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Iron metabolism and ferroptosis in health and diseases: the crucial role of mitochondria in meta-bolically active tissues

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PII: S0955-2863(25)00051-8
DOI: https://doi.org/10.1016/j.jnutbio.2025.109888
Reference: JNB 109888

To appear in: *The Journal of Nutritional Biochemistry*

Received date: 17 May 2024
Revised date: 15 November 2024
Accepted date: 27 February 2025

Please cite this article as: Angela Catapano , Fabiano Cimmino , Lidia Petrella , Amelia Pizzella , Margherita D'Angelo , Katia Ambrosio , Francesca Marino , Annarita Sabbatini , Massimiliano Petrelli , Barbara Paolini , Lucio Lucchin , Gina Cavaliere , Luigia Cristino , Marianna Crispino , Giovanna Trinchese , Maria Pina Mollica , Iron metabolism and ferroptosis in health and diseases: the crucial role of mitochondria in meta-bolically active tissues, *The Journal of Nutritional Biochemistry* (2025), doi: https://doi.org/10.1016/j.jnutbio.2025.109888

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Highlights:

- Iron homeostasis is tightly regulated in the cell
- Ferroptosis is iron-dependent non-apoptotic regulated cell death
- Mitochondria play a crucial role in iron metabolism and ferroptosis
- Ferroptosis is involved in the pathophysiology of metabolic disorders

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Iron metabolism and ferroptosis in health and diseases: the crucial role of mitochondria in meta-bolically active tissues

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Running title: Ferroptosis and mitochondria

Funding: Project funded under the National Recovery and Resilience Plan (NRRP), Mission 4
Component 2 Investment 1.3 - Call for proposals No. 341 of 15 March 2022 of Italian Ministry of University and Research funded by the European Union – NextGenerationEU; Award Number: Project code PE00000003, Concession Decree No. 1550 of 11 October 2022 adopted by the Italian Ministry of University and Research, CUP D93C22000890001, Project title: "ON Foods - Research and innovation network on food and nutrition Sustainability, Safety and Security – Working ON Foods"; PRIN 2022 PNRR, European Union-Next Generation EU (project n. P20225W97A).

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Abstract

Iron is essential in various physiological processes, but its accumulation leads to oxidative stress and cell damage, thus iron homeostasis has to be tightly regulated. Ferroptosis is an iron-dependent non-apoptotic regulated cell death characterized by iron overload and ROS accumulation. Mitochondria are organelles playing a crucial role in iron metabolism and involved in ferroptosis. MitoNEET, a protein of mitochondrial outer membrane, is a key element in this process. Ferroptosis, altering iron levels in several metabolically active organs, is linked to several non-communicable diseases. For example, iron overload in the liver leads to hepatic fibrosis and cirrhosis, accelerating NAFLD progression, in the muscle cells contributes to oxidative damage leading to sarcopenia, and in the brain is associated to neurodegeneration. The aim of this review is to investigate the intricate balance of iron regulation focusing on the role of mitochondria and oxidative stress, and analyzing the ferroptosis implications in health and disease.

Keywords: Iron; Ferroptosis; Mitochondria; MitoNEET; Obesity

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1. Iron metabolism

Iron is an oligoelement essential for life, being part of a broad spectrum of metabolic processes. Nonetheless, it may also produce detrimental effects **[1]**. Iron has two stable oxidation states, ferrous iron (Fe^{2+}) and ferric iron (Fe^{3+}). Its oxidoreductive properties and its propensity to exchange electrons, make this element essential for life, and a key factor for the functioning of numerous proteins **[2]**. Indeed, iron is acting as a metal cofactor for many enzymes, for hemoproteins or non- heme iron-containing proteins **[3]**. Hemoproteins are implicated in a variety of biological functions, including oxygen binding (hemoglobins), oxygen metabolism (oxidases, peroxidases, catalases, etc.), and electrons transfer (cytochromes). Nonheme iron-containing proteins catalyze reactions related to energy metabolism (mitochondrial aconitase and [Fe-S] proteins of the electron transport chain), and DNA synthesis **[3]** (Table 1). Furthermore, iron-containing proteins are required for the metabolism of collagen, tyrosine, and catecholamines **[3]**. However, the same chemical properties that make iron crucial for biological functions can be harmful for living organisms. Iron, if is not adequately chelated, through the Fenton reaction($Fe^{++} + H_2O_2 = Fe^{+++} + OH° + OH^-$), produces superoxide anion and hydroxyl radical reacting with biological molecules, including proteins, lipids and DNA, thus inducing peroxidative damage to vital cell structures **[4,5]**. Therefore, organisms are facing one of the paradoxes of life, that is to maintain level of "free iron" (including both ferrous and ferric iron) low enough to be protected from oxidative stress, but high enough to allow the synthesis of hemoproteins and other iron-containing molecules. This delicate balance is maintained by several specialized molecules and mechanisms that control iron homeostasis modulating cellular iron uptake, transfer and storage. In particular, systemic iron homeostasis is maintained by: i) regulation of intestinal iron absorption; ii) recycling of heme iron from senescent erythrocytes; iii) mobilization of body reserves **[6,7]**.

Non-heme iron enzymes	**Function**
Succinate dehydrogenase	Krebs cycle
Aconitasis	Krebs cycle
Ribonucleotide reductase	Reduction of NTPs into dNTPs for DNA synthesis
Xanthine dehydrogenase	Purine catabolism
Adrenodoxin	Synthesis of steroid hormones
Δ9 - desaturases	Synthesis of unsaturated fatty acids
NADH dehydrogenase	Respiratory chain
CoenzymeQ reductase	Respiratory chain
Lipoxygenase	Synthesis of leukotrienes and eicosanoids

Table 1. Non-Heme Iron Enzymes. Non-heme iron-containing proteins catalyze reactions related to energy metabolism and DNA synthesis.

1.1 Iron bioavailability

Although iron is one of the most abundant elements on Earth, it is poorly bioavailable since its soluble form Fe^{2+}, primarily used in biological processes, is rapidly oxidized to Fe^{3+} in aerobic environments. However, the insoluble Fe^{3+} at neutral pH can be efficiently dissolved at acidic pH. Thus, organisms have evolved two mechanisms to manage iron, i.e. the acidification of environment and the reduction of Fe^{3+} to Fe^{2+}.

In physiological conditions, iron content in adult human organisms is ~ 4–5 g, with up to 80% of each in erythrocyte hemoglobin, and the remaining ~ 20% stored within liver, spleen and bone marrow. The cellular iron is stored into the protein ferritin, able to bind and release iron in a controlled manner. About 5% of the iron is present in the myoglobin in muscle cells, while less than 1% is in heme-containing proteins (e.g., cytochromes), iron–sulfur cluster (ISC)-containing proteins (e.g., succinate dehydrogenase) and non-heme/non-ISC iron-containing proteins (e.g., iron- and 2-oxoglutarate-dependent dioxygenases) [8] (Table 2).

The physiological daily iron requirement of an adult is about 1 mg for males and about 2 mg for females, balancing the daily iron loss through feaces and exfoliation of enterocytes and skin cells [6], as well as menstruation and childbirth for women of reproductive age. Iron loss processes lack homeostatic control and are independent from the iron status of the body. Thus, the regulation of intestinal iron absorption is the primary mechanism for iron homeostasis [9].

Iron distribution in human body				
		Weight (mg)	**%**	**Location**
Heme iron	Hemoglobin	200-2500	75-80	Erythrocytes
	Myoglobin	150-200	3-5	Myocytes
	Hemic enzymes	8-15	0-3	Enzymes
Non-heme iron	Non-hemic enzymes			
	Transferrin	3-4	0,1	Plasma
	Reserve iron (ferritin, hemosiderin)	300-1200	15-20	Liver, spleen, bone marrow
	Total	3000-4000		

Modified from Hercberg et al., 1988 [10]

Table 2. Iron distribution in human body.

1.2 Iron absorption

Iron in the food is present as: i) inorganic nonheme iron that is mostly Fe^{3+}; ii) organic heme iron, from animal origin, and ferritin iron from animal and plant origin. In alkaline and neutral condition iron is mainly present in Fe^{3+}, making insoluble complexes with OH- and anions. Instead, in acidic condition, iron is mainly in Fe^{2+} form that is highly soluble and bioavailable [11].

The primary site for iron absorption is in the duodenum and the upper jejunum. In the duodenum, receiving the acidic gastric chyme, iron is mainly absorbed as Fe^{2+}. More distally in the jejunum, pH becomes neutral or alkaline, and iron uptake declines [12]. Heme iron is estimated to contribute 10–15% of total iron intake in meat-eating populations, but, because of its higher absorption it could contribute ≥40% of total absorbed iron. Nonheme iron absorption is usually lower than heme iron absorption. The bioavailability of non-heme iron from the diet is increased by duodenal acidity, ascorbic acid, citric acid. In general, all the substances that can promote the conversion from Fe^{3+} to Fe^{2+} induce a greater iron absorption. On the other hand, iron availability is inhibited by [13]:

- phytates, phytic acid (cereals, legumes, oilseeds, nuts)
- oxalates (spinach, purslane)
- Tannins (tea, coffee, cocoa, pomegranate juice, red wine)
- Polyphenols (fruits, berries, vegetables, species, legumes and whole grains, tea, coffee, cocoa)
- Calcium

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• Milk protein, eggs, soy (rich in phytic acid and calcium)
• Other metals (copper, zinc)
• Proton pump inhibitors (gastric reflux) such as antacids, gastro-protectants
• Infection by Helicobacter pylori

Considering the limited absorption of the iron, the recommended intake of dietary iron in healthy individuals is about 18-20 mg [12], to fulfill the daily requirement of about 1-2 mg.

Iron, to be absorbed, has to pass through both the apical and basolateral membranes of enterocytes. This process is influenced by the amount of iron in the diet, the chemical state of the iron (Fe^{2+} and Fe^{3+}), and the existing iron reserves within the body [13]. In the human diet, iron is mainly present in form of heme, ferritin, and ferric iron. Heme and non-heme iron seem to be absorbed by distinct mechanisms. Moreover, another pathway is involved in ferritin absorption [6].

Heme iron is highly bioavailable and up to 40% of each is easily absorbed [14] in the intestine through a dedicated carrier, not yet identified [15]. This transporter must be coupled to a cytoplasmic heme oxygenase (HO) which extracts iron from heme [16].

Non-heme iron uptake occurs at the apical brush border of enterocytes in the small intestine, mainly by dimetal transporter-1 (DMT1), an integral membrane protein predicted to have 12 transmembrane domains, expressed not only in the enterocytes, but also in the endosomes of all cells. At the apical membrane of enterocytes, DMT1 recognizes exclusively Fe^{2+}. Fe^{3+} is reduced to Fe^{2+} either by gastric acid pH, reducing components in the meal, or by the ferric reductase enzyme duodenal cytochrome b (DCYTB) [12]. Interestingly, for this reduction DCYTB uses ascorbic acid during the electron transfer, explaining the importance of vitamin C for iron absorption [17] (Figure 1).

DMT1 operates through a proton-coupled mechanism to transport Fe^{2+} and other divalent metals including zinc, manganese, cobalt, cadmium, copper, nickel, and lead. Protons, the driving force for iron transport, are supplied by a sodium/hydrogen exchanger (NHE3) [18]. Knock-out mice for SLC11A2 gene, coding for DMT1 protein, experience severe anemia since they display a deficit in iron absorption [19].

1.3 Iron Export

Fe^{2+} in enterocytes can be incorporated into the cytosolic iron-storage molecule ferritin or can be transported across the basolateral surface of enterocytes into the plasma by ferroportin [6] (Figure 1). Ferroportin, the exclusive cellular iron exporter, is expressed in all the cells involved in iron metabolism, encompassing the duodenal mucosa cells, macrophages, and placental cells [20]. Ferroportin exports Fe^{2+} as well as Zn^{2+} [21].

Following export from the enterocytes, Fe^{2+} is converted to Fe^{3+} by the oxygen-dependent ferroxidases, hephaestin, zyklopen and ceruloplasmin, and then loaded into the iron carrier transferrin (Tf) [22], that use molecular oxygen to oxidize Fe^{2+} to Fe^{3+} [23] (Figure 1). Hephaestin and zyklopen are proteins expressed mainly in enterocytes and placenta respectively, while ceruloplasmin is highly expressed in the liver and the retina. All three ferroxidases are found also in the brain. The ferroxidase-mediated conversion of Fe^{2+} to Fe^{3+}, remove Fe^{2+} from external medium, creating the driving force for ferroportin-mediated iron export. Thus, in absence of ferroxidase, Fe^{2+} does not get exported through ferroportin and accumulates in the cytosolic iron-storage molecule ferritin. Ferroportin is a highly regulated protein: its internalization and degradation mainly depend on hepcidin [12,24] (Figure 1).

1.4 Iron distribution - delivery to tissues and organs

Iron exported from cells by ferroportin gets bound to transferrin, an 80-kDa glycoprotein necessary for the transfer of circulating iron. It is synthesized in the liver, retina, testis and brain and is secreted into the plasma. Transferrin has two binding sites, binding exclusively Fe^{3+} [3]. The iron-free form of transferrin is referred as apo-transferrin. Transferrin binds iron with high affinity, limiting the ability of iron to generate toxic free radicals, thus preventing the Fenton reaction.

Once bound to transferrin, iron is transported to various organs and tissues: bone marrow, muscle, liver etc. [25]. The transferrin–Fe^{3+} complex circulating in plasma gets access into the cells through the cell-surface transferrin receptor (transferrin receptor-1 or TfR), a gatekeeper in charge of physiological iron acquisition

by most cell types in the organism. The transferrin receptor consists of a disulfide-linked transmembrane glycoprotein homodimer and each subunit binds to one transferrin molecule [26]. Only iron-saturated transferrin, diferric transferrin, is recognized by its TfR and is internalized by the target cells. The internalization of the complex Fe^{3+}–transferrin–transferrin-R1 depends on receptor-mediated endocytosis via clathrin-coated pits. The product of the endocytosis is an internalized vesicle (a clathrin-coated endosome called siderosome). After removal of clathrin, the siderosomes is acidified (pH 5.5) by ATP-dependent proton influx, leading to conformational changes in both transferrin and TfR1 and variation in the transferrin affinity for iron. This mechanism promotes the release of Fe^{3+} from transferrin. Afterwards, Fe^{3+} is reduced to Fe^{2+} by a ferrireductase and exported from the siderosome to the cell cytoplasm by DMT1-like conveyor, while TfR1 is recycled to the cell membrane and transferrin is shed back into the circulation [27] (Figure 2). During its lifespan of about two days, transferrin completes this cycle about 100 times.
Depending on the specific cell, iron in the cytosol can bind ferritin creating iron storage, as it happens in the liver, or participate to the synthesis of hemoglobin in the bone marrow and myoglobin in the muscle tissue.

1.5 Iron storage

Iron absorbed by enterocytes through DMT1 is either exported by ferroportin or stored inside the cell bound to ferritin. Ferritin, a ubiquitous cytosolic iron-storage protein, is particularly abundant in the spleen, liver and bone marrow, but present at very low level in serum (less than 1%, 12-40 microg/L). Nevertheless, serum iron is an important clinical indicator, being directly proportional to the body's iron reserves [12]. Moreover, since ferritin is an acute phase protein, its values may vary during an inflammatory process.
Ferritin is a globular protein of 24 subunits, and each ferritin molecule is able to incorporate about 4500 iron atoms. Ferritin not combined with iron is known as apoferritin. When the amount of iron exceeds the normal ferritin binding capacity some of the iron is shunted into another storage form, hemosiderin, present in the macrophages of the liver and bone marrow. Hemosiderin, a condensation product of ferritin molecules, proteins, lipids, sialic acid, and porphyrins, is a less bioavailable storage form of iron [5].

1.6 Iron recycling

Although the iron daily requirement is about 1-2 mg, the total content of iron in the body is much higher. Erythrocytes are the cells containing the greatest concentration of iron, bound to haemoglobin. Senescent erythrocytes are phagocytosed by macrophages which degrade haemoglobin and recycle iron back into plasma where it binds the iron-transporting protein transferrin. Despite the rapid turnover of iron and changes in its utilization, plasma iron content is stably maintained at 2-4 mg bound to transferrin, suggesting that the delivery of iron from recycling macrophages into plasma has to be under homeostatic control [6]. If the amount of iron released into the plasma is higher than the iron-binding capacity of transferrin, the excess non-transferrin-bound iron is deposited in parenchymal tissues [25]. Over a day, ~0.8% (or ~15–25 mg) of iron erythrocyte is recycled, considering: i) the amount of circulating blood (5 L), ii) the body erythrocytes count and iii) their average lifespan of 120 days. A smaller amount of iron is retrieved by macrophages from other cell types.
Thus, the control of systemic iron levels occurs through the regulation of iron absorption which depends on mobilization of body reserves and iron storage, and through the control of iron recycling from senescent erythrocytes. There is no known physiologic regulatory mechanism for iron excretion [25].

2. Regulation of systemic iron

The iron absorption in the gut is regulated by iron needs and availability. Upon exposure to an amount of iron beyond a threshold, enterocytes become refractory to absorbing additional iron. This phenomenon is referred to as "mucosal block" [28], and might depend on downregulation of DMT1 [25] (Figure 1). Another mechanism controlling the level of iron in the enterocytes is the "stores regulator" mechanism in

which duodenal mucosal cells adjust their absorptive capacity based on the body's iron stores. Indeed, iron absorption is enhanced in response to conditions like ineffective erythropoiesis or hypoxia.
The influx of iron into the bloodstream from enterocytes, but also from macrophages, is influenced by the iron status or demands of tissues. A key component of systemic iron metabolism is hepcidin, a circulating peptidic humoral factor that signals body iron levels, and regulates the entry of iron into plasma. Hepcidin is a member of the family of defensins; its bioactive form is a 25-amino-acid peptide primarily secreted by hepatocytes [28]. Hepcidin play a crucial role in iron homeostasis negatively regulating the iron transfer protein ferroportin. Hepcidin binds ferroportin leading to ferroportin phosphorylation, internalization, ubiquitylation and degradation in lysosomes. High serum level of hepcidin leads to downregulation of ferroportin in enterocytes, macrophages (holding significant amounts of iron from erythrocyte recycling), and hepatocytes (acting as an iron reservoir). As a consequence, iron export from the cells decreases and serum iron is overall reduced. In addition, this also causes an increase in cytosolic iron stored in ferritin [29], leading to a reduced iron absorption. Regulation of hepcidin expression seems to occur at the level of transcription [25] (Figure 1).
A deficiency in hepcidin in both mice and humans leads to increased absorption of iron and results in iron overload in various parenchymal organs such as the liver, pancreas, and heart. Paradoxically, this deficiency also causes the loss of iron stores within macrophages [30,31]. In contrast, higher expression level of hepcidin results in reduced iron absorption and the development of iron-limited anemia [32]. Accordingly, hepcidin overexpression during fetal life can impair iron transfer to the fetus, causing severe iron deficiency anemia at birth, and higher incidence of perinatal mortality [33]. Altogether, these data indicate that hepcidin is a negative regulator of iron transport into the plasma [25]. Notably, the phenotype associated with hepcidin deficiency is mimicked by heterozygous mutations in human ferroportin that disrupt its interaction with hepcidin [34]. These data confirm the crucial role of the hepcidin-ferroportin interaction in iron homeostasis.
The appropriate regulation of hepcidin expression depends on the ability of the liver to sense intracellular and extracellular iron and to relay these signals to the hepatocyte nucleus where hepcidin expression can be appropriately modulated to maintain homeostasis. Hepatocyte transferrin receptor (TFR) 1, TFR2, and human hemochromatosis protein (HFE) may function as sensors of extracellular iron, and plasmatic levels of transferrin-bound iron (iron-TF). These proteins potentiate the signaling through the bone morphogenetic protein (BMP) pathway to stimulate hepcidin transcription based on iron-TF concentrations [35].
Iron stores are potent regulators of hepcidin, but less is known about how they regulate hepcidin transcription, and the BMP receptor may be involved in this pathway [36]. Iron metabolism is regulated at cellular level by iron regulatory proteins (IRPs) 1 and 2, engaged in the post-transcriptional regulation of genes involved in intracellular iron accumulation/release and import/export [28]. In particular, when the concentration of iron is low, IRP does not bind iron, but works as postranscriptional regulator, binding specific IRE (iron responsive elements) sequences of mRNAs coding for transferrin receptor and ferritin, with opposite effects. Binding of IRP to 3' UTR of transferrin receptor mRNA stimulates its translation, while binding to 5' UTR of ferritin mRNA inhibits its translation, (Figure 3). Thus, low iron leads to low ferritin level, allowing a rapid transport of iron in the blood. The iron entrance in the cells is favored to the increased level of transferrin receptor [37]. Instead, when the iron concentration is high, the IRP1 protein binds to a prosthetic group, formed by cubes with 4 iron atoms and 4 sulfur atoms alternating at the vertices, and acquires antioxidant aconitase activity. Instead, IRP2 is polyubiquinated and degraded in the cell proteosome. In absence of IRP, transferrin receptor mRNA is degraded, while ferritin mRNA translation is stimulated (Figure 3).

3. Ferroptosis

Historically, cell death was considered a passive and unregulated process, until apoptosis was discovered in the 70s as the first form of regulated cell death pathways (RCDs) [38]. Over the years, other modalities of RCDs have been identified, such as autophagy and necrotic apoptosis. Ferroptosis, defined for the first time

by Dixon on 2012 [39], is an iron-dependent and non-apoptotic cell death process, driven by massive membrane lipid peroxidation and mediated by iron overload and accumulation of reactive oxygen species (ROS) [40].

Ferroptosis was observed for the first time in cells treated with erastin, a small molecular inducer of ferroptosis capable of inhibiting cystine uptake by the cystine/glutamate antiport [41]. Later on, it was identified another compound able to activate ferroptosis, lethal synthetic RAS 3 (RSL3). Indeed, cell death caused by RSL3 undergoes an iron-dependent non-apoptotic pathway [42,43].

Although an initial study indicated that ferroptosis is morphologically, biochemically, and genetically distinct from apoptosis, necrosis and autophagy [39]. Most researchers agree that cells undergoing ferroptosis usually exhibit morphological changes similar to necrosis [44]. These features include loss of plasma membrane integrity, cytoplasmic swelling (oncosis), swelling of cytoplasmic organelles, increase in autophagosomes, and moderate chromatin condensation [40].

Ferroptosis involves several key proteins that regulate iron metabolism, including ferritin, transferrin receptor 1 (TfR1), ferroportin, and iron-responsive element binding protein 1 (IREB1). Ferritin serves as the primary iron storage protein, sequestering excess of iron to prevent oxidative damage; however, during ferroptosis, autophagic degradation of ferritin, termed ferritinophagy, leads to the release of free iron, which can catalyze the formation of reactive oxygen species (ROS) and promote cell death [45–47]. Conversely, it has been demonstrated that promoting the expression of the iron storage protein ferritin, leads to reduced iron content, and decreases the susceptibility to ferroptosis [48]. Moreover, it has been shown that the inhibition of TfR1, responsible for the uptake of transferrin-bound iron into cells, leads to ferroptosis [49]. Ferroportin is responsible for exporting excess iron out of cells, and its downregulation can contribute to iron accumulation and subsequent ferroptosis [50]. IREB1 plays a regulatory role in iron homeostasis by modulating the expression of genes involved in iron metabolism, including those encoding TfR1 and ferroportin, influencing the susceptibility to ferroptosis [51,52].

Ferroptosis cellular and molecular mechanisms have been analyzed extensively elsewhere [53]. The main focus of this review will be to illustrate the link between ferroptosis, mitochondria and oxidative stress, as well as to investigate the ferroptosis implications in health and disease.

Ferroptotic cells are characterized by mitochondrial abnormalities such as increased membrane density, reduction or disappearance of mitochondrial crests, as well as rupture of the outer membrane [54]. Despite these significant changes in mitochondrial morphology, the role of these organelles in ferroptosis remains controversial.

Mitochondria are the center of metabolism and an important source of reactive oxygen species (ROS) in most mammalian cells [55–57]. In contrast to an initial study indicating that mitochondria-mediated ROS production is not necessary for ferroptosis, more recent evidence indicates that ROS production, DNA stress, and metabolic reprogramming are key factors for lipid peroxidation and ferroptosis induction [58].

Ferroptosis depends on the delicate balance between ferroptosis-inducing and ferroptosis-protecting factors.

The factor inducing ferroptosis are the peroxidation of phospholipids containing polyunsaturated fatty acids (PUFA-PL), iron metabolism and mitochondrial metabolism [59,60]. Excessive level of iron initiates the non-enzymatic reaction of Fenton and acts as an essential cofactor for arachidonate lipoxygenase (ALOX) and cytochrome P450 oxidoreductase (POR), enzymes that promote lipid peroxidation, leading to the formation of reactive lipid oxygen species (lipid ROS or phospholipid hydroperoxides, PLOOH) [61]. The propagation of the oxidative process leads to the formation of numerous secondary products, including the degradation products of lipid peroxides (such as 4-hydroxynonenal and malondialdehyde), and oxidized and modified proteins that, altering the integrity of cell membranes, lead to the cell death [62].

Ferroptosis defense systems primarily include the glutathione peroxidase 4 (GPX4)-reduced glutathione (GSH) system, the ferroptose suppressor protein 1 (FSP1)-ubiquinol (CoQH 2) system, the dihydroorotate dehydrogenase (DHODH)-CoQH 2 system and the GTP cyclohydrolase 1 (GCH1)-tetrahydrobiopterin (BH 4) system. GPX4 is the main enzyme that neutralizes PLOOH, catalyzing the reduction of hydrogen peroxide, organic hydroperoxides and lipid peroxides at the expense of reduced glutathione (GSH). The oxidized form of glutathione (GSSG), which is generated during the reduction of hydroperoxides by GPX4,

is recycled by glutathione reductase and NADPH/H [63]. There are three isoforms of GPX4 with distinctive subcellular localization, namely: cytosolic, mitochondrial and nuclear GPX4 [64,65]. The ferroptosis suppressor protein 1 (FSP1)-ubiquinol (CoQH 2) system is localized on the plasma membrane and acts as an oxidoreductase, using nicotinamide adenine dinucleotide phosphate (NAD(P)H) to reduce ubiquinone (coenzyme Q10, CoQ10) to ubiquinol CoQH2. In addition to its well-known function in mitochondrial electron transport, CoQH2 can also trap lipid peroxyl radicals, thereby suppressing lipid peroxidation and ferroptosis [66,67]. Dihydroorotate dehydrogenase (DHODH)-CoQH 2 is a recently discovered antioxidant defense system located in mitochondria that can compensate the loss of GPX4 in mitochondrial lipid peroxidation detoxification. DHODH is an enzyme involved in pyrimidine synthesis that can reduce CoQ to CoQH2 in the inner mitochondrial membrane. When GPX4 is inactivated, the flow through DHODH is increased, resulting in increased generation of CoQH2 that neutralizes lipid peroxidation and defends against ferroptosis in the mitochondria [68]. Thus, cells have developed at least four defense systems with different subcellular localizations to detoxify lipid peroxides and thus protect cells from ferroptosis, in which cytosolic GPX4 (GPX4cyto) collaborates with FSP1 on the plasma membrane (and other non-mitochondrial membranes), and mitochondrial GPX4 (GPX4 mito) collaborates with DHODH in mitochondria to neutralize lipid peroxides [69]. It should be noted that, while mitochondrial GPX4 and DHODH can compensate each other to suppress mitochondrial lipid peroxidation, cytosolic GPX4 and FSP1 fail to do so, apparently because they are not localized in the mitochondria and therefore cannot detoxify the lipid peroxides accumulated in the inner mitochondrial membrane, highlighting the importance of compartmentalization in the defense of ferroptosis [54].

Therefore, when cellular activities promoting ferroptosis significantly exceed the detoxifying abilities provided by the ferroptosis defense systems, a lethal accumulation of lipid peroxides on cell membranes leads to membrane rupture and cell death by ferroptosis. Given iron's central role in cell viability and death, it is not surprising that its cellular homeostasis is finely controlled by the balance between iron import, storage and export [70]. On the other hand, it is important to underline that ferroptosis may also have adapted to play life-saving roles. Indeed, growing evidence suggests that multiple diseases, such as tumors, neurological diseases and organ injuries can be treated with ferroptosis inducers or inhibitors [69].

4. Homeostasis iron-mitochondria and ferroptosis

The relationship between iron and mitochondria is complex and multifaceted, as iron plays a crucial role in various mitochondrial functions. Mitochondria are double-membraned organelles of eukaryotic cells, responsible for energy production through oxidative phosphorylation. Iron is an essential element for this process, as it is a key component of heme, a prosthetic group present in proteins such as hemoglobin and cytochromes, which are part of the electron transport chain (ETC), a protein complexes embedded in the inner mitochondrial membrane. Heme is synthesized through a series of enzymatic reactions known as the heme biosynthetic pathway, which involves the incorporation of iron into the heme molecule, and partly takes place in the inner mitochondrial membrane [71]. Moreover, iron is essential for the biogenesis of iron-sulfur clusters, which are critical cofactors in the activity of various mitochondrial enzymes involved in the tricarboxylic acid cycle, ETC, and in various cellular functions, including DNA repair. These clusters are assembled in the mitochondrial matrix and then incorporated into proteins in the mitochondrial inner membrane [72]. The ETC complexes contain iron-sulfur clusters and heme groups, both of which are essential for electron transfer during oxidative phosphorylation. Iron serves as an electron carrier in these complexes, facilitating the flow of electrons along the chain [73].

Since maintaining proper iron homeostasis within mitochondria is crucial for their function, these organelles are endowed with mechanisms to import and export iron, which are tightly regulated to ensure that iron levels are appropriate [74]. Accordingly, dysregulation of mitochondrial iron levels can lead to oxidative stress and cell damage [75].

In summary, iron is intimately linked to mitochondrial functions, playing a critical role in heme synthesis, electron transport, iron-sulfur cluster biogenesis, and overall iron homeostasis. These processes are essen-

tial for the production of ATP and the overall energy metabolism of the cell, highlighting the intricate relationship between iron and mitochondria in maintaining cellular health and function.
A protein with a crucial role in the mitochondria-iron homeostasis is MitoNEET, also known as CISD1 (CDGSH iron-sulfur domain-containing protein 1). MitoNEET is a small mitochondrial protein, containing a specialized iron-sulfur (Fe-S) cluster-binding domain known as the CDGSH domain, which is able to inhibit iron transport inside the mitochondria [76]. This unique feature allows this protein to serve as a key player in the regulation of mitochondrial iron-sulfur cluster biogenesis. Proper iron-sulfur cluster biogenesis is essential for efficient energy production, as these clusters are cofactors in this metabolic pathway. MitoNEET was identified for the first time in white adipose tissue (WAT) adipocytes. Its overexpression in WAT or liver has been shown to reduce iron levels in the mitochondrial matrix, consequently reducing the functionality of the ETC, fatty acid oxidation, and ROS production. Instead, the reduction of MitoNEET expression level results in an increase of mitochondrial iron levels leading to increased oxidative stress and ROS production [77]. In addition, MitoNEET binds to 2Fe-2S iron-sulfur clusters by functioning as an iron reservoir for these clusters within the mitochondria [78]. Interestingly, MitoNEET is able to sense changes in the redox state of mitochondria and to modulate mitochondrial functions in response to cellular metabolism [77]. Impacting both energy metabolism and redox state, MitoNeet plays a crucial role in cellular and mitochondrial health. Accordingly, dysregulations of this protein can lead to mitochondrial dysfunction, which is associated with a wide range of diseases [79] (Figure 4).

4.1 Mitochondria and ferroptosis

Ferroptosis, as a form of regulated cell death characterized by the iron-dependent accumulation of lipid peroxides, leading to membrane damage, primarily involves lipid peroxidation, and it is significantly connected to altered mitochondrial functions. Mitochondria are crucial organelles in the regulation of ferroptosis because they contain abundant polyunsaturated fatty acids (PUFAs), particularly cardiolipin, which is highly susceptible to lipid peroxidation. The iron-catalyzed lipid peroxidation, which characterize ferroptosis, leads to the oxidation of mitochondrial membrane lipids, compromising the integrity and function of these organelles [60]. Mitochondria are also involved in the regulation of intracellular iron homeostasis. Excess iron accumulation within mitochondria can lead to increased oxidative stress and lipid peroxidation, which are key triggers of ferroptosis. Moreover, mitochondrial iron transporters, such as mitoferrins, play a role in modulating intracellular iron levels and ferroptosis susceptibility [80] (Figure 5). Recent studies highlighted that lipid peroxidation significantly increases membrane tension, which in turn activates the mechanosensitive Piezo1 ion channel. This activation facilitates cation influx, contributing to the collapse of transmembrane ion gradients, a critical step in ferroptosis [81]. Piezo1 not only responds to increased membrane tension, but also cooperates with other ion channels to enhance cation permeability, exacerbating the ferroptotic process [81,82]. Mitochondrial glutathione peroxidase 4 (mGPx4) plays a pivotal role in mitigating ferroptotic cell death. Elevated levels of mGPx4 have been shown to confer resistance against ferroptosis, as this enzyme is crucial in reducing lipid peroxides and maintaining cellular redox balance. Mitochondrial dysfunction, including accumulation of ROS, is triggering ferroptosis [83]. Thus, lipid peroxidation and consequent membrane tension, Piezo1 activation, and mitochondrial mGPx4 may work together to orchestrate the cellular response to ferroptotic stimuli [81]. Interestingly, it has been demonstrated that activation of Small conductance calcium-activated potassium (SK) channel prevents ferroptosis and excitotoxicity, suggesting that this channel may be a therapeutic target for neurodegenerative diseases involving ferroptosis [84].

4.2 Mitochondrial Reactive Oxygen Species (ROS) and Ferroptosis

Mitochondria are a major source of intracellular ROS production. In ferroptosis, excessive lipid peroxidation can lead to increased ROS generation within mitochondria, creating a positive feedback that amplifies oxidative damage and further contributes to ferroptotic cell death [85]. Mitochondria contain their own pool of the antioxidant molecule glutathione (GSH). GSH is involved in protecting mitochondrial lipids and

proteins from oxidative damage. Depletion of mitochondrial GSH levels, which can occur in ferroptosis, makes mitochondria more susceptible to lipid peroxidation and promote ferroptotic cell death [66].
In summary, mitochondria play a central role in the regulation of ferroptosis through their involvement in lipid peroxidation, iron homeostasis, ROS production, and the maintenance of antioxidant defenses. Understanding the interplay between mitochondria and ferroptosis is crucial for elucidating the mechanisms underlying this form of cell death and exploring potential therapeutic strategies for related diseases, including cancer and neurodegenerative disorders (Figure 5).

5. Obesity and altered iron metabolism

Emerging studies have highlighted the crucial role of iron metabolism and ferroptosis in the onset and development of obesity and non-communicable diseases (NCDs) [86] which are characterized by altered mitochondrial functions. Interestingly, mitochondrial impairments promotes ferroptosis through disrupted iron and lipid metabolism, linking it to the progression of these diseases [87].

5.1 Obesity and iron deficiency

Obesity is one of the major health problem worldwide, resulting from a chronic excessive caloric intake and insufficient energy expenditure [88,89]. Increasing evidence indicates a connection between obesity and iron deficiency [90–92]. In 1962, it was demonstrated, for the first time, iron deficiency in obese adolescents [93]. Subsequent research has confirmed this association in children, adolescents, as well as adult subjects [94]. Similar findings have been reported in obese postmenopausal women that exhibited a higher level of soluble transferrin receptors, compared to non-obese postmenopausal women [75,95]. However, the relationship between iron metabolism and obesity is still unclear, although several hypotheses have been proposed.
Numerous studies suggested that obesity play a significant role in iron deficiency due to increased serum levels of low-grade markers of chronic inflammation [96]. To date several evidence shown a close involvement of inflammation processes in iron homeostasis. Indeed, a negative correlation was detected between iron absorption and c-reactive protein (CRP) serum levels, in healthy premenopausal women [97]. Serum iron and transferrin saturation in obese subjects was significantly lower than in lean individuals [98]. The iron deficiency observed in obesity condition is attributable to high pro-inflammatory cytokines released from adipocytes [99,100] (Figure 5). It is well known that adipose tissue of the obese individuals presents a major quantity of macrophages and producers of pro-inflammatory molecules [99]. Visceral adipose tissue is more extensively infiltrated by macrophages that release inflammatory cytokines, compared to peripheral fat [101]. Furthermore, visceral adipose tissue secretes the pro-inflammatory cytokines into the portal circulation, which drains directly to the liver. In the liver, interleukyne-6 (IL-6) stimulates hepcidin production, by activating the Janus kinase [102–104]. Hepcidin serves both as a homeostatic regulator of systemic iron metabolism and as a mediator of host defence and inflammation [105]. The impact of hepcidin on iron metabolism [106] depends on its ability to inhibit the intestinal iron uptake and to decrease its outflow from splenic and hepatic macrophages. Hepcidin exerts its action binding the cellular iron export channel ferroportin-1, present in enterocytes, hepatocytes, and macrophages, thus causing its internalization and degradation into lysosome [107]. As a result, ferroportin expression decreases and cellular iron stores increase [108], resulting in deficiency of iron serum levels. It was observed a significant increase in serum hepcidin levels in obese women and children compared to lean subjects [109,110] (Figure 1). Serum hepcidin levels is inversely related to iron absorption and positively related to serum levels of leptin, an adipokine present in high concentration in obese people [111]. The increased serum hepcidin levels observed in overweight and obese subjects explain the lower efficacy of iron supplementation in these individuals compared to those with normal body weight [97,112]. Therefore, a reduction in adipose tissue, associated with a change in pro-inflammatory cytokine levels, would result in a decrease of hepcidin release and an improvement in iron status in overweighted and obese people [113] (Figure 5). Indeed,

several evidence demonstrated that diet-induced weight loss can improve iron homeostasis and aid obese individuals in correcting and resolving iron deficiency [114,115]. In obese subjects, a reduction in BMI index results in decreased hepcidin levels, which in turn improves iron absorption and metabolism [116]. Accordingly, in overweight obese children and adolescents, after an eight-month physical exercise programme, it was shown an increase in serum iron concentration and a decrease in BMI index, body fat mass, CRP, soluble transferrin receptor, interleukin-6 and hepcidin levels [117].
In obese subjects, besides increased hepcidin levels also increased levels of lipocalin-2 have been identified [118]. Lipocalin 2, a possible crucial factor in obesity-related iron deficiency, is an acute-inflammatory phase-related mediator, quickly secreted in response to inflammation [119]. It plays a crucial role in the defense against bacterial infections through the regulation of iron accumulation in the cell. In detail, when inflammation occurs, the liver, pancreas, and adipose tissue produce Lipocalin-2, which sequestering iron, contributes to innate immunity and prevents the availability of iron for pathogenic bacteria [120].

5.2 Obesity and ferroptosis

Obesity is a complex disease, characterized by increased macrophage numbers in adipose tissue and subsequent augmented secretion of inflammatory factors leading to chronic low-grade inflammation [121]. In obese patients, displaying low grade inflammation, proinflammatory adipokines (e.g. IL-6) can stimulate the expression of hepcidin, leading to reduced iron level in the serum [122]. Indeed, the hepcidin high levels mediate the inhibition of ferroportin, the primary iron export protein found in surface of macrophages, enterocytes, and hepatocytes. When ferroportin is inhibited, the export of iron from cells into the bloodstream decreases, leading to systemic iron deficiency. At the same time, due to the inhibited exporting system, the iron levels inside the cells increase, preventing further import of iron. In particular, in enterocytes with iron overload conditions, the mucosal block of DMT-1 (transmembrane transporter that mediate the uptake of iron from the lumen of the intestine into the enterocyte) leads to decreased iron absorption from the gut [123]. In this condition of blocked DMT1, even when dietary iron is sufficient or supplemented, the iron cannot be effectively absorbed into the enterocyte, and as a result, it cannot be exported by ferroportin into the blood stream [124]. Thus, this inflammatory condition lead to iron deficiency anemia, despite adequate iron intake (Figure 1).
Therefore, it is possible to conclude that obesity linked to low grade inflammation leads to paradoxical conditions characterized by low level of iron in the serum and high levels of iron inside the cells [125]. Interestingly, the iron buildup occurring inside the cells as a result of high fat diet-dependent inflammation [87] may trigger the ferroptosis in cells of different organs [53,126,127]. The development of ferroptosis has been demonstrated in adipose tissue, with adipocytes and macrophages being involved in this process [128]. Chronic feeding overload leads to the expansion of adipose tissue, increase in the size of adipocytes, and the consequent stress condition of these cells [129,130]. In fact, adipocytes have a saturation point at which they lose their ability to store other lipids. At this stage, adipocytes completely swollen with lipids, express stress signals that trigger the release of chemoattractant proteins for macrophages, resulting in macrophage infiltration [131]. The relationship between adipocytes and macrophages appears to play a key role in adipose tissue's ferroptosis. Indeed, it has been observed that a high fat diet induces iron entrance into adipocytes and inhibits the ability of macrophages to process iron [128]. Moreover, exposure of primary peritoneal macrophages to saturated fatty acids alters their gene expression related to iron metabolism. Altered iron management by macrophages parallels with iron overload in adipocytes of obese mice [128]. In polygenic obese and diabetic mice it was observed that iron accumulation occurs in the epididymal adipose tissue [132], and iron chelating agents reduces inflammatory factors, oxidative stress, macrophage infiltration, and improve adipocyte hypertrophy in epididymal fat depot [133]. This emphasizes the key role played by iron accumulation in oxidative stress damage in adipose tissue.
Macrophages are important players in obesity-related inflammation and in controlling iron metabolism [134,135]. In physiological condition, they play an important role in recycling the iron by phagocytosis of red blood cells. In obesity condition, the number of macrophages increases in adipose tissue, as does their release of pro-inflammatory cytokines. Macrophages secrete IL-6, TNF-α, IL-1β, which promote the pro-

cess of ferroptosis [136,137]. IL-6 promotes the transcription of hepcidin via the activation of JAK-STAT3 pathway [138], thus affecting macrophage-stored iron release and reducing intestinal absorption of iron. Hepcidin also reduces transferrin expression, exacerbating iron accumulation [139]. TNF-α upregulates acyl-CoA synthetase 3 (ACSL3), a key enzyme in the synthesis of acyl-CoA, thus promoting the lipid accumulation in the cells, and creating a favorable condition for ferroptosis [140].
IL-1b can upregulate both hepcidin transcription, through increased expression of CCAAT enhancer-binding protein (C/EBP) [141,142], and hepcidin expression through phosphorylated c-Jun N-terminal kinase and its substrates c-jun and JunB [143]. These changes result in ferroportin degradation and iron overload.
Furthermore, iron buildup in macrophages, along with the release of ROS and the formation of lipid peroxidation through Fenton Reaction, leads to ferroptosis [144]. More recent studies highlighted that ferroptosis may indirectly promote the development of obesity through the inflammatory response and insulin resistance, involving neuroimmune regulation [87].

6. Ferroptosis and liver diseases

Liver plays an important role in iron homeostasis, as it synthesizes numerous proteins implicated in iron metabolism. It is noteworthy that liver is the most metabolically active organ in our body, with high concentration of mitochondria, playing a key role in ferroptosis. Hepatocytes, which account for about 80% of the liver mass, are the liver cells mainly involved in iron metabolism, and are the main site of iron accumulation. In particular, hepatocytes synthesize ferritin and transferrin, involved in iron accumulation and transport respectively [145], as well as hepcidin, the main negative regulator of iron homeostasis [146–148].
The Kupffer cells, the liver macrophage population, play an essential role in the maintenance and the regulation of iron homeostasis, being involved in red blood cell clearance and heme iron recycling [149]. The Kupffer cell, present in hepatic sinusoids, express iron regulatory genes, and are considered the first cells to take up excess iron to buffer hepatocyte overload [150]. Iron produced by heme catabolism from macrophages is stored inside the cells bound to ferritin, or it is exported outside the cell via ferroportin [151]. Therefore, macrophages maintain steady-state iron levels and prevent the buildup of toxic iron in the body. Furthermore, macrophages can release hepcidin in the site of infection reducing the iron availability for pathogens.
Increasing evidence indicate that ferroptosis plays a variety of roles in a range of liver diseases, such as non-alcholic fatty liver diseases (NALFD), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) [152–154]. NAFLD, whose prevalence rate has been steadily increasing worldwide [155], is a spectrum of liver diseases caused by metabolic stresses and characterized by steatosis, which can evolve into cirrhosis and liver cancer [156,157]. Iron overload is a common feature in patients with NAFLD, and iron-induced lipid peroxidation is a major determinant of NAFLD [158]. Ferroptosis accelerates the progression of hepatic lesions in NAFLD [159,160]. In fact, high-iron diet aggravated oxidative stress, leading to the progression of NAFLD in animal models [161]. Accordingly, ferroptosis inhibitors, such as liproxstatin-1, suppress hepatic lipid peroxidation and related cell death, thereby reducing the severity of nonalcoholic steatohepatitis (NASH) [162,163].
Several studies have highlighted the involvement of ferroptosis in liver fibrosis, a disease arising from the liver response to chronic injury, and characterized by activation of hepatic stellate cells (HSCs) and excessive extracellular matrix (ECM) deposition in the liver [164]. In the fibrotic liver increased iron in HSCs and lipid peroxidation have been observed [165]. Moreover, iron boosted the proliferation of rat HSC cells, selectively increased collagen synthesis [166], and increased TGF-β expression in rats livers [167], inducing collagen deposition in rodents liver [168] and promoting cirrhosis in mice [169].
Liver diseases, characterized by mitochondrial dysfunctions, oxidative stress and lipid peroxidation, which are key elements in ferroptosis. In hepatocytes with oxidative stress, excess of iron in the mitochondria exacerbates lipid peroxidation, leading to cell death and liver damage. This connection makes ferroptosis a

potential target for therapeutic strategies in treating various liver diseases, including NAFLD and HCC, where mitochondrial health is crucial in managing disease progression and preventing liver cell loss [170].

7. Ferroptosis and skeletal muscle diseases

Ferroptosis is believed to be a crucial factor in a variety of skeletal muscle disorders, including sarcopenia, rhabdomyolysis and exhaustion-induced fatigue, although the relationship between ferroptosis and skeletal muscle diseases has not yet been fully elucidated.

Sarcopenia is an age-related degenerative loss of skeletal muscle strength and quality [171] due to an imbalance of muscle cells synthesis and degradation [172], which is closely related to the decrease in satellite cells (SCs) number/function [173,174]. When muscle is damaged, activation and proliferation of SCs occurs, promoting muscle regeneration and damage repair [175,176]. With aging, SCs decrease in number and their function is impaired. Thus, their ability to self-renew and to regenerate is decreased, leading to sarcopenia [177,178]. Iron accumulation in skeletal muscle during aging promotes muscle damage through down-regulation of SCs, augmenting the progression of sarcopenia [179].

Rhabdomyolysis (RML) is an acute syndrome resulting from the injury of skeletal muscle cells and the release of intracellular components into the systemic circulation [180]. Ferroptosis can be related to the progression of RML. Indeed, in RML mice have been detected hallmarks of ferroptosis, such as decreased GSH levels and accumulation of lipid peroxidation products [181]. Accordingly, treatment of RML mice with ferrostatin 1, a ferroptosis inhibitor, has a significant improvement effect on muscle cell death [181].

Prolonged and/or intense physical exercise leads to increased ROS production in skeletal muscle as a response to increased mitochondrial activity in this tissue, which, in turn, induce lipid peroxidation [182], associated with the development of ferroptosis.

In skeletal muscle diseases, mitochondrial dysfunction exacerbates ROS production and iron dysregulation, leading to enhanced lipid peroxidation and triggering ferroptosis. As a consequence, these diseases are characterized by progressive loss of muscle fibers and decline of muscle strenght. Furthermore, mitochondrial impairment in skeletal muscle cells lowers the level of glutathione, an antioxidant critical for neutralizing ROS and protecting cells from lipid peroxidation. In absence of adequate antioxidant defenses, muscle cells become more susceptible to ferroptosis, leading to muscle degradation and atrophy [183].

8. Ferroptosis and heart diseases

Ferroptosis plays various roles in the pathophysiology of cardiovascular diseases (CVDs), such as e.g., atherosclerosis, myocardial infarction, and ischemia/reperfusion (I/R) injury. Several studies shown increased levels of iron in atherosclerotic lesions both in human and animal models [184]. Excessive iron induces free radical generation that can promote low-density lipoprotein (LDL) oxidation [185]. Oxidized LDL can be taken up by macrophages to form foam cells, which, in turn, upregulate certain proteolytic enzymes involved in the breakdown of extracellular matrix leading to atherosclerotic plaque rupture. Interestingly, it was demonstrated that, in vivo, the ferroptosis inhibitor ferrostatin-1 (Fer-1) alleviates atherosclerotic lesions and lipid peroxidation induced by a high-fat diet in ApoE−/− mice [186]. Similarly, in vitro studies have demonstrated that Fer-1 can improve ferroptosis and endothelial dysfunction induced by oxidized LDL and can delay the progression of atherosclerosis [186].

Mitochondria in heart cells are vital for maintaining energy production and cellular health, but under stress conditions, such as ischemia or hypertrophy, mitochondrial impairment disrupts iron metabolism and produces excess ROS. This oxidative environment promotes lipid peroxidation, a hallmark of ferroptosis, which damages cardiomyocytes and contributes to the progression of heart diseases like ischemic heart disease, heart failure, and cardiomyopathies [187].

Myocardial infarction (MI) is defined as an injury caused by acute and/or continuous ischemia and hypoxia of the coronary artery and is a leading cause of death in patients with CVDs. Recent studies have demontrated that the expression of GPX4 is significantly decreased in the early and middle stages of MI, contributing to the ferroptosis of cardiomyocytes under metabolic stress. GPX4 deletion led to lipid peroxide

accumulation and cardiomyoblast cell death through ferroptosis [188]. A study revealed that ferroptosis happens during myocardial reperfusion rather than during ischemia [189]. Accordingly, in I/R model has been demonstrated a significant decrease in cell death caused by ferrostatin-1, suggesting that reperfusion injury can lead to ferroptosis [190]. In the same I/R model, has been showed that ferritin depletion activates the synthesis of numerous antiferroptotic proteins, and among them HO-1. The increase in HO-1 causes the induction of SLC7A11 and GSH, reducing ferroptosis and preserving cardiac function [191]. It is noteworthy that HO-1 activation is primarily regulated by Nrf2 in response to oxidative stress [192]. Although the HO-1 was demonstrated to have a protective role against ferroptosis, it may also act as a contributor to ferroptosis by facilitating the processes that increase iron availability and promote lipid peroxidation [193]. In the context of luteolin-triggered ferroptosis in clear cell renal cell carcinoma (ccRCC), the luteolin can stimulate the expression of HO-1, leading to the degradation of heme and to the release of free iron. This increase of the labile iron pool can enhance the availability of iron for Fenton reactions, which generate reactive oxygen species (ROS) and promote oxidative stress. The elevated levels of ROS and free iron can lead to increased lipid peroxidation, a hallmark of ferroptosis [194]. Different studies have shown that increased HO-1 expression can enhance or mediate ferroptosis induced by anti-cancer agents like Bay 11-7085 and withaferin A, by promoting iron accumulation and ROS production [195,196]. Thus, HO-1 acts as a cytoprotective or as a driving mechanism for ferroptotic progression depending on the level of ROS production and subsequent oxidative damage in response to specific stimuli [197].
Interestingly, ferroptosis has been recently identified as a promising target in oncology. In cancer treatment, inducing ferroptosis not only inhibits tumor growth but also enhances immunotherapy responses and helps overcome resistance to current cancer therapy [198,199]. However, excess of iron may also support tumor growth by fueling cancer cell metabolism [200]. Thus, inducing ferroptosis can be beneficial in killing cancer cells, but this treatment should be carefully managed to avoid adverse effects on normal tissues.

9. Iron metabolism in the brain

Brain, one of the most metabolically active organs, is particularly sensitive to iron homeostasis [201]. Iron homeostasis is tightly controlled, since even slight iron unbalance may affect organs' integrity and physiology [202]. Iron is able to cross the blood brain barrier (BBB) by receptor-mediated endocytosis. Indeed, iron, bound to transferrin (holotransferrin, HTf), interacts with the transferrin receptor 1 (TFR1), a specific receptor in the capillary endothelium, and crosses the BBB by endocytic vesicle [203]. Peripheral iron concentration strongly influences the level of iron in the brain since majority of brain iron is coming from the blood flow. Iron fulfils numerous tasks in the brain, as for instance: i) it is essential for intracellular metabolism, as component of the cytochrome C oxidase, an enzyme of the oxidative phosphorylation pathway [204], ii) iron levels is particularly relevant for hippocampal myelination [205,206], iii) iron affects neurotransmitter synthesis, since monoamine production requires iron as co-factor [207]. As iron is so important for several brain functions, its brain levels have to be finely regulated. Indeed, iron deficiency affects neurotransmitter synthesis, axonal myelination, and synaptic plasticity [208,209], and may impact cognition and social behavior [210]. Conversely, iron accumulation was found in Alzheimer's and Parkinson's disease patients [211], where iron overloading has been associated with dysregulation of neural circuitries. Moreover, it has been shown that iron's capability of modulating neurotransmitter release contributes to exacerbate behavioral and cognitive alterations in anxiety and depression [210,212].
In the brain there is a massive production of ROS, mainly due to the great abundance of substrates for lipid peroxidation, as for instance PUFAs of plasma membranes [213]. This lipid peroxidation leads to ferroptosis [214,215]. In the brain, glutathione peroxidase (GPx), the enzyme protecting the cells from oxidative stress, is expressed in neurons and glial cells. In particular, GPx4 is the most widely expressed isoform in the brain, acting as an antioxidant [216]. Particularly important in brain iron maintenance is the Xc- system, a cysteine/glutamate antiporter that supplies cells with cysteine. Cysteine is required for glutathione (GSH) synthesis, which is involved in oxidative protection. Inhibition of Xc- system leads to decrease in intracellular GSH, with subsequent decrease in GPx4 activity and accumulation of lipid peroxides. The accumulation of lipid-derived ROS, and subsequent neuroinflammation and DNA alterations leads to ferrop-

totic cell death [217]. This inflammatory profile triggers premature aging and neuronal death, and it has been associated with the development of neurodegenerative disease [214,218,219].

10. Ferroptosis in neurodegenerative diseases

Iron accumulation, GSH depletion and lipid peroxidation are common features of several neurodegenerative diseases, strongly suggesting the involvement of ferroptosis in the pathophysiology of these disorders [220].

10.1 Ferroptosis and Neurodegeneration with Brain Iron Accumulation Disorders

The Neurodegeneration with Brain Iron Accumulation (NBIA) disorders are a heterogeneous group of genetic neurological diseases with an incidence of 2:1.000.000 people, affecting both children and adults [221]. NBIA are characterized by iron inclusions in the brain, occurring mainly in the globus pallidus [222], a subcortical basal ganglia structure that coordinate proprioception and voluntary movements [223]. In the later stages of the disease, also the substantia nigra accumulate iron [222]. The iron accumulation is detectable by magnetic resonance imaging (MRI) and post-mortem examination [224] . Another important feature of NBIA is the presence of spheroid bodies in the CNS, indicating degenerating axons that exhibit an atypical morphology [225]. The spheroid bodies accumulate mainly in the globus pallidus and in the surrounding structures [226]. NBIA also exhibit oxidative stress, altered phospholipid metabolism, neuroinflammation and mitochondrial dysfunction [227,228]. It is particularly interesting that NBIA and ferroptosis display common features, as for instance mitochondria impairments, with an altered morphology, decreased membrane potential and lipid peroxidation. Moreover, several genes linked to NBIAs, as PANK2, COASY, PLA2G6, and C19ORF12, are also related to mitochondrial functions. One of this gene-associated protein, PLA2G6, play a protective role against ferroptosis detoxifying lipid peroxides.

10.2 Ferroptosis in Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disorder associated with aging. AD is characterized by memory and cognitive impairments correlated with loss of neurons and deficits of synaptic connection. Two of the key features of AD are β-amyloid (Aβ) accumulation in extracellular plaques, and intracellular neurofibrillary tangles (NFTs) formed by aggregation of hyper-phosphorylated tau proteins [229,230]. In addition, inflammation, oxidative stress, altered metal homeostasis and mitochondrial dysfunction have been implicated in AD [211,231–233]. Several pathological changes characterizing AD, including unbalance of iron homeostasis, increased lipid peroxidation and altered XC- activity, are all hallmark of ferroptosis [234,235]. In AD brain, both Aβ plaques and NFTs display iron accumulation [235], which has been associated with the cognitive decline [236]. In presence of iron, ROS production in Aβ plaques is exacerbated, with subsequent increment of protein oxidation, lipid peroxidation and DNA damage [237]. Furthermore, iron regulates tau phosphorylation and induces aggregation of hyperphosphorylated tau leading to NFTs [238,239]. In a P301S tau transgenic mouse, model of tauopathy, the supplementation with α-lipoic acid was able to limit tau hyperphosphorylation at several tau phosphorylation sites related to AD. Interestingly, α-lipoic acid administration was shown to mitigate ferroptosis features, like iron overload and subsequent lipid peroxidation and neuroinflammation [240]. The ferroptosis role in AD was supported also by experiments in which normal dietary PUFAs were replaced by deuterated PUFAs (D-PUFA) that are relatively resistant to lipid peroxidation [241]. In a mouse model of AD (APP/PS1 transgenic mice), the administration of D-PUFA reduced brain lipid peroxidation and decreased the Aβ- peptide levels [242,243], suggesting that the reduced ferroptosis ameliorates Aβ- pathology in AD mouse model.

Recently, it was demonstrated, both in AD mouse model and in AD patients, a reduction in the brain expression of ferroportin (FPN), a transmembrane iron exporter [244]. FPN knockout hippocampal neurons and AD mice with downregulation of FPN display morphological ferroptosis characterized by ruptured mitochondria, low hippocampal levels of GSH and higher levels of malondialdehyde (MDA). Interestingly,

restoration of FPN ameliorates ferroptosis and memory alteration in AD transgenic mice (APPswe/PS1dE9) [244].

Moreover, in cerebrospinal fluid of human patients, the levels of ferritin, a protein necessary for iron stocking, was predicting mild cognitive impairment conversion to AD [236].

In AD, mitochondrial dysfunction is a central contributor to neuronal damage, creating a high oxidative environment that leads to ferroptosis [245]. Impaired mitochondria in AD-affected neurons generate excess ROS and disrupt iron homeostasis, promoting lipid peroxidation and cell death [246]. This mitochondrial-triggered ferroptosis accelerates neurodegeneration and worsens cognitive decline [247].

10.3 Ferroptosis and Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disease mainly characterized by loss of dopaminergic neurons in the substantia nigra pars compacta. Clinical features of the disease are movement impairments such as bradykinesia, muscular rigidity, and rest tremor [248,249]. At the molecular level, several genes are responsible for the familial PD, such α-synuclein, Parkin, PINK1, DJ-1/PARK7, LRRK2 [250].

It has been known that daily exposure to elevated iron levels is a risk factor for PD development [251], and several sign of ferroptosis have been reported in PD, like mitochondrial dysfunction, glutathione deficiency and high levels of ROS production [252]. Interestingly, glial cells and dopaminergic neurons of PD patients display accumulation of iron. Moreover, several genes and proteins related to iron metabolism and genes coding for essential proteins that modulate pathways related to ferroptosis sensitivity are mutated in the brain of PD patients, strengthening the correlation between iron metabolism and PD [253–256].

Noteworthy, mutation in PARK7 gene, which encode for the protein DJ-1, is known to cause early-onset PD [257]. It was recently demonstrated that DJ-1 is a negative regulator of ferroptosis in a cancer cell model [255], suggesting that mutation in PARK7 gene could increase ferroptosis in PD.

Recently, it has been shown that α-synuclein (α-syn) aggregation (a common feature of PD) is responsible for ROS production leading to lipid peroxidation in an iron-dependent manner, and consequent increased calcium influx and cell death [258]. α-syn oligomers can also alter complex I, inducing oxidation of ATP synthase and mitochondrial lipid peroxidation [259,260].

Parkin knock-down cells, which accumulate α-syn, displayed mitochondrial dysfunction and cell death, similarly to what was observed in wild-type cells exposed to iron. The same study also demonstrated that endogenous and exogenous iron could be a trigger for neurodegeneration in PD [261]. In human stem cell-derived models of synucleinopathy it was demonstrated that α-syn oligomers, associated with high cytosolic calcium influx, lead to ferroptosis through lipid peroxidation [262]. In absence of lipid peroxidation, the α-syn-induced calcium dysregulation is abolished [263]. The importance of α-syn in neuronal survival was confirmed in another study, demonstrating that, in dopaminergic neurons, the level of α-syn regulates phospholipid membrane composition and consequently resistance to ferroptosis. Reduced level of α-syn decreased the concentration of ether-phospholipids in the plasma membrane, reducing the resistance to ferroptosis [264]. At the same time, elevated levels of α-syn in human neuronal precursor cell, made neurons more vulnerable to ferroptosis induced by lipid peroxidation and cell death [260].

Interestingly, it was demonstrated that overexpression of ferritin heavy chain 1 (FTH1), a subunit of ferritin complex, mitigate ferroptosis in a PD cell model [265]. Conversely, FTH1 degradation increases intracellular iron levels leading to ROS formation and subsequent mitochondria damage. In a different series of experiments, in vivo (rat with intraperitoneal injection of 6-hydroxydopamine (6-OHDA)), and in vitro (PC12 cells stimulated 24h with 6-OHDA) models of PD were treated with miR-335 that decreases GPx4 and FTH1 expression levels. It was observed an increased intracellular iron concentration, as well as accumulation of lipid peroxidation, promoting ferroptosis and aggravating PD pathology [266]. Postmortem analysis of the brain of PD patients revealed high levels of iron regulatory proteins 1 (IRP1), which may limit ferritin levels and enhance neuronal iron uptake through transferrin receptor 1 (TfR1), sensitizing neurons to iron-associated oxidative damage [267]. Furthermore, it was demonstrated that the ferroptosis inhibitor, ferrostatin-1, can prevent neuronal loss and behavioural impairment in a mouse model of PD

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[268]. These data strongly support the hypothesis that ferroptosis is one of the molecular mechanisms underlying PD.

10.4 Ferroptosis in Huntington's disease

Huntington's disease (HD) is a neurodegenerative disorder characterized by involuntary movements, emotional, cognitive and psychiatric impairments. The pathology is mainly caused by an abnormal CAG repeat in the first exon of the Huntingtin (HTT) gene encoding for the Htt protein. Precisely, triplet repeats less than or equal to 26 are not associated with the pathology, while triplet repeats more than 36 are pathogenic [269]. The mutate protein can aggregate in macromolecules causing neuronal damage and death. This aggregation can be found in different cell compartments causing different damages: in the cytoplasm proteins aggregation results in inhibition of chaperones, proteasomes and autophagy, while macromolecules crossing nuclear membrane can interfere with the transcription of proteins necessary for mitochondrial function and cellular energy metabolism [270]. In general, huntingtin aggregations may lead to mitochondrial dysfunction, decreased ATP generation and increased ROS production [271]. Moreover, mutated Htt (mHtt) protein in glial cells stimulates the secretion of pro inflammatory cytokines by immune cells, worsening mitochondria dysfunction and altering neuronal redox state [272], while mHtt in striatal neurons of HD patients increased oxidative stress [273].
Several data directly suggest the involvement of ferroptosis in the development of the disease. For instance, enhanced lipid peroxidation was colocalized with mHtt inclusions in striatal neurons of R6/2 HD mouse model [274] and in corticostriatal brain slices of mN90Q73 HD mouse model [275]. Also 4-hydroxy-2-nonel (4-HNE), a lipid peroxidation product, showed an increased immunoreactivity in HD mouse models [274]. Interestingly, HD patients have lower plasma levels of GSH [276], and a deregulation of GSH and GSH-dependent enzymes [273,277]. Interestingly, it has been reported that iron accumulates in HD mitochondria as the disease progresses, leading to alteration in mitochondrial membrane potential, oxygen consumption and lipid peroxidation products, all signs of mitochondrial dysfunction. Accordingly, a membrane-permeable iron selective chelator, deferiprone, rescues these deficits in a mouse model of HD [278]. In addition, an increased expression of ferroportin was detected in brain of HD mice model [279].

10.5 Ferroptosis in Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease characterized by degeneration of motoneurons, leading to paralysis and death [229]. Only 10% of ALS cases are caused by gene mutations, but more than 40 genes have been implicated in the disease [230]. Among them, several genes are associated with mitochondrial functions, such as oxidative phosphorylation, ROS production, altered mitochondrial dynamics and calcium buffering capacity. The most common mutations regard the genes encoding superoxide dismutase protein 1 (SOD1) [231], RNA-binding protein fused in sarcoma (FUS), and trans-active response DNA-binding protein 43 (TDP-43) [232].
TDP-43, a ubiquitously RNA-binding protein, with nuclear and cytoplasmatic location, is the main constituent of abnormal aggregation of proteins, known as "cytoplasmic inclusions", a cytological hallmark of ALS [233].
Several experimental evidence indicate that ferroptosis plays a role in ALS pathogenesis. Iron accumulation was detected in the spinal cord of 12 months old SOD1 transgenic mice [234]. In neuronal cell cultures, it was recently demonstrated that two SOD1 mutations cause the formation of atypic amyloid fibrils structures, that results to be more toxic and responsible for mitochondrial alteration and for promoting ferroptosis [280]. ASL patients display decreased GSH levels in motor cortex [235] and increased serum levels of lipid peroxidation and 4-HNE, which correlate with the stage of the disease [236]. Depletion of GPX4 was observed in postmortem spinal cords of both sporadic and familiar ALS patients [237].

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11. Conclusions

Ferroptosis is a complex cellular response involving different mechanisms, some of which are still unknown. A key role in ferroptosis is played by mitochondria, ROS productions and defences. Thus, the susceptibility of cells to ferroptosis depends on the alteration of iron metabolism, and mitochondrial functions that modulate ROS levels.

Based on these considerations, it is possible to hypothesize that the ferroptosis is a common mechanism underlying numerous metabolic and neurodegenerative diseases characterized by altered mitochondrial functions and redox status. Nonetheless, it is important to note that ferroptosis, in some conditions, may also have beneficial effects, as for instance in inhibiting tumor growth, although further investigations are necessary to elucidate these aspects.

As mitochondrial health is essential for preventing ferroptosis, the comprehensive investigation of the associated molecular pathways will pave the way for the identification of innovative therapeutic strategies, targeting mitochondrial function and iron metabolism, for slowing the progression of several disorders in which ferroptosis is involved.

CRediT authorship contribution statement.

Angela Catapano: Writing – original draft. **Fabiano Cimmino**: Writing – original draft, Conceptualization. **Lidia Petrella**: Writing – original draft. **Amelia Pizzella**: Writing – original draft. **Margherita D'Angelo**: Writing – original draft. **Katia Ambrosio**: Writing – original draft. **Francesca Marino**: Writing – original draft. **Annarita Sabbatini**: Writing – original draft. **Massimiliano Petrelli**: Writing – original draft. **Lucio Lucchin**: Writing – original draft. **Gina Cavaliere**: Writing – original draft. **Luigia Cristino**: Writing – original draft. **Marianna Crispino**: Writing – original draft, Writing – review & editing, Supervision. **Giovanna Trinchese**: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Maria Pina Mollica**: Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Conflict of Interest

Declaration of interest: none

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Figure legends

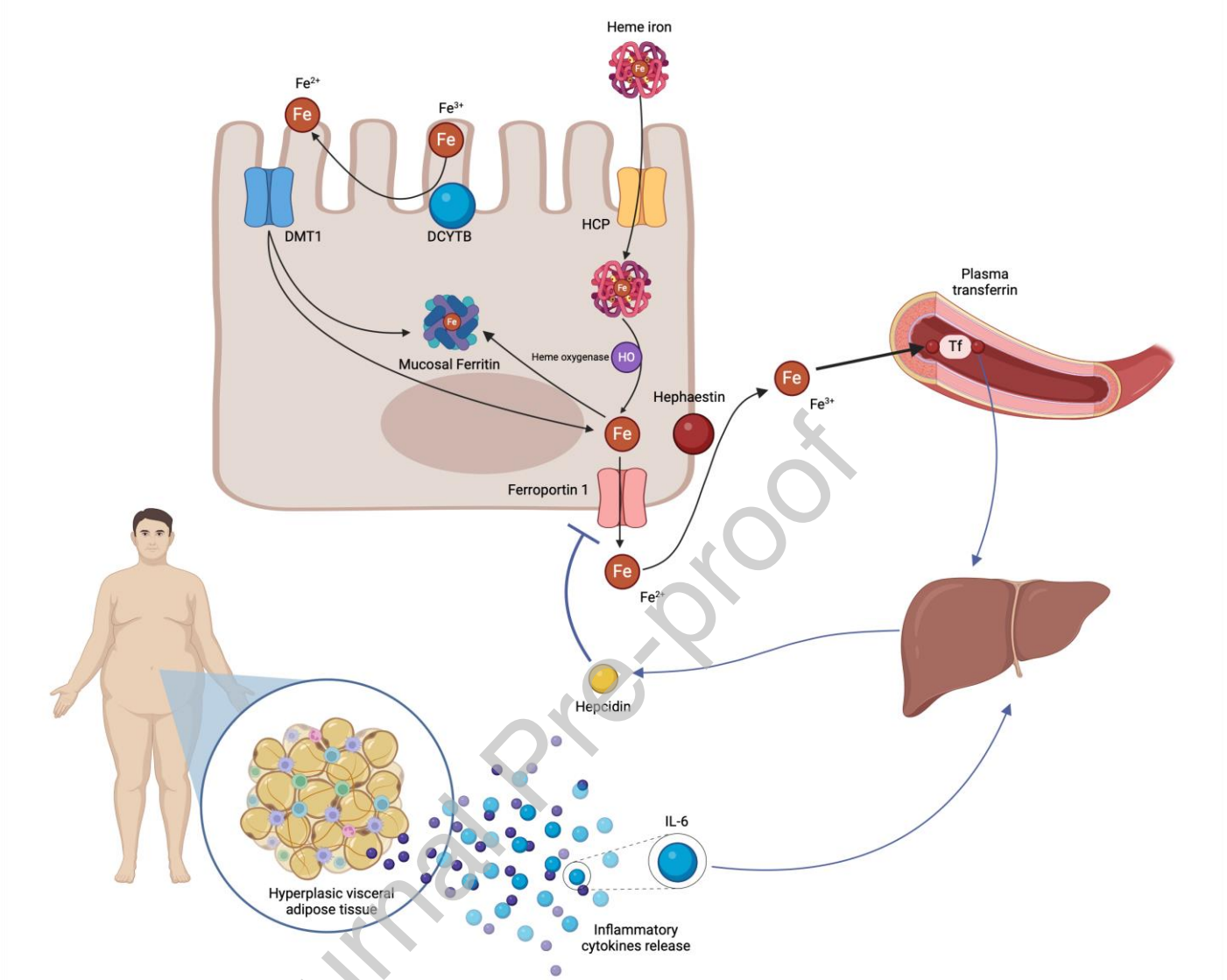

Figure 1. Intestinal iron absorption and "mucosal block" in obesity. Heme iron is easily absorbed in the intestine through a dedicated Heme-Carrier-Protein (HCP). This transporter is coupled to a cytoplasmic heme oxygenase which extracts iron from heme. Non-heme iron uptake occurs at the apical brush border of enterocytes in the small intestine, mainly by Dimetal Transporter-1 (DMT1), which operates through a proton-coupled mechanism and recognizes exclusively ferrous iron (Fe2+). Ferric iron (Fe3+) may be reduced to Fe2+ by the duodenal cytochrome B (DCYTB). Fe2+ in enterocytes can be incorporated into the cytosolic iron-storage molecule, ferritin, or can be transported across the basolateral surface of enterocytes by ferroportin. Following export from the enterocytes, Fe2+ is converted to Fe3+ by the oxygen-dependent ferroxidases, hephaestin, and then loaded into the plasmatic iron carrier transferrin. The liver senses intracellular and extracellular iron and regulates hepcidin expression levels. High serum hepcidin levels lead to downregulation of ferroportin, and iron export from the cell is reduced leading to a decrease in circulating iron. In obesity, hyperplastic visceral adipose tissue produces inflammatory cytokines, including IL-6, which increases hepcidin release from the liver. Therefore, in this condition, even if dietary iron intake is adequate or even supplemented, circulating iron levels may be decreased.

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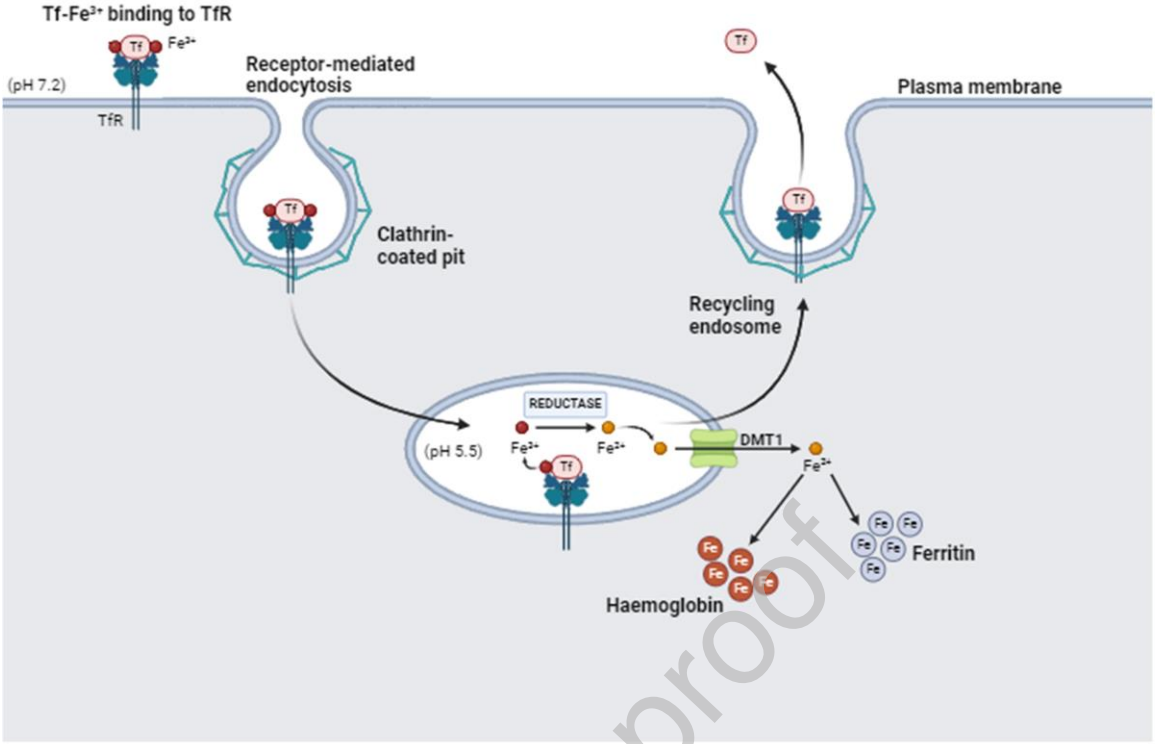

Figure 2. Absorption of iron through Transferrin receptor. The internalization of the complex Fe3+–transferrin–transferrin receptor (TfR) depends on receptor-mediated endocytosis via clathrin-coated pits which leads to the formation of a siderosome. The siderosomes is acidified (pH 5.5) by ATP-dependent proton influx, leading to conformational changes in both transferrin and TfR and variation in the transferrin affinity for iron. This mechanism promotes the release of Fe3+ which is reduced to Fe2+ by a ferrireductase and exported from the siderosome to the citoplasm by DMT1-like conveyor. TfR is recycled to the cell membrane and transferrin is shed back into the circulation. Iron in the cytosol can bind ferritin creating iron storage or participate to the synthesis of hemoglobin in the bone marrow, and myoglobin in the muscle tissue.

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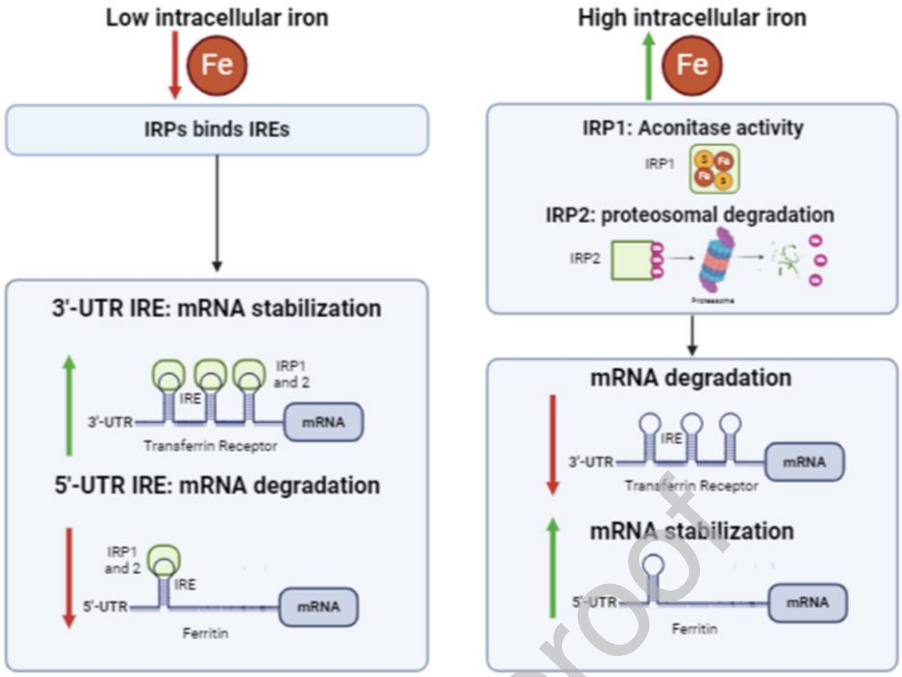

Figure 3. Iron regulatory proteins. Iron metabolism is regulated at cellular level by iron regulatory proteins (IRPs) 1 and 2. If the iron concentration is high, the IRP1 protein binds to a prosthetic group, formed by cubes with 4 iron atoms and 4 sulfur atoms, and acquires antioxidant aconitase activity. Instead, IRP2 is polyubiquinated and degraded in the cell proteosome. If the concentration of iron is low, IRPs bind to specific IRE (iron responsive elements) sequences of mRNAs coding for transferrin receptor and ferritin, with opposite effects: binding to 5' UTR of ferritin mRNA inhibits its translation, while binding to 3' UTR of transferrin receptor mRNA stimulates its translation.

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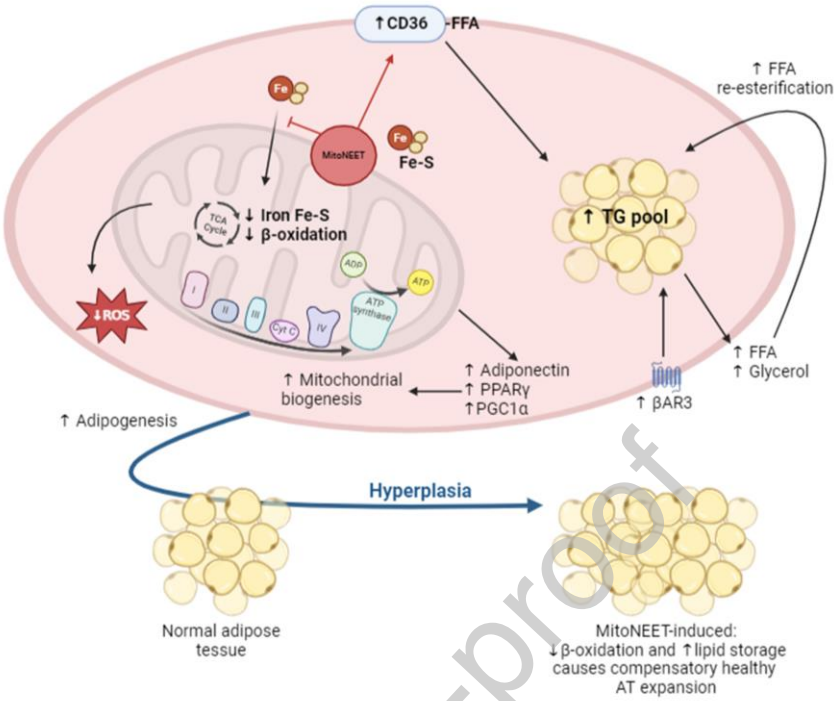

Figure 4. Role of MitoNEET. MitoNEET is a protein with a crucial role in the mitochondria-iron homeostasis. It is a small mitochondrial protein, containing a specialized iron-sulfur (Fe-S) cluster-binding domain, which is able to inhibit iron transport inside the mitochondria. Its overexpression in WAT or liver has been shown to reduce iron levels in the mitochondrial matrix, consequently reducing the functionality of the ETC, fatty acid oxidation, and ROS production. MitoNEET also enhances FA-uptake by signaling via CD36. Compromised mitochondrial function therefore triggers a compensatory upregulation of adipogenesis, β-3 adrenergic signaling and mitochondrial biogenesis. The cellular decrease in mitochondrial activity further enhances lipid-influx into the cell. The inability to utilize these lipids effectively in mitochondria shunts surplus substrates into the TG pool. Consequently, low β-oxidation rates, high Ppar-γ activity accompanied by excess lipid storage, results in hyperplasia of adipose tissue.

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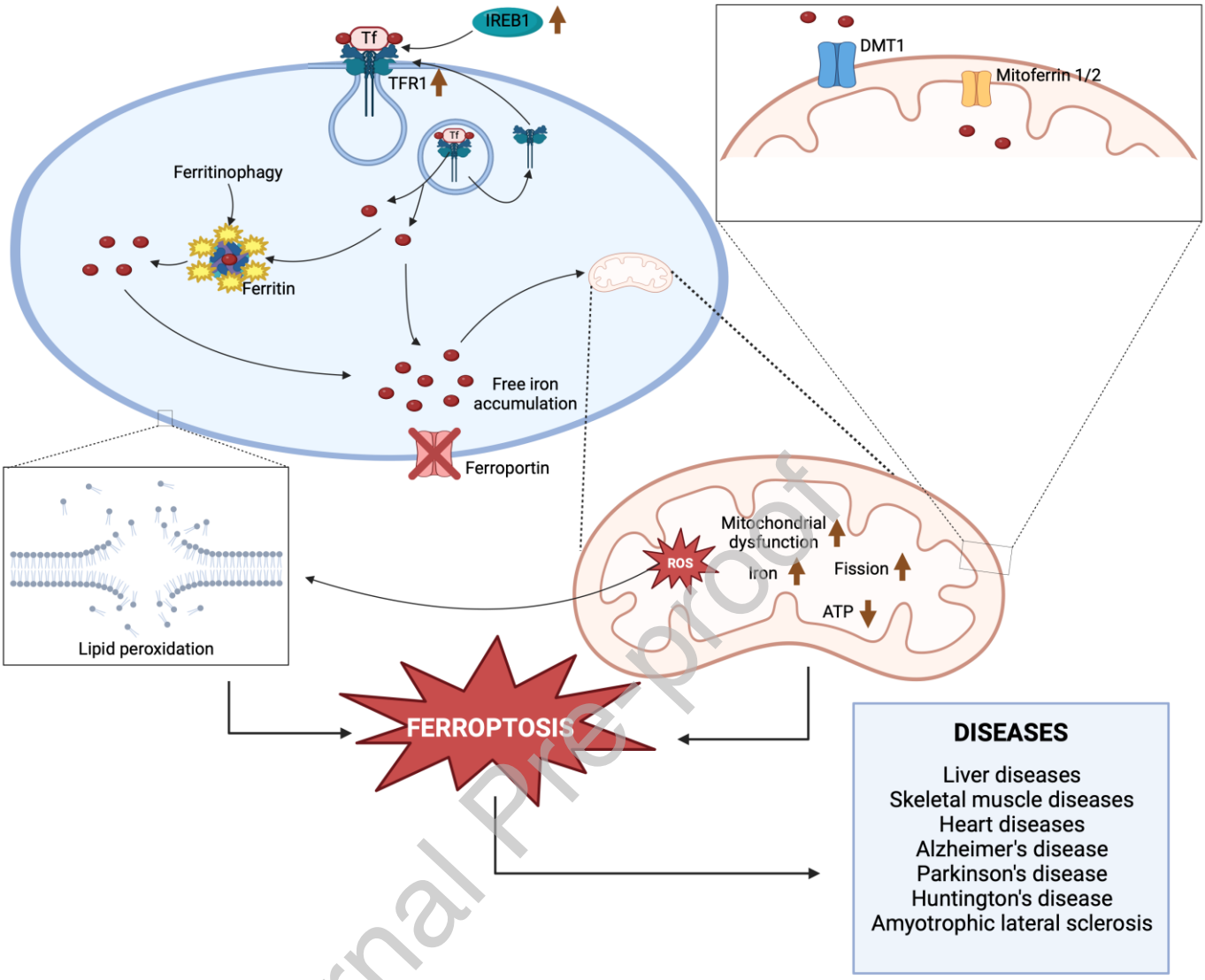

Figure 5. Mitochondria involvement in ferroptosis mechanisms: influence on peripheral and neurodegenerative diseases. Iron overload, ferroportin inhibition, and consequent autophagic degradation of ferritin worsen the free iron accumulation and promote iron import inside the mitochondria through DMT1 and Mitoferrin 1 and 2. Excess iron levels in mitochondria leads to mitochondrial dysfunction, altered mitochondrial dynamics (increase of fission processes), reduced ATP production and increase in ROS production. ROS release induces membrane lipid peroxidation and trigger ferroptosis mechanisms fueling the pathogenesis of peripheral disorders and neurodegenerative diseases.

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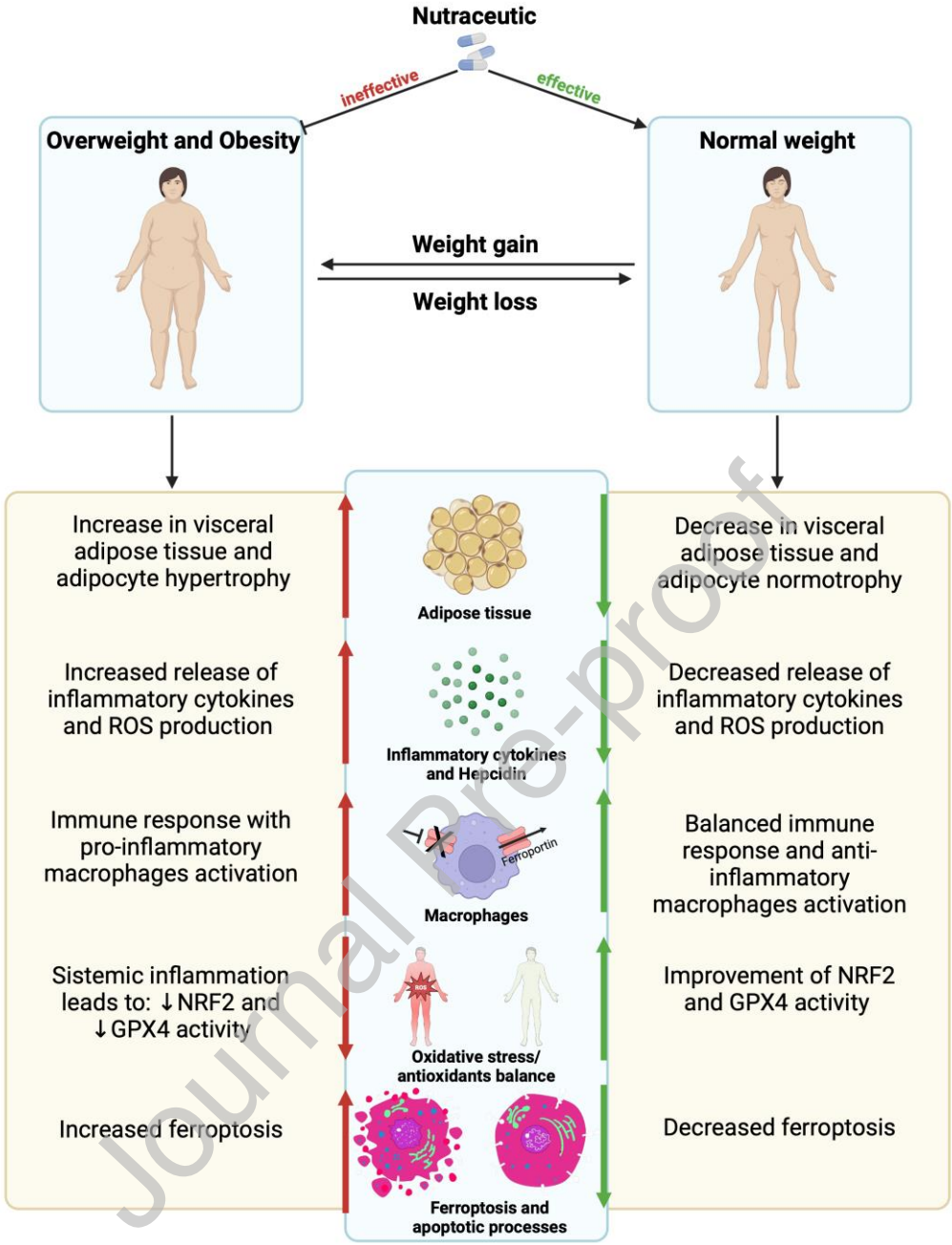

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Figure 6. Obesity and iron deficiency. In overweight and obese people, the increase in adipose tissue and adipocyte hypertrophy results in: increased release of pro-inflammatory cytokines from adipocytes, increased release of hepcidin from the liver, increased iron sequestration by macrophages. Furthermore, in these subjects, normal intestinal absorption is damaged, therefore iron uptake is compromised, and the use of nutraceuticals is futile. As a result, lowered circulating iron levels and iron deficiency occur. Conversely, weight loss involves: less release of inflammatory cytokines from adipocytes (which become normotrophic), less release of hepcidin from the liver and normal release of iron from macrophages. Furthermore, in these subjects, the normal intestinal absorption of nutrients is restored, therefore iron uptake becomes optimal, and the use of nutraceuticals is effective. As a result, circulating iron levels normalize.

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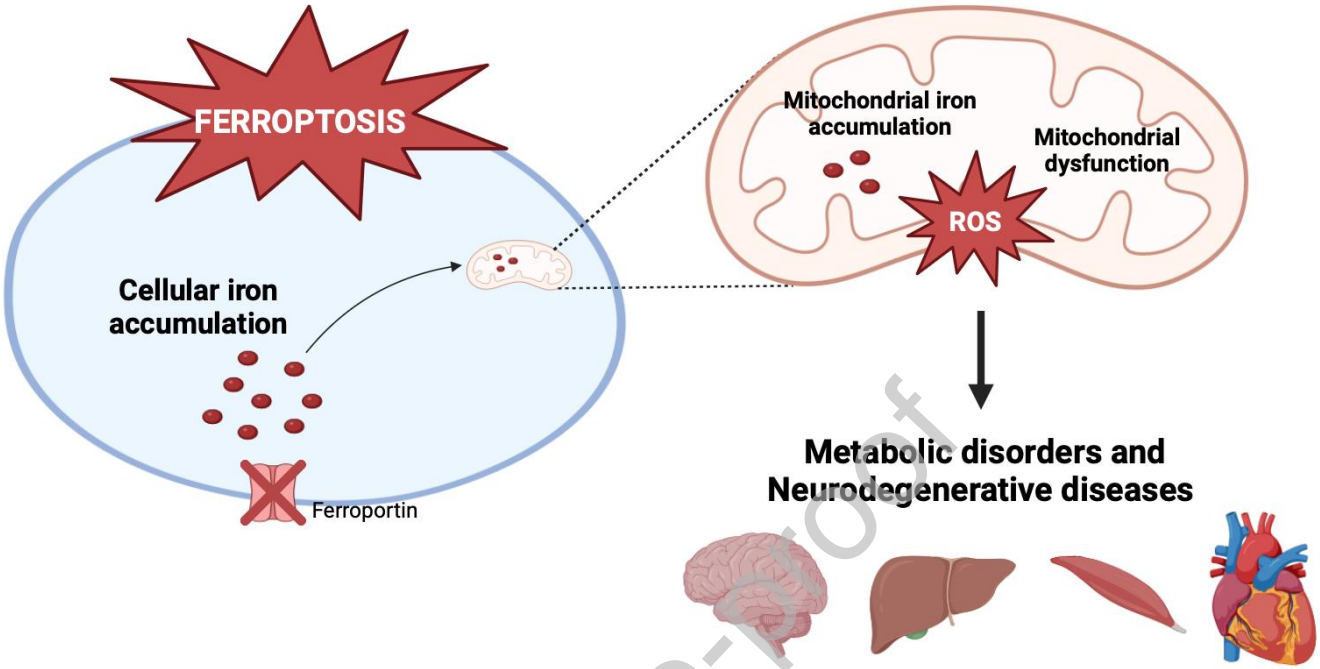

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Declaration of interests

☒ 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.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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