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REVIEW PAPER

The Emerging Roles of Ferroptosis in Huntington's Disease

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Abstract
Huntington's disease (HD) is an autosomal dominant and fatal neurodegenerative disorder, which is caused by an abnormal CAG repeat in the huntingtin gene. Despite its well-defined genetic origin, the molecular mechanisms of neuronal death are unclear yet, thus there are no effective strategies to block or postpone the process of HD. Ferroptosis, a recently identified iron-dependent cell death, attracts considerable attention due to its putative involvement in neurodegenerative diseases. Accumulative data suggest that ferroptosis is very likely to participate in HD, and inhibition of the molecules and signaling pathways involved in ferroptosis can significantly eliminate the symptoms and pathology of HD. This review first describes evidence for the close relevance of ferroptosis and HD in patients and mouse models, then summarizes advances for the mechanisms of ferroptosis involved in HD, finally outlines some therapeutic strategies targeted ferroptosis. Comprehensive understanding of the emerging roles of ferroptosis in the occurrence of HD will help us to explore effective therapies for slowing the progression of this disease.

Keywords Huntington's disease · Ferroptosis · Mutant Huntingtin · Lipid peroxidation · Iron accumulation

Introduction of Huntington's Disease

Huntington's disease (HD) is a rarely autosomal dominant neurodegenerative disorder. In the western world, the prevalence of HD is about 4–10 per 100 000 (Pringsheim et al. 2012). A survey of the Chinese HD Collaborative Network estimates that there are approximately 30 000 patients in China. Most ages of onset are between 30 and 40 years. The motor dysfunction, cognitive decline, and mental disorders will be progressively developed, with death occurring 10–20 years from onset (Vonsattel and DiFiglia 1998). Due to the autosomal dominant inheritance, their children have a 50% risk of developing HD. The genetic factor is that the gene encoding Huntingtin (Htt) on chromosome 4 is mutated. There is an abnormal CAG triplet repeat expansion in the first exon of Htt, which encodes an expanded polyglutamine stretch in the Htt protein (MacDonald et al. 1993). HD exhibits significant individual variance that is likely due to genetic background and environment. In general, longer CAG repeats cause earlier onset and more severe symptoms in patients (Wexler et al. 2004; Rosenblatt et al. 2006).

The pivotal trigger factor and pathological signature of HD is that mutant Htt (mHtt) is easily cleaved and aggregated into toxic macromolecules, which in turn lead to neuronal degeneration and cell death. In detail, the N-terminal of mHtt is truncated and can be cleaved at several points to generate monomeric or small oligomeric fragments with abnormal conformations such as β-sheet structures. These toxic fragments in cytoplasm may impair the systems for handling abnormal proteins such as proteasome, chaperone, and autophagy in neurons. The toxic macromolecules entering the neuronal nuclear can also show interference with antioxidative gene transcription (Ross and Tabrizi 2011). Therefore, both cytoplasm and nuclear located toxic fragments can cause mitochondrial abnormalities such as decrease of ATP and increase of reactive oxygen species (ROS) (Ayala-Pena 2013). Although, the pathological mechanism of HD is very complicated, more and more evidence show that oxidative stress is the initial factor in the pathogenesis (Browne and Beal 2006). Meanwhile, some intervention strategies against

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oxidative stress have partially achieved therapeutic effects (Velusamy et al. 2017). However, the specific mechanisms and signaling molecules involved in oxidative damage and subsequent neuronal degeneration have not been fully elucidated. Recently, ferroptosis has been known to play an essential role in oxidative damage and HD.

Ferroptosis

Ferroptosis is a new form of cell death that was recently recognized in 2012 (Dixon et al. 2012). Ferroptosis is completely distinct from apoptosis, necroptosis, and autophage-induced cell death. There are no triggered morphological changes or biochemical processes that characteristically occurred in apoptosis (Table 1). Cell membrane is lack of rupture and blebbing, and the cytoplasm is rounding-up. The nuclear size is normal, and there is no chromatin condensation and margination or cleavage of poly ADP-ribose polymerase (Xie et al. 2016). Notably, as observed under transmission electron microscopy, mitochondria is smaller with increased density of membrane and reduction even vanishment of crista as well as outer mitochondrial membrane rupture in ferroptosis (Cao and Dixon 2016; Xie et al. 2016). Biochemically, iron and ROS accumulation can be detected. Activation of mitogen-activated protein kinase (MAPK), glutathione (GSH) depletion, and increased nicotinamide adenine dinucleotide phosphate (NAPDH) oxidation are also characteristics of ferroptosis (Xie et al. 2016). In addition, induction of ferroptosis depends on an unique set of genes which are different from cell death triggered by pro-apoptotic or pro-necrotic agents (Dixon et al. 2012). And this unique cell death cannot be attenuated by deletion of apoptotic effectors, by suppression of caspases, by inhibitors of necroptosis, or by blockage of autophagy (Yang and Stockwell 2008). However, the iron chelators and the lipophilic antioxidants can be used to prevent cell from ferroptosis (Yagoda et al. 2007).

At present, it is believed that the mechanism of ferroptosis is that polyunsaturated fatty acids of lipid membranes transform to lipid peroxides under the accumulation of ROS. And then in the presence of divalent iron, a chemical reaction which is generally referred to as the Fenton reaction occurs, resulting in a large number of lipid-related ROS that causes ferroptosis in cells. Under physiological conditions, glutathione peroxidase 4(Gpx4) can rapidly remove excess lipid peroxides and inhibit ferroptosis. Therefore, when oxidative damage makes a massive production of lipid peroxides, or GSH is depleted, which in turn causes a decrease of GSH-dependent Gpx4 activity, or excessive iron is accumulated, ferroptosis will irreversibly occur (Yang and Stockwell 2016). In view of the correlation between ferroptosis and oxidative stress, mechanisms of oxidative injury and glutamate excitotoxicity-induced cell death are partially attributed to ferroptosis (Wu et al. 2018).

Among the ferroptosis regulators mentioned above, Gpx4 attracts most scientists' attention as the key inhibitor of ferroptosis (Yang et al. 2014). Ferroptosis is seen as the final imbalance between the rate of lipid peroxidation and reduction (Maiorino et al. 2017). Gpx4 is a selenoprotein glutathione peroxidase that can reduce peroxidation of membrane lipids, then maintain membrane stability and prevent the generation of lipid peroxidation-derived ROS (Girotti 1998). Consistently, a recent research published in Cell also elucidated that selenocysteine utilization by Gpx4 was required to prevent hydroperoxide-induced ferroptosis (Ingold et al. 2018). Cortical neurons from mutant E15.5 embryos proved that Gpx4 deletion caused a novel form of non-apoptotic cell death with lipid peroxidation which could be effectively prevented by the lipophilic antioxidant vitamin E (Seiler et al. 2008). Similarly, spinal motor neuron of Gpx4 ablation exhibited features of ferroptosis, including no caspase-3 activation, no positive TUNEL staining and activation of ERKs (Chen et al. 2015). In addition, the GSH-Gpx4 system has been suggested to regulate activities of lipoxygenase (LOX) and

Table 1 A comparison between ferroptosis and apoptosis

Type	Morphological features	Biochemical features	Core regulators
Ferroptosis	Cell membrane: lack of rupture and blebbing Cytoplasm: mitochondria is smaller, increased density of mitochondrial membrane, reduction of crista, rupture of outer membrane Nuclear: normal size, no chromatin condensation and margination	Iron and ROS accumulation GSH depletion Increased NAPDH oxidation MAPK activation	Ras TFR Gpx4 Nrf2 Iron
Apoptosis	Cell membrane: blebbing Cytoplasm: retraction of pseudopods, reduction of cellular volume Nuclear: smaller and fragmentation, chromatin condensation and margination	Phosphatidylserine exposure Endonuclease activation and DNA fragmentation Cytochrome c release Caspases activation	Caspases p53 Bax Bcl-2

Gpx4 glutathione peroxidase 4, *GSH* glutathione, *MAPK* mitogen-activated protein kinase, *NAPDH* nicotinamide adenine dinucleotide phosphate, *Nrf2* nuclear transcriptional factor-2, *ROS* reactive oxygen species, *TFR* transferrin receptor

prostaglandin-endoperoxide synthase (PTGS). Meanwhile, both LOX and PTGS enzymes have pro- and anti-inflammatory effects, which contribute to the ferroptotic process; this biological event is called as necroinflammation (Proneth and Conrad 2018). Accumulative studies suggest that Gpx4 plays pivotal roles in neurodegeneration diseases (Cardoso et al. 2017). Consistently, large amount of data demonstrate that ferroptosis maybe a major driver of neuronal death in diverse neurodegenerative disorders. This is not hard to understand for that nervous system contains the highest content of polyunsaturated fatty acids (Angeli et al. 2017). Furthermore, lipid peroxidation, GSH metabolism and the level of Gpx4 are abnormal in several pathologies such as Alzheimer's disease (Joshi et al. 2015), Parkinson's disease (Deas et al. 2016) and HD (Paul et al. 2014). Among them, the studies between ferroptosis and HD draw our attention.

Some Ferroptotic Signs in HD

The evidence of ferroptosis involved in HD of different animal models or human patients have been summarized in the Table (2). In transgenic HD mouse models and patients, neuronal death did not exhibit blebbing of the nuclear or cytoplasm, apoptotic bodies, or DNA fragmentation, suggesting that it was a novel cell death which was neither apoptosis nor necrosis (Yang and Stockwell 2016). A higher level of lipid peroxidation was a principal characteristic in HD patients (Klepac et al. 2007). In R6/2 HD mouse model, this increased lipid peroxidation was colocalized with mHtt inclusions in the striatal neurons (Lee et al. 2011). Consistently, increased lipid peroxidation could be detected in corticostriatal brain slices of mN90Q73 HD mouse model (Skouta et al. 2014). And increased lipid peroxidation had been also found in cerebrospinal fluid of HD (Reddy and

Table 2 Some ferroptotic signs in HD

Features	Comments	Subject
Cell death is neither apoptosis nor necrosis	Neuronal death did not develop blebbing of the nucleus or cytoplasm, apoptotic bodies, or DNA fragmentation	Transgenic mouse model and human patient
Fer-1 is beneficial	Fer-1 inhibited lipid peroxidation and cell death	mN90Q73 HD mouse model
Increased lipid peroxidation	Patients had higher plasma lipid peroxidation levels; increased lipid peroxidation was colocalized with mHtt inclusions in the striatal neurons; lipid peroxidation increased in corticostriatal brain slices	Human patient; R6/2 HD mouse model; mN90Q73 HD mouse model
Inhibition of lipid peroxidation is beneficial	Modulation of lipid peroxidation improved neuropathology	R6/2 HD mouse model
Decreased GSH	Patients had lower GSH level; reduced GSH was detected in the striatum, cortex and hippocampus in HD mouse	Human patient; 3-NP induced rat HD model
Reduced GSH-S-transferase	Reduced GSH-S-transferase in the striatum, cortex and hippocampal regions	3-NP induced rat HD model
Cystamine and cysteamine are beneficial	Cystamine and cysteamine attenuated 3-NP induced cell death and GSH decreasing	STHdhQ111/HdhQ111 striatal cell lines
Decreased Gpx	Activities of erythrocyte Gpx reduced in peripheral tissues	Human patient
Increased iron	MRI showed iron deposition in putamen, pallidum and occipital cortex; ferritin iron levels significantly increased in striatum; Quantitative Susceptibility suggested increased iron levels in nucleus, putamen, and globus pallidus	Human patient
Change of iron related protein	Area of ferritin labeling increased in striatum and cortex in patients; decreased IRPs, TFR and increased FPN in HD mouse model	Human patient; R6/2 HD mouse model
Iron supplement deteriorates neurodegeneration	Neonatal iron supplement decreased striatal volumes and neuronal cell body volumes	R6/2 HD mouse
DFO is beneficial	Intraventricular delivery of DFO improved motor phenotype	R6/2 HD mouse

3-NP 3-nitropropionic acid, *DFO* iron chelator deferoxamine, *Ferrostatin-1* Fer-1, *FPN* ferroportin, *HD* Huntington's disease, *IRPs* iron response proteins, *mHtt* mutant huntingtin, *MRI* magnetic resonance imaging, *TFR* transferrin receptor

Shirendeb 2012). Inhibition of lipid peroxidation with ferrostatin-1(Fer-1) significantly improved neuropathology of R6/2 HD mouse model (Lee et al. 2011).

Lower GSH level is another characteristics in HD patients (Klepac et al. 2007). Consistently, the study of Kumar et al. showed that decreased GSH and GSH-S-transferase were detected in the striatum, cortex and hippocampus in 3-nitropropionic acid (3-NP)-induced HD mouse (Kumar et al. 2010). While, supplement of cystamine and cysteamine could attenuate 3-NP induced neuronal death and decrease of GSH in this HD model (Mao et al. 2006).

Redundant iron accumulation is a major cause of oxidative stress in neurons, and is also another pivotal trigger of ferroptosis in HD. Due to its redox activity and electron spin states, excess iron can be readily detected (Muller and Leavitt 2014). Magnetic resonance imaging (MRI) of HD patients showed excessive iron deposition in occipital cortex, globus pallidum, and putamen (Rosas et al. 2012). Quantitative susceptibility mapping also showed increased iron in putamen, nucleus, and globus pallidus (van Bergen et al. 2016). Accordingly, the level of ferritin iron also notably increased in striatum (Bartzokis et al. 2007). Furthermore, change of iron related proteins could be detected. For example, increased ferritin in striatum and cortex of HD patients, decreased iron response proteins (IRPs) and transferrin receptor (TFR), and increased ferroportin (FPN) could be detected in R6/2 HD mouse model (Simmons et al. 2007; Chen et al. 2013). In addition, the expression of Fe–S enzymes was reported to be altered in HD striatum (Roze et al. 2008). Iron supplement further decreased striatal volumes and deteriorated neurodegeneration of HD mouse (van Bergen et al. 2016). In contrast, intraventricular administration of iron chelator deferoxamine (DFO) improved striatum pathology and motor phenotype in R6/2 HD mouse (Chen et al. 2013).

Possible Regulatory Mechanism of Ferroptosis in HD

Observing the close correlation between ferroptosis and HD, it should be thought that which molecule or signaling pathway initiates this biological event. Firstly, mHtt is cleaved at several points to generate various forms of toxic fragments concluding monomer or small oligomers in neurons. Secondly, these cytoplasmic toxic fragments inhibit proteasomes and autophagy, and then give rise to abnormal accumulation of folded proteins and mitochondrial dysfunction (Ross and Tabrizi 2011). Finally, excessive ROS, massive lipid peroxidation and iron accumulation lead to ferroptosis together.

Accumulative data suggest that mHtt can interact with the outer membrane of mitochondria, and then lead to calcium abnormalities (Choo et al. 2004). mHtt also influences transcription of mitochondrial genes and mitochondrial homeostasis. For example, inhibition of peroxisome proliferator-activated receptor-C coactivator-1a (PGC-1a), which regulates the expression of genes that mediate mitochondrial biogenesis and respiration (Cui et al. 2006), and depletion of the enzymes are necessary for cysteine synthesis (Paul et al. 2014). In addition, mHtt interacts and inhibits TIM23, which is a component of the inner membrane transport complex, then disturbs the transportation of proteins into mitochondria, and finally contributes to respiratory dysfunction (Yano et al. 2014). The equal balance between fission and fusion of mitochondria is important for a healthy neuron. Mitochondrial fission is regulated by dynamin-related protein 1 (Drp-1), and Drp1 localized to the mitochondrial outer membrane promotes mitochondrial fragmentation (Reddy et al. 2011). One study reports that mHtt could interact with Drp1 and lead to mitochondrial fragmentation (Guo et al. 2013). mHtt also interacts with proteins localized in axons and impairs axonal transport. Some studies of axonal transport reported that impaired mitochondrial transport could be found in HD neurons, and motility of mitochondria significantly decreased in the neurons from HD mice compared to wild-type neurons (Orr et al. 2008; Shirendeb et al. 2012).

All the factors mentioned above contribute to mitochondrial dysfunction and aberrant production of ROS which is the initial cause for oxidative stress and lipid peroxidation. Some researchers suggested that increased 4-hydroxynonenal (4-HNE) deposition could be treated as a marker of the excessive lipid peroxidation in a cellular model of HD. 4-HNE is more stable than free radicals and can pass more easily among subcellular compartments. Interestingly, 4-HNE positive signals distributed in nuclear foci were spatially colocalized with mHtt in striatal neurons of the R6/2 mice. Moreover, 4-HNE can modify mHtt and substantially increase its toxicity and accelerate the formation of inclusion body (Lee et al. 2011).

One study that the phenotype of the mouse whose mHtt was expressed in both astrocytes and neurons was worse than neuronal-only expression, confirmed the contribution of astrocytes to HD (Bradford et al. 2010). The toxic fragments in astrocytes can reduce glutamate transporter protein-1 (GLT-1), and decrease GLT-1 dependent reuptake of glutamate, then considerable glutamate over-stimulate extrasynaptic glutamate receptors, and then lead to excitotoxicity (Prasad and Bondy 2016). On the one hand, glutamate-induced excitotoxicity can promote Ca^{2+} release, and then also cause mitochondrial dysfunction and oxidative stress (Cheng et al. 2018). On the other hand, extracellular glutamate accumulation inhibits cystine to transport into neurons, followed by the decrease of GSH, and then causes a great amount of lipid peroxidation and ferroptosis (Dixon 2017). In addition, growing evidence has implicated that increased

secretion of pro-inflammatory cytokines and chemokines in astrocytes plays a role as neuroinflammation in neurodegeneration of HD (Wild et al. 2011). Moreover, mHtt expressed in microglia also could activate these immune cells to secret pro-inflammatory cytokines (Crotti et al. 2014), and microglia exhibited reduced migration ability in response to chemotactic signals (Kwan et al. 2012). These immunoinflammatory responses in glias will exacerbate mitochondrial dysfunction and imbalance of redox state in neurons. A recent study further suggested that ferroptotic neuron itself also could release pro-inflammatory damage-associated molecular patterns (DAMPs), which then triggered the innate immune system in brain tissues (Proneth and Conrad 2018).

Dexamethasone induced Ras-related protein 1 (Dexras1) has been reported to sustain iron homeostasis in neurons via *N*-methyl-D-aspartate receptor (NMDAR)-NO transmission pathway (Cheah et al. 2006). As mentioned above, mHtt leads to NMDAR activation, which then causes calcium increase and activates neuronal nitric oxide synthase (nNOS). nNOS produces excess NO which transducts signals via *S*-nitrosylation of cysteines. Among them, NO *S*-nitrosylation activates Dexras1, which can interact with the Golgi resident protein Acylcoenzyme A binding domain containing 3 proteins (ACBD3). And then, ACBD3 binds to the divalent metal transporter (DMT1), and induces iron uptake into the neurons (Cheah et al. 2006). The Ras homolog enriched in striatum (Rhes) protein which is selectively localized to the striatum shares 67% homology to Dexras1 (Vargiu et al. 2004). Rhes directly interacts with mHtt, sumoylates mHtt, and then increases the soluble toxic form (Subramaniam et al. 2009). Moreover, activation of NMDARs increases expression level of Rhes. In addition, Rhes can interact with the scaffolding protein between Dexras1 and ACBD3, and activation of Rhes increases the uptake of iron (Choi et al. 2013). Some evidence support that wild-type Htt has a role in transport of vesicles and endosomes, and thus Htt may be involved in making endocytosed iron available for cell utilization and sustaining iron homeostatsis (Muller and Leavitt 2014). Consistently, other findings show that ions are primarily localized in secondary lysosomes in HD, and mHtt has a toxic effect on the transport of endosomes (Muller and Leavitt 2014).

The nuclear factor erythroid 2-related factor (Nrf2) is an antioxidant agent (Baird and Dinkova-Kostova 2011), and modulates the onset and outcomes of ferroptosis (Abdalkader et al. 2018). Interestingly, muted Nrf2 activation response could be detected in neural stem cells of human HD (Quinti et al. 2017). Normally, Nrf2 resides in the cytoplasm and bounds to its negative regulator Kelch-like ECH-associated protein 1 (Keap1). In striatal neurons of HD, mHtt-induced abnormal folded protein and increased oxidative stress facilitated the dissociation of Nrf2 from Keap1, and then promoted Nrf2 translocation to nuclear. In the nucleus, Nrf2 interacted with antioxidant response elements (AREs) in the promoter region of target genes and then influenced the transcriptional activities of these genes (Yamamoto et al. 2018). These genes are involved in GSH regulation and NADPH regeneration which are both important for Gpx4 activity, iron regulation, and lipids metabolism regulation. In addition, Nrf2 regulates mitochondrial dynamics such as biogenesis and mitophagy (Merry and Ristow 2016; East et al. 2014).

Treatment Strategies Targeted Ferroptosis

Currently, there are not yet disease-modifying drugs available for HD. Treatment is just improving patients' symptoms such as choreiform movements, cognitive problems, and psychiatric symptoms (Jimenez-Sanchez et al. 2017). Some therapeutic strategies based on pathologic mechanisms are on trial, such as silencing the expression of the mHtt gene, anti-apoptotic treatment and caspase inhibition, transglutaminase inhibition, up-regulating autophagy, and transplantation for neurons. Unfortunately, these trials were just performed on animal models, and somewhat disappointed in large clinical trials of patients, even stopped early due to a combination of futility and safety concerns (McBride et al. 2011; Grondin et al. 2012).

Since ferroptosis is very likely involved in HD process, therapies targeted ferroptosis are encouraging. Coenzyme Q10 (CoQ10), which is located in the cellular and mitochondrial membranes, is the only endogenous lipid-soluble antioxidant preventing the initiation and propagation of lipids peroxidation (Varela-Lopez et al. 2016; Morris et al. 2013). Thus, CoQ10 maybe the most promising candidate for ferroptosis inhibition. In vivo experiment, supplementation of CoQ10 could effectively extend to the brain of mice, up-regulated GSH and reduced lipids peroxidation (Barbiroli et al. 1997; Matthews et al. 1998; Kim et al. 2007). Other studies also established the safety and efficacy of high dose supplementation of CoQ10 in several neuropsychiatric disorders in humans (Gerwyn and Maes 2017; Morris et al. 2016).

Targeting iron is another treatment strategy. Iron chelation treatments concluding DFO, deferiprone (DFP), and deferasirox (DFX), have been successfully to decrease iron over-accumulation, reduce lipid peroxidation and improve mitochondrial function (Grolez et al. 2015; Kuo and Mrkobrada 2014). Animal evidence indicated that DFP in combination with *N*-acetylcysteine (NAC) was notably more effective in reducing levels of non-transferrin-bound iron (NTBI) in the brain than monotherapy respectively. Meanwhile, the dose of DFP could be reduced (Sripetchwandee et al. 2016; Wongjaikam et al. 2016).

Chemical activation of antioxidant transcript factor Nrf2 could increase expression of target gene such as hemeoxygenase-1 (HO-1), and then enhance antioxidant defense (Dinkova-Kostova et al. 2018). Therefore, some strategies designed to activate Nrf2 have been used as a novel method for treatment of several ferroptosis based neurodegenerative diseases (Prasad and Bondy 2016). Activation of Nrf2 by the cyanoenone triterpenoids CDDO-ethyl amide and CDDO-trifluoroethyl amide could induce significant antioxidant effects of brain and ameliorate the neurological symptoms in HD mouse (Stack et al. 2010). Disrupting the interaction between Keap1 and Nrf2 could be also treated as a potential protective agent for HD (Quinti et al. 2016).

Conditional deletion of neuronal Gpx4 in adult mice led to rapid degeneration of spinal motor neurons which was most likely ferroptosis, and rapid onset and progression of paralysis. Interestingly, lipid peroxidation and abnormal mitochondria involved in ferroptosis could be clearly observed in motor neurons (Chen et al. 2015). Due to the key role as a cytoplasmic peroxidation inhibiting protein, Gpx4 has been treated as an intervention target in nervous degenerative diseases (Friedmann Angeli et al. 2014; Yang and Stockwell 2016). Therefore, Gpx4 maybe the promising therapeutic target of HD in the future. Considering Gpx4 as a GSH-dependent enzyme and GSH is also showed to be dysregulated in HD, more and more studies for treatment are focusing on GSH. However, some researchers indicate that GSH itself can not to effectively cross the blood brain barrier (BBB) to promote an increase of intracellular GSH in neurons or glias (Johnson et al. 2012). Therefore, as the precursor of GSH, NAC has been treated as the best drug candidate penetrating from blood to brain. Sandhir et al. reported that NAC could reverse mitochondrial dysfunction in 3-NP treated HD rats (Sandhir et al. 2012).

Conclusion

In this review, sufficient evidence of human and animals were collected for the possible correlation between ferroptosis and HD, and the molecular mechanism of ferroptosis in HD was summed up from the key regulators Gpx4, Nrf2-mediated signaling pathways, the abnormalities of iron transportation, and glutamate-mediated excitotoxicity. Meanwhile, the effect of the mHtt-ferroptosis network on the fate of striatal neurons was clarified from different functions of mHtt in neurons, astrocytes, and microglias (Fig. 1). This review provides basic research data for targeted intervention against HD, and opens up new windows for the study of neurodegenerative diseases that are based on oxidative stress and iron accumulation.

Ferroptosis is a novel mechanism involved in HD initiation and procession, but it is not the only cause for neuronal

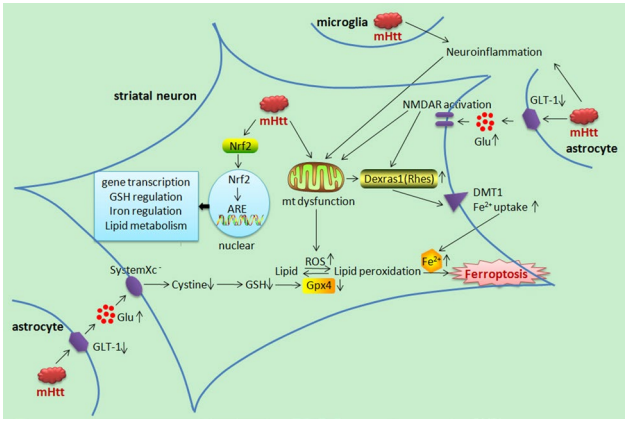

Fig. 1 The potential mechanism of ferroptosis in Huntington's disease. *AREs* antioxidant response elements, *Dexras1* dexamethasone induced Ras-related protein 1, *DMT1* divalent metal transporter, *GLT-1* glutamate transporter protein-1, *Glu* glutamate, *Gpx4* glutathione peroxidase 4, *GSH* glutathione, *MAPK* mitogen-activated protein kinase, *mHtt* mutant huntingtin, *mt* mitochondria, *NAPDH* nicotinamide adenine dinucleotide phosphate, *NMDAR N*-methyl-D-aspartate receptor, *Nrf2* nuclear transcriptional factor-2, *ROS* reactive oxygen species; system Xc^- cystine/glutamate antiporter system

deaths in this disease. In HD post-mortem striatum, a small percentage of dark neurons had previously been found to be TUNEL-positive in both neurons and glias. Of course, due to lack of ultrastructural analysis, the TUNEL-positive nuclei are not currently recognized as definitive apoptosis (Turmaine et al. 2000). One study suggested that wild-type Htt exerted an anti-apoptotic role both in vitro cell models and in vivo HD mice models (Ho et al. 2001; Leavitt et al. 2006). And overexpression of Htt could suppress the apoptosome complexes formation and consequent of caspases activation (Zhang et al. 2006). Jimenez-Sanchez et al. have demonstrated that mHtt interferes with mitochondrial dynamics, and increases the enzymatic activity of Drp-1, and leads to mitochondrial fragmentation which then activates caspase and induces apoptosis (Jimenez-Sanchez et al. 2017). Another two studies also suggest that the expression of mHtt induces apoptosis by caspase activation via mitochondrial cytochrome *c* release (Jana et al. 2001; Majumder et al. 2007).

Gpx4 is considered as an pivotal inhibitor of ferroptosis, and Gpx4 activity in the brain tissue has been used as a marker for ferroptosis and neurodegeneration (Cardoso et al. 2017). However, not all types of neurons are equally sensitive to Gpx4 activity, this may be due to different redox systems, different phospholipid metabolism, and different expression of lipid-related enzymes, such as ACSL4 (Conrad et al. 2018). In addition, Gpx4 has also been shown to regulate apoptosis, for observing that Gpx4 can suppress cytochrome *c* dissociation from the inner membrane of mitochondria and then release to the cytoplasm to induce

apoptosis (Ran et al. 2004). At present, the selectivity of Gpx4 in inhibiting apoptosis or ferroptosis maybe depend on the cell types and stress conditions (Chen et al. 2015). Ravikumar et al. have shown that mHtt sequesters mammalian target of rapamycin (mTOR), decreases mTOR activity and enhances autophagy. Meanwhile, Rhes protein has also been reported to influence autophagy (Mealer et al. 2014). Therefore, the types of neuronal death in HD may be more complicated and this maybe depends on the length of CAG triplet repeat expansion, the degree of toxic proteins accumulation, and the pathological progression of the disease.

Comprehensive understanding the basic mechanisms of HD would be helpful to exploit effective disease-modifying therapies that maybe bring clinical benefits in the future. Obviously, the utilization of a single strategy will not effectively improve the pathology and symptoms in HD patients. Therefore, it should be necessary to simultaneously inhibit ferroptosis, decrease oxidative stress, and reduce glutamate release, at the same time increase the activities of antioxidant enzymes and signaling pathways together. It is undeniable that using Crisper/Cas9 and adenovirus infection to safely and effectively remove the mutated genes Htt is the most fundamental treatment in the future. For clinical diagnosis, it is significant to develop multiple detecting methods for early onset markers such as lipid peroxidation, iron accumulation in brain, and decreased activity of Gpx4.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

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