^- antiporter), RSL3-induced inactivation of GPX4, as well as cystine starvation. Inactivation of GPX4, either directly or indirectly, leads to an accumulation of lipid peroxide species in both the plasma and organelle membranes (Friedmann et al., 2014; Xu et al., 2019; Yang et al., 2014).

It is important to note that GPX4 is not the only ferroptosis inhibitor. Ferroptosis suppressor protein 1 (FSP1), discovered in 2019, is a cytosolic oxidoreductase that reduces ubiquinone (also known as coenzyme Q10 or CoQ) to a radical-trapping antioxidant at the plasma membrane (Bersuker et al., 2019). FSP1 operates in parallel to cytosolic GPX4, and while inactivation of FSP1 alone does not trigger a strong ferroptosis

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response (most likely due to functional overlap with GPX4), it does sensitize cells to GPX4 inhibitors (Bersuker et al., 2019; Pontel et al., 2022). In addition, FSP1 has shown to compensate for GPX4 activity and promote tumor growth in *GPX4* knockout lung cancer cell lines by preventing ferroptotic cell death (Bersuker et al., 2019; Pontel et al., 2022). Dihydroorotate dehydrogenase (DHODH) represents another ferroptosis defense mechanism with specific intracellular activities. While FSP1 is localized to the plasma membrane, DHODH is expressed in the inter-membrane space of mitochondria, where it protects against lipid oxidation of the mitochondrial inner membrane by coupling the oxidation of dihydroorotate (DHO) to orotate (OA) with the reduction of CoQ to ubiquinol ($CoQH_2$) in pyrimidine biosynthesis. DHODH and mitochondrial specific GPX4 (mtGPX4) show complementary activities, as only inactivation of both enzymes resulted in increased mitochondrial membrane oxidation (Mao et al., 2021).

Another recently discovered ferroptotic inhibitor, GTP cyclohydrolase-1 (GCH1), is the rate-limiting enzyme for the synthesis of the antioxidant tetrahydrobiopterin (BH_4). As with FSP1, inactivation of GCH1 alone does not produce a strong ferroptotic response in non-oncogenic cells, but overexpression of *GCH1* or exogenous administration of BH_4 in *GPX4* knockout cells is able to inhibit ferroptosis by selectively protecting certain phosphatidylcholines (PCs) with two polyunsaturated fatty acid (PUFA) tails from oxidation (Kraft et al., 2020). Perhaps the most shocking observation is the oxidation of other phospholipids in those same *GPX4* knockout cells. While PCs with only one PUFA tail are degraded in *GCH1* overexpression cells, PC 20:4_20:4, PC 20:4_20:5, and PC 20:4_22:6 show no significant depletion (in phospholipid notation, PC 20:4_22:6 corresponds to a phosphatidylcholine containing 20 carbons and 4 double bonds in chain one and 22 carbons with 6 double bonds in chain two - this can also be written in shorthand as PC 42:10). Clearly GCH1 only prevents the oxidation of a specific subset of PUFA-containing phospholipids, yet ferroptosis is still inhibited (Kraft et al., 2020). Inactivation of GCH1 has also been shown to promote erastin-induced ferroptosis in colorectal cancer – a cancer type that is generally resistant to pharmacologically induced ferroptosis (Hu et al., 2022). GCH1 targeting has also demonstrated tumor-suppressive activity in glioblastoma stem cells (Jiang et al., 2022). Long story short: ferroptosis is regulated by several anti-oxidizing proteins, of which GPX4 is the most well-studied and arguably has the strongest impact on preventing cell death. FSP1, DHODH, and GCH1 represent additional ferroptosis inhibitors, but specific phospholipids protected by GCH1 indicate lipid composition to be a determinant of ferroptotic sensitivity.

While it would be simpler to say that GPX4 dysregulation is the sole cause of ferroptosis, the picture is never that simple. Ferroptosis is an iron-dependent programmed cell death. Accumulation of iron in cells results in the production of reactive oxygen species (ROS) that react with phospholipids of the plasma membrane via the Fenton reaction. Iron is transported into the cell by binding to transferrin (TF), which is recognized by transferrin receptor 1 (TFR1) on the plasma membrane (Mf et al., 2021; Xu et al., 2019). Once transported into the cell by TFR1-mediated endocytosis, cytosolic iron binds to ferritin. Stored in ferritin, iron poses no threat to the lipid species of the plasma membrane. However, NCOA4-, ATG5-, and ATG7-mediated autophagy (called ferritinophagy) releases iron from ferritin, allowing for the interaction with hydrogen peroxide and the formation of ROS. Thus, inactivation of autophagy genes (*NCOA4*, *ATG5*, *ATG7*) inhibits ferroptosis by preventing the release of free iron (Hou et al., 2016). While iron is primarily exported from the cell through ferroportin-1 (FPN1), ferroptosis can also be inhibited by inducing prominin-2 expression, which contributes to the formation of ferritin-containing exosomes (Brown et al., 2019). A delicate balance between iron import (TF and TFR1), iron storage (ferritin), and iron export (FPN1) contributes to ferroptotic activity through the ROS levels generated by Fenton reaction.

3. Execution of ferroptosis: oxidation of polyunsaturated fatty acids (PUFAs)

While reviewing the mechanisms of ferroptosis activation and inhibition, it may have become apparent that the lipid composition in the plasma membrane plays a defining role in ferroptosis sensitivity. Recall that iron accumulation generates ROS through Fenton reaction (conversion of H_2O_2 into hydroxyl radicals). These radicals are then free to interact with the phospholipids (PLs) of the cell membranes to produce lipid peroxides.

$$e^- + O_2 \rightarrow O_2^{\bullet-} \rightarrow H_2O_2 + Fe^{2+} \rightarrow \bullet OH + PL \rightarrow PL\bullet + O_2 \rightarrow PL\text{-}OO\bullet \rightarrow PL\text{-}OOH$$

Thus far we have characterized ferroptosis as a cell death resulting from the oxidation of lipids by ROS, but specifically, it is the PUFAs found in the plasma membrane that have the greatest impact on ferroptotic induction (Yang et al., 2016). PUFAs are long-chain fatty acids that are easily oxidized by ROS due to the weak C–H bonds found at the bis-allylic positions. Oxidation of PUFAs produces toxic byproducts that disrupt membrane permeability and lead to cell death (Gaschler & Stockwell, 2017). PUFAs are inserted into the plasma membrane by acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3), where they are vulnerable to ROS attack (Xu et al., 2019). While inactivation of GPX4 is known to induce ferroptosis, *GPX4-ACSL4* double knockout cells demonstrate that ACSL4 inhibition results in significant ferroptotic resistance, indicating the lipid composition of the plasma membrane as a determining factor in ferroptosis initiation. This sensitivity to ferroptosis can be restored in *GPX4-ACSL4* double knockout cells when supplemented with exogenous PUFAs, such as omega-6 arachidonic acid (AA – 20:4) and omega-3 docosahexaenoic acid (DHA – 22:6), both of which are enriched in the brain (Doll et al., 2017). ACSL4 activation has also been implicated in ischemia-reperfusion related ferroptosis (Li et al., 2019). It is important to note that only an increase in PUFAs is likely to initiate ferroptosis, as exogenous administration of monounsaturated fatty acids (MUFAs) produce ferroptosis-resistant cells by reducing the concentration of PUFAs at the plasma membrane. Incorporation of MUFAs into the plasma membrane via ACSL3 has been shown to displace PUFAs, reducing plasma membrane oxidation and, in turn, ferroptosis sensitivity (Magtanong et al., 2019).

Even free PUFAs, not incorporated into phospholipids, can sensitize cells to ferroptosis. In the case of AA, this is accomplished through the activity of the tumor suppressor protein Fas-associated factor 1 (FAF1). The UAS domain of FAF1 interacts with free AA to induce polymerization and sequester lipids into a globular structure, preventing interaction with free iron (Cui et al., 2022). Cultured cells deficient in FAF1 showed increased sensitivity to ferroptosis when treated with physiological levels of AA and/or RSL3 (compared to FAF1 competent controls), but this sensitivity was rescued through *FAF1-ACSL4* double knockout. Intriguingly, AA treatment had no effect on the incorporation of AA into phospholipids, yet increased production of malondialdehyde (MDA), a lipid peroxide intermediate, in both cultured cells and *Faf1*−/− mice (Cui et al., 2022). Thus, a lack of PUFAs (either in the plasma membrane or the cytosol) is sufficient to prevent ferroptosis regardless of GPX4 activity. It is important to note that PUFAs can also be enzymatically oxidized by lipoxygenases, which generate hydroperoxides, and cyclooxygenases, which generate endoperoxides (Dyall et al., 2022; Yang et al., 2016). Lipoxygenases are particularly sensitive to peroxidation of AA with arachidonate 5-lipoxygenase (ALOX5) being responsible for oxidizing AA at carbon 5 (Gaschler & Stockwell, 2017; Rouzer et al., 1986). In summary, due to their innate structure, PUFAs are easily oxidized by ROS and oxygenases, disrupting membrane permeability and contributing to ferroptosis. ACSL4 inhibition demonstrates the

importance of PUFAs in the cell membranes, with increased PUFA concentrations sensitizing cells to ferroptosis, whereas decreased PUFA concentrations promote ferroptotic resistance.

4. Lipid composition of the brain: clue to neural sensitivity

As previously mentioned, ferroptosis has been linked to several diseases, including cancer, ischemia-reperfusion, and neurodegeneration (Reichert et al., 2020; Tian et al., 2020; Yan et al., 2021). The frequency with which ferroptosis is seen in cancer can be explained by high iron and high ROS correlated with oncogenic transformation. The proliferative cell growth of tumors requires an increase in iron and lipid metabolism to meet the energy demands of continuous cell division, which also predisposes them to ferroptosis by generating more ROS (Hassannia et al., 2019; Li & Li, 2020). Reperfusion of ischemic tissue can lead to ischemia-reperfusion injury when reoxygenation of ischemic tissue results in a significant increase in mitochondrial ROS. This rapid accumulation of ROS can lead to cell death linked to ferroptosis, especially in myocardial injury (Cadenas, 2018; Li et al., 2021). However, the association with neurodegeneration begs the question – why neurons? Why do neurons show higher sensitivity to ferroptosis? What makes them more prone to an iron-dependent cell death than other tissue types? Given that the brain has the second highest concentration of lipids in the human body (50–60% of dry weight) after adipose tissue (Larrieu & Layé, 2018), a possible explanation may lie in the differential lipid composition of the brain, which increases neuronal sensitivity to lipid peroxidation and thus to ferroptosis.

While all cells possess a plasma membrane, the lipid composition of these membranes varies across tissue type. For example, erythrocytes are known to have a high concentration of cholesterol, making their plasma membranes more rigid, but also increasing O_2 permeability – a necessary feature for oxygen transport and gas exchange (Al-Samir et al., 2021; Alberts et al., 2002). However, studies have linked oxidation of cholesterol (known as oxysterols) in red blood cells to increased ROS production, GSH depletion, and an oxidative stress-dependent cell death (Tesoriere et al., 2014). Following a similar logic, neurons of the central nervous system (CNS) show a signature enrichment of two PUFAs, AA (20:4) and DHA (22:6) (Dyall, 2015; Mota-Martorell et al., 2022). In rats, DHA accounts for 10–15% of the fatty acid volume of the brain (depending on region), while <5% of liver, 7% of heart, and <1% of adipose tissue are composed of DHA (Sugasini et al., 2019). Note that adipose tissue has the highest lipid concentration of all tissues, yet only <1% is PUFAs characteristically enriched in the brain. The same study measured comparable amounts of AA in both the heart and brain, supporting lipid composition as a determining factor in ferroptosis susceptibility observed in heart failure, including ischemia-reperfusion (Yang et al., 2022).

As free unesterified PUFAs, both AA and DHA can be incorporated into phospholipids when esterified at the sn-2 position. The lack of saturation and increased number of double bonds in PUFAs endow neuronal membranes with flexibility and hyperplasticity, which are necessary for brain development, learning, memory, and formation of new synaptic circuitry (Cutuli, 2017; Denis et al., 2013). DHA and AA accretion in the brain is highest during the final prenatal trimester and the first 2 postnatal years. Once accumulated to high enough levels, PUFA concentrations remain constant throughout childhood and adulthood, but some studies note a slight drop in PUFA levels later in life, which is associated with age-related cognitive decline (Lauritzen et al., 2016; Martínez & Mougan, 1998). However, lipid profiling of different regions of the brain indicate that the lipid composition is generally maintained throughout adulthood with only minor changes (i.e., a slight decrease in omega-6 and an increase in omega-3 PUFAs) in selected regions. These changes are most pronounced in adults aged 80 years and older (Mota-Martorell et al., 2022). Why these PUFA levels decrease is likely due to the increased lipid peroxidation that results from increased oxidative stress associated with aging. Interactions with ROS convert DHA into 4-hydroxyhexanal (4-HHE) and AA into 4-hydroxynonenal (4-HNE) (Ionescu-Tucker & Cotman, 2021; Sun et al., 2018), but increased dietary DHA intake showed mostly mixed results on memory and learning in elderly populations (Cutuli, 2017; McNamara et al., 2018; Power et al., 2022). Less research has been done on the effects of dietary AA supplementation, but some studies have shown improved hippocampal functioning in senescent rats (Inoue et al., 2019). However, treatment with AA or linoleic acid (a metabolic precursor of AA) sensitizes cells to RSL3-induced ferroptosis, suggesting a delicate balance between the neuroprotective and neurodestructive effects of PUFA (Yang et al., 2016).

A significant portion of the research focused on brain cell sensitivity to oxidative stress has centered on the interaction between astrocytes and neurons (Bélanger et al., 2011). As the most abundant glial cell in the brain, astrocytes have many supportive roles to neuronal function, including maintaining the blood-brain barrier, clearing synaptic glutamate to prevent neurotoxicity, and GSH synthesis (Barber & Raben, 2019; Dringen, 2000). Astrocytes appear to play a protective role in reducing oxidative stress in neurons due to the preferential expression of nuclear factor erythroid-2-related factor 2 (Nrf2), which activates several antioxidant related genes, including those involved in ferroptosis inhibition (Ali et al., 2009; Shih et al., 2003; Vargas & Johnson, 2009). The increased neuronal glucose and oxygen demand, especially when under oxidative stress, lead to dysregulation in Nrf2 expression and reduced antioxidant protection in both astrocytes and neurons (Albert-Garay et al., 2022; Ishii et al., 2019).

In both mono- and tri-cultures, microglia were the most sensitive to erastin and RSL3-induced ferroptosis, followed by astrocytes and neurons (Jiao et al., 2022; Ryan et al., 2023). Expression analysis of cells treated with RSL3 showed a consistently decreased expression of *ACSL4*, but a diverse pattern of ferroportin-1, namely a reduction in microglia while an increase in neurons. From this, RSL3 treatment may attenuate neuronal susceptibility to ferroptosis by promoting iron export. The authors thus propose differential iron metabolism as an explanation for varying ferroptosis sensitivities (Jiao et al., 2022), however, this is in contrast to pantothenate kinase-associated neurodegeneration (PKAN)-derived cells in which iron accumulation is found in neurons and astrocytes (lesser in neurons) but not in microglia and oligodendrocytes, yet astrocytes (having greater iron accumulation) survive longer (Kruer et al., 2011; Santambrogio et al., 2022). In addition, PKAN-derived astrocytes appear to exert a cytotoxic effect on PKAN-derived neurons rather than the antioxidant protection previously discussed (Santambrogio et al., 2022).

Despite the lack of clear data from humans, lipidomic analysis of rodent cerebellar cells reveals distinct profiles between astrocytes and neurons. At least 17 phospholipids differ between the two cell types, with astrocytes showing a significant enrichment in PE O- 34:2, PE 38:2, and PE O- 36:2 and neurons showing elevated levels of PC 38:6, PC 40:6, PC 36:2, PE 36:4, and PC O- 36:2 (Neumann et al., 2019). Due to the limitations of current technology, we cannot yet know for certain if these phospholipids contain AA (20:4) or DHA (22:6) as the same total carbon and double bond number can be achieved by various fatty acid compositions. However, the number of double bonds in PC 38:6, PC 40:6, and PE 36:4 confirm one or more PUFA chains (potentially AA or DHA). The remaining phospholipids with 2 double bonds may or may not contain PUFAs, depending on the lipid species. These results are consistent with the enrichment of PC in the neurons and astrocytes of mice brains when compared with microglia and oligodendrocytes; however, with shorter chain lengths, the lesser the total carbon and fewer double bonds. In general, astrocytes were enriched in PE species, oligodendrocytes in sulfatide or hexosylceramide species, microglia in sphingomyelin species, and neurons in phosphatidylglycerol species (Fitzner et al., 2020). Further analysis of the fatty acid chains within these lipid species would reveal a more conclusive role of AA and DHA in the differential susceptibility of neurons and glia to ferroptosis.

While the characteristic lipid composition of the CNS is necessary for both structural and functional capabilities, it also renders the plasma

membranes vulnerable to increased peroxidation. The specific enrichment of AA (20:4) and DHA (22:6) in the brain is particularly noteworthy when considering the inhibitory effects of GCH1. Kraft et al., found that *GPX4* knockout cells overexpressing GCH1 exhibited increased ferroptotic resistance by preventing the oxidation of PC 20:4_20:4, PC 20:4_20:5, and PC 20:4_22:6 (Kraft et al., 2020). In their study, oxidation of phospholipids containing AA or DHA tails was more likely to induce ferroptosis. This opens GCH1 as a potential target to inhibit neuronal ferroptosis by preventing the oxidation of these PUFAs that are preferentially expressed in greater amounts in the brain. In conclusion, we favor the following explanation: brain-specific enrichment of PUFAs, such as DHA and AA, is likely to determine ferroptosis sensitivity and promote the iron-dependent cell death, which is disproportionally observed in neurons (Fig. 1).

5. PUFAs and ferroptosis in human neurological diseases

5.1. Parkinson's disease (PD)

PD represents the second most common neurodegenerative disease. It is a movement disorder characterized by the loss of dopaminergic neurons in the *substantia nigra* of the brain. This progressive neuron loss causes bradykinesia, tremor, and other motor function impairments (Tysnes & Storstein, 2017). The exact cause of PD remains largely unknown and varies by familial (autosomal dominant and recessive) and sporadic forms. The best-studied monogenic forms include mutations in the *PARK2* (*PRKN*) and *PARK6* (*PINK1*) genes, which encode proteins involved in mitochondrial quality control mechanisms (Pickrell & Youle, 2015), and the aggregation of α-synuclein proteins (Lewy bodies) encoded by the *SNCA* gene (Shahnawaz et al., 2020). Other genes linked to monogenic and sporadic PD include *LRRK2*, *ATXN2/3*, *GCH1*, *PARK7*, and *PANK2,* where GCH1 is directly associated with ferroptosis and PANK2 is the overarching genetic contributor to the aforementioned PKAN (Houlden & Singleton, 2012).

Recently, ferroptosis has been linked to PD in both laboratory and clinical settings (Ko et al., 2021; Mahoney-Sánchez et al., 2021), with many studies preventing dopaminergic neuron loss and/or motor impairments by targeting the ferroptosis pathways (Hu et al., 2023; Huang et al., 2021; Lin et al., 2022; Yue et al., 2022). Why this programmed cell death is so commonly in neurodegenerative diseases such as PD may be due to lipid composition and altered lipid metabolism of the brain. Based on a recent study, dietary intake of omega-3 and omega-6 fatty acids appears to have no effect on plasma PUFA levels or disease severity in PD patients, but plasma levels of DHA and AA are positively correlated with the severity of non-motor symptoms (Yoo et al., 2021). Generally, PD patients exhibit abnormal PUFA composition in their brains, but whether these levels are higher or lesser than normal physiological levels is inconclusive. Previous studies have shown decreased PUFA levels in the *substantia nigra* of PD when compared to other brain regions and healthy controls; and increased levels of MDA (the lipid peroxide intermediate), 4-HNE (product of AA peroxidation and ferroptosis biomarker), and more dopaminergic neuron loss (Brion & Saffar, 1979; Dexter et al., 1986; McCormack et al., 2005). These results indicate decreased PUFA concentrations and increased cell death as the results of excessive lipid

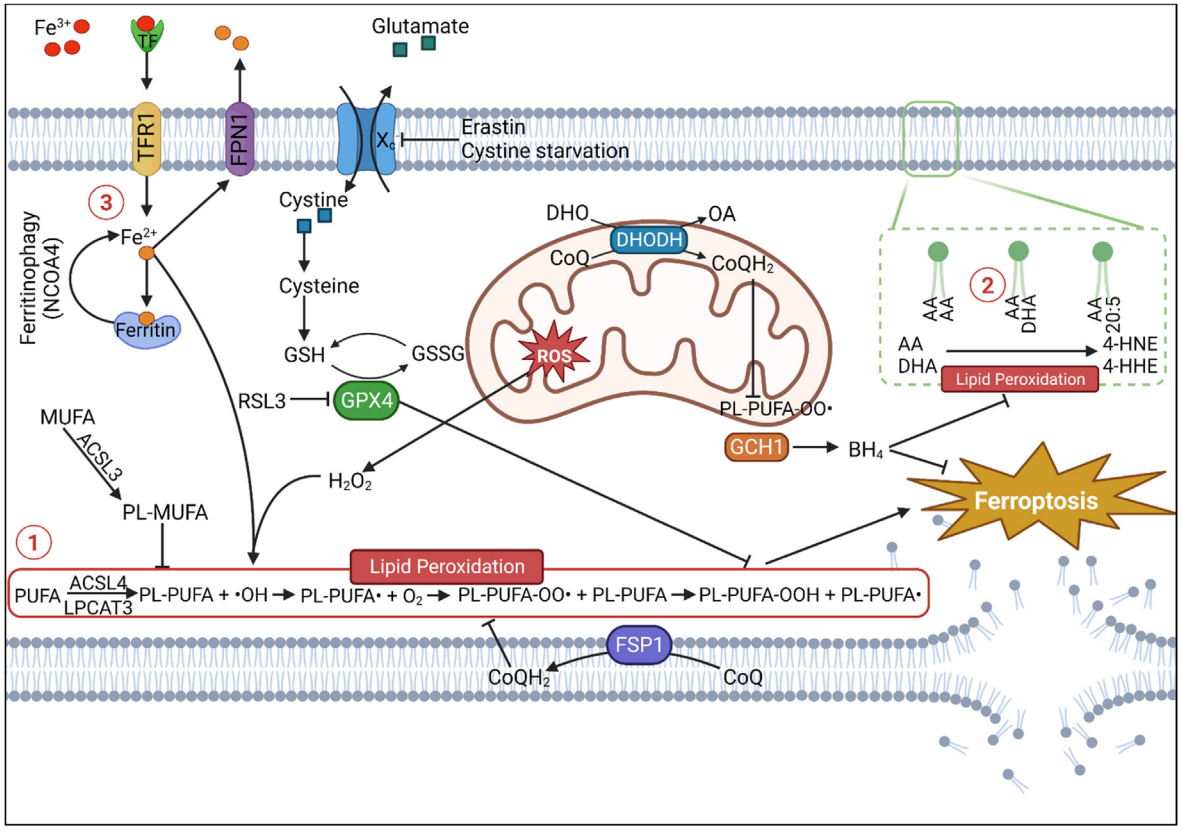

Fig. 1. Molecular details during ferroptosis. The process of ferroptosis can be triggered, determined and regulated by multiple factors, for instance: the abundance/activity of genetic or protein factors such as system Xc-, GPX4, DHODH, GCH1, FSP1, TF, TFR1, Ferritin; content/metabolism of small molecules (including ions) such as iron (Fe), glutamate, cystine/cysteine, GSH/GSSG, BH4, H_2O_2 and CoQ; and the rate of chemical reactions such as Fenton reactions. ①, ②, ③ indicate the three possible factors summarized in the manuscript that may sensitize neurons to ferroptosis

Abbreviations: TF, Transferrin; TFR1, Transferrin receptor 1; GSH, glutathione; GSSG, glutathione disulfide; BH4, tetrahydrobiopterin; AA, arachidonic acid; DHA, docosahexaenoic acid; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; 4-HNE, 4-hydroxynonenal; 4-HHE, 4-hydroxyhexanal; CoQ, coenzyme Q10.

peroxidation; meanwhile post-mortem studies of PD patients have shown increased cytosolic and membrane PUFA levels (including DHA) in dopaminergic neurons overexpressing α-synuclein (Sharon et al., 2003).

Much of the research on altered lipid metabolism in PD centers on the interaction of α-synuclein with PUFAs, which induces oligomerization of synuclein proteins (Perrin et al., 2001; Sharon et al., 2003). In animal models, DHA readily induces α-synuclein aggregation, and these oligomers are especially toxic to dopaminergic neurons (De Franceschi et al., 2011). More recent studies have indicated that the interaction between α-synuclein and PUFAs determines susceptibility to ferroptosis by altering the composition of phospholipid membranes. It has been shown that reduced α-synuclein production coincided with decreased ether-phospholipid (PL) levels, lipid peroxidation, and ferroptosis sensitivity in dopaminergic neurons at levels comparable to *ACSL4* knockdown. Supplementation with AA restored ether-PL levels and ferroptosis susceptibility, providing evidence that ether-PLs are required for neuronal ferroptosis (Mahoney-Sanchez et al., 2022). In addition to altered lipid metabolism, intracellular superoxide and hydrogen peroxide production and aberrant calcium signaling have been reported to be associated with α-synuclein oligomerization. The results also demonstrated that lipid peroxidation allows the insertion of α-synuclein aggregates into the plasma membrane, which further induces lipid peroxidation due to ROS generation (Angelova et al., 2020). AA peroxidation appears to play a significant role in neurodegeneration, as evidenced by HNE toxicity presented in the brain tissue of AD, PD, Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) patients and/or models (Di Domenico et al., 2017).

The exact nature of altered lipid metabolism in PD remains a complex mystery. While it is well established that PUFAs such as AA and DHA are significantly enriched in the brain, how these levels are affected varies. AA and DHA appear to correlate with disease severity in several studies, yet decreased in others (Sharon et al., 2003; Yoo et al., 2021). Notably, in studies where AA and DHA appear to be decreased, peroxidation markers such as MDA and 4-HNE are significantly increased (Brion & Saffar, 1979; Dexter et al., 1986; Di Domenico et al., 2017; McCormack et al., 2005). These results indicate that the naturally high concentrations of AA and DHA in the brain are a risk factor for ferroptosis. However, the rate of peroxidation may eventually exceed the rate of PUFA incorporation into the plasma membrane (due to increased iron, increased oxidative stress, self-perpetuating autooxidation, α-synuclein accumulation, etc.), thus showing reduced levels of AA and DHA – a pattern also observed in AD (Fonteh et al., 2020). Analysis of PUFA levels and peroxidation at various stages of disease progression would provide a more complete understanding for the role of AA and DHA in PD.

Although there are still many gaps to be filled in, evidence does support a link between brain lipid composition and ferroptosis in PD. Proteomic analysis revealed several differentially regulated ferroptosis-related genes in PD patients, including *GCH1* and *GPX4* (Jian et al., 2022). Downregulation of *GCH1* has also been found in a *Drosophila* model for α-synucleinopathies, and this differential expression appeared to enhance its pathogenesis (Sarkar et al., 2020). To summarize, lipid composition and peroxidation of signature PUFAs present in high concentrations in the brain seem to determine susceptibility to neuronal ferroptosis and play a role in PD progression through phospholipid-aggregate interactions.

5.2. Alzheimer's disease (AD)

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the accumulation of extracellular amyloid (Aβ) plaques, intracellular neurofibrillary (tau) tangles, and synaptic loss in the hippocampus (Khan et al., 2020). The most prominent symptom of AD is cognitive decline (especially with regard to learning and memory), which is caused by neuron loss and shrinkage of the hippocampus and cerebral cortex. While the characteristic protein aggregates certainly contribute to cell death and disease progression, the actual cause of AD is largely unknown in both familial and sporadic cases. Aging is probably the most significant risk factor with over 90% of cases occurring after the age of 65, along with mutations in autosomal dominant genes such as *APP*, *PSEN-1*, *PSEN-2* and *APOE* (Breijyeh & Karaman, 2020).

As with PD, AD displays altered lipid metabolism in the CNS (Bégin et al., 2010; Corsinovi et al., 2011; Grimm et al., 2017), but whether AD is correlated with an increase or decrease in PUFA content of the brain is still up for debate. Several AD mouse models cite elevated levels of AA and/or DHA (Ates et al., 2020), while a recent study reported significantly increased AA metabolism and turnover in the brain of AD patients, with AA incorporation into the brain most pronounced in areas of high neuritic plaque density and microglial activation (Esposito et al., 2008). These results are consistent with an ANOVA analysis of cerebrospinal fluid that showed AA and DHA enrichment in pre-symptomatic AD patients (identified by normal cognitive functioning but abnormal Aβ and tau protein levels), yet noticeably lower levels in cognitively impaired AD patients. In both control and pre-symptomatic AD patients, AA and DHA were positively correlated with Aβ and tau protein levels (Fonteh et al., 2020). These results suggest an underlying role for high PUFA concentration in AD that varies based on disease progression. Higher levels of PUFA may contribute to the development of abnormal Aβ and tau protein aggregates, but these lipids decrease in concentration when oxidative stress (a possible cause or contributor of AD) reaches a threshold to cause extensive peroxidation that exceeds the rate of PUFA incorporation or synthesis in symptomatic AD. Increased DHA peroxidation has been observed in the temporal and occipital lobes of AD patients (Nourooz-Zadeh et al., 1999), while 4-HNE is elevated in the brain tissue of AD, PD, HD, and ALS patients and/or models (Di Domenico et al., 2017). Extensive lipid peroxidation (along with iron accumulation) results in ferroptosis in both AD patients and models (Li et al., 2022; Ma et al., 2022; Wang et al., 2022; Zhu et al., 2022). Neuron specific *Gpx4* knockout models reveal that the hippocampus is particularly sensitive to ferroptosis (Hambright et al., 2017).

Due to the potential neuroprotective effects of DHA and its effect on neural plasticity, several studies have been conducted to test the effects of dietary PUFA supplementation on cognitive function in AD with mixed results. An analysis of multiple randomized studies with a total of 632 participants found no evidence of efficacy of omega-3 PUFA supplements in treating mild to moderate AD (Burckhardt et al., 2016). In another double-blind, randomized clinical trial, participants who received a combination of dietary eicosapenteinoic acid (EPA – 20:5, another omega-3 PUFA) and DHA showed no improvement in cognitive decline. Interestingly, despite similar doses, the relative amounts of EPA in plasma was higher than that of DHA, suggesting differential metabolism and/or incorporation (Phillips et al., 2015). Meanwhile, supplementation on fly diets with hydroxylated DHA (DHA-H) in a *Drosophila* model of AD improved mortality, locomotive, and cognitive capacity, and results were successfully replicated in a familial AD mouse model (Mohaibes et al., 2017). Once again, these results suggest a delicate balance between the neuroprotective and neurodestructive effects of PUFAs. Although not as conclusive as the evidence surrounding PD development, PUFA composition remains a possible explanation for ferroptotic sensitivity, given that DHA concentrations are highest in synaptic membranes that are characteristically lost in AD progression (Tanaka et al., 2012) and AA, which has specific increase in the hippocampus with age (Mota-Martorell et al., 2022). The characteristic protein aggregates of AD and altered lipid metabolism are parallel to the lipid-aggregate interactions seen in PD studies, suggesting a similar role of PUFA composition in ferroptosis.

5.3. Other neurodegenerative diseases

Given the similarities in various neurological diseases (iron accumulation, oxidative stress, lipid peroxidation, protein aggregation, etc.), signs of ferroptotic activity can be found in several other forms of neurodegeneration (Dugger & Dickson, 2017; Erkkinen et al., 2018). In Huntington's diseases (HD), patients exhibit increased lipid peroxidation

(4-HNE), increased oxidative stress, and decreased GSH levels (Klepac et al., 2007). In transgenic HD mouse models (R6/2, N171-82Q and CAG140), inhibition of lipid peroxidation improved mortality, mitochondrial morphology, and synapse structure, while reducing HNE toxicity; likewise, cultured neurons having similar treatments were also resistant to oxidative stress-induced cell death (Klepac et al., 2007). HNE toxicity in HD models is particularly interesting as 4-HNE appears to interact with the mutant huntingtin protein (mtHTT, the protein aggregates characteristic of HD) to increase toxicity in a manner similar to the lipid-α-synuclein interactions observed in PD (Angelova et al., 2020; Klepac et al., 2007; Mahoney-Sanchez et al., 2022). HD is also linked with differential expression of several ferroptosis-related genes briefly discussed in the following section (Chen et al., 2013; Simmons et al., 2007).

In amyotrophic lateral sclerosis (ALS), mutations in the radical-trapping superoxide dismutase (SOD1) are found in 15% of familial cases (Abati et al., 2020). Mutant SOD1 mouse models show upregulated *TFR1* and downregulated *GPX4* expression, while *Drosophila* SOD1-related ALS models show increased sensitivity to hydrogen peroxide in motor neurons and glial cells with decreased lifespans and increased lipid peroxidation (Chen et al., 2021; Jeong et al., 2009; Kumimoto et al., 2013). In *Drosophila* mutant models, the majority of differentially expressed genes pertained to oxidative stress response, lipid metabolism, and neurodevelopment (Kumimoto et al., 2013). GPX4 deficiency has also been observed in sporadic ALS patients (Chen et al., 2021), while plasma 4-HNE levels have been shown to be an effective biomarker for predicting neuronal degeneration in ALS patients (Devos et al., 2019). Lastly, in PKAN, the characteristic accumulation of iron in the *globus pallidus* of the brain coincides with signs of ferroptosis in the form of MDA accumulation and decreased GPX4 activity (Gregory & Hayflick, 1993; Santambrogio et al., 2022). Intriguingly, although we discuss neuronal pathology in diseases, ferroptosis in PKAN models is more likely to occur in astrocytes rather than neurons (Santambrogio et al., 2022). HD, ALS, and PKAN share the same neurodegenerative features seen in PD and AD (iron accumulation, oxidative stress, lipid peroxidation, etc.) and are likely to experience the same sensitivity to ferroptosis due to differential lipid composition (Table 1).

5.4. Other determinants of neuronal ferroptosis

Lipid composition presents a promising explanation for neuronal sensitivity to ferroptosis, but other aspects of brain physiology should be considered. Perhaps the most likely alternative is iron accumulation, a notable feature found in several forms of neurodegeneration. Brain iron accumulation in select regions (namely the *substantia nigra*, basal ganglia, and cortices) is part of the normal aging process (Sato et al., 2022; Ward et al., 2014). However, iron accumulation in abnormally high amounts or in regions not normally found to possess significant iron levels has been linked with neurodegenerative disease (Dauer Née Joppe et al., 2021; Lei et al., 2017; Wise et al., 2022). Brain iron accumulation can even be used to indicate the severity of cognitive decline in PD patients (Thomas et al., 2020). As previously discussed, iron accumulation results in the generation of ROS and lipid peroxidation, leading to ferroptotic cell death.

In addition to iron accumulation, neurodegenerative diseases are often associated with differential expression of ferroptosis-related genes. In the 6-OHDA induced PD rat model, ferritin heavy chain 1 (subunit of the ferritin complex involved in iron storage) was downregulated and inversely correlated with α-synuclein levels, suggesting a role in PD pathogenesis (Tian et al., 2020). Mutations in PSEN1 are believed to cause autosomal dominant familial AD and sensitize cells to ferroptosis by altering GPX4 expression through decreased selenium uptake (Greenough et al., 2022). Downregulation of FPN1 (iron exporter) has been cited in both human AD patients and AD mouse models and increased expression of FPN1 resulted in ferroptotic resistance and cognitive improvement in mouse models (Bao et al., 2021). HD mouse models and some patients show elevated ferritin and FPN1 levels and reduced TFR1 expression (Chen et al., 2013; Simmons et al., 2007). It has been recently reported that astrocytes from AD patients contain elevated levels of ROS-producing NOX4. This upregulation coincided with increased lipid peroxidation (as indicated by 4-HNE and MDA levels), iron accumulation, and ferroptosis. The authors were able to replicate these results in the APP/PS1 mice model and concluded that upregulation of NOX4 causes oxidative stress-induced lipid peroxidation that contributes to ferroptosis in AD (Park et al., 2021). However, changes in gene expression can only explain disease-specific susceptibility to

Table 1
Evidence linking lipid composition to ferroptosis sensitivity in neurodegenerative disease.

	Parkinson's Disease	Alzheimer's Disease	Other
Altered Lipid Metabolism	4-HNE toxicity (product of AA peroxidation)	4-HNE toxicity (product of AA peroxidation)	4-HNE toxicity (product of AA peroxidation) in HD and ALS
	Increased DHA and AA that positively correlates with disease symptoms	Increased DHA and AA	4-HNE used to predict neuronal degeneration in ALS patients
	Decreased PUFA due to increased lipid peroxidation	Decreased PUFA due to increased lipid peroxidation (symptomatic AD patients)	Increased lipid peroxidation (HD and ALS)
		DHA concentration highest in synaptic membranes (characteristically lost in AD)	Increased H_2O_2 sensitivity (ALS)
		AA increases with age in hippocampus (region of high degeneration in AD)	
Lipid-Aggregate Interactions	Increased DHA in dopaminergic neurons overexpressing α-synuclein	Increased DHA and AA that is positively correlated with Aβ and tau protein levels (pre-symptomatic AD patients)	4-HNE interacts with mtHTT protein aggregates (HD)
	DHA induced α-synuclein oligomerization	Increased AA metabolism highest in regions of significant neuritic plaque density and microglial activation	
	α-synuclein positively correlated with ether-PL, lipid peroxidation, and ferroptosis sensitivity in DA neurons		
	Lipid peroxidation allows for α-synuclein insertion, resulting in further peroxidation		
Differentially Regulated Ferroptosis Genes	*GCH1* and *GPX4* downregulation	*GPX4* downregulation	*GPX4* downregulation (ALS and PKAN)
	Downregulation of ferritin heavy chain 1, inversely correlated to α-synuclein	*FPN1* downregulation	Ferritin and *FPN1* upregulation and *TFR1* downregulation (HD)
		Increased expression of *NOX4* in astrocytes coinciding with increased 4-HNE, MDA, iron accumulation, and ferroptosis	*TFR1* upregulation (ALS)
			Reduced GSH (HD)
			Genes involves in oxidative stress and lipid metabolism (ALS *Drosophila* model)

ferroptosis, but seldom contribute to a good understanding of why it occurs in a wide variety of CNS diseases with diverse etiologies.

6. Conclusion

In conclusion, ferroptosis represents a type of iron-dependent cell death commonly linked to neurodegeneration. PUFA content appears to play a significant role in ferroptosis, as interaction with ROS from mitochondrial dysfunction and iron accumulation result in the generation of cytotoxic lipid peroxides in cell membranes. Even in cases where ferroptotic sensitivity appears to be determined more by iron levels or ROS generation, the highly oxidizable PUFAs concentrated in the brain play a role in this cell death, indicating a multifactorial process. Based on these observations, this review proposes lipid composition as a determining factor in ferroptosis susceptibility. The higher PUFA content in neurons, while necessary to ensure neuronal plasticity; when combined with mitochondrial dysfunction/ROS accumulation, may also predispose the brain to greater amounts of lipid peroxidation not seen in other cell. This vulnerability could explain the neuronal sensitivity to ferroptosis observed in PD, AD, and other age-related diseases that are associated with increased oxidative stress.

Author contributions

JS and ZW wrote the manuscript. ZW provided funding.

Declaration of competing interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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