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Electromagnetic fields regulate iron metabolism: From mechanisms to applications

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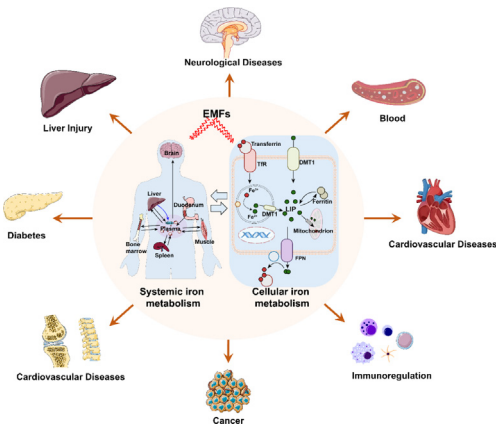
HIGHLIGHTS

- Electromagnetic fields (EMFs) can influence the progression of various diseases by regulating iron metabolism.
- The regulation of iron metabolism by EMFs is highly parameter-specific and varies across different tissues and cells.
- The electromagnetic properties of iron-containing molecules/proteins and iron-rich tissues influence iron metabolism modulation by EMFs.
- EMFs can modulate iron metabolism through their effects on membrane structure and ion channels.
- EMFs can modulate iron metabolism by regulating the generation and activity of Reactive Oxygen Species (ROS).

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Electromagnetic fields (EMFs), as a form of physical therapy, have been widely applied in biomedicine. Iron, the most abundant trace metal in living organisms, plays a critical role in various physiological processes, and imbalances in its metabolism are closely associated with the development and progression of numerous diseases. Numerous studies have demonstrated that EMF exposure induces significant changes in both systemic and cellular iron metabolism.

Aim of Review: This review aims to summarize the evidence and potential biophysical mechanisms underlying the role of EMFs in regulating iron metabolism, thereby enhancing the understanding of their biological mechanisms and expanding their potential applications in biomedical fields.

Key Scientific Concepts of Review: In this review, we have synthesized research findings and proposed the hypothesis that the biophysical mechanisms of EMFs regulate iron metabolism involve the special electromagnetic properties of iron-containing proteins and iron-enriched tissues, as well as the modulation

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of membrane structure and function, ion channels, and the generation and activity of Reactive Oxygen Species (ROS). Then, the review summarizes the latest advances in the effects of EMFs on iron metabolism and their safety, as well as their impact on immunoregulation, cardiovascular diseases, neurological diseases, orthopedic diseases, diabetes, liver injury, and cancer.

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Introduction

Electromagnetic fields (EMFs) are natural environmental factors essential to all living organisms. Earth is a giant magnet, enveloping all life on the planet within a geomagnetic field (GMF) of 20–70 μT, where organisms survive, evolve, reproduce, and die [1]. Meanwhile, advancements in technology have led to increasing exposure to various types of artificial EMFs. These artificial EMFs are now extensively utilized not only in industrial production and communication but also in biomedical applications. For instance, magnetic resonance imaging (MRI), a representative application of EMFs in biomedicine, has revolutionized medical diagnostic technology. In recent years, the biological effects and mechanisms of EMFs, as well as their applications in the treatment of various diseases, have gained growing attention. Various types of EMFs have been increasingly applied in both research and clinical treatment across a range of conditions, including immunoregulation, cardiovascular diseases, neurodegenerative disorders, orthopedic conditions, and cancers [2–6].

Iron is the most abundant transition metal in humans, and the balance of its metabolism is vital and essential for health [7]. On one hand, iron is an essential component of various proteins and a cofactor for many key enzymes, participating in critical physiological processes such as oxygen transport, DNA synthesis and repair, and the maintenance of mitochondrial function, among others [8]. Systemic iron deficiency has been considered as the direct cause of iron-deficiency anemia and related complications. Additionally, brain iron deficiency has been associated with irre-

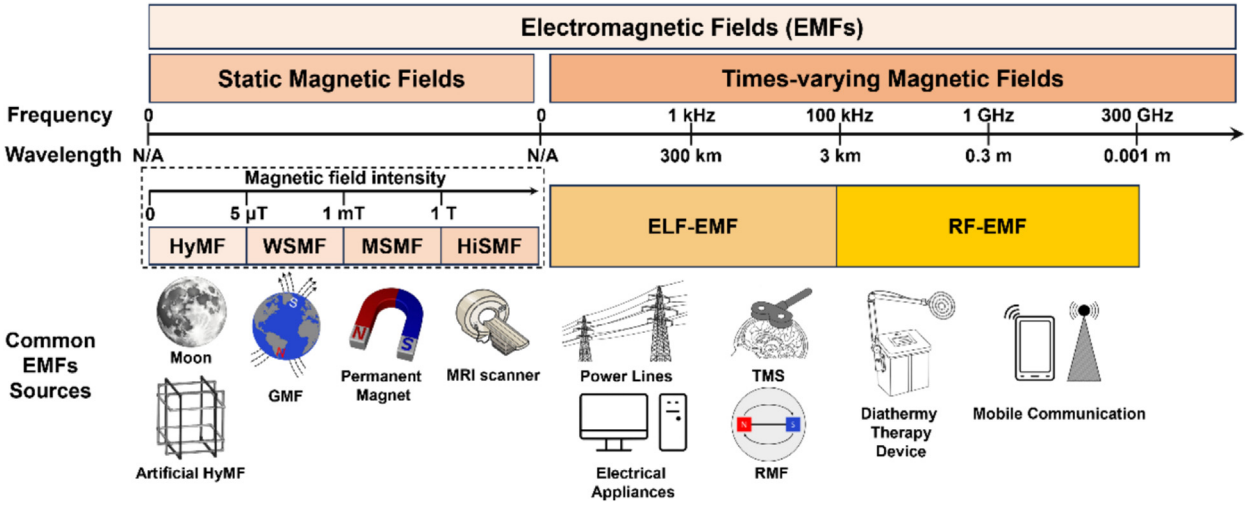

Fig. 1. The characteristics and classification of electromagnetic fields (EMFs). According to whether the magnetic field intensity varies with time, EMFs can be divided into static magnetic field (SMF) and times-varying magnetic field. SMFs can be further categorized by increasing magnetic field intensity into hypomagnetic fields (HyMFs, <5 μT), weak static magnetic fields (WSMFs, 5 μT to 1 mT), moderate static magnetic fields (MSMFs, 1 mT to 1 T), and high static magnetic fields (HiSMFs, >1 T). HyMFs include natural environments, such as the lunar surface, as well as artificial environments, which can be generated using devices like Helmholtz coils. The geomagnetic field (20–70 μT) is the most commonly encountered WSMF for living organisms. MSMFs are typically produced by permanent magnets, while HiSMFs are primarily generated by superconducting devices such as MRI systems. Time-varying magnetic fields are further subdivided by increasing frequency into extremely low-frequency electromagnetic fields (ELF-EMFs, 0–100 kHz) and radiofrequency electromagnetic fields (RF-EMFs, 100 kHz–300 GHz), among others. ELF-EMFs in daily life commonly originate from power transmission lines and electrical appliances. In the biomedical field, devices like Transcranial Magnetic Stimulation (TMS) systems and rotating magnetic field (RMF) generators also produce ELF-EMFs. RF-EMFs from mobile communication systems are the most common form of RF-EMF exposure in daily life. Additionally, RF-EMFs are widely used in the medical field, such as in diathermy devices for therapeutic applications.

versible cognitive and developmental delays [9]. On the other hand, abnormally increased iron levels in tissues and cells are recognized as triggers for redox imbalance. Iron can also convert relatively inactive O_2 and H_2O_2 molecules into highly active oxygen free radical and hydroxyl radicals by participating in the Fenton reaction, thereby increasing intracellular oxidative stress, and involved in various pathological processes [10]. Iron overload is a pathological condition characterized by the excessive accumulation of iron in tissues and organs, often resulting from genetic disorders, chronic blood transfusions, or metabolic dysregulation [11]. Many studies have demonstrated that iron overload is closely involved in the pathological processes of various orthopedic disorders such as osteoporosis, neurodegenerative diseases like Alzheimer's disease, and cardiovascular diseases like atherosclerosis, etc [11]. Moreover, the excessive accumulation of intracellular Reactive Oxygen Species (ROS) caused by iron could induce a novel form of iron-dependent programmed cell death—ferroptosis [12]. Ferroptosis is one of the key biological mechanisms underlying many iron overload-related diseases [13]. Furthermore, due to the fragile redox balance characteristic of most cancer cells, ferroptosis has emerged as a promising target for cancer therapy.

The regulation of ion transport and metabolism is recognized as one of the biophysical mechanisms of EMFs [14,15]. Firstly, iron and some iron-containing proteins, owing to their strong natural magnetic moments, are considered key targets of the biological effects of EMFs. Meanwhile, the effects of EMFs on cellular membrane potential and transmembrane ion channels may also be an important pathway to regulate iron metabolism. Moreover, considering the close association between iron and ROS, as well as the substantial research evidence about the modulation of ROS by EMFs, it has been suggested that iron metabolism could be a critical target of EMF-induced biological effects [16,17]. In addition, EMFs have been shown to regulate cellular and systemic iron metabolism by influencing the enrichment, uptake, and release of iron-containing agents, including iron-based nanoparticles (NPs) [18,19]. Notably, the effects of EMFs on iron metabolism are not solely determined by the exposure parameters of the field, such as intensity, frequency, and duration, but also influenced by the physiological status of the organism and tissue-specific variations. For example, in our previous study, continuous exposure to 10 T–12 T static magnetic fields (SMFs) for 28 days increased iron levels in the kidneys and liver of mice. 2T- 8 T SMFs exposure also resulted in an elevation of iron content in the kidneys, but did not significantly change iron levels in the liver of mice [20]. Burchard JF et al also found that 60 Hz, 30 μT EMFs exposure for 30 days did not change iron levels in the cerebrospinal fluid of ovariectomized cows but reduced iron content in the cerebrospinal fluid of nonlactating pregnant cows [21]. Overall, although the diverse effects of EMFs on iron metabolism make it difficult to systematically summarize, the findings from relevant studies provide valuable insights for the safety assessment of EMFs and their applications in the biomedical field.

This review focuses on the effects of EMFs on iron metabolism and their potential applications in the prevention and treatment of diseases related to iron homeostasis disorders. We first describe the classification and characteristics of EMFs, along with the fundamental concepts of systemic and cellular iron metabolism. Subsequently, we propose several potential biophysical mechanisms through which EMFs regulate iron metabolism. Furthermore, we discuss the applications and underlying biological mechanisms of EMFs in blood and immunoregulation, and management of iron homeostasis disorders-related diseases such as cardiovascular diseases, neurological conditions, orthopedic diseases, and cancer, among others.

The classification of EMFs

EMFs can be classified into static magnetic fields (SMFs, 0 Hz) and time-varying magnetic fields based on whether the magnetic field intensity and orientation varies with time [22] (Fig. 1).

According to the different magnetic field intensity, the SMFs could be further divided into hypomagnetic fields (HyMF, <5 μT), weak static magnetic fields (WSMF, 5 μT to 1 mT), moderate static

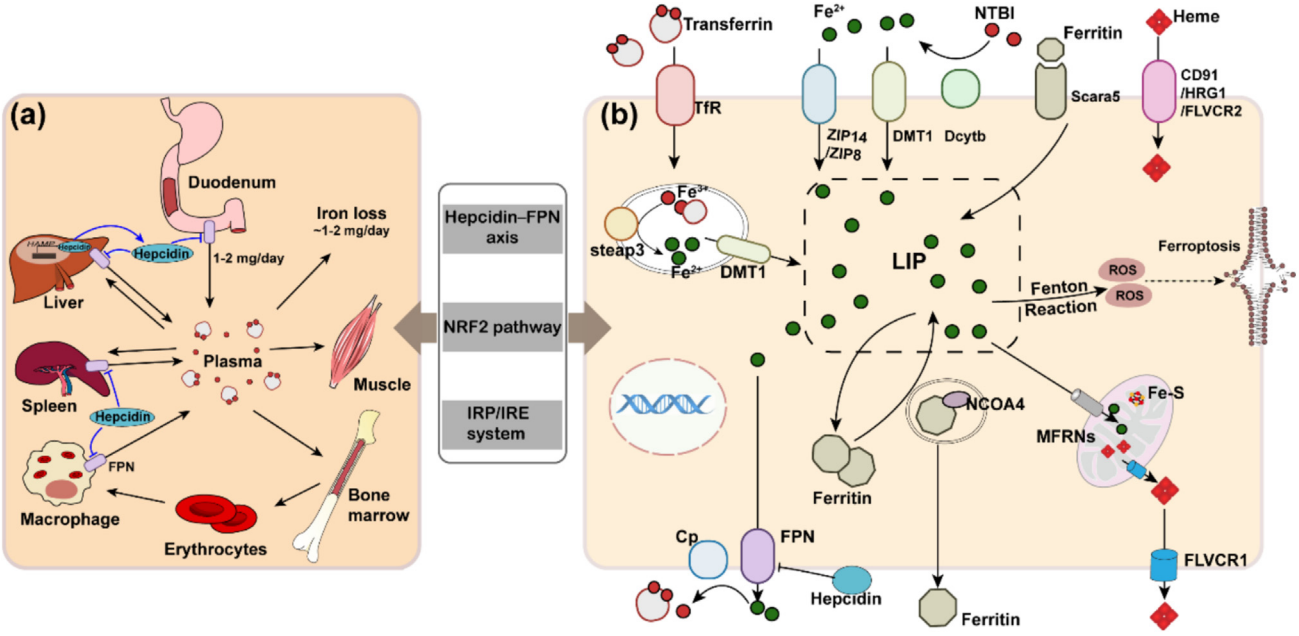

Fig. 2. Systemic and cellular iron metabolism. **(a),** The duodenal enterocytes absorb approximately 1–2 mg of dietary iron daily to compensate for nonspecific iron losses. Plasma iron is bound to transferrin, the majority of which is utilized for hemoglobin synthesis in erythroid cells in the bone marrow, while a smaller portion is stored or used by other cells in various tissues. Macrophages can phagocytose damaged or senescent red blood cells, releasing the iron from hemoglobin back into the plasma, which accounts for more than 90 % of the plasma iron pool. The unused iron is reversibly stored in liver and spleen. Hepcidin, the core regulator of systemic iron metabolism, is primarily produced in hepatocytes and can inactivate ferroportin (FPN) in target cells, thereby inhibiting iron efflux to the bloodstream. **(b),** Transferrin-bound iron is taken up through Transferrin Receptor (TfR), then the iron is reduced from Fe3 + to Fe2 + by six-transmembrane epithelial antigen of prostate3 (STEAP3) in vesicles and enters the cytoplasm via dalent metal transporter 1 (DMT1). Cells can also take up the Non-Transferrin-Bound Iron (NTBI) directly through ion channels like DMT1, Zinc transporters Zrt- and Irt-like protein 8 (ZIP8) and ZIP14. Moreover, heme and ferritin can be transported directly into the cell by specific molecules, including CD91, HRG1, FLVCR2, and Scara5. Fe^{2+} in the Labile Iron Pool (LIP) can be stored in ferritin and can also be utilized in various biochemical processes. Iron in ferritin can be released back into the LIP through Nuclear receptor coactivator 4 (NCOA4) mediated ferritinophagy. Most active iron enters the mitochondria via mitoferrins (MFRNs) for the synthesis of Fe-S clusters and heme. FPN exports excess Fe^{2+} from cells, where it is oxidized to Fe^{3+} by ceruloplasmin (Cp) and subsequently binds to transferrin. Additionally, NCOA4 can mediate the export of ferritin, while FLVCR1 is believed to mediate the extracellular export of heme. Hepcidin-FPN axis, Iron-Regulatory Protein (IRP)–Iron-Responsive Element (IRE) network, and nuclear factor erythroid 2-related factor 2 (NRF2) pathway are critically involved in the regulation of systemic and cellular iron metabolism.

magnetic fields (MSMF, 1 mT to 1 T), and high static magnetic fields (HiSMF, >1 T) [23]. Natural HyMFs are mainly exist in locations distant from the Earth's surface and in extraterrestrial space, such as the magnetic field intensity on the Moon is less than 300 nT [24]. The artificial HyMF environments on Earth are primarily typically achieved using shielding systems made of soft magnetic materials or compensation systems based on Helmholtz coils. The geomagnetic field can be classified as a WSMF, while the magnetic fields generated by common permanent magnets are considered MSMFs. The most common HiSMF environments are primarily produced by superconducting technology, such as the main magnetic field in MRI devices. Currently, artificial HiSMF can exceed 45 T [25].

Based on the difference in frequency, time-varying magnetic fields can be further classified into extremely low-frequency electromagnetic fields (ELF-EMFs, 0–100 KHz) and radiofrequency electromagnetic fields (RF-EMFs, 100 KHz to 300 GHz), etc [26]. The terahertz fields, infrared, visible light, ultraviolet, and higher-frequency fields such as X-rays and γ rays are considered within the scope of EMFs in physics, but these fields fall outside the scope of this review. Time-varying magnetic fields can be generated by varying currents. For example, alternating current (AC) can produce sinusoidal EMFs, while modulated currents can generate pulsed electromagnetic fields (PEMFs). Additionally, some time-varying magnetic fields, such as rotating magnetic fields (RMFs), can be produced using moving SMF devices. Common sources of ELF-EMFs include power systems and electrical appliances. Notably, ELF-EMFs have significant biomedical applications, such as RMFs for regulating chronic diseases and Transcranial Magnetic Stimulation (TMS) for treating neurological disorders [27–29]. The RF-EMFs are not only widely used in mobile communication technologies, including current 5G communication devices, but also extensively applied in diathermy therapy [30,31].

Iron metabolism

Iron metabolism is precisely regulated in the body to maintain a relatively balanced state. Approximately 2 % of human genes encode iron--containing proteins, and over 6 % of all enzymes are dependent on iron [32]. Both iron deficiency and iron overload at the tissue, organ, or cellular levels are associated with impairments in normal physiological functions [7,33]. Iron metabolism in organisms can be broadly categorized into systemic iron metabolism and cellular iron metabolism, which are interconnected and regulated through multiple signaling pathways. These include the hepcidin-ferroportin (FPN/SLC40A1) axis, the Iron-Regulatory Protein (IRP)–Iron-Responsive Element (IRE) network, and the nuclear factor erythroid 2-related factor 2 (NRF2) regulatory hub, among others. Additionally, as an iron-dependent form of programmed cell death, ferroptosis has recently emerged as a key focus in the study of iron metabolism [34] (Fig. 2).

Systemic iron metabolism

Systemic iron metabolism refers to the regulatory processes involved in the absorption, transport, storage, and reutilization of iron throughout the body. In humans, systemic iron is primarily absorbed by the epithelial cells of the duodenum from the diet,

at a rate of approximately 1–2 mg per day [8]. Within duodenal epithelial cells, iron is processed, transported, and released into the bloodstream through the basolateral membrane. Then, iron bound to transferrin (Tf) in blood, and is transported to tissues for storage or utilization. Iron in the body can be broadly categorized into functional iron and storage iron. Functional iron mainly exists in the heme structures such as hemoglobin (Hb) and myoglobin (Mb), with Hb iron in red blood cells accounting for approximately 70 % of the total body iron. The damaged or senescent red blood cells could be phagocytosed by macrophages, and Hb iron is released and reused, which supplied more than 90 % of the iron for utilization in organism [35].

Excess iron in the organism is primarily stored in hepatocytes in the liver and in the reticuloendothelial systems of the spleen and bone marrow. Notably, the human body lacks a specific iron excretion pathway, and iron loss is primarily via shedding of cells and bleeding to maintain a relatively stable total organism iron level. Systemic iron metabolism is mainly regulated by the hepcidin-FPN axis [36]. Hepcidin, encoded by the HAMP gene, is a key regulator in the systemic iron metabolism and is primarily secreted by the liver. FPN, a membrane iron transporter, is currently the only known channel for iron export in mammals. Duodenal epithelial cells, stem cells, and macrophages all express high levels of FPN, participating in the regulation of systemic iron metabolism. Hepcidin binds to the extracellular domain of FPN on the cell membrane, triggering its internalization and subsequent degradation in lysosomes, thereby reducing cellular iron efflux. Abnormal expression and function of hepcidin is often accompanied by severe systemic iron metabolism disorders. For instance, hepcidin deficiency can lead to iron overload disorders such as hereditary hemochromatosis, while elevated hepcidin levels are associated with conditions like iron-refractory iron deficiency anemia (IRIDA) and anemia of inflammation [37].

Cellular iron metabolism

Cellular iron metabolism can be divided into iron uptake, utilization, storage, and efflux [8]. The majority of cellular iron uptake is mediated by the Transferrin Receptor (TfR), which binds to iron-loaded transferrin (Tf) and facilitates the internalization of the Tf–TfR complex. Within the acidic environment of endosomes, Fe^{3+} is released from Tf-TfR complex, subsequently reduced to $Fe^{2+}$by six-transmembrane epithelial antigen of the prostate 3 (STEAP3), and then transported into the cytoplasm via divalent metal transporter 1 (DMT1/SLC11A2). DMT1 is also the primarily mediator of the uptake of Non-Transferrin Bound Iron (NTBI). Additionally, the zinc transporters Zrt- and Irt-like protein 8 (ZIP8) and ZIP14 can also mediate NTBI uptake. Moreover, heme can be directly absorbed by cells via prolow-density lipoprotein receptor-related protein 1 (LRP1; also known as CD91), heme-responsive gene 1 protein (HRG1/SLC48A1), and feline leukemia virus subgroup C receptor 2 (FLVCR2/SLC49A2). Furthermore, some cells can directly uptake ferritin via Scara5 [38]. Once inside the cell, iron can be directly utilized in critical physiological processes such as enzymatic activity and cellular respiration. In this process, a large fraction of iron enters mitochondria through mitoferrins (MFRNs) to participate in the assembly of Fe–S cluster and the synthesis of heme. Unutilized intracellular iron exists in the Labile Iron Pool (LIP), which can be directly used by the cell and is also an important source of intracellular ROS [38].

Excess intracellular iron is stored in ferritin, a protein capable of housing up to 4,500 iron atoms. Ferritin consists of 24 subunits, primarily categorized into heavy (FTH) and light (FTL) chains. Nuclear receptor coactivator 4 (NCOA4) could mediate the autophagic degradation of ferritin within lysosomes, and released iron back into the LIP, which progress termed ferritinophagy [39]. During cellular iron efflux, Fe^{2+} is primarily transported to the extracellular space by FPN, and oxidized to Fe3 + by ceruloplasmin (Cp) or heparan sulfate, allowing it to rebind to Tf. Additionally, ferritin could be secreted to extracellular environment by lysosome during ferritinophagy in hepatocytes, macrophages, and renal tubular cells. Furthermore, despite ongoing debate, FLVCR1 on the cell membrane is believed to directly export heme from the cell, a process important for preventing excessive heme accumulation and enabling its transfer from macrophages to developing erythroblasts.

Regulatory pathways of iron metabolism

The balance of systemic and cellular iron metabolism is maintained through a complex regulatory system. In addition to the previously mentioned hepcidin-FPN axis, the IRP/IRE network and the NRF2 regulatory hub also play crucial roles in this process [37]. IRPs include two homologous factors: IRP1 (also known as cytoplasmic aconitase) and IRP2. IRP1 and IRP2 can bind to IREs located in the untranslated regions (UTRs) of target mRNAs encoding iron metabolism-related proteins, thereby regulating both the translation of ferritin and FPN mRNA and the stability of TfR and DMT1 mRNA. Under iron-deficient conditions, the interaction between IRPs and the IREs of target mRNAs prevents the small ribosomal subunit from binding to the mRNA, thereby inhibiting the translation of ferritin and FPN. Conversely, when intracellular iron levels are sufficient, iron binds to IRPs, causing their dissociation from IREs, thereby promoting the translation of ferritin and FPN while reducing the stability of TfR and DMT1 mRNA [40]. NRF2 was initially identified for its role in erythropoiesis and was later recognized as a central regulator of iron metabolism. NRF2 regulates the intracellular Labile Iron Pool (LIP) by upregulating ferritin and Ferroportin (FPN) expression, while its inhibition promotes NCOA4-mediated ferritinophagy [41,42]. Additionally, NRF2 can regulate hepatic hepcidin synthesis by modulating bone morphogenetic protein 6 (BMP6), thereby indirectly regulating systemic iron metabolism. NRF2 also modulates macrophage heme uptake via HRG1 expression and regulates heme degradation through heme oxygenase 1 (HMOX1). Furthermore, as a key regulator of cellular redox homeostasis, NRF2 plays a protective role against ferroptosis by upregulating genes such as quinone oxidoreductase 1 (NQO1) and heme oxygenase-1 (HO-1) [43].

Ferroptosis

Ferroptosis is a non-apoptotic form of programmed cell death, with one of the key triggering factors is the accumulation of excess redox iron due to dysregulated iron metabolism [44]. Compared to other types of programmed cell death, increased intracellular membrane lipid peroxides due to the reaction of iron or iron-containing enzymes with oxygen and polyunsaturated fatty acid (PUFA) is the defining characteristic of ferroptosis [45]. The regulation of LIP levels has been shown to influence cellular sensitivity to ferroptosis, and iron chelators such as Deferoxamine (DFO) and deferiprone (DFP) can protect cells from ferroptosis [46]. Therefore, although the exact role of iron in ferroptosis remains unclear, ferroptosis is still considered an essential component of iron metabolism research.

The potential biophysical mechanisms and characteristics of EMFs in regulating iron metabolism

As a form of physical stimulation, the effects of EMFs on iron metabolism are not limited to the regulation of iron metabolism-related molecular expression but also involve multiple biophysical

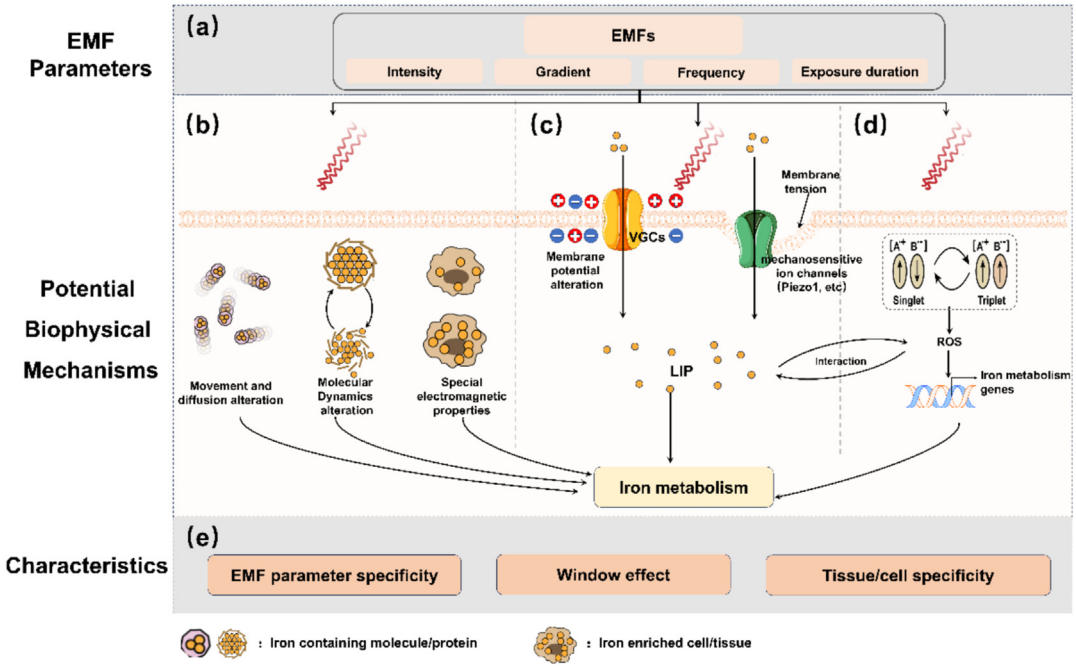

Fig. 3. The potential biophysical mechanisms and characteristics of electromagnetic fields (EMFs) in regulating iron metabolism. (**a**) EMF exposure involves various parameters, including field intensity, gradient, frequency, and exposure duration. **(b-d)** Potential biophysical mechanisms of EMF regulation of iron metabolism. (**b**) The direct effects of EMFs on iron-containing tissue and proteins. Iron content influences the electromagnetic properties of tissue and cells, including magnetic permeability, electrical conductivity, and dielectric constants, thereby affecting their response to EMFs; EMFs alter the movement of iron-containing proteins and molecules, such as hemoglobin and ferritin, thus impacting iron metabolism; Furthermore, EMFs modulate the dynamic characteristics of iron-containing proteins/molecules, thereby regulating iron metabolism, such as regulating the release and storage of iron in ferritin. (**c**) EMFs regulate iron metabolism by influencing transmembrane transport of iron through the modulation of cell membranes and ion channels. EMFs could regulate voltage-gated ion channels (VGCs) mediated iron uptake by adjusting membrane potential, and mechanosensitive ion channels (piezo1, etc) mediated iron uptake by inducing membrane deformation. (**d**) Due to the close interplay between Reactive Oxygen Species (ROS) and iron metabolism, EMFs can regulate iron metabolism by altering intracellular ROS levels through mechanisms such as affecting the spin state of radical pairs. (**e**) The regulation of iron metabolism by EMFs exhibits distinct characteristics, including parameter specificity, window effects, and tissue- and cell- specificity.

mechanisms. First, EMFs directly interact with various iron-containing biomacromolecules, including numerous iron-binding proteins, while differences in iron content among tissues may also influence tissue responses to EMF exposure. Additionally, EMFs modulate membrane structures and the states of ion channels, thereby regulating iron transmembrane transport. Furthermore, due to the intricate relationship between intracellular iron and Reactive Oxygen Species (ROS), EMFs can regulate iron metabolism by modulating oxidative stress levels, particularly influencing the spin states of radical pairs. Due to the complex interactions among these biophysical mechanisms, the regulation of iron metabolism by EMFs varies depending on parameters such as intensity, gradient, frequency, and exposure duration, while also exhibiting characteristics of dose dependence, window effects, and specificity for different tissues and cell types (Fig. 3).

The direct effects on iron enriched protein and tissues

Iron in proteins can alter their magnetism, thereby affecting their movement and physiological functions in the presence of EMFs. For instance, Hb, as the most well-known iron-containing protein, provides the necessary oxygen for the body to maintain normal energy metabolism. The magnetism of Hb is related to its state, oxyhemoglobin (oxyHb) and carbonmonoxyhemoglobin are diamagnetic, while deoxyhemoglobin (deoxyHb) is magnetic [47]. When moving in an inhomogeneous magnetic field, red blood cells containing paramagnetic hemoglobin exhibit noticeable displacement toward the stronger magnetic field. This displacement is proportional to the square of the paramagnetic moment of hemoglobin in the cells [48]. Furthermore, studies have found that sufficiently high EMFs can affect Hb diffusion. When the magnetic field strength exceeding 22.8 T, the diffusion of deoxyHb is impacted, while fields stronger than 25.7 T influence the diffusion of oxyHb [49]. Accordingly, EMFs could mediate the transport of oxygen and the fate of red blood cells through interactions with Hb, thereby regulating systemic iron metabolism. Meanwhile, the function of iron-containing protein can also be regulated by EMFs. As iron storage protein, ferritin consists of a cage-like structure composed of 24 subunits. The iron is mainly stored in the cage as form of a ferrihydrite-like mineral core, which gives ferritin its superparamagnetic properties [50]. Oscar et al. found that 1 MHz, 30 μT RF-EMFs exposure significantly decreased the iron intake rate of ferritin. This effect is non-thermal and depends on the frequency-amplitude product of the magnetic field [51,52]. Hernández-Morales M et al. also found that exposure to 180 MHz, 12 μT RF-EMF increased LIP and upregulated intracellular ROS level in a ferritin-dependent manner, suggesting that EMF exposure promotes iron release from ferritin [53]. In these studies, it was observed that due to magnetization lag, ferritin's internal energy increases when exposed to time-varying magnetic fields. This increased energy will diffuse to the surroundings, altering the molecular dynamics and functioning of the protein cage's subunits, and changing iron intake and release of ferritin. Besides, SMFs have been shown to alter the release of iron from ferritin. Chen et al. found that 1.4 mT – 5.0 mT SMF exposure increased intracellular ROS levels by promoting the release of iron from ferritin, which could be attenuated by the addition of ROS inhibitors or iron chelator [54]. However, it remains uncertain whether this process is due to changes in the molecular dynamics and function of ferritin itself, as our previous study found that exposure to a 0.2–0.4 T SMF increased the LIP level by promoting ferritinophagy [55]. Furthermore, iron-sulfur cluster assembly 1 (IscA1), also known as magne-

toreceptor (MagR), is an important magnetic sensitive protein in organisms, which have been indicated contains a very high iron content and serves as a scaffold protein and iron donor, participating in the assembly of iron-sulfur clusters [56]. Moreover, the overexpressing of pigeon MagR has been shown to increase the expression of iron uptake related genes in *E.* coli cells [57]. Therefore, the role of magR in the regulation of EMFs on iron metabolism also deserves further investigation.

The iron content of tissues may influence their electromagnetic properties, thereby affecting their response to EMFs. The biological effects of EMFs may primarily be attributed to differences in magnetic susceptibility (χ) under SMFs. Dubiel et al. found that the distinct uniaxial magnetic anisotropy characteristics of brain and liver are related to variations of iron content and its existing forms tissue [58]. Studies have found that the major organs of iron-overloaded mice exhibit higher magnetic susceptibility [59]. Additionally, the increased tissue iron content has been proved to be a major contributing factor to the elevated magnetic susceptibility of the spleen and liver in NRF2−/− mice [60]. In time-varying magnetic fields, dielectric properties appear to play a more prominent role [61]. Compared to normal tissues, tumor tissues typically exhibit higher dielectric permittivity and conductivity values [62–64]. It can be attributed not only to the higher water content in tumor tissues but also to the higher iron content.

However, magnetism is an intrinsic property of matter, and virtually all molecules can be influenced by EMFs, although their sensitivity and responses vary depending on their magnetic properties. Notably, some non-iron-containing molecules, such as ROS and certain metal enzymes, also exhibit relatively high magnetic susceptibility, making them sensitive to EMF exposure. Given the current limited understanding of the magnetic properties and EMF responsiveness of molecules involved in iron metabolism, it is possible that EMFs may regulate iron metabolism indirectly through interactions with non-iron-containing biomacromolecules or structural components of tissues.

Membrane permeability, potential and ion channels

Cellular iron uptake, utilization, and efflux involve the transmembrane transport of iron ions and iron-binding proteins. Meanwhile, membrane structure and membrane potential, and the state of ion channels on the membrane can all affect the transport of iron, thereby influencing iron metabolism. The biological effects of EMFs are related to their regulation of membrane potential and ion channels [65,66]. Firstly, EMFs can mediate the ion diffusion and transport via the Lorentz force and alter the membrane potential [67,68]. On one hand, EMF exposure can reorganize the permanent phospholipid dipoles in the membrane structure, influencing its shape and potential [69]. On the other hand, the membrane structure has a higher electrical resistance, while transmembrane proteins have higher charge permeability making the conformation of these proteins more susceptible to changes induced by EMF exposure [70]. Voltage-gated ion channels (VGCs) are crucial pathways for ion transport in cells, containing domains rich in charged residues, known as voltage-sensing domains (VSDs), which undergo conformational changes in response to voltage fluctuations across the membrane [71]. Many studies have indicated that both acute and chronic EMFs exposure can enhance ion transport mediated by various VGCs, which may be attributed to the effects of EMFs on the VSD and pore-forming domain of VGCs [66,72–74]. Although no specific iron-VGCs have been identified, iron can non-specifically enter cells through various types of VGCs [75–77]. Additionally, EMFs can regulate cellular iron uptake by regulating mechanosensitive ion channels on the cell membrane [78]. Piezo1 primarily recognized as a mechanosensitive calcium ion channel, has also been implicated in iron uptake [79]. Studies have shown that EMFs can influence the expression and activation state of Piezo1 [80,81]. These conformational changes of Piezo1 may not be directly caused by EMF induced mechanical stimulation, as such stimulation requires forces exceeding the pN, which is far greater than the magnitude of forces generated by the EMFs in these studies [82]. However, it is still possible for EMFs to directly affect the opening of mechanosensitive ion channels either through direct interaction or indirectly through cell membrane deformation, as long as the intensity gradient or energy of EMFs is sufficient. For example, external EMFs have been reported to induce ion oscillations, leading to membrane oscillations and subsequent alterations in the activity of mechanosensitive channels [83].

The interaction between ROS and iron metabolism

EMFs can modulate intracellular ROS levels through multiple pathways [84–87]. Radicals, important components of ROS, are characterized by unpaired electrons in their outer shells. The effect of EMFs on radical pairs is hypothesized to be a key physical mechanism underlying the biological effects of EMFs and one of the fundamental bases for biological sensitivity to magnetic fields [88,89]. Studies have shown that the singlet–triplet transitions and recombination of radical pairs can be regulated by magnetic fields, thereby influencing intracellular ROS levels [90,91].. Additionally, EMFs have been reported to alter intracellular ROS levels by modulating the activity of antioxidant enzymes [16]. The intracellular ROS levels are closely associated with iron metabolism. On one hand, intracellular iron can increase ROS levels by participating in the Fenton reaction, and iron deposition within ferritin is accompanied by the generation of a small amount of hydroxyl radicals. On the other hand, ROS can actively regulate the process of iron metabolism [92–94]Hydrogen peroxide can promote the binding of IRP1 to IREs and induce the iron atom release from cytosolic aconitase by directly reacting with [4Fe–4S] cluster, thereby influencing iron metabolism [95,96]. Superoxide and hydroxyl radicals can also facilitate the release of iron from transferrin and enhance cellular iron uptake [97,98]. Additionally, studies have shown that ROS (including radical pairs) can regulate the expression and function of iron metabolism-related genes and proteins [98,99]. Moreover, ROS can indirectly modulate iron metabolism by reducing the activation of the IRP/IRE network and promoting NRF2 expression [100]. Many studies focus on the regulation of iron metabolism by EMFs has also reported concurrent changes in ROS levels [101–104]. The increase in intracellular ROS levels induced by EMFs is typically accompanied by upregulated expression of iron uptake-related genes and an elevated LIP. In contrast, the decrease in intracellular ROS levels under EMF exposure is associated with the upregulation of iron storage and export-related genes, along with a reduction in LIP levels. Although the upstream–downstream regulatory relationship between intracellular iron metabolism and ROS levels under EMFs exposure remains unclear, we speculate that EMF-mediated ROS regulation is an important biophysical mechanism underlying its modulation of iron metabolism.

The characteristics of EMFs in regulating iron metabolism

Due to the complex interactions among these biophysical mechanisms, the regulation of iron metabolism by EMFs varies depending on parameters such as intensity, gradient, frequency, and exposure duration, while also exhibiting characteristics of window effects and specificity for different tissues and cell types.

One of the most prominent features of EMF-mediated regulation of iron metabolism is its dependence on EMF parameters. For intensity, HyMF have been shown to increase serum and femur iron content in mice, whereas 1–2 T HiSMF can decrease

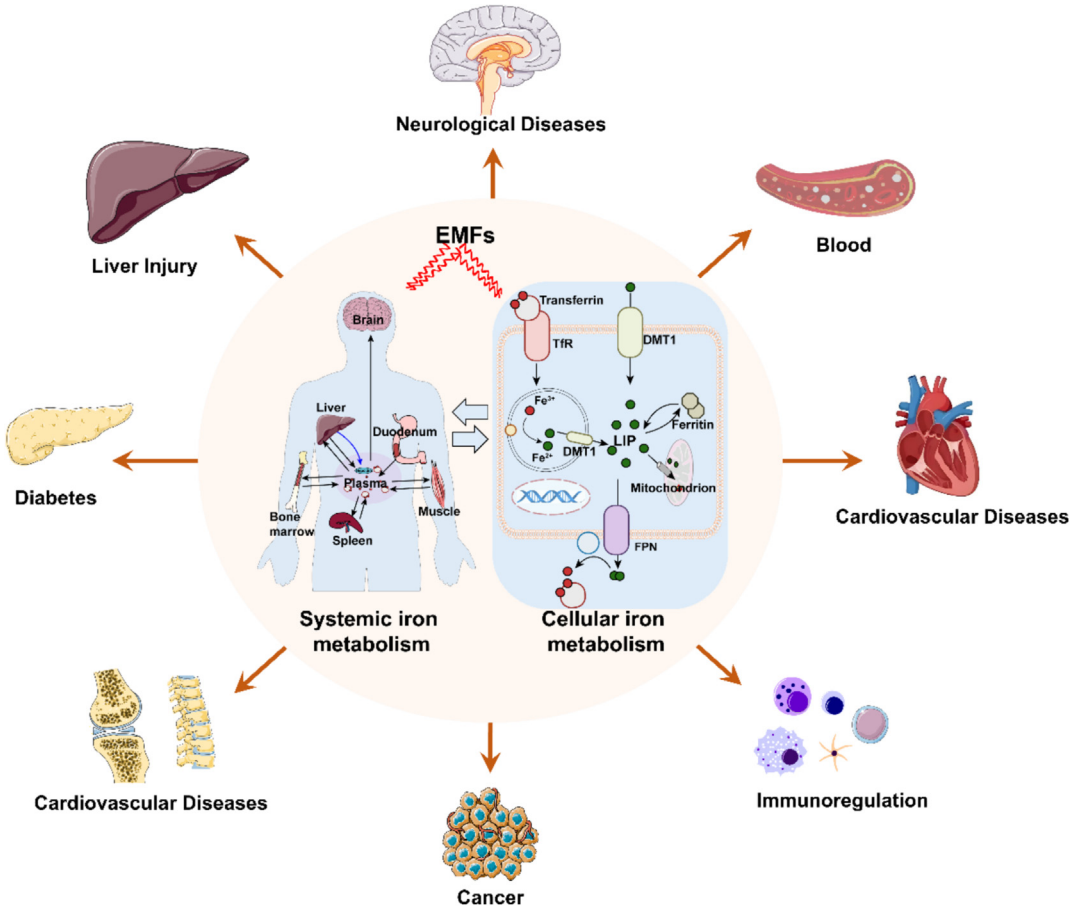

Fig. 4. Electromagnetic fields influence various physiological processes and the progression of diseases by regulating iron metabolism.

iron levels in these organs [105,106]. For gradient, MSMFs with lower gradients have been shown to reduce iron overload in diabetic mice, whereas high-gradient SMFs fail to produce the same effect [102,107]. For frequency, ELF-EMF at 7.5 Hz have been shown to reduce intracellular iron levels, and its inhibitory effects on tumor cells were mitigated by ferric ammonium citrate (FAC), while the antitumor effects of 134 kHz RF-EMFs were attenuated by iron chelators [108,109]. The differential responsiveness of iron-containing proteins to EMFs is a key factor underlying the parameter-specific regulation of iron metabolism by EMFs. For instance, hemoglobin remains largely unaffected under low EMF strength or gradient, while its movement becomes subject to magnetic control in high-gradient EMFs, which has even been exploited for applications such as red blood cell separation [49,110]. The differential responsiveness of membranes and membrane-bound ion channels to EMFs is another critical reason for the parameter-specific regulation of iron metabolism by EMFs [111]. On one hand, different types of ion channels require distinct membrane potential thresholds or force for activation. On the other hand, EMFs with varying parameters exert different levels of electrical stimulation, tension on membrane structures, thereby leading to diverse biological effects. Additionally, the sensitivity of ion channels to EMF exposure is also related to their type and the frequency of the EMF. Furthermore, the effects of EMFs on ROS have shown varying results depending on the exposure parameters and cell types [16,106,112–119]. Therefore, the differential regulation of ROS by various EMF parameters is also one of the key reasons underlying the parameter-specific effects of EMFs on iron metabolism.

The specificity of EMF-regulated iron metabolism in different tissues and cell types is also a significant manifestation of the complex interplay among the various biophysical mechanisms through which EMFs exert their effects on iron homeostasis. First, the iron content and the distribution of iron-containing proteins vary across different tissues. The liver and spleen, which are rich in iron, and often exhibit more pronounced changes in iron metabolism–related indicators under EMF exposure [17]. It was reported that the enriched iron content in many types cancer cells results in a higher magnetic susceptibility ($\chi_{cancerous} > \chi_{healthy}$), making them more sensitive to SMFs [120]. In addition, the distribution of membrane ion channels and the levels of intracellular ROS also vary across different tissues and cell types. For example, neuronal cells typically possess a higher density of membrane-bound ion channels, the metabolically active cells—such as tumor cells tend to exhibit elevated intracellular ROS levels [121,122]. Moreover, the organism's inherent homeostatic mechanisms allow it to gradually adapt to external stimuli, thereby reducing sensitivity to EMFs. This adaptive capacity may be one of the key reasons underlying the "window effect" observed in the regulation of iron metabolism by EMFs. In addition, studies have shown that intracellular levels of ions such as potassium and calcium exhibit periodic fluctuations, and EMFs with specific frequencies can induce resonance-like responses with these ions, thereby eliciting biological effects [123]. Although it remains unclear whether intracellular iron levels exhibit periodic changes, they have been shown to undergo dynamic fluctuations [124]. Furthermore, the resonance frequencies of different iron metabolism-related molecules and ion channels lead to their differential responses to EMFs of varying

frequencies [125–127]. Therefore, resonance-like interactions between intracellular iron ions or iron metabolism-related molecules and electromagnetic fields may also represent a potential reason for the window effects of EMFs on the regulation of iron metabolism, influenced by factors such as intensity, frequency, and exposure duration.

The effects of EMFs on iron metabolism and its relationship to diseases

The safety of EMFs and their potential therapeutic applications in various diseases have garnered increasing attention, with research into their biological mechanisms advancing steadily. Recently, changes in iron metabolism have become a focal point in studies on the biological effects of EMFs [17]. Many studies on the biosafety of EMFs have reported changes in iron metabolism. Meanwhile, iron metabolism is involved in the regulation of EMFs on immunoregulation, and the progression of neurological diseases, cardiovascular diseases, orthopedic diseases, diabetes, liver injury, and cancer [102,118,128–138] (Fig. 4). Additionally, studies have demonstrated that that iron metabolism is involved in the regulation of EMFs on ROS and ferroptosis [55,112,119,139]. Moreover, in combination with iron metabolism-regulating drugs or iron oxide nanoparticles, EMFs have been observed to exhibit synergistic or antagonistic effects on iron metabolism regulation [108,140–143].

The relationship between EMFs biosafety and its regulation on iron metabolism

Current research on the relationship between electromagnetic field (EMF) biosafety and its regulation of iron metabolism primarily focuses on iron metabolism-related indicators in the nervous system and blood. Red blood cells, hemoglobin (Hb), transferrin, and other iron-related parameters in the blood are all important indicators of systemic iron metabolism. Thalassemia, a hereditary hemolytic anemia, necessitates regular blood transfusions to maintain adequate Hb levels. However, due to the lack of efficient iron elimination mechanisms in the human body, thalassemia patients are often experience iron overload and require additional iron chelation therapy [144]. Various studies have reported that 1 h per day 128 mT SMF exposure increased the transferrin content in serum and iron content in spinal cord, while decreased Hb and iron concentration in plasma [128,145–148]. It is suggested the potential of EMF-based therapies to exacerbate iron overload in patients receiving blood transfusions. Conversely, the risk of EMF-induced anemia has also been extensively studied. 50 Hz, 1.35 mT ELF-EMF exposure for 2 h per day over a period of 2 months did not significantly affect the serum Fe^{3+} concentration in SD rats [129]. Similarly, Devevey L et al. found that long-term exposure (3 to 16 weeks) to a 50 Hz, 500 μT ELF-EMF decreased the total percentage of cells in the red cell lineage in blood without inducing anemia-related symptoms [130]. Furthermore, a study reported that exposure to EMFs near 50 Hz high-voltage transmission lines, although it did not cause anemia, led to a decrease in serum iron levels in more than 48 % (15/31) of males and more than 38 % (13/34) of females [149]. In addition, the effects of RF-EMFs generated by mobile devices on iron status in blood have also been explored. Çetkin M et al. reported that the RF-EMF generated by GSM mobile phone systems reduced the serum transferrin unsaturated iron-binding capacity and total iron-binding capacity in rats [150]. El-Maleky NF et al. found that 60 min per daily mobile phone EMFs exposure for 6 months increased the serum ferritin and iron concentration in rats, while simultaneously reducing serum iron, plasma Hb, hematocrit (HCT), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) levels [30]. Overall, these studies indicate that EMFs can influence iron metabolism markers and components in the blood. These findings suggest the therapeutic potential of EMFs in treating iron metabolism disorders in blood, while emphasizing the importance of addressing these effects in EMF safety and risk management.

Due to the changes in electrical potentials accompanying neural signal conduction, the nervous system is very responsive to EMFs stimulation. Changes in iron metabolism within the nervous system have been observed in many studies assessing the biological safety of EMFs. Kopani M found that exposure to 1788 MHz RF-EMF generated by GSM mobile phone systems increased iron deposition in the cerebellum of rabbits [31]. Meanwhile, studies have indicated that EMFs could regulate the function and status of brain by altering the blood–brain barrier permeability to iron [151,152]. Furthermore, 60 Hz, 10 μT ELF-EMF exposure for 24 h has been shown to increase the occurrence of DNA single-strand and double-strand breaks in rat brain cells, and these effects could be inhibited by the iron chelator deferiprone [153]. In addition, the effects of the EMFs on behavior may be related to its regulation of iron metabolism in the nervous system. Abdelmelek et al. conducted a study using the plus-maze test and found that treatment with $FeSO_4$ alone did not affect the activity patterns of mice. However, when combined with 128 mT SMF exposure, it significantly reduced the number of entries and time spent in the open arms, indicating higher anxiety levels in the mice [154]. Interestingly, their related studies found that both the SMF and FeSO4 treatment alone impaired the spatial learning abilities of mice in morris water maze test, while combined treatment significantly improved the spatial memory abilities of mice compared to the SMF treatment alone [155]. Several studies have also reported that electromagnetic fields exert no significant influence on iron metabolism within the nervous system. For example, Aldinucci Cet al. found that 50 Hz, 2 mT ELF-EMF exposure had no significant changed free iron release in synaptosomes [135,156]. Maaroufi et al. also found that 900 MHz RF-EMF exposure interfered spontaneous exploratory behavior in rats, and the intraperitoneal injection of ferrous sulfate induced iron overload has not exacerbated these effects [157]. Nevertheless, the effects of EMFs on iron metabolism should still be considered an important factor when assessing their safety for the nervous system.

In addition, some epidemiological research reported that EMFs may be a risk factor for cancer and male infertility [158,159]. Dysregulated iron metabolism is a hallmark of cancer cells and also a significant contributor to male infertility [160–162]. However, the relationship between EMFs exposure, its potential role in cancer development and reproductive health, and its regulatory effects on iron metabolism remains to be further investigated.

Overall, the safety risks associated with EMFs are closely linked to their impact on iron metabolism, with oxidative stress resulting from iron dysregulation being one of the primary sources of damage. Therefore, to mitigate the biosafety risks posed by EMFs, potential protective strategies may include not only limiting EMF exposure and administering iron-regulating agents, but also supplementing with antioxidants to reduce oxidative stress.

The effects of EMFs on iron metabolism in immunoregulation

The immune system plays a crucial regulatory role in various physiological processes, including infection, wound healing, aging, and cancer. Iron not only participates in innate immune responses by regulating macrophage polarization, neutrophil recruitment, and Natural Killer (NK) cell activity but it also involved in adaptive immunity through modulating lymphocytes activation [163]. Extensive studies indicated that EMFs mediated immunoregulation by regulating iron metabolism and redox status. Some studies sug-

gested that EMFs exposure was closed to immune system disturbance and may pose health risks [164,165]. Nevertheless, the immunomodulatory potential of EMFs has also been extensively explored in research aimed at treating various disease [166,167].

Innate immunity

Macrophages, a type of innate immune cells, play a crucial role in inflammation, wound healing, and tumor immunity. It can be broadly classified into two subtypes: classically activated (M1) phenotype and alternatively activated (M2) phenotype. M1 macrophages mainly exert pro-inflammatory functions, whereas M2 macrophages mainly exert anti-inflammatory functions. Iron availability influences macrophage polarization, with iron abundance promoting M1 polarization and iron deficiency favoring M2 polarization [163,168]. Macrophages are key cells in the systemic regulation of iron metabolism, supplying the majority of plasma iron. RAW264.7 cells, a mouse mononuclear macrophage cell line, are widely used in in vitro studies of macrophage polarization and can differentiate into osteoclasts when induced by receptor activator of nuclear factor-kappa B ligand (RANKL). Our previous study found that 16T SMF decreased the iron content and the expression of TfR1, DMT1, and FTH1 in RANKL-induced RAW264.7 cells, while increasing FPN expression [131]. It suggests the potential for EMFs to regulate the fate of macrophages by regulating iron metabolism. Notably, the effects of EMFs on macrophage polarization vary depending on parameters such as intensity and frequency [169]. However, the effects of EMFs with different parameters on macrophage iron metabolism and polarization are still unclear. In addition, EMFs have been shown to modulate the functions of NK cells and neutrophils by regulating ROS levels. Various studies showed that ELF-EMFs exposure decreased the activity of Natural Killer (NK) cells, whereas SMF enhances their cytotoxic capacity [170–172]. Intracellular ROS levels, which are closely related to iron metabolism, play a pivotal role in the function of NK cells and neutrophils [173,174]. Excessive accumulation of ROS under inflammatory or oxidative conditions could impair the physiological function of monocytes. Patruno et al. reported that 50 Hz, 1 mT ELF-EMF exposure for 1 h decreased intracellular ROS reduced intracellular ROS levels in human monocyte THP-1 cells by promoting NRF2 nuclear translocation and activating the NRF2/HO-1 signaling pathway [112]. As mentioned above, NRF2 is widely regarded as a key regulator of iron metabolism. Moreover, the NRF2/HO-1 pathway is also considered a crucial regulatory signaling pathway in ferroptosis. Therefore, the above evidence suggest that EMFs could influence the fate of macrophages, NK cells, neutrophils and monocytes via regulating iron metabolism.

Adaptive immunity

Adaptive immunity, primarily mediated by lymphocytes, is a crucial immune mechanism for combating infectious and malignant diseases [175]. Lymphocytes are highly sensitive to EMFs and are commonly used to assess the biological safety of EMFs. Studies have shown that EMFs can exacerbate lymphocyte damage caused by iron overload. 7 mT SMF and 1.5 W/kg, 930 MHz RF-EMF acute (5 and 15 min) exposure did not significantly affect physiological state of lymphocytes, but intensified the increase in intracellular ROS levels and apoptosis induced by $FeCl_2$ [132,176]. Furthermore, 7 mT SMF and 50 Hz ELF-EMF have been indicated caused DNA damage in lymphocytes when combined with $FeCl_2$ [113]. These findings demonstrate that EMFs can synergistically enhance intracellular ROS generation when used with iron preparations, leading to cell damage. However, several studies have also found that certain EMFs reduced intracellular oxidative stress levels, and increased activity of lymphocytes. Zmyslony M et al. found that 50 Hz, 40 mT ELF-EMF parallel to the GMF direction exposure decreased intracellular ROS in lymphocytes [177]. Additionally, several studies have indicated that combination treatment of EMFs and iron-based NPs enhanced the activation and antitumor effects of T cells [178]. All the above results suggested that the effects of EMFs on lymphocyte iron metabolism and ROS represented a significant risk factor for adaptive immunity. However, optimizing EMF parameters and regulating iron levels in the lymphocyte environment could help mitigate these risks and potentially enhance adaptive immunity.

The effects of EMFs on iron metabolism in cardiovascular diseases

Abnormal iron metabolism has been identified as a trigger for various cardiovascular diseases (CVDs), including hypertension, thrombosis, atherosclerosis, and myocardial ischemia–reperfusion injury [133]. While EMFs have been considered a potential risk factor for cardiovascular diseases, they are also widely applied in the prevention and treatment of these conditions [5].

Hypertension, thrombosis, and atherosclerosis

Epidemiological studies have shown that serum iron levels are negatively correlated with the prevalence of hypertension, while transferrin levels are positively correlated with hypertension prevalence. Both excessively low and high serum ferritin levels have been associated with an increased risk of hypertension [179]. Systemic iron deficiency is widely recognized as one of the causative factors of thrombosis, while chronic use of iron supplements, such as dextran iron, has also been shown to increase thrombosis risk by inducing vascular oxidative stress [180,181]. The regulatory effects of EMFs exposure on blood flow and blood pressure had been widely confirmed by both animal and clinical studies [182,183]. Meanwhile, studies have shown a mitigating effect on iron-induced hypertension and related thrombosis in animal models. Li Q et al. found that 400 mT and 600 mT SMFs exposure for 60 days decreased the blood pressure in $FeCl_3$ treated rats. Moreover, 200 mT SMF increased the thrombolytic agent tissue-type plasminogen activator (tPA) content, and 600 mT SMF decreased thrombus protein content in $FeCl_3$-induced arterial thrombosis rats [184]. These findings indicate that EMFs have the potential for therapeutic effects in the processes of hypertension and thrombosis caused by iron metabolism disorders.

Atherosclerosis is a prevalent cardiovascular disease worldwide, characterized by high morbidity and mortality rates [185]. Although the relationship between abnormal iron metabolism and atherosclerosis remains controversial, many atherosclerotic patients exhibit symptoms of iron overload. Moreover, both animal and clinical studies have indicated that alleviating iron overload were contributed to mitigating the symptoms of atherosclerosis [186,187]. Many studies indicated that EMFs inhibit the progression of atherosclerosis by biologically reducing the oxidation rate of low-density lipoprotein (LDL), as well as physiologically decreasing blood viscosity and enhancing blood shear stress [188,189]. Although direct evidence linking EMFs to the alleviation of atherosclerosis through their regulation of iron metabolism is still lacking, studies have demonstrated the involvement of EMFs in the inhibition of atherosclerosis through their influence on calcium ion metabolism [190]. During the progression of atherosclerosis, the proliferation, migration, and adhesion of vascular smooth muscle cells (VSMCs) was excessively activated. Li et al. found that 5 mT SMF exposure suppressed the proliferation, migration, and adhesion of human umbilical artery smooth muscle cells (hUASMCs) by inhibiting integrin β1 clustering and reducing cytosolic free calcium concentration [191]. The regulation of ion channel opening states on the cell membrane by EMFs is a key mechanism for modulating intracellular calcium levels, and most calcium ion channels can nonspecifically mediate the transmembrane transport of iron ions [77,192]. Therefore, the regulation of

Table 1
The effects of EMFs on iron metabolism in nervous system.

EMF type		Parameters	Objects	Exposure time	Iron metabolism change	Outcome	Reference
SMF	**MSMF**	128 mT	Rats	1 h/day, for 5 days	Brain iron content/ unchanged	Synergistically exacerbated anxiety levels in rats when combined with FeSO4, but no synergistic effects on spatial learning abilities	[147,154,155]
	MSMF	0.23 T–0.28 T	PC12	1 h	Iron uptake/ decreased	Counteracted several PD-relevant endpoints exacerbated by A(2A)R agonist CGS21680	[221]
Time-varying magnetic fields	**ELF-EMF**	25 Hz rTMS	Mice	14 days and 28 days	FTH1, NRF2 / increased TfR1 and hippocampal iron content/ decreased	Enhanced cognitive function and augments cerebral activity	[101]
	ELF-EMF	17.96 μT, 50 Hz	Rats	2 h/day for 8 weeks	Iron content in injury area/ increased	Promoted vascular regeneration, reduce lesion volume and inflammation following spinal cord injury	[200]
	ELF-EMF	60 Hz, 10 μT	Rats	24 h		Increased the DNA damage in brain, which inhibited by iron chelator deferiprone	[153]
	ELF-EMF	50 Hz, 17.96μT	Rats	2 h/day for 5 weeks		Synergistically promoted the repair of spinal cord injury with nanoparticles	[206]
	ELF-EMF	60 Hz, 0.7 T	Rats	4 h/day for 8 days	NRF2 / increased		[223]
	RF-EMF	900 MHz, 100 mW	Rats	1 h/day for 21 days		No synergistic effect between 900 MHz EMF and FeSO4 on spatial learning	[157]
	RF-EMF	1788 MHz	Rabbits	150 min	iron deposition in cerebellum/ increased		[31]
	ELF-EMF	60 Hz, 30 μT	Nonlactating pregnant Holstein cows	2.05 h/day, 30 days	Iron in blood plasma/ unchanged Iron in cerebrospinal fluid/decreased		[21]
	ELF-EMF	60 Hz, 30 μT	Nonlactating nonpregnant ovariectomized heifers	2.05 h/day, 30 days	Iron in blood plasma/ unchanged Iron in cerebrospinal fluid/ unchanged		[21]
	ELF-EMF	50 Hz, 1 mT	hBMSCs	6 days		Synergistic Promoted neural Differentiation with Fe3O4 nanoparticles	[116]
	ELF-EMF	50 Hz, 1 mT	hBMSCs	12 days	FTH1 and FTL / increased	Promoted the neural differentiation	[136,204]
	ELF-EMF	50 Hz, 1 mT	$SOD1^{G93A}$ mutant SH-SY5Y cells	24–72 h	TFR1, IRP1, and MFRN1 / decreased		[137]
	ELF-EMF	50 Hz, 2 mT	Synaptosomes	2 h	Iron release/ unchanged	Physiological behavior of cortical synaptosomes was unaffected	[135,156]

iron metabolism by SMF may also be involved in inhibiting the proliferation, migration, and adhesion of VSMCs.

Ischemia-reperfusion injury

Ischemia-reperfusion injury is a common clinical complication observed in various organs, including the heart, liver, kidneys, and brain. Ferroptosis is one of the main driving factors underlying ischemia–reperfusion injury [193]. Ferroptotic oxidized phosphatidylethanolamine species was accumulated in the mitochondria of heart during ischemia–reperfusion injury, while iron chelators and ferroptosis inhibitors effectively alleviated acute and chronic myocardial ischemia–reperfusion injury [133]. Ma F et al found that 30 Hz PEMF (X-axis 0.22 ± 0.05 mT, Y-axis 0.20 ± 0.05 mT, Z-axis 0.06 ± 0.02 mT) exposure reduced the apoptosis of myocardial cells and improved myocardial ischaemia–reperfusion injury in rats. Meanwhile, PEMF exposure significantly decreased ROS levels in primary neonatal rat cardiac ventricular myocytes (NRCMs) induced by hypoxia/reoxygenation (H/R) in vitro [114]. Similarly, 20 Hz, 4.5 mT PEMF exposure suppressed ROS generation and enhanced cell viability in neonatal rat cardiomyocytes treated with hypoxia/reoxygenation in vitro [194]. The Fe^{2+} involved Fenton reaction is the major source of ROS during ferroptosis. Therefore, the protective effect of the EMFs on ischemia–reperfusion injury may also be related to its regulation of iron metabolism.

The effects of EMFs on iron metabolism in neurological diseases

Iron is an essential element in neurodevelopment, and research has shown that iron deficiency anemia can impair central nervous

system development [195]. Conversely, iron accumulation has been closely linked to the pathogenesis of various genetic and neurodegenerative diseases [196]. Besides, some psychiatric diseases, including depression, cognitive impairments, schizophrenia, and post-traumatic stress disorder (PTSD) may also be associated with systemic iron metabolism dysregulation [197]. EMFs have been widely applied for both enhancing nervous system function and promoting injury repair. TMS, as a non-invasive electromagnetic field based technique, has been extensively used in the treatment of various neurological disorders [27]. In addition to the previously mentioned interest in the relationship between EMF regulation of iron metabolism and the neurobiological safety of EMF exposure, the therapeutic potential of EMF effects on iron metabolism in neurological disorders has also been widely explored. The effects of EMFs exposure on iron metabolism in nervous system are shown in Table 1.

Neural injury

Iron overload can interfere with the recovery process of spinal cord injury and has been closely linked to neuronal ferroptosis [198]. In recent years, the role of EMFs in neural injury repair has gained increasing attention. Wincek A., through clinical studies, found that repetitive transcranial magnetic stimulation (rTMS) can enhance neural signal transmission within residual spinal cord neurons, thereby promoting motor control recovery in patients with incomplete spinal cord injury (SCI) [199]. The relationship between the effects of EMFs on neuronal cells and their regulation of iron metabolism and ROS is an important research direction in the application of EMFs for neural injury repair. Dey S et al. found that 2 h per day 50 Hz, 17.96 μT ELF- EMFs exposure for 8-week increased iron content, promoted vascular regeneration, reduced lesion volume and inflammation in the spinal cord injury area of rats [200]. Mesenchymal stem cells (MSCs) have been extensively investigated as a novel cell-therapeutic solution for neurodegenerative diseases and neural injury due to their ability to differentiate into neuronal-like cells [201]. The differentiation of neural stem cells is accompanied by an increase in FTL expression [202]. 50 Hz, 1 mT ELF-EMF exposure has been shown to promote the neural differentiation of human bone marrow mesenchymal stem cells (hBMSCs) and increase the expression of IRP1, FTH1 and FTL [136,203,204]. Notably, ROS levels increased during the astrocytic differentiation of BMSCs under 50 Hz, 1 mT ELF-EMF exposure. FTL is involved in iron storage from the Labile Iron Pool (LIP) and the release of iron from ferritin through electron transfer, thus maintaining the dynamic equilibrium of intracellular LIP and redox balance [205]. The upregulation of FTL expression can induced a mild increase in ROS levels without causing significant oxidative stress damage. Furthermore, studies have shown that both 50 Hz, 1 mT ELF-EMF exposure and its combination with iron-based nanoparticles (NPs) can promote neural differentiation of hBMSCs, which is associated with a mild increase in intracellular ROS levels [115,116]. Pal A et al. also found that 50 Hz, 17.96 μT ELF-EMF exposure promoted the repair of spinal cord injury in albino Wistar rats. Moreover, the ELF-EMF combined with iron-based NPs had a synergistically effect on enhancing spinal cord injury repair in vivo, and reducing oxidative stress induced by H_2O_2 in vitro [206]. Therefore, the upregulation of FTL caused by EMFs could promote neural differentiation of MSCs by inducing a mild increase in intracellular ROS levels, and inhibit oxidative stress damage caused by excessive accumulation of exogenous iron (iron based- NPs) and H_2O_2.

Neurodegenerative diseases

Neurodegenerative diseases encompass a spectrum of disorders characterized by neuronal death or impaired neuronal function, including Parkinson's disease (PD), Alzheimer's disease (AD), Amyotrophic Lateral Sclerosis (ALS), and Huntington's disease [207]. Recent studies have revealed a close association between the progression of neurodegenerative diseases and abnormalities in iron metabolism, with different types of these diseases exhibiting distinct iron metabolism characteristics [208].PD is a neurodegenerative disorder characterized by both motor and non-motor symptoms, resulting from the loss of dopaminergic neuronal function. Iron deposition in substantia nigra pars compacta (SNpc) is a hallmark pathological feature in PD patients, and ferroptosis has been identified as a contributing factor to the progressive loss of dopaminergic neuronal function and cell death [209]. AD is the is the leading cause of dementia. Studies have shown that brain tissue slices from AD patients typically exhibit higher magnetic iron oxide magnetite (Fe_3O_4) content, and iron deposition in the cortex and hippocampus is a key pathological feature of AD. Iron accumulates in neurons, glia, as well as in Aβ plaques and neurofibrillary tangles, leading to abnormal expression of Aβ and phosphorylated tau, which are important triggers for the progression of AD [210,211]. ALS is a rare neurodegenerative disease characterized by the progressive loss of motor neurons, with iron deposition in motor neurons and glial cells being one of its pathological characteristics [212]. Additionally, increased iron in subcortical structures and the surrounding white matter have been identified as a feature of early HD [213]. Therefore, targeting iron metabolism and ferroptosis has become a major focus in recent research on the treatment of neurodegenerative diseases. Iron chelators and ferroptosis inhibitors have demonstrated therapeutic potential for neurodegenerative diseases in cellular and animal models [214]. However, the iron chelator deferoxamine has been shown to inhibit the progression of AD but not PD in clinical studies [215,216].

A large number of clinical trials have demonstrated the therapeutic effects of EMFs on neurodegenerative diseases, such as improving motor function in PD patients, enhancing cognitive function in AD patients, and alleviating muscle decline in ALS patients [217–219]. Meanwhile, the regulation of iron metabolism and Reactive Oxygen Species (ROS) in neural cells by EMFs has been shown to involve in counteracting neurodegenerative diseases. Studies have shown that 0.23 T to 0.28 T SMF exposure reduced the expression of the PD biomarker adenosine A(2A) receptor (A(2A)R) in PC12 cells, similar to the effects of the PD drug candidate ZM241385. Furthermore, SMF exposure decreased cAMP levels, nitric oxide production, p44/42 MAPK phosphorylation, cell proliferation, and iron uptake in PC12 cells [220,221]. Xu et al. demonstrated that 25 Hz rTMS treatment increased the expression of glutathione peroxidase 4 (GPX4) and system Xc-, reduced oxidative stress levels in brain, enhanced cognitive function and augments cerebral activity, and ameliorated AD-like symptoms in SAMP8 mice [101]. Moreover, rTMS decreased the expression of TfR1 and reduced levels of Fe^{2+}, while increased the expression of NRF2 and FTH1. Superoxide dismutase 1 (SOD1) is a key antioxidant enzyme that maintains redox homeostasis, and its dysfunction can result in excessive ROS accumulation. Mutations in SOD1 induced neuronal dysfunction are the causative actors for ALS [222]. Consales et al. found that while 50 Hz, 1 mT ELF-EMF exposure did not significantly decrease the generation of superoxide and H_2O_2 in $SOD1^{G93A}$ mutants SH-SY5Y cells, it reduced the expression of TFR1, IRP1, and MFRN1 [137]. Tasset I et al. also found that 60 Hz, 0.7mT TMS treatment increased the expression and nuclear translocation of NRF2 in neuronal cells in Huntington's disease-like rats induced by 3-nitropropionic acid [223]. Weiler M. et al. found that TMS significantly upregulated TfR1 expression in hippocampal cells ex vivo, a phenomenon associated with enhanced myelination processes [224]. Additionally, they found that TMS increased the expression of hemoglobin-related genes in the hippocampal cells of young rats but decreased their expres-

Table 2
The effects of EMFs on iron metabolism in orthopedic diseases.

EMF type		Parameters	Objects	Exposure time	Iron metabolism change	Outcome	Reference
SMF	**HyMF**	300 nT	Mice	28 days	Liver, spleen, bone marrow, diaphysis, and serum iron content/increased Serum ferritin content/ increased Hepcidin in liver/ increased FPN in liver/decreased TfR1, FTH1, and FPN in tibia/ decreased	Aggravated HLU induced bone loss; Inhibited the recovery of HLU induced bone loss	[105,253]
	HyMF	300 nT	Rats	28 days	Serum iron content/ increased	Aggravated HLU induced bone loss	[254]
	MSMF	0.05 T ~ 0.5 T	Mice	14 days, 28 days	Serum hepcidin/increased Serum ferritin/decreased iron content in callus/ decreased	Promoted fracture healing	[134]
	MSMF	0.4 T-0.7 T	Type 1 diabetic mice	4 h/day for 6 weeks	Tibial iron content/ increased TfR1, FTH1, and FPN in tibia /increased	Inhibited diabetes induced boss	[248]
	HiSMF	1 T-2 T	Mice	1 h/day, 28 days	Serum iron/decreased Iron in femur/decreased	Inhibited hindlimb unloading induced bone loss and bone resorption	[106]
	HyMF	500 nT	MC3T3-E1	48 h	Iron content, TfR1 / increased FTH1, FTL, and FPN/ unchanged	Increased ALP and COL-1 expression; Decreased DMP1 expression	[246]
	HyMF	500 nT	MC3T3-E1	10 days	iron content/increased	Inhibited osteogenic differentiation	[255]
	MSMF	0.2 T	MC3T3-E1	48 h	Iron content, TfR1, and FTL / unchanged FTH1, FPN/increased	Decreased ALP and DMP1 expression	[246]
	HiSMF	16 T	MC3T3-E1	48 h	Iron content, TfR1/ decreased FPN/increased FTH1 and FTL/ unchanged	Increased ALP, OCN, COL-1, DMP1, and OPN expression	[246]
	HiSMF	16 T	MLO-Y4	48 h	Iron content, DMT1/ increased FPN/decreased FTH1/unchanged	Increased CX43 expression; Deceased sost expression and secretion	[247]
	HiSMF	1 T-2 T	RAW264.7	1 h/day for 28 days	TfR1 and FPN/unchanged FTH1/decreased iron uptake of IONPs/ decreased	Inhibited osteoclastogenesis	[106]
	HiSMF	16 T	RAW264.7	48 h	Iron content, TfR1, DMT1, and FTH1/ decreased FPN/increased	Inhibited osteoclast differentiation	[131]
Time-varying magnetic fields	**RMF**	6.72 Hz and 8.97 Hz, 0.4 T,	Rats	2 h/time, twice a day for 30 days	Serum iron content and transferrin/ increased	Alleviated RA induced joint swelling	[267]
	ELF-MF	50 Hz, 1 mT	Amniotic epithelial cells	30 min/ time, twice a day for 21 days	NRF2/increased	Promoted osteogenic differentiation	[250]
	RF-MF	1 MHz	Mouse primary chondrocytes		FTH1 /increased NCOA4/decreased	Inhibited *tert*-butyl hydroperoxide-induced ferroptosis	[140]

sion in aged rats. Notably, unlike extracellular hemoglobin, which may induce neuronal damage through oxidative stress and iron accumulation, endogenously expressed hemoglobin in neurons plays a crucial role in maintaining normal mitochondrial function and protecting against oxidative stress-related damage in the brain [225,226]. Therefore, the relationship between EMFs-mediated regulation of neuronal hemoglobin expression and its potential impact on neurodegenerative diseases remains to be further elucidate. Collectively, these observations and studies suggest that EMFs could improve oxidative stress levels, inhibits ferroptosis in neural cells by regulating iron metabolism, plays a protective role in the nervous system, and suppresses the progression of neurodegenerative diseases. However, some studies suggests that electromagnetic fields could influence the progression of neurodegenerative diseases by modulating neuronal electrical activity, which is independently from iron homeostasis [227,228]. Consequently, when considering electromagnetic field-based interventions for neurodegenerative disorders, it is essential to monitor not only iron metabolism but also electrophysiological parameters associated with neuronal activity.

Additionally, Transcranial Magnetic Stimulation (TMS) can synergistically enhance its protective effects against neurological diseases when combined with iron-based NPs. Studies have demonstrated that intravenous administration of iron-based NPs enhances TMS-induced Motor Evoked Potential (MEP) and improves the therapeutic effects of low-frequency rTMS (LF-

rTMS) on prenatal Valproic Acid (VPA)-induced autism spectrum disorder (ASD) in rats [58,135]. Intravenous administration of iron-based NPs enhanced TMS-induced Motor Evoked Potential (MEP), and therapeutic effects of low-frequency rTMS (LF-rTMS) on prenatal Valproic Acid (VPA)-induced ASD in rats [141,229].

The effects of EMFs on iron metabolism in orthopedic diseases

Orthopedic diseases primarily include bone and mineral disorders such as osteoporosis, fractures, and osteogenesis imperfecta, as well as osteoarticular diseases like osteoarthritis (OA), rheumatoid arthritis (RA), and intervertebral disc degeneration (IVDD). The use of EMFs as a therapeutic approach for orthopedic diseases has a history spanning over fifty years [230]. With advancing insights into the pathogenesis and mechanisms underlying orthopedic diseases, iron metabolism and ferroptosis have emerged as key therapeutic targets for these diseases [231,232]. Consequently, regulating iron metabolism has become a critical focus for enhancing the efficacy of EMF-based treatments in orthopedic diseases.

Bone and mineral disorders

Iron metabolism disorders are closely associated with bone and mineral disorders [231,233]. On one hand, iron is an essential component of various enzymes involved in collagen synthesis, which is crucial for bone formation [234]. On the other hand, excessive iron could suppress osteoblast mediated bone formation by inhibiting the activation of the Wnt/β-catenin signaling pathway, and promotes osteoclast differentiation and bone resorption by activating the NF-κB signaling pathway through the generation of ROS [235,236]. For instance, long-term transfusion-related systemic iron overload has been implicated in the development of osteoporosis in thalassemia patients and hypophosphataemic osteomalacia [144,237]. Sickle cell anemia, an inherited Hb disorder disease characterized by low hemoglobin levels and elevated serum ferritin level [238]. Studies found that sickle cell anemia patients have lower bone mass in children, and higher prevalence of osteoporosis [239,240]. Furthermore, iron accumulation in the body increases with age, especially after menopause in women. Clinical studies have demonstrated a positive correlation between serum ferritin levels and both the rate of bone loss and the occurrence of vertebral fractures in postmenopausal women [241,242]. The influence of EMFs on bone remodeling is closely associated with the regulation of iron metabolism [4,243]. Our previous clinical study revealed that, compared to the control group, 90-day MSMF intervention exhibited a greater increase in BMD, accompanied by a more pronounced reduction in serum ferritin levels in postmenopausal osteoporosis patients [104]. As shown in Table 2, the effects of EMFs on iron metabolism of cells involved in bone remodeling vary depending on cell types and magnetic field parameters.

During the bone remodeling, bone formation is primarily mediated by osteoblasts, and bone resorption is primarily mediated by osteoclast. Our previous studies found that 0.2T-0.4 T SMF exposure promoted the recovery of hindlimb unloading (HLU) induced bone loss, increased femoral microstructure and serum bone formation marker OCN levels, whereas decreased the distribution of osteoclasts on femoral bone surface and serum bone resorption marker TRAP-5b levels in mice [244]. Meanwhile, 0.2T-0.4 T SMF exposure reduced iron content, and promoted osteogenic differentiation while inhibited adipogenic differentiation of BMSCs [245]. 16T SMF exposure increased the mineralized nodules formation and ALP activity, as well as the expression of osteogenic markers such as Col-1, DMP1, and OCN during osteogenic differentiation of MC3T3-E1 cells. Concurrently, SMF exposure decreased the iron content and TfR1 expression while increased FPN expression in MC3T3-E1 cells [246]. In contrast, as previously describe,16 T SMF exposure increased the FPN expression, decreased the expression of FTH1, TfR1, and DMT1, as well as reduced intracellular iron content in RANKL-induced RAW264.7 cells [131]. Additionally, 16 T SMF inhibited RANKL-induced osteoclast differentiation. Furthermore, studies showed that 1 T-2 T SMF exposure inhibited HLU-induced bone loss and osteoclast activation in mice, reduced iron content in bone and osteoclasts, and decreased the FTH1 expression during RAW264.7 cells osteoclastic differentiation [106]. Collectively, these findings suggest that SMF exposure reduces iron content in both osteoblasts and osteoclasts, although its effects on the expression of iron metabolism-related proteins differ between cell types. Given that excess iron inhibits osteoblast differentiation but promotes osteoclast differentiation, SMFs appear to prevent bone loss by simultaneously promoting bone formation and suppressing bone resorption. Osteocytes, as the primary regulatory cells in bone tissue, modulate the functions of osteoblasts and osteoclasts through the secretion of various cytokines. Yang J et al found that 16 T SMF exposure increased cell viability and intracellular iron content in MLO-Y4 osteocyte-like cells. Furthermore, 16 T SMF increased the expression of the bone remodeling mediator PGE2 and the bone resorption promoter RANKL in bone cells while reducing the expression of the bone formation inhibitor sclerostin in MLO-Y4 cells [247]. However, the regulatory effect of osteocytes on osteoclasts mainly depends on the ratio of RANKL/osteoprotegerin (OPG). Further studies are needed to assess the levels and ratios of RANKL and OPG secreted by osteocytes to elucidate their role in bone resorption under SMF exposure. Additionally, the promotion of cell viability and ALP expression induced by 16 T SMF exposure was mitigated by FAC. However, the 16 T SMF exposure induced increase in NO secretion was enhanced by both DFO and FAC. This further confirms that the regulation of osteocyte morphology and function by SMF is related to the changes in iron metabolism. Interestingly, the effects of EMFs on iron metabolism in bone remodeling do not appear to be static. Rather, they exhibit a context-dependent nature, with varying effects on iron metabolism tailored to meet the requirements for correcting imbalances in bone remodeling.

Osteoporosis is a common complication of diabetes. Our previous study found that the serum ferritin has been increased, whereas tibial total iron content was decreased in streptozotocin induced type 1 diabetic mice [248]. Meanwhile, 0.4–0.7 T SMF exposure inhibited bone loss, increased bone iron content, and upregulated the expression of FPN, TfR1, and FTH1 in type 1 diabetic mice. Moreover, 0.4T-0.7T SMF enhanced bone turnover in type 1 diabetic mice, as well as promoted both osteoblast and osteoclast differentiation under high-glucose conditions in vitro. Furthermore, our previous study found that 0.05 T-0.5 T SMF exposure promoted fracture healing, reduced iron content at the bone callus site, decreased serum ferritin levels, and increased serum hepcidin levels in mice [134]. Notably, 0.05 T–0.5 T SMF exposure not only enhanced bone formation but also facilitated the transition from cartilage callus to hard callus. The transition from cartilage callus to hard callus not only not only conventional osteoblast-mediated bone formation and osteoclast-mediated bone resorption but also processes such as the chondrogenic differentiation of MSCs, apoptosis of chondrocytes, and chondrocyte-to-osteoblast transdifferentiation [249]. These results suggest that SMFs could regulate functionality and fate of chondrocytes by modulating iron metabolism. Time-varying magnetic fields have also been shown to regulate bone remodeling by modulating iron metabolism. Wang Q et al. found that PEMF promoted osteogenic differentiation and increased the NRF2 expression in amniotic epithelial cells [250]. Melatonin has garnered significant attention in the study of iron accumulation and iron overload-related diseases due to its unique structure, which allows it to exhibit both iron-chelating and antioxidant properties. Huang et al. found that

the PEMF enhanced the anti-bone loss effect of melatonin in OVX mice [251,252].

In contrast, the absence of the GMF could disrupt the balance of bone remodeling by modulating iron metabolism. Artificial HyMF environments are widely used to evaluate the biological effects of absence of geomagnetic field. Our previous studies found that the HyMF exposure did not directly induce bone loss but exacerbated HLU-induced deterioration of bone microstructure, reductions in mechanical performance and bone formation, and increased bone resorption in rats and mice [253,254]. Meanwhile, HyMF increased serum ferritin, liver iron content, and bone iron content in HLU rats and mice. Furthermore, HyMF inhibited the recovery of femoral microstructure and mechanical properties ofi n HLU-pretreated mice, which was attenuated by iron chelator DFO [105]. In addition, HyMF increased the intracellular iron content and inhibited mineralized nodules formation in MC3T3-E1 cells during osteogenic differentiation in vitro [255]. These findings indicate that HyMF exacerbates inducible bone loss by promoting iron accumulation.

EMFs can also be used in combination with iron preparations and iron metabolism regulators to regulate bone remodeling. The Ferumoxytol, an iron-based NP and FDA approved iron supplement, has been observed alleviated HLU induced bone loss by inhibiting osteoclast differentiation and bone resorption. Further investigations revealed that the combination of 1–2 T SMF and Ferumoxytol inhibited the activation of NF-κB and MAPK pathways during osteoclast differentiation by reducing intracellular iron content and Reactive Oxygen Species (ROS), exhibiting a synergistic anti-bone loss effect in vivo [106]. The combination of 0.2 T SMF and iron-based NPs promoted osteoblast differentiation and induced apoptosis in osteoclasts in vitro [142].

Osteoarticular diseases

Iron metabolism disorders are also implicated in the onset and progression of osteoarticular diseases, including OA, RA, and IVDD [232]. Many clinical studies have reported that age-related and post-traumatic osteoarthritis were usually accompanied by iron deposition at the site of pathology [256]. Meanwhile, the incidence of knee OA and IVDD is significantly higher in individuals with hemochromatosis compared to the general population [257,258]. Furthermore, studies have showed that iron overload disrupted the normal function of chondrocytes and induced ferroptosis, while interventions such as iron chelator DFO and ferroptosis specific inhibitor ferrostatin-1 suppressed the progression of OA [259–261]. In addition, iron deficiency anemia is the most common haematological manifestation of patients with RA (30–60 %), and iron deficiency itself may accelerate the progression of IVDD [262–264].

Numerous studies have demonstrated that EMFs alleviate OA, RA, and IVDD by regulating the differentiation and the physiological functions of chondrocytes and intervertebral disc cells [265,266]. Although direct evidence of EMFs modulating the progression of osteoarticular diseases through iron metabolism regulation is currently lacking, several studies have reported changes in iron metabolism and ROS levels during EMF treatments for these conditions [117]. Bi et al found that RMFs alleviated of RA, and increased serum iron and transferrin levels, as well as total iron-binding capacity in rats [267]. Besides, Lv Z et al found the combination of 1 MHz RF-EMF and iron-based NPs-TRPV1 increased the FTH1 expression, decreased the NCOA4 expression, and inhibited *tert*-butyl hydroperoxide (TBHP)-induced ferroptosis in chondrocyte in vitro. Meanwhile, the 1 MHz EMF and iron-based NPs-TRPV1 treatment attenuated osteoarthritis progression in mice [140]. Therefore, iron metabolism represents a crucial research target in the study of EMF-based therapies for osteoarticular diseases and should not be overlooked.

The effects of EMFs on iron metabolism in diabetes

Iron plays a critical role in glucose and lipid metabolism through pathways such as regulating metabolic rates, gluconeogenesis, insulin action, and adipocyte signaling [268]. Serum ferritin levels are correlated with an increased risk of type 2 diabetes (T2D), and iron overload is associated with decreased insulin secretion, insulin resistance, and increased hepatic gluconeogenesis in type 2 diabetes mellitus (T2DM) [269]. Blood transfusions induced iron overload has been shown to increase the incidence of diabetes in β-thalassemia patients. Furthermore, phlebotomy has been reported to improve insulin secretion in diabetes patients, Iron chelators and ferroptosis inhibitors have also been shown to have therapeutic effects in alleviating diabetes and its associated complications [270]. EMF therapy has demonstrated efficacy in the clinical treatment of diabetic complications, such as diabetic peripheral neuropathy and diabetic foot ulcers [271]. In recent years, growing attention has been given to the relationship between the effects of EMFs on diabetes progression and their role in regulating iron metabolism. Yu B et al found that the downward 100 mT SMF exposure for 12 consecutive weeks reduced iron levels and ROS in pancreatic cells, and prevented the development of high-fat diet (HFD)-induced T2D and ameliorated related symptoms [102]. Meanwhile, the combined exposure to 3 mT SMF and 7 kV/m electric fields for 30 days was shown to inhibit the progression of type 2 diabetes by reducing intracellular ROS level [272]. These results proved the potential of EMFs in diabetes treatment by regulating iron metabolism. However, some studies have also reported that extreme SMFs exposure may exacerbate diabetes and related tissue damage. High gradient (up to 55.5 T/m) 1.0 T-8.6 T SMFs exposure elevated glycosylated serum protein and blood glucose levels, and exacerbated the spleen, hepatic, and renal tissue impairment in both T1D and T2D mice. Moreover, gradient SMFs did not significantly alter iron levels in serum, while increased the levels of oxidative stress in kidney tissue of diabetic mice [107]. These findings suggest that the effects of SMF exposure on iron metabolism and diabetes are parameter-specific. Simply increasing the intensity and gradient of SMFs could lead to adverse reactions, underscoring the importance of optimizing exposure parameters in potential therapeutic applications. Overall, EMFs can influence the physiological function of pancreatic cells and the body's glucose metabolism by regulating iron metabolism, offering a new approach for the physical treatment of diabetes.

The effects of EMFs on iron metabolism in liver injury

Liver is one of the primary iron storage organs and serves as the regulator of systemic iron metabolism. Studies have shown that the changes of external magnetic field environments can regulate systemic iron metabolism by altering liver iron content. Our previous studies found that 300nT HyMF exposure increased liver iron content in mice during both HLU and the reloading process [105,253]. Drago M et al. reported that 16 mT SMF with different orientation exposure for 28 days reduced liver iron content in mice [273]. Similarly, our earlier research found that 0.05T-0.5 T SMF exposure reduced liver iron content in mice with fractures [134]. Moreover, 2 T-4T and 6 T-8T SMF exposure for 28 days had no significant effect on liver iron content, whereas 10 T-12 T SMF exposure increased liver iron content in mice [20]. These findings demonstrate that the effects of EMFs on liver iron metabolism display a distinct "window effect," wherein specific magnetic field parameters determine their regulatory outcomes. In addition, certain EMFs exposure showed the protective potential against liver damage caused by iron metabolism disorders. Dietary iron overload has been found to decrease hepatic mitochondrial oxidative phosphorylation and exacerbate mitochondrial dysfunction induced by oxidative stress in

Table 3
The effects of EMFs on cancer iron metabolism.

EMF type		Parameters	Objects	Exposure time	Iron metabolism change	Outcome	Reference
SMF	**MSMF**	10 mT	MCF-7	24 h, 48 h	Iron content/ decreased	Inhibited proliferation	[118]
	MSMF	0.2–0.4 T	K7M2 stem cells, MG63 stem cells	7 days	LIP / increased FTH1/ decreased NCOA4/ increased	Improved self-renewal ability	[55]
	HiSMF	12 T	MNNG/HOS, U-2 OS, and MG63	48 h	Iron content, LIP/increased FTH1, DMT1/ increased TfR1, FPN/ unchanged	Inhibited proliferation	[103]
Time-varying magnetic fields	**ELF-EMF**	7.5 Hz. 0.4 T	LLC	2 h/day, 3 days	TfR1, FTH1/ decreased	Inhibited proliferation	[108]
	ELF-EMF	7.5 Hz, 0.4 T	Lewis lung cancer murine model	2 h/day, 35 days	TfR1, FTH1/ decreased	Inhibited lung cancer growth	[108]
	ELF-EMF	50 Hz, 1 mT	SH-SY5Y		NRF2/ increased	Increased resistance to doxorubicin and H2O2	[316]
	ELF-EMF	50 Hz, 5.1 mT	G401, A549 cells	2 h/day, 3 days		Inhibited proliferation, which could be attenuated by ferrostatin-1	[119]
	RF-EMF	134 KHz	Molt-4, BT474, and HepG2	1 h		Inhibited proliferation, which could be attenuated by deferoxamine	[109]
		3 kW, 60 min	HCC-70		FTH1, NRF2/ decreased	Enhanced the inhibitory ability of Fe3O4 NPs on cell viability and cell migration.	[311]

mice [274]. Meanwhile, some patients with alcoholic liver disease exhibit disruptions in iron metabolism [275]. Ethanol suppresses the hepcidin expression in hepatocytes, facilitating duodenum iron absorbed, while simultaneously promoting the expression of TfR in hepatocytes, thereby increasing hepatic iron uptake [276,277]. Excessive iron accumulation in the liver can elevate oxidative stress levels within hepatocytes, thereby aggravating liver damage and potentially triggering iron-induced ferroptosis [278]. Zhang X et al found the 0.1 T ~ 0.2 T and 3 T SMFs exposure reduced alcohol-induced inflammation, ROS levels, and oxidative stress in the liver of mice [138,279]. Similarly, Lv et al. found that 0.6 T SMF exposure reduced hepatic iron content in obesity and diabetes mice, and balanced hepatic redox status via the regulation of MAPKs/Nrf2/HO-1 antioxidant pathways, and mitigated liver injury associated with obesity and diabetes [280]. However, some studies have described that t that the decrease in liver iron content under EMF exposure is associated with increased iron release from the liver into the bloodstream [281]. Therefore, although EMFs hold considerable potential for modulating hepatic iron metabolism and preventing associated liver damage, it is crucial to consider their broader effects on iron metabolism in other tissues when designing therapeutic strategies.

The effects of EMFs on iron metabolism in cancer

Although several studies have suggested the potential carcinogenicity of EMFs, many others have demonstrated therapeutic potential of EMFs in combating cancers [282–284]. Abnormal iron metabolism is a hallmark of cancer cells, and the targeted regulation of iron metabolism has become a focal point in cancer treatment. Numerous studies have shown that the regulation of iron metabolism by EMFs is closely associated with its effects on cancer progression, which not limited to standalone treatments, but also extend to combination therapies involving chemotherapy drugs or iron-based NPs (Table 3).

Iron metabolism and cancer

The majority of malignant cancer cells are characterized by dysregulated iron metabolism, where tumor growth, proliferation, invasion, and metastasis require elevated levels of iron [285]. Intracellular iron contributes to the formation of DNA strand breaks and oxidizing DNA bases, as well as generation of intracellular free radicals, further inducing genetic mutations. Consequently, the abnormally elevated intracellular iron is carries a risk for carcinogenesis [286]. The high expression of iron uptake-related genes, such as TFR1 and DMT1, as well as iron storage-related genes like FTH1, have been reported in various cancers, including hepatocellular carcinoma, lung cancer, breast cancer, colorectal cancer, and pancreatic cancer [287–290]. Meanwhile, reduced iron efflux also contributes to the maintenance of elevated intracellular iron levels in cancer cells. Decreased expression of FPN has been observed in cell lines and human samples of breast, lung, and prostate cancers [291–294]. Besides, the low FPN expression is strongly correlated with poor pathology and prognosis in cancers. On one hand, inhibiting iron uptake and facilitating iron efflux have shown promise in suppressing cancer progression. For example, iron chelators and the decreased local hepcidin expression contribute to improving cancer prognosis. On the other hand, the "iron addiction" of cancer cells induced the increasing of intracellular ROS, renders these cells more vulnerable to redox imbalances, renders it more vulnerable to redox imbalance. This vulnerability offers novel therapeutic targets for selectively eliminating cancer cells, such as through ferroptosis [37].

The relationship between the effects of EMFs on iron metabolism and cancer progression

EMFs, as a standalone or adjunctive therapy, have demonstrated efficacy in the clinical treatment of various cancers, such as improving the quality of life for patients with hepatocellular carcinoma and advanced lung cancer [284,295]. However, the effects of EMFs on cancer-related iron metabolism are diverse, with studies highlighting their dual roles in modulating intracellular iron levels. Many studies have demonstrated that EMFs exert anti-cancer effects by reducing intracellular iron content. Hajipour Verdom B et al. found that 10 mT SMF exposure inhibited the proliferation, and decreased intracellular iron content in MCF-7 and HFF cells [118]. Interestingly, that the SMF exposure increased intracellular ROS levels in MCF-7 and HFF cells, although intracellular iron,

the important source of ROS generation, was significantly decreased. Ren J et al. found that the 7.5 Hz, 0.4T ELF-EMF inhibited the LCC cells proliferation in vitro and tumor growth in vivo by arresting the cell cycle at the G1 phase and promoting p53 expression. Meanwhile, ELF-EMF exposure reduced iron content, and decreased the TfR1 and FTH1 expression in both LCC cells in vitro and in lewis lung cancer murine model in vivo. Moreover, the anti-lung cancer effects of the ELF-EMF were mitigated by FAC [108]. Iron is essential for maintaining the activity of ribonucleotide reductase and DNA polymerase. The S phase and G2 phase of the cell cycle are critical stages for DNA synthesis and repair during mitosis. Therefore, the inhibitory effect of 7.5 Hz, 0.4 T ELF-EMF on cell proliferation may be linked to suppressed DNA synthesis due to cellular iron deficiency.

Nevertheless, there are also many studies have shown that EMFs can suppress cancer progression by regulating the expression of iron metabolism-related genes and increasing intracellular iron levels. Our previous study found that 12 T SMF exposure inhibited proliferation, and increased the intracellular iron content, LIP and ROS levels in MNNG/HOS, U-2 OS, and MG63 osteosarcoma cell lines in vitro [103]. The anti-osteosarcoma effects of 12 T SMF were attenuated by antioxidants (NAC) and iron chelators (DFO) but enhanced by FAC. This indicates that the primary mechanism of 12 T SMF's anti-osteosarcoma effects lies in the disruption of redox homeostasis due to increased intracellular iron and ROS. Meanwhile, 12 T SMF exposure increased the expression of FTH1 and DMT1 without significantly affecting the expression of TfR1 and FPN in osteosarcoma cells. These findings suggest that increased LIP under 12 T SMF exposure may result from enhanced uptake of NTBI, which is primarily mediated by DMT1, and that FTH1 upregulation reflects a protective response to the excessive accumulation of intracellular free iron. Lai HC et al. also reported that the 134 KHz RF-EMFs exposure inhibited the proliferation of Molt-4, BT474, and HepG2 cells in vitro, with the effects was suppressed by iron chelator DFO and ROS scavenger N-*tert*-butyl-alpha-phenylnitrone (PBN) [109]. Accordingly, the anti-cancer cell effects of RF-EMFs may involve promoting iron-related ROS production and disrupting the cellular redox balance. The excessive accumulation of ROS generated by intracellular iron through the Fenton reaction is a key inducer of ferroptosis. Furthermore, EMFs have been indicated could induce ferroptosis in cancer cells. Yuan LQ et al. found that the 50 Hz, 5.1 mT ELF-EMF exposure increased intracellular ROS and inhibited the proliferation of G401 and A549 cells, with the effects could be attenuated by the ferroptosis inhibitor, ferrostatin-1 [119]. These results suggest that utilizing electromagnetic fields to regulate iron metabolism and induce ferroptosis in cancer cells holds potential as a direction for cancer treatment research.

Cancer stem cells (CSCs), a subpopulation of cancer cells, possess remarkable proliferative, self-renewal, and differentiation capability. CSCs play pivotal role in cancer progression and metastasis, making it garnered significant attention as a therapeutic focus of drug resistance of cancer [296]. Compared to general cancer cells, CSCs have higher LIP and ferritin levels. Meanwhile, CSCs often exhibit enhanced redox adaptation and regulatory capabilities, whereas general cancer cells tend to experience fragile redox balance due to increased intracellular iron levels [297]. Zhao et al. found that 0.2–0.4 T SMF exposure increased LIP and intracellular ROS in K7M2 and MG63 osteosarcoma stem cells by promoting NCOA4 mediated ferritinophagy. Meanwhile, the SMF improved the self-renewal ability of osteosarcoma stem cells [55]. It suggests that changes in CSC-related markers should not be overlooked when using EMFs to regulate iron metabolism for cancer treatment. Therefore, additional combination approaches may be necessary to effectively harness EMFs in modulating iron metabolism-induced ROS accumulation, thereby targeting and eliminating CSCs.

Combined effects of EMFs, chemotherapeutic drugs, and iron-based nanoparticles on iron metabolism in cancer

The combination of EMFs with chemotherapeutic drugs has been widely studied in cancer treatment. In recent years, with the deepening understanding of the biological effects of EMFs and the increasing research on ferroptosis- related cancer treatment, the interplay between the effects of EMFs and chemotherapeutic drugs on iron metabolism in cancer cells has attracted significant attention. Cisplatin, a conventional chemotherapy drug, has been found to reduce intracellular iron levels in cancer cells. Furthermore, various studies have demonstrated that cisplatin acts as a ferroptosis inducer [298,299]. Several EMFs have been shown to enhance the anti-cancer effects of cisplatin both in vitro and in vivo [300–304]. Doxorubicin, another broad-spectrum anticancer drug, has also been studied in combination with EMFs. Hajipour Verdom B et al. found that the combination of 10 mT SMF and doxorubicin synergistically reduced intracellular iron content and increased intracellular ROS levels in MCF7 cells [118]. Therefore, the utilization of regulatory effect of EMFs on iron metabolism holds significant potential as an adjunctive therapy in cancer chemotherapy.

Due to inherent electromagnetic properties of iron-based NPs, which can be locally accumulated by EMFs. Studies have indicated that EMFs enhance the targeted aggregation, the binding to the cell membrane, and internalization of iron-based NPs in vitro and in vivo [305–307]. Meanwhile, various types of exogenous EMFs can alter the iron release rate of iron-based NPs. Consequently, extensive studies have been conducted on the synergistic effect of EMFs and iron-based NPs in inducing ferroptosis in cancer cells. Magnetic hyperthermia therapy (MHT) refers to a therapeutic approach that utilizes the heat generated by magnetic nanoparticles under external time-vary magnetic fields to increase the temperature in the target area. MTH has gained significant attention in tumor treatment due to its non-invasive property, excellent tissue penetration, and demonstrated remarkable anti-tumor efficacy [308]. Iron-based NPs are the most commonly used magnetic NPs in MHT. Sadhukha et al. found that 386 kHz, 7.56 mT EMF in combination with iron-based NPs effectively reduced the proportion of cancer stem cells subpopulations in A549 and MDA-MB-231 cells [309]. Meanwhile, compared to conventional heat therapy established by water bath heating, MHT increased intracellular ROS levels in a time-dependent manner. The heating effect of EMF exposure, along with its interaction with iron-based NPs, improved the sensitivity of cells to oxidative stress, which has been associated with changes in iron metabolism and decreased GPX4 expression [310]. It has reported that during MHT, the EMFs interact with intracellular NPs, accelerating the glutathione consumption mediated by iron and facilitating the iron-catalyzed generation of ·OH, which induces oxidative damage and trigger ferroptosis in cancer cells [139]. Li ZF et al. found that compared to Fe_3O_4 NPs treatment alone, the MHT by combination with EMFs inhibited proliferation and migration of HCC-70 cells and suppressed the growth of triple-negative breast cancer (TNBC) in mice. Furthermore, the MHT increased apoptosis levels, and decreased the expression of NRF2 and FTH1 of TNBC cells both in vitro and in vivo [311]. Additionally, the GPX4 expression was significantly decreased, suggesting that MHT induced ferroptosis in TNBC. Ji et al. found that the 30 min, 25 W microwave exposure promoted the iron releases from NPs and induced lipid peroxidation, leading to ferroptosis in vitro and in vivo [143]. EMFs can also induce ferroptosis in cancer cells by altering the configuration of nanoparticles, enhancing their chemical activity. Recently, some iron-based NPs with unique

structural characteristics have been found to exhibit intrinsic peroxidase (POD) or oxidase (OXD)-like activities, catalyzing the generation of intracellular ROS, and referred to as magnetic nanozymes [312]. Studies have shown that EMFs can enhance the ferroptosis-inducing effect of magnetic nanozymes [313]. Yuan et al. reported that the catalytic velocity, Michaelis constant, and catalytic efficiency marker K_{cat}/K_M value of nanozyme under alternating magnetic fields exposure were significantly elevated with increasing magnetic field intensity ranging from 0 to 350 μT [314]. This effect was associated with EMFs exposure promoting electron transfer and increasing the Fe^{2+}/Fe^{3+} ratio in nanozymes. They also found that alternating magnetic fields promoted ferroptosis induced by the combined treatment of nanozymes with Xenon lamp in HeLa and MCF-7 cells, and suppressed tumor growth in HeLa-tumor-bearing mice. Moreover, EMFs can synergistically regulate iron metabolism in conjunction with iron-based NPs and facilitate the release of carried drugs, thereby augmenting their anti-cancer effects. Orel V et al. found that compared to conventional doxorubicin treatment, the combination of SMF and RF-EMFs inductive hyperthermia below 40 °C with doxorubicin-loaded iron-based NPs demonstrated superior efficacy in inhibiting lung cancer growth and metastasis in mice. Meanwhile, RFH decreased the activity of FeS-protein electron transport chains in mitochondria [315]. T The anti-cancer effect of this combined treatment may be attributed to its regulation on iron metabolism in mitochondrion, specifically inhibiting electron transfer in mitochondrial iron-sulfur proteins and increasing in non-heme iron complexes with nitric oxide.

Conclusion and perspective

EMFs have been widely applied as a non-invasive physical alternative or adjunctive therapy in translational medicine. The regulation of iron metabolism by EMFs is a crucial mechanism underlying their biological effects and plays a significant role in their translational applications. On one hand, iron metabolism-related indicators can be used to evaluate the biological safety of EMFs. On the other hand, the effects of EMFs on iron metabolism have potential applications in the research and treatment of various diseases, including immunoregulation, cardiovascular diseases, neurological diseases, orthopedic diseases, diabetes, liver injury, and cancer. Moreover, the synergistic regulation of iron metabolism through the combination of EMFs with drugs—particularly iron-based NPs—has notably enhanced the potential of EMFs in the biomedical field. However, conflicting results in many studies regarding the effects of EMFs on iron metabolism make it challenging to systematically summarize the regulatory patterns of EMFs on iron metabolism. Despite these inconsistencies, several general characteristics of EMF-mediated regulation of iron metabolism can still be summarized. First, the effects of EMFs on iron metabolism vary depending on the properties of the EMFs (such as intensity, gradient, frequency, etc.) and exposure time [17]. Additionally, the effects of EMFs on iron metabolism appear to exhibit a biological "window". It has been reported that the biological effects induced by EMFs of specific intensities, frequencies, and exposure durations within this "window" may differ significantly from those outside it [123]. Furthermore, the regulation of iron metabolism by EMFs also shows significant tissue- and cell-type specificity. Compared to changes in biochemical indicators, biophysical mechanisms are typically used to provide a deeper explanation of the biological effects and patterns of EMFs. In this review, we have summarized several potential biophysical mechanisms through which EMFs regulate iron metabolism, aiming to better understand the underlying reasons for the complex regulatory characteristics of EMFs on iron metabolism, and to provide research insights for utilizing EMFs in the modulation of iron metabolism in the future. Furthermore, the descriptions of EMFs parameters and exposure forms in many studies are often vague, which limits the comparability of results across different studies. Therefore, more precise descriptions of EMF parameters and exposure methods are needed in future research on the effects of EMFs on iron metabolism and related diseases. We expect that with extensive and in-depth studies on the effects and mechanisms of EMFs in iron metabolism, the scope of EMF applications in disease prevention and treatment is likely to expand.

CRediT authorship contribution statement

Shenghang Wang: Conceptualization, Data curation, Writing – original draft, Funding acquisition. **Jiancheng Yang:** Supervision, Writing – review & editing. **Chenxiao Zhen:** Writing – original draft, Software. **Huiru Wang:** Data curation, Software. **Peng Shang:** Conceptualization, Supervision, Writing – review & editing, Funding acquisition.

Declaration of competing interest

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

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