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The role of mitochondria in iron overload-induced damage

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Abstract
Iron overload is a pathological condition characterized by the abnormal accumulation of iron within the body, which may result from excessive iron intake, disorders of iron metabolism, or specific disease states. This condition can lead to significant health complications and may pose life-threatening risks. The excessive accumulation of iron can induce cellular stress, adversely affecting the structure and function of mitochondria, thereby compromising overall organ function. Given the critical role of mitochondria in cellular metabolism and homeostasis, it is imperative to investigate how mitochondrial dysfunction induced by iron overload contributes to disease progression, as well as to explore mitochondrial-related pathways as potential therapeutic targets for various iron overload disorders. This review examines the mechanisms by which mitochondria are implicated in iron overload-induced damage, including increased oxidative stress, mitochondrial DNA damage, and disruptions in energy metabolism. Additionally, it addresses the relationship between these processes and various forms of programmed cell death, as well as alterations in mitochondrial dynamics. Furthermore, the review discusses strategies aimed at alleviating and mitigating the complications associated with iron overload in patients by targeting mitochondrial pathways.

Keywords Iron overload, Mitochondria, Oxidative stress, Programmed cell death

Introduction

Iron is an essential trace element that is vital for the physiological functioning of the human body. It plays a significant role in the biosynthesis of iron-sulfur (Fe–S) clusters and heme within mitochondria; these iron-containing structures serve as cofactors for numerous enzymes [1–3]. Mitochondria, which operate as endosymbionts, along with the cell nucleus and other organelles, collectively form the mitochondrial information processing system [4–7]. The functionality of mitochondria, which is responsible for biosynthesis and signal transduction, can be compromised by various diseases, resulting in mitochondrial dysfunction that often coincides with the progression of pathological conditions [8, 9]. Mitochondria are central to cellular iron metabolism, necessitating an adequate supply of iron to maintain proper iron homeostasis [10]. Iron overload can occur at both the cellular and mitochondrial levels, leading to mitochondrial dysfunction [11]. Disruptions in mitochondrial iron metabolism are correlated with the onset of numerous diseases [3, 12, 13]. Mitochondrial damage resulting from iron overload is a multifaceted process that encompasses various factors and stages, including, but not limited to, oxidative stress, DNA damage, and disruptions in

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energy metabolism. As research in this field progresses, new mechanisms are being identified, such as the dysregulation of autophagy, the interaction between ferroptosis and apoptosis, and changes in mitochondrial dynamics. Although the importance of mitochondria in the context of iron overload is well recognized, a thorough understanding of these emerging mechanisms provides valuable insights that may guide future therapeutic approaches. This review offers an overview of the current advancements in research concerning the diverse mechanisms of mitochondrial damage associated with iron overload, with a particular emphasis on mitochondrial reactive oxygen species (mtROS) as a critical component linking the various pathways of damage.

Iron overload stimulates the generation of non-transferrin bound iron

Transferrin plays a crucial role in binding iron within the bloodstream. When transferrin reaches iron saturation, a condition known as iron overload occurs, resulting in increased levels of non-transferrin bound iron (NTBI) and labile plasma iron (LPI) [14]. NTBI consists of potentially deleterious iron complexes in plasma, predominantly Fe^{3+}-citrate or albumin complexes [14]. LPI is a subset of NTBI that exhibits both redox activity and chelatable, which increase in conjunction with NTBI levels and possess the ability to permeate cells and tissues. LPI exhibits a loose binding affinity to proteins and, due to its enhanced redox activity, is acknowledged as a significant factor contributing to iron-induced oxidative damage [15]. The initial stage in NTBI absorption involves the reduction of Fe^{3+} to Fe^{2+} facilitated by a membrane-associated ferrireductase [16]. NTBI/LPI can readily penetrate the heart, liver, spleen, pancreas, and other tissues through various transporters, including divalent metal transporter 1 (DMT1), ZRT/IRT-like protein 14 (ZIP14), lipocalin-2 (LCN-2), T-type calcium channels (TTCC), and L-type calcium channels (LTCC), resulting in an increase in labile cellular iron (LCI) [14, 17–20]. Surplus free iron or NTBI absorbed by cells is integrated into the labile iron pool (LIP), from where iron can be transferred to mitochondria via DMT1, mitoferrin, and sideroflexin 1 [21, 22]. Excess free iron within the LIP is stored in ferritin, which can subsequently be transported to lysosomes for degradation, thereby replenishing the LIP [22]. A relatively stable LIP is typically maintained through careful regulation of iron absorption, storage, utilization, and export within cells [23, 24].

Diseases associated with iron overload

Iron overload may arise from genetic predispositions, such as hereditary hemochromatosis [25] or ferroportin disease [26], as well as from acquired factors, including repeated red blood cell (RBC) transfusions due to anemia, increased intestinal iron absorption and ineffective erythropoiesis [27]. Prolonged alterations in iron metabolism can lead to organ dysfunction, particularly affecting the liver and potentially resulting in heart failure [28]. Each unit of RBC transfusion introduces approximately 250 milligrams of iron into the body, which is 100 times greater than the daily iron absorption observed in healthy individuals. Initially, iron overload from transfusions accumulates in the spleen; however, the distribution of iron within cells evolves over time. As iron stored in the spleen is gradually released, plasma transferrin becomes saturated, leading to the presence of NTBI in the plasma. Transfusion-induced iron overload is characterized by elevated levels of NTBI, which has a strong affinity for parenchymal cells [29]. NTBI may serve as a distinctive biomarker for iron overload in clinical patients [30]. Conditions necessitating frequent transfusions, such as myelodysplastic syndromes (MDS), β-thalassemia, and sickle cell disease (SCD), can result in transfusional iron overload [31–37]. This excess free iron can lead to complications such as iron overload cardiomyopathy (IOC), endocrine issues, and liver failure [31, 38, 39]. Patients receiving repeated blood transfusions for hematopoietic stem cell transplantation are at risk of developing iron overload, which may remain undetected until years later when significant methemoglobinemia is diagnosed [40]. IOC is a leading cause of mortality in individuals with chronic anemia-related disorders, such as β-thalassemia and SCD, who undergo long-term transfusions, affecting approximately 2.5% of chronically transfusion-dependent SCD patients [19, 36, 41]. While the toxicity of iron overload is less pronounced in SCD patients compared to those with β-thalassemia, iron accumulation primarily occurs in the liver rather than in the heart and endocrine organs [35, 42]. Iron can also enter the brain from the bloodstream through the blood-brain barrier. Transfusion-dependent β-thalassemia patients may experience brain iron overload, potentially leading to cognitive impairment, in contrast to non-transfusion-dependent patients [43]. Further research is necessary to elucidate the neurotoxic mechanisms associated with brain iron overload in patients with β-thalassemia. Furthermore, research has demonstrated that patients experiencing transfusion-related acute lung injury display an imbalance in iron homeostasis within the lungs, particularly characterized by iron overload [44].

Certain diseases and pharmacological treatments may contribute to iron overload in patients. Metabolic hyperferritinemia is associated with iron accumulation, which heightens the risk of hepatic and cardiometabolic diseases [45]. Iron overload is particularly prevalent in individuals with metabolic syndrome, especially among the aging population [46]. Furthermore, an imbalance in iron homeostasis has been linked to respiratory diseases,

with iron overload and mitochondrial dysfunction playing significant roles in pulmonary dysfunction and pulmonary fibrosis [47]. In the context of neurodegenerative diseases, such as Friedreich's ataxia (FA), mitochondrial iron overload is implicated in both cardiac and neurological pathologies; deficiencies in frataxin lead to detrimental changes in iron metabolism, resulting in oxidative stress and cellular injury [48, 49]. Additionally, the cardiac toxicity associated with the chemotherapeutic agent doxorubicin (DOX) and myocardial infarction may be connected to the accumulation of iron within cells and mitochondria [50]. The phenomenon of iron overload, whether of genetic origin or acquired through external factors, provides a basis for a renewed investigation into the pathophysiological mechanisms underlying iron-related disorders.

Iron overload disrupts mitochondrial metabolism and increases oxidative stress

In instances of iron overload, surplus intracellular iron may be transferred to the mitochondria [11]. Mitoferrin (Mfrn), which includes Mfrn1 and Mfrn2, plays a crucial role in facilitating the transport of iron across the inner mitochondrial membrane [51, 52]. Mfrn1, a protein with a molecular weight of 38 kDa, is predominantly expressed in erythroid cells, while its expression in other tissues is minimal. In contrast, Mfrn2, a 39 kDa protein, is primarily located in non-erythroid tissues [53–55]. Cytoplasmic iron can enter the mitochondria from the cytoplasm through Mfrn2 and the mitochondrial calcium uniporter (MCU) [56]. Mitochondria require a continuous supply of iron to support the synthesis of heme and Fe-S cluster synthesis, thereby preventing the initiation of the Fenton reaction and the subsequent generation of ROS. The capacity for iron transport into the mitochondria is augmented in states of iron overload. However, the normal utilization and release of iron are constrained, resulting in elevated production of ROS and a decrease in the biosynthesis of heme and Fe-S clusters during conditions of iron overload [57].

The electron transport chain (ETC) is integral to aerobic respiration in eukaryotic cells, located within the inner mitochondrial membrane (IMM). It consists of a series of protein complexes (I, II, III, IV) and electron carriers that facilitate the oxidation of electrons derived from nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) through a series of biochemical reactions, ultimately reducing molecular oxygen (O_2). The energy released during this process is harnessed to transport protons across the IMM, generating a proton motive force that drives oxidative phosphorylation (OXPHOS), culminating in ATP production by ATP synthase [58, 59]. Elevated levels of ROS can be induced by excessive free iron or LIP through the Haber-Weiss and Fenton reactions, with ROS originating from various sources, including xanthine oxidase, NADPH oxidase, and mitochondria [60–62]. Mitochondria function not only as sites of significant redox activity but also as key contributors to the generation of ROS in response to iron [41]. The incomplete reduction of O_2 during respiration within the ETC can trigger the production of ROS, a process that is catalyzed by iron ions. Specifically, the combination of hydrogen peroxide and superoxide results in the formation of hydroxyl radicals [63]. And mtROS are primarily produced at complex I or complex III of the ETC [64]. The mitochondrial respiratory chain is closely linked to intracellular iron, particularly intramitochondrial iron [65]. An excess of iron can disrupt the function of proteins within the mitochondrial respiratory chain, thereby impairing electron transport and proton pumping. The accumulation of intracellular iron may lead to reduced activity of respiratory enzymes, resulting in incomplete reduction of O_2 and an increase in free radical production. The lipid components of mitochondrial membranes are abundant in polyunsaturated fatty acids, and free radicals may interact with these lipids, causing peroxidative damage. The absence of cardiolipins and other essential lipid constituents of the mitochondrial membrane may hinder the assembly and functionality of the respiratory chain. As a result, oxidative inactivation of enzymes involved in the mitochondrial respiratory chain can create a detrimental feedback loop [41].

Iron overload exacerbates oxidative stress and lipid peroxidation by adversely affecting mitochondrial function and structural integrity, ultimately resulting in tissue damage. The mitochondrial dysfunction induced by iron overload in cardiac tissue is a significant contributor to IOC [17]. Mitochondrial dysfunction is a prevalent risk factor for various cardiovascular diseases, with the heart being particularly susceptible due to its high oxygen consumption and limited antioxidant capacity, necessitating a substantial number of mitochondria. Damage to mitochondria resulting from iron overload leads to a reduction in ATP synthesis, which may impair cardiac contractility [66, 67]. Additionally, iron overload has been shown to increase mitochondrial iron accumulation and the production of mtROS, contributing to insulin resistance in H9c2 cardiomyoblast cells [68]. MitoNEET is a protein that effectively mitigates mitochondrial iron accumulation in the presence of excess extracellular or intracellular iron [69]. Overexpression of MitoNEET in cardiomyoblast cells or the application of the mitochondrial antioxidant Skq1 can alleviate insulin resistance induced by ferric ammonium sulfate [68]. Furthermore, iron overload exacerbates atherosclerosis and vascular aging by increasing NTBI, which leads to excessive mtROS production [34, 61]. The specific knockout

of the endothelial cell iron transporter Mfrn2 in ApoE-/- mice has been shown to reduce the formation of atherosclerotic lesions and levels of intercellular adhesion molecule-1 (ICAM-1) in the aorta, indicating that Mfrn2 deficiency alleviates endothelial dysfunction by lowering mitochondrial iron levels and reducing mitochondrial dysfunction [55]. NTBI can damage liver and kidney function through oxidative stress and mitochondrial dysfunction [70, 71]. Iron overload generates excessive hydroxyl radicals and induces oxidative stress, leading to structural and functional abnormalities in mitochondria, which may be a key factor in the dysfunction of various lung cells and further contribute to the progression of pulmonary fibrosis [47, 72].

Heightened oxidative stress resulting from an excess of iron is a significant contributor to cellular damage. The primary strategy for managing iron overload involves iron chelation therapy, which employs agents such as Desferrioxamine, Deferiprone (DFP), and Deferasirox to facilitate the removal of excess free iron from the body. These chelating agents function by forming complexes with iron; however, they exhibit limitations in terms of oral bioavailability and plasma half-life, and they are unable to completely prevent iron-mediated oxidative stress [73]. Current research is investigating the potential benefits of combining iron chelators with other pharmacological interventions to enhance treatment efficacy. A limitation of the DFP is its lack of specificity for mitochondria. The application of antioxidants, particularly those that target mitochondria, can alleviate the harmful effects of excessive iron accumulation across various cell types and tissues. For example, MitoTEMPO, a mitochondria-specific antioxidant, exhibits greater efficacy in mitigating iron-induced mitochondrial dysfunction compared to the general antioxidant N-acetyl cysteine (NAC) [74]. The use of mitochondria-targeted tri-catechol-based iron chelators, in combination with mitochondria-homing Szeto-Schiller (SS) peptides, enables the precise delivery of iron-selective chelating agents to mitochondria. This strategy provides a means to protect cells by chelating excess mitochondrial iron in conditions of iron overload [75].

Oxidative stress worsens mitochondrial damage

The elevated production of ROS has been shown to induce depolarization of the mitochondrial membrane potential (ΔΨm) and the subsequent opening of the mitochondrial permeability transition pore (mPTP) [76, 77]. This process may facilitate the release of various mitochondrial components and their metabolic byproducts, which possess immunogenic characteristics, such as mitochondrial DNA (mtDNA) and cytochrome C, into the cytoplasm. Consequently, this release can initiate an immune response characterized by the presence of damage-associated molecular patterns (DAMPs) [78–81]. Notably, mtDNA is situated near the inner mitochondrial membrane, a critical site for ROS generation; thus, iron overload may result in damage to mtDNA and its release [71, 82–84]. Damage and mutations in mtDNA have been associated with diseases related to iron overload, such as FA [85]. In addition to the direct damage caused by oxidative stress, elevated iron levels have been shown to disrupt the synthesis and function of respiratory subunits by affecting mtDNA [86]. Furthermore, excessive iron can induce apoptosis in liver and kidney cells by causing mtDNA damage [71].

The phenomenon known as ROS-induced ROS release (RIRR) describes a mechanism whereby iron overload triggers a surge of ROS in the liver [87]. The mPTP is a multi-protein complex that, when persistently open, causes mitochondrial swelling, potentially leading to rupture of the mitochondrial outer membrane. When iron overload results in an increase in ROS that reaches a threshold sufficient to trigger mPTP opening, this, in turn, causes a simultaneous collapse of the ΔΨm and a transient increase in ROS production within the ETC. The release of ROS into the cytosol may serve as a second messenger, activating RIRR in adjacent mitochondria. Consequently, mitochondrial-to-mitochondrial RIRR constitutes a positive feedback mechanism that enhances ROS production, potentially resulting in severe mitochondrial and cellular damage (Fig. 1) [87, 88]. A recent finding indicated that acute iron overload induces mtROS and depolarization of ΔΨm, leading to mPTP opening and promoting calcium waves and arrhythmias, thereby positioning mPTP as a target for mitigating the arrhythmic effects of iron overload [89]. Iron homeostasis is crucial for maintaining normal lung function [47].

Iron overload-induced programmed cell death

The academic community has consistently recognized the mechanisms related to increased mitochondrial oxidative stress and impaired energy metabolism in the context of iron overload. As research has progressed, the association between mitochondrial dysfunction and programmed cell death (PCD) in conditions of iron excess has become more clearly defined. Importantly, processes such as autophagy and ferroptosis have emerged as critical areas of focus in current research (Fig. 1).

Apoptosis

Apoptosis involves intricate intrinsic and extrinsic signaling pathways [90]. The intrinsic pathway, which is reliant on mitochondrial function, is initiated by various intracellular stimuli, including DNA damage, deprivation of growth factors, and oxidative stress. The primary regulatory components of intrinsic apoptosis are the B-cell lymphoma-2 (BCL-2) protein family, which encompasses

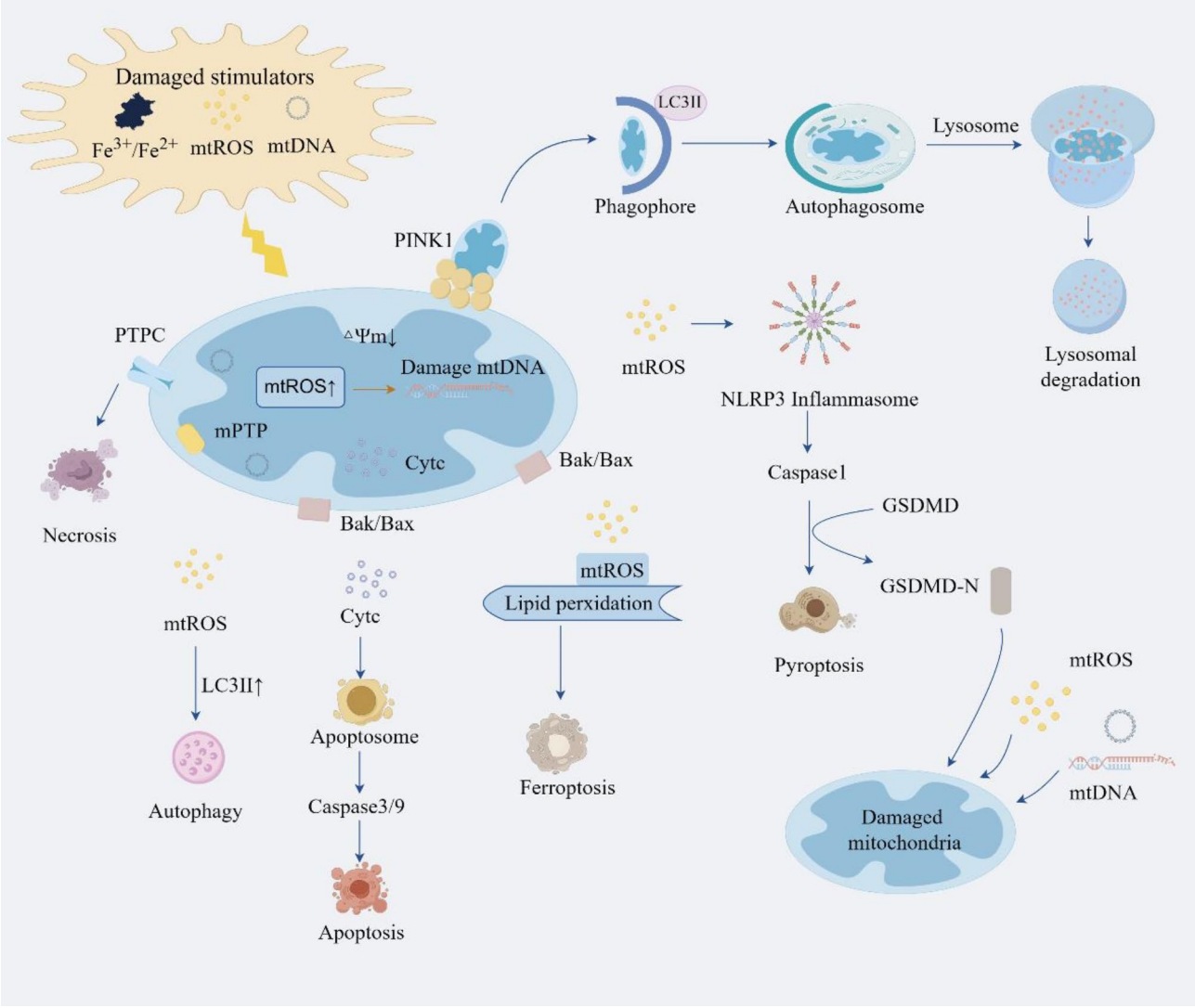

Fig. 1 The pathways of damage that occur following mitochondrial damage and the introduction of mitochondrial reactive oxygen species into the cytoplasm. **Abbreviations**: PTPC, permeability transition pore complex; PINK1, PTEN-induced putative kinase 1; mPTP, mitochondrial permeability transition pore; GSDMD, gasdermin D; GSDMD-N, GSDMD N-terminal; mtROS, mitochondrial reactive oxygen species; mtDNA, mitochondrial DNA; ΔΨm, mitochondrial membrane potential; Cytc, Cytochrome c; BAX, B-cell leukemia/lymphoma 2 (BCL2)-associated X; BAK, BCL2 antagonist/killer

both pro-apoptotic and anti-apoptotic proteins. The activation of intrinsic apoptosis leads to the release of cytochrome c, which subsequently activates caspase-9 and caspase-3 [91–93]. Conversely, the extrinsic pathway of apoptosis is initiated by the binding of death ligands to death receptors, which activates downstream effector caspase-8, ultimately resulting in the activation of caspase-3, -6, and −7, thereby inducing direct cell death [94]. Cytochrome c plays a central role in the process of mitochondria-dependent apoptosis [90, 91]. Furthermore, mitochondria are essential for maintaining intracellular calcium ion (Ca^{2+}) homeostasis by regulating calcium channels and sodium-calcium exchangers located on the membrane, as well as by interacting with organelles such as the endoplasmic reticulum [95]. Variations in Ca^{2+} concentration can significantly affect mitochondrial function, and an imbalance in Ca^{2+} may initiate apoptosis [96]. Additionally, iron overload can impair mitochondrial dynamics, leading to abnormal morphology and functionality, thereby increasing cellular susceptibility to apoptosis and ferroptosis signals.

In instances of iron overload, a significant correlation exists between apoptosis and mitochondrial function. Research utilizing a mouse model of chronic iron overload has demonstrated that excess iron acts as a ROS stimulant, thereby exacerbating mitochondrial damage [97]. Elevated levels of iron within mitochondria can lead to membrane depolarization, which facilitates the release of cytochrome c. This release subsequently activates the caspase cascade pathway, culminating in apoptosis [97].

An increasing body of clinical evidence indicates that iron overload is a significant factor contributing to the death of bone marrow cells in patients with hematologic diseases [98, 99]. Bone marrow mesenchymal stromal cells (BMMSCs) are essential for maintaining bone marrow homeostasis and providing hematopoietic support [100]. Studies employing mouse models indicate that iron overload induces ROS production in both mitochondria and the cytoplasm, resulting in apoptosis of BMMSCs and osteoblasts [101, 102]. In the investigation of iron overload-induced bone marrow cell death, the levels of ROS and the initiation of apoptosis are primarily linked to the mitogen-activated protein kinase (MAPK) pathway [98]. Additionally, iron overload induces endoplasmic reticulum stress in MC3T3-E1 osteoblasts by elevating ROS levels and disrupting calcium homeostasis, which leads to mitochondrial fission and subsequent apoptosis due to excessive calcium accumulation in mitochondria [103]. In conclusion, mitochondria are pivotal in mediating apoptosis induced by iron overload through various mechanisms.

Ferroptosis

Ferroptosis is a type of PCD by the production of ROS and lipid peroxidation [104] Mitochondria function as both initiators and amplifiers of ferroptosis. The process of iron-dependent phospholipid peroxidation is modulated by various cellular metabolic pathways, with iron and mitochondrial metabolism playing pivotal roles in the regulatory network associated with ferroptosis. When mitochondrial structure is compromised and function is impaired, these organelles can disrupt energy metabolism and the balance between excitatory and inhibitory signals.

The susceptibility to ferroptosis is influenced by cell type and is contingent upon the antioxidant capacity present within cells [98, 105]. Prior research has indicated that ferroptosis inhibitors can confer protection against myocardial disease in SCD mouse models [106]. The pathophysiology of doxorubicin and ischemia/reperfusion-induced myocardial injury in mice may be primarily associated with increased mitochondrial iron levels and lipid peroxidation, suggesting that mitochondrial oxidative damage is a principal mechanism underlying ferroptosis in this context [107]. The uptake of mitochondrial iron can be mediated by the MCU, which plays a critical role in mitochondrial calcium absorption [108]. Studies investigating the regulation of ion channels relevant to mitochondrial iron transport and cardiac dysfunction due to iron overload have demonstrated that the MCU facilitates the transport of Fe2+into the mitochondria, while Mfrn2 may serve a regulatory function in this process [11]. In models of acute iron overload, ferroptosis induced by lipocalin-2 exhibits characteristics that diverge from classical ferroptosis. Specifically, this includes the generation of mtROS, alterations in mitochondrial morphology and function, increased calcium ion uptake, and the regulation of specific genes, all of which collectively contribute to ferroptosis. Notably, lipocalin-2-induced ferroptosis in the liver initiates the production of mtROS and enhances mitochondrial calcium absorption, culminating in ferroptosis [109].

Current research regarding the impact of ferroptosis on diseases associated with iron overload is still relatively limited. The insights derived from these investigations could enhance the development of novel therapeutic strategies for conditions related to iron overload by improving our understanding of the mechanisms underlying both classical and non-classical ferroptosis induced by excess iron. Ferroptosis can be inhibited by various agents, including iron chelators, antioxidants, Trolox, MitoTEMPO (which specifically targets mitochondria), and Ferrostatin-1 (a lipophilic scavenger of free radicals) [11, 110, 111]. Additionally, natural antioxidants such as chebulagic and chebulinic acids have been shown to prevent ferroptosis without causing harm [112]. It is crucial to acknowledge that the use of antioxidants, such as vitamins C and E, for disease prevention may, in some instances, increase the risk of mortality [113, 114].

Autophagy

Autophagy exhibits dual roles in conditions characterized by iron overload. Within cellular contexts, autophagy can function as a protective compensatory mechanism in response to elevated iron levels, thereby mitigating cell death associated with oxidative stress and other detrimental factors [115]. Recent studies have demonstrated that mtROS can induce autophagy [116, 117]. Specifically, ROS generated due to iron overload are pivotal in triggering mitochondria-dependent apoptosis. In an iron overload model in L6 skeletal muscle cells, these cells respond to the perturbation by attempting to activate autophagy to maintain optimal homeostasis and functionality. Defects in autophagy, such as those observed in Atg5K130R/Atg7 knockout cells, iron overload-induced ROS and apoptosis. Although elevated iron levels may initially enhance autophagic activity, they ultimately disrupt the autophagy, thereby compromising the self-protective capabilities of autophagy [118]. For another, Zhou et al. et al. found that under iron overload conditions, increases expression and GFP-LC3-positive autophagosomes in bone marrow cells, leading significantly reducing viability. They discovered that that iron overload-induced damage to bone marrow is exacerbated by the inhibition of Sirtuin 3 (SIRT3) activity and expression. This inhibition leads to an increase in the acetylation of superoxide dismutase 2, which subsequently regulates the accumulation of mtROS and promotes

autophagy [99]. Curcumin, a natural yellow pigment derived from the rhizomes of Curcuma longa, exhibits anti-inflammatory, antioxidant, and iron-chelating properties [119]. It has been shown to protect bone marrow by reversing the mtROS-dependent autophagy pathway [99]. In conclusion, under conditions of iron overload, the interplay between autophagy and mitochondria creates a complex regulatory network. Further investigation is necessary to enhance our understanding of the role of autophagy in the progression of iron overload-related damage and to develop innovative therapeutic strategies that target autophagic pathways.

It is noteworthy that sublethal permeabilization of the mitochondrial outer membrane induces mitophagy, which serves to limit the release of mtDNA and ROS by facilitating the degradation of dysfunctional mitochondria via lysosomal pathways. This process subsequently inhibits pattern recognition receptor (PRR) signaling and mitigates inflammatory responses [120, 121]. Furthermore, Parkin-dependent mitophagy can produce mitochondrial-derived vesicles from mitochondrial DAMPs (mtDAMPs), thereby suppressing inflammation in neighboring cells [122]. Nevertheless, insufficient autophagy or systemic abnormalities may result in pathological inflammation as a consequence of mitochondrial dysfunction [123].

In summary, mtROS serve as primary DAMPs that activate inflammasomes in the context of iron overload conditions. They play a pivotal role in a complex pathway that intersects with the molecular mechanisms governing PCD at various junctures. The excessive generation of mtROS resulting from iron overload can initiate diverse forms of cellular demise, each characterized by intricate and distinct PCD processes. Although multiple cell death pathways, including apoptosis, autophagy, and ferroptosis, have been investigated, the majority of studies have focused on individual mechanisms. Given that mtROS can induce varying degrees and types of PCD under different stress scenarios, future research should prioritize the exploration of the interplay and modulation of these cell death pathways in the context of mitochondrial oxidative stress.

The impact of iron overload on mitochondrial dynamics

Mitochondria are dynamic organelles within cells, characterized by processes of fusion and fission. The equilibrium between these processes is crucial for shaping the mitochondrial network and influencing its functionality [124]. These dynamics are meticulously regulated by specific proteins. Mitochondrial fusion is mediated by Mfn1, Mfn2, and optic atrophy 1 (OPA1), whereas mitochondrial fission is governed by dynamin-related protein 1 (Drp1) and fission 1 (Fis1) [125]. An imbalance in mitochondrial dynamics has been observed in conditions of iron overload [126]. Mitochondrial fragmentation is essential for generation of ROS and inducing cell death [127, 128]. Khamseekaew et al. demonstrated that during ischemia-reperfusion injury, the ratio of Drp-1/Mfn-2 in the hearts of both wild-type and β-thalassemia mice was significantly elevated [126]. The precise regulation of Drp1 is vital for cellular health, as excessive activation of Drp1 under pathological conditions triggers mitochondrial fission and the release of cytochrome c, ultimately leading to apoptosis [129]. Numerous studies have indicated that in scenarios of iron overload, there is an increase in mitochondrial stress, which results in mitochondrial fragmentation and a disruption of the fission and fusion [68, 130]. This cascade of events subsequently elevates ROS levels within the mitochondria and the intracellular environment, contributing to the onset of ferroptosis [131, 132]. Therefore, strategies aimed at inhibiting or promoting mitochondrial fission may represent potential therapeutic approaches to mitigate IOC. Certain NTBI species are taken up by tissues through TTCC and LTCC, which may lead to increased intracellular calcium levels in instances of iron overload [133]. Iron-induced Ca^{2+} signals control mitochondrial dynamics via the Ca^{2+}/calmodulin and Ca^{2+}/calpain pathways, resulting in the dephosphorylation of Drp1(Ser637), which leads to mitochondrial fragmentation and neuronal death in iron-related neurodegenerative diseases. This underscores the potential significance of Ca^{2+}-mediated calcineurin signaling in the regulation of mitochondrial dynamics during neuronal damage induced by iron overload [134].

In recent decades, calcium channel blockers and modulators of mitochondrial dynamics, such as mitochondrial division inhibitor 1 (Mdivi-1) and the mitochondrial fusion promoter M1, have demonstrated cardioprotective and neuroprotective properties in various experimental models [129, 135, 136]. Recently, Mdivi-1 has shown potential roles that extend beyond its function in mediating mitochondrial fission; it has been found to reversibly inhibit complex I and mitigate ROS production associated with reverse electron transport (RET). Furthermore, Mdivi-1 has been observed to reduce neuronal damage by decreasing oxidative stress and depolarizing mitochondrial membranes through a mechanism that is independent of Drp1 [129]. However, further investigation is required to validate the efficacy and safety of these approaches for future clinical applications.

Therapeutic

Mitochondrial transplantation

Mitochondrial transplantation represents a novel therapeutic strategy that involves the transfer of healthy mitochondria into damaged recipient cells with the aim of restoring tissue function [137]. Preclinical studies have

indicated the potential efficacy of this approach across a range of diseases, including ischemia-reperfusion injury, neurodegenerative disorders, kidney diseases, acute respiratory distress syndrome, and cancer [124, 138–143]. This technique has the capacity to restore dysfunctional mitochondria by introducing healthy counterparts, thereby improving cellular energy metabolism and overall cellular function. Consequently, it is posited that mitochondrial transplantation may provide therapeutic advantages in mitigating tissue mitochondrial damage resulting from iron overload.

Pharmacology

Iron overload induces mitochondrial dysfunction in recipient cells, leading to tissue injury. This process can be addressed through the development of targeted pharmacological interventions that modulate mitochondrial function. Currently, the primary strategies for mitochondrial intervention include inhibiting the entry of iron into mitochondria, regulating mitochondrial redox status, enhancing mitochondrial biogenesis, and managing mitochondrial dynamics.

As of the present time, specialized therapies aimed at mitochondrial targets have yet to receive approval for clinical use. Consequently, treatment strategies remain primarily within the preclinical and clinical trial phases [137]. The therapeutic category most frequently referenced in the domain of mitochondrial medicine is mitochondrial-targeted complexes, particularly antioxidants, which are designed to mitigate the pathological accumulation of mtROS and to preserve mitochondrial function [144, 145]. Antioxidants based on quinone, including coenzyme Q10 (CoQ) analogs such as idebenone and EPI-743, act as mitochondria-targeted antioxidants and show promising prospects in preclinical studies; as well as vitamin E derivatives, such as the water-soluble sonlicromanol, are employed to address mitochondrial oxidative damage [146–148]. Efforts to inhibit the permeabilization of the mitochondrial inner or outer membrane may reduce the release of ROS and occurrences of PCD [92, 123, 149]. For instance, compounds like cyclosporin A (CsA) act as inhibitors of the mPTP by obstructing the peptidyl-prolyl cis/trans isomerase active site of Cyclophilin D [150]. Additionally, Furthermore, a specific inhibitor of BCL-2 has been approved for clinical use, functioning by directly modulating the mitochondrial outer membrane permeabilization (MOMP) molecular pathway [151, 152]. Lipophilic cations present a viable solution to the challenge of mitochondrial targeting in drug delivery. These molecules exhibit low transmembrane activation energy, allowing them to penetrate the phospholipid bilayer and accumulate within mitochondria without necessitating an uptake mechanism [153, 154]. Examples of lipophilic cations include MitoQ and SKQ1, which effectively target mitochondria by autonomously entering the phospholipid bilayer [155, 156]. The SS peptide family comprises oligopeptides that specifically target mitochondria, thereby safeguarding their function by stabilizing the inner mitochondrial membrane and inhibiting the formation of mtROS [157]. Triphenylphosphonium (TPP+) is another lipophilic cation utilized in the development of numerous mitochondria-targeted drugs, such as mitoQuinone and mitoTEMPO [158, 159]. Several compounds have been identified for their ability to selectively target the complex I site in mitochondria, thereby inhibiting the generation of ROS and retarding the production of RET without disrupting normal OXPHOS processes [160–162]. The field of mitochondrial-targeted therapy is continuously advancing, with ongoing research dedicated to the exploration of new compounds, peptides, and nanoparticles that exhibit improved specificity for mitochondria [153, 163–165]. This pursuit aims to develop more efficient and precise intervention approaches.

Mitochondrial biogenesis is a critical cellular process that facilitates the generation of new mitochondria, which is essential for preserving tissue homeostasis. The peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α) is a key regulatory factor in this biological mechanism [166]. Various pharmaceutical agents that promote mitochondrial biogenesis target specific regulatory pathways to enhance mitochondrial production, presenting potential therapeutic avenues for conditions associated with mitochondrial dysfunction [167, 168]. AMP-activated protein kinase (AMPK) activators have been shown to increase the transcriptional activity of PGC-1α, thereby facilitating mitochondrial biogenesis. For instance, PXL770 has been shown to restore mtDNA copy number and PGC-1α mRNA expression in a mouse model of autosomal dominant polycystic kidney disease (ADPKD) [169]. Resveratrol, a sirtuin-activating compound, enhances the activity of the SIRT1-PGC-1α axis and promotes muscle remodeling in mice with Duchenne muscular dystrophy [170]. Peroxisome proliferator-activated receptor (PPAR) agonists are critical for mitochondrial biogenesis. For example, Bezafibrate activates PPARs and enhances the transcription of genes associated with mitochondrial biogenesis [171]. Pioglitazone, a PPAR-γ agonist, has been shown to positively influence mitochondrial biogenesis in individuals with diabetes and exhibits neuroprotective effects in mouse models of Alzheimer's disease [172]. Additionally, metformin enhances mitochondrial biogenesis by activating AMPK, which increases PGC-1α expression and activation. Nicotinamide mononucleotide (NMN), an NAD+supplement, also activates PGC-1α [173, 174]. Mdivi-1 and other pharmacological agents target the balance of mitochondrial dynamics. A synergistic effect has

been reported in Alzheimer's disease cell models with the combined treatment of SS-31 and Mdivi-1 [175]. The Drp1 antagonist peptide has demonstrated therapeutic effects in an in vitro model of Parkinson's disease [176].

Diet and exercise

In addition to pharmacological interventions, individuals requiring prolonged RBC transfusions may improve mitochondrial dysfunction through lifestyle modifications. Research has demonstrated that physical activity and athletic training can enhance mitochondrial function [177, 178]. It is essential to select appropriate exercises tailored to individual tolerance levels under medical supervision, as this can contribute to the overall well-being of patients. Furthermore, dietary adjustments, such as the adoption of a Mediterranean diet rich in antioxidants, omega-3 fatty acids, and polyphenols, may have a positive impact on mitochondrial health [179, 180]. Nutritional supplements, including carnitine, CoQ, creatine, and vitamin B2, also provide potential benefits [181–186]. Modifying dietary composition, as exemplified by the ketogenic diet (KD), which emphasizes high fat and low carbohydrate intake, may simulate a fasting state by stimulating ketone production. The KD has been shown to elicit antioxidant and anti-inflammatory responses in cells, thereby alleviating mitochondrial stress [187–189].

The lifestyle modifications discussed herein include a variety of intervention strategies designed to improve health and reduce tissue damage linked to mitochondrial dysfunction by enhancing mitochondrial function. However, additional randomized controlled trials are required to confirm their efficacy and safety. Furthermore, it is essential to consider the potential side effects associated with long-term dietary and pharmacological interventions, while also accounting for individual differences when implementing these changes under the guidance of healthcare professionals.

Conclusions and future directions

Mitochondria not only represent a therapeutic target for tissue damage induced by iron overload but also play a pivotal role in modulating the physiological response to such overload. The established mechanisms provide substantial insights into the pathogenesis of diseases related to iron overload, while the recent mechanisms introduce innovative avenues for exploring potential therapeutic targets. Through complex mechanisms involving oxidative stress, mitochondrial dynamics, and their effects on PCD, mitochondria have emerged as key regulators in the context of iron overload-related damage. Despite the limited research available on the interplay between mitochondria and iron overload, their critical function in maintaining iron homeostasis and managing associated damage underscores their importance in the pathological processes of both congenital and acquired iron overload. Further research is essential to clarify the specific roles of mitochondria in the adverse reactions elicited by iron overload and to uncover the underlying mechanisms involved. Moreover, mitochondrial transplantation represents a novel strategy for addressing tissue damage resulting from iron overload. Therapeutic approaches such as antioxidant therapy, mitochondrial-targeted compounds, and lifestyle modifications present promising opportunities to mitigate mitochondrial dysfunction and alleviate the side effects associated with iron overload. The complex nature of clinical monitoring for adverse reactions, combined with the multifaceted characteristics and elusive phenotypic thresholds of mitochondrial dysfunction, complicates our understanding of its role in various diseases. As the field of mitochondrial medicine progresses, the translation of research findings into clinical practice will require interdisciplinary collaboration to bridge the gap between molecular insights and therapeutic innovations. This collaboration is crucial for improving the prognosis and survival rates of patients facing complications related to iron overload from diverse etiological sources.

Abbreviations

MDS	Myelodysplastic syndromes
SCD	Sickle cell disease
IOC	Iron overload cardiomyopathy
NTBI	Non-transferrin-bound iron
LPI	Labile plasma iron
DMT1	Divalent metal transporter 1
ZIP14	ZRT/IRT-like protein 14
LCN-2	Lipocalin-2
TTCC	T-type calcium channels
LTCC	L-type calcium channels
LCI	Labile cellular iron
LIP	Labile iron pool
Fe–S clusters	Iron-sulfur clusters
DFP	Deferiprone
ETC	Electron transport chain
IMM	Inner mitochondrial membrane
OXPHOS	Oxidative phosphorylation
ROS	Reactive oxygen species
Mfrn	Mitoferrin
MCU	Mitochondrial calcium uniporter
RIRR	ROS-induced ROS release
mPTP	Mitochondrial permeability transition pore
ΔΨm	Mitochondrial membrane potential
mtDNA	Mitochondrial DNA
BCL-2	B-cell lymphoma-2
SS	Szeto-Schiller
PCD	Programmed cell death
BMMSCs	Bone marrow mesenchymal stromal cells
MAPK	Mitogen-activated protein kinase
MOMP	Mitochondrial outer membrane permeabilization
DAMPs	Damage-associated molecular patterns
OPA1	Optic atrophy 1
Drp1	Dynamin related protein 1
Fis1	Fission 1
RET	Reverse electron transport
CoQ	Coenzyme Q10
TPP+	Triphenylphosphonium

PGC-1α	Peroxisome proliferator-activated receptor-gamma coactivator-1alpha
KD	Ketogenic diet
PPAR	Peroxisome proliferators-activated receptor
SIRT	Sirutin

Supplementary Information

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Supplementary Material 1

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Author contributions
Yangyang Zhao wrote the manuscript. Xiaoxue Liang and Mengjiao Yang collected the related literature and edited. Yangyang Zhao, Mengjiao Yang, Xiaoxue Liang participated in the design of the review and revised the manuscript. All authors have read and approved the final manuscript.

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Declarations

Consent for publication
Not applicable.

Conflict of interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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