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IRON OVERLOAD AND FERROPTOSIS IN HEREDITARY HEMOCHROMATOSIS: MOLECULAR MECHANISMS AND THERAPEUTIC PERSPECTIVES

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ABSTRACT

Hereditary hemochromatosis (HH) is a common inherited disorder of iron metabolism characterized by excessive systemic iron accumulation resulting from dysregulation of the hepcidin–ferroportin axis. Persistent iron overload promotes oxidative stress, mitochondrial injury, chronic inflammation, and progressive damage to the liver, pancreas, heart, endocrine glands, and other organs. In recent years, ferroptosis, an iron-dependent form of regulated cell death driven by lipid peroxidation and impaired antioxidant defenses, has emerged as a key mechanism linking iron accumulation to tissue injury. Growing evidence suggests that ferroptosis contributes substantially to the pathogenesis and clinical manifestations of hereditary hemochromatosis. This review summarizes current knowledge regarding the molecular mechanisms of iron overload and ferroptosis in hereditary hemochromatosis, emphasizing the roles of reactive oxygen species, mitochondrial dysfunction, lipid peroxidation, glutathione metabolism, and glutathione peroxidase 4 (GPX4). The review also discusses emerging therapeutic strategies targeting iron metabolism and ferroptotic pathways, including iron chelation, hepcidin replacement therapies, ferroptosis inhibitors, and antioxidant approaches. A better understanding of the relationship between iron overload and ferroptosis may provide new opportunities for precision medicine and the development of targeted interventions for hereditary hemochromatosis.[1–5]

KEYWORDS: Hereditary hemochromatosis; iron overload; ferroptosis; oxidative stress; lipid peroxidation; hepcidin; ferroportin; GPX4; reactive oxygen species; iron metabolism.

INTRODUCTION

Iron is an essential micronutrient involved in oxygen transport, electron transfer reactions, mitochondrial respiration, DNA synthesis, and numerous enzymatic processes. Because of its ability to alternate between ferrous and ferric states, iron serves as a critical cofactor in cellular metabolism. However, this same redox activity can become detrimental when iron accumulates beyond physiological requirements, leading to oxidative damage and cellular dysfunction.[1,2]

Systemic iron homeostasis is tightly regulated because humans lack an active pathway for iron excretion. The hepcidin–ferroportin axis constitutes the principal mechanism controlling iron absorption and distribution. Disruption of this regulatory pathway results in excessive intestinal iron absorption and progressive iron deposition in tissues.[3]

Hereditary hemochromatosis is most commonly associated with mutations in the HFE gene, particularly C282Y and H63D variants, which lead to inappropriately low hepcidin expression despite increasing body iron stores.[4] The consequent increase in ferroportin activity promotes continuous release of iron into the circulation and progressive accumulation of iron within parenchymal organs.

The toxic effects of iron overload are primarily mediated by oxidative reactions. Redox-active iron catalyzes the generation of reactive oxygen species through Fenton chemistry, initiating lipid peroxidation, protein oxidation, DNA damage, and mitochondrial

dysfunction.[6] These events contribute to fibrosis, endocrine dysfunction, cardiomyopathy, diabetes mellitus, and carcinogenesis observed in patients with hereditary hemochromatosis.

Recent advances in cell death research have identified ferroptosis as an important mechanism underlying iron-induced tissue injury. Ferroptosis is characterized by iron-dependent accumulation of lipid hydroperoxides, depletion of glutathione, impaired activity of glutathione peroxidase 4, and irreversible membrane damage.[7,8] Increasing evidence indicates that ferroptotic pathways participate in the progression of liver disease, pancreatic dysfunction, myocardial injury, and neurodegeneration associated with iron overload conditions.[8–10]

The present review aims to provide a comprehensive overview of the molecular relationship between iron overload and ferroptosis in hereditary hemochromatosis and to discuss potential therapeutic approaches targeting iron metabolism and ferroptotic signaling pathways.

MATERIALS AND METHODS

This study was designed as a narrative review aimed at synthesizing current evidence regarding the relationship between iron overload and ferroptosis in hereditary hemochromatosis. A comprehensive literature search was performed using PubMed, Scopus, Web of Science, and Google Scholar databases. Original investigations, review articles, meta-analyses, and experimental studies published in peer-reviewed journals were considered eligible. Studies investigating molecular mechanisms of iron homeostasis, cellular consequences of iron overload, ferroptotic signaling pathways, and emerging therapeutic interventions were critically evaluated and integrated to provide a comprehensive overview of the current understanding of ferroptosis in hereditary hemochromatosis.[12–14]

RESULTS AND DISCUSSION

The pathophysiology of hereditary hemochromatosis is characterized by persistent dysregulation of systemic iron homeostasis resulting from insufficient hepcidin activity and sustained ferroportin-mediated iron export. Consequently, excessive amounts of dietary iron are absorbed and progressively accumulate within parenchymal tissues. Increased transferrin saturation eventually leads to the appearance of non-transferrin-bound iron (NTBI), which can readily enter cells through alternative transport systems and significantly enlarge the intracellular labile iron pool. Unlike protein-bound iron, the labile iron pool is highly redox-active and represents the major source of iron-mediated cellular toxicity.[15]

The excessive accumulation of redox-active iron profoundly alters cellular homeostasis. Ferrous iron catalyzes the Fenton reaction, converting hydrogen peroxide into highly reactive hydroxyl radicals. These radicals possess extremely short half-lives but exhibit remarkable reactivity toward biological macromolecules. Proteins, phospholipids, carbohydrates, and nucleic acids become susceptible to oxidative modifications, leading to widespread cellular dysfunction. Oxidative damage to DNA contributes to genomic instability and carcinogenesis, whereas protein oxidation alters enzyme activity, receptor signaling, and intracellular communication pathways. Simultaneously, peroxidation of membrane lipids disrupts membrane integrity and changes the physicochemical properties of cellular membranes.[16]

Persistent oxidative stress represents a critical pathogenic mechanism underlying organ injury in hereditary hemochromatosis. The liver is particularly vulnerable because it serves as the principal site of iron storage and hepcidin synthesis. Excessive iron accumulation promotes hepatocyte injury, activation of hepatic stellate cells, extracellular matrix deposition, and progressive fibrosis. Similar mechanisms operate in the pancreas, where oxidative injury and β-cell dysfunction impair insulin secretion and contribute to diabetes mellitus. In the myocardium, iron-induced oxidative stress disrupts mitochondrial function and excitation–contraction coupling, ultimately resulting in cardiomyopathy and heart failure. Iron deposition in endocrine tissues and the central nervous system may further contribute to hormonal abnormalities and neurodegenerative manifestations.[15,16]

Recent discoveries have identified ferroptosis as a major mechanism linking iron overload to progressive tissue damage in hereditary hemochromatosis. Ferroptosis is a distinct form of regulated cell death that is fundamentally dependent on iron-catalyzed lipid peroxidation. Unlike apoptosis, ferroptosis is not characterized by chromatin condensation, caspase activation, or DNA fragmentation. Instead, it is associated with overwhelming accumulation of lipid hydroperoxides, depletion of intracellular glutathione reserves, and functional inactivation of glutathione peroxidase 4 (GPX4). Once antioxidant defenses become insufficient, phospholipid hydroperoxides accumulate uncontrollably and induce irreversible membrane damage, culminating in cell death.[17]

The biochemical basis of ferroptosis is intimately associated with membrane biology. Cellular membranes contain large quantities of polyunsaturated fatty acids that are particularly susceptible to free radical attack. The hydrogen atoms present at bis-allylic positions are easily abstracted by reactive oxygen species, initiating chain reactions of lipid peroxidation. The resulting products, including malondialdehyde and 4-hydroxynonenal, not only disrupt membrane architecture but also form covalent adducts with proteins and nucleic acids. These processes alter membrane fluidity, increase membrane permeability, impair ion transport systems, and interfere with intracellular signaling networks. Consequently, ferroptosis may be viewed not only as a biochemical

process but also as a phenomenon involving profound alterations in membrane structure and cellular biophysical properties.[18]

Mitochondria occupy a central position in iron-induced ferroptotic injury. Excessive intracellular iron can accumulate within mitochondria and amplify reactive oxygen species generation through disturbances in the electron transport chain. Morphologically, ferroptotic cells exhibit characteristic mitochondrial alterations, including reduction in mitochondrial volume, increased membrane density, diminished or absent cristae, and rupture of the outer mitochondrial membrane. Functionally, these changes impair ATP production, disrupt redox homeostasis, and establish a vicious cycle in which oxidative stress promotes further mitochondrial dysfunction and lipid peroxidation. Increasing evidence indicates that mitochondrial metabolic pathways substantially modulate ferroptotic sensitivity and may determine the severity of tissue injury in hereditary hemochromatosis.[18,19]

The recognition of ferroptosis as a central mechanism of iron-mediated injury has important therapeutic implications. Conventional treatment of hereditary hemochromatosis relies primarily on phlebotomy and, in selected cases, iron chelation therapy to reduce body iron stores. However, the emerging understanding of ferroptotic pathways has generated interest in novel therapeutic strategies targeting downstream mechanisms of cellular injury. Experimental studies have demonstrated protective effects of ferroptosis inhibitors such as ferrostatin-1 and liproxstatin-1, which suppress lipid peroxidation and preserve membrane integrity. Restoration of glutathione metabolism, enhancement of GPX4 activity, and administration of mitochondria-targeted antioxidants have also shown promising results in reducing iron-induced oxidative damage. Furthermore, therapeutic modulation of the hepcidin–ferroportin axis through hepcidin agonists or ferroportin inhibitors may provide additional opportunities for preventing iron accumulation and limiting ferroptotic tissue injury. These approaches support the emerging concept that precision medicine strategies integrating genetic profiling, biomarkers of iron metabolism, and ferroptosis-related molecular signatures may substantially improve the management of hereditary hemochromatosis in the future.[20]

CONCLUSION

Hereditary hemochromatosis is no longer regarded merely as a disorder of excessive iron accumulation but rather as a complex systemic disease in which iron-mediated oxidative stress and ferroptosis play central roles in the development of organ dysfunction. Persistent expansion of the intracellular labile iron pool promotes the generation of reactive oxygen species, initiates lipid peroxidation, disrupts membrane integrity, and induces mitochondrial dysfunction, ultimately culminating in ferroptotic cell death. Increasing evidence indicates that ferroptosis constitutes a fundamental pathogenic mechanism linking iron overload to hepatic fibrosis, diabetes mellitus, cardiomyopathy, and neurodegenerative complications. A deeper understanding of the molecular interplay between iron metabolism, oxidative stress, and ferroptotic pathways may facilitate the identification of novel biomarkers and therapeutic targets. Future investigations integrating molecular, cellular, and translational approaches are expected to advance precision medicine strategies and improve clinical outcomes in patients with hereditary hemochromatosis.

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