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Review Article

Ferroptosis-mediated immune responses in osteoporosis

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ABSTRACT

Osteoporosis is a common systemic metabolic disease, characterized by decreased bone mass and susceptibility to fragility fractures, often associated with aging, menopause, genetics, and immunity. Ferroptosis plays an underestimated yet crucial role in the further impact of immune function changes on osteoporosis. Cell ferroptosis can induce alterations in immune function, subsequently influencing bone metabolism. In this context, this review summarizes several mechanisms of ferroptosis and introduces the latest insights on how ferroptosis regulates immune responses, exploring the interactions between ferroptosis and other mechanisms such as oxidative stress, inflammation, etc. This review elucidates potential treatment strategies for osteoporosis, emphasizing the promising potential of ferroptosis as an emerging target in the treatment of osteoporosis. In conclusion, preparations related to ferroptosis exhibit substantial clinical promise for enhancing bone mass restoration.

The translational potential of this article: This review elucidates a nuanced conversation between the immune system and osteoporosis, with ferroptosis serving as the connecting link. These findings underscore the potential of ferroptosis inhibition as a therapeutic strategy for osteoporosis.

1. Introduction

Osteoporosis is a disease characterized by reduced bone mass and microstructural damage to bone tissue, leading to decreased bone strength and increased risk of fractures [1]. The global impact of osteoporosis is significant. According to recent estimates, approximately 200 million people worldwide are affected by osteoporosis, especially among the elderly population [2]. Furthermore, the global burden of osteoporosis is immense. The estimated annual medical expenses caused by osteoporosis in the United States exceed $20 billion [3]. It is expected that by 2025, this cost will increase to $25 billion [4]. It is evident that the current efforts in the prevention and treatment of osteoporosis are far from satisfactory. Therefore, exploring new causes of osteoporosis and discovering innovative prevention and treatment methods is of utmost importance [5].

There is a close relationship between the immune system and osteoporosis [6]. Bone tissue is not only a structural support, but also has immune regulatory functions [7]. The hematopoietic stem cells and bone matrix in the bone marrow have a certain impact on the function and development of immune cells [8]. Overactivation of the immune system may lead to the release of inflammatory factors, such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), which can stimulate osteoclasts activity [9]. Certain immune cells such as T cells and B cells can directly participate in bone metabolism [10]. Activated T cells can promote the differentiation and function of osteoclasts and enhance bone resorption by secreting specific cytokines [11]. However, the specific mechanism by which immune cells affect bone metabolism is still unclear.

Ferroptosis is a novel form of programmed cell death that was first discovered and named in 2012 [12]. Its characteristic is the excessive accumulation of intracellular iron and the generation of lipid peroxides, leading to cell death [13]. Recently, studies have suggested that ferroptosis is involved in osteoporosis, including the role of iron in bone metabolism and how its induced lipid peroxidation affects bone metabolism [14]. The functions of osteoblasts and osteoclasts are regulated by ferroptosis have also been elaborated [15]. Therefore, ferroptosis can regulate bone metabolism.

On the other hand, ferroptosis also plays a significant role in the immune system. It can impact the survival and functionality of immune cells, such as T cells and macrophages, potentially leading to a diminished immune response [16]. Additionally, ferroptosis may also contribute to regulating inflammatory responses. By mediating specific

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cell death, it affects the recruitment and activity of inflammatory cells, thereby coordinating immune responses [17]. Ferroptosis typically occurs alongside an increase in oxidative stress. Moderate oxidative stress can activate immune responses, but excessive oxidative stress may result in damage and dysfunction of immune cells [18]. In summary, ferroptosis is correlated with immune regulation and bone metabolism, and ferroptosis may serve as a bridge for the immune system to regulate bone homeostasis [19]. Therefore, in this review, we describe the roles of ferroptosis in immune regulation and bone metabolism, and elucidate the possible mechanisms by which ferroptosis affects osteoporosis in the immune system.

2. The mechanism of ferroptosis

2.1. Definition and characteristics of ferroptosis

Since the discovery of "ferroptosis" in 2012, this new form of cell death has been widely studied in the fields of tumors and metabolic diseases [12]. Subsequently, the International Cell Death Nomenclature Committee defined ferroptosis as a form of cell death regulated by GPX4 in 2018 [20]. Ferroptosis is different from classical cell apoptosis and necrosis, characterized by excessive intracellular iron and the failure of specific antioxidant mechanisms, leading to lipid oxidation of the cell membrane and ultimately resulting in cell death. It does not involve DNA breakage or changes in the nucleus, and is usually not accompanied by inflammatory reactions [21]. The occurrence of ferroptosis is directly related to the concentration of iron in cells. In ferroptosis, the antioxidant defense mechanism of cells is inhibited or disabled, making it difficult to effectively eliminate excessive reactive oxygen species (ROS), leading to cell death.

There are also some sub-cellular changes in ferroptosis. Mitochondria in ferroptotic cells become smaller, denser, and show condensed cristae structures. The mitochondrial membrane potential is disrupted, leading to impaired mitochondrial function [12]. Endoplasmic reticulum (ER) may become dilated or swollen as a result of lipid peroxidation. ER stress can activate the unfolded protein response (UPR) pathway, which may contribute to ferroptosis by increasing ROS production [22]. In addition, the plasma membranes become leaky, resulting in cell rupture and release of cellular contents [12]. The nuclear membranes and lysosomal membranes can be damaged by ROS, leading to leakage of lysosomal enzymes into the cytoplasm, which further exacerbates cell death [13]. Therefore, ferroptosis not only leads to an increase in ROS, but also affects physiological activities through many pathways.

2.2. Pathways of ferroptosis

There are multiple pathways to induce ferroptosis. System Xc^- is an amino acid transport system responsible for intracellular cysteine transport. When system Xc^- is inhibited, the uptake of cysteine decreases, leading to insufficient synthesis of glutathione (GSH). GSH is an important antioxidant that can clear ROS [23]. Cysteine deficiency makes cells prone to accumulate lipid peroxides, inducing ferroptosis [24]. Glutathione peroxidase 4 (GPX4) is a key enzyme in the antioxidant system, mainly used for reducing lipid peroxides. If the function of GPX4 is impaired, it can lead to a large accumulation of lipid peroxides, ultimately resulting in cell death [25]. Some compounds, such as RSL3, can directly inhibit the activity of GPX4 and induce cell death by iron [26]. The storage and utilization of iron are the foundation of ferroptosis. Iron accumulation leads to the enhancement of the Fenton reaction, which generates hydroxyl radicals, further promoting lipid oxidation and cell membrane damage [27]. Excessive use of metal ions such as manganese, copper, nickel, zinc, cobalt, and iron carriers may promote an increase in intracellular free iron, thereby inducing ferroptosis [28]. Of course, ferroptosis may also be regulated in different organs and tissues in different ways. The sensitivity of different cell types to inducing factors may vary. In addition, certain signaling pathways are also involved in the regulation of ferroptosis, such as the NF-κB and p53 signaling pathways [29]. NF-κB is an important transcription factor that is associated with cell survival and death signals. P53 participates in the regulation of ferroptosis by affecting iron metabolism and regulating oxidative stress status [30]. Specific information was listed in Table 1.

2.3. Regulation factors

SLC7A11, a transmembrane cysteine transporter, helps maintain intracellular GSH levels by promoting cysteine uptake. GSH can enhance the antioxidant capacity of cells and lower the risk of ferroptosis [41]. When it is inhibited, the levels of cysteine and GSH decrease, increasing the sensitivity of cells to ROS, thereby promoting the occurrence of ferroptosis [42]. Ferroptosis repressor protein 1 (FSP1) enhances antioxidant capacity by converting coenzyme Q10 (CoQ10) into its reduced form. CoQ10 can capture lipid peroxides and reduce intracellular ROS [43]. The activity of FSP1 can inhibit the generation of lipid peroxides, thereby preventing cells from ferroptosis [44]. Acyl CoA synthetase long chain family member 4 (ACSL4) promotes the synthesis of cell membrane phospholipids by increasing the supply of intracellular unsaturated fatty acids. These unsaturated fatty acids are more easily oxidized, making cells more susceptible to damage when facing ROS and increasing the risk of ferroptosis [33].

Table 1
Reported pathways of ferroptosis in different cell types.

Role	Pathway	Regulating medium	Description
Stimulation	Fenton reaction	Fe^{2+}, H_2O_2	Iron ions generate free radicals through Fenton reaction, promote lipid peroxidation, and induce ferroptosis [31].
	P53 signaling pathway	P53, Fatty acid synthase	P53 enhances cell sensitivity to ferroptosis by regulating fatty acid metabolism and catalyzing ferroptosis reactions [32].
	ACSL4 pathway	ACSL4, Linoleic acid	ACSL4 promotes the synthesis of polyunsaturated fatty acids such as linoleic acid and enhances the occurrence of ferroptosis [33].
	ER stress pathway	CHOP, GRP78	Endoplasmic reticulum stress-induced ferroptosis is associated with enhanced lipid peroxidation [34].
	NF-κB signaling pathway	NF-κB, TNF-α	NF-κB can regulate inflammatory response and promote the expression of ferroptosis related genes [35].
Inhibitation	SLC7A11 pathway	SLC7A11, Cysteine	SLC7A11 transporter promotes cysteine uptake, increases glutathione synthesis, and inhibits ferroptosis [36].
	Regulation of intracellular iron homeostasis	FPN, DMT1	By regulating the uptake and excretion of iron within cells, maintaining iron homeostasis can help inhibit ferroptosis [37].
	GPX4 antioxidant	GPX4, GSH	GPX4 is an inhibitor of lipid peroxides, which inhibits ferroptosis [38].
	NRF2 signaling pathway	NRF2, HO-1, NQO1	NRF2 transcription factor regulates the expression of antioxidant genes and inhibits cell ferroptosis [39].
	FSP1 antioxidant	FSP1, Coenzyme Q_{10}	FSP1 prevents ferroptosis by inhibiting lipid peroxidation [40].

Other proteins are also involved in the regulation of ferroptosis. The products of cysteine dioxygenase (CDO1) and cystathionine β-synthase (CBS) regulate ferroptosis by affecting GSH levels [45]. Z-DNA binding protein 1 (ZBP1) affects ferroptosis by regulating immune response and apoptosis pathways [46]. Exportin 1 (XPO1) regulates cell sensitivity to ferroptosis by affecting the nuclear efflux of transcription factors [47]. The downstream target genes of nuclear factor E2 related factor 2 (NRF2) include antioxidant enzymes, which can indirectly affect the occurrence of ferroptosis [48]. These proteins interact through various mechanisms to regulate cellular responses to iron overload and oxidative stress, making them a key area of research in ferroptosis.

Overall, the regulatory mechanism of ferroptosis is very complex. We presented in Fig. 1 the regulatory mechanisms of ferroptosis reported in previous studies. However, research on ferroptosis is still in its infancy, and the subsequent mechanisms need to be updated, especially in the field of osteoporosis. Understanding these theories can help develop new treatment strategies for osteoporosis.

3. Immune system and osteoporosis

The relationship between the immune system and osteoporosis is a complex interactive network involving multiple cells, factors, and signaling pathways. Changes in the immune system can disrupt the balance of bone metabolism by promoting inflammation, dysregulated immune cell function, and microenvironmental changes, leading to the occurrence of osteoporosis.

3.1. Release of pro-inflammatory cytokines

The activation of the immune system (such as chronic inflammation) can lead to the release of pro-inflammatory factors such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which can upregulate the generation and activity of osteoclasts, enhance bone resorption, and lead to bone loss [49]. TNF-α is one of the main pro-inflammatory factors. It can promote osteoclast activity by activating the MAPK, PI3K/Akt, and NF-κB pathways, as well as activate osteoblast apoptosis and inhibit the bone morphogenetic protein (BMP) signaling pathway by binding to their receptors, thereby suppressing bone formation [50]. Interleukin-1 (IL-1) and interleukin-6 (IL-6) promote the transformation of bone marrow monocytes into osteoclasts by enhancing the expression of receptor activator nuclear factor kappa B ligand (RANKL) [51]. IL-17 secreted by TH17 cells can stimulate osteoblasts to secrete pro-inflammatory cytokines, enhance osteoclast generation, and disrupt bone formation [52].

3.2. Dysfunction of immune cells

The relationship between T cells and osteoporosis mainly involves the regulation of bone metabolism by the immune system. The activation of T cells can promote osteoclastogenesis by secreting RANKL and binding to RANK on the surface of osteoclast precursors [53]. The inactivation of T cells may lead to the downregulation of RANKL, thereby affecting bone metabolism. T cells can secrete various cytokines, such as interferon-γ (IFN-γ), TNF-α, etc., which can affect bone metabolism through multiple pathways [54]. When T cells become inactive, the balance of these cytokines is affected, leading to an imbalance between osteoblastic and osteoclastic activities. Wnt/β-catenin signaling pathway plays an important role in the development of osteoblasts. T cells indirectly affect the Wnt signaling pathway by secreting RANKL. When T cells are inactivated, it may lead to inhibition of Wnt signaling pathway, thereby affecting bone formation [55]. In addition, there is an interaction between immune and bone, which affects bone metabolism. The inactivation of T cells may prevent this interaction, leading to osteoporosis [56].

The main functions of B cells include antibody production and regulation of immune responses, but they can also affect bone metabolism by secreting cytokines and interacting with other cells in the bone marrow microenvironment. Under normal circumstances, activation of B cells can promote the production of osteoprotegerin (OPG), thereby inhibiting the action of RANKL and reducing the generation of

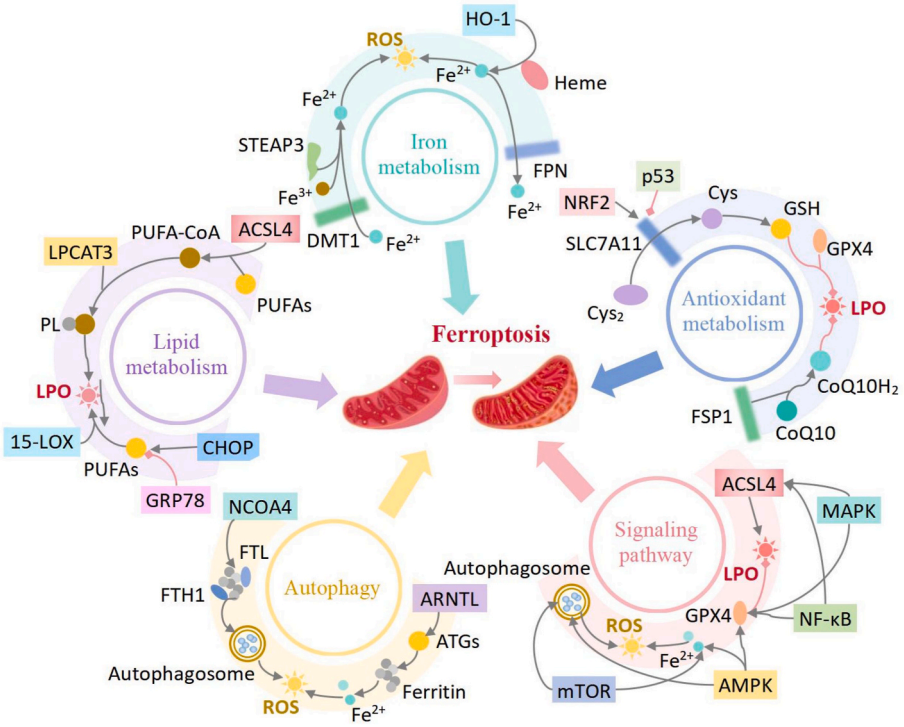

Fig. 1. Reported regulatory mechanisms of ferroptosis. Ferroptosis can occur through several major pathway, including antioxidant metabolism, iron metabolism, lipid metabolism, autophagy, cell signaling pathway, etc.

osteoclasts [57]. Inactivated B cells can also lead to dysregulation of the release of inflammatory factors, such as TNF-α, IL-6, etc., which can promote the formation and activity of osteoclasts [58]. Studies have shown that certain cytokine signaling pathways, such as JAK/STAT and NF-κB, are involved in regulating bone metabolism [59]. Inactivated B cells may lead to dysregulation of these signaling pathways, affecting the function of osteoblasts and osteoclasts. In addition, osteoblasts synthesize and actively release collagen and other matrix components within vesicles. If B cells are inactivated, it may lead to the inhibition of this secretion mechanism, reduce the formation of matrix vesicles, and decrease collagen synthesis, thereby reducing the quality and strength of bone matrix [60].

Other immune cells also participate in bone metabolism. Macrophages, as precursor cells of osteoclasts, can differentiate into mature osteoclasts under RANKL induction. Macrophage polarization is associated with osteoporosis. M1 macrophages promote osteoclastogenesis by secreting pro-inflammatory factors, while M2 macrophages promote osteoblast differentiation. In osteoporosis, the M1/M2 polarization balance of macrophages is disrupted, and M1 macrophages dominate, leading to increased bone resorption [16]. Neutrophils release various pro-inflammatory factors during inflammation, promoting osteoclast differentiation by activating NF-κB pathway. It also produces ROS, which participates in ferroptosis and osteoclast differentiation processes [9]. Proteases released by neutrophils can degrade bone matrix, disrupt the structural integrity of bone tissue, and lead to reduced bone mass. Therefore, the dysregulation of immune cells can lead to an imbalance of bone homeostasis and promote osteoporosis.

3.3. Bone marrow microenvironment

Changes in the microenvironment of the bone marrow, such as aging or pathological conditions, can affect the development and function of immune cells, leading to immune system dysfunction and subsequently affecting bone metabolism. The bone marrow microenvironment provides a supportive 'host' for hematopoietic stem cells, maintaining self-renewal and differentiation through various extracellular matrix components, intercellular signaling pathways, and cytokines [61]. The differentiation status of stem cells directly affects the production of various immune cells. Meanwhile, the bone marrow is also a critical site for the development of B cells and certain types of T cells [62]. Fibroblasts, adipocytes, and other immune cells (such as dendritic cells and macrophages) in the bone marrow regulate immune responses by releasing cytokines and chemokines, affecting the migration and activation status of immune cells [63].

On the contrary, the immune system can also affect the bone marrow microenvironment. Immune cells can infiltrate into the bone marrow, altering the cellular composition of its microenvironment [64]. The immune system affects the bone marrow microenvironment by releasing cytokines and chemokines. These molecules can not only affect the self-renewal and differentiation of hematopoietic stem cells in the bone marrow, but also alter the function of bone marrow stromal cells [65]. In an inflammatory or infectious state, the immune system may cause remodeling of the bone marrow microenvironment. For example, the activation of macrophages can promote the inflammatory response of bone marrow stromal cells, leading to changes in the local microenvironment [66]. It can be seen that there is a complex feedback mechanism between immune cells and the bone marrow microenvironment. The differentiation and function of certain immune cells may be regulated by the bone marrow microenvironment, and the state of the bone marrow microenvironment continuously affects the activity of immune cells.

We counted all the literature related to immune cells (T cells, B cells, macrophages, neutrophils), inflammatory factors (TNF-α, interleukins, chemokines, prostaglandins, TGF-β, IFN-γ), and bone metabolism cells (osteoblasts, osteoclasts) in PubMed (search equation: (A [Title/Abstract]) AND (B [Title/Abstract]), where A and B are the search terms mentioned above), and calculated the proportion of literature. We also drew a Sankey plot to observe the popularity of the correlation between each keyword. According to Fig. 2, macrophages have the highest number of studies in immune cells, while interleukins have the highest number of inflammatory factors. They may be the focus of immune response affecting the process of osteoporosis.

Overall, changes in the immune system have a certain impact on the occurrence and development of osteoporosis. The relevant molecular mechanisms involve the release of pro-inflammatory cytokines, dysfunction of immune cells, and changes in the bone marrow microenvironment. In addition, an increasing number of studies suggest that ferroptosis may also be involved in bone—immune interactions.

4. Ferroptosis in the immune system

Recent studies have shown that the immune system plays an important role in the occurrence and regulation of ferroptosis. In some cases, immune cells may experience ferroptosis. There are many reasons for this phenomenon. The immune system can induce ferroptosis through multiple mechanisms such as iron uptake and utilization, oxidative stress, and intercellular interactions.

4.1. Iron accumulation

Immune cells increase their demand for iron during activation and proliferation. Because iron is essential for DNA synthesis and cell division, a lack of iron can lead to limited cell proliferation. Meanwhile, iron is an important component in the synthesis of hemoglobin and a key metal ion for many enzymes [67]. During the activation and proliferation of immune cells, it is necessary to increase the synthesis of hemoglobin and enzymes to support metabolic activity. Activated immune cells require more energy, and iron, as an important component of the cellular respiratory chain, is a key substance in energy metabolism, which increases the demand for iron by immune cells during the activation process [68]. Therefore, macrophages and other immune cells uptake and store more iron in response to infection or inflammation. Excessive iron accumulation promotes the generation of free radicals, leading to lipid peroxidation, which provides conditions for ferroptosis [69].

4.2. ROS

Immune cells produce a large amount of ROS when participating in inflammatory reactions, as ROS are important weapons used by immune cells to kill pathogens. In the inflammatory response, immune cells are activated by recognizing signals from pathogens or damaged tissues, such as pathogen-associated molecular patterns and injury-associated molecular patterns [70]. Activated immune cells can increase the production of ROS through certain signaling pathways, such as activation of NADPH oxidase, mitochondrial respiratory chain, cytochrome P450, autophagy, and lysosomes [71]. These excessive ROS can directly induce lipid peroxidation within cells, promoting the occurrence of ferroptosis.

4.3. Lipid metabolism

Immune cells play an important role in regulating lipid metabolism and ferroptosis, often adapting to the environment by altering lipid metabolism when activating and responding to pathogens. In ferroptosis, peroxidation of cell membrane phospholipids and changes in lipid metabolism are key factors. These changes can be regulated by signals within immune cells and the microenvironment. For example, macrophages may increase the uptake of unsaturated fatty acids (such as linoleic acid and arachidonic acid) after stimulation, which are more prone to peroxidation reactions and promote ferroptosis [72]. When activated, immune cells may deplete antioxidant substances such as GSH and vitamin E, making them more susceptible to the toxic effects of lipid

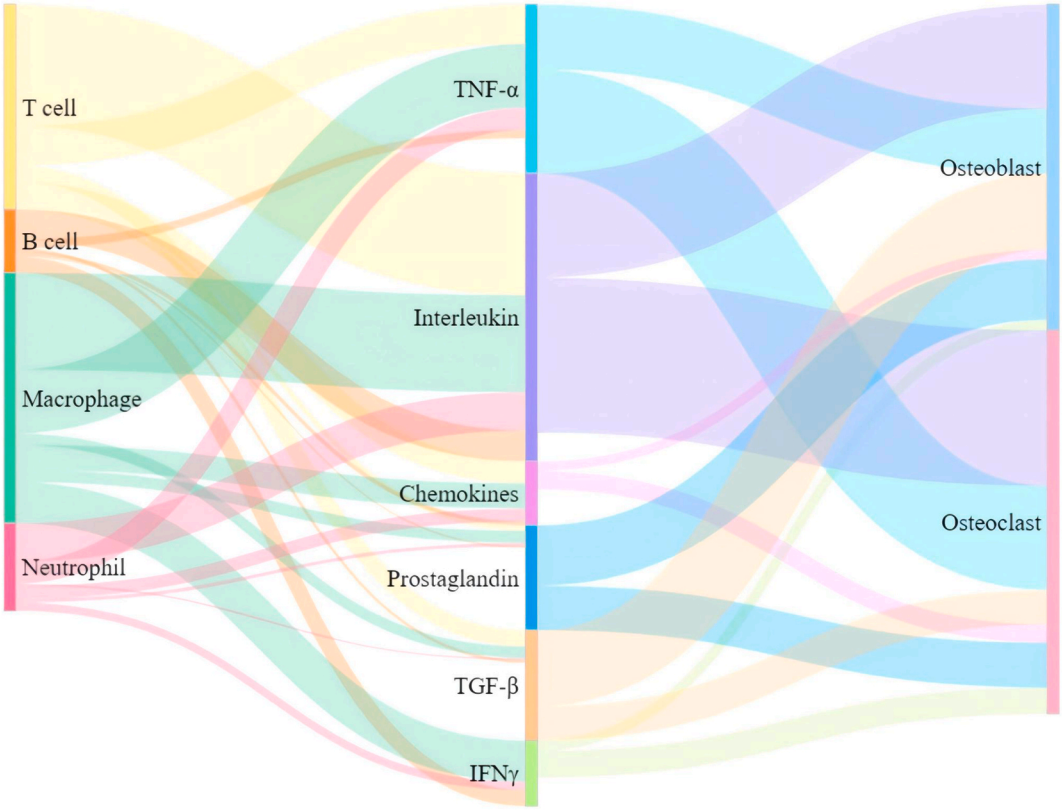

Fig. 2. Sankey plot of the proportion of literature on (I) immune cells and inflammatory factors; and (II) inflammatory factors and bone metabolism cells. TNF-α, tumor necrosis factor alpha; TGF-β, transforming growth factor beta; IFN-γ, interferon gama.

peroxides and inducing ferroptosis [73].

4.4. Cytokine and chemokine

During the immune response, the secretion of certain chemokines can affect iron metabolism, thereby promoting ferroptosis. The most common is TNF-α, which enhances the expression of iron transporters by activating downstream signaling pathways such as NF-κB, leading to intracellular iron accumulation and promoting ferroptosis [74]. IFN-γ is mainly secreted by activated T cells and natural killer cells (NK cells), and it can upregulate the expression of genes related to iron metabolism, leading to iron accumulation [75]. IL-1 and IL-6 can promote liver synthesis of transferrin, which in turn affects intracellular iron levels and promotes ferroptosis [76]. Chemokines such as CCL2 and CXCL10 can attract monocytes and T cells to gather at the site of inflammation, which further increases local iron levels [77]. Other cytokines and chemokines (such as IL-12, IL-17, etc.) may also indirectly affect iron metabolism and the occurrence of ferroptosis by regulating the activity of immune cells or signaling pathways related to iron metabolism [78].

4.5. Weakening of antioxidant defense

During immune activation, cells will preferentially call upon some resources for secreting cytokines, proliferation, and other processes that mediate immune responses, which may lead to a weakened ability to synthesize and maintain antioxidant molecules. For example, the synthesis of GSH may be inhibited, causing cells to lack sufficient antioxidant capacity [79]. Antioxidant defense relies on various antioxidant enzymes, and immune activation may lead to a decrease in the expression or activity of these enzymes. Under sustained immune stimulation and inflammatory conditions, immune cells may experience functional exhaustion, which reduces the effectiveness of antioxidant responses [80]. The microenvironment activated by immune response, such as tumor microenvironment or chronic inflammatory environment, may be rich in pro-oxidative components, including certain enzymes, metal ions, and harmful compounds [81]. These microenvironmental factors can accelerate the consumption of antioxidant substances and reduce local antioxidant capacity. Therefore, during the immune response process, the antioxidant defense mechanism will weaken, indirectly leading to an increase in ROS and inducing ferroptosis.

4.6. The effect of ferroptosis on immune cells

The core feature of ferroptosis is the accumulation of lipid peroxides, as well as ROS generated by iron overload and inhibition of GPX4 function. The impact of ferroptosis on different immune cells varies. In macrophages, ferroptosis can induce macrophage death. After ferroptosis, the cell membrane is disrupted and High Mobility Group Box 1 (HMGB1) is released from the nucleus to the extracellular space, leading to the transformation of macrophages from M1 to M2 [82]. Ferroptosis can weaken the killing ability of Th1 cells against tumor cells, leading to immune suppression and reducing macrophage activation. It can also reduce the secretion of IL-4 and IL-13 by Th2 cells, weaken allergic reactions, and decrease the ability to clear parasites. Ferroptosis of Th17 cells weakens their ability to clear bacteria and fungi. Ferroptotic regulatory T cells (Tregs) can lead to overactivation of immune responses, which may exacerbate the progression of autoimmune diseases such as systemic lupus erythematosus [73]. Ferroptosis induces dendritic cell (DC) death, reduces its antigen presentation ability, and further weakens T cell activation. It also induces the death of B cells and neutrophils, reducing their ability to produce antibodies and weakening their antibacterial properties [83]. Therefore, ferroptosis can lead to immune suppression, exacerbate inflammation and tissue damage, and may promote immune tolerance by inducing immune cell death or dysfunction. The mechanism of immune response regulating ferroptosis was shown in Fig. 3.

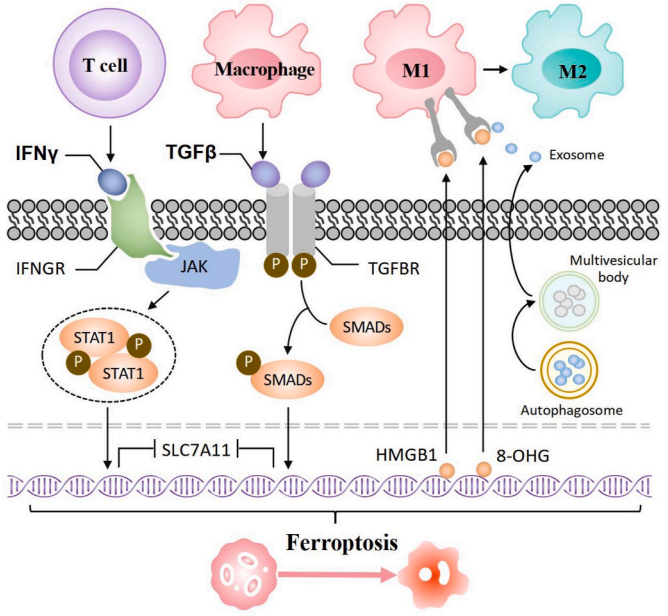

Fig. 3. Relationship between ferroptosis and immunity. IFNγ released by T cells induces ferroptosis by activating the JAK-STAT pathway, which regulates the expression of SLC7A11. TGFβ released by macrophages promotes ferroptosis by activating SMAD proteins. Ferroptotic cells release damage-associated molecular patterns, such as high mobility group protein B1 (HMGB1), and 8-hydroxyguanosine (8-OHG), which affect the function of immune cells.

5. Role of ferroptosis in osteoporosis

Recent research has found a certain correlation between ferroptosis and osteoporosis. Firstly, iron overload and subsequent oxidative stress may have a negative impact on the function of bone cells. In osteoporosis, excessive iron may enhance the activity of osteoclasts, leading to increased bone resorption [84]. Secondly, patients with osteoporosis often have chronic inflammation, which may promote iron deposition and ferroptosis [85]. Inflammatory mediators can stimulate the differentiation of osteoclasts, leading to increased bone resorption. In addition, ferroptosis may also affect the function of osteoblasts. In cases of osteoporosis, the number of osteoblasts usually decreases, further limiting the regenerative ability of bone [86]. We will provide a comprehensive review of the impact of ferroptosis on osteoporosis related cells as follows.

5.1. Osteoblast

Ferroptosis of osteoblasts is a programmed cell death that relies on iron. When the GSH level decreases and lipid peroxides increase, ferroptosis is initiated. At this point, GPX4, which is responsible for inhibiting lipid peroxidation, experiences ferroptosis in osteoblasts due to its reduced activity [87]. Osteoporosis patients often suffer iron accumulation, and iron accumulation in osteoblasts generates hydroxyl radicals through the Fenton reaction, which in turn triggers lipid oxidation and promotes ferroptosis [88]. The SLC7A11/SLC3A2 complex is an important transporter for the exchange of glutamate and cysteine. When this channel is inhibited in osteoblasts, intracellular cysteine levels decrease, thereby affecting GSH synthesis and promoting ferroptosis [89]. NRF2 is an important transcription factor in osteoblasts, and its activation can enhance the cell's tolerance to ROS by upregulating antioxidant genes to inhibit ferroptosis [90]. Recent studies have reported that abnormal elevation of DNMT and subsequent inhibition of GPX4 play a decisive role in osteoblast ferroptosis. Due to the reversible nature of epigenetic modifications, intervening in ferroptosis through DNMT may be an effective strategy for treating osteoporosis [15].

After ferroptosis occurs in osteoblasts, the number of cells decreases, further leading to a decrease in the generation of bone matrix, which directly affects the ability of bone formation. Even if some osteoblasts survive, they may still suffer functional impairment due to the stress associated with ferroptosis, leading to a decrease in mineralization ability [91]. The death of osteoblasts may trigger changes in the local microenvironment, such as an increase in inflammatory response and alterations in the extracellular matrix, which are detrimental to bone formation. At the same time, it may also affect osteogenic precursor cells, leading to a decrease in their ability to differentiate into mature osteoblasts, further reducing bone formation. Therefore, ferroptosis of osteoblasts directly affects bone metabolism, leading to osteoporosis.

5.2. Osteocyte

The main cause of osteoporosis is ferroptosis in osteoblasts. This process not only affects the function of osteoblasts, but may also have a significant impact on the signaling pathway of osteocytes. Firstly, osteocytes play an important role in bone remodeling and mineralization processes, and the Wnt/β-catenin signaling pathway has a significant impact on bone formation. When ferroptosis affects osteoblasts, this signaling pathway is inhibited, leading to changes in the number and activity of osteocytes and a decrease in bone formation ability [92]. Secondly, ferroptosis can trigger cellular stress response, thereby activating the NF-κB signaling pathway and leading to the release of inflammatory factors such as TGF-β, PGE2, MMPs, etc. [93]. These inflammatory factors can affect the function of osteocytes and inhibit bone formation. Ferroptosis may lead to osteocytes apoptosis by activating the Mitogen Activated Protein Kinase (MAPK) signaling pathway [94]. The PI3K/Akt signaling pathway plays an important role in cell growth, survival, and metabolism. Ferroptosis inhibits the activation of this pathway, leading to a decrease in the phosphorylation level of Akt and a reduction in downstream survival signals such as mTOR and Bcl-2 [95]. This will reduce the survival ability of cells and promote osteocytes death. Then, ferroptosis may also be associated with other cell death mechanisms such as apoptosis and necrosis, affecting the survival of osteocytes. In addition, ferroptotic osteocytes further promote bone loss by regulating osteoclast mediated bone resorption. Among them, Nrf2 serves as a key regulatory pathway, and the Nrf2/Dnmt3a/RANKL axis in osteocytes is a novel mechanism for osteoporosis [92].

5.3. Osteoclast

Osteoclasts are responsible for bone resorption in bone remodeling and work together with osteoblasts to maintain bone balance. Ferroptosis can cause endoplasmic reticulum stress (ER stress), activate related signaling pathways, such as IRE1α, PERK, and further lead to the death of osteoclast precursor cells [96]. Meanwhile, autophagy also plays an important role in regulating cell survival and death processes. Ferroptosis can indirectly regulate the activity of osteoclast precursor cells by altering autophagy activity, ultimately affecting bone resorption. The ROS generated by ferroptosis can promote the formation of osteoclasts through the NF-κB signaling pathway [97]. When iron accumulation leads to excessive cell death, inflammatory factors formed in the local environment promote the generation of osteoclasts. This situation can lead to an imbalance in the normal bone resorption mechanism, thereby exacerbating the degree of osteoporosis [98]. In addition, ferroptosis can affect the survival and function of osteoclasts by affecting apoptotic signals within the cells, such as the Bcl-2/Bax ratio and activation of caspases [99]. Similar to osteoblasts, ferroptosis can alter the composition of the bone microenvironment, affecting the interaction between osteoblasts and osteoclasts. This imbalance promotes bone resorption and inhibits bone formation.

5.4. Bone marrow mesenchymal stem cell

Ferroptosis also has a certain impact on bone marrow mesenchymal stem cells (BMSCs). Ferroptosis is accompanied by a significant increase in intracellular ROS, and this oxidative stress can cause damage to BMSCs, affecting their proliferation and differentiation abilities. The lipid peroxidation induced by ferroptosis can affect the integrity of the cell membrane, resulting in changes in the composition and fluidity of the BMSCs membrane, leading to inhibition of its differentiation into osteoblasts. Ferroptosis inhibits the PI3K/Akt signaling pathway, activates the p38, JNK, and NF-κB pathways in BMSCs, and reduces the survival and differentiation potential of stem cells [100]. Autophagy can clear damaged organelles and proteins, while ferroptosis inhibits autophagy, accumulates damaged cellular components, and ultimately affects the function of BMSCs [101]. Recent studies have suggested that ferroptosis can further regulate the function of BMSCs by affecting the expression of miRNAs such as miR-21, miR-34a, miR-22, and miR-411a [102].

In summary, cells related to bone metabolism exhibit ferroptosis. When these cells undergo ferroptosis, the balance between bone formation and resorption is disrupted, leading to osteoporosis. We have listed the recent reported possible mechanisms by which ferroptosis affects the activity of various bone metabolism related cells in Fig. 4. Regulating ferroptosis related genes and further regulating bone metabolism may be a new target for the prevention and treatment of osteoporosis in the future.

6. Challenges and future directions

Ferroptosis is a unique mode of cell death that differs significantly from classical cell death modes such as apoptosis, necrosis, and autophagy. Apoptosis depends on Caspases, during which the cell membrane remains intact, forming apoptotic bodies that can clear abnormal or damaged cells. Necrosis is passive cell death accompanied by a strong inflammatory response, typically caused by acute injury. Autophagy is mediated by the autophagosome-lysosome system, involved in the degradation and reuse of cellular components, and plays a protective role under stress conditions. Ferroptosis relies on iron and lipid peroxidation. It may indirectly regulate bone metabolism by affecting the function and survival of immune cells. In addition, it may further regulate bone metabolism by affecting the production and release of inflammatory factors. Therefore, ferroptosis may play a bridging role in the interaction between immune response and bone metabolism.

Anti osteoporosis drugs are widely used in clinical practice, but long-term use of these drugs may be accompanied by certain side effects. RANKL inhibitors and bisphosphonates can cause hypocalcemia, mandibular necrosis, and bisphosphonates can also cause flu like symptoms such as fever and muscle pain. Parathyroid hormone analogs also pose a risk of hypercalcemia and osteosarcoma. Romosozumab may increase the risk of myocardial infarction, stroke, and cardiovascular death. Therefore, the development of new anti osteoporosis drugs is crucial.

Immune cells have current or potential clinical application in the prevention and treatment of osteoporosis. Denosumab is a monoclonal antibody targeting RANKL and has been widely used in the treatment of osteoporosis. BMSCs have strong immune regulatory abilities and can reduce the release of inflammatory cytokines. Its transplantation has become a research hotspot in the treatment of osteoporosis [103]. At present, clinical research on ferroptosis in osteoporosis is still in its early stages, but iron chelators and antioxidants have shown certain therapeutic effects. Iron chelators (such as Deferoxamine) can reduce intracellular free iron levels, while antioxidants can clear lipid peroxides. Both can inhibit ferroptosis and protect osteoblasts [86]. It can be speculated that GPX4 activators may have protective effects on bone metabolism and become potential drugs for treating osteoporosis in the future.

This review mainly focuses on the relationship between immune response, ferroptosis, and osteoporosis. Ferroptosis, as a form of cell death, plays a regulatory role in immune response and bone metabolism, but its application in the prevention and treatment of osteoporosis still

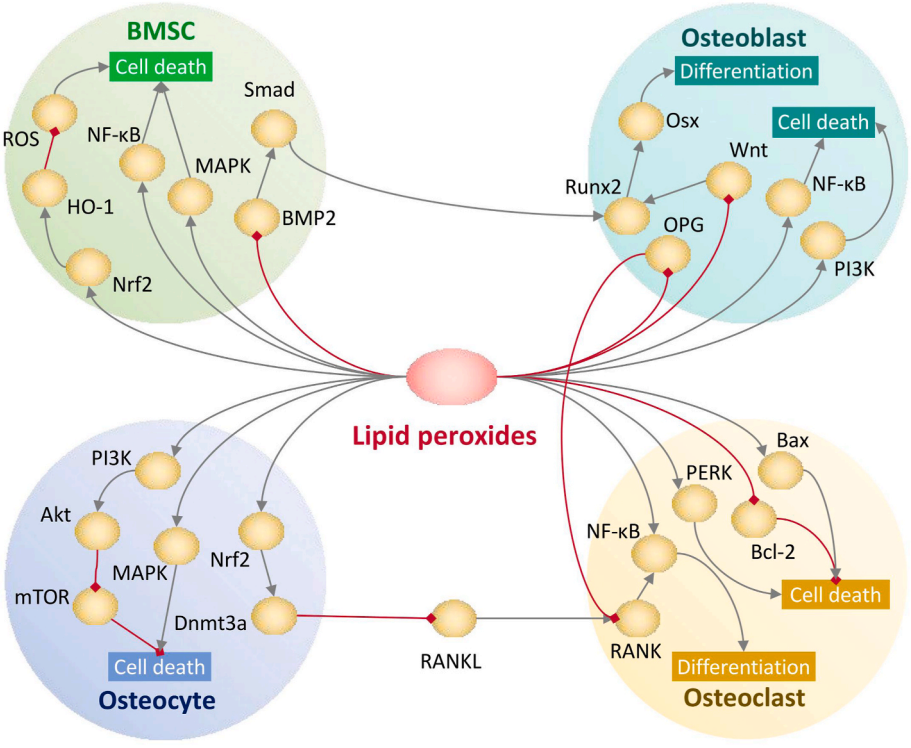

Fig. 4. Ferroptosis plays an important role in the progression of osteoporosis. Possible signaling mechanisms affecting osteoblast, osteoclast, bone marrow mesenchymal stem cells (BMSCs), and osteocyte during ferroptosis.

faces many challenges. (I) The complexity of ferroptosis mechanism: Ferroptosis involves the interaction of multiple molecules and signaling pathways, including iron metabolism, lipid peroxidation, antioxidant system, etc. The complexity of these factors makes it difficult to fully understand the regulatory mechanisms of ferroptosis. In addition, different types of cells (such as osteoblasts, osteoclasts and immune cells) may have different sensitivity and response to ferroptosis, which increases the difficulty of regulating ferroptosis in specific cell types. (II) The balance between ferroptosis and immune response: Inhibitors of ferroptosis may reduce the death of immune cells, thereby enhancing immune response. However, excessive enhancement of immune response may lead to overactivation of the immune system, triggering autoimmune diseases or inflammatory reactions. Ferroptosis plays an important role in inflammation regulation, but how to suppress ferroptosis while avoiding excessive inflammatory response is an important challenge. (III) The balance between ferroptosis and bone metabolism: Ferroptosis may affect the function of osteoblasts and osteoclasts, thereby affecting bone metabolism. How to maintain a balance between osteogenesis and osteoclastogenesis while inhibiting ferroptosis, and avoid excessive reduction or increase in bone mass, is a key issue. As mentioned previously, the cytokine profile and cell interactions in the bone marrow microenvironment are complex, and the regulation of ferroptosis may affect these microenvironmental factors, further increasing the difficulty of regulation. (IV) Clinical translation and safety: Currently, research on inhibitors and activators of ferroptosis is mainly focused on the basic research stage, and clinical translation faces challenges in drug development and safety evaluation. Inhibitors of ferroptosis may have potential side effects such as iron overload, lipid metabolism disorders, etc., and require strict safety evaluations in clinical applications. (V) Individual differences and precision medicine: Different individuals may have varying sensitivities and responses to ferroptosis, which increases the difficulty of precision medicine. The genetic polymorphism of ferroptosis related genes (such as GPX4) may also affect an individual's response to ferroptosis, and these factors need to be considered in clinical applications.

The following solutions have been proposed to address the aforementioned challenges. (I) Regarding the complexity of ferroptosis mechanism: Through multi-level research methods, including genomics, proteomics, metabolomics and materials science, comprehensively analyze the regulatory network of ferroptosis. Establish in vitro and in vivo models for different cell types to study the specific regulatory mechanisms of ferroptosis in different cell types. Using systems biology methods, integrating multi-level data, constructing a systematic regulatory model of ferroptosis, and revealing its complexity. (II) Balancing ferroptosis and immune response: Developing ferroptosis regulators that target specific immune cells to avoid non-specific effects on other immune cells. Combining other immunomodulatory drugs, such as anti-inflammatory drugs and immunosuppressants, to balance ferroptosis regulation and immune response. By dynamically monitoring the function of immune cells and levels of inflammatory factors, real-time adjustment of ferroptosis regulation strategies can be made to avoid excessive immune activation. (III) Targeting the balance between ferroptosis and bone metabolism: Developing ferroptosis regulators that simultaneously affect osteoblasts and osteoclasts to maintain the balance of bone metabolism. Study the impact of ferroptosis on the bone marrow microenvironment, develop drugs to regulate the bone marrow microenvironment, and optimize bone metabolism. Clinical trials can also be conducted to evaluate the effects of ferroptosis regulators on bone metabolism and optimize treatment plans. (IV) Regarding clinical translation and safety: Based on the mechanism of ferroptosis regulation, develop new drugs such as small molecule inhibitors and activators, and conduct preclinical and clinical trials. Ensure the safety of ferroptosis regulators through systematic safety assessments, including toxicology and pharmacology studies. Develop personalized treatment plans based on individual differences to improve treatment effectiveness and safety. (V) Targeting individual differences and precision medicine: studying the polymorphism of ferroptosis related genes, identifying gene variations associated with ferroptosis sensitivity, and providing a basis for personalized treatment. Develop biomarkers related to ferroptosis and evaluate individuals' sensitivity and response to ferroptosis through blood or imaging testing. Establish a precision medicine platform that integrates genomics, proteomics, and clinical data to provide support for personalized treatment.

7. Summary

In conclusion, the study of ferroptosis presents a promising avenue for understanding and treating various diseases, particularly those involving bone metabolism and the immune system. However, the complexity of ferroptosis mechanisms, the intricate balance between ferroptosis and bone metabolism, and the challenges of clinical translation and safety evaluation necessitate a multidisciplinary approach. Future research should focus on developing targeted therapies that can modulate ferroptosis with precision, while minimizing adverse effects and considering individual genetic variations. The integration of basic science with clinical practice will be crucial for advancing the field and ultimately improving patient outcomes. As our understanding of ferroptosis deepens, it is anticipated that this knowledge will lead to innovative strategies for osteoporosis management and treatment.

Authorship

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Each author certifies that this material or part thereof has not been published in another journal, that it is not currently submitted elsewhere, and that it will not be submitted elsewhere until a final decision regarding publication of the manuscript in Journal of Orthopaedic Translation has been made.

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Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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