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Review

IRON OXIDE NANOPARTICLES FOR DIAGNOSING AND TREATING DEGENERATIVE ORTHOPAEDIC DISEASES: A REVIEW

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Abstract

The prevalence of degenerative orthopaedic diseases, such as osteoarthritis, osteoporosis, and intervertebral disc disease, has increased due to the increasing prevalence and unsatisfactory therapeutic methods. Recently, different types of bioactive nanomaterials, such as iron oxide nanoparticles (IONPs), have raised much concern due to their ability to positively regulate the bone remodelling balance. Due to their magnetic characteristics, IONPs have been applied in magnetic resonance imaging in the clinic, but their ability to treat degenerative orthopaedic diseases has recently been shown both *in vitro* and *in vivo*. However, a comprehensive review of the potential utilization of IONPs in the orthopaedic field is lacking. Here, we summarize previous works in this review and discuss future research directions in this field.

Keywords: Iron oxide nanoparticles, magnetism, molecular diagnosis, orthopaedic diseases.

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1. Introduction

With the acceleration of ageing, the prevalence of degenerative orthopaedic diseases has increased rapidly, which has raised much concern. Degenerative orthopaedic diseases, which include many highly prevalent diseases, such as bone-featured osteoporosis (OP) and cartilage-featured osteoarthritis (OA)/intervertebral disc disease (IDD), are characterized by senescence of bone and cartilage tissues. These diseases cause many elderly people to suffer, which is also the main cause of disability and death.

OP is a common degenerative orthopaedic disease seriously threaten the survival quality of elderly (Agrawal and Garg, 2023; Ensrud and Crandall, 2024). Researchers have reported that fragility fractures occur more often in OP patients, especially in the hip and centrum, which can cause long-term bedrest and eventually death. Although many drugs, such as bisphosphonates, denosumab and teriparatide, are available, their side effects and limited therapeutic effects are still unsatisfactory (Pant *et al*., 2023; Wei *et al*., 2022; Zheng *et al*., 2022). For example, in the treatment of OP, the patients with long-termed application of bisphosphonates might suffer from atypical fracture in the shaft of femur (Aouad *et al*., 2023; Black *et al*., 2020). The fracture is always defined as low energy damage due to the patients' own gravity, which might owing to the over-inhibition of bone resorption, which affects the bone remodeling for the trabeculae bone with appropriate micro-architectural structure for load-bearing (Kordoni *et al*., 2018; Lisnyansky *et al*., 2018; Saleh *et al*., 2013; Schilcher *et al*., 2011).

OA is also a common degenerative disease of the whole joint characterized by pathological cartilage damage, which is the most common cause of joint disability and pain in elderly individuals and affects more than 250 million people worldwide (Allen *et al*., 2022; Prieto-Alhambra *et al*., 2014). In the clinic, stepped therapeutic methods highlight the importance of pharmacotherapy. However, the drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), glucosamine sulfate and sodium hyaluronate are always "safe but ineffective", which cannot intervene the

process of diseases, which makes it difficult to achieve a satisfactory therapeutic effect (Eckstein *et al*., 2006; Ibrahiem *et al*., 2023; Liu *et al*., 2021; Moseng *et al*., 2024; Pei *et al*., 2023; Shavlovskaya *et al*., 2023; Wu *et al*., 2023). Those patients can barely avoid receiving the surgical treatment due to the progression of diseases and the disease-modifying drugs is still in development (Li *et al*., 2023; Makarczyk *et al*., 2021; Shavlovskaya *et al*., 2023). The situation of IDD is similar to that of OA. Hence, the novel pharmacological therapeutic method is in urgent need for those degenerative orthopedic diseases.

Recently, with the development of nanotechnology, the treatment of degenerative orthopaedic diseases has become possible. These nanomaterials easily pass through physiological barriers due to their unique physicochemical properties, such as a high surface-to-volume ratio, which allows them to be applied in drug delivery and enhances their therapeutic effect (Bartkowski *et al*., 2024; Liang *et al*., 2023b). As a typical nanomaterial, iron oxide nanoparticles (IONPs), including Fe_3O_4, y-Fe_2O_3, and hybrid ferrites, have garnered much attention. These nanoparticles can carry iron, which can be detected by existed medical device such as magnetic resonance imaging (MRI). Also, it can induce biological activities due to the releasion of iron ions and the properties of nanoparticles. In previous translational research, IONPs exhibited excellent biocompatibility and biodegradability *in vivo* (Paik *et al*., 2015; Patil *et al*., 2015). Additionally, they are sensitive to magnetic fields, enabling their use in both diagnostic and therapeutic approaches, especially for the cellular and subcellular diagnosis (Kim *et al*., 2020; Shi *et al*., 2020; Vallabani *et al*., 2019; Wu *et al*., 2015). Meanwhile, due to the modifiable property, the IONPs have been used to prepare a lot of multi-functional agents with the integration of diagnosis and treatment have been developed, especially in the oncological field.

Although the IONPs have been maturely applied in the biomedical field, the research is in its infancy in orthopedic field. According to previous reports, IONPs has been explored to be applied in the diagnosis and treatment of different orthopedic diseases, such as OA, OP, bone tumors, fractures, osteolysis, and bone defects (Fig. 1) (Guo *et al*., 2020; Pang *et al*., 2021; Sadeghzadeh *et al*., 2023; Vergnaud *et al*., 2022; Wang *et al*., 2021a; Zhang *et al*., 2024). The nanoparticles exhibited great bioactivity when locally administrated in bone tissues alone or combined with other motifs, such as the enhancement of osteogenic and chondrogenic differentiation. Also, the unique magnetic properties make the IONPs could be used for magnetic-respond drug/stem cell tracing and delivery in orthopedic diseases (Chang *et al*., 2021; Xia *et al*., 2019b). When combined with the intervention of external magnetic field, the IONPs might translate the magnetic into other stimulation via different electromagnetic effect, such as the magnetocaloric effect, magneto-force effect (Del Bianco *et al*., 2022; Hamad *et al*., 2021; Ma *et al*., 2022; Wang *et al*., 2021b). The physical intervention is especially emphasized in the abundance of bone matrix, which finally act on the cells and induced the alteration in the cellular behaviors, such as the regulation of osteogenic and chondrogenic differentiation (Harris *et al*., 2015).

Although the IONPs is a promising agent due to the magnetic properties and biological activity, the biosafety and efficiency in diagnosing and treating degenerative orthopedic diseases are still worrying. As is known, the iron ions are tightly related to the ferroptosis, which has been regarded as the key pathological process in the inflammation and senescence (Coradduzza *et al*., 2023; Fan *et al*., 2024; Sun *et al*., 2024). In the oncological field, the ferroptosis is an effective weapon for killing the tumor cells. However, in the treatment of degenerative diseases, it might be regarded as a "double-edged sword", which might contribute to the acceleration of pathological process. Also, too many kinds of IONPs have been developed for the biomedical application due to the excellent extensibility. However, how to use an appropriate IONPs agent to intervene the determined pathological process in the degenerative orthopedic disease is still unclear. Briefly, a retrospective review based on the translational application perspective in orthopaedic field is still in lack. Herein, we summarize the application of IONPs in diagnosing and treating degenerative orthopaedic diseases, which might provide new insights for future research in this field.

2. The Preparation of IONPs

IONPs can be prepared by various methods, including physical, chemical and biological methods, which is tightly linked with the physicochemical properties (Laurent *et al*., 2008; Wu *et al*., 2015). Due to the lack of ability to precisely control the size of IONPs in the nanoscale, the physical approachs, such as the electron beam litography, aerosol, gase phase deposition, and powder ball milling, are not widely applied (Ling *et al*., 2015). The biological process relies on the redox reaction, which is more promising to be explored in the future. We considered that the *in-situ* synthesis of IONPs *in vivo* might be a ultimate aim of the biological method. However, the present application is still limited, and the application of physical and biological methods account for less than 10% in the preparation of IONPs (Ali *et al*., 2016; Revathy *et al*., 2023; Samrot *et al*., 2021). Hence, we focus on introducing the chemical synthesis routes.

The co-precipitation method is among the most simple and efficient synthesis procedures, which involves the mixing of multiple metal salts and precipitants to trigger a reaction, ultimately leading to the formation of a mixture comprising iron oxide and metal ions in the reaction solution (Sharouf and Saffour, 2024; Wahfiudin *et al*., 2024). The adjustment of factors such as pH value, reaction time, precipitant type, and solution concentration en-

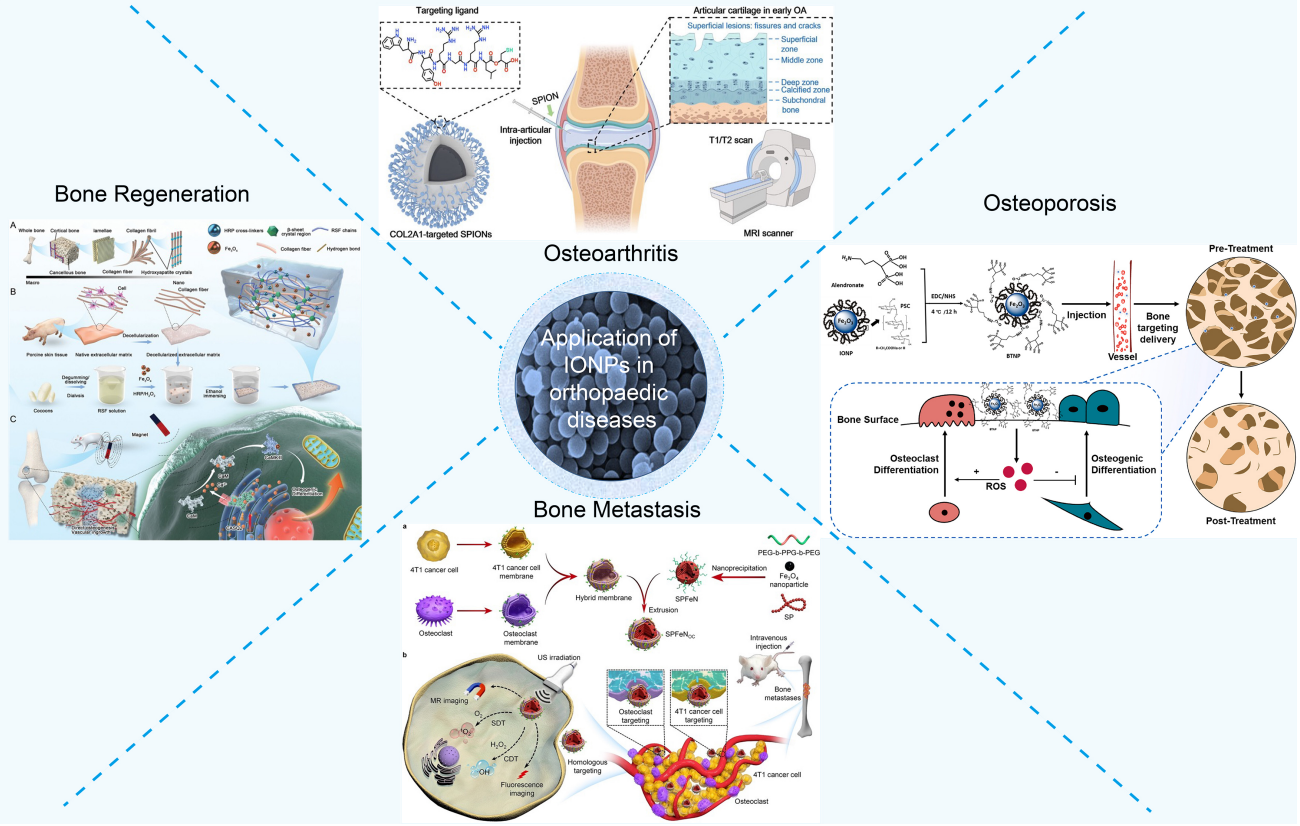

Fig. 1. Application of iron oxide nanoparticles (IONPs) for treating orthopaedic diseases.

ables the achievement of control over product particle size and composition (Wahfiudin *et al*., 2024). Nevertheless, this method is associated with a broad particle size distribution and challenges in precisely controlling product composition. To overcome these challenges, the improved co-precipitation techniques with the assistance of magnetic field, ultrasound, or functionalized bases have been developed (Liu *et al*., 2011; Pereira *et al*., 2012; Petcharoen and Sirivat, 2012; Remya *et al*., 2016; Roy *et al*., 2016; Suh *et al*., 2012; Wu *et al*., 2011).

To precisely control the size and shape of IONPs, the solvothermal method, which is also named as thermal decomposition, was developed (Hufschmid *et al*., 2015; Park *et al*., 2004). The method entails the heating of a solution comprising a mixture of metal ions and surfactants to yield IONPs with tunable particle sizes. By manipulating parameters such as temperature, concentration, surfactant type, and heating duration, this method allows for the precise attainment of desired product particle sizes and shape (Sharifi *et al*., 2012). However, this approach necessitates high temperatures and a complex preparation process, which make it not environmentally friendly. Also, the application of toxic chemicals in the synthesis processes make its own a risk in biocompatibility to be directly applied in the medical scene (Roy *et al*., 2021).

The sol-gel method is also a common method for the preparation of IONPs, which involves the swelling of metal ions in an organic solvent, followed by hydrolysis and repolymerization to form an iron oxide gel system (Darmawan *et al*., 2010; Puscasu *et al*., 2016). Subsequent heat treatment leads to the production of nanoparticles. This approach exhibits high precision and controllability, enabling the regulation of product morphology and crystal form through the manipulation of conditions such as hydrolyzing agent type and concentration (López-Sánchez *et al*., 2022; Panda *et al*., 2024; Waqas *et al*., 2024). However, it necessitates a prolonged preparation time, a complex process, and may result in environmental pollution due to the use of organic solvents.

Besides, a lot of methods such as microemulsion, hydrothermal, sonochemical and electrochemical deposition methods were employed for the preparation of IONPs. The microemulsion method used two immiscible liquids to form a confined environment for the nucleation and controlled growth of nano- and micro-particles (Hwang, 2024; Morán *et al*., 2023; Rahman *et al*., 2024). Although the size of the IONPs could be easily controlled by regulating the micelles, the limited crystallinity and yield make it hard to be translated in clinic use (Chaudhari and Panda, 2023). The hydrothermal method is relatively low-cost and easy to be performed. However, the final size of particles is not easy to be controlled (Hang *et al*., 2024; Ta *et al*., 2024). We have listed the advantages and disadvantages of different methods in the Table 1 for the future reference. The more

Table 1. The comparison of different synthesis method of iron oxide nanoparticles (IONPs).

Method	Complexity	Energy intensity	Homogeneity	Shape control	Crystallinity	Yield
Co-precipitation	Very simple	Low	Bad	Bad	Low	High
Solvothermal	Very complicated	High	Excellent	Excellent	High	High
Sol-gel	Relatively simple	Low	Good	Good	Low	Low
Microemulsion	Complicated	Low	Good	Good	Low	Low
Hydrothermal	Relatively simple	High	Good	Bad	High	High

preparation methods with ability to balance the yield and the ability to control the size and shape of IONPs is still in need to be developed.

3. The Biocompatibility of IONPs

When IONPs are applied in biomedical applications, biosecurity, which includes adverse effects when animals are exposed to nanoparticles, is highly important. Thus, we used a single section to exhibit the biocompatibility of IONPs before the application in orthopedic field. A previous review reported the therapeutic efficacy, migration and metabolism of IONPs *in vivo* (Malhotra *et al*., 2020). Although IONPs have been used in different ways in the biomedical field, toxicity is still a challenge that hinders their clinical translation. Although many types of IONPs exist, they have similar structures, including iron oxide cores, polymer coatings, and external layers. Previous work has shown that the toxicity of IONPs is mostly dependent on the shape and size of the nanoparticles and the presence of coating materials (Hussain *et al*., 2005; Jeng and Swanson, 2006; Karlsson *et al*., 2008; Karlsson *et al*., 2009; Malehmir *et al*., 2023). Herein, we separately introduce the aspects for the reference to prepare more bio-friendly IONPs for treating degenerative orthopaedic diseases.

The size of IONPs is an important factor affecting the cellular toxicity, which is mainly related to metabolism *in vivo*. In general, smaller IONPs (<10 nm) are metabolized by renal extravasation, while larger IONPs (>200 nm) are captured by the spleen, which indicates that IONPs with a size of 10-100 nm are more suitable for application *in vivo* (Choi *et al*., 2007; Gupta and Gupta, 2005). Additionally, many studies have shown that different shapes of IONPs are linked to toxicity. For example, spherical IONPs have been observed to have lower toxicity than other shapes, while rod-shaped IONPs have been reported to have greater toxicity (Ran *et al*., 2015).

Previously, it was reported that a polymer coating is the most important structure for relieving the toxicity of iron oxide and could also prevent the aggregation of nanoparticles (Gupta and Gupta, 2005). The possible potential mechanisms include enhancing the stability of IONPs and reducing the speed of iron ion release from the iron oxide core. Previous results have shown that the albumin nanoparticle coating provides a stable biocompatible shell and prevents the cytotoxicity of magnetite nuclei. After prolonged exposure (48 hours), IONPs become cytotoxic due to the production of free radicals, but this toxic effect can be neutralized by the use of polyethylene glycol (Abakumov *et al*., 2018). Previously, we found that polymer coatings could relieve iron overload-induced OP by scavenging reactive oxygen species (ROS) (Yu *et al*., 2020). As is widely known, the ferroptosis is a kind of cellular death based on the lipid peroxidation and the generation of ROS, which means that the ROS-scavenging polymers are also promising in reducing the toxicity by intervene the cellular behavior (Cao *et al*., 2024; Endale *et al*., 2023; Teschke, 2024). So, a lot of polymer materials with excellent antioxidant properties is also promising to be used for the synthesis of novel IONPs with more excellent biocompibility and diversified bioactivity, and the area is worth to be explored in the future. Each coating material has its own advantages and disadvantages, and we should pay attention to the selection (Abakumov *et al*., 2018). However, studies on the relationship between coating materials and toxicity in different microenvironments are still limited, and more studies need to be conducted.

The biosafety of IONPs is a crucial aspect that should be thoroughly examined and addressed for their successful clinical translation (Wang *et al*., 2024a; Yang *et al*., 2023). While IONPs offer immense potential in various biomedical applications, such as drug delivery, magnetic resonance imaging, and hyperthermia treatment, their long-term safety profile remains a significant concern (Marycz *et al*., 2020; Moacă *et al*., 2023). IONPs are typically designed to degrade over time, releasing iron ions that are subsequently metabolized by the body. However, uncontrolled degradation can lead to excessive accumulation of iron, potentially causing oxidative stress and cellular damage. Therefore, strategies to precisely regulate the degradation rate of IONPs are crucial. As is shown in Fig. 2, a work used a continuous flow system to unveil the biologically degradation behavior *in vivo* and characterize the degraded products, which is important in promoting the clinical application of IONPs (Yang *et al*., 2024). The improvement of biosafety can be realized by the application of novel coatings or modifications that stabilize the nanoparticles for a desired duration, ensuring that they degrade only when needed (Gu *et al*., 2024; Natarajan and Tomich, 2020; Zhong *et al*., 2019). Moreover, the use of targeting ligands that specifically deliver IONPs to target cells while minimizing accumulation in healthy tissues could also be explored (Israel *et al*., 2020; Liao *et al*., 2015; Park *et al*., 2008; Riegler *et al*., 2013; Zhi *et al*., 2020; Zhou *et al*.,

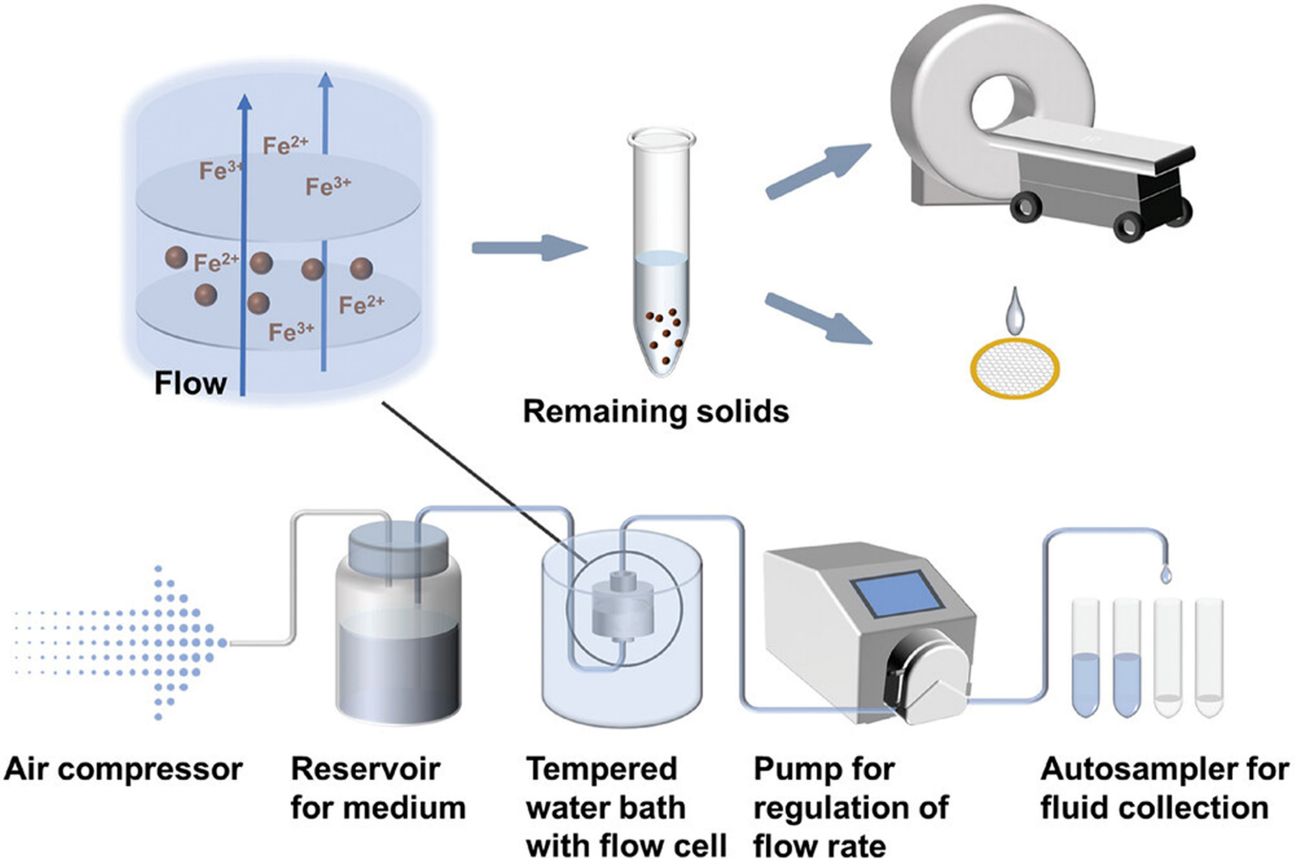

Fig. 2. A flow system which can dynamically monitor the degradation behavior of IONPs *in vivo*. Image cited from Yang *et al*. (2024).

2022). The biosafety of IONPs is a multifaceted issue that requires a comprehensive approach to address. By controlling the degradation rate, avoiding long-term accumulation, and mitigating potential toxic side effects, researchers can enhance the safety profile of IONPs and pave the way for their successful clinical translation.

4. Magnetic Nanoparticles for Imaging Innovations

In enhanced Magnetic Resonance (MR) detection, the most widely applied contrast agent is gadolinium (III). However, its high toxicity, especially in patients with liver and kidney failure, has raised significant concerns and limited its clinical application (Chen *et al*., 2011; Di Marco *et al*., 2017). In previous work, ultra-superparamagnetic iron oxide nanoparticles (SPIONs) were shown to significantly reduce the transverse relaxation time (T2) during MRI (Ajayi *et al*., 2023), and these materials have the potential to be applied as novel contrast agents. Recently, the imaging properties of newly prepared IONPs have been shown to be similar to those of gadolinium-based contrast agents, which are in the process of clinical translation (Liu *et al*., 2013)

IONPs can be used for MRI of different tissues. Usually, nanoparticles less than 10 nm in size are excreted in the urine, while a large number of nanoparticles larger than 200 nm are engulfed by the digestive system. This phenomenon indicated that the IONPs used for imaging different organs need to be of different sizes and shapes. Larger IONPs accumulate in the reticuloendothelial system (RES), which enables the imaging of the liver and spleen (Dadfar *et al*., 2019). Moreover, particles with sizes between 20 and 150 nm tend to deposit in connective tissues (bone, tendons, and muscles), stomach, and kidneys, as reported previously (Wang *et al*., 2022a). As mentioned above, the size of IONPs could be easily controlled by adjusting the preparation process. Determining the relationship between the size of IONPs and their enrichment in organs is important for future research and is highly valuable for preparing individual products for organ imaging.

In bone tissue imaging, imaging depth is still a challenge that limits imaging technology, but IONPs might provide a possible solution. Recently, magnetic particle imaging (MPI) technology, which aims to evaluate the electromagnetic properties of IONPs according to the gradient relationship between the magnetic field and concentration of IONPs, has been developed. IONPs saturate according to the direction of the magnetic gradient, except in a field without a magnetic field (Graeser *et al*., 2019; Panagiotopoulos *et al*., 2015; Saritas *et al*., 2013). The oscillating be-

haviours of IONPs make it possible to visualize and quantify the imaging results, which eliminates common issues in optical imaging, such as the disturbance of autofluorescence and signal attenuation in tissues (Bulte *et al*., 2015; Saritas *et al*., 2013). Moreover, MPI technology is not dependent on negative contrast for screening IONPs, which could avoid confusion in visualization at the air medium and tissue interfaces (Talebloo *et al*., 2020). Moreover, MPI enables continuous longitudinal screening of signals in samples, which is vital for cell tracing *in vivo* (Kang *et al*., 2014; Rana *et al*., 2010). Previously, the IONPs conjugated with collagen-binding peptides and IONPs can be detected via MRI methods for the diagnosis and treatment of osteoarthritic joints (Guan *et al*., 2023). We hope similar studies will contribute to the diagnosis of the pathological process of orthropedic diseases.

5. Application of IONPs in the Treatment of OA

OA is a representative degenerative orthopaedic disease characterized by the deterioration of cartilage and subchondral bone (Abdelbari *et al*., 2023). Cartilage tissues are regarded as avascular connective tissue without a self-renewal ability, but cartilage regeneration has become a challenge (Bullock *et al*., 2018). Herein, we investigated the application of IONPs in the treatment of OA and in the treatment of cartilage-derived degenerative orthopaedic diseases, including as nanocarriers and diagnostic/therapeutic agents.

Due to the absence of the vasculature, the entry of agents into the joint carve has been regarded as a complex problem. Methods to deliver drugs into the joint carve have raised much concern. The systemic administration of drugs is limited by systemic side effects and low bioavailability (Abbas *et al*., 2022b; Mosallam *et al*., 2022; Yang *et al*., 2011). Local intra-articular injection is a promising method for directly delivering bioactive agents to cartilage lesions. However, repeated punctures increase the risk of iatrogenic infection. Nanocarriers have been developed for efficient drug delivery via the joint route to address these challenges, and they improve drug delivery efficiency while minimizing adverse effects on other organs and tissues (Abbas *et al*., 2022a; Mohamed *et al*., 2020). Magnetic targeting combined with IONPs has been shown to be efficient for drug delivery (Ong *et al*., 2020, Suryadevara *et al*., 2023). IONPs, which are easy to fabricate, play a vital role in the controlled delivery of bioactive agents to the determined area and have shown advantages in terms of biocompatibility and surface functionalization (Abbas *et al*., 2022a, Das *et al*., 2019, Son *et al*., 2015). Molecular drugs can easily bind directly to the iron oxide surface for local delivery (Ibrahiem *et al*., 2023; Partain *et al*., 2020). In addition, Mei *et al*. (2016) prepared IONPs with superparamagnetic properties using a high-temperature thermal decomposition method and subsequently coated them with PEG. The modified IONPs had a particle size of 5.9 ± 1.1 nm and could easily penetrate into cartilage for drug delivery. Additionally, other works have used WYRGRL, which is a short peptide that combines with COL2A1 in the extracellular matrix of cartilage (Papadimitriou *et al*., 2014; Yarmola *et al*., 2016). Also, the IONPs conjugated with C5-24 peptides increased the retention of hyline cartilage when administrated in OA knees in a previous study (Guan *et al*., 2023). Additionally, IONPs contribute to cartilage repair and regeneration by recruiting bone mesenchymal stem cells (BMSCs) to specific locations and promoting their expression while causing fewer inflammatory responses (Yang *et al*., 2019a and Yang *et al*., 2019b). These innovative approaches present promising avenues for advancing OA treatment.

In addition to drug delivery, IONPs have also been widely used directly for diagnosing and treating OA (Fig. 3). The use of COL2A1-targeting IONPs can aid in the use of MRI to distinguish cartilage with early degenerative characteristics from healthy cartilage to achieve molecular-level diagnosis (Wu *et al*., 2023). Additionally, chitosan-modified IONPs have been shown to be efficient at labelling cells without altering their differentiation ability, which can be useful for intra-articular imaging. Interestingly, a team used IONPs to collect CTX-II, an important biomarker in osteoarthritic joint carves, which is called “magnetic capture” and is helpful for the early-stage diagnosis of OA (Garraud *et al*., 2016; Yarmola *et al*., 2016). As metal oxide nanoparticles, IONPs were proven to significantly improve histopathological damage to rat knee joints by regulating OPG, RANKL, ERK1, and MAPK levels (Ibrahiem *et al*., 2023). In addition, IONP-containing biomaterials, such as diphasic magnetic nanocomposite scaffolds, nanovehicles, and PLGA microspheres, have been developed for the treatment of OA (Butoescu *et al*., 2009; Huang *et al*., 2018; Zhang *et al*., 2020; Wang *et al*., 2024b). *In vitro* experiments have shown that IONPs can promote the differentiation of BMSCs into chondrocytes and upregulate the Ihh/PTHrP signaling pathway, providing a potential therapeutic approach for treating cartilage degeneration-related diseases (Jiang *et al*., 2017). Additionally, studies have explored the effects of IONPs on the chondrogenic differentiation of human bone marrow stromal cells (HBMSCs), neonatal, and adult chondrocytes. It was found that the viability of all cell types was unaffected; however, the cell morphology shifted to a “stretched” phenotype after SPIO uptake, and the proliferation of neonatal chondrocytes decreased after SPIO uptake (Saha *et al*., 2013). *In vivo* studies have found that 12.75 μg/mL M-SPIO can successfully label human articular cartilage-derived chondroprogenitor cells with minimal impact on cell viability, MSC marker expression, and differentiation potential (Vinod *et al*., 2019). It also does not affect the production of major cartilage matrix components (Ramaswamy *et al*., 2009). However, the potential regulatory mechanism has not been elucidated

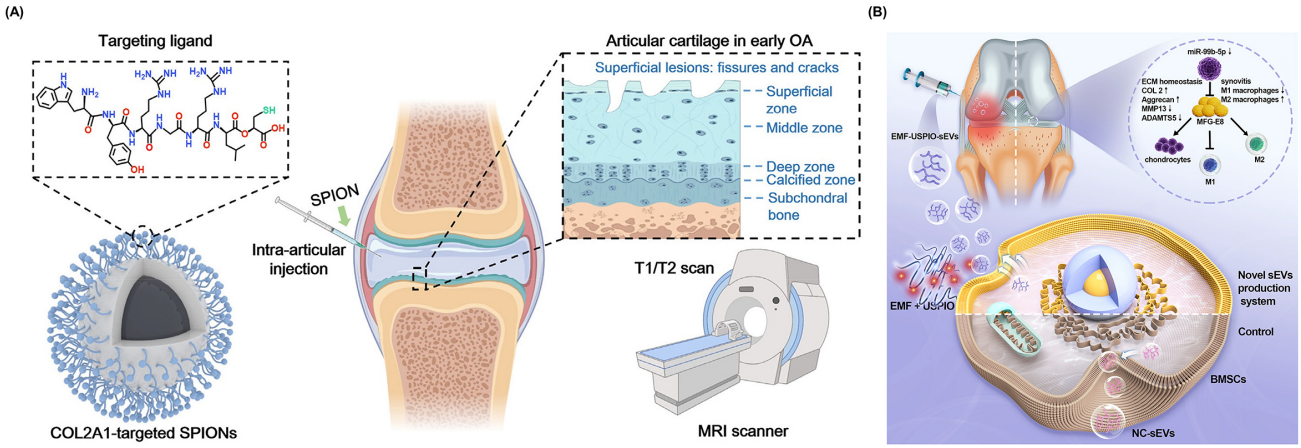

Fig. 3. IONPs have been proven effective in treating osteoarthritis (OA). (**A**) COL2A1 targeted IONPs for treating OA. Image cited from Wu *et al*., (2023). (**B**) IONPs based hybrid system for treating OA. Image cited from Wang *et al*. (2024b).

well, and whether the therapeutic effects are due to nanoparticle properties or degradation products remains unclear and is worth exploring (Table 2).

In addition to the application of IONPs as drugs to treat OA, IONPs are more likely to be applied in combination with stem cells or chondrocytes in the cell tracing field and can exhibit therapeutic effects. IONPs combined with MRI T2 imaging can maintain the stemness of adipose-derived stem cells (ADSCs), which is promising for application in MRI-assisted cartilage tissue engineering (Xie *et al*., 2019). Naosuke Kamei *et al*. prepared a cell delivery system to deliver mesenchymal stem cells (MSCs) to the cartilage defect area for cartilage repair (Kobayashi *et al*., 2008). They subsequently conducted clinical work and reported that IONP-labelled autologous MSCs were safe for repairing cartilage defects in the knee, while newly formed cartilage was observed 48 weeks after surgery (Kamei *et al*., 2018). Additionally, IONP-labelled chondrocytes can also be guided by a magnetic field to the cartilage defect area for cartilage repair (Gong *et al*., 2018). As the autologous chondrocyte implantation (ACI) technique has been regarded as effective for treating cartilage defects, the use of IONP-labelled chondrocytes is similar to that of chondrocyte transplantation, which seems to have the advantage of minimal invasion. Briefly, IONPs combined with stem cells or chondrocytes are easy to translate in the clinic. However, long-term studies on the safety and effectiveness of these treatments are still needed.

6. Application of IONPs in the Treatment of OP

OP is a common bone degenerative disease with an extremely high prevalence in elderly individuals. OP can be divided into two subtypes: decreased bone formation activity and increased bone resorption activity (Compston *et al*., 2019; Ensrud and Crandall, 2024). Previously, IONPs were shown to be effective in regulating the behaviour of osteoblasts and osteoclasts. Chitosan-coated IONPs modified with chitosan and hydroxyapatite were reported to be effective at enhancing the proliferation of osteoblasts while protecting the cells from exogenous stimuli and promoting osteogenic differentiation (Shi *et al*., 2012; Tran *et al*., 2012; Tran and Webster, 2011). Similar osteogenic-enhanced effects of IONPs were found in osteoporotic fracture models, while implant osseointegration was significantly enhanced (Anjum *et al*., 2023; Fouad-Elhady *et al*., 2020; Hedvičáková *et al*., 2023, Paun *et al*., 2018). Moreover, with the assistance of a magnetic field, IONPs can be guided to any bone area needed to enhance the formation of bone tissue, which could reverse the process of OP (Tran and Webster, 2013). In the same period from approximately 2012-2015, bone-targeting IONPs were developed for the radiological evaluation of bone metabolic activity (Panahifar *et al*., 2013). Additionally, the inhibitory effect of IONPs on osteoclasts was reported to be dependent on the TRAF6-p62-CYLD pathway (Li *et al*., 2021; Liu *et al*., 2019). However, with the increased awareness of iron overload-induced OP, the application of IONPs in treating this disease is controversial. In 2020, we reported that IONPs coated with antioxidative polysaccharides can release iron ions in bone mass without causing iron accumulation-related OP, which might be explained by the ROS scavenging effect of polysaccharides (Yu *et al*., 2020). Subsequently, IONPs combined with typical anti-OP drugs, such as bisphosphonates, were prepared for the treatment of OP in our and other works (Lee *et al*., 2016; Zheng *et al*., 2022, Panseri *et al*., 2012). Furthermore, Guan H *et al*. (2023) combined IONPs, Piezo1 activators and zoledronic acid in a hybrid system for the treatment of OP, which was shown to have an excellent therapeutic effect. Also, Yuanyuan Guo *et al*. (2021) used the IONPs to remote-controllable deliver estradiol to treat OP in rats models and achieved a success. However, the potential mechanism by which IONPs regulate OP is still unclear.

Table 2. The researches of the effect of IONPs on chondrogenic differentiation.

IONPs	Magnetic field intensity	Cell type	The effect of IONPs on the chondrogenic differenetiation	Reference
Magnetospirillum sp-isolated IONPs	0.25 mT	BMSCs	Enhanced	(Son *et al*., 2015)
Crbon quantum dots-doped IONPs	0.05 T	WJ-MSCs	Enhanced	(Das *et al*., 2019)
Ferumoxytol	None	MSCs	Enhanced	(Suryadevara *et al*., 2023)
Superparamagnetic iron oxide	None	BMSCs	Transient inhibition	(Saha *et al*., 2013)
Superparamagnetic iron oxide	1 T	ADSCs	Inhibited	(Kolecka *et al*., 2017)
Kartogenin-loaded ultrasmall super-paramagnetic iron-oxide	None	BMSCs	Enhanced	(Suryadevara *et al*., 2023)

BMSCs, bone mesenchymal stem cells; MSCs, mesenchymal stem cells; ADSCs, adipose-derived stem cells; WJ-MSCs, Wharton's jelly mesenchymal stem cells.

In our previous work, we found that IONPs could regulate the inflammatory microenvironment in bone tissues, which is beneficial for bone renewal and the function of bisphosphonates (Fig. 4). IONPs can be combined with different materials, such as calcium phosphate cement (CPC) (Xia *et al*., 2019a), or synthesized into mesoporous silica-coated magnetic (Fe_3O_4) nanoparticles (M-MSNs) (Jia *et al*., 2019), both of which enhance the osteogenic activity of stem cells through the WNT/β-catenin signaling pathway. Marycz K *et al*. (2020) synthesized the α-Fe_2O_3/γ-Fe_2O_3 nanocomposite does not induce an immune response and regulates integrin expression; it also enhances the osteogenic differentiation of osteoblasts and triggers apoptosis of osteoclasts. The combined use of a 1-2 T static magnetic field (SMF) and IONPs reduces iron uptake by osteoclasts and decreases oxidative stress levels during osteoclast differentiation. At the molecular level, the 1-2 T SMF combined with IONPs inhibits the expression of the NF-κB and MAPK signaling pathways (Zhang *et al*., 2022). Meanwhile, the appropriate ratio of Fe/Ca = 1:15, mol/mol (SPIO@15HA) inhibited the formation of osteoclasts through the TRAF6-p62-CYLD pathway. Besides, the osteogenic differentiation process was enhanced by the regulation of TGF-β, PI3K-AKT, and calcium signaling pathways. Furthermore, the overexpressed cytokines such as OPG, CSF2, and CCL2 also contributed to the maintainence of bone remodeling balance (Li *et al*., 2021). The senescence-associated secretory phenotype of immune cells and bone-related cells is widely recognized as an important source of inflammatory cytokines that contribute greatly to the progression of OP. Whether IONPs have a regulatory effect on the production of inflammation still needs to be explored.

7. Application of IONPs in Intervertebral Disc Diseases

The intervertebral disc is another site that is linked to orthopaedic degenerative diseases and is also a leading cause of disability in elderly individuals, and the common clinical manifestation is low back pain (Xin *et al*., 2022). The exploration of IONPs in intervertebral discs has focused mainly on diagnosis or combination with stem cell therapy for IDD. For example, Guillaume Bierry *et al*. (2009) used IONP-enhanced MRI to identify infectious and degenerative vertebral disorders, which could distinguish between the two diseases according to the quantitative results. In other studies, IONPs were used to mark MSCs to evaluate their survival and differentiation (Handley *et al*., 2015; Hang *et al*., 2017; Saldanha *et al*., 2008). Additionally, recent research has used IONPs as a magnetofection system to deliver miR-21 into stem cells for intervertebral fusion operations, which is the only therapeutic application of IONPs in IDD (Wang *et al*., 2023a). Studies have shown that inflammation, mitochondrial DNA damage and apoptosis play an important role in the pathological process of intervertebral disc cell degeneration (Zhou *et al*., 2024). Silence-activated transcription factor 3 (ATF3) blocks the pathological process of IVDD by regulating iron apoptosis, apoptosis, inflammation, and extracellular matrix (ECM) metabolism in nucleus pulposus cells (NPCs) (Wang *et al*., 2024c). Sirtuins/SIRTs and their related activators regulate autophagy, myeloid apoptosis, oxidative stress and extracellular matrix degradation, and have positive effects on the treatment of IVDD (Shen *et al*., 2024). Prolonged exposure to high concentrations of IONPs may induce oxidative stress and inflammatory translation (Vidya Balakrishnan *et al*., 2024), but there is insufficient evidence of INOPs and inflammatory response in the treatment and imaging of IDD. Overall, the application of IONPs for treating degenerative diseases of the spine is still in the initial stages. Based on the similar pathogenesis of IDD and OA, future work on the spine is warranted.

8. Discussion

In the field of biomaterials, nanoparticles have been widely applied due to their unique physicochemical properties (Zheng *et al*., 2024). These nanoparticles can be widely used for diagnosing, treating and preventing or-

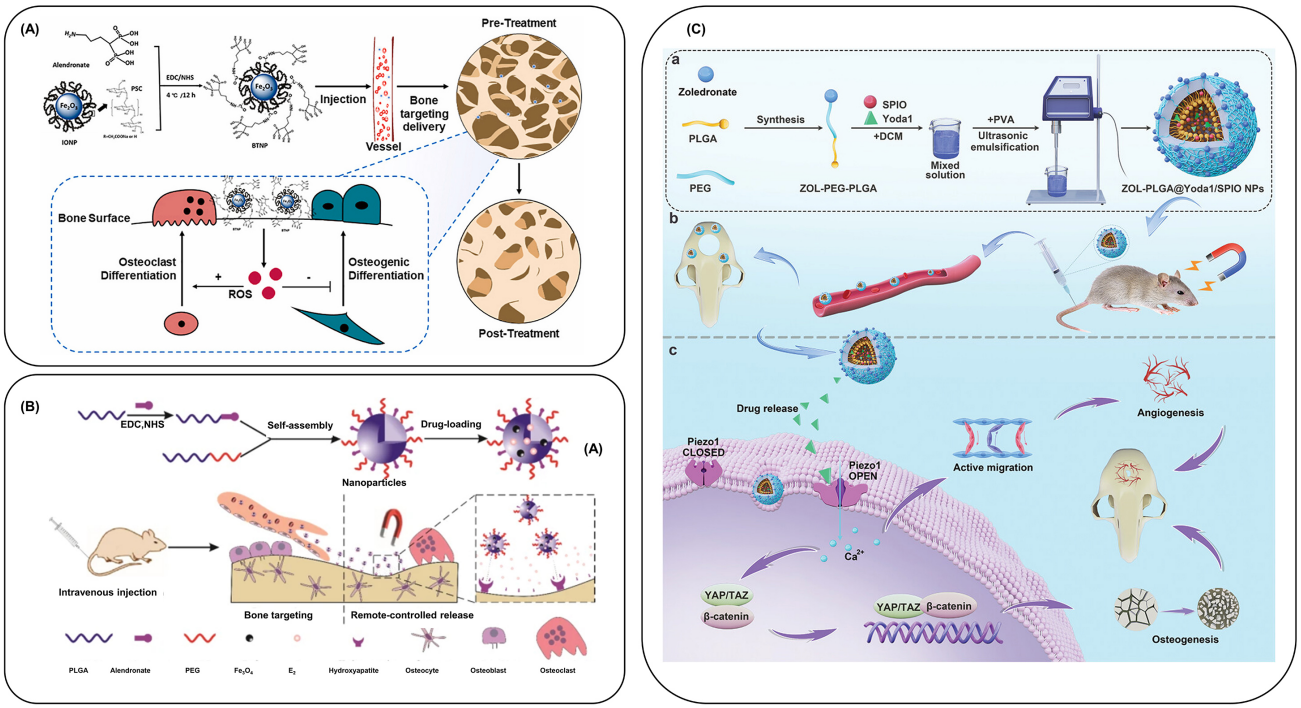

Fig. 4. Modified IONPs for treating osteoporosis. (**A**) Bone-targeting IONPs for treating postmenopausal osteoporosis; images were obtained from Zheng *et al*., (2022). (**B**) Bone-targeting IONPs combined with estradiol for treating postmenopausal osteoporosis; images were obtained from Guo *et al*., (2021). (**C**) Bone-targeting IONPs combined with Yoda1 for treating osteoporosis, images were obtained from Guan *et al*., (2023). Abbrevations: EDC, 1-Ethyl-3-(3- dimethylaminopropyl) carbodiimide; NHS, N-hydroxysuccinimide.

thopaedic diseases. Herein, we chose IONPs as representative nanoparticles and summarized their application in the orthopaedic field. Compared with other types of nanoparticles, IONPs have the unique advantage of magnetic properties and are also an important trace element in the human body. Iron metabolism in humans is a complex process involving duodenal enterocytes, plasma, erythroid bone marrow, the spleen, and the liver (Chifman *et al*., 2014). Many degenerative diseases have been linked to ferroptosis, which is a unique type of cell death mediated by iron-dependent lipid superoxidation (Jiang *et al*., 2021). Thus, the biosecurity of IONPs has been challenged. However, in our and others' previous work, suitable polymer coatings that can scavenge the existing ROS produced during ferroptosis can help to prevent iron accumulation-induced degenerative diseases (Guan *et al*., 2023; Yu *et al*., 2020; Zheng *et al*., 2022). Recently, many biosynthetic polymers with antioxidant activity, such as lignin, chitosan, and functional lipidosomes, have been identified (Pei *et al*., 2023; Zheng *et al*., 2021a; Zheng *et al*., 2021b). Surprisingly, we also found that IONPs can prevent the senescent secretion phenotype (data not published), which means that the intracellular delivery of Fe^{2+} might involve an independent pathway to improve the inflammatory microenvironment. The crosstalk between IONPs and the immune system is worth exploring.

In addition to their direct effects, the synergistic effects of IONPs with typical therapeutic methods attracted our attention. The most common application is the combination of IONPs with stem cells, in which the IONPs play a multimodal role. In the process of clinical translation of stem cell therapy, the greatest obstacle is the risk of tumorigenicity, while the IONPs can act as surveillants. In preclinical and clinical experiments, IONPs can be used to collect data for the analysis of the proliferation and differentiation of stem cells. On the other hand, the IONPs could directly act on stem cells and regulate their behaviour, enhancing their ability to promote osteogenesis/chondrogenesis for tissue repair to treat degenerative orthopaedic diseases (Table 3). In addition to the advantage of integration of IONPs with stem cells, several distinct challenges still remained to be addressed. A major challenge lies in achieving high-efficiency labeling of stem cells with IONPs while maintaining cell viability and functionality (Berman *et al*., 2011; Küstermann *et al*., 2008; Lin *et al*., 2017; Zheng *et al*., 2016). It was reported that the surface modified IONPs performed better in the long-term trancing of stem cells, such as the application of glucosamine, self-assembled peptide amphiphile, high-molecular polymers, amine and silica (Guldris *et al*., 2017; Yang *et al*., 2016; Yao *et al*., 2020; Liang *et al*., 2023a, Liu *et al*., 2020). Current methods often result in variable labeling efficiencies, which can limit the accuracy of tracking and monitoring stem cells, which could be improved by the development of device to generate focusing magnetic field and IONPs with more precise magnetic properties (Liu and Ho, 2017; Wang *et al*., 2020; Wang

Table 3. The researches of the effect of IONPs on osteogenic differentiation.

IONPs	Magnetic field intensity	Cell type	Animal model	Conclusions	Reference
Collagen–chitosan–hydroxyapatite–Fe_2O_3	250 mT	MG-63 osteoblast-like cells	None	Enhances ALP activity, osteocalcin synthesis and new bone tissue formation	(Paun *et al*., 2018)
PLA-nHA-Fe_2O_3	0.05-25 mT	None	Rabbit model of lumbar transverse defects	Accelerates new bone tissue formation and remodelling *in vivo*	(Meng *et al*., 2013)
ECM-RSF-Fe_2O_3	1 mT-1 T	Rat BMSCs	Critical-sized femur defect in a rat model	Enhances the osteogenic differentiation of BMSCs *in vitro* and new bone formation *in vivo*	(Liang *et al*., 2023a)
R-IONPs-HA	Not clear	MC3T3-E1	None	Promotes proliferation and osteogenic differentiation	(Wang *et al*., 2021a)
Fe-HA	320 mT	Saos-2 human osteoblast-like cells	A rabbit critical bone defect model	Promotes cell proliferation and osteoblast activity *in vivo*	(Panseri *et al*., 2012)
APTES -nHAp -IONPs	Not clear	MC3T3-E1 and 4B12	None	Enhances the metabolic activity of osteoblasts and diminishes osteoclasts' metabolism	(Marycz *et al*., 2022)
IONP-CPC	Not clear	hDPSCs	Subcutaneous implantation in mice	Enhances ALP activity and bone mineral synthesis *in vitro* and enhances osteogenesis *in vivo*	(Xia *et al*., 2019b)
Silk fibroin–hydroxyapatite–IONPs	Not clear	BMSCs	Subcutaneous implantation in mice	Promotes cell adhesion, growth, and osteogenesis *in vitro* and facilitates bone formation *in vivo*	(Liu *et al*., 2020)

et al., 2022b). Furthermore, the translation of IONP-based stem cell therapies from the laboratory to clinical settings faces numerous hurdles, including concerns regarding biocompatibility, long-term safety, and regulatory approval.

IONPs exhibit significant potential when integrated with drugs, genes, and biomaterials to form multifunctional nanoplatforms aimed at synergistic therapeutic outcomes. As drug carriers, IONPs facilitate precise delivery via magnetic targeting, enhancing bioavailability and therapeutic efficacy. They also function as sustained-release agents, extending drug release and therapeutic duration (Tran *et al*., 2022). The multifunctional hybrids are used to treat cancers and achieved a lot of success (Ghadimi Darsajini *et al*., 2023; Feng *et al*., 2023; Hasani *et al*., 2023; Wang *et al*., 2023b). However, in the orthopedic field, the application of multifunctional IONPs containing hybrids in diagnosing and treating diseases is still in the early stage. Previously, the combination application of IONPs with different drugs, such as salicylic acid, dexamethasone, folic acid, alendronate, and exosomes were proven efficient in treating OA and OP (Ibrahiem *et al*., 2023; Marycz *et al*., 2020; Shah *et al*., 2017; Tran *et al*., 2022, Marycz *et al*., 2022, Meng *et al*., 2013). However, current work are more likely to use the IONPs as a drug which can synergetically perform therapeutic effect with the typical drugs. As we previous reported, the multifunctional nanoplatforms can be obtained as two styles: the multifunction of one single functional unit, and the combination of different functional units (Zheng *et al*., 2024). Due to the complex structure and physicochemical properties, IONPs are easily to be used as therapeutic core and nano-vechiles which is easily to be translated to treat diseases with different pathologies, such as OA. However, various factors, such as charge, particle size, and surface modifications, influence the nanoplatform preparation methods based on IONPs. Also, drug-IONPs integration may alter physicochemical properties, affecting stability and bioactivity. The integration process requires careful consideration of compatibility, stability, biological activity, and safety of the nanoplatforms.

In conclusion, IONPs are novel nanoagents that could be translated to the clinic for the treatment and diagnosis of orthopaedic degenerative diseases. However, some unsolved questions worth studying persist, such as the improvement of biosecurity and potential molecular mech-

anisms involved in regulating cellular behaviours. After these obstacles are solved, more clinical trials are needed in the future.

List of Abbreviations

ACI, autologous chondrocyte implantation; ADSCs, adipose-derived stem cells; ATF3, activated transcription factor 3; BMSCs, bone mesenchymal stem cells; CPC, calcium phosphate cement; ECM, extracellular matrix; EDC, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide; HBMSCs, human bone marrow stromal cells; IDD, intervertebral disc disease; IONPs, iron oxide nanoparticles; MPI, magnetic particle imaging; MR, Magnetic Resonance; MSCs, mesenchymal stem cells; NHS, N-hydroxysuccinimide; NPC, nucleus pulposus cell; NSAIDs, nonsteroidal anti-inflammatory drugs; OP, osteoporosis; OA, osteoarthritis; RES, reticuloendothelial system; ROS, reactive oxygen species; SMF, static magnetic field; SPIONs, superparamagnetic iron oxide nanoparticles.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization: XLZ, LFJ, LMZ. Methodology: XLZ, QCF, LMZ. Investigation: XLZ, QCF. Visualization: XLZ, QCF, LMZ. Supervision: LFJ, and LMZ. Writing—original draft: XLZ, and QCF. Writing—review and editing: LFJ, LMZ. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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