Chapter

The "Irony" of Ferroptosis: A Review on Neurological Challenges

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Abstract

Ferroptosis in recent days has gained high impact due to its implication in inducing several neurological challenges. Impairment of iron homeostasis (mainly surplus iron deposition) is the key reason for the induction of the ferroptotic cell death. This type of programmed cell death in the neurons can trigger neuropathological abnormalities. Ferroptosis has been given clinical importance, where biomedical researchers are working on the pathological detection of ferroptosis and finding clinical ways to arrest it. In this review, we have elucidated the impact of ferroptotic cell death on the pathophysiology of several neurological challenges.

Keywords: Ferroptosis, cell death, neurological challenges, oxidative stress, iron

1. Introduction

Ferroptosis is recently discovered non-apoptotic, iron-dependent programmed cell death instigated by the upsurge of intracellular lipid reactive oxygen species. Despite of the importance of iron in the body, the proper cellular homeostasis is important. The cellular mechanistic pathways which are related to ferroptosis are majorly iron metabolism and lipid peroxidation. Ferroptosis has been reported to have direct execution for several neurological disorders. As we know that ferroptosis is rather a very new area of research, intricate research is needed to work on the molecular crosstalk between ferroptosis, apoptosis, autophagy, and necrosis. A comparative molecular mechanism of ferroptotic pathophysiology in several neurological diseases needs to be revealed. Furthermore, research on the establishment of ferroptosis as a therapeutic approach for several neurological diseases is also important [1].

The ideal purpose of iron homeostasis in body must be established in the system, which not only transfers iron in the brain but also reduces its concentration, if exceed the optimum level. Irregularities in iron homeostasis, especially for surplus iron, relates to several critical cellular dysfunction and signifies a serious stage for neurodegenerative physiology. Ferroptosis is characterised by iron-dependent oxidative damage in the lipid bilayer. It is mainly instigated by the disparity in the oxidation and anti-oxidation proportion in the cell. Disturbances in iron and

lipid metabolism cause excessive accumulation of lipid peroxides within the lipid bilayer, causing oxidative destruction of the cell membrane. Disorder in the cellular antioxidant procedures results in the incapability to remove the lipid peroxides which is generated from the induction of oxidative stress. Eventually which is the reason for the massive annihilation of the lipid bilayer membrane and eventually causes programmed cell death. As accumulation of iron and lipid peroxides play the major roles in the triggering of ferroptosis, thus it can be decreased by the administration of iron chelators or by lipophilic antioxidants in the system. Recent findings have specified its major role in the brain maturation and adverse effects on the nervous system and its pathophysiology eventually initiating neural dysfunctions.

Lipid hydroperoxides are formed in the process of lipid peroxidation [2]. Glutathione peroxidase (GPX4) is a glutathione (GSH) dependent enzyme that acts to reduce lipid hydroperoxides (L-OOH) to from lipid alcohols (L-OH). This can inhibit the iron induced formation of toxic lipid reactive oxygen species (L-ROS). GSH is a cofactor of GPX4 and effectively sustains the GPX4 level through cystine/glutamate antiporter system known as the Xc- system. The inhibition of Xc- system or GSH synthesis, or GPX4 activity will eventually initiate the accumulation of lipid peroxides and initiation of ferroptotic cell death. The dysfunction of iron metabolism system, iron uptake (transferrin receptor), iron export (ferroportin), iron accumulation (ferritin) induces surplus of iron load and which results in the catalysis of hazardous L-ROS production [3]. The antiporter is a 12-pass transmembrane subunit (SLC7A11) where anionic cystine enters inside the cell via facilitated diffusion and in exchange, anionic glutamate moves out of the cell by facilitated diffusion. This antiporter also has 1-pass transmembrane subunit (SLC3A2), connected to the transporter by a disulfide bond. The capability of glutamate analogues to provoke ferroptosis in neurons is straightway correlated with their capability to inhibit cystine uptake in the cell. Cysteine in the extracellular domain is quickly oxidised to cystine where two molecules of cysteines are linked covalently by a disulfide bond. After transportation inside the cell, cystine is reduced to cysteine by glutathione reductase. Inhibition of cystine uptake results in the exhaustion of cysteine and eventually related exhaustion of GSH [4].

In this chapter, we have reviewed the impact of ferroptotic cell death on the pathophysiology of several neurological challenges.

2. Mechanistic overview of the pathophysiological manifestation during ferroptosis-induced neurological challenges

The propagation of ageing in nervous system, induces clinical conditions like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), anxiety, depression, stroke, and traumatic brain injury which appears to be predominant in a population. The molecular mechanism of neurological disorders is multifarious, and there is lack of applicable therapeutic protocols. Molecules, manifesting ferroptosis-induced neurological disorders, such as reactive oxygen species (ROS), nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE), iron ion (Fe^{2+}), nicotinamide adenine dinucleotide phosphate (NADPH), NADPH oxidase (NOX), play crucial role in the pathophysiology. In the cells, due to the activity of acyl-CoA synthetase long chain family member 4 (ACSL4), cytochrome p450 oxidoreductase (POR), lipoxygenases (ALOX), polyunsaturated fatty acids (PUFA) produce phospholipid hydroperoxides (PLOOH) over a sequence of biochemical reactions, eventually from which, PLOO is generated.

This results in lipid peroxidation. GPX4 activity can reduce PLOOH to PLOH to constrain lipid peroxidation occurrence. Mitochondria generates reactive ROS through, which causes oxidative stress. Fe^{2+} is oxidised to ferric ion (Fe^{3+}) after absorption in the duodenum. Fe^{3+} enters the cell by combining with transferrin (Tf) and transferrin receptor (Tfr) to procedure a complex. Iron decomposition from endosome can induce ferroportin (FPN) protein activation on the cell membrane, where iron ions enter iron pool. Tf-Tfr complex triggers for the next cell cycle. During neurological disorders, excessive iron produces a large volume of ROS, which cause ferroptosis [5].

Neurodegeneration, cardiovascular disease, and diabetes, where ferroptosis might provoke the neuronal, cardiomyocyte, and β-cell loss. Regarding ferroptosis research, the transcription factor Nrf2 and its transcriptional target genes play in the inhibition process or in certain situations activating of the ferroptotic cascade. This concludes that cautious attention should be given in terms of Nrf2 pathway, which signify practical targets to recruit ferroptosis in tumour cell types, without damaging their normal cell types. Another therapeutic option is using the activation of Nrf2 or other essential anti-ferroptotic moderators in terms of avoiding ferroptosis. In homeostatic circumstances, Nrf2 is ubiquitylated and embattled for proteasomal.

degradation by a KEAP1-CUL3-RBX1 E3 ubiquitin ligase complex. During the pathophysiology of oxidative stress, or mutations occurred in Nrf2 or KEAP1/CUL3, the Nrf2 is not degraded, which in turn allows nuclear translocation and activation of antioxidant response element encompassing genes. Nrf2 is involved in iron metal metabolism, along with the detoxification system of the cell through glutathione synthesis, all of these play a crucial key role in the inhibition of ferroptosis. In the circulation (blood), Fe^{3+} is transported by Tf. Fe^{3+}-Tf is bound by tfr1 and endocytosed. In the endosome, the acidic pH promotes detachment of Tfr and Fe^{3+}. This is further reduced to Fe^{2+} by the activity of metalloreductase STEAP3. Fe^{2+} is further transported to the cytosol by divalent metal transporter 1 (DMT1), donating to the iron pool. FPN1 plays a role in exporting of Fe^{2+} out of the cell by incorporating it into iron-containing proteins or storing by ferritin as Fe^{3+}. Ferritinophagy is the autophagic mechanism which regulates the degradation of ferritin through nuclear receptor coactivator 4 (NCOA4). The degradation of ferritin, results in the reduction of Fe^{3+} to Fe^{2+} by STEAP3 and eventually exported from the lysosome to the cytosol by DMT1 to contribute to the iron pool. Notably, the physiology of iron metabolism, storage, and transport, along with ferritinophagy are transcriptionally controlled by Nrf2 [6].

Both oxidative and nitrosative stress can unfavourably disturbs the mechanistic pathways and effective proteins regulating cellular iron homeostasis, like iron controlling protein/iron response element system, and can eventually be a basis of unusually high levels of iron and a cause of lethal levels of lipid membrane peroxidation. Moreover, neuroinflammation governs the upregulation of bivalent metal transporter-1 on the surface of astrocytes, microglia, and neurones, which make them extremely sensitive to excess iron in the occurrence of elevated levels of non-transferrin bound iron, therefore, initiation of iron mediated neuropathology occurs. Mechanisms regulating the iron homeostasis physiology and the effectiveness of ferritin and mitochondria are important. Negative regulation of ferroptosis by GSH, GPX4, the cystine/glutamate antiporter system, heat shock protein 27 and Nrf2 is crucial. The possible role of deglycase (DJ-1) inactivation in the reduction of ferroptotic cell death is simultaneously critical. Therapeutic approach in terms of coenzyme Q10, iron chelation therapy, deferiprone, deferoxamine (desferrioxamine) and deferasirox, and N-acetylcysteine is of high clinical importance [7].

3. Ferroptotic influence on the manifestation of neurological challenges

Iron overload in cell (dysregulation of iron homeostasis) is contemplated to be a precarious situation for neurodegeneration. The current findings, emphasise β-amyloid, tau proteins, α-synuclein, and demyelination process connected to ferroptosis which induces neurodegeneration. The theory built on the possible role of dysregulation of iron homeostasis and ferroptosis in the pathophysiology of neurodegenerative diseases can be further supported by clinical experiments and epidemiological analyses [8].

Despite of the fact that ferroptosis was first defined in cancer cells, however, developing indications, include this cell death process with cerebral ischemia and brain haemorrhage also. Neonatal brain injury is a significant reason for the developmental damage and everlasting neurological insufficiencies. Different cell death processes, including iron-dependent ferroptotic pathways, have been identified for neonatal brain injury. Iron chelators and erythropoietin have been acknowledged as neuroprotective agents against neonatal brain injury. Generally, ferroptosis is principally defined through activators and inhibitors. Ferroptosis in adults are reported to generate ischemic and intraventricular haemorrhage-induced neuronal cell death. The inhibition of ferroptosis decreases the rate of neuronal death and behavioural abnormalities. Contemplating the recent paradigms in ferroptotic research, investigation on the relation between neonatal brain injury and ferroptosis should be considered seriously [9].

The propagation of ferroptosis incorporates the pathophysiology of autophagy as well as the inclusion of the activities of well-studied proteins such as Nrf2, p53 etc. The manifestation and regulatory molecular pathways of ferroptosis are constantly developing. There are indications that ferroptosis and its correlated genes may be concerned in a sequence of neural maturation, maintenance, and ageing physiology. In turn these genes can play a critical role in the pathophysiology of neurodegenerative diseases, neurological disorders, strokes, epilepsy, brain tumours etc. Investigating the incidence and expansion of ferroptosis in the brain tumours and endeavouring to stimulate tumour cell death with ferroptosis inducers are expected to collaborate with traditional tumour therapeutics and immunotherapy protocols. However, in the perspective of glioma treatment by endorsing ferroptosis, it is possible for the destruction of neuronal cells simultaneously, thus provoking the collective neurodegenerative diseases, stroke, and other neurological disorders, which will result to the similar indications in glioma patients [10].

In ferroptosis, a cloud of pharmacological modulators has been discovered considering the target proteins involved in iron homeostasis, in terms of origination and reduction of lipid peroxides or cystine import and GSH metabolism. Several machineries of the ferroptosis cascade are target genes of the transcription factor Nrf2, representing its analytical role in facilitating the ferroptotic reaction. Ferroptosis, is controlled by various cellular metabolic pathways. Research on the effect of ferroptotic cell death in inducing numerous neurological disorders has gained acceleration nowadays. Genetic regulation behind ferroptosis-induced neurological disorders and the probable functioning of ferroptosis in the development of brain is of serious concern. There are reports on 42 ferroptosis genes, which play crucial roles in the brain development and the gene co-expression system for the human dorsolateral prefrontal cortex development, where cluster of 22 genes actively participate. 12 genes out of these 22 genes are considered for the conservation of elementary cellular functions (non-transitional), which include RNA processing.

The rest 10 genes with postnatal line are effective for the upgradation of patterns in neuron and glial cells. Stress affects the differential gene expression pattern during the process of brain development [11].

Cumulative substantiation designates a probable connection between neuroinflammation and neurological disorders, including AD, PD, HD, and stroke. Ferroptosis can possibly explain this connection. Research have shown that disorders of iron homeostasis, glutamate excitative toxicity, L-ROS, and some other factors related to ferroptosis can be detected in several neurological disorders which is caused by neuroinflammation. Convincing indication regarding the damage-associated molecular pattern molecules, like ROS, generated during the pathophysiological process of ferroptosis, trigger glial cells by stimulating neuroimmune pathways and then generate a sequence of inflammatory factors which initiate neurological disorders. Complicated biochemical reactions occur throughout ferroptosis. Activated microglia, reactive astrocytes, invasive T-cells, and overproduction of inflammatory molecules, establish the neuroinflammatory response. During the early phase, acute inflammatory responses cause trauma in the central nervous system, which can have a defensive role, restraining the strictness of the injury thus augmenting neuronal repair. If the acute inflammatory response does not decrease adequately, it will be directed into chronic inflammation which can be uncontrollable. In this situation, glial cells incline to intensify oxidative stress on neurons. Neuroinflammation is not essential during the early stage of neurological disorders, however, a constant inflammatory response can produce aggravation of the diseases. The detail pathophysiology of ferroptosis and its connection with neuroinflammation, have been understood in a rudimentary level. The practice of inhibitors of ferroptosis in investigational animal models can improve the rigorousness of the neural diseases. However, medications targeting ferroptosis can play a critical role in the medical treatment of chronic neuroinflammatory diseases. This needs rigorous clinical trials [12].

The active equilibrium of cardiomyocytes and neurons is vital to continue the normal physiological functions of heart and brain. If unnecessary cell death occurs in the tissues, severe cardio-cerebrovascular diseases (CCVD) like, hypertension, myocardial infarction, and ischemic stroke happens. The mechanistic regulation of cell death possesses a key role in endorsing these diseases. Worldwide, major mortalities and morbidities occur due to CCVDs. Excess of iron has been established to be a crucial element for pathogenic response in cardiocerebrovascular toxicity and manifest diverse CCVDs, thus ferroptosis, has received serious attention for its pathophysiology for CCVDs. Many studies have shown that ferroptosis occurs in atherosclerosis, heart failure, diabetic cardiomyopathy, hypertensive brain injury, ischemic stroke, and myocardial infarction. Inhibitors of ferroptosis may stop these diseases by inhibiting the ferroptotic pathway both in cardiac tissue and neurons. Cardio-cerebrovascular cell death is a central pathophysiological procedure and in fact, ferroptosis strikes throughout the CCVDs. However, in terms of abridged level of ferroptosis inhibitors (like GSH, GPX4, and Nrf2) and alterations in the gene expression levels, which are known to be expressed during CCVDs, the existing assays are not totally appropriate for predictable and routine clinical diagnosis. Damaged mitochondrial structure is an important feature of ferroptosis. Growing figure of inducers and inhibitors of ferroptosis have been showed. However, the best therapeutic agent among these inducers and inhibitors are still to known properly. Ferroptosis leads to pathophysiological alterations like inflammation and endoplasmic reticulum stress. However, it is a complex issue to explain the whole pathway across which ferroptosis works with the initiation of ischemia and hypoxia, iron discharges

through the upregulation of heme oxygenase 1 (Hmox1), thus stimulating ferroptosis, resulting in myocardial pathologic modification and myocardial cell damage. Heart failure enthused by enhancement of the iron pool resulting in the surplus iron and the incidence of ferroptosis, eventually which leads to myocardial edema, arrhythmia, and cardiomyocyte cell death [13].

Intracerebral haemorrhage (ICH) is another critical medical condition with high morbidity and mortality. Brain injury due to ICH is primarily recognised due to oxidative stress and haemoglobin lysate (which include iron), indicates unalterable harm to neurons. Therefore, ferroptosis has become a recent paradigm in neuronal cell death research after ICH [14].

The blood–brain barrier (BBB) is crucial in regulating the homeostasis within the CNS. Brain microvascular endothelial cells are effectively arrayed to make the vessel walls and have tight junction complexes that restrict the paracellular pathways of BBB. These walls effectively controls the movement of ions, molecules, and cells between the blood and the brain. This is extremely important for the protection of the neural tissues in the brain from hazardous toxins and pathogens. Primary damage due to the ill functioning of BBB can damage the tight junctions, transport proteins and leukocyte adhesion molecules, which can cause brain edema, imbalance in ion homeostasis, changed signalling pathways and immune infiltration, leading eventually to neuronal cell death. Several neurological disorders can happen due to BBB dysfunction. Ferroptosis can play a key role in BBB dysfunction [15].

Severe central nervous system (CNS) injuries, like stroke, traumatic brain injury, and spinal cord injury is a serious cause of concern for clinicians due to high morbidity and mortality. In fact, the therapeutic strategies for these diseases are not sufficient some time. Oxidative stress, neuroinflammation, excitotoxicity, and programmed cell death (including ferroptosis) plays crucial roles in the pathophysiology of acute CNS damages. Reports develop relations between acute CNS injuries and ferroptosis. Pharmaceutical agents, such as iron chelators, ferrostatin-1 (Fer-1), and liproxstatin-1 (Lip-1), can have inhibitory effect on the ferroptosis and may have neuroprotective capabilities even after acute CNS injuries. Till date, edaravone is the single approved medicine with accepted clinical effectiveness and safety for the CNS injury [16].

4. Conclusion

Recent research on programmed cell death complemented by ferroptosis, is indicating to find novel theories on ferroptotic mechanism to design therapeutic protocols for ferroptosis-related neurological diseases. A medical perception is indeed necessary for the treatment strategy to combat the dysregulation of iron homeostasis and/or inhibition of ferroptosis to reduce the rate of neurodegenerative pathophysiology induced by ferroptosis. Our knowledge on ferroptosis is still at the base level. It is extremely important to depict a ferroptotic biomarkers for biomedical identification. Ferroptosis has distinctive process which has produced abundant chemotherapeutic potentials for treating cancers. The concrete pathophysiological implication of ferroptotic pathway, encompassing reasonable translational methods is still evolving. Growing data propose that the inhibition of ferroptosis may efficiently avoid neuronal diseases.

DOI: http://dx.doi.org/10.5772/intechopen.108737

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