INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD)
© 2026 IJNRD | Volume 11, Issue 8, August 2026 | ISSN: 2456-4184 | IJNRD.ORG

FERROPTOSIS IN HUMAN DISEASES

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ABSTRACT:

Iron is an indispensable trace element that supports a wide range of biological functions, making the regulation of iron homeostasis essential for maintaining normal physiological processes. Disturbances in iron balance, whether due to deficiency or excessive accumulation, can lead to numerous pathological conditions. One of the most significant consequences of disrupted iron metabolism is ferroptosis, a distinct form of regulated cell death that relies on iron-dependent lipid peroxidation. Unlike classical forms of programmed or accidental cell death, ferroptosis is primarily driven by abnormalities in iron metabolism, excessive lipid oxidation, and impairment of cellular antioxidant defence mechanisms**.** The susceptibility of cells to ferroptosis is controlled through multiple regulatory levels, including transcriptional, translational, and post-translational mechanisms, which collectively influence the expression and activity of key ferroptosis-related proteins. Over the past decade, increasing evidence has established ferroptosis as a critical contributor to the pathogenesis of a broad spectrum of human diseases. These include cancer, metabolic disorders, autoimmune diseases, cardiovascular diseases, neurological disorders, and musculoskeletal conditions. The growing understanding of ferroptosis has identified numerous ferroptosis-associated proteins as promising therapeutic targets for diseases that currently lack effective treatments. Furthermore, several pharmacological agents that modulate ferroptosis have demonstrated encouraging therapeutic outcomes in preclinical studies and early clinical trials, although additional research is required to confirm their long-term efficacy and safety in clinical practice.

Introduction:.

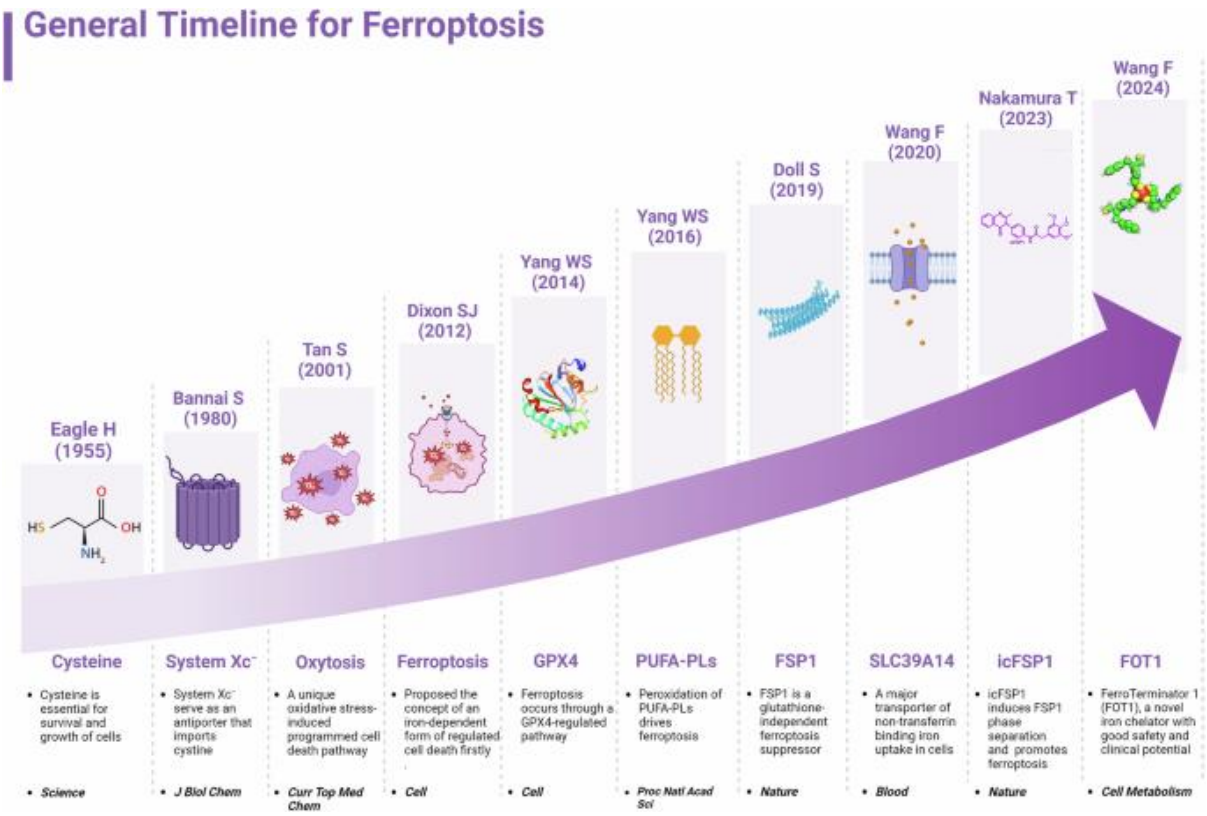
Ferroptosis is a distinct form of regulated cell death that is driven by iron-dependent lipid peroxidation and characterised by the accumulation of reactive oxygen species (ROS) and oxidative damage to cellular membranes. Unlike apoptosis, necrosis, or autophagy, ferroptosis displays unique morphological, biochemical, and metabolic features, with its initiation and progression being closely associated with disturbances in iron metabolism, redox homeostasis, and lipid metabolism. The availability of intracellular iron is a critical determinant of ferroptotic sensitivity because excess ferrous iron catalyses the Fenton reaction, generating ROS that oxidise polyunsaturated fatty acid-containing phospholipids and trigger membrane lipid peroxidation. Consequently, alterations in systemic or cellular iron homeostasis have a profound impact on ferroptosis.

Several proteins involved in iron metabolism regulate ferroptosis by controlling iron uptake, storage, transport, and utilisation. Molecules such as transferrin, metal ion transporters, and iron-responsive element-binding protein 2 (IREB2) influence intracellular iron availability and thereby modulate ferroptotic signalling. Similarly, exposure to exogenous iron sources, including ferric ammonium citrate (FAC), enhances ferroptosis by increasing intracellular iron levels, whereas iron-chelating agents such as deferoxamine (DFO) suppress ferroptosis through the reduction of iron overload. The extent of membrane lipid unsaturation further determines cellular susceptibility to ferroptotic damage, as polyunsaturated phospholipids are highly vulnerable to oxidative attack.

To counteract lipid peroxidation, cells possess several antioxidant defence systems that maintain redox balance. Among the best-characterised pathways are the glutathione (GSH)/glutathione peroxidase 4 (GPX4) axis, which detoxifies lipid hydroperoxides, and the coenzyme Q10 (CoQ10)/ferroptosis suppressor protein 1 (FSP1) pathway, which inhibits lipid radical propagation independently of GPX4. Alterations in the expression or activity of these regulatory molecules are widely used as molecular indicators of ferroptosis and provide valuable insights into its underlying mechanisms.

Since ferroptosis was first identified over a decade ago, extensive research has demonstrated its involvement in numerous physiological and pathological processes. Increasing evidence indicates that ferroptosis contributes to tumour initiation and progression, immune regulation and immune escape, neurodegeneration, skeletal muscle wasting, and tissue injury associated with ischaemia-reperfusion. These findings suggest that ferroptosis plays a central role in maintaining metabolic and redox homeostasis while also participating in the pathogenesis of a wide range of human diseases.

Fig. 1



Biological functions of iron homeostasis:

Iron is an essential trace element that supports numerous physiological functions required for normal growth, metabolism, and cellular survival. It plays indispensable roles in oxygen transport through haemoglobin and myoglobin, mitochondrial respiration, DNA synthesis, cytochrome enzyme activity, and cellular energy production. Because both iron deficiency and iron overload are detrimental to health, iron homeostasis is tightly regulated to ensure an adequate supply for biological processes while preventing iron-mediated toxicity.

The human body contains no active mechanism for iron excretion; therefore, systemic iron balance is maintained primarily through intestinal absorption. Approximately 1–2 mg of dietary iron is absorbed each day to compensate for unavoidable losses resulting from the shedding of intestinal epithelial cells, skin desquamation, and minor blood loss. Dietary iron exists in two principal forms: haem iron and non-haem iron. Haem iron is readily absorbed by intestinal epithelial cells through haem carrier protein 1 (HCP1), whereas

non-haem iron is predominantly present in the ferric (Fe^{3+}) state .Iron absorption occurs mainly in the duodenum and proximal jejunum, where enterocytes regulate the amount of iron entering the circulation.

Following intestinal uptake, intracellular iron has two possible fates. A proportion is stored within enterocytes as ferritin, while the remainder is exported across the basolateral membrane by ferroportin (FPN), the only known iron exporter in mammalian cells. During this process, ferrous iron is oxidised to ferric iron by ferroxidases, enabling its binding to transferrin (TF), the principal iron transport protein in plasma. Transferrin delivers iron to peripheral tissues by interacting with transferrin receptor 1 (TFR1) on the cell surface. The transferrin–TFR1 complex is internalised through clathrin-mediated endocytosis, after which iron is released within endosomes, reduced to the ferrous form, and transported into the cytoplasm by DMT1. Cytoplasmic iron is subsequently utilised for metabolic processes or stored in ferritin to prevent oxidative damage. Under conditions of iron overload, cells also acquire non-transferrin-bound iron (NTBI) through transporters such as SLC39A14, contributing to increased intracellular iron accumulation.

Iron storage and recycling are equally important for maintaining systemic iron homeostasis. Ferritin functions as the primary intracellular iron storage protein, safely sequestering excess iron and limiting its participation in oxidative reactions. During periods of iron deficiency, ferritin is selectively degraded through NCOA4-mediated ferritinophagy, releasing stored iron into the labile iron pool for cellular utilisation. Excess iron is predominantly deposited as ferritin and hemosiderin within hepatocytes and macrophages of the reticuloendothelial system, particularly in the liver, spleen, and bone marrow, where it serves as a readily mobilisable reserve.

Iron metabolism is also regulated at the cellular level through the iron-responsive element/iron regulatory protein (IRE/IRP) system, which maintains intracellular iron balance by controlling the translation and stability of mRNAs encoding proteins involved in iron uptake, storage, and export, including ferritin, TFR1, DMT1, and ferroportin. In addition, hypoxia-inducible factors regulate the transcription of several iron-related genes by binding to hypoxia-responsive elements. The stability of HIF proteins is controlled by prolyl hydroxylase domain (PHD) enzymes, whose activity depends on intracellular ferrous iron concentrations. This close relationship between iron availability and HIF signalling has attracted considerable attention as a potential therapeutic target in disorders associated with abnormal iron metabolism.

Iron deficiency:

Iron is an indispensable micronutrient that functions as a catalytic cofactor for numerous enzymes and forms an integral component of several structural proteins. It is essential for a wide range of biological processes, including oxygen transport by haemoglobin, oxygen storage by myoglobin, mitochondrial electron transport, oxidative phosphorylation, and the activity of various oxidoreductase enzymes. Owing to these diverse physiological functions, adequate iron availability is critical for maintaining cellular metabolism, tissue oxygenation, and normal organ function.

Iron deficiency is the most prevalent nutritional deficiency worldwide and generally results from insufficient dietary intake, impaired intestinal absorption, chronic blood loss, or increased physiological demand. When iron stores become depleted, haem synthesis declines, leading to reduced haemoglobin production and ultimately hypochromic microcytic anaemia. Beyond its role in haemoglobin synthesis, haem is an iron-containing tetrapyrrole that participates in multiple biological processes, including oxygen transport, gas sensing, mitochondrial respiration, xenobiotic metabolism, and the regulation of microRNA processing. Consequently, inadequate iron availability disrupts haem biosynthesis, compromises oxygen delivery to tissues, and reduces aerobic energy production. These effects commonly manifest as fatigue, diminished

exercise tolerance, and impaired endurance performance, particularly among adolescents, women of reproductive age, and athletes who have increased iron requirements.

In addition to supporting oxygen metabolism, haem also acts as an important signalling molecule that regulates the transcription of genes involved in circadian rhythm, cellular proliferation, apoptosis, oxidative stress responses, mitochondrial function, and ion channel activity. Therefore, iron deficiency not only impairs oxygen transport but also influences multiple intracellular signalling pathways that are essential for maintaining normal cellular homeostasis.

Iron is equally important for mitochondrial integrity, DNA synthesis and repair, endoplasmic reticulum function, and numerous iron-dependent enzymatic reactions required for cell survival. As a result, iron deficiency adversely affects both cellular metabolism and organ function. Clinical manifestations frequently include reduced physical performance, muscle weakness, cognitive impairment, and decreased work capacity. In individuals with chronic inflammatory disorders, these effects are often more pronounced because inflammation restricts iron availability while simultaneously increasing metabolic demands, thereby accelerating disease progression and worsening clinical outcomes.

Iron also plays a fundamental role in skeletal health through its involvement in vitamin D metabolism and collagen synthesis. Reduced intracellular iron levels disrupt the balance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption, resulting in impaired bone remodelling and progressive bone loss. Consequently, iron deficiency, irrespective of the presence of anaemia, has been associated with osteopenia, osteoporosis, and an increased risk of fractures.

Iron metabolism is also profoundly altered during cancer development. Many patients with malignancies develop functional iron deficiency or anaemia of chronic disease, largely driven by inflammation-induced overproduction of hepcidin and further aggravated by chemotherapy or other anticancer treatments. At the cellular level, tumour cells frequently remodel iron metabolism to satisfy their increased metabolic demands. Transferrin receptor 1 (TFR1) is commonly overexpressed, enhancing iron uptake, while divalent metal transporter 1 (DMT1), which mediates intestinal iron absorption and endosomal iron transport, is frequently upregulated in colorectal cancer. Ferritin, traditionally regarded as an intracellular iron storage protein, may also be secreted by tumour cells and subsequently internalised through TFR1, providing an additional source of iron. In contrast, ferroportin (FPN), the only known cellular iron exporter, is often downregulated in breast and prostate cancers, resulting in intracellular iron accumulation that supports tumour growth and proliferation. These alterations highlight the importance of iron-regulatory proteins as potential therapeutic targets in oncology.

Iron overload:

Although iron is indispensable for numerous physiological processes, excessive iron accumulation is highly detrimental because of its potent pro-oxidant properties. Iron readily cycles between its ferrous (Fe^{2+}) and ferric (Fe^{3+}) oxidation states, enabling it to catalyse redox reactions that generate reactive oxygen species (ROS). Through the Fenton and Haber–Weiss reactions, excess free iron promotes the formation of highly reactive hydroxyl radicals that oxidise lipids, proteins, nucleic acids, and cellular organelles, including mitochondria and lysosomes. Consequently, uncontrolled iron accumulation disrupts redox homeostasis, impairs cellular function, and ultimately contributes to tissue injury and organ dysfunction.

Under physiological conditions, circulating iron is tightly bound to transferrin, which limits the availability of redox-active iron and prevents oxidative damage. However, when transferrin saturation exceeds approximately 60–70%, its binding capacity becomes exhausted, resulting in the appearance of non-transferrin-bound iron (NTBI). This highly reactive iron fraction constitutes the labile iron pool and is readily transported into cells

through multiple pathways, including calcium channels in cardiomyocytes. Once inside the cell, NTBI accelerates ROS generation, amplifies lipid peroxidation, and initiates oxidative damage that predisposes tissues to ferroptosis and other forms of cell injury.

Iron overload disorders comprise a heterogeneous group of inherited and acquired diseases characterised by excessive iron deposition in tissues. Hereditary haemochromatosis (HH) represents the most common inherited form and is primarily caused by mutations affecting genes involved in systemic iron regulation, including *HFE*, *HAMP*, *HJV*, *TFR2*, and *SLC40A1* (encoding ferroportin). These genetic defects reduce hepcidin production or impair ferroportin regulation, leading to excessive intestinal iron absorption and progressive iron accumulation throughout the body. Acquired iron overload most frequently develops following repeated blood transfusions, chronic haemolytic disorders, or diseases associated with ineffective erythropoiesis. Diagnosis relies on a combination of clinical findings, elevated serum ferritin concentrations, increased transferrin saturation, genetic testing, and assessment of tissue iron burden.

Quantification of iron overload has become increasingly important for disease management and therapeutic monitoring. Liver iron concentration closely reflects total body iron stores and is therefore regarded as a reliable indicator of systemic iron burden. Magnetic resonance imaging (MRI) has emerged as the preferred non-invasive technique for estimating tissue iron deposition in the liver, heart, and other organs, allowing accurate assessment of disease severity and monitoring of treatment response.

Persistent iron overload has widespread pathological consequences because virtually every organ is susceptible to iron-mediated oxidative injury. The liver is particularly vulnerable owing to its central role in iron storage. Progressive hepatic iron accumulation induces chronic oxidative stress, promotes inflammation and fibrosis, and may eventually progress to cirrhosis and hepatocellular carcinoma. Similarly, excessive myocardial iron disrupts mitochondrial respiration, impairs mitochondrial dynamics, and compromises cardiac contractility, thereby increasing the risk of cardiomyopathy, arrhythmias, and heart failure.

The cardiovascular system is also affected through mechanisms extending beyond direct myocardial toxicity. Iron accumulation within vascular macrophages alters their phenotype and influences inflammatory signalling, oxidative stress, and atherosclerotic plaque development. Furthermore, iron can catalyse the oxidation of low-density lipoprotein (LDL), an important event in atherogenesis. Although iron deposition has been identified within atherosclerotic plaques, whether iron accumulation represents a primary driver of vascular disease or merely a consequence of plaque progression remains an area of ongoing investigation.

Excessive iron deposition in the central nervous system has been implicated in the development of several neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and certain neurodevelopmental disorders. Increased brain iron promotes oxidative stress, mitochondrial dysfunction, and neuronal death, all of which contribute to progressive neurological decline. Following intracerebral haemorrhage, haemoglobin degradation releases large amounts of iron into the surrounding brain tissue, where the abundant polyunsaturated lipids of neuronal membranes become highly susceptible to iron-dependent lipid peroxidation. This process promotes ferroptosis, exacerbating neuronal injury, cerebral oedema, mitochondrial dysfunction, and secondary neurological damage. During haemorrhagic transformation after cerebral ischaemia, disrupted iron metabolism further aggravates oxidative injury by increasing free radical production and impairing mitochondrial energy metabolism, thereby establishing a self-perpetuating cycle of neuronal damage.

Iron overload also influences immune function and host susceptibility to infectious diseases. Because iron is an essential nutrient for many microorganisms, increased systemic iron availability can facilitate microbial proliferation and enhance pathogen virulence. Clinical studies have demonstrated an association between iron overload and an increased incidence of bacterial and fungal infections. Elevated ferritin concentrations and

disorders characterised by abnormal iron metabolism have additionally been linked with poorer outcomes in viral infections, including coronavirus disease 2019 (COVID-19), suggesting that dysregulated iron homeostasis may contribute to excessive inflammatory responses and disease progression.

Accumulating evidence indicates that excessive iron also contributes to carcinogenesis. Chronic oxidative stress induced by iron overload causes DNA damage, genomic instability, and disruption of normal cell-cycle regulation, thereby promoting malignant transformation. Individuals with hereditary haemochromatosis have a markedly increased risk of hepatocellular carcinoma, particularly in the presence of advanced liver fibrosis or cirrhosis. Whether iron overload similarly increases the incidence of extrahepatic malignancies remains controversial, with epidemiological studies producing inconsistent findings. Further investigation is therefore required to clarify the role of iron metabolism in tumour initiation, progression, and therapeutic response across different cancer types.

Metabolic disorders are likewise influenced by abnormal iron accumulation. Elevated dietary or tissue iron has been associated with an increased risk of type 2 diabetes mellitus, primarily through oxidative stress-mediated pancreatic β-cell dysfunction and impaired insulin secretion. Excess iron also disrupts adipocyte metabolism, alters systemic energy balance, and activates inflammatory signalling pathways that contribute to insulin resistance and metabolic dysfunction.

Age-related increases in skeletal muscle iron content have emerged as an important contributor to sarcopenia. Excess intracellular iron impairs mitochondrial function, promotes lipid peroxidation, and disrupts cellular redox balance, leading to progressive muscle weakness and atrophy. Iron overload also sensitises skeletal muscle cells to ferroptosis and compromises the regenerative capacity of muscle stem cells, thereby limiting muscle repair following injury. Chronic inflammation frequently coexists with iron accumulation in ageing muscle, further accelerating degenerative changes.

Bone tissue is similarly affected by excessive iron deposition. Experimental studies have demonstrated that iron overload increases oxidative stress within bone, alters mineralisation, and disrupts bone microarchitecture. More recent evidence suggests that iron acts as an independent regulator of bone metabolism by disturbing the balance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption. Consequently, chronic iron overload has been recognised as an important risk factor for osteoporosis and other metabolic bone disorders.

Collectively, these findings demonstrate that iron overload has systemic consequences extending far beyond disturbances in iron metabolism alone. Through persistent oxidative stress, mitochondrial dysfunction, chronic inflammation, and ferroptosis, excessive iron contributes to the pathogenesis of cardiovascular, neurological, hepatic, metabolic, musculoskeletal, and malignant diseases. A comprehensive understanding of the molecular mechanisms governing iron toxicity will facilitate the development of targeted therapeutic strategies aimed at restoring iron homeostasis and preventing iron-mediated tissue damage.

Overview of ferroptosis:

Ferroptosis is a distinct form of regulated cell death characterised by iron-dependent lipid peroxidation and excessive oxidative damage to cellular membranes. Unlike apoptosis, autophagy, necroptosis, or pyroptosis, ferroptosis is initiated by the accumulation of iron-catalysed reactive oxygen species (ROS) and the subsequent oxidation of phospholipids enriched with polyunsaturated fatty acid (PUFA) chains. This process overwhelms the cellular antioxidant defence system, ultimately resulting in irreversible membrane damage and cell death.

The development of ferroptosis depends on the coordinated interaction of three key factors: dysregulated iron metabolism, increased lipid peroxidation, and impaired antioxidant capacity. Under physiological conditions, intracellular antioxidant systems effectively neutralise lipid peroxides and maintain redox homeostasis.

However, excessive iron accumulation enhances ROS generation through Fenton chemistry, leading to oxidative stress that exceeds the cell's antioxidant buffering capacity. As lipid hydroperoxides continue to accumulate, membrane integrity is progressively compromised, culminating in ferroptotic cell death.

Conclusion:

Disruption of intracellular iron homeostasis results in the accumulation of labile iron, which promotes oxidative stress and triggers ferroptosis, a distinct form of regulated cell death that is mechanistically different from apoptosis, autophagy, pyroptosis, and other cell death pathways. Although ferroptosis possesses unique molecular and morphological characteristics, increasing evidence indicates that it does not function in isolation. Instead, extensive crosstalk exists between ferroptosis and other regulated cell death mechanisms, with these interconnected pathways collectively influencing cell fate under both physiological and pathological conditions. Such interactions contribute to the complexity of ferroptosis and help explain its diverse roles in the onset and progression of numerous human diseases.Recent advances in molecular biology, genomics, and therapeutic technologies have substantially accelerated research into ferroptosis, leading to a deeper understanding of its regulatory mechanisms and disease-specific functions. These developments have identified novel molecular targets and pharmacological modulators, raising the possibility of translating ferroptosis-based interventions into personalised therapeutic strategies. Continued investigation of the signalling pathways, regulatory networks, and interactions between ferroptosis and other forms of cell death across different physiological and pathological settings will further clarify its biological significance and support the development of more effective treatments for a broad spectrum of human diseases.

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