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Ferroptosis: Implications in Diseases and Potential Treatment Approaches

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Ferroptosis is a recently recognized iron dependent form of regulated cell death. Ferroptotic cells are smaller than normal mitochondria and are usually cristae in structure. Ras-selective lethal small molecule (RSLs) induced cell death is blocked by anti-oxidants and iron chelators. Thus, the term ferroptosis often refers to a non-apoptotic, iron dependent form of regulated cell death (RCD). In 2016, it was found that there are 4 classes of inducers of ferroptosis which includes erastin, glutamate, sorafenib, RSL-3, FIN 56, etc and other reagents like CCL4 and artesunate may induce ferroptosis in liver and pancreatic cancer cells. Age-related and degenerative diseases necessarily cause an increase in brain iron levels, which can be seen in both post-mortem and living samples. Hepatochromatosis and other tissues and illnesses with ferroptosis have both been researched. The presence of ferroptosis is consistent with a variety of clinicopathologic dementia characteristics. Other neurodegenerative illnesses have comparable symptoms. A variety of pharmacological treatment for inhibiting ferroptosis in diseases have been reported like iron chelators, lipophilic antioxidant and ß-mercaptoethanol.

Keywords: Apoptosis; Degenerative disease; Erastin; Ferroptosis; Iron chelators; Regulated cell death.

Ferroptosis is a relatively new kind of cell death that is characterised by excessive iron buildup and lipid peroxidation during the cell death process. Ferroptosis is a form of controlled necrosis that is more immunogenic than apoptosis and is iron-dependent. Few research have examined ferroptosis' natural roles, although the majority of studies to present reveal that it is caused by degenerative processes or may be therapeutically induced in some tumours.[1,33] Ferroptosis is an adaptive and planned kind of cell death that occurs, for example, during development, although its physiological role is not yet known. It is known as controlled necrosis and it is more immunogenic than apoptosis. Amino acid, iron and polyunsaturated fatty acid metabolism, as well as the synthesis of glutathione, phospholipids, NADPH, and coenzyme, are all associated with ferroptosis vulnerability.[1]Before the term "ferroptosis" was coined, ferroptosis inducers were discovered.[5,33]

History

Erastin was first identified as a feroptosis inducers in the year 2003, A little chemical called erastin has the ability to trigger ferroptotic cell death. Erastin functionally inhibits the cystine-

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glutamate antiporter system Xc via binding to and activating voltage-dependent anion channels (VDAC) through reversing tubulin's regulation of VDAC2 and VDAC3. Erastin treatment deprives cells of cysteine, which prevents them from producing glutathione, an antioxidant. Eventually, severe lipid peroxidation and cell death result from glutathione depletion.

Small chemical inhibitors of apoptosis, necrosis, necroptosis, and autophagy (e.g., Z-VAD-FMK, BOC-D-FMK, wortmannin, and necrostatin-1) are unable to prevent RSL-induced cell death. So the iron chelators and the antioxidants induce the RSL cell death. Finally, ferroptosis is a non-apoptotic, iron-dependent form of RCD.[2]At last in 2012 the term ferroptosis was coined.[4]

Ferroptosis Induced Disorders

Pathological diseases induced by ferroptosis are affecting both the age groups either in younger individuals (below 15 years) or chronic disabilities in elderly people. As immature brain is unique in its growth, the individuals under the age of fifteen years are more vulnerable to traumatic brain injury [TBI] which has worsened the death and morbidity rate as one of the major causes .[6-8]Other neurological diseases afflicting the elderly include Alzheimer's disease, Parkinson's disease and Huntington's disease. The key mechanisms that cause disorders include iron accumulation, upregulation of genes, defective iron and lipid metabolism, and a reduction in glutathione peroxidase activity[8]

Ischemic stroke, acute kidney failure, brain tumors, intracerebral hemorrhage have also been recognized in patients associated with ferroptosis.[7,8]

Types of regulated cell death

As previously stated, ferroptosis is one of twelve kinds of controlled cell death, including apoptosis, necrosis, pyroptosis, and necroptosis.[6,12,36] Mainly, ferroptosis is regulated by numerous genes like ACSL4, AKRICI-3,CARS, ALOXs and furthermore which serves as a marker for contributing a part in the fundamental mechanism of (RCD) regulated cell death.[5,9]Through various studies it has been confirmed that ferroptosis is also triggered by few enzymes and decrease in endogenous inhibitors [GSH, NADPH, GPX4 or Vit E]. Drugs used to treat various ailments acts as inducers and have vulnerability to affect the elderly patients.[5]

Inducers of Ferroptosis

Erastin

Iron chelators like deferoxamine and antioxidants such as á-tocopherol, butylated hydroxytoluene, and â-carotene significantly decrease cell death triggered by erastin. This suggests that erastin-induced ferroptosis relies on signaling pathways dependent on reactive oxygen species (ROS) and iron.[9,10,37]Specifically, erastin-induced ferroptosis relies on six key genes linked to iron or mitochondrial fatty acid metabolism. These genes include Ribosomal protein L8, IREB2, ATP synthase F0 complex subunit C3, citrate synthase, tetratricopeptide repeat domain, and andacyl-CoA synthetase family member 2 (ACSF2).[2,3,11]In tumor cells expressing oncogenic Ras, the RAF/MEK/ERK signaling pathway seems to play a crucial role in enabling erastin to induce ferroptosis.[10] Piperazine erastin has been shown to possess greater stability and water solubility than erastin in vivo, demonstrating its ability to inhibit cancer growth more effectively.[12]

Sulfasalazine

Chronic inflammation of the gastrointestinal tract, joints, and retina is commonly treated with sulfasalazine. Sulfasalazine not only blocks the ~~NF-B~~ ***NF-êB*** signalling pathway but also the system Xc transporter. The inhibition of system Xc-mediated cystine absorption by substances like sulfasalazine and erastin induces ferroptosis in cancerous cell lines such as BJeLR and HT1080.

Sorafenib

Sorafenib induces ferroptosis in certain cancer cells like hepatocellular carcinoma (HCC) cells. Sorafenib's mode of action in ferroptosis may be dependent on inhibiting system Xc function rather than GPX4 activity. ER stress is elevated throughout this procedure. Further analysis of the structure-activity relationship of 87 sorafenib analogs reveals that sorafenib inhibits system Xc activity through a non-kinase target.[5]

RSL3 and RSL5

For RSL3 and RSL5 to cause ferroptosis in tumour cells containing oncogenic Ras, iron, ROS, and MEK are necessary. [3] Ferroptosis caused by RSL5 but not RSL3 requires VDAC2/3. [3] RSL3

inhibits GPX4 directly but not system Xc. [12] RSL3 binds to GPX4 and deactivates it, causing GPX4 to produce ROS as a result of lipid peroxidation. [12] RSLs come in at least two different varieties. Type I RSLs, such as erastin and RSL5, can trigger ferroptosis by targeting upstream regulators like VDAC and system Xc, while Type II RSLs like RSL3 induce ferroptosis by blocking downstream regulators such as GPX4. Protein synthesis appears essential for Type I RSL-induced ferroptosis, as demonstrated by the significant suppression of RSL5-induced ferroptosis by the protein synthesis inhibitor cycloheximide, while RSL3-induced ferroptosis remains unaffected.[3]

Buthioninesulfoximine

The rate-limiting enzyme for GSH production, glutamyl cysteine synthetase is irreversibly inhibited by buthioninesulfoximine (BSO). Ras-mutant cells undergo ferroptosis as a result of BSO's inhibition of GSH production, which is accompanied by decreased GPX activity and elevated ROS levels. [12]

Morphology of Ferroptosis

In response to erastin, ferroptotic cancer cells are typically gathered and separated. [2,9,10] Ferroptotic cells have altered cristae and mitochondrial morphology. After administering erastin to BJeLR cells, observations revealed alterations characteristic of ferroptosis, including a reduction in mitochondrial size, heightened mitochondrial membrane density, and a decrease or disappearance of mitochondrial cristae.[2,9,10]Genetic disruption of GPX4 has been observed through transmission electron microscopy, leading to the induction of ferroptosis in immortalized fibroblasts and kidney tissue. This induction is associated with the rupture of the outer mitochondrial membrane.[11,38] In contrast, after erastin treatment, cancer cells maintain their nucleus' structural integrity. [2] In cancer cells treated with erastin, neither nuclear condensation nor chromatin margination are seen.[2] We can distinguish ferroptosis from apoptosis, necroptosis, and autophagy thanks to these morphological characteristics.

Role of ferroptosis in various diseases

Major roles for ferroptosis are played by highly vascularized organs, which are linked to a variety of system disorders, including those affecting the liver, gastrointestinal tract, lungs, kidneys, pancreas, neurological and cardiovascular

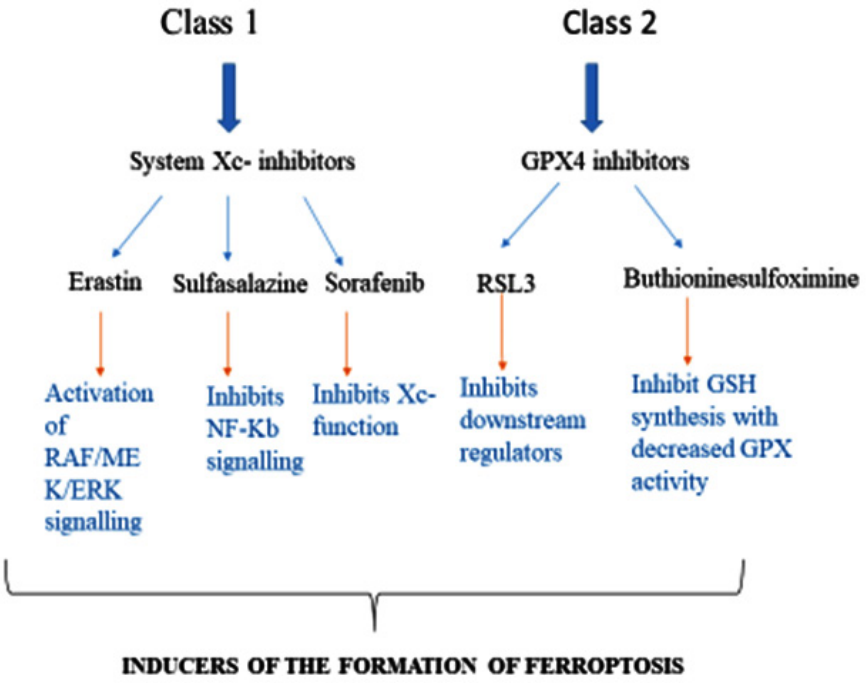

Fig. 1. Represents the inducers of the formation of ferroptosis

systems, and these organs also have a higher risk of developing tumors.

Ferroptosis is thought to be the primary mechanism of cell death in Alzheimer's disease due to the observed rise in lipid peroxidation and the growing body of data linking elevated iron levels in the brains of these patients to cognitive impairment.[14-18]

Before the identification of ferroptosis, previous indications pointed toward lipid peroxidation and oxidative stress as contributors to various neurological conditions.Historically, cell death in neurological and neuropsychiatric disorders was associated with apoptosis, while acute incidents resulting in cell death within the central nervous system (CNS), like infection and traumatic brain injury, were linked to necrosis. However, recent findings challenge this paradigm by suggesting that ferroptosis might be the principal mechanism responsible for cellular demise in diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD).[19-22]

Development of techniques for cancer therapy through induction of ferroptosis is supported by recent discoveries of drugs that induce ferroptosis as well as additional identification of the regulating mechanisms and genes involved in ferroptosis induction.[23]The heightened sensitivity of cancer cells to ferroptosis induction is proposed due to the iron-enriched (ferroptosis-promoting) environment within tumors. This susceptibility is further supported by increasing evidence indicating the overexpression of mechanisms that inhibit ferroptosis in cancer cells. However, this inhibition is counteracted by cancer cells' reliance on tumor suppressor pathways.[12,24]

Iron chelators

Research on the pathogenic nature of iron following Traumatic Brain Injury (TBI) has been advanced through pharmacological approaches involving iron chelation. Various iron chelators have been the subject of study, targeting free iron present either within cells, outside cells, or both. Among these chelators are Deferoxamine, which chelates both intracellular and extracellular ferric iron, 2,3-dihydroxybenzoic acid, primarily focusing on extracellular ferric iron chelation, and 2,2-bipyridine, specifically designed as an intracellular ferrous iron chelator. These compounds, along with others, were examined for their impact on brain edema and the preservation of the blood-brain barrier integrity in a model simulating brain injury induced by cold exposure.[5,25,35,39]

Deferoxamine

Deferoxamine (DFO) is a drug used off-label to treat aluminum toxicity and iron overload (authorized indication). It belongs to the chelator drug class. Deferoxamine chelates ferritin, hemosiderin, and iron in transit between

Table 1. Represents the Role of Ferroptosis in various diseases

Disease	Role of Ferroptosis
Cancer	Ferroptosis is linked to the development of cancer and resistance to treatment. Oxidative stress and chemotherapy are two extreme environments that cancer cells can withstand by using ferroptosis resistance mechanisms. One interesting approach to cancer treatment may be to target the ferroptosis pathways.[19]
Neurological	Stroke, Parkinson's disease, Alzheimer's disease, and other neurological conditions have all been related to ferroptosis. Under these circumstances, neuronal death and neurodegeneration are facilitated by excessive iron buildup and lipid peroxidation, two essential aspects of ferroptosis. Neuroprotection and therapeutic advantages could result from ferroptosis inhibition.[22]
Cardiovascular	Ferroptosis contributes to cardiovascular disorders such as ischemia-reperfusion damage, heart failure, and atherosclerosis. Iron-mediated oxidative damage and lipid peroxidation promote myocardial injury and vascular dysfunction, aggravating cardiovascular disease.[20]
Liver Diseases	Ferroptosis plays a role in the development of several liver illnesses, including non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), and liver fibrosis. Hepatic lipid peroxidation and iron excess induce hepatocyte injury and inflammation, resulting in liver dysfunction and fibrogenesis.[19]

transferrin and ferritin (labile chelating iron pool), as well as non-transferrin bound iron (free iron). The most extensively studied iron-chelator in the context of brain damage is deferoxamine, which provides neuroprotection via a variety of pathways. In addition to the hydroxyl radical and the peroxy nitrite anion, deferoxamine scavenges ferrous iron. In cultured neurons and astrocytes, it reduces oxidative stress, most likely as a result of less iron being available to produce free radicals.[5,26]

A key element of human physiology is iron. It is an essential component of several proteins, including cytochrome, myoglobin, and hemoglobin, and it also serves as an enzyme cofactor. Ferritin stores it, and transferrin distributes it throughout the serum. There is no physiological system in place to eliminate iron. Instead, hepcidin levels are changed by humans to control GI intake. By elevating hypoxia-inducible factor-1, there is a potential for promoting cell survival through the activation of molecules such as erythropoietin and vascular endothelial growth factor. This mechanism could potentially offer additional protection to the developing injured brain in juvenile individuals.[5,27]

Ferrostatin- 1 (fer1)

It has been established that Fer1 is a powerful and particular inhibitor of ferroptosis [9]. Acute brain damage, Huntington's disease, periventricular leukomalacia, and renal failure are a few cellular disease models that studies have indicated Fer-1 inhibits cell death in [31]. Other research has demonstrated that Fer1 prevented ferroptosis linked to stroke and Parkinson's disease in animal models and decreased glutamate-induced ferroptosis in organotypic hippocampal slices [28-31]. In a recent research, Fer-1-treated TBI rats showed decreased iron buildup and reduced neuronal deterioration.

Treatment with Fer1 also decreased neuronal cell death and enhanced cognitive and

Table 2. Represents the Management of Ferroptosis in various diseases

Management	Targeted Iron Type	Disease	Management Strategy
Iron chelators Deferoxamine	Intracellular and extracellular ferric iron	Traumatic Brain Injury (TBI)	Neuroprotection by scavenging ferrous iron and lowering oxidative stress. Maintains blood-brain barrier integrity and lowers cerebral edema.[5,25,26]
2,3-Dihydroxybenzoic Acid	Primarily extracellular ferric iron	Traumatic Brain Injury (TBI)	To prevent brain damage and protect the blood-brain barrier, target extracellular ferric iron.[35]
2,2-Bipyridine	Intracellular ferrous iron	Not specified	It inhibitsthe intracellular ferrous iron to prevent cell damage and death.[35]
Ferrostatin-1 (Fer1)	Ferroptosis inhibitor	Traumatic Brain Injury (TBI), Huntington's disease, periventricular leukomalacia, stroke, Parkinson's disease	It inhibits ferroptosis in various cellular disease models, including TBI. Reduces iron buildup, neuronal deterioration, and improves cognitive and motor performance.[28-31]
Liproxstatin-1	Ferroptosis inhibitor	Ischemia-Reperfusion Injury (IRI), renal damage	It Suppresses the ferroptosis in renal proximal tubule epithelial cells and models of IRI. Reduces tissue damage and inflammation.[33]

motor performance over the long term. These results therefore revealed a distinct kind of TBI-related cell death and offer a fresh therapeutic target for preserving the wounded brain. In order to establish the therapeutic window of Fer1 and create medications that are clinically viable, more research is currently required.[28-31]

Liproxstatin-1

In humans, Liproxstatin-1 has demonstrated its ability to impede ferroptosis in renal proximal tubule epithelial cells, Gpx4-deficient kidneys, and in a model of tissue damage induced by ischemia-reperfusion injury (IRI). Additionally, compounds categorized as lipid peroxidation inhibitors, such as lysyl oxidase (LOX) inhibitors, have shown the capacity to suppress ferroptosis.[34] To investigate the effect of ferroptosis inhibition in Ischemic / Reperfusion injury, mice were given liproxstatin-1, a powerful and selective ferroptosis inhibitor that has previously been demonstrated to reduce I/R damage. Liproxstatin-1 therapy ischemia increased GPx4 expression while decreasing COX2 expression in vivo.[33]

CONCLUSION

Understanding the role of ferroptosis in these diseases has opened up new avenues for therapeutic intervention. Strategies targeting key regulators of ferroptosis, such as GPX4, ACSL4, and system xc-, have shown promise in preclinical studies. Small molecules and compounds that modulate iron metabolism, lipid peroxidation, and antioxidant defenses are being explored as potential treatments to induce ferroptosis in cancer cells or to prevent neuronal cell death in neurodegenerative diseases. Additionally, combination therapies incorporating ferroptosis-inducing agents with conventional treatments like chemotherapy or radiation therapy hold potential for synergistic effects in cancer treatment. However, further research is needed to fully elucidate the role of ferroptosis in different diseases and to optimize therapeutic strategies targeting this cell death mechanism.

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Conflicting Interest

None.

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