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# FERROPTOSIS AND THEIR EMERGING ROLE IN DISEASE PROGRESSION AND TREATMENT

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## ABSTRACT

The iron dependent pathways known as Ferroptosis that's started by uncontrolled lipid peroxidation and is directed by atomic systems which incorporate different atoms and organelles. Ferroptosis has ended up a basic component in various physiological and obsessive scenarios, driving to significant restorative advance in a wide run of diseases. Ferroptosis may be a modified type of cell death mechanism. This current article represent the brief role Ferroptosis and its part within the pathogenesis of numerous maladies.

**KEYWORDS:** Ferroptosis, Cancer, Neuronal Disease, Diabetes, Ischemia; NAFLD.

## INTRODUCTION

Ferroptosis is distinguished from programmed cell death by its distinct characteristics, including its unique appearance, biochemistry, genetics, and immunological responses. Mitochondrial enlargement, decreased cristae, increased membrane density, and outer mitochondrial membrane rupture are recognised morphological characteristics of ferroptosis. Ultimately, cell death results from an iron-dependent process that encompasses three key metabolic pathways related to lipids, thiol, and iron. The enzymatic reaction of two primary antioxidant systems can effectively prevent ferroptosis. (1).

Programmed cell death is essential for the development of normal tissues, the selection of immune cells, and the removal of damaged and infected cells. These processes encompass the removal of damaged and diseased cells. Accidental cell death and regulated cell death two pathways followed by any cells. In accidental cell death it is transpires independently of human influence and is initiated by irreversible external stimuli, whereas Regulated cell death, governed by molecular network mechanisms and influenced by either experimental or therapeutic substances. Ferroptosis is a metabolic process associated with various metabolic abnormalities and is regulated by a specific set of genes. To enhance research initiatives, it is crucial to recognise these modifications, which act as indicators of ferroptosis(1,2).

## THE FUNDAMENTAL MECHANISM OF FERROPTOSIS

Ferroptosis begins with an increase in iron buildup and a rise in lipid peroxidation. Two mechanisms that work to prevent ferroptosis are the first chelation of excess iron and the second activation of antioxidant pathways that are either dependent on or not dependent on GPX4. As will be explained later on, ferroptosis revolves on a disturbance in redox equilibrium. The peroxidation of lipid that is commonly known as lipid peroxidation play very crucial role in the activation of Ferro ptosis mediated cell death. There are various external and internal factors for the activation of lipid peroxidation such as free radicals of oxygen, $H_20_2$, and $cl^{\cdot}$. These by products directly damage the cellular lipid and play important role in iron mediated death pathways. Lipid peroxidation, which can be caused by an increase in reactive oxygen species (ROS) generation or stimulation, can lead to several types of controlled cell death (RCD). Numerous processes, play important role in ROS generation such as Fenton reaction, Glycolysis and TCA cycle, mitochondrial respiratory chain, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX. In a wide variety of cell types and tissues, reactive oxygen species can either trigger ferroptosis or make it more likely to occur(3,4).

## FERROPTOSIS AND DISEASE

Recently, it was found that ferroptosis may be

activated and has been linked to practically all organ-system illnesses. Ferroptosis is involved in cancer, neurological disorders, infection, ischemia-reperfusion injury, stress, autoimmune diseases, biopolar disorder and metabolic disorders. The peroxidation and free radicals of iron mainly activates and disrupted GPX4 pathway and enhanced ferritinophagy enable ferroptosis in these disorders and others disease conditions (5).

## TUMOUR CELLS AND FERROPTOSIS

Apoptosis has long been the main way cancer cells die. Apoptosis-based cancer treatments often fail due to dysregulation of apoptotic pathways, especially anti-apoptotic mechanisms. Recent research have linked ferroptosis to many cancers, particularly drugs that target cancer-related genes and KRAS mutation-associated signalling pathways. Ferroptosis targeting may help fight cancer, especially apoptosis-resistant ones, through different ways. Cancer cells have developed several methods to reduce ferroptosis' metabolic and oxidative stresses (1,6). The Stress-inducible nuclear protein 1 basically increases the lipocalin 2 expression, and inhibit or reducing iron buildup due to this free radical of oxygen generates and oxidative damage occurs. This makes human and mouse pancreatic ductal adenocarcinoma (PDAC) cells more ferroptosis-resistant. In PDAC cells and mice models, HSPA5 stabilises GPX4, inhibiting ferroptosis. Radiotherapy is a common cancer treatment that uses ferroptosis. Radiation induces ferroptosis-mediated immunogenic death in cells, which is connected to its anticancer effects. When irradiated tumour cells produce the Ataxia-Telangiectasia mutant gene, lipid peroxidation increases, blocking SLC7A11. This blocks cystine absorption. (7).

## DEMYELINATION

Neurodegenerative disorders are becoming more common, which is a huge problem for society and a major source of stress for those dealing with them. However, there is still a lack of effective treatments for many disorders. The relationship between pathogenic features, disease processes, and neuronal death must thus be further investigated. The primary focus of this research is on ferroptosis and its association with both Alzheimer's disease as well as Parkinson's disease. The pathophysiology of Alzheimer's disease and Parkinson's disease extensively exhibit ferroptosis traits, such as iron dyshomeostasis and lipid peroxidation. Iron builds up in the brain with age, making it a major risk factor for neurodegenerative disorders. Evidence of iron buildup in certain areas of the brain has been found in many neurodegenerative disorders (8,9).

## REPERFUSION AND ISCHEMIA MYOCARDIAL ISCHEMIA

Myocardial ischemia is a serious medical disorder that can lead to serious complications and sometimes patient may die. Reduced blood flow to tissues, known as ischemia, happens when arteries are either blocked or ruptured. Cell death is caused by energy depletion and the end of blood flow (10). Returning blood flow as soon as possible is critical. However, once blood flow returns to normal, more substantial functional and structural alterations become noticeable. Myocardial infarction, acute renal injury, circulatory arrest, and sleep apnea are all possible outcomes of the pathological process. However, IRI poses a significant obstacle to organ transplantation, and reducing its negative consequences in real-world settings is no easy feat. As a potential target for treating ischemia-reperfusion injury, iron shows promise (10,11). Children who suffer from severe ischemic-anoxic insults have significantly higher iron levels in different parts of the brain, according to clinical research. Tissue damage in ischemia-reperfusion injury may also be caused by high iron levels during ischemia/reperfusion. Iron chelation was shown to reduce IRI damage in many animal models of the disease. Reactive oxygen species (ROS) can increase upon reperfusion of ischemic tissue, which is known to further worsen tissue damage and deterioration. There is evidence that antioxidants can protect against ischemia-reperfusion injury in a variety of settings. Lipid peroxidation occurs in tandem with the rise in oxidation (12).

## FERROPTOSIS AND DIABETES

There are basically two types of diabetes Type 1 diabetes mellitus (T1DM) in which the immune system's attack on and destruction of pancreatic β-cells, leading to a deficiency in insulin production and type 2 diabetes (T2DM) the modest reduction in insulin secretion from pancreatic β-cells. Relative insulin insufficiency, resulting from dysfunctional pancreatic β-cells, aging and other health issues are a significant contributor to type 2 diabetes mellitus (T2DM) and insulin resistance. Studies indicate that individuals with diabetes mellitus exhibit irregularities in iron metabolism and frequently accumulate excess iron in their bodies, and iron overload may be a critical factor in the development of the disease (13). Individuals with diabetes, as well as animal models, exhibit low plasma concentrations of antioxidant enzymes such as glutathione (GSH) and superoxide dismutase (SOD).The reduced amount of antioxidant enzyme play very important role in the

Pancreatic β-cells exhibit susceptibility to oxidative stress-induced damage and activation of ferroptopsis pathways. A study by Liu et al. demonstrated that ferroptosis contributes to pancreatic damage, glucose intolerance, iron accumulation, and diabetic symptoms in mice with type 2 diabetes. The study indicates that islet function may be restored through the inhibition of ferroptosis (13). Type 1 diabetes patients may undergo ferroptosis following islet transplantation, a treatment that has become increasingly favored for its potential to enhance pancreatic β-cell mass, and normal secretion of insulin and mitigate long-term complications (13-15).

## NAFALD AND ROLE OF FERROPTOSIS

NAFLD, is a conditions of hepatic steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) are all parts of this chronic, progressive illness. A large body of evidence suggests that ferroptosis has a role in the development of NAFLD (16). One of the main factors that contribute to the development of NAFLD is the abnormal buildup of lipids, which in turn causes oxidative stress. Research by Zhang et al.(17) in 2021 proved that ferroptosis causes inflammation, which propels NASH development and progression. Improvements in liver function, inhibition of inflammatory reactions, and hepatocyte death reversal are all possible side effects of ferroptosis inhibitors (18).

## EFFECTS OF OSTEOPOROSIS ON FERROPTOSIS

One prevalent metabolic disorder that affects bones is osteoporosis. A growing body of research is attempting to clarify the role of ferroptosis in the development of osteoporosis. Having too much iron in your system might be harmful. Animal studies have shown that iron excess can lead to osteoporosis and increased oxidative stress in mice (19). Postmenopausal women may have high iron levels in addition to estrogen insufficiency, both of which can lead to PMOP. Overconsumption of iron causes reactive oxygen species (ROS) to build up. In osteoporosis, ROS trigger the NF-κB/NLRP3 signaling pathway, causing osteoclasts to cause bone loss. Reactive oxygen species may help maintain metabolic bone homeostasis, according to Gao et al. (12,20).

## CONCLUSION

There has been a rising realization in recent years that ferroptosis is an important disease mechanism in the pathogenesis of practically every organ system disease. This recognition has occurred in the course of recent years. Ferroptosis is commonly found in a wide range of diseases, including cancer, neurodegeneration, ischemia-reperfusion injury, metabolic abnormalities, and other associated conditions. These disorders are extremely prone to ferroptosis because they contain a large amount of lipids and iron, both of which are factors that promote lipid peroxidation on the cell surface. Because of the discovery of ferroptosis, new channels have been opened in the knowledge of the processes that lead to cell death. As a result, the possibilities for therapeutic intervention have been expanded. This is particularly true in situations where dysregulated cell death is a significant component, such as in the case of neurodegenerative illnesses and cancer. For the purpose of determining whether or whether there is a potential therapeutic advantage, researchers are conducting extensive research on pharmacological and genetic approaches to controlling ferroptosis. However, despite the fact that it shows promise, research on ferroptosis is severely hindered by a multitude of issues that restrict our capacity to fully comprehend and exert control over this cell death mechanism.

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