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Review

Unraveling the interplay between iron homeostasis, ferroptosis and extramedullary hematopoiesis

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ABSTRACT

Iron participates in myriad processes necessary to sustain life. During the past decades, great efforts have been made to understand iron regulation and function in health and disease. Indeed, iron is associated with both physiological (e.g., immune cell biology and function and hematopoiesis) and pathological (e.g., inflammatory and infectious diseases, ferroptosis and ferritinophagy) processes, yet few studies have addressed the potential functional link between iron, the aforementioned processes and extramedullary hematopoiesis, despite the obvious benefits that this could bring to clinical practice. Further investigation in this direction will shape the future development of individualized treatments for iron-linked diseases and chronic inflammatory disorders, including extramedullary hematopoiesis, metabolic syndrome, cardiovascular diseases and cancer.

1. An overview of iron and ferroptosis: it all starts from *ferrum*

1.1. Some historical milestones in the study and understanding of iron

For biological entities, the precise regulation of iron homeostasis is critical for the proper functioning of the cellular machinery and for preventing the toxicity derived from an overload of this trace element. Iron deficiency is a unique condition within a group of disorders of similar etiology. It is the depletion of absolute body iron content, especially of hepatocyte and macrophage iron stores, and its diagnosis is straightforward unless the setting is masked by an inflammatory milieu. Iron deficiency often resembles iron-deficiency anemia, as anemia is its more evident sign; however, it is a broader concept [1–3]. Iron overload or excess storage, an opposite condition to iron deficiency, can be classified based on different criteria such as the access route within the body, the predominant site of storage, or the cause of its overload. Regarding the latter classification, iron overload can be primary (often inherited) or secondary to other pre-existing factors/conditions such as hemolysis, transfusion, or excessive parenteral and/or dietary consumption of iron [4–6]. Iron has many crucial functions in mammalian cells, including the catalysis of metabolic redox reactions and oxidative phosphorylation, DNA synthesis, heme formation, oxygen transport and

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storage, and erythrocyte fate. By enhancing the release of reactive oxygen species (ROS), it is also a major contributor to tissue damage through its effects on lipids, proteins and even DNA [7,8].

While the importance of iron has been recognized since ancient times (and from its knowledge by the ancient Egyptian, Hindu, Greek and Roman cultures) [7], we have to fast-forward to the 1990 s when the study of its biology began to flourish through seminal studies by Finch and Feder. Finch was the first to describe the role of erythropoiesis and iron stores in the regulation of systemic iron metabolism, hypothesizing the existence of erythroid and iron store regulators [9]. Feder and colleagues identified the mutation in the *HFE* (homeostatic iron regulator) gene related to classical hereditary hemochromatosis, which results in excess iron deposition and consequent multi-organ damage [10]. These findings, added to earlier research on ferrokinetics and subsequent studies using molecular and genetic approaches, led to a better understanding of iron regulation disorders, which can lead to the development of serious diseases that are among the most common in humans [7, 1112].

1.2. Iron regulation

Iron modulates itself through regulatory proteins (and the genes that encode them), which regulate its uptake, recycling and storage. Among them, the acute-phase peptide hepcidin, which is synthesized in the liver, is an important modulator of iron homeostasis owing to its control by mediators dependent on the iron stores present in macrophages [13], erythropoiesis and inflammation [14,15]. Hepcidin expression in hepatocytes is controlled mainly by the bone morphogenetic protein-SMAD (BMP-SMAD) pathway [16]. Functionally, hepcidin promotes the degradation of the iron exporter ferroportin (FPN) in gut enterocytes and in macrophages, which reduces iron uptake [3,8,12]. Other important molecules involved in the cellular regulation of iron include the iron storage and release protein ferritin and the iron transporter glycoprotein transferrin. Ferritin is present in the cytoplasm in almost every cell, whereas transferrin is synthesized and secreted by the liver. Interestingly, similar to transferrin, ferritin can also be released into circulation, albeit at moderate levels [17,18]. Both proteins contribute to iron redistribution, maintaining it in a nonreactive form that prevents the release of oxygen radicals; ferritin stores most of the iron in the body. The process by which iron is released from ferritin has recently attracted attention for its association with human diseases. This process has been defined as ferritinophagy [19–21], a selective autophagy pathway. It is triggered by nuclear receptor coactivator 4 (NCOA4) on the surface of autophagosomes, which targets ferritin for lysosomal destruction [22,23]. Levels of iron inversely modulate the levels of NCOA4 and, therefore, the number of ferritin molecules to be processed and the released iron. This is a key process in the regulation of erythropoiesis, in which hepcidin plays a significant role by regulating the cellular iron levels (6). The aforementioned mechanisms are important for the global flow of iron inside the body through the participation of the small intestine, the bone marrow, the liver, the spleen and the circulatory system, among others [12,19,22,24]. Fascinatingly, the microbiota (now considered as a human organ [25,26]) has been recently related to iron homeostasis and bioavailability [27,28]. The gut microbiota depends on iron, and its deficiency negatively influences the microbial ecosystem and can harm the health of the host. Iron is also essential for pathogenic bacteria, but there are different requirements for this metal owing to the considerable variability of microorganisms [27,29]. Iron accumulation and lipid peroxidation in the brain has been linked to cryptococcal meningitis [28], and both processes are the main characteristics of iron-programmed cell death, or ferroptosis.

2. Iron-dependent cell death

Recent studies have defined ferroptosis as a new type of non-apoptotic cell death characterized by high levels of iron accumulation and lipid peroxidation [5,30–33]. The term was first coined in a landmark paper by Brent R. Stockwell and colleagues in 2012 [34], where they described a type of oxidative cell death that results from a pronounced decrease in the antioxidant capacity of cells and an increase in lipid-related ROS due to the sum of factors that affect the activity of glutathione (GSH) peroxidases. In this regard, lipoxygenases (LOXs) and their products, lipid hydroperoxides, are thought to be key participants in the initiation and progression of ferroptosis through the induction of lipid autoxidation. Pharmacological inhibition of LOX isoforms (5-LOX, p12-LOX and 15-LOX-1) is protective against ferroptosis [35].

Cell morphology and function differentiate ferroptosis from other types of cell death (apoptosis, necrosis, autophagy, necroptosis, pyroptosis, oxidative glutamate toxicity or parthanatos) [33,36–39]. Moreover, ferroptosis has unique morphological characteristics including shrunken mitochondria with increased membrane density and loss or reduction of mitochondrial cristae, and ruptured outer membrane, normal-sized nuclei and non-condensation of chromatin. From a biochemical perspective, ferroptosis is defined by the depletion of intracellular GSH and reduced activity of glutathione peroxidase 4 (GPX4), which hinders the reduction of lipid peroxides and leads to ROS generation through the Fenton reaction-dependent oxidation of lipids by Fe^{2+} [40]. The basic mechanisms regulating ferroptosis and phospholipid peroxidation have been studied in depth in recent years [33]. Ferroptosis is considered as an important downstream pathway of oxidative stress [32,41]. In addition to this, oxidative and metabolic stress are connected to human diseases [42,43] and this includes altered bone marrow hematopoiesis and extramedullary hematopoiesis (EMH) [44,45].

3. Iron, ferroptosis and EMH: an undefined link possibly connected to severe clinical outcomes

Iron biology and ferroptosis likely have a relevant impact on inflammation, chemotherapy, photodynamic therapy and neurodegeneration. Yet, few studies have examined the relationship between iron, ferroptosis (reviewed in [46]) and EMH, which is the topic discussed in the present review (see graphical abstract).

EMH is defined as the development and growth of hematopoietic cells outside the medullary spaces of the bone marrow [45,47–49], with the most common sites being the spleen and liver [47]. This manifestation of compensatory hematopoiesis typically occurs under adverse conditions, such as the insufficient or inappropriate formation of blood cell components by the bone marrow (i.e., chronic hemolytic anemias, thalassemias, atherogenesis, and lymphomas or leukemias) [45], but excessive EMH can trigger inflammatory diseases [45]. EMH can also occur when the bone marrow becomes an inhabitable niche for stem and progenitor cells due to the replacement of the niche by collagenous fibers (such as in myelofibrosis) [48].

Interestingly, enhanced erythroid EMH in the spleen (mainly occurring in the red pulp) contributes to decrease the synthesis and release of hepcidin [50] and lowers iron availability [49]. All blood cell lineages are generated and replenished during hematopoiesis by hematopoietic stem cells (HSCs) [51]. As an example of the potential link between iron, ferroptosis and EMH, we recently described the contribution of the immune receptor nucleotide-binding oligomerization domain 1 (NOD1), which is associated with leukocyte ontogeny and recruitment, to iron metabolism and ferroptosis regulation in the spleen, a relevant organ in EMH [52,53]. The potential interplay between iron, EMH and ferroptosis is discussed in the following subsections.

3.1. Iron and hematopoietic cells

3.1.1. Erythrocytes

Mature red blood cells (RBCs) are highly specialized cells that are the result of a complex maturation process from HSCs. Given that 200

billion of these mature cells are generated daily, requiring 25 mg of iron, it is not surprising that iron physiology is important for the regulation of the erythroid lineage.

Erythroid precursors contain molecules, such as transferrin receptors (TFR), whose main functions are the transport, use and storage of iron [54,55]. They are characterized by their enormous requirements for iron to maintain hemoglobin synthesis, and the recycling of iron from senescent RBCs by macrophages is crucially important for internal iron flux. Iron homeostasis is also controlled by the absorption of iron from the diet, which can balance iron requirements when levels are low (i.e., during childhood, hypoxia, or pregnancy) or iron is lost (as in bleeding) [56,57]. These finely regulated molecular and cellular mechanisms are essential to support the supply of oxygen (and iron) to cells and all body tissues, and have motivated the study of the mechanisms involved. As an example, the erythroid hormone erythroferrone suppresses hepcidin, which enhances the bioavailability of iron for hemoglobin synthesis in times of erythropoietic stress [3,58]. In addition, iron deficiency impairs erythropoietin production through the iron regulatory protein 1-hypoxia inducible factor 2α (IRP1-HIF2α) pathway, which prevents the wasteful use of iron for erythropoiesis during iron restriction conditions [56].

3.1.2. Other hematopoietic cells

In addition to its well-recognized roles in erythropoiesis and erythrocyte homeostasis, iron also contributes to the development of other hematopoietic cell lineages. Accordingly, changes in iron levels (either due to deficiency or over-abundance) can negatively influence hematopoietic flow, affecting the normal biology of different hematopoietic cell lineages and leading to several diseases [4,11,59–65].

3.1.3. Iron: from its deficiency to its excess

Iron deficiency impairs embryonic hematopoiesis by inhibiting proliferation, clonogenic capacity and survival of progenitor cells. It does not, however, affect the endothelial-to-hematopoietic transition, which is the first stage of hematopoiesis [58]. Erythroid-myeloid progenitors appear to be more influenced by iron deficiency than primitive erythroid cells [64].

In contrast to iron deficiency, more studies have been carried out on iron overload, both primary and genetically determined or secondary to other conditions, [31–38]. It is widely known that iron can be very toxic to the bone marrow, leading to ROS accumulation, changes in the expression of hematopoiesis-regulatory genes and the deterioration of the hematopoietic microenvironment (Fig. 1).

3.1.3.1. *Promising strategies for iron overload at a glance.*

Iron chelation therapies, such as deferasirox, have been developed to mitigate the deleterious effects of iron overload [4,65]. NADPH oxidase 4 and p38-MAPK (p38 mitogen-activated protein kinase) signaling pathways have been identified as being responsible for the ROS-dependent damage in bone marrow hematopoietic cells under iron overload [59]. Other studies demonstrated that both p38-MAPK and JNK (Jun N-terminal kinase) pathways are involved in disturbances in hematopoietic stem/-progenitor cells and natural killer cells during iron overload in myelodysplastic syndromes [61]. The impact of iron excess in myelodysplastic disorders has been studied in depth [6,61,62]. Other approaches for the treatment of iron overload, some in the preclinical phase, include antioxidants (flavonoid compounds such as quercetin), calcium channel blockers (nifedipine or amlodipine acting on divalent metal transporter-1 [DMT1]) [66], ebselen (DMT1 inhibitor; [67]), erythropoiesis modulation inhibitors (such as luspatercept, ACE-536; and sotatercept, ACE-011) [68], phytochemicals and phytochelants [69], minihepcidin peptides (alone or in combination) or other strategies, such as targeting TMPRSS6, a type II transmembrane serine protease that is primarily expressed in the liver and downregulates hepcidin expression through the BMP-SMAD pathway [3,70].

3.1.3.2. *Iron deficiency/overload: the importance of iron regulation in cardiovascular diseases.*

Cardiovascular diseases, which are responsible for ~30% of all global deaths, are known to be affected by hematopoiesis and leukocyte accumulation [52,53,71]. Interestingly, both the deficiency or the excess of iron are frequently observed in a many of these diseases, favoring their onset and determining their development and fate [72]. Cellular uptake of iron occurs by the binding of iron-laden transferrin, containing two ferric iron molecules, to transferrin receptor protein 1 (TFR 1). This triggers the endocytosis of the protein complex dependent on clathrin. Acidification of the endosome by vacuolar ATPase leads to reduction to ferrous iron, which is then released into the

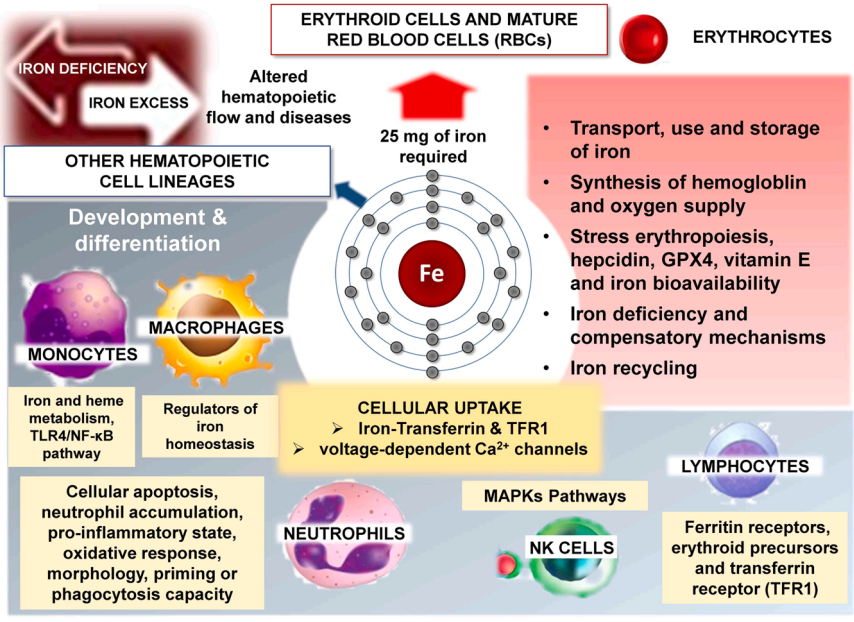

Fig. 1. Iron dependence and regulation of hematopoietic cells and derived lineages. Virtually all organisms require iron to carry out their functions. Subtle changes in the body's iron concentrations, including its deficiency or overabundance, have consequences for physiological processes, such as hematopoiesis. Iron dysregulation affects hematopoietic cell lineages and can cause different diseases.

cytoplasm by the DMT1 transporter. This underscores the potential for DMT1-targeted approaches in iron-overload cardiovascular diseases. There is some controversy about whether non-transferrin-bound iron is transported into cardiomyocytes by voltage-dependent calcium channels [73]. As an example of this process, it has been described that L-type Ca^{2+} channels have a role in iron transport and iron-overload cardiomyopathy. These channels can take-up ferrous iron in cardiomyocytes in a highly effective manner and especially under iron excess conditions. Indeed, L-type Ca^{2+} channels may also contribute to iron uptake in other excitable cells including pancreatic β-cells and neurons. Accordingly, inhibitors of these types of channels represent a promising new therapy to diminish the adverse effects of iron overload [74]. Curiously, calcium has been demonstrated to inhibit iron absorption. Firstly, $CaCO_3$ was demonstrated to inhibit Fe absorption in experimental models, and later studies showed that several sources of Ca (including $CaCO_3$, $CaCl_2$, calcium phosphate and calcium lactate) reduced the retention of Fe and the rate of hemoglobin regeneration in animals [75]. Among the mechanisms responsible for these inhibitory effects of calcium, the presence of one-site competitive binding at a receptor has been suggested, making it an interesting target in iron-related diseases and especially in those involving iron overload [75].

3.1.4. Iron regulation and immune cells

Several receptors for iron-regulation proteins are expressed by hematopoietic immune cells. For example, lymphocytes express ferritin receptors [76], whereas activated lymphocytes, erythroid precursors and most rapidly dividing cells express the classical transferrin receptor (TFR1) [5,12,77]. Megakaryocytes, which generate thrombocytes/platelets, and the myeloid lineage, particularly phagocytic cells (macrophages and neutrophils), have been tightly linked to iron homeostasis. In the case of neutrophils, their link to iron includes the control of cellular apoptosis (the intrinsic pathway) and oxidative responses. However, because macrophages are the main players in iron homeostasis and erythroid cell proliferation and differentiation, most of the research has focused on these populations [60,77]. As a recent example, the role of iron and heme metabolism has been studied in inflammatory responses mediated by TLR4/NF-κB (Toll-like receptor 4/ nuclear factor κB) signaling in human monocytes [78].

3.2. Hematopoiesis, iron and inflammation

Hematopoiesis has long been associated with inflammation and infection [79–81]. Given the breadth of studies in these fields, we will only briefly touch upon the relationship between iron and these processes.

3.2.1. Hematopoietic cells and inflammatory milieu in EMH: a role for damage signals, cytokines and growth factors

HSCs are exposed to inflammatory or damaging signals that allow them to replenish mature immune cells under conditions of infection or tissue injury. HSC proliferation and differentiation are essential during these inflammatory processes, but they need to be tightly regulated to avoid immunopathology. Indeed, prolonged exposure to inflammatory signals triggers HSC aging and the selection of malignant-prone HSC clones [80,82]. As an example of stem cell exposure to inflammatory signals, HSCs are the main target of the IL-23 (interleukin-23)-dependent inflammatory pathway in colitis, a disease that presents with an abnormal intestinal accumulation of inflammatory monocytes and neutrophils. This indicates that inflammatory cytokines mediate hematopoiesis dysregulation. Also, interferon-γ (IFN-γ) participates in the medullar and splenic accumulation of proliferating HSCs, which promotes EMH [47]. More recently, it has been shown that granulocyte-macrophage-colony stimulating factor (GM-CSF) causes HSC dysregulation and pathogenic EMH in experimental models of spondyloarthritis. This disease is characterized by systemic inflammation and comprises different inflammatory arthropathies, such as psoriatic or enteropathic arthritis. In this regard, HSCs and both bone marrow and EMH play important roles [83].

3.2.2. Inflammatory-derived EMH sites

EMH sites can be established in areas of local inflammation, injury, ischemia or tissue repair. This is made possible by the molecular, cellular or stromal factors and/or the changes associated with these complex processes, which mimic those contributing to hematopoiesis. Along this line, a large number of inflammatory mediators and cytokines can enhance the number of peripheral HSCs, leading to their establishment in damaged tissues and their participation in local inflammatory or regenerative processes [49].

3.2.3. Oxidative stress and HSCs

HSC function is not only affected by acute and chronic lesions or infectious processes, but also by auto-inflammatory pathologies, irradiation, and physiological or pathological states such as aging, obesity or cardiovascular diseases [82,84]. Oxidative stress is a principal underlying mechanism in these settings. Indeed, both experimental and clinical research have identified ROS and Nrf2 (nuclear factor erythroid 2-related factor 2) as important participants in the functional and transcriptional regulation of HSC biology and hematopoiesis [85]. HSCs are mainly located in the hypoxic niche of the bone marrow and their function is modulated by both intrinsic (signaling pathways) and extrinsic (multiple, with the most influential derived from the micro-environmental niche) factors. ROS can behave as either intrinsic (endogenous ROS, mainly derived from oxidative metabolism in mitochondria, inflammatory pathways or metabolic processes) or extrinsic (external sources) mediators. ROS levels in HSCs contribute to their mobilization, migration, proliferation, repopulation potential and differentiation, and ROS overload damages DNA and triggers cell cycle arrest. In this regard, Nrf2 acts as a master modulator of cellular antioxidant responses, being key in the metabolism of ROS and redox modulation of HSCs [85]. Nrf2 is now considered as a master transcription factor in ameliorating lipid peroxidation and ferroptosis through its regulation of downstream targets, such as several redox enzymes (e.g., glutathione-S-transferases pi-1 and α-1, GSTP1 and GSTA1, thioredoxin reductase, TXNRD1, and even GPX4) or, perhaps more importantly, by regulating ferritin and FPN. It is also an essential transcriptional modulator of anti-ferroptotic genes that play roles in mitigating lipid peroxidation and ferroptosis [86,87]. These data provide a link between iron and ferroptosis with the modulation of oxidative stress and subsequent tissue damage. Notably, inflammation is also considered a hallmark of tissue injury.

3.2.4. Anemia of inflammation

Among the many debilitating disorders related to iron deficiency, anemia of inflammation (AI) (or anemia of chronic disease) is arguably the most studied link between iron and inflammation [14,18,57,88–90]. AI is an acquired, multifactorial disorder of iron regulation associated with prolonged immune activation such as infections, inflammatory diseases or malignancies. It is a typically normocytic normochromic anemia characterized by macrophage-mediated iron retention due to diminished iron export. During inflammation, enhanced levels of serum hepcidin are induced through the IL-6/STAT3 (interleukin-6/signal transducer and activator of transcription 3) axis, which triggers FPN degradation. Cytokines such as IL-1β also participate in this process. Inflammation similarly promotes iron-binding proteins including haptoglobin, lactoferrin, hemopexin and lipocalin 2, which limit iron availability for erythropoiesis, [57,89]. AI is the most common anemia in chronically ill and hospitalized patients [14]; however, at the onset of inflammation, AI and iron-deficiency anemia can be difficult to differentiate, and the two can also coexist [89].

3.2.5. Anemia, inflammatory diseases, iron levels and hepcidin, and heme regulation

Anemia has also been linked to other inflammatory diseases such as inflammatory bowel disease [91–93] (wherein the gut microbiota seems to have an important role in the regulation of the hepcidin-FPN axis [57]), rheumatic disorders [94], or splenomegaly linked to EMH [95]. In addition, inflammatory cytokines and hepcidin, as a master regulator of iron homeostasis, block the intestinal absorption of iron and its retention by reticuloendothelial cells, leading to iron-restricted erythropoiesis and further contributing to AI [14]. Interestingly, hepcidin expression is not only regulated by anemia, serum iron levels and erythropoiesis, but also by hypoxia, infection and inflammation [90,96]. Hepcidin is closely related to inflammatory diseases [15]. Furthermore, heme catabolism is also associated with inflammation and its immunomodulation, and appears to have a leading regulatory function in various physio- and pathological processes, particularly cell protection and apoptosis. Among these intricate mechanisms, heme oxygenase 1 (HO-1) is prominent, as it can catabolize free heme into Fe^{2+}, CO and biliverdin/bilirubin [97].

3.3. Iron, ferroptosis and EMH

3.3.1. Ferritinophagy

Several recent reviews have updated the molecular mechanisms associated with ferroptosis and their potential therapeutic control [19,31,98,99]. As an example of these pathways, ferritinophagy is known to induce ferroptosis by triggering iron overload following ferritin degradation. Excess Fe^{2+} promotes the peroxidation of lipids, favoring plasma membrane damage and further ferroptotic cell death. Indeed, it is thought that ferritinophagy may directly impact the activity and function of metabolic enzymes that contain Fe^{2+}, such as phenylalanine hydroxylase, by delivering Fe^{2+} to the cytoplasm. Accordingly, the inhibition of this specific type of autophagy may help to mitigate metabolic and inflammatory diseases whose underlying cause is ferroptosis [19,100,101].

3.3.2. Iron and EMH

Despite their obvious connection and the many pieces of evidence outlined in previous sections, there are scarcely any studies that link iron with EMH. For example, it is known that the absence of cardiac iron correlates with EMH in patients with thalassemia who have been polytransfused [47]. In this study, patients with EMH were all splenectomized and presented higher concentrations of the soluble form of the transferrin receptor and a higher nucleated RBC count. In addition, the patients had a lower transfusional iron intake and an elevated hemoglobin level after transfusion [44]. Most of them were highly predisposed to thrombotic events. With regard to the improved red blood cell counts mentioned above, it has been shown that GPX4 and vitamin E indirectly regulate stress erythropoiesis, iron biology, and reticulocyte maturation. Indeed, deficiency of *Gpx4* in murine hematopoietic cells triggers iron excess in the bloodstream [58].

3.3.2.1. Iron-EMH-macrophage axis: a ferroptosis perspective. As we briefly mentioned earlier, macrophages perform essential immune-metabolic functions and also regulate iron flow, and so their involvement in ferroptosis (and EMH) is fundamental. Macrophages are known to maintain a very close relationship with erythroid cells from their origin until their death. Erythrocyte development is favored by a specialized subclass of macrophages (the nurse macrophages), mainly under stressful settings, and they are also responsible for their own destruction when senescent and for iron recycling to maintain erythropoiesis [102]. Indeed, heme per se can stimulate the differentiation of monocytes into iron-recycling macrophages by activating the heme-binding transcriptional repressor BACH1 (Btb and Cnc homology 1). This, in turn, induces a specific cell differentiation program through the transcription factor SPI-C [57,103]. As an example of the role of macrophages in iron-related cell death, recent evidence has indicated that differential activation signals in macrophages establish sensitivity to lipid peroxidation process and ferroptosis [104]. We also recently described an important link between iron, ferroptosis and macrophage regulation dependent on NOD1 activation [52,53,105,106]. In this work it is shown that under hypercholesterolemic and athero-prone conditions in mice, the spleen shows elevated counts of macrophages in the absence of NOD1, while iron levels in this tissue are decreased [49]. In addition, in these mice, splenic mRNA levels of iron-related genes such as *Slc40a1* (which encodes for ferroportin 1, FPN1), *Spic* and *Slc7a11* are enhanced [52,53]. Interestingly, Gpx4 levels increase upon NOD1 activation, pointing to a protective role of this immune receptor against ferroptosis in the spleen [52]. These findings allow us to suggest that ferroptosis is closely related to EMH despite the paucity of studies directly linking the two concepts. As we will discuss in the next section, more research in this field would add clarity and might inform new clinical practice treatments.

4. Ferroptosis and inflammation: benefits from their association with EMH and novel strategies to combat important diseases

Ferroptosis is pro-inflammatory due to its immunogenicity, as it triggers the release of different damage-associated molecular patterns, such as high-mobility group box 1 and lipid metabolites, which function to modulate immune response but ultimately induce a type of immunogenic cell death. As an example, ferroptosis-derived immunogenicity plays an important role in inflammation following ischemia-reperfusion injury [107,108]. Not surprisingly, agents that inhibit ferroptosis have been shown to have anti-inflammatory activity in several diseases [108].

The new field of ferroptosis and inflammation has been studied in depth in recent years [26,32,38]. Ferroptotic cell death has been described at sites of inflammation in different severe disorders, including inflammatory bowel disease and acute pancreatitis. This is based on the concurrence of lipid peroxidation metabolites (e.g., malondialdehyde) and gene expression profiles associated with ferroptosis [26]. Both deficient or excessive ferroptotic cell death contributes to a wide range of physio- and pathological mechanisms and are linked to impaired immune responses [26]. Ferroptosis-specific necrotic signaling pathways produce harmful factors that dysregulate the immune system by activating immune cells. Subcellular structures such as destructive peroxisomes or ruptured mitochondria are also upregulated under these conditions [38].

Ferroptosis is directly and closely associated with the biological processes of relevant diseases as varied as kidney injury, cancer, nervous system dysfunctions, or blood-related pathologies [40]. In the latter case, ferroptosis is considered a novel key regulator of blood cells and their differential functions, including neutrophils, T-cells, B-cells, or platelets [109].

Of note, most of the aforementioned diseases are also related to inflammatory processes involving the recruitment of myeloid cells and the release of chemoattractants and inflammatory cytokines. Because of this, specific approaches that focus on regulating ferroptotic cell death might be promising tools in many areas of precision medicine, as described below.

4.1. Ferroptosis, metabolic syndrome and diabetes

Of all the metabolic diseases, patients with diabetes might derive the most benefit from the study of ferroptosis regulation [110–115]. Hyperglycemia and insufficient endogenous insulin (or its misuse) are the main characteristics of diabetes, and several mechanisms linked to ferroptosis have been studied in the development of diabetic disease. For example, ferroptotic cell death contributes to impaired glucose-stimulated insulin secretion and pancreatic damage induced by arsenic [116].

Diabetic complications like myocardial ischemia or diabetic cardiomyopathy are also worsened with ferroptosis [111,114]. Indeed, recent evidence correlates poor wound healing, involving oxidative stress and inflammation at the wound site, with ferroptosis. Specifically, fibroblasts and vascular endothelial cells exhibited altered survival and migration under these conditions of diabetic ferroptosis [110].

Other studies again link oxidative stress, Nrf2 and HO-1 in the setting of hyperglycemia with ferroptosis [113,115], and a mitochondrial regulation of ferroptosis has also been proposed [117]. Ferroptosis is also considered an important player in other metabolic diseases [118]. Ferroptosis-regulating molecules participate in complex metabolic networks that modulate, for instance, cysteine use, GSH status, nicotinamide adenine dinucleotide phosphate function, lipid peroxidation, or iron homeostasis, which all of contribute to human health or disease when impaired [119]. As an example, enhanced levels of hepcidin, iron and ferroptosis are all well-known markers of obesity, in addition to chronic and systemic low-grade inflammation [7].

4.2. Ferroptosis, cardiovascular diseases and atherosclerosis

Cardiovascular diseases, including ischemic heart disease, stroke and atherosclerosis, are the leading cause of mortality and morbidity worldwide [120,121]. The relationship between cardiovascular diseases and ferroptosis has been extensively studied in recent years because of its potential therapeutic applications [32,46,122–128]. Myocardial infarction, heart failure, cardiomyopathy, ischemia/reperfusion injury and atherosclerosis are all tightly related to iron-dependent cell death. As an example, cardiac mTOR inhibits ferroptosis and ROS release in the setting of myocardial infarction, whereas its deficiency triggers iron-induced cell death. Indeed, ferroptosis was found in the infarcted myocardium and cardiomyocytes after hypoxic injury. However, both iron overload and iron deficiency are related to heart failure and cardiomyocyte function [124,126,127,129]. Another recent study found a direct relationship between ferritinophagy-derived iron and cardiomyocyte death and heart failure induction [130].

In the setting of atherosclerosis, which is profoundly influenced by lipid homeostasis and peroxidation, GPX4 overexpression was shown to alleviate aortic atheroma lesions in an *Apoe*$^{-/-}$ mouse model [131]. Other studies have examined the link between atherosclerosis and ferroptosis, involving oxLDL, NOD1 and enzymes such as cyclooxygenase 2 and or ACSL4 (acyl-CoA synthetase long-chain family member 4), among others [52,132]. Ferroptosis also affects other atherosclerosis-related cells such as vascular endothelial cells, macrophages and vascular smooth muscle cells [122,124,128,133]. Accordingly, targeting ferroptosis emerges as promising approach to treat or prevent cardiovascular diseases.

Accumulating evidence suggests that iron chelators, ferroptosis inhibitors, genetic manipulations and antioxidant molecules can be used to block ferroptosis and alleviate vascular and myocardial injury. For instance, deferoxamine is an approved very high-affinity iron chelator with cardioprotective properties that can protect against ferroptotic cell death. In addition, dexrazoxane is the only FDA-approved iron-chelator drug, and it also shows cardioprotective benefits and ferroptosis inhibition characteristics in animal models of doxorubicin-induced cardiomyopathy [32,123,125].

4.3. Ferroptosis and other inflammatory diseases

Inflammatory diseases can occur in almost all human tissues and organs including the liver, lungs and heart [134], and ferroptotic cell death has been reported in these different anatomical sites (Fig. 2).

Ferroptosis has been studied in severe liver inflammatory diseases [20,135,136], including nonalcoholic steatohepatitis [137–139] and fibrosis [140,141]. These important discoveries have opened up new research fields on potential pharmacological strategies, such as studies using the anti-malarial drug artesunate to ameliorate liver fibrosis through its modulation of ferroptosis [21,30].

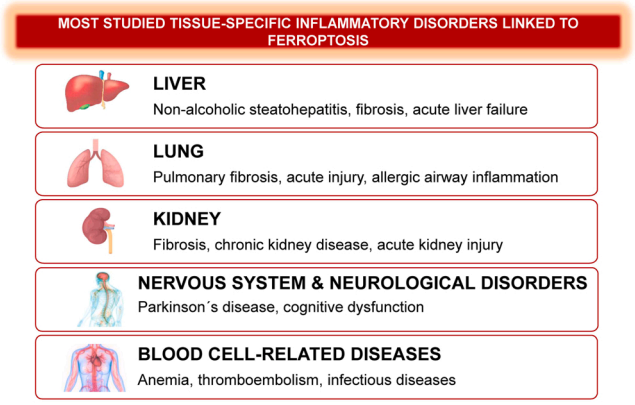

Fig. 2. Inflammation, tissue dysfunction and ferroptosis. Relationship between ferroptosis, inflammatory processes and tissue damage. Interestingly, the same organs are also studied (but independently) in the context of cancer and ferroptosis.

Beyond the liver, ferroptosis is also being studied in kidney disorders (mainly involving ROS-dependent mechanisms, lipid accumulation and subsequent ferroptotic cell death leading to kidney injury [142–144]), lung dysfunction, where oxidative stress and uncontrolled inflammatory responses can occur after sepsis, injury, smoking or toxic gas inhalation, among others [145–147]), and blood cell-related diseases, as ferroptosis influences the function of blood cells and ferroptosis impairment affects erythropoiesis and the development of erythrocytes, causing anemia.

Ferroptosis also contributes to neutrophil recruitment, formation of neutrophil extracellular traps, B-cell differentiation and antibody responses, T-cell polarization and function [109]), and nervous system and neurological diseases. Indeed, ferroptosis has been studied as a key mechanism of cell death in intracerebral hemorrhage, stroke, acute brain injuries and degenerative brain dysfunctions [148,149]. In the latter case, several features of Parkinson's disease are similar to ferroptosis processes, including iron accumulation, lipid peroxidation, oxidative stress and damage [150,151].

In addition, it should be noted that both hematopoiesis (classical or extramedullary), and the functions exerted by hematopoietic cells and derived leukocytes are essential regarding the generation, regulation, protection and regeneration of these organs (liver, kidney, brain, etc.) [152–154], reinforcing the suggested ferroptosis-hematopoiesis interplay.

4.4. Ferroptosis and cancer

Cancers present with a high inflammatory component, but beyond inflammation, ferroptosis mechanisms play crucial roles in their biology [136]. A new compound, erastin, was discovered in 2003, presenting a lethal and selective effect on RAS-expressing cancer cells [40]. Additionally, later studies showed that iron-chelating molecules inhibited this new type of cell death, thus linking it to iron regulation, and to cancer biology [155]. In this line, a new compound called RSL3 (RAS-selective lethal 3) was further found to trigger iron-dependent cell death [40]. Cancer cells need significantly more iron to survive than normal cells and, accordingly, they are more susceptible to iron-dependent cell death. This holds promise for new therapies, as targeting ferroptosis arises as a valuable molecular strategy to fight therapy-resistant cancers [37,156].

Ferroptosis is garnering more attention in oncological research and it has been investigated in many types of cancer, including colorectal, breast, lung, and pancreatic cancer, and also metastasis [37,157–161]. Given the breadth of recent studies in this field and the different metabolic pathways involved, such as PI3K-AKT-mTOR signaling [162,

163], we will only cite some examples of interest (Fig. 3).

For lung tumors, ferroptosis has become a novel target with promising clinical potential. Lung cancer patient samples (serum, bronchoalveolar lavage fluid and exhaled air condensate) show elevated ferritin levels, and TFR1 is highly expressed in most non-small-cell lung cancers, suggesting enhanced iron intake by lung cancer cells. Indeed, ferroptosis and lung cancer cells are connected by signaling pathways and molecules as varied as lymphoid-specific helicase (LSH), NFS1 (mitochondrial cysteine desulfurase) enzyme, long noncoding RNAs, Nrf2/HO-1, serine/threonine tyrosine kinase 1/novel oncogene with kinase domain (STYK1/NOK), ferroptosis suppressor protein 1 (FSP1) or p53 [77,156,164–167].

As a key protein in stress and cancer regulation, p53 has been studied in the context of ferroptosis. Protein polymorphisms in p53 are known to affect the response to cell fate [148]. The so-called cancer-related p53 has been further investigated in other tissues where ferroptosis has been demonstrated to have preeminent roles, such as the liver [168]. These findings contribute to the establishment of novel tumor prognostic or therapeutic modalities and different strategies [37,169]. For instance, manipulation of tumor-associated macrophages to a ferroptosis-enhanced state endows potent tumoricidal activity [170]. Novel combination therapies along these lines include the use of both ferroptosis and immune-based strategies, such as myeloid-derived suppressor cells, again pointing to the importance of studying the links between ferroptosis and hematopoiesis [37,169]. Table 1 summarizes ferroptotic processes linking cancer and hematopoiesis. It is known that molecules such as erastin, and the more recently discovered RSL3, trigger RAS activation, which has been widely studied in cancer research. Interestingly, the oncogenic RAS pathway, which is involved in iron metabolism, and the activation of ferroptotic responses remains an open issue depending on the involvement of other molecules such as TFR1, ROS synthesis, and activation of the MAPK and PI3K/Rac1 signaling [171], as shown in Table I. Notably, the indicated pathways are also closely related to the hematopoietic process. For instance, TFRC is a relevant protein in hematopoiesis by binding diferric transferrin and providing iron to cells. Moreover, the MAPK, PI3K/AKT and RAS/-Raf/MEK/ERK signal transduction pathways are imperative for the transmission of signals from plasma membrane receptors to downstream targets, leading to the modulation of essential cellular processes such as cell growth, differentiation, gene expression and apoptosis. This also occurs in hematopoietic cells, in which MAPK signaling cascades are key for their regulation. Additionally, cysteine depletion, considered as a

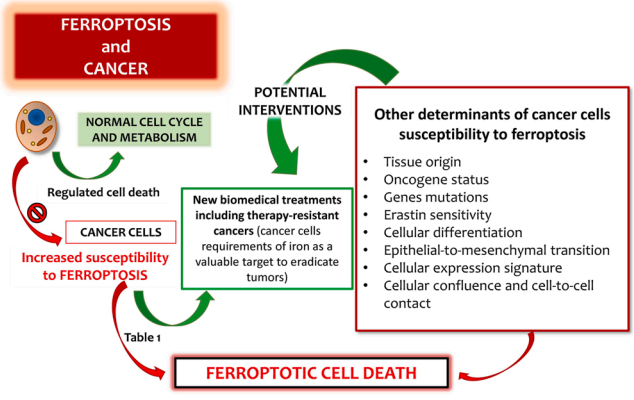

Fig. 3. Ferroptosis: at the forefront of cancer research. Impairment in programmed cell death pathways, such as apoptosis, necroptosis, autophagy-dependent cell death or pyroptosis, can trigger physiological dysfunction. This fact can be translated into the biology and regulationof cancer cells, which require high levels of iron to survive and, therefore, are susceptible to ferroptotic cell death. This involves several mechanisms (described in Table 1). The tendency for ferroptosis in tumor cells can be used to develop targeted treatments to combat resistant cancers.

Table 1
Proposed models for ferroptotic responses associated with cancer and linked to hematopoiesis.

Cause/triggering stimuli	Mechanisms	References
RAS signaling induced by molecules such as erastin or RSL3 (RAS-selective lethal 3)	↑TFR1 (transferrin receptor 1) **↑Intracellular iron** **ROS and p38-MAPK-dependent oxidative response** **NOXs (NADPH oxidases)** **PI3K**/Rac1 (**phosphoinositide 3-kinase**/ RAS-related C3 botulinum toxin substrate 1) **RAS-Raf-MEK-ERK pathway**	[55,60, 189] [190–193]
Cystine/cysteine deprivation	**MAPK pathways,** **iron sulfur cluster generation,** **heme biosynthesis,** **central carbon metabolism,** **production of several intracellular metabolites (i.e., taurine and CoA)**	[190, 194–196]
Hippo signaling pathway	**YAP/TAZ (yes-associated protein 1/ transcription adaptor putative zinc finger)**	[197–199]
Multidrug resistance-associated protein 1 (MRP1)	**Disturbance in glutathione efflux**	[58,177, 200]
Ionizing radiation (IR), ATM (ataxia-telangiectasia mutated)/ATR (ATM and Rad3-related), and tumor suppressor p53	**DNA damage response**	[179–181]
Ferroptosis-inducing molecules (e.g., artesunate)	**Such as GPX4 (glutathione peroxidase 4) and/or the amino acid antiporter SLC7A11/System Xc^- (cystine-glutamate solute carrier family 7 member 11/ System Xc^-) inhibitors** **Ferroptosis and iron- and ROS-dependent manner**	[162,175, 182] [21,59,63, 183]

bold terms are also linked to hematopoiesis

potential therapeutic approach in cancer, has also been associated with MAPK pathways, heme biosynthesis, iron-sulfur cluster generation, regulation of central carbon metabolism, and in the increase of intracellular metabolites such as taurine and coenzyme A.

Interestingly, ferroptosis is also dependent on cell density and confluence through the tumor suppressor Hippo-YAP/TAZ pathway (controlled by TAZ activity), a process linked to the progression of several cancer types [172]. This pathway also promotes ferroptosis, via the E3 Ligase SKP2 in a YAP-dependent manner [173]. Both pathways are required for the normal division and fate of hematopoietic cells, connecting ferroptosis with Hippo signaling and basic physiological processes such as cell proliferation, survival and differentiation.

It is well known that elevated GSH levels suppress ferroptosis; however, the regulation of the intracellular content of GSH and how it modifies ferroptosis sensitivity remains an open issue [41,174–176]. Inhibition of the multidrug resistance-associated protein 1 (MRP1), encoded by the *ABCC1* gene in humans and important in the establishment of therapeutic resistance mechanisms in tumor cells, prevents GSH efflux, thereby, protecting against ferroptosis. In this context, other GSH-dependent enzymes are important in the control of hematopoiesis. A good example is the microsomal glutathione-transferase 1 (MGST1) which inhibits ferroptosis via the Nrf2 pathway and is required for hematopoiesis [177]. In the same category of ferroptosis-regulating molecules, inhibitors of GPX4 or SLC7A11 cystine-glutamate antiporter/system Xc^- promote ferroptosis and play a role in cancer through enhanced lipid peroxidation [162]. They trigger ferroptosis induction but also contribute to the fate of hematopoietic stem and progenitor cells [87,178].

Conditions associated with DNA damage, such as ionizing radiation or the pathways regulated by the ATM (ataxia-telangiectasia mutated)/

ATR (ATM and Rad3-related), or the tumor suppressor p53, in addition to regulating ferroptosis in cancer are associated with DNA-damage responses in hematopoietic stem cells, being involved in normal hematopoiesis but also in the development of different malignancies [179–181]. Finally, alterations in intracellular ROS have been identified in hematopoietic progenitors of patients with myelodysplastic syndrome, establishing an association with iron overload and blast count [21,59,63,162,175,182,183].

5. Conclusions, facts and open questions

5.1. Conclusions

The above evidence points to ferroptosis regulation as an unexplored therapeutic avenue. Not only may iron chelators, ferroptosis inhibitors, or antioxidant molecules [32,37,123,125,156,169] help to fight human diseases such as cardiovascular diseases or cancer, but also other ferroptosis-related responses. With this aim, it is essential to understand the links between iron-related cell death and the target disease [184, 185]. As an example, a recent study demonstrated that the regulation of heat stress combined with the use of iron oxide nanoparticles destroy tumor homeostasis, determining the cell fate to ferroptosis in cancer therapy [186]. In addition, inhibition of ferroptosis-dependent genes may promote iron-dependent cell death in other clinical interventions [174]. Undoubtedly, the modulation of iron and ferroptosis-regulatory proteins represents an interesting milestone in many biomedical research fields [187,188]. Additional focus on iron-related inflammatory and hematopoietic processes promises further successful therapeutic strategies [47,126]. Research into these complex connections will be needed to establish the role of iron and the subsequent iron-derived metabolism (including ferroptotic pathways) under clinical contexts. We suggest that the hematopoietic-inflammation-iron metabolism axis is a promising hub for future ferroptosis research. A better understanding of these biological and metabolic scenarios should lead to effective preventive and therapeutic opportunities for human diseases.

5.2. Facts

- Iron homeostasis is tightly regulated to prevent harmful effects on organs due to iron overdose or deficiency.
- While iron deficiency can be controlled via oral supplements to prevent anemia, the deleterious effects of excess iron remain an open field of research.
- Ferroptosis, a form of non-apoptotic cell death, occurs after iron accumulation and induction of lipid peroxidation.
- Extramedullary hematopoiesis depends on the bioavailability of iron and is involved in the outcome of several inflammatory diseases.

5.3. Open questions

- What are the molecular links involved in the control of extramedullary hematopoiesis associated with altered iron bioavailability?
- Is there a connection between iron homeostasis and extramedullary hematopoiesis?
- Is it possible to identify biomarkers associated with the prevention of ferroptosis in patients with metabolic syndrome, diabetes or iron-overload cardiomyopathy?
- Is it possible to introduce ferroptosis-specific cell death strategies to eradicate cancer cells?

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Author contributions

V.F.-G. wrote the paper, designed the figures and revised the manuscript. S.G.-R. provided new ideas and improvements and revised the text. P.M.-S. and A.C. provided intellectual input. L.B. provided funding and intellectual input and discussed the information.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Data Availability

No data was used for the research described in the article.

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