Histol Histopathol (2021) 36: 383-397
http://www.hh.um.es

Histology and Histopathology

REVIEW Open Access

Targeting NRF2 to suppress ferroptosis in brain injury

Shunchen Song, Yaxuan Gao, Yi Sheng, Tongyu Rui and Chengliang Luo
Department of Forensic Medicine, Medical College of Soochow University, Suzhou, Jiangsu, China

Summary. Brain injury is accompanied by serious iron metabolism disorder and oxidative stress. As a novel form of regulated cell death (RCD) depending on lipid peroxidation caused by iron overload, ferroptosis (FPT) further aggravates brain injury, which is different from apoptosis, autophagy and other traditional cell death in terms of biochemistry, morphology and genetics. Noteworthy, transcriptional regulator NRF2 plays a key role in the cell antioxidant system, and many genes related to FPT are under the control of NRF2, including genes for iron regulation, thiol-dependent antioxidant system, enzymatic detoxification of RCS and carbonyls, NADPH regeneration and ROS sources from mitochondria or extra-mitochondria, which place NRF2 in the key position of regulating the ferroptotic death. Importantly, NRF2 can reduce iron load and resist FPT. In the future, it is expected to open up a new way to treat brain injury by targeting NRF2 to alleviate FPT in brain.

Key words: Nuclear Factor Erythroid 2-Related Factor 2 (NRF2), Brain Injury, Ferroptosis (FPT)

Introduction

Ferroptosis (FPT) is a form of regulated cell death (RCD), which is characterized by a lethal level of iron-dependent lipid peroxidation (Stockwell et al., 2017). A large body of research on FPT has been conducted over the past few decades (Stockwell et al., 2017). Until 2012, this particular cell death was coined by Dixon et al. and there is an independent system of FPT which is different from apoptosis, autophagy and other traditional cell death in terms of biochemistry, morphology and genetics (Dixon et al., 2012).

The involvement of iron is a key feature of FPT (Dixon et al., 2012). Reactive oxygen species (ROS) refer to partially reduced oxygen-containing substances, including superoxide (O^{2-}), peroxides (H_2O_2 and ROOH) and free radicals (·OH and RO), etc. Iron, a transition metal with strong redox activity, is responsible for excessive hydroxyl radicals through Fenton reaction in cells (Fig. 1). The Fenton reaction is a string of relatively complex reactions, mostly used for sewage disposal in industry (Dixon et al., 2012). The reaction mainly takes $Fe^{2+}+H_2O_2=Fe^{3+}+\cdot OH+OH^-$, where ·OH is produced to turn organic compounds into inorganic ones. This kind of reaction is only detected in aqueous solution *in vitro* due to problems such as concentration and PH value. For example, the Fenton reaction can help to accelerate the process of nano drugs killing cancerous cells via FPT (Dong et al., 2019), despite lack of evidence in neurological diseases related to iron accumulation (Ratan, 2019). Hydroxyl radicals and ferrous iron can attack lipids and cause lipid peroxidation, as well as potentiate FPT. Remarkably, FPT is a complicated cascade of intracellular metabolic disorders, including but not limited to iron metabolism disorder. Cell injury caused by FPT is mostly attributed to lipid peroxidation of membrane phospholipids containing polyunsaturated fatty acids (PUFAs) (Dixon et al., 2012). It is currently known that there are two approaches to lipid peroxidation in FPT: enzymatic oxidation (responsible for initiating lipid peroxidation) and autoxidation (responsible for driving lipid peroxidation) (Shah et al., 2018) (Fig. 2). The former approach includes lipoxygenases (LOXs) which prefer free PUFAs as substrates instead of PUFAs bound to membrane phospholipids (Kuhn et al., 2015). However, phosphatidylethanolamine (PE) bound to the membrane can form a non-bilayer arrangement, which facilitates the enzymatic oxidation of LOXs (van den Brink-van der Laan et al., 2004). In PUFAs, arachidonic acid (AA) / adrenic acid (AdA) contains bis-allylic hydrogen atoms which can be easily abstracted (Shah et al., 2018); this may account for the fact that AA/AdA PE is much more favored in lipid peroxidation. Additionally, PEBP1 can be combined with 15LOX to form a PEBP1/15LOX complex, amplifying the function of 15LOX (Wenzel et al., 2017) (Fig. 2). Moreover, a set of enzymatic reactions mediated by ACSL4 and LPCAT3 are essentially important for FPT because they help to combine PUFAs to membrane phospholipid (Doll et al., 2017) (Fig. 2).

In the anti-FPT system, one important factor is

Corresponding Author: Chengliang Luo, Department of Forensic Medicine, Medical School of Soochow University, 178 Ganjiang East Road, Suzhou 215123, China. e-mail: clluo@suda.edu.cn
DOI: 10.14670/HH-18-286

GSH-GPX4 antioxidant axis (which belongs to the thiol-dependent antioxidant system) by virtue of the potential capability of glutathione peroxidase 4 (GPX4) to resist FPT (Brigelius-Flohe and Maiorino, 2013), and recently peroxidase 6 (PRDX6) has been found with similar functions to GPX4 in terms of repairing damaged membrane caused by lipid peroxidation (Fisher et al., 2018) (Fig. 2). Additionally, it is also observed that the thioredoxin (TXN) system, another important thiol-dependent system, can compensate for the functional impairment of the GSH system (Lu and Holmgren, 2014) (Fig. 2). Moreover, the mevalonate (MVA) pathway has its own place in the anti-FPT system, which synthesizes two important components to inhibit FPT, including coenzyme Q10 (responsible for targeted inhibition of lipid peroxidation cooperating with FSP1) and IPP (necessary for the maturation of GPX4) (Shimada et al., 2016b) (Fig. 2). Altogether, these findings support the knowledge of the extension of the single GSH-GPX4 anti-FPT axis.

Brain injury is hallmarked by high incidence, high fatality rate, and high disability rate, as a major public health problem that attracts much attention. It is well accepted that brain injury is often accompanied by iron metabolism disorder and FPT in nerve cells (Magtanong and Dixon, 2018). Therefore, how to control or even reverse FPT has undoubtedly become the key to the treatment and prognosis of brain injury.

The structure of the brain determines that the threshold of FPT after brain injury is much lower than that of other organs, in other words, the brain is more sensitive to FPT (Fig. 3), due to the existence of many FPT risk factors in brain. First of all, an abundance in phospholipids containing PUFAs, not only ensures neuron plasticity, synapse connections, and neurotransmitter release and the development of a sophisticated neural network (Ingold et al., 2018), but also presents the Achilles' heel of the brain for its contribution to lipid peroxide in the brain as well as an increased risk of FPT (Anthonymuthu et al., 2018). Additionally, as the most abundant transition metal in the brain, iron is necessary for neurotransmitter

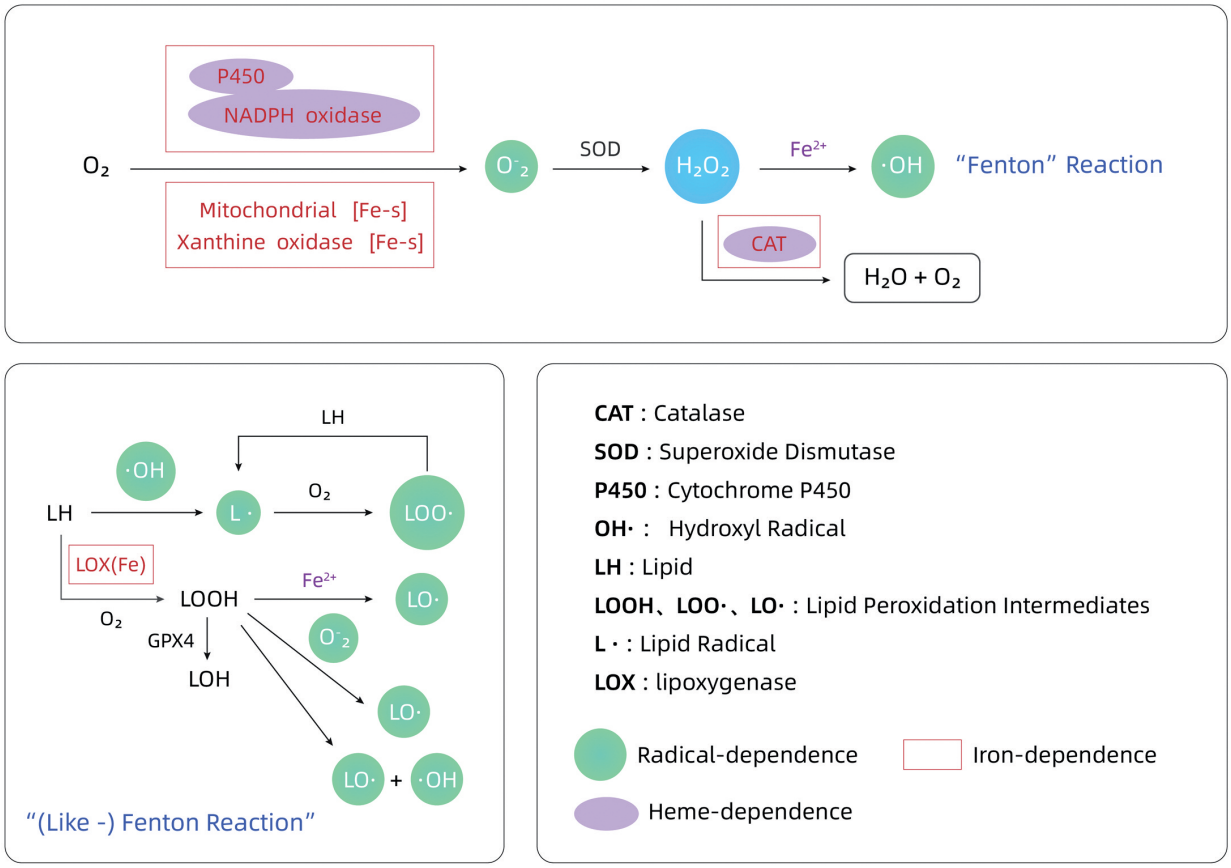

Fig. 1. Fenton Reaction-based transformation. Oxygen produces O_2^- under the action of cytochrome P450, NADPH oxidase, mitochondrial and xanthine oxidase; it also produces hydrogen peroxide triggered by superoxide dismutase (SOD). On one hand, catalase (CAT) can degrade harmful hydrogen peroxide, but divalent iron can produce a large number of peroxides based on ·OH through Fenton reaction. Then, the ·OH attack lipid (LH), produce toxic LOO· and destroy cells. On the other hand, oxygen and oxides react with LH and produce toxic LOOH. Under physiological conditions, GPX4 can degrade LOOH into non-toxic LOH, but there also exists the possibility of a further Fenton-like reaction which produces free radicals such as LOO·, LO,· and ·OH, damaging the structure of the membrane.

synthesis, neuron development (Nikseresht et al., 2019), brain mitochondrial respiration, and monoamine oxidase (Snyder and Connor, 2009; Crichton et al., 2011).

A powerful anti-FPT mechanism confronts with FPT risk factors in the brain from an evolutionary point of view. Firstly, the brain is on the priority list of selenium supply, which is a vital anti-FPT element, among all the others (Conrad and Proneth, 2020). Secondly, Apolipoprotein E receptor 2 (APOER2), also known as low- density lipoprotein receptor-associated protein 8 (LRP8), facilitates the entry of selenoprotein P into testis and brain (Chiu-Ugalde et al., 2010) and APOER2 mRNA mainly exists in the central nervous system (CNS), placenta, and testis (Ueta et al., 2012). Taken together, these findings may be one reason that some brain cells are highly dependent on the antioxidant function of GPX4, whose active site needs a selenium supply (Ueta et al., 2012). Examples of these brain cells include pyramidal cells in the hippocampus, glutamatergic neurons in the cortex, Purkinje cells, and

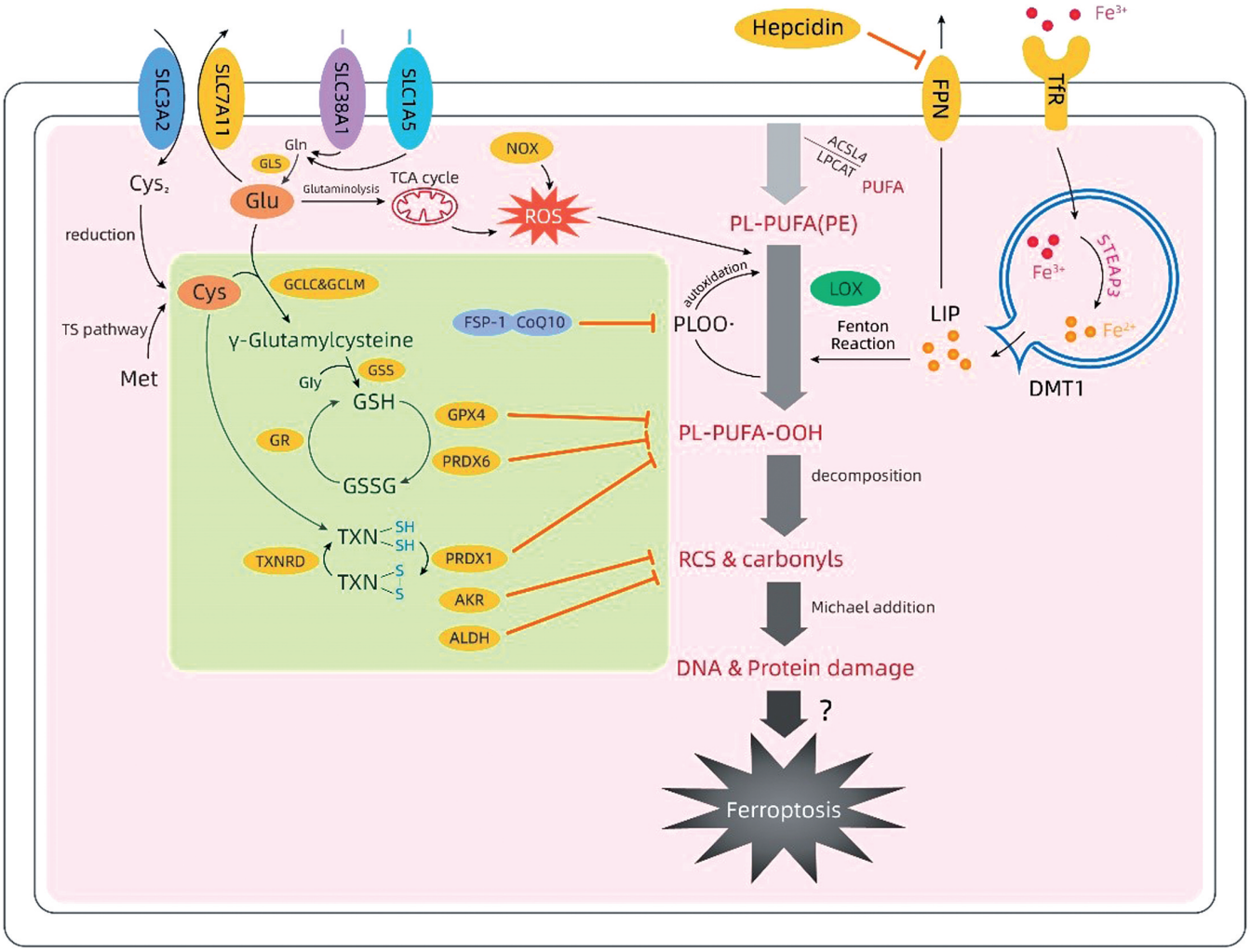

Fig. 2. Pathway for regulating FPT. In the process of lipid peroxidation of FPT, ACSL4 and LPCAT3 are needed for PUFA to bind to the membrane phospholipid. There are two ways for PL-PUFA to render lipid peroxidation, which are the enzymatic oxidation and autoxidation. The former serves to initiate the process; as its name suggests, 15-LOX is combined with PEBP-1 to enhance the efficacy of oxidation. The latter autoxidation serves to drive the process, and it can be inhibited by coenzyme 10 (CoQ10). Excessive iron accumulation in the labile iron pool (LIP) can promote lipid peroxidation through Fenton reaction. The glutamine (Gln) input through amino acid transporters SLC38A1 and SLC1A5 may enable mitochondrial TCA to produce ROS through glutaminolysis. Additionally, NOXs in the cytoplasm also contribute to ROS. Then, lipid peroxides are further decomposed into RCS and carbonyls, which may eventually execute FPT by damaging DNA and protein via Michael addition. Lipid peroxides are found to be targeted by GPX4; PRDX6 and PRDX1 can exert similar effects. Furthermore, downstream products of lipid peroxidation—RCS and carbonyls—can be inhibited by AKR and ALDH. The intracellular cysteine can be supplemented when system XC imports cystine (This section is unclear and requires revision)- or derived from the TS pathway. Afterward, intracellular cysteine can be used to synthesize GSH or TXN in the two major thiol-dependent systems, ultimately involved in the anti-FPT cascade as the cofactors of GPX4, PRDX6, and PRDX1.

motor neurons in the cerebellum (Conrad et al., 2018). As shown in Fig. 3, in a physiological state, there already exists an unstable balance between FPT risk factors in the brain and the power to fight against FPT compared with other organs with low-sensitivity to FPT, and brain injury will undoubtedly exacerbate the unstable balance. Interestingly, neurons and some tumor cells seem to have striking similarities—both have a strong anti-FPT system to defend against FPT risk factors, though the difference is that neurons use it to enable complex metabolic activities of the brain while tumors use it to promote survival, proliferation, or even malignant transformation (Conrad and Proneth, 2020).

NRF2 (NF-E2 p45 related factor 2), a basic leucine zipper (bZIP) transcription factor that can bind to small MAF proteins (Hayes and Dinkova-Kostova, 2014), regulates hundreds of antioxidant genes and plays an important role in the endogenous antioxidant defense system (Baird and Dinkova-Kostova, 2011; Zhang et al., 2013). In most cases, NRF2 binds to its negative regulatory molecule kelch-like ECH-associated protein 1 (Keap1) to maintain a low level through ubiquitination and degradation. Intracellular increased oxidative stress promotes NRF2 dissociation and translocation of Keap1 to nucleus and then NRF2 interacts with antioxidant response elements (AREs) located in the promoter region of the target gene, increasing its transcription (Silva-Islas and Maldonado, 2018).

This review focuses on analysis of FPT caused by brain injury and mechanism of NRF2 modulating FPT, looking forward to opening up a new road to treat FPT in brain injury.

Evidence for ferroptosis in brain injury

Ferroptosis in traumatic brain injury

Traumatic brain injury (TBI) is the main cause of death and disability worldwide, as well as a formidable burden for patients and caregivers both economically and psychologically (Wachelder et al., 2009; Humphreys et al., 2013), and lack of effective drug therapy makes TBI a Gordian knot (Abou-Abbass et al., 2016; Brazinova et al., 2018). TBI is defined as a brain injury caused by external mechanical forces (vibration, explosion, extrusion or penetrating external objects), which is clinically categorized into mild, moderate, and severe levels and further leads to temporary or permanent damage in cognition, physiology, and psychology (Blennow et al., 2016; Capizzi et al., 2020). The brain successively experiences two waves of injury once external mechanical forces operate on it. The primary injury is the direct result of mechanical force, while secondary injury includes a complex series of iron accumulation, glutamate excitotoxicity, inflammation, diffuse axonal injury (DAI), and oxidative stress (Werner and Engelhard, 2007; Al Nimer et al., 2011; McGinn and Povlishock, 2016; Rostami, 2016; Anthonymuthu et al., 2018). Given the pervasive outlooks on TBI, there are different kinds of cell death involved in the pathophysiological process of TBI, including necrosis, apoptosis, necroptosis, and pyroptosis (Jia et al., 2009;

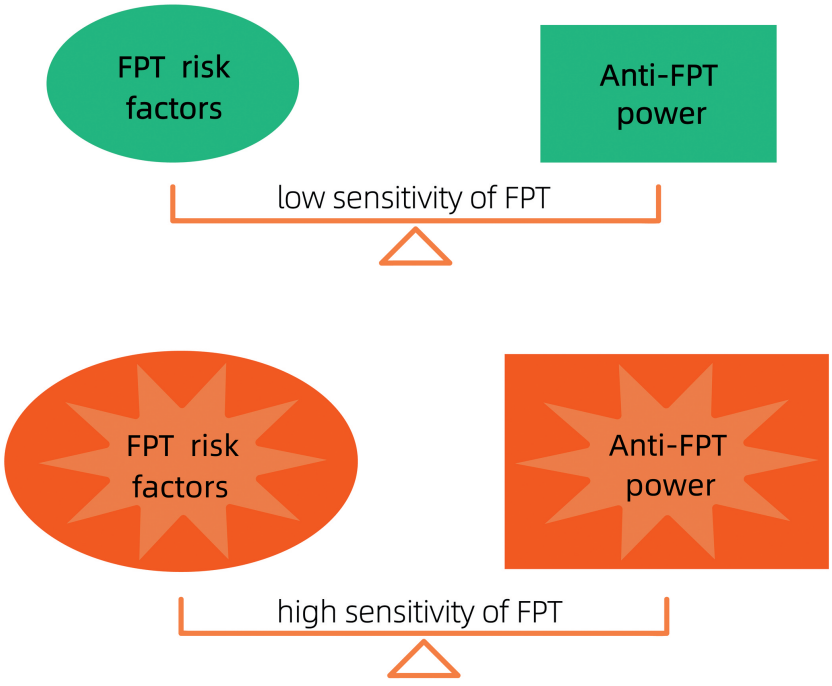

Fig. 3. The balance between FPT risk factors and anti-FPT power lays the foundation of FPT sensitivity. When FPT risk factors (rich in PL-PUFA, iron, and so forth) are low and cells do not need to be highly dependent on the anti-FPT power (supply of Se, GPx4, etc.), FPT sensitivity is low. When FPT risk factors are high and cells are highly dependent on the anti-FPT power, FPT sensitivity is high.

Adamczak et al., 2014; Liu et al., 2016). The intervention for primary injury is preventive and comparatively the intervention for secondary injury has a longer therapeutic window, winning its unique status in clinical treatment (Blennow et al., 2016). Such targeted intervention, however, meets with obstruction due to the mysterious pathophysiological process of TBI.

Recent years have witnessed the important role of FPT in fostering TBI. The 15-LOX/PEBP1 complex (Wenzel et al., 2017) and markers of lipid peroxidation (Bayir et al., 2002, 2004; Yen et al., 2015) was found to increase significantly in ferroptotically dying neurons after TBI. TBI animals using a controlled cortical impact model (CCI) were accompanied by iron accumulation, iron metabolism disorder, accumulation of lipid peroxidation, depletion of GSH, and decreased activity of GPX4 (Kenny et al., 2019; Xiao et al., 2019; Xie et al., 2019a). Moreover, the typical morphological feature of FPT—shrunken mitochondria—was observed using transmission electron microscopy 3 days after TBI (Dixon et al., 2012). Additionally, the application of baicalein (inhibiting 12/15-LOX) and Fer-1 (targeting lipid peroxidation products) significantly alleviated FPT and improved particular brain function of the damaged areas (Kenny et al., 2019; Xie et al., 2019a). Nevertheless, it is noteworthy that antioxidant therapy is largely ineffective in clinical treatment of TBI although lipid peroxidation plays a crucial role in FPT (Anthonymuthu et al., 2018), and the underlying causes need to be further explored.

Beyond direct empirical support for FPT involvement in TBI, the mechanism of FPT also seems to overlap with that of TBI. Firstly, erastin- induced FPT and oxidative glutamate toxicity (OGT) seem to share a lot of similarities (Tan et al., 2001). OGT is among the secondary injuries of TBI (Bullock et al., 1998; Robertson et al., 2001), and its level is closely related to cognitive function after TBI (Mao et al., 2019). It seems that extracellular high-concentration glutamate caused by TBI can be a natural FPT inducer (Stockwell et al., 2017). Secondly, inactivation of tau protein, for example, a high level of phosphorylated tau and abnormal tau oligomers, were observed in plasma after TBI (Gerson et al., 2016; Rubenstein et al., 2017; Wang and Han, 2018), having the potential to inhibit FPN-dependent iron output regulated by APP and cause intracellular iron accumulation, as well as an increased risk of FPT (Tuo et al., 2017). Thirdly, Apolipoprotein E (APOE) among the circulation of plasma lipoproteins during regeneration and repairment after brain injury (Huang et al., 2004), could be seen as a double-edged sword, and its ε 4 allele was clinically significantly correlated with poor prognosis after TBI for approximately 6-12 months, especially in severe TBI (Zeng et al., 2014). The underlying mechanism may be that ε 4 allele has the power to decrease brain selenium level (Cardoso et al., 2017) which is important for production of selenocysteine (Sec), the active site of GPX4 (Alim et al., 2019; Conrad and Proneth, 2020). In a word, these studies show that many features promoting FPT are present in TBI, and inhibiting FPT is a valid therapeutic strategy for TBI. However, these overlapping mechanisms between FPT and TBI call for the request for more comprehensive and deeper research.

Ferroptosis in stroke

Stroke is a group of life-threatening diseases hallmarked with high mortality and serious sequelae, and it can be classified into two major categories: ischemic stroke and hemorrhagic stroke (Wu et al., 2018). The vast majority is ischemic stroke, accounting for approximately 80% (Wu et al., 2018). FPT has been reported to be critical to ischemia-reperfusion injury (IRI) of some peripheral organs, such as liver, kidney, and heart (Friedmann Angeli et al., 2014; Linkermann et al., 2014; Gao et al., 2015; Fang et al., 2019), as well as the central nervous system. ACSL4, which plays an important role in the production of lipid ROS in FPT, was involved in the pathological process of cerebral ischemic injury (Gubern et al., 2013). What's more, carvacrol inhibited FPT by increasing GPX4 expression, thus protecting hippocampal neurons from IRI (Guan et al., 2019) and iron-targeted intervention significantly alleviated IRI induced by middle cerebellar artery occlusion (MCAO) model (Tuo et al., 2017).

Intracerebral hemorrhage (ICH) refers to non-traumatic intracerebral hemorrhage. Despite making up merely 15%, it is known for highest mortality among all the stroke subtypes (Feigin et al., 2009). Nevertheless, there is a lack of feasible and effective treatment for ICH currently (Zille et al., 2017). Previous studies have provided solid evidence for FPT engagement in ICH and the level of GPX4 was observed to decrease after ICH while overexpression of GPX4 gene or a single dose of selenium (Se) supply alleviated oxidative stress and inflammation and improved behavior in ICH (Zhang et al., 2018a,b; Alim et al., 2019). It is noteworthy that Hb/heme/iron (especially Fe^{2+}) and nuclear ALOX5 played an important role in the formation of lipid ROS in ICH (Katsu et al., 2010; Hu et al., 2016; Wang et al., 2016; Zou et al., 2017; Imai et al., 2019), which was inhibited by Fer-1in organotypic hippocampal slice cultures (Li et al., 2017). Additionally, shrunken mitochondria, the classic morphological feature of FPT, was also observed in ICH (Li et al., 2017).

Taken together, this evidence provides some insight into the connection between FPT and brain injury and inhibition of FPT can be a potential and effective treatment for brain injury, one of which is to enhance the endogenous anti-FPT mechanism of cells. That is why NRF2 as a potential transcription factor regulating iron metabolism and FPT has attracted our attention. The following section will discuss the role of transcription factor NRF2 in the regulation of endogenous anti-FPT

mechanism.

The role of NRF2 in preventing ferroptosis

NRF2 and iron metabolism

NRF2 regulates iron metabolism in cells, including iron intake, output, storage, recycling (mainly the synthesis and degradation of heme containing iron), ultimately alleviating the abnormal iron overload in cells and inhibiting FPT (Fig. 5). Firstly, iron input to the brain is mainly through transferrin and transferrin receptor 1 (TF-TFR1). TF is responsible for iron reception (Gomme et al., 2005) and is widely distributed in the brain, especially in the blood-brain barrier (BBB), which is the most important channel for iron to enter the brain. Its transcription is affected by NRF2-ARE (Lee et al., 2003b). Secondly, ferroportin (FPN) is the only known protein so far to export intracellular iron (Donovan et al., 2005; Zhang et al., 2011; Drakesmith et al., 2015) and hepcidin indirectly reduces iron efflux by acting on FPN (Nemeth et al., 2004) (Fig. 2). Proteins (FPN, hepcidin) that either directly or indirectly regulate iron output are regulated by NRF2. Thirdly, ferritin is the main iron storage protein in cells consisting of 24 heavy chains (H-ferritin, FTH1) and light chains (L-ferritin, FTL) (Muckenthaler et al., 2017). The upstream of FTH1 and FTL DNA contains ARE sequence which can be combined by NRF2 for upregulating transcription. Fourthly, iron can be used to synthesize heme in mitochondria, and the relevant enzymes involved in this process are regulated by NRF2, including ABCB6 (ATP binding cassette subfamily B member 6) on the outer membrane of mitochondria and ferrochelatase (FECH) on the inner membrane (Paul et al., 2017) (Fig. 4). Moreover, NRF2 is considered to be a key regulator of heme oxygenase (HO-1) in the brain (Johnson et al., 2008) (Fig. 4), which is the rate-limiting enzyme responsible for heme degradation, allowing iron to be recycled (Maines, 1988). Biliverdin, which is one of the degradation products, can be converted into bilirubin through biliverdin reductase (BLVRA and BLVRB) and their genes are positively regulated by NRF2 (Holowiecki et al., 2016). The end product bilirubin can serve to scavenge free radicals and resist lipid peroxidation when used with an appropriate dose (Stocker et al., 1987; Mancuso, 2017) (Fig. 4). However, it is noteworthy that overexpression of HO-1 can cause the opposite effects—exacerbating the imbalance of intracellular redox homostasis and inducing FPT (Bansal

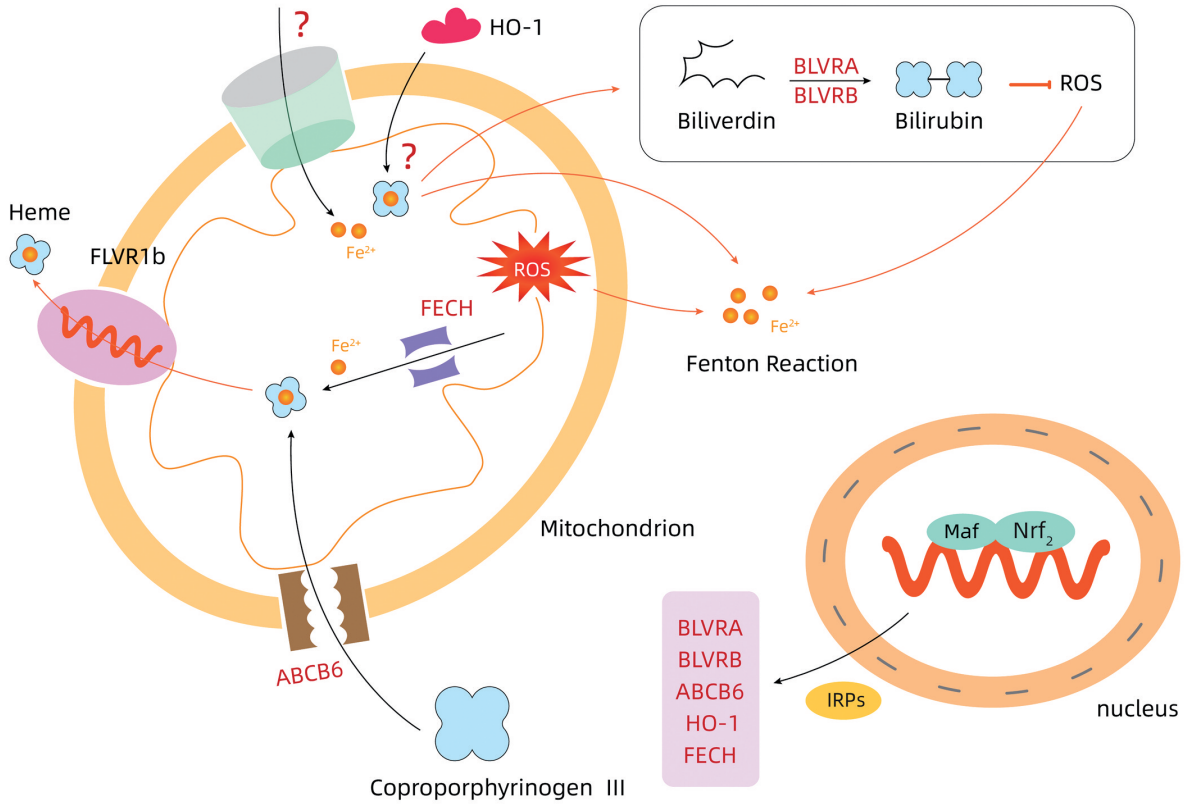

Fig. 4. Synthesis and Metabolism of NRF2-related Heme in Brain. Generally, the synthesis and metabolism of heme are carried out in mitochondria after the transportation of ferrous and coproporphyrinogen III by FECH and ABCB6 respectively into mitochondria. Under the effect of heme oxygenase (HO-1), heme mainly decomposes into biliverdin and Fe^{2+}. A minority of metabolites can help to protect nerve cells, but ROS produced by Fe^{2+} and mitochondria can lead to FPT through Fenton reaction. Those marked in red are regulated by NRF2.

et al., 2014). The rationale behind it may be associated with the accumulation of iron, mitochondrial dysfunction, and excessive ROS (Chang et al., 2018).

In addition, NRF2 has some shortcomings in regulating iron metabolism disorder in the brain. NRF2 regulates iron metabolism by regulating gene transcription, which has a long-term effect but is relatively too slow to cope with immediate changes of redox state and plays a very timely therapeutic role in acute brain injury. Moreover, iron metabolism in the brain is not under the complete control of NRF2 and there are many other factors involved. For example, iron regulatory proteins (IRPs) (Pantopoulos and Hentze, 1995; Bogdan et al., 2016; Zhou and Tan, 2017), lactoferrin (LF) (MacGillivray et al., 1983; Ke and Qian, 2007) and transferrin receptor 2 (TFR2) (Mastroberardino et al., 2009; Rhodes et al., 2014; Muckenthaler et al., 2017; Kawabata, 2019) are not regulated by NRF2, which weakens the regulation of iron metabolism by NRF2 to some extent.

NRF2 and thiol-dependent antioxidant system

NRF2 functions as a regulator in the thiol-dependent antioxidant system, which is mainly composed of the GSH and TXN systems (Fig. 2). The GSH system makes tremendous contributions to resisting FPT as GSH itself has strong antioxidant power and is a necessary cofactor of GPX4 (Dixon et al., 2012). First of all, all the genes coding key enzymes in GSH biosynthesis (GCLC, GCLM, GSS, SLC7A11) and reduction of oxidized GSH (GR) are the target genes of NRF2 (Hayes and Dinkova-Kostova, 2014, Dodson et al., 2019). Additionally, NRF2 is also involved in the regulation of gamma-glutamyl transferase (GGT1), a key enzyme of gamma-glutamyl cycle responsible for recycling of GSH (Hayes and Dinkova-Kostova, 2014). However, it is worth mentioning that although GPX4 is confirmed as one of the target genes of NRF2 (Osburn et al., 2006; Hirotsu et al., 2012), there remains a lack of experimental evidence supporting that NRF2 can inhibit FPT by increasing GPX4 expression (Shin et al., 2018; Ursini and Maiorino, 2020), and thereby future studies should put more attention on the regulation of GPX4 by NRF2 considering its critical role in anti-FPT system.

The TXN system, composed of NADPH, thioredoxin reductase (TXNRD), and thioredoxin (TXN), is a vital antioxidant system preventing oxidative stress (Lu and Holmgren, 2014) under regulation of NRF2. Although the TXN system gains less attention

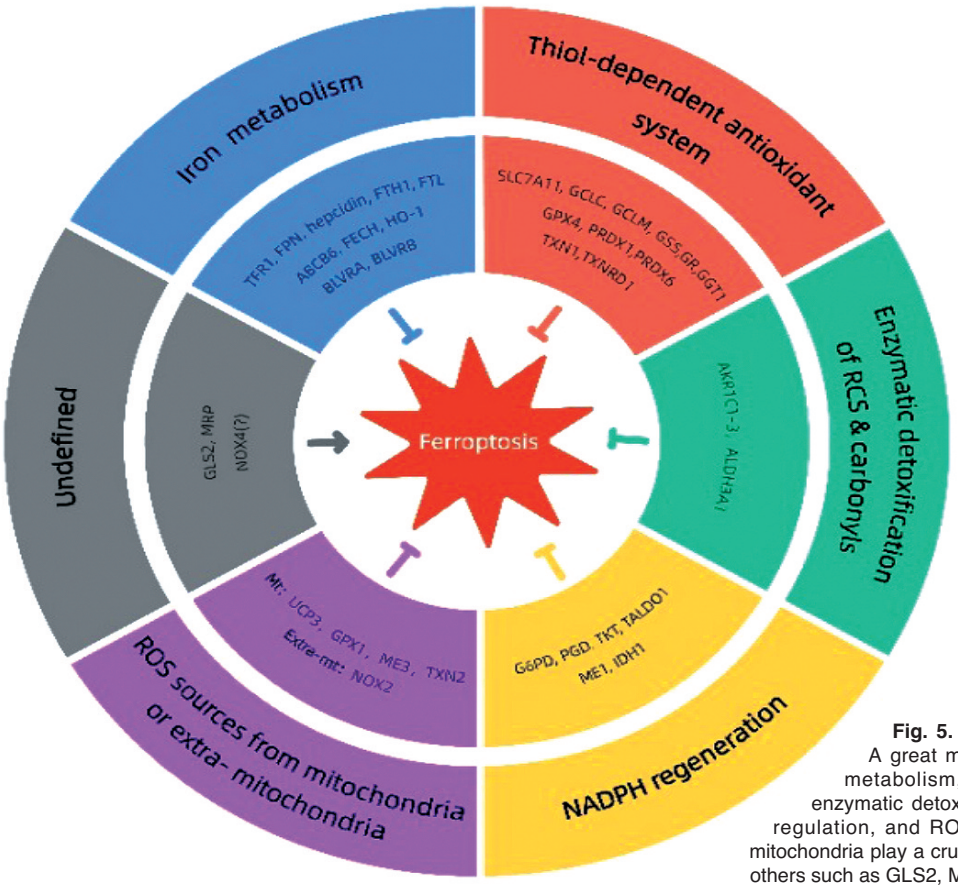

Fig. 5. FPT-related Genes Regulated by NRF2. A great many target genes of NRF2 such as iron metabolism, thiol- dependent antioxidant system, enzymatic detoxification of RCS and carbonyls, NADPH regulation, and ROS sources from mitochondria or extra mitochondria play a crucial role in inhibiting FPT. However, some others such as GLS2, MRP, NOX4 seem to promote FPT.

than the GSH system in the area of FPT inhibition, the direct and indirect relationship between TXN1 or TXNRD1 and FPT has come to the surface (Hayes and Dinkova-Kostova, 2014; Abdalkader et al., 2018; Dodson et al., 2019). A drug coming from pleuromutilin and targeting TXN was proved effective in inducing FPT (Llabani et al., 2019) and the TXN system provides support when the GSH system loses or weakens its function to inhibit FPT indirectly (Tan et al., 2010). For example, Telorack et al. found that cysteine supplemented with SLC7A11 could not be used to synthesize GSH in keratinocytes lacking GCLC but could be incorporated into TXN as an ROS/RNS scavenger to compensate for GSH deficiency (Telorack et al., 2016) (Fig. 2).

The peroxidases (PRDXs) family consists of six members (Rhee et al., 2001, 2005), among which PRDX1 and PRDX6 are regulated by NRF2 (Hayes and Dinkova-Kostova, 2014). PRDX6 uses GSH, the same as GPX4 as a physiological reductant of peroxidase activity, while PRDX1-5 uses TXN (Fig. 6). Strikingly, PRDX6 and GPX4 seem to share the similar function of repairing damaged cell membranes (Fisher et al., 2018). Moreover, PRDX6 has been confirmed as a negative regulator of FPT (Fig. 10), which can remove lipid peroxide (LOOH) through its iPLA2 activity (Lu et al., 2019). Additionally, PRDX1 prevented lipid peroxidation of corneal endothelial cells (CEnCs) and the level of lipid peroxidation of B4G12-CEnCs showed a significant increase if depleted by the PRDX1 gene. However, a similar outcome did not show up in those lacking GPX4 (Lovatt et al., 2020). This not only indicates that the major regulator of lipid peroxidation in B4G12-CEnCs is PRDX1 instead of GPX4 (Lovatt et al., 2020), but also suggests that NRF2 can inhibit FPT by regulating a GPX4-dependent or GPX4-independent system depending on the context of different tissues.

However, it is noteworthy that NRF2 may be a double-edged sword and can deteriorate FPT in some cases. For example, NRF2 regulates GLS2, the key enzyme gene for glutaminolysis (Hirotsu et al., 2012) which was observed to exacerbate FPT in mouse embryonic fibroblasts (MEFs) cultured under deprivation of cysteine, and depletion of GLS2 gene prevented FPT (Gao et al., 2015). This may be attributed to the fact that glutaminolysis involves the mitochondrial tricarboxylic acid (TCA) cycle, ultimately causing accumulation of intracellular ROS and FPT (Gao et al., 2019) (Fig. 2). Another example is that NRF2 promoted the outfllux of GSH by increasing expression of multidrug resistance-associated protein (MRP) to decline intracellular GSH and thereby increase the risk of FPT (Vollrath et al., 2006; Franco and Cidlowski, 2012) (Fig. 2).

NRF2 and enzymatic detoxification of RCS and carbonyls

Previous research on the downstream of FPT has been limited to lipid peroxidation (especially lipid hydroperoxide), and there are few studies focusing on the ultimate executor of FPT. Lipid peroxides are decomposed into active derivatives, including reactive carbonyl species (RCS) and carbonyls, which attack proteins and DNA through Michael addition (Gaschler and Stockwell, 2017) and may play a more central role in the execution of FPT (Hajdinak et al., 2019) (Fig. 2). This indicates that detoxification of lipid peroxidation downstream product may be a new direction for treating FPT. RCS detoxification genes regulated by NRF2 include AKR1C1-3 and ALDH3A1 (Hayes and Dinkova-Kostova, 2014; Dodson et al., 2019) (Fig. 6), and their coding products are potential inhibitors acting upon FPT downstream. For example, AKRs (AKR1C1-3) and ALDHs are highly expressed in some FPT-resistant tumor cells (Dixon et al., 2014; Okazaki et al., 2018; Gagliardi et al., 2019; Otsuki et al., 2020) and this resistance may be partly attributed to the involvement of NRF2 despite lack of research conducted in the brain

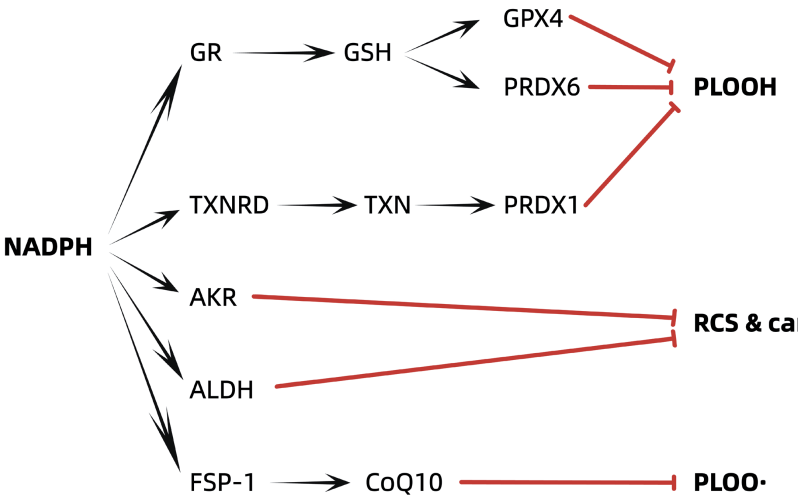

Fig. 6. NADPH-dependent Enzymes in FPT regulation. NADPH has strong reducing power, which provides electrons for enzymes to inhibit FPT. These enzymes can effectively inhibit FPT from different aspects, such as the upstream of lipid peroxidation (PLOOH), the downstream of lipid peroxidation (RCS and carbonyls), or the autoxidation process (PLOO·).

injury context (Gagliardi et al., 2019).

NRF2 and NADPH regeneration

Through ARE, NRF2 can directly activate genes related to the pentose phosphate (PPP) pathway (G6PD, PGD, TKT, TALDO1) and some other metabolic pathway (ME1, IDH1) to supply NADPH (Mitsuishi et al., 2012; Hayes and Dinkova-Kostova, 2014) (Fig. 5). The FPT-related enemy (such as GR, TXNRD, FSP1, AKR, ALDH) functions with the aid of NADPH (Mano, 2012; Deponte, 2013; Lu and Holmgren, 2014; Doll et al., 2019) (Fig. 6), indicating the potential connection between NADPH and FPT. Moreover, a decrease of NADPH level was observed to be the downstream consequence of lipid peroxidation in FPT, and NADPH (rather than NADH) was identified as a biomarker of the sensitivity of FPT inducer (FIN56) across 12 cell lines (Shimada et al., 2016a). According to Shimada et al. cell lines resistant to FPT had high levels of NADPH or capability for regenerating NADPH (Shimada et al., 2016a). Altogether, this evidence directly or indirectly demonstrates the feasibility of targeting NRF2 to regenerate NADPH for treating FPT.

NRF2 and ROS sources from mitochondria or extra-mitochondria

It is well accepted that mitochondria are important sources of intracellular ROS, excessive accumulation of which can contribute to lipid peroxidation of FPT (Fig. 2). However, the role of mitochondria in FPT remains controversial. On one hand, the typical morphological feature of FPT is shrunken mitochondria, indicating that mitochondria do participate in FPT (Dixon et al., 2012). Moreover, cysteine deprivation led to mitochondria membrane potential hyperpolarization and lipid peroxide accumulation, culminating in FPT (Gao et al., 2019). On the other hand, mitochondria seem to be less important in FPT induced by GPX4-targeted inhibition (Gao et al., 2019). Taken together, mitochondria seem to be mainly involved in the upstream of FPT instead of the downstream part. What's more, NRF2 regulation of mitochondrial ROS is also an enigma. Under stress conditions, NRF2 is activated to counteract increased ROS by transcriptionally modulating uncoupling protein 3 (UCP3), GPX1, malic enzyme 3 (ME3), and TXN2 in mitochondria (Greco et al., 2011; Dinkova-Kostova and Abramov, 2015). However, Dinkova-Kostova et al. found that NRF2 had a restricted role in the regulation of mitochondrial ROS (Dinkova-Kostova and Abramov, 2015) and that no increase was observed in the FPT sensitivity of tumor cells removed by mitochondrial DNA (Dixon et al., 2012). Moreover, total ROS increase in NRF2-KO cells was more prominent than mitochondrial ROS in primary glio-neural and brain explant slice cultures (Kovac et al., 2015). In a word, these findings mix the role of NRF2 in regulating mitochondrial ROS and further research is in urgent need.

As a heme-dependent enzyme, NADPH oxidase (NOX) is an important source of extracellular ROS and plays a unique role in maintaining intracellular redox homeostasis (Droge, 2002). Recent discoveries have shown that NOX has the potential to contribute to lipid peroxidation of FPT. For example, NOX was reported to be involved in neurodegenerative diseases and heart failure through autophagy and FPT (Chen et al., 2019; Hou et al., 2019) and inhibiting NOX in human mammary epithelial (HME) cells helped to prevent FPT (Poursaitidis et al., 2017; Dangol et al., 2019). The possible mechanism may be attributed to NOX contribution to total ROS increase (Fig. 2). NOX-induced oxidative stress has been reported to activate NRF2 (Kovac et al., 2015), but the transcriptional effect of NRF2 on NOX has been little studied. Current research considers NRF2 a negative regulator of NOX2 (Kovac et al., 2015), while the transcriptional effect of NRF2 on NOX4 remains controversial. Theoretically, NRF2 as an antioxidant should serve to inhibit NOX4 transcription, but plenty of studies reveal that NOX4 is positively regulated by NRF2 (Pendyala et al., 2011) and lack of NRF2 resulted in NOX4 transcription decline. The reason for such a condition may be that absence of NRF2 creates an environment that is friendly to oxidation and thereby contributes to deactivation of redox-sensitive cysteine in HDAC4 (Matsushima et al., 2013), terminating with decline of NOX4 transcription (Siuda et al., 2012). Therefore, the positive regulation of NOX4 by NRF2 has the potential to promote FPT, despite lack of empirical support (Fig. 5). In short, the relationship between NRF2 and NOX (especially NOX4) is complicated and further study will be required for elucidating it (Wu et al., 2011; Mitsuishi et al., 2012; Singh et al., 2013).

Considering the crucial role NRF2 plays in the regulation of FPT-related genes, we will probe into the feasibility of targeting NRF2 to suppress FPT for treating brain injury in the next section.

Targeting NRF2 to mitigate ferroptosis as a therapy for brain injury

As mentioned before, NRF2 is located in the key position of mitigating FPT, so it is of great significance to explore drugs that can target NRF2 to inhibit FPT for treating brain injury. Recent studies have shown connections between NRF2 and brain injury treatment. For example, Edaravone injected into the lateral ventricle reduced brain edema in rats with intraventricular hemorrhage (IVH) through the increase of NRF2/HO-1 signal (Zhang et al., 2018a) and the NRF2/ARE pathway was activated to suppress oxidative stress in TBI (Cheng et al., 2013). It is worth mentioning that NRF2-mediated neuroprotection is mainly attributed to astrocytes in the brain (Lee et al., 2003a,b; Kraft et al., 2004; Shih et al., 2005), and the regulation of the NRF2 signaling pathway is highly dependent on the interaction

between neurons at the neuron- astrocyte tripartite synapse and astrocytes (Habas et al., 2013). Though astrocytes were not completely relieved from neurotoxicity, it was regarded as a self-defense mechanism when astrocytes overloaded with iron activated NRF2 (Cui et al., 2016). Notably, research on brain injury should not merely separate one or two particular type of brain cells considering the variety of brain cells and their complicated interaction between each other (Linkermann et al., 2014; Stockwell et al., 2017).

There are three ways to activate NRF2 in the brain: (1) Drugs of NRF2 activator enter the brain through BBB, such as dimethyl fumarate (DMF) (Satoh and Lipton, 2017), bardoxolone methyl (Zhang, 2013), ML334, Cpd16, AN-465/14458038, and CPUY192018 (Silva-Islas and Maldonado, 2018). However, such a method is not easy because the BBB has highly selective permeability determined by its biological structure (Xie et al., 2019b). TFR which is only expressed in the cerebral vascular endothelial cells in the BBB offers a natural target (Jefferies et al., 1984; Fishman et al., 1987). Drugs targeting TFR can be delivered across the BBB to the brain with nanocarriers, monoclonal antibodies, lipid carriers and so forth (Johnsen et al., 2019). (2) Under one typical condition, brain cells can be activated to secrete NRF2 autonomously free of continuous exotic NRF2 activators. Lactoferrin (LF) itself is a natural iron chelator in the brain, which serves to exert neuroprotection. The increase of apo-LF not only promoted NRF2 synthesis and nuclear translocation but also induced EPO production which can contribute to the accumulation of NRF2 in brain cells (Genc et al., 2010; Zakharova et al., 2018), forming a positive feedback loop for autonomous and continuous NRF2 activation. (3) Drugs can be injected through the lateral ventricles bypassing the BBB. Zhang et al. injected antibodies and nano drugs into the lateral ventricles of the brain and the drugs were allowed to spread throughout the whole brain parenchyma through the action of reception enhanced delivery (CED) (Zhang et al., 2017), opening up a new approach to regulating NRF2 in the brain. Additionally, besides these mainstream ways, there are more options, such as intravenous injection, intrathecal injection, and oral administration. Nevertheless, the regulation of NRF2-targeted drugs into the brain has been a big challenge for clinical treatment during the last few years and more attention should be focused on the practical problems, to avoid staying at the theoretical level.

The role NRF2 plays in the context of cancer has always been a hot topic. Cancer can "kidnap" the function of NRF2 for proliferation and malignant transformation (Mitsuishi et al., 2012; Kim and Keum, 2016; Gagliardi et al., 2019), but it also presents the Achilles' heel of cancer cells and thereby renders an effective therapeutic target available (Anandhan et al., 2020). For example, bursal, a NRF2 inhibitor, enabled sorafenib-resistant hepatoma cells to regain the sensitivity of FPT for its inhibition of metallothionein-1G (MT-1G) (Sun et al., 2016). One of the differences between how NRF2 works in tumor cells and normal cells is that NRF2 activation in tumor cells is continuous and uncontrolled, while in normal cells it is limited and controlled. This suggests that clinical practice of NRF2 activators for brain injury treatment must not be overused in case of potential side effects. Furthermore, it is notable that NRF2 seems not to be a 'customized' transcription factor to resist FPT and it also plays a regulatory role in other RCDs, such as apoptosis and autophagy (Stępkowski and Kruszewski, 2011). However, there is a reason to believe that NRF2 can adjust the cell antioxidant system to defend against different types of cell death.

Conclusion and further research

Since FPT was coined in 2012, research on it has made rapid progress. Its system has been expanding, and recent studies have shown connections between FPT and other RCDs. A large amount of experimental evidence has proved that FPT is involved in the process of brain injury, and NRF2 as a transcription factor regulating redox homeostasis plays a key role in the regulation of FPT. Taken together, it is of vital significance to explore new ways of using drugs to target NRF2 for brain injury treatment. The clinical treatment and prognosis of brain injury has always been a hard nut to crack in the medical field. Because of the severe side effects of NRF2 activators, these drugs are rarely applied in clinical treatment currently and more attention should be focused on the practical problems, to avoid staying at the theoretical level.

Is FPT scheduled to happen under gene coding and of physiological significance like apoptosis, or is it just a defense loophole caused by brain injury? One viewpoint concerning the question considers ferroptotic death an evolved anti-cancer function of cells (Gao et al., 2019). In any case, understanding the role of FPT in brain injury in essence is of more profound significance for brain injury treatment.

In a word, targeting NRF2 to suppress FPT may be a promising therapeutic strategy for the treatment of brain injury, but more research in this field is needed in order to apply this new idea to clinical treatment.

Acknowledgements. This review was supported by the National Natural Science Foundation of China (81971163, 81400999), Suzhou Science and Technology for People's Livelihood (SYS2019027), Hui-Chun Chin and Tsung-Dao Lee Chinese Undergraduate
Research Endowment (CURE), and a Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

References

Abdalkader M., Lampinen R., Kanninen K.M., Malm T.M. and Liddell

J.R. (2018). Targeting NRF2 to suppress ferroptosis and mitochondrial dysfunction in neurodegeneration. Front. Neurosci. 12, 466.

Abou-Abbass H., Bahmad H., Ghandour H., Fares J., Wazzi-Mkahal R., Yacoub B., Darwish H., Mondello S., Harati H., El Sayed M.J., Tamim H. and Kobeissy F. (2016). Epidemiology and clinical characteristics of traumatic brain injury in lebanon: A systematic review. Medicine (Baltimore) 95, e5342.

Adamczak S.E., de Rivero Vaccari J.P., Dale G., Brand F.J. 3rd, Nonner D., Bullock M.R., Dahl G.P., Dietrich W.D. and Keane R.W. (2014). Pyroptotic neuronal cell death mediated by the AIM2 inflammasome. J. Cereb. Blood Flow Metab. 34, 621-629.

Al Nimer F., Beyeen A.D., Lindblom R., Strom M., Aeinehband S., Lidman O. and Piehl F. (2011). Both MHC and non-MHC genes regulate inflammation and T-cell response after traumatic brain injury. Brain Behav. Immun. 25, 981-990.

Alim I., Caulfield J.T., Chen Y., Swarup V., Geschwind D.H., Ivanova E., Seravalli J., Ai Y., Sansing L.H., Ste Marie E.J., Hondal R.J., Mukherjee S., Cave J.W., Sagdullaev B.T., Karuppagounder S.S. and Ratan R.R. (2019). Selenium drives a transcriptional adaptive program to block ferroptosis and treat stroke. Cell 177, 1262-1279 e1225.

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

Anthonymuthu T.S., Kenny E.M., Lamade A.M., Kagan V.E. and Bayir H. (2018). Oxidized phospholipid signaling in traumatic brain injury. Free Radic. Biol. Med. 124, 493-503.

Baird L. and Dinkova-Kostova A.T. (2011). The cytoprotective role of the Keap1-Nrf2 pathway. Arch. Toxicol. 85, 241-272.

Bansal S., Biswas G. and Avadhani N.G. (2014). Mitochondria-targeted heme oxygenase-1 induces oxidative stress and mitochondrial dysfunction in macrophages, kidney fibroblasts and in chronic alcohol hepatotoxicity. Redox Biol. 2, 273-283.

Bayir H., Kagan V.E., Tyurina Y.Y., Tyurin V., Ruppel R.A., Adelson P.D., Graham S.H., Janesko K., Clark R.S. and Kochanek P.M. (2002). Assessment of antioxidant reserves and oxidative stress in cerebrospinal fluid after severe traumatic brain injury in infants and children. Pediatr. Res. 51, 571-578.

Bayir H., Marion D.W., Puccio A.M., Wisniewski S.R., Janesko K.L., Clark R.S. and Kochanek P.M. (2004). Marked gender effect on lipid peroxidation after severe traumatic brain injury in adult patients. J Neurotrauma 21, 1-8.

Blennow K., Brody D.L., Kochanek P.M., Levin H., McKee A., Ribbers G.M., Yaffe K. and Zetterberg H. (2016). Traumatic brain injuries. Nat. Rev. Dis. Primers 2, 16084.

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

Brazinova A., Rehorcikova V., Taylor M.S., Buckova V., Majdan M., Psota M., Peeters W., Feigin V., Theadom A., Holkovic L. and Synnot A. (2018). Epidemiology of traumatic brain injury in europe: A living systematic review. J. Neurotrauma 33, 1-30.

Brigelius-Flohe R. and Maiorino M. (2013). Glutathione peroxidases. Biochim. Biophys. Acta 1830, 3289-3303.

Bullock R., Zauner A., Woodward J.J., Myseros J., Choi S.C., Ward J.D., Marmarou A. and Young H.F. (1998). Factors affecting excitatory amino acid release following severe human head injury. J. Neurosurg. 89, 507-518.

Capizzi A., Woo J. and Verduzco-Gutierrez M. (2020). Traumatic brain injury: An overview of epidemiology, pathophysiology, and medical management. Med. Clin. North Am. 104, 213-238.

Cardoso R.B., Hare D.J., Lind M., McLean C.A., Volitakis I., Laws S.M., Masters C.L., Bush A.I. and Roberts B.R. (2017). The APOE epsilon4 allele is associated with lower selenium levels in the brain: Implications for alzheimer's disease. ACS Chem. Neurosci. 8, 1459-1464.

Chang L.C., Chiang S.K., Chen S.E., Yu Y.L., Chou R.H. and Chang W.C. (2018). Heme oxygenase-1 mediates bay 11-7085 induced ferroptosis. Cancer Lett. 416, 124-137.

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

Cheng Z.G., Zhang G.D., Shi P.Q. and Du B.S. (2013). Expression and antioxidation of nrf2/are pathway in traumatic brain injury. Asian Pac. J. Trop. Med. 6, 305-310.

Chiu-Ugalde J., Theilig F., Behrends T., Drebes J., Sieland C., Subbarayal P., Kohrle J., Hammes A., Schomburg L. and Schweizer U. (2010). Mutation of megalin leads to urinary loss of selenoprotein p and selenium deficiency in serum, liver, kidneys and brain. Biochem J. 431, 103-111.

Conrad M. and Proneth B. (2020). Selenium: Tracing another essential element of ferroptotic cell death. Cell Chem Biol. 27, 409-419.

Conrad M., Kagan V.E., Bayir H., Pagnussat G.C., Head B., Traber M.G. and Stockwell B.R. (2018). Regulation of lipid peroxidation and ferroptosis in diverse species. Genes Dev. 32, 602-619.

Crichton R.R., Dexter D.T. and Ward R.J. (2011). Brain iron metabolism and its perturbation in neurological diseases. J. Neural Transm. (Vienna) 118, 301-314.

Cui Z., Zhong Z., Yang Y., Wang B., Sun Y., Sun Q., Yang G.Y. and Bian L. (2016). Ferrous iron induces NRF2 expression in mouse brain astrocytes to prevent neurotoxicity. J. Biochem. Mol. Toxicol. 30, 396-403.

Dangol S., Chen Y., Hwang B.K. and Jwa N.S. (2019). Iron- and reactive oxygen species-dependent ferroptotic cell death in rice-magnaporthe oryzae interactions. Plant Cell 31, 189-209.

Deponte M. (2013). Glutathione catalysis and the reaction mechanisms of glutathione-dependent enzymes. Biochim. Biophys Acta 1830, 3217-3266.

Dinkova-Kostova A.T. and Abramov A.Y. (2015). The emerging role of NRF2 in mitochondrial function. Free Radic. Biol. Med. 88, 179-188.

Dixon S.J., Patel D.N., Welsch M., Skouta R., Lee E.D., Hayano M., Thomas A.G., Gleason C.E., Tatonetti N.P., Slusher B.S. and Stockwell B.R. (2014). Pharmacological inhibition of cystine-glutamate exchange induces endoplasmic reticulum stress and ferroptosis. Elife 3, e02523.

Dixon S.J., Lemberg K.M., Lamprecht M.R., Skouta R., Zaitsev E.M., Gleason C.E., Patel D.N., Bauer A.J., Cantley A.M., Yang W.S., Morrison B. 3rd and Stockwell B.R. (2012). Ferroptosis: An iron-dependent form of nonapoptotic cell death. Cell 149, 1060-1072.

Dodson M., Castro-Portuguez R. and Zhang D.D. (2019). NRF2 plays a critical role in mitigating lipid peroxidation and ferroptosis. Redox Biol. 23, 101107.

Doll S., Proneth B., Tyurina Y.Y., Panzilius E., Kobayashi S., Ingold I., Irmler M., Beckers J., Aichler M., Walch A., Prokisch H., Trumbach D., Mao G., Qu F., Bayir H., Fullekrug J., Scheel C.H., Wurst W., Schick J.A., Kagan V.E., Angeli J.P. and Conrad M. (2017). ACSL4

dictates ferroptosis sensitivity by shaping cellular lipid composition. Nat. Chem. Biol. 13, 91-98.

Doll S., Freitas F.P., Shah R., Aldrovandi M., da Silva M.C., Ingold I., Goya Grocin A., Xavier da Silva T.N., Panzilius E., Scheel C.H., Mourao A., Buday K., Sato M., Wanninger J., Vignane T., Mohana V., Rehberg M., Flatley A., Schepers A., Kurz A., White D., Sauer M., Sattler M., Tate E.W., Schmitz W., Schulze A., O'Donnell V., Proneth B., Popowicz G.M., Pratt D.A., Angeli J.P.F. and Conrad M. (2019). FSP1 is a glutathione-independent ferroptosis suppressor. Nature 575, 693-698.

Dong Z., Feng L., Chao Y., Hao Y., Chen M., Gong F., Han X., Zhang R., Cheng L. and Liu Z. (2019). Amplification of tumor oxidative stresses with liposomal fenton catalyst and glutathione inhibitor for enhanced cancer chemotherapy and radiotherapy. Nano Lett 19, 805-815.

Donovan A., Lima C.A., Pinkus J.L., Pinkus G.S., Zon L.I., Robine S. and Andrews N.C. (2005). The iron exporter ferroportin/slc40a1 is essential for iron homeostasis. Cell Metab. 1, 191-200.

Drakesmith H., Nemeth E. and Ganz T. (2015). Ironing out ferroportin. Cell Metab. 22, 777-787.

Droge W. (2002). Free radicals in the physiological control of cell function. Physiol. Rev. 82, 47-95.

Fang X., Wang H., Han D., Xie E., Yang X., Wei J., Gu S., Gao F., Zhu N., Yin X., Cheng Q., Zhang P., Dai W., Chen J., Yang F., Yang H.T., Linkermann A., Gu W., Min J. and Wang F. (2019). Ferroptosis as a target for protection against cardiomyopathy. Proc. Natl. Acad. Sci. USA 116, 2672-2680.

Feigin V.L., Lawes C.M., Bennett D.A., Barker-Collo S.L. and Parag V. (2009). Worldwide stroke incidence and early case fatality reported in 56 population-based studies: A systematic review. Lancet Neurol. 8, 355-369.

Fisher A.B., Vasquez-Medina J.P., Dodia C., Sorokina E.M., Tao J.Q. and Feinstein S.I. (2018). Peroxiredoxin 6 phospholipid hydroperoxidase activity in the repair of peroxidized cell membranes. Redox Biol. 14, 41-46.

Fishman J.B., Rubin J.B., Handrahan J.V., Connor J.R. and Fine R.E. (1987). Receptor-mediated transcytosis of transferrin across the blood-brain barrier. J. Neurosci. Res. 18, 299-304.

Franco R. and Cidlowski J.A. (2012). Glutathione efflux and cell death. Antioxid. Redox Signal 17, 1694-1713.

Friedmann Angeli J.P., Schneider M., Proneth B., Tyurina Y.Y., Tyurin V.A., Hammond V.J., 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 G.W., Geissler E.K., Thomas S.B., Stockwell B.R., O'Donnell V.B., Kagan V.E., Schick J.A. and Conrad M. (2014). Inactivation of the ferroptosis regulator GPX4 triggers acute renal failure in mice. Nat. Cell Biol. 16, 1180-1191.

Gagliardi M., Cotella D., Santoro C., Cora D., Barlev N.A., Piacentini M. and Corazzari M. (2019). Aldo-keto reductases protect metastatic melanoma from er stress-independent ferroptosis. Cell Death Dis. 10, 902.

Gao M., Monian P., Quadri N., Ramasamy R. and Jiang X. (2015). Glutaminolysis and transferrin regulate ferroptosis. Mol. Cell 59, 298-308.

Gao M., Yi J., Zhu J., Minikes A.M., Monian P., Thompson C.B. and Jiang X. (2019). Role of mitochondria in ferroptosis. Mol. Cell 73, 354-363 e353.

Gaschler M.M. and Stockwell B.R. (2017). Lipid peroxidation in cell death. Biochem. Biophys. Res. Commun 482, 419-425.

Genc K., Egrilmez M.Y. and Genc S. (2010). Erythropoietin induces nuclear translocation of Nrf2 and heme oxygenase-1 expression in SH-SY5Y cells. Cell Biochem. Funct 28, 197-201.

Gerson J., Castillo-Carranza D.L., Sengupta U., Bodani R., Prough D.S., DeWitt D.S., Hawkins B.E. and Kayed R. (2016). Tau oligomers derived from traumatic brain injury cause cognitive impairment and accelerate onset of pathology in htau mice. J. Neurotrauma 33, 2034-2043.

Gomme P.T., McCann K.B. and Bertolini J. (2005). Transferrin: Structure, function and potential therapeutic actions. Drug Discov. Today 10, 267-273.

Greco T., Shafer J. and Fiskum G. (2011). Sulforaphane inhibits mitochondrial permeability transition and oxidative stress. Free Radic. Biol. Med. 51, 2164-2171.

Guan X., Li X., Yang X., Yan J., Shi P., Ba L., Cao Y. and Wang P. (2019). The neuroprotective effects of carvacrol on ischemia/reperfusion-induced hippocampal neuronal impairment by ferroptosis mitigation. Life Sci. 235, 116795.

Gubern C., Camos S., Ballesteros I., Rodriguez R., Romera V.G., Canadas R., Lizasoain I., Moro M.A., Serena J., Mallolas J. and Castellanos M. (2013). MiRNA expression is modulated over time after focal ischaemia: Up-regulation of mir-347 promotes neuronal apoptosis. FEBS J. 280, 6233-6246.

Habas A., Hahn J., Wang X. and Margeta M. (2013). Neuronal activity regulates astrocytic nrf2 signaling. Proc. Natl. Acad. Sci. USA 110, 18291-18296.

Hajdinak P., Czobor A. and Szarka A. (2019). The potential role of acrolein in plant ferroptosis-like cell death. PLoS One 14, e0227278.

Hayes J.D. and Dinkova-Kostova A.T. (2014). The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. Trends Biochem. Sci. 39, 199-218.

Hirotsu Y., Katsuoka F., Funayama R., Nagashima T., Nishida Y., Nakayama K., Engel J.D. and Yamamoto M. (2012). Nrf2-MAFG heterodimers contribute globally to antioxidant and metabolic networks. Nucleic Acids Res. 40, 10228-10239.

Holowiecki A., O'Shields B. and Jenny M.J. (2016). Characterization of heme oxygenase and biliverdin reductase gene expression in zebrafish (danio rerio): Basal expression and response to pro-oxidant exposures. Toxicol. Appl. Pharmacol. 311, 74-87.

Hou L., Huang R., Sun F., Zhang L. and Wang Q. (2019). NADPH oxidase regulates paraquat and maneb-induced dopaminergic neurodegeneration through ferroptosis. Toxicology 417, 64-73.

Hu X., Tao C., Gan Q., Zheng J., Li H. and You C. (2016). Oxidative stress in intracerebral hemorrhage: Sources, mechanisms, and therapeutic targets. Oxid Med. Cell Longev. 3215391.

Huang Y., Weisgraber K.H., Mucke L. and Mahley R.W. (2004). Apolipoprotein E: Diversity of cellular origins, structural and biophysical properties, and effects in alzheimer's disease. J. Mol. Neurosci. 23, 189-204.

Humphreys I., Wood R.L., Phillips C.J. and Macey S. (2013). The costs of traumatic brain injury: A literature review. Clinicoecon Outcomes Res. 5, 281-287.

Imai T., Iwata S., Hirayama T., Nagasawa H., Nakamura S., Shimazawa M. and Hara H. (2019). Intracellular Fe(2+) accumulation in endothelial cells and pericytes induces blood-brain barrier dysfunction in secondary brain injury after brain hemorrhage. Sci. Rep. 9, 6228.

Ingold I., Berndt C., Schmitt S., Doll S., Poschmann G., Buday K.,

Roveri A., Peng X., Porto Freitas F., Seibt T., Mehr L., Aichler M., Walch A., Lamp D., Jastroch M., Miyamoto S., Wurst W., Ursini F., Arner E.S.J., Fradejas-Villar N., Schweizer U., Zischka H., Friedmann Angeli J.P. and Conrad M. (2018). Selenium utilization by GPX4 is required to prevent hydroperoxide-induced ferroptosis. Cell 172, 409-422.e421.

Jefferies W.A., Brandon M.R., Hunt S.V., Williams A.F., Gatter K.C. and Mason D.Y. (1984). Transferrin receptor on endothelium of brain capillaries. Nature 312, 162-163.

Jia F., Mao Q., Liang Y.M. and Jiang J.Y. (2009). Effect of post-traumatic mild hypothermia on hippocampal cell death after traumatic brain injury in rats. J. Neurotrauma 26, 243-252.

Johnsen K.B., Burkhart A., Thomsen L.B., Andresen T.L. and Moos T. (2019). Targeting the transferrin receptor for brain drug delivery. Prog. Neurobiol. 181, 101665.

Johnson J.A., Johnson D.A., Kraft A.D., Calkins M.J., Jakel R.J., Vargas M.R. and Chen P.C. (2008). The Nrf2-ARE pathway: An indicator and modulator of oxidative stress in neurodegeneration. Ann. NY Acad. Sci. 1147, 61-69.

Katsu M., Niizuma K., Yoshioka H., Okami N., Sakata H. and Chan P.H. (2010). Hemoglobin-induced oxidative stress contributes to matrix metalloproteinase activation and blood-brain barrier dysfunction *in vivo*. J. Cereb. Blood Flow Metab. 30, 1939-1950.

Kawabata H. (2019). Transferrin and transferrin receptors update. Free Radic. Biol. Med. 133, 46-54.

Ke Y. and Qian Z.M. (2007). Brain iron metabolism: Neurobiology and neurochemistry. Prog. Neurobiol. 83, 149-173.

Kenny E.M., Fidan E., Yang Q., Anthonymuthu T.S., New L.A., Meyer E.A., Wang H., Kochanek P.M., Dixon C.E., Kagan V.E. and Bayir H. (2019). Ferroptosis contributes to neuronal death and functional outcome after traumatic brain injury. Crit. Care Med. 47, 410-418.

Kim J. and Keum Y.S. (2016). Nrf2, a key regulator of antioxidants with two faces towards cancer. Oxid. Med. Cell Longev. 2746457.

Kovac S., Angelova P.R., Holmstrom K.M., Zhang Y., Dinkova-Kostova A.T. and Abramov A.Y. (2015). Nrf2 regulates ROS production by mitochondria and NADPH oxidase. Biochim. Biophys. Acta 1850, 794-801.

Kraft A.D., Johnson D.A. and Johnson J.A. (2004). Nuclear factor E2-related factor 2-dependent antioxidant response element activation by tert-butylhydroquinone and sulforaphane occurring preferentially in astrocytes conditions neurons against oxidative insult. J. Neurosci. 24, 1101-1112.

Kuhn H., Banthiya S. and van Leyen K. (2015). Mammalian lipoxygenases and their biological relevance. Biochim. Biophys. Acta 1851, 308-330.

Lee J.M., Shih A.Y., Murphy T.H. and Johnson J.A. (2003a). NF-E2-related factor-2 mediates neuroprotection against mitochondrial complex I inhibitors and increased concentrations of intracellular calcium in primary cortical neurons. J. Biol. Chem. 278, 37948-37956.

Lee J.M., Calkins M.J., Chan K., Kan Y.W. and Johnson J.A. (2003b). Identification of the NF-E2-related factor-2-dependent genes conferring protection against oxidative stress in primary cortical astrocytes using oligonucleotide microarray analysis. J. Biol. Chem. 278, 12029-12038.

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

Linkermann A., Skouta R., Himmerkus N., Mulay S.R., Dewitz C., De Zen F., Prokai A., Zuchtriegel G., Krombach F., Welz P.S., Weinlich R., Vanden Berghe T., Vandenabeele P., Pasparakis M., Bleich M., Weinberg J.M., Reichel C.A., Brasen J.H., Kunzendorf U., Anders H.J., Stockwell B.R., Green D.R. and Krautwald S. (2014). Synchronized renal tubular cell death involves ferroptosis. Proc. Natl. Acad. Sci. USA 111, 16836-16841.

Liu T., Zhao D.X., Cui H., Chen L., Bao Y.H., Wang Y. and Jiang J.Y. (2016). Therapeutic hypothermia attenuates tissue damage and cytokine expression after traumatic brain injury by inhibiting necroptosis in the rat. Sci. Rep. 6, 24547.

Llabani E., Hicklin R.W., Lee H.Y., Motika S.E., Crawford L.A., Weerapana E. and Hergenrother P.J. (2019). Diverse compounds from pleuromutilin lead to a thioredoxin inhibitor and inducer of ferroptosis. Nat. Chem. 11, 521-532.

Lovatt M., Adnan K., Kocaba V., Dirisamer M., Peh G.S.L. and Mehta J.S. (2020). Peroxiredoxin-1 regulates lipid peroxidation in corneal endothelial cells. Redox Biol. 30, 101417.

Lu J. and Holmgren A. (2014). The thioredoxin antioxidant system. Free Radic. Biol. Med. 66, 75-87.

Lu B., Chen X.B., Hong Y.C., Zhu H., He Q.J., Yang B., Ying M.D. and Cao J. (2019). Identification of PRDX6 as a regulator of ferroptosis. Acta Pharmacol. Sin. 40, 1334-1342.

MacGillivray R.T., Mendez E., Shewale J.G., Sinha S.K., Lineback-Zins J. and Brew K. (1983). The primary structure of human serum transferrin. The structures of seven cyanogen bromide fragments and the assembly of the complete structure. J. Biol. Chem. 258, 3543-3553.

Magtanong L. and Dixon S.J. (2018). Ferroptosis and brain injury. Dev. Neurosci. 40, 382-395.

Maines M.D. (1988). Heme oxygenase: Function, multiplicity, regulatory mechanisms, and clinical applications. FASEB J. 2, 2557-2568.

Mancuso C. (2017). Bilirubin and brain: A pharmacological approach. Neuropharmacology 118, 113-123.

Mano J. (2012). Reactive carbonyl species: Their production from lipid peroxides, action in environmental stress, and the detoxification mechanism. Plant Physiol. Biochem 59, 90-97.

Mao Y., Zhuang Z., Chen Y., Zhang X., Shen Y., Lin G. and Wu R. (2019). Imaging of glutamate in acute traumatic brain injury using chemical exchange saturation transfer. Quant Imaging Med. Surg. 9, 1652-1663.

Mastroberardino P.G., Hoffman E.K., Horowitz M.P., Betarbet R., Taylor G., Cheng D., Na H.M., Gutekunst C.A., Gearing M., Trojanowski J.Q., Anderson M., Chu C.T., Peng J. and Greenamyre J.T. (2009). A novel transferrin/TFR2-mediated mitochondrial iron transport system is disrupted in parkinson's disease. Neurobiol. Dis. 34, 417-431.

Matsushima S., Kuroda J., Ago T., Zhai P., Park J.Y., Xie L.H., Tian B. and Sadoshima J. (2013). Increased oxidative stress in the nucleus caused by Nox4 mediates oxidation of HDAC4 and cardiac hypertrophy. Circ. Res. 112, 651-663.

McGinn M.J. and Povlishock J.T. (2016). Pathophysiology of traumatic brain injury. Neurosurg Clin. N. Am. 27, 397-407.

Mitsuishi Y., Taguchi K., Kawatani Y., Shibata T., Nukiwa T., Aburatani H., Yamamoto M. and Motohashi H. (2012). Nrf2 redirects glucose and glutamine into anabolic pathways in metabolic reprogramming. Cancer Cell 22, 66-79.

Muckenthaler M.U., Rivella S., Hentze M.W. and Galy B. (2017). A red carpet for iron metabolism. Cell 168, 344-361.

Nemeth E., Tuttle M.S., Powelson J., Vaughn M.B., Donovan A., Ward D.M., Ganz T. and Kaplan J. (2004). Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science 306, 2090-2093.

Nikseresht S., Bush A.I. and Ayton S. (2019). Treating alzheimer's disease by targeting iron. Br. J. Pharmacol. 176, 3622-3635.

Okazaki S., Shintani S., Hirata Y., Suina K., Semba T., Yamasaki J., Umene K., Ishikawa M., Saya H. and Nagano O. (2018). Synthetic lethality of the ALDH3A1 inhibitor dyclonine and xCT inhibitors in glutathione deficiency-resistant cancer cells. Oncotarget 9, 33832-33843.

Osburn W.O., Wakabayashi N., Misra V., Nilles T., Biswal S., Trush M.A. and Kensler T.W. (2006). Nrf2 regulates an adaptive response protecting against oxidative damage following diquat-mediated formation of superoxide anion. Arch. Biochem. Biophys. 454, 7-15.

Otsuki Y., Yamasaki J., Suina K., Okazaki S., Koike N., Saya H. and Nagano O. (2020). Vasodilator oxyfedrine inhibits aldehyde metabolism and thereby sensitizes cancer cells to xCT-targeted therapy. Cancer Sci. 111, 127-136.

Pantopoulos K. and Hentze M.W. (1995). Rapid responses to oxidative stress mediated by iron regulatory protein. EMBO J. 14, 2917-2924.

Paul B.T., Manz D.H., Torti F.M. and Torti S.V. (2017). Mitochondria and iron: Current questions. Expert Rev. Hematol. 10, 65-79.

Pendyala S., Moitra J., Kalari S., Kleeberger S.R., Zhao Y., Reddy S.P., Garcia J.G. and Natarajan V. (2011). Nrf2 regulates hyperoxia-induced Nox4 expression in human lung endothelium: Identification of functional antioxidant response elements on the Nox4 promoter. Free Radic. Biol. Med. 50, 1749-1759.

Poursaitidis I., Wang X., Crighton T., Labuschagne C., Mason D., Cramer S.L., Triplett K., Roy R., Pardo O.E., Seckl M.J., Rowlinson S.W., Stone E. and Lamb R.F. (2017). Oncogene-selective sensitivity to synchronous cell death following modulation of the amino acid nutrient cystine. Cell Rep. 18, 2547-2556.

Ratan R.R. (2019). Does iron loading of oxygen-sensing prolyl hydroxylases rather than random fenton-driven radical formation drive programmed ferroptosis and degeneration in neurological diseases? Curr. Opin. Physiol. 7, 60-65.

Rhee S.G., Kang S.W., Chang T.S., Jeong W. and Kim K. (2001). Peroxiredoxin, a novel family of peroxidases. IUBMB Life 52, 35-41.

Rhee S.G., Chae H.Z. and Kim K. (2005). Peroxiredoxins: A historical overview and speculative preview of novel mechanisms and emerging concepts in cell signaling. Free Radic. Biol. Med. 38, 1543-1552.

Rhodes S.L., Buchanan D.D., Ahmed I., Taylor K.D., Loriot M.A., Sinsheimer J.S., Bronstein J.M., Elbaz A., Mellick G.D., Rotter J.I. and Ritz B. (2014). Pooled analysis of iron-related genes in parkinson's disease: Association with transferrin. Neurobiol. Dis. 62, 172-178.

Robertson C.L., Bell M.J., Kochanek P.M., Adelson P.D., Ruppel R.A., Carcillo J.A., Wisniewski S.R., Mi Z., Janesko K.L., Clark R.S., Marion D.W., Graham S.H. and Jackson E.K. (2001). Increased adenosine in cerebrospinal fluid after severe traumatic brain injury in infants and children: Association with severity of injury and excitotoxicity. Crit. Care Med. 29, 2287-2293.

Rostami E. (2016). Traumatic brain injury models in animals. Methods Mol. Biol. 1462, 47-59.

Rubenstein R., Chang B., Yue J.K., Chiu A., Winkler E.A., Puccio A.M., Diaz-Arrastia R., Yuh E.L., Mukherjee P., Valadka A.B., Gordon W.A., Okonkwo D.O., Davies P., Agarwal S., Lin F., Sarkis G., Yadikar H., Yang Z., Manley G.T., Wang K.K.W., the T.-T.B.I.I., Cooper S.R., Dams-O'Connor K., Borrasso A.J., Inoue T., Maas A.I.R., Menon D.K., Schnyer D.M. and Vassar M.J. (2017). Comparing plasma phospho tau, total tau, and phospho tau-total tau ratio as acute and chronic traumatic brain injury biomarkers. JAMA Neurol. 74, 1063-1072.

Satoh T. and Lipton S. (2017). Recent advances in understanding NRF2 as a druggable target: Development of pro-electrophilic and non-covalent NRF2 activators to overcome systemic side effects of electrophilic drugs like dimethyl fumarate. F1000Res 6, 2138.

Shah R., Shchepinov M.S. and Pratt D.A. (2018). Resolving the role of lipoxygenases in the initiation and execution of ferroptosis. ACS Cent Sci. 4, 387-396.

Shih A.Y., Imbeault S., Barakauskas V., Erb H., Jiang L., Li P. and Murphy T.H. (2005). Induction of the NRF2-driven antioxidant response confers neuroprotection during mitochondrial stress *in vivo*. J. Biol. Chem. 280, 22925-22936.

Shimada K., Hayano M., Pagano N.C. and Stockwell B.R. (2016a). Cell-line selectivity improves the predictive power of pharmacogenomic analyses and helps identify nadph as biomarker for ferroptosis sensitivity. Cell Chem. Biol. 23, 225-235.

Shimada K., Skouta R., Kaplan A., Yang W.S., Hayano M., Dixon S.J., Brown L.M., Valenzuela C.A., Wolpaw A.J. and Stockwell B.R. (2016b). Global survey of cell death mechanisms reveals metabolic regulation of ferroptosis. Nat. Chem. Biol. 12, 497-503.

Shin D., Kim E.H., Lee J. and Roh J.L. (2018). NRF2 inhibition reverses resistance to GPX4 inhibitor-induced ferroptosis in head and neck cancer. Free Radic. Biol. Med. 129, 454-462.

Silva-Islas C.A. and Maldonado P.D. (2018). Canonical and non-canonical mechanisms of NRF2 activation. Pharmacol. Res. 134, 92-99.

Singh A., Happel C., Manna S.K., Acquaah-Mensah G., Carrerero J., Kumar S., Nasipuri P., Krausz K.W., Wakabayashi N., Dewi R., Boros L.G., Gonzalez F.J., Gabrielson E., Wong K.K., Girnun G. and Biswal S. (2013). Transcription factor NRF2 regulates mir-1 and mir-206 to drive tumorigenesis. J. Clin. Invest. 123, 2921-2934.

Siuda D., Zechner U., El Hajj N., Prawitt D., Langer D., Xia N., Horke S., Pautz A., Kleinert H., Forstermann U. and Li H. (2012). Transcriptional regulation of Nox4 by histone deacetylases in human endothelial cells. Basic Res. Cardiol. 107, 283.

Snyder A.M. and Connor J.R. (2009). Iron, the substantia nigra and related neurological disorders. Biochim. Biophys Acta 1790, 606-614.

Stępkowski T.M. and Kruszewski M.K. (2011). Molecular cross-talk between the NRF2/KEAP1 signaling pathway, autophagy, and apoptosis. Free Rad. Biol. Med. 50, 1186-1195.

Stocker R., Yamamoto Y., McDonagh A.F., Glazer A.N. and Ames B.N. (1987). Bilirubin is an antioxidant of possible physiological importance. Science 235, 1043-1046.

Stockwell B.R., Friedmann Angeli J.P., Bayir H., Bush A.I., Conrad M., Dixon S.J., Fulda S., Gascon S., Hatzios S.K., Kagan V.E., Noel K., Jiang X., Linkermann A., Murphy M.E., Overholtzer M., Oyagi A., Pagnussat G.C., Park J., Ran Q., Rosenfeld C.S., Salnikow K., Tang D., Torti F.M., Torti S.V., Toyokuni S., Woerpel K.A. and Zhang D.D. (2017). Ferroptosis: A regulated cell death nexus linking metabolism, redox biology, and disease. Cell 171, 273-285.

Sun X., Niu X., Chen R., He W., Chen D., Kang R. and Tang D. (2016). Metallothionein-1G facilitates sorafenib resistance through inhibition of ferroptosis. Hepatology 64, 488-500.

Tan S., Schubert D. and Maher P. (2001). Oxytosis: A novel form of programmed cell death. Curr. Top Med. Chem. 1, 497-506.

Tan S.X., Greetham D., Raeth S., Grant C.M., Dawes I.W. and Perrone G.G. (2010). The thioredoxin-thioredoxin reductase system can function *in vivo* as an alternative system to reduce oxidized glutathione in saccharomyces cerevisiae. J. Biol. Chem. 285, 6118-6126.

Telorack M., Meyer M., Ingold I., Conrad M., Bloch W. and Werner S. (2016). A glutathione-NRF2-thioredoxin cross-talk ensures keratinocyte survival and efficient wound repair. PLoS Genet 12, e1005800.

Tuo Q.Z., Lei P., Jackman K.A., Li X.L., Xiong H., Li X.L., Liuyang Z.Y., Roisman L., Zhang S.T., Ayton S., Wang Q., Crouch P.J., Ganio K., Wang X.C., Pei L., Adlard P.A., Lu Y.M., Cappai R., Wang J.Z., Liu R. and Bush A.I. (2017). Tau-mediated iron export prevents ferroptotic damage after ischemic stroke. Mol. Psychiatry 22, 1520-1530.

Ueta T., Inoue T., Furukawa T., Tamaki Y., Nakagawa Y., Imai H. and Yanagi Y. (2012). Glutathione peroxidase 4 is required for maturation of photoreceptor cells. J. Biol. Chem. 287, 7675-7682.

Ursini F. and Maiorino M. (2020). Lipid peroxidation and ferroptosis: The role of gsh and GPX4. Free Radic. Biol. Med. 152, 175-185.

van den Brink-van der Laan E., Killian J.A. and de Kruijff B. (2004). Nonbilayer lipids affect peripheral and integral membrane proteins via changes in the lateral pressure profile. Biochim. Biophys. Acta 1666, 275-288.

Vollrath V., Wielandt A.M., Iruretagoyena M. and Chianale J. (2006). Role of NRF2 in the regulation of the Mrp2 (ABCC2) gene. Biochem. J. 395, 599-609.

Wachelder E.M., Moulaert V.R., van Heugten C., Verbunt J.A., Bekkers S.C. and Wade D.T. (2009). Life after survival: Long-term daily functioning and quality of life after an out-of-hospital cardiac arrest. Resuscitation 80, 517-522.

Wang B. and Han S. (2018). Exosome-associated tau exacerbates brain functional impairments induced by traumatic brain injury in mice. Mol. Cell Neurosci. 88, 158-166.

Wang G.Q., Hu W.M., Tang Q.P., Wang L., Sun X.G., Chen Y.L., Yin Y.F., Xue F. and Sun Z.T. (2016). Effect comparison of both iron chelators on outcomes, iron deposit, and iron transporters after intracerebral hemorrhage in rats. Mol. Neurobiol. 53, 3576-3585.

Wenzel S.E., Tyurina Y.Y., Zhao J., St Croix C.M., Dar H.H., Mao G., Tyurin V.A., Anthonymuthu T.S., Kapralov A.A., Amoscato A.A., Mikulska-Ruminska K., Shrivastava I.H., Kenny E.M., Yang Q., Rosenbaum J.C., Sparvero L.J., Emlet D.R., Wen X., Minami Y., Qu F., Watkins S.C., Holman T.R., VanDemark A.P., Kellum J.A., Bahar I., Bayir H. and Kagan V.E. (2017). PEBP1 wardens ferroptosis by enabling lipoxygenase generation of lipid death signals. Cell 171, 628-641 e626.

Werner C. and Engelhard K. (2007). Pathophysiology of traumatic brain injury. Br. J. Anaesth 99, 4-9.

Wu K.C., Cui J.Y. and Klaassen C.D. (2011). Beneficial role of NRF2 in regulating NADPH generation and consumption. Toxicol. Sci. 123, 590-600.

Wu J.R., Tuo Q.Z. and Lei P. (2018). Ferroptosis, a recent defined form of critical cell death in neurological disorders. J. Mol. Neurosci. 66, 197-206.

Xiao X., Jiang Y., Liang W., Wang Y., Cao S., Yan H., Gao L. and Zhang L. (2019). Mir-212-5p attenuates ferroptotic neuronal death after traumatic brain injury by targeting Ptgs2. Mol. Brain. 12, 78.

Xie B.S., Wang Y.Q., Lin Y., Mao Q., Feng J.F., Gao G.Y. and Jiang J.Y. (2019a). Inhibition of ferroptosis attenuates tissue damage and improves long-term outcomes after traumatic brain injury in mice. CNS Neurosci. Ther. 25, 465-475.

Xie J., Shen Z., Anraku Y., Kataoka K. and Chen X. (2019b). Nanomaterial-based blood-brain-barrier (BBB) crossing strategies. Biomaterials 224, 119491.

Yen H.C., Chen T.W., Yang T.C., Wei H.J., Hsu J.C. and Lin C.L. (2015). Levels of F2-isoprostanes, F4-neuroprostanes, and total nitrate/nitrite in plasma and cerebrospinal fluid of patients with traumatic brain injury. Free Radic. Res. 49, 1419-1430.

Zakharova E.T., Sokolov A.V., Pavlichenko N.N., Kostevich V.A., Abdurasulova I.N., Chechushkov A.V., Voynova I.V., Elizarova A.Y., Kolmakov N.N., Bass M.G., Semak I.V., Budevich A.I., Kozhin P.M., Zenkov N.K., Klimenko V.M., Kirik O.V., Korzhevskii D.E., Menshchikova E.B. and Vasilyev V.B. (2018). Erythropoietin and NRF2: Key factors in the neuroprotection provided by apo-lactoferrin. Biometals 31, 425-443.

Zeng S., Jiang J.X., Xu M.H., Xu L.S., Shen G.J., Zhang A.Q. and Wang X.H. (2014). Prognostic value of apolipoprotein e epsilon4 allele in patients with traumatic brain injury: A meta-analysis and meta-regression. Genet. Test Mol. Biomarkers 18, 202-210.

Zhang D.D. (2013). Bardoxolone brings NRF2-based therapies to light. Antioxid. Redox Signal. 19, 517-518.

Zhang Z., Zhang F., An P., Guo X., Shen Y., Tao Y., Wu Q., Zhang Y., Yu Y., Ning B., Nie G., Knutson M.D., Anderson G.J. and Wang F. (2011). Ferroportin1 deficiency in mouse macrophages impairs iron homeostasis and inflammatory responses. Blood 118, 1912-1922.

Zhang M., An C., Gao Y., Leak R.K., Chen J. and Zhang F. (2013). Emerging roles of NRF2 and phase II antioxidant enzymes in neuroprotection. Prog. Neurobiol. 100, 30-47.

Zhang C., Mastorakos P., Sobral M., Berry S., Song E., Nance E., Eberhart C.G., Hanes J. and Suk J.S. (2017). Strategies to enhance the distribution of nanotherapeutics in the brain. J. Control Release 267, 232-239.

Zhang J., Shi X., Chen Z., Geng J., Wang Y., Feng H., Zhu G. and Chen Q. (2018a). Edaravone reduces iron-mediated hydrocephalus and behavioral disorder in rat by activating the Nrf2/Ho-1 pathway. J. Stroke Cerebrovasc. Dis. 27, 3511-3520.

Zhang Z.W., Wu Y., Yuan S., Zhang P., Zhang J.Y., Li H.Y., Li X., Shen H.T., Wang Z. and Chen G. (2018b). Glutathione peroxidase 4 participates in secondary brain injury through mediating ferroptosis in a rat model of intracerebral hemorrhage. Brain Res. 1701, 112-125.

Zhou Z.D. and Tan E.K. (2017). Iron regulatory protein (IRP)-iron responsive element (IRE) signaling pathway in human neurodegenerative diseases. Mol. Neurodegener. 12, 75.

Zille M., Karuppagounder S.S., Chen Y., Gough P.J., Bertin J., Finger J., Milner T.A., Jonas E.A. and Ratan R.R. (2017). Neuronal death after hemorrhagic stroke *in vitro* and *in vivo* shares features of ferroptosis and necroptosis. Stroke 48, 1033-1043.

Zou X., Wu Z., Zhu W., Chen L., Mao Y. and Zhao F. (2017). Effectiveness of minocycline in acute white matter injury after intracerebral hemorrhage. J. Neurosurg. 126, 1855-1862.

Accepted November 26, 2020