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Recent advances of nanoparticles on bone tissue engineering and bone cells

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With the development of biotechnology, biomaterials have been rapidly developed and shown great potential in bone regeneration therapy and bone tissue engineering. Nanoparticles have attracted the attention of researches and have applied in various fields especially in the biomedical field as the special physicochemical properties. Nanoparticles were found to regulate bone remodeling depending on their size, shape, composition, and charge. Therefore, in-depth research was necessary to provide the basic support to select the most suitable nanoparticles for bone relate diseases treatment. This article reviews the current development of nanoparticles in bone tissue engineering, focusing on drug delivery, gene delivery, and cell labeling. In addition, the research progress on the interaction of nanoparticles with bone cells, focusing on osteoblasts, osteoclasts, and bone marrow mesenchymal stem cells, and the underlying mechanism were also reviewed. Finally, the current challenges and future research directions are discussed. Thus, detailed study of nanoparticles may reveal new therapeutic strategies to improve the effectiveness of bone regeneration therapy or other bone diseases.

Introduction

Medicine is defined as the applied science of detecting and diagnosing, treating, and preventing diseases. Nanomedicine is different from other types of medicine in that it refers to the development and application of nanoscale materials and technologies, and is an interdisciplinary field involving the interaction of nanoscience, nanoengineering, nanotechnology and

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life sciences.[1] Nanoparticles (NPs) are main components of nanomedicine. Currently, nanoparticles can be divided into organic nanoparticles and inorganic nanoparticles based on their composition. Such as organic nanoparticles include lipid-based nanoparticles, polymeric-based nanoparticles, dendrimers, chitosan, and inorganic nanoparticles include metal nanoparticles carbon-based nanoparticles, magnetic-based nanoparticles, silica-based nanoparticles, calcium phosphate-based nanoparticles, quantum dot *etc.*[2,3] With the development of biotechnology, the properties of nanoparticles have been greatly improved and have been used in several fields. However, the properties of nanoparticles depend mainly on the methods of synthesis, purification, and characterization.[4,5]

In recent years, some functional bio-nanomaterial molecules have been used in bioengineering and tissue engineering.[6] The research of nanoparticles is mainly focus on the field of bone tissue engineering, as the drug delivery, gene delivery, cell labeling, and especially in some experimental studies related to bone regeneration methods. Angiogenesis and osteogenesis are critical stages of bone regeneration, both of which require the regulation of multiple growth factors. The mechanical properties, biocompatibility, and bone integration properties of biomaterials are the priority factors for bone tissue regeneration engineering. To better mimic the nanostructures in the natural bone extracellular matrix (ECM), nanofibers, nanotubes, nanoparticles, and hydrogels have emerged as effective candidates to produce resemble the ECM and tissue scaffolds.[7,8] For example, carbon nanotubes of tubular nanomaterials accelerate tissue healing and bone regeneration through orchestrated cell and tissue-regulatory responses.[9] And nanoparticles as a carrier material for bone implants improved the osseointegration of the implants and reduced the risk of infection.[10] Nanoparticles were found to regulate bone remodeling depending on their size, shape, composition, and charge *in vitro*. In the meantime, the biocompatibility, low toxicity, biodegradability, and precise targeting of nanoparticles are the key factors to evaluate safety *in vivo*.[6,11] In addition, nanoparticles have made breakthroughs in cancer diagnosis and treatment, and it have developed targeted cell markers for nanoparticles used in the treatment of cancer.[12] Therefore, in-depth research was necessary to provide the basic support to select the most suitable nanoparticles for bone relate diseases treatment.

This article reviews the current development of nanoparticles in bone tissue engineering, and the research progress

Table 1 Characteristics of different types of nanoparticles

Type of nanoparticles	Advantages	Disadvantages	Applications	Ref.
Liposomes	Biocompatible and biodegradable Reducing drug toxicity	Rapid absorbed and removing from the bloodstream	Bone regeneration Osteoporosis Drug/gene delivery Cell labeling	13–15
Polymeric NPs	Biocompatible and biodegradable Easy to synthesize and functionalize Synthesis flexibility	Scale-up issues	Bone regeneration Osteoporosis Drug/gene delivery Cell labeling	21
Dendrimers	Good biocompatible Large number of surface functional Monodispersity	Low drug retention Size-dependent toxicity	Bone regeneration Drug/gene delivery Cell labeling	26–28
Gold NPs	Good biocompatible Easy functionalization Lower cytotoxicity Unique optical property	Biosafety need to improving by long-term cytotoxicity	Bone regeneration Osteoporosis Drug/gene delivery Cell labeling	30
Magnetic NPs	Good biocompatible Easy functionalization Stability and monodispersity	Potential toxic	Bone regeneration Osteoporosis Drug/gene delivery Cell labeling	37 and 38
Bioactive glasses NPs	Good biocompatibility Bioactive Biostability Osteoconductivity	Complex synthesis process	Bone regeneration Wound healing Bone grafting	14
Silica NPs	Biocompatible and biodegradable Chemical stability Uniform morphology	Toxicity	Bone regeneration Osteoporosis Drug/gene delivery Cell labeling	46–48
Hydroxyapatite NPs	Good biodegradability Biocompatibility and osteoconductive capabilities	Not easy to process Potential toxic	Bone regeneration Osteoporosis Drug/gene delivery Cell labeling	52 and 53
Quantum dots	Wide absorption spectrum and narrow emission spectrum Good photostability Multi-color imaging	Toxicity	Bone regeneration Drug/gene delivery Cell labeling	63–65

on the interaction of nanoparticles with bone cells, focusing on osteoblasts, osteoclasts, and bone marrow mesenchymal stem cells (BMSCs), and the underlying mechanism were also reviewed. The physicochemical properties of nanoparticles change depending on their size, dimensions, and surface markers, which affects their function. Therefore, to enhance the role of nanoparticles in bone-related diseases, further studies on the composition of nanoparticles are needed to reveal new therapeutic strategies to improve the effectiveness of bone regeneration therapy or other bone diseases.

Different types of nanoparticles

At present, various nanoparticles have been used in bone tissue engineering related experimental studies. The function of nanoparticles can be enhanced by continuously improving the bioavailability of nanoparticles. Currently commonly used nanoparticles and their advantages and disadvantages are shown in Table 1.

Organic NPs

Liposomes. Liposomes is a kind of artificial membrane, which is the first nano-delivery system applied in clinical trials and is considered the most successful drug delivery system.[3,13] Liposomes are double-stratified vesicles that formed in water by phospholipids and additives in water. Usually, each layer of the liposomes bounds water by the hydrophilic groups of phospholipids, and the lipid molecules in the hydrophobic tails are squeezed together and self-assembled.[14] Liposomes are used for drug delivery to target cells as their good biocompatibility and biodegradability, and it have the characteristics of slowing down or reducing drug toxicity, and enhancing stability.[15] The functional properties of liposomes are influenced by their components, surface charge, size, and preparation method.[13] For example, the preparation method affects the assembly of phospholipids and produces different types of liposomes, and the lipid composition determines the fluidity and charge of the bilayer membrane, and the response to external stimuli.[16] Moreover, functionalized liposomes respond to certain stimuli as pH, enzymatic cleavage, or light. It was shown that dextran-modified liposomes can be effectively absorbed by cells under certain pH response, and subcutaneous administration of this liposomal formulations enhanced antigen-specific immune response and inhibit tumor growth in mice.[17]

In general, liposomes are used as carriers for delivery systems. For example several liposomal formulations 3β-(*N*-[*N*′,*N*′-dimethyl aminoethane]-carbamoyl) cholesterol (DCChol) and dimethyl diocta decylammonium (DDA) have been used for delivery of antibodies in cancer immunotherapy.[18] Therefore, it is necessary to integrate the desired molecules into the liposome. Considering the properties of the loaded substance, hydrophilic molecules can be incorporated and retained within the liposome *via* an aqueous solution, and hydrophobic molecules must be mixed with an organic solvent and bound to the hydrophobic sits.[14] The size of liposomes directly impacts the circulation half-life, and a disadvantage of the liposomes is that they are rapidly absorbed by the reticuloendothelial system (RES), and removes them from the bloodstream. To solve this problem, the researcher found that it can be combined with the hydrophilic polyethylene glycol (PEG) lipid to reduce the absorption by RES and increase the time in the bloodstream.[3,13] Most bone-targeting liposomes are conducted based on the binding interactions between the cationic and negatively charged phosphates in bone tissue. Such as, bone-targeting liposomes with targeted fragments of phosphorylated cholesterol are being developed to accelerate fracture healing. In addition, specific ligands on the liposomes enabled them to locate target site and promote osteogenic differentiation.[19] In short, it is need to find further strategies to overcome the shortcomings and give full play to its advantages in the field of bone tissue engineering in the future.

Polymeric NPs. In recent years, polymeric NPs have received significant attention due to their special physical properties and biodegradability. Polymer are organic materials composed of long chains of atoms connected by covalent bonds. Both natural and synthetic polymers are valuable material types in bone tissue engineering, and synthetic polymers offer more possibilities for chemical modifications and molecular alterations. For example, the natural polymers collagen and gelatin are the main protein components of natural bone, and poly (lactic-co-glycolic acid) (PLGA) is a candidate material for bone tissue engineering. Polymer NPs are prepared from polymer materials, the size range of polymeric NPs is about 1–1000 nm, but it can be appropriately adjusted according to the actual application to provide more effective and targeted polymeric NPs to improve the application efficiency. So far, polymeric NPs have been applied in several forms, such as nanofibers, nanocapsules and polymer micelles.[14,20] Polymeric NPs also have the advantages of good biocompatible, easy functionalization, flexible synthesis, and the ability to bind different types of molecules. Thereby, polymeric NPs show greater advantage and promise in the treatment of various diseases.[21]

Polymeric NPs can bind different types of molecules and have high drug-carrying capacity. To data, these vectors have been used for molecular transport and delivery in areas such as inflammation, cancer, and tissue regeneration.[20,22,23] Furthermore, the method of synthesizing polymeric NPs depends on the types of molecules loaded. In the case of small molecule ligands, it can be attached prior to self-assembly, and if the macromolecule ligands, it is usually linked to the surface of assembled nanoparticles.[14] At present, chitosan is one of the most common used polymers in drug delivery filed as the good biocompatibility, biodegradability, non-toxicity and safety.[3] Moreover, PLGA nanoparticles is one of the most successful polymers due to its good biodegradability and biocompatibility, sustained release, and other advantages.[24] Since different polymeric NPs are produced depending on the type of drug-loaded. Currently, drug-loaded polymeric NPs delivery systems have rarely been studied in clinical trials. Therefore, it is necessary to further study about the toxicity and drug-loading mechanism of polymeric NPs are needed *in vivo*, which provide a valuable basis for clinical application.

Dendrimers. Dendrimers were first discovered by Fritz Vogtle in 1978, while Donald Tomalia and his colleagues discovered the presence of dendrimers in the early 1980s.[25] Dendrimers are nano-sized and radial symmetric molecules with a good nanotree structures. From the center core subdivided into layered units, ending with periphery covers units.[26] This unique dendrimer structure allows them to be used in multiple fields such as nanomedicine, diagnostics, drugs gene delivery system. In general, there are two approaches used for drug delivery of dendritic macromolecules: formulation and nanostructure. In the formulation method, drugs are encapsulated in dendrimers through non-covalent interactions, while drugs are linked on dendrimers by covalent coupling in the nanostructure approach. Drug loading and release from dendrimers can be regulated by modifying the surface and generation of dendrimers.[27]

Dendrimers are a new type of polymeric NPs with good biocompatibility, monodispersity, and multiple surfaces functional groups. However, they suffer from size-dependent toxicity (cationic dendritic macromolecules) and poor drug retention. Typically, dendrimers are delivered to target sites for drug targeting by binding to peripheral moieties to enhance drug solubility.[25,26] Compared with traditional polymeric NPs, dendrimers have distinct advantages in drug delivery system. For example, high-efficiency drug loading capacity, precise peripheral size control, good targeting and multivalency of bind drugs. Therefore, dendrimers have become ideal carriers for studying the influence of polymer size and charge on biological effects such as cytotoxicity, biological distribution and retention time.[28]

Inorganic NPs

Gold NPs. Metal nanoparticles have received increasing attention for their unique properties and potential applications in biochemistry, imaging, optics, and electronics. In particular, the gold NPs has become an option for various biotechnology applications, such as drug delivery, imaging, and biosensing applications.[29] Gold NPs have been widely used in the biological field because of their good biocompatibility, easy functionalization, and low cytotoxicity, but long-term toxicity tests are needed to improve their biosafety. Gold nanoparticles are available in various shapes, including gold nanospheres, nanorods and nanostars, and different shapes and sizes also affect their biological effects.[30]

Currently, gold NPs are the most widely used inorganic nanoparticles due to their unique physicochemical properties. For example, the surface plasmon resonance (SPR) effect, which is an optical phenomenon caused by the interaction of electromagnetic waves with electrons in metals. The shape, size, charge, ligand, and surface temperature of nanoparticles will affect SPR effect, and this unique property makes them valuable in biomedical therapeutics and bio-diagnostic tools.[14,31] Moreover, it also has significant advantages in bioimaging, which can be absorbed in the near-infrared range and improve the visualization of deep tissues through imaging techniques.[32,33] Although gold nanoparticles have low toxicity and safety compared with other metal nanoparticles, long-term cytotoxicity, biocompatibility and biodistribution tests are still needed before application *in vivo* to improve the efficiency.

Magnetic NPs. Magnetic nanomaterials include iron, nickel, cobalt, and their metal oxides, typically include superparamagnetic nanoparticles (SPIONs), magnetic cationic liposomes, and single domain ferromagnetic nanoparticles.[34] Magnetic nanoparticles (MNPs) have received extensive attention due to their special properties and have been applied in imaging, drug delivery, cell tracking, gene delivery, magnetic resonance imaging (MRI), biosensors and thermotherapy.[35,36] The composition, shape, size, and magnetic behavior of MNPs is a key factor that affects its biological effects.

MNPs have good biocompatibility, low cost, stability and monodispersity. Moreover, it also has good targeting properties, which can be precisely targeted to the target location under the external magnetic field. Therefore, they can be used as good MRI contrast agents and an effective carrier for tumor drug delivery.[37,38] For example, a study has shown that dimercaptosuccinic acid (DMSA) coated (SPIONs) effectively delivered IFN-γ (an anti-tumorigenic cytokine) at the tumor site under the external magnetic field to inhibit tumor growth.[39] In recent years, cell-free therapies have received more attention, but the high heterogeneity of cell-free therapeutic-based EVs has limited their current clinical translation. Magnetic nanomaterials also play an important role in facilitating the separation, delivery, monitoring, and imaging of EVs for biomedical application. For example, MNPs can increase MRI *in vivo* for the tracking of EVs, combined with magnetic hyperthermia to control the spatiotemporal release of biomolecules, and thus precisely deliver EVs to realize the therapeutic potential of drugs.[40] Although MNPs have been applied in various research fields, it still faces great challenges in practical applications. MNPs have showed a potential toxicity, so surface-modified coatings (such as nickel ferrite) are necessary to ensure safety and efficacy in clinical applications.

Bioactive glasses NPs. Bioactive glasses are amorphous silicate-based material that has good biocompatibility, biostability, bioactive and osteoconductivity, which can form chemical bonds with bone tissue and it has been successfully used for bone regeneration.[14] The first bioactive glass was developed by Larry Hench *et al.* in 1969 and it has been used in clinical since 1985. They can rapidly degrade in the body, and through a combination of apatite crystallization and ion release on the surface to stimulate bone cell proliferation, which resulting in the formation of new bone.[41]

The new generation of mesoporous bioactive glass (MBG) has a higher specific surface area and allows biomolecular adsorption, which provides a new material for bone regeneration.[42] Patel K. D. *et al.*[43] found that the combinatory cues provided by nanotopology (25 nm roughness) and ions released from of MBG nanoparticles could effectively stimulate osteoblast differentiation and enhance the expression of bone-associated genes (ALP, OPN, and OCN). In addition, boron is a necessary trace element that plays an important role in the human body. Borate bioactive glasses (BBGs) are produced by replacing silica ions with boron ions in the glass networks, and

is mainly focused on the bone regeneration and wound healing applications, which an effective biological material.[44]

Silica NPs. Silicon is one of the most abundant elements in the earth's crust, which is mainly in the form of compounds. It is an essential nutrient and a basic element in many minerals.[45] In recent years, silica NPs have been used in the fields of drug delivery, imaging, diagnostics, and therapeutics as their good biocompatibility and biodegradability, chemical stability, and uniform morphology. The physical properties of silica NPs are related to their shape, size, charge, and surface modification. Although silica NPs are widely used in biomedicine and they are a good choice for bone regeneration materials, their potential toxicity cannot be ignored. Studies have shown that the toxicity of silica NPs is related to their particle size, concentration, and surface charge.[46–48]

Silica NPs can be divided into mesoporous silica NPs (MSNPs) and core/shell silica particles (C/S NPs) based on their applications. For example, C/S NPs are mainly used for molecular imaging because their unique shell structure can defend the imaging agent inside the nanoparticles, which enables the nanoparticles to precisely target to the sites.[49] Compared to other silica NPs, MSNPs have good drug delivery and release and biomedical applications. MSNPs with large surface area and pores are conductive to drug adsorption and loading, adjustable-sized pores control drug release, and easily functionalized surfaces contribute to drug targeting control, improving drug efficacy, and reducing toxicity.[50] In addition, studies have shown that dietary silica intake are positively correlated with human bone mineral density (BMD), and MSNPs can regulate the process of bone remodeling, which have a certain impact on the development of bone.[3] Singh R. K. *et al.* developed novel nanofibrous hybrid scaffolds of polycaprolactone shelled with mesoporous silica (PCL@MS). The results have shown that growth, proliferation, and the osteogenic differentiation of rat mesenchymal stem cells were significantly improved on the scaffolds, and the hybrid scaffolds was a novel nanobiomatrix platform for bone regeneration.[51]

Hydroxyapatite NPs. Hydroxyapatite (HA) is one of the main components of human teeth and bone matrix. HA nanoparticles (HA NPs), as a representative of bio-ceramic NPs with great biodegradability, and osteoconductive property, which has been widely used in bone tissue engineering, bioimaging and hyperthermia treatment fields.[52,53] Moreover, HA NPs also has low cytotoxicity and easy to prepare and modify, and are considered ideal carriers for drugs and gene delivery.[54] At present, HA NPs have become an ideal alternative for orthopedic implants due to their unique properties. The physicochemical properties of HA NPs are mainly related to particle size, shape, and surface functional groups, charge, and morphology.[55]

Although pure hydroxyapatite has excellent biocompatibility and bioactivity, it has poor mechanical properties and cannot be used as load-bearing implant materials, which is related to the physicochemical properties. However, hydroxyapatite nanoparticles overcame the traditional hydroxyapatite difficult plasticity, brittleness, slow degradation, with high chemical activity, which is conducive to cell attachment and growth, enabling bone cells to secrete varieties of osteogenic differentiation factors, and they also provide crystal nucleus for bone cell calcification and plays the role of osteoconductivity. In addition, HA NPs could improve the performance of scaffolds and increase bone mineral deposition in bone tissue engineering. When calcium and phosphorus are implanted in the body, they will be released from the surface of the material and absorbed by tissues.[56] In addition, HA NPs have also been applied in cancer therapy to inhibit tumor growth and metastasis through the release of loaded drugs.[57,58]

Quantum dots. Quantum dots (QDs) are nanoscale inorganic semiconductor particles with sizes ranging from 1 nm to 10 nm. In recent years, with the rapid development of nanotechnology in the field of biomedical, new nanomaterials such as QDs have been widely used in medical diagnostics, imaging, gene therapy and drug delivery due to their unique physical properties.[59–62] Since the properties of wide absorption spectrum and narrow emission spectrum of QDs are related to the size and surface coating, the emission spectrum can be controlled by adjusting the size and coating to make it more suitable for application imaging.[63,64] Although QDs have good photostability and multicolor imaging properties, which facilitate long-term cell labeling, they also have certain biological toxicity.[65] Since they may release metal ions that lead to cell death, the specific underlying cytotoxic mechanism needs to be further research and discussed, which makes them face some challenges in clinical application.[66]

Applications of nanoparticles in bone regeneration

In recent years, the discovery of novel biologically active compounds that could be used to treat diseases has degraded, with fewer new drugs entering the market every year. At present, NPs have become a focus of interest as a versatile and multifaceted drug delivery vehicle. NPs have good pharmacokinetic properties, sustained release, and target specific cells or tissues to enhance the efficacy of existing drugs through aggressive targeting and enhanced permeability and retention effect. In recent years, nanoparticles have been found to be effective drug carriers for the treatment of skeletal-related diseases (osteoporosis, osteoarthritis, osteosarcoma, and bone defect/repair) and have been applied in bone tissue engineering (drug/gene delivery and cell labeling/MRI) (Fig. 1). As the drug and gene delivery system as a carrier can be more accurately targeted to specific tissues, thereby improving the efficiency of treatment. Cell labeling can more accurately and permanently perform *in vivo* cell tracking and monitoring, and the application of diagnostic techniques can improve disease prevention functions. As shown in Table 2, the experimental study of nanoparticles in the field of bone tissue engineering.

Drug delivery

With the development of bone biology research, several different drugs are currently available for therapeutic intervention. However, some drugs are blocked in delivery by

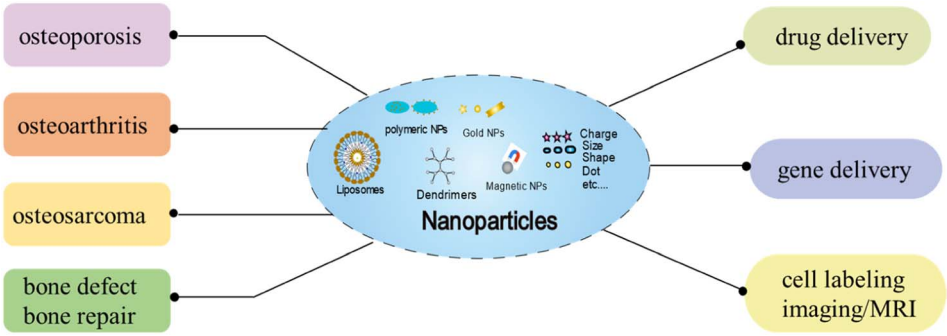

Fig. 1 Schematic illustration of the effects of NPs on different type of bone diseases, and the applications of NPs in bone regeneration as drug/gene delivery, and cell labeling/imaging (MRI).

gastrointestinal (oral) related enzymes and may be cleared from the body, making it difficult to reach specific tissue and diminishing the effects of the drug. Higher or more frequent drug doses to ensure the effectiveness of the treatment. However, higher drug concentrations may also have toxic effects on other organs and cause a series of adverse reactions. Research have shown that people develop new drug vectors to treat complex diseases by improving technology. Nanomaterials have unique structure, which can improve cell uptake and blood circulation, enable continuous controlled release of drugs, prolong the retention time of drugs in the body, and reduce the toxicity of drugs. In general, loading specific targeting ligands on the surface of nanoparticles is the most common form, and these targeting ligands can be in the form of small molecules, antibodies, peptides.[67,68] Typically, the drug is dissolved, captured, adsorbed, or covalently attached to the surface of nanocarrier, and it also can be encapsulated into it. The nanomedicine delivery system will be implemented by using active or passive targeting mechanisms. Once, the drug is released from the nanocarriers after they reach the target location by identifying specific ligands. In general, the rate of drug release is related to the physiological environment (such as temperature, pH, osmolality, and enzymatic activity), the solubility of the drug, and the degree of drug diffusion through the nanoparticle matrix.[69,70]

Usually, nanoparticles were combined with scaffolds such as protein hydrogels or biodegradable polymer matrices to promote application in bone tissue. On the one hand, growth factors could be delivered by nanoparticles to promote the osteogenic process. On the other hand, specific inhibitors could be released locally to regulate the function of osteoclasts, and the balance of bone remodeling was regulated.[6,14] Studies have shown that bone morphogenetic proteins (BMPs), members of the transforming growth factor (TGF)-β superfamily, were suitable for promoting osteogenic differentiation. Among the many BMPs, BMP-2 and BMP-7 are the most used and have been approved by FDA for clinical applications. Zhao *et al.*[71] found that chitosan-polyethyleneimine (CS-PEI) nanoparticle loaded with hBMP-2 could effectively promote the proliferation and differentiation of MC3T3-E1 cells *in vitro* without cytotoxicity. In addition, the CS-PEI/hBMP-2 nanoparticle significantly accelerated new bone formation at the bone defect area 12 weeks after implantation *in vivo*. Yi *et al.*[72] found that mesoporous silica nanoparticles-chitosan-loaded BMP-2 could effectively promote the repair of bone defects in chronic osteomyelitis and promote the osteogenic differentiation of BMSCs. Shen *et al.*[73] found that Cefazolin/BMP-2 loaded mesoporous silica nanoparticles significantly promoted the repair of open fractures and reduced inflammation with bone defects in mice, and increased the osteogenic differentiation ability of BMSCs *in vitro*. Qiu *et al.*[74] prepared silk fibroin/chitosan scaffolds containing mesoporous hydroxyapatite nanoparticles (mHANPs) of BMP-2 (SCH-L). The results showed the interaction of BMP-2/m HANPs heightened the binding ability of BMP-2 to cellular receptors, and the osteogenic differentiation of BMSCs *in vitro* and bone formation of rat calvaria defect *in vivo* were significantly promoted with the SCH-L scaffold. It has been shown that nanoparticle-embedded electrospun nanofiber scaffold encapsulated with BMP-2 and dexamethasone (DXMS) promote the repair of critical-sized rat calvarial defect.[75] In contrast to the BMP2, BMP7 plays an important role in the late stages of bone formation. It has been shown that biopolymer nanoparticle loaded with BMP7 could release BMP7 with long-acting and promoted osteogenic differentiation of adipose mesenchymal stem cells (ADSCs). Polylactic acid (PLA) and polyhydroxyalkanoate (PHA) nanoparticles loaded with BMP2 and BMP7, respectively, and modified with soybean lecithin (SL) as biosurfactants, enhanced osteogenic differentiation process of ADSCs in simulated microgravity.[76,77] In addition, a microporous silica nanoparticle for loading DXMS and ECM-derived peptides-poly(*N*-isopropylacrylamide-*b*-(2-(dimethylamino)ethyl methacrylate) promoted osteoblast mineralization and ectopic bone formation. DXMS-loaded liposomes induced osteogenic differentiation of hBMSCs.[78,79]

In addition to affecting osteoblasts, nanoparticles loaded with drugs could also manipulate of osteoclasts. Currently, bisphosphonates, a clinical anti-osteoporosis drug, reduce the risk of osteoporosis by inhibiting osteoclast activity. However, the bioavailability of oral bisphosphonates is poor. Therefore, bisphosphonate-loaded nanoparticles are feasible for local bone regeneration. It has been shown that IONPs loaded with alendronate could inhibit osteoclastogenesis and alleviated OVX-induced mice osteoporosis.[80] HA NPs loaded with risedronate could be effectively used for bone-targeted drug delivery

Table 2 Researches of nanoparticle in bone tissue engineering

Application	Type of NP	Outcome	Ref.
Drug delivery	CS-PEI NPs	CS-PEI loaded with hBMP-2 promoted the proliferation and differentiation of MC3T3-E1 cells *in vitro* and accelerated new bone formation *in vivo*	71
	Mesoporous silica NPs	Mesoporous silica NPs loaded with BMP-2 promoted the repair of bone defects and open fractures, and promoted the osteogenic differentiation of BMSCs	72 and 73
	Nanoparticle-embedded electrospun nanofiber scaffold	The scaffold encapsulated with BMP-2 and DXMS promote the repair of critical-sized rat calvarial defect	74, 75
	Biopolymer NPs	PLA and PHA loaded with BMP7 enhanced osteogenic differentiation of ADSCs	76 and 77
	Liposomes	Liposomes loaded with DXMS induced osteogenic differentiation of hBMSCs	78 and 79
	IONPs	IONPs loaded with alendronate inhibited osteoclastogenesis and alleviated OVX-induced mice osteoporosis	80
	HA NPs	HA NPs loaded with BMP-2 heightened osteogenic differentiation of BMSCs *in vitro* bone formation of rat calvaria defect *in vivo*; HA NPs loaded with risedronate inhibited OVX-induced reduction of bone density and mechanical properties in mice	74 and 81
Gene delivery	Mesoporous silica NPs	Mesoporous silica nanoparticles with BMP2 plasmid DNA (pDNA) increased transfection efficiency and osteogenic differentiation of MSCs	83
	Bioactive glass	BGN loaded with BMP2 plasmid DNA increased osteogenic differentiation of MSCs and promoted bone regeneration at the rat calvaria defect model	84
	Ionizable lipid nucleic acid NPs	Ionizable lipid nucleic acid NPs loaded BMP-9 gene delivery to BMSCs to promote osteogenic differentiation and increase bone density in OVX mice	85
	Lipopolysaccharide amine nanovesicles and nanopolymersomes	Lipopolysaccharide amine nanovesicles and nanopolymersomes, loaded gene pBMP-2 could induce osteogenic differentiation of BMSCs and MC3T3-E1 cells *in vitro*	86 and 87
	Gold NPs	Gold NPs mediated c-myb gene delivery to promote osteogenic differentiation of MC3T3-E1 cells and inhibite osteoclast differentiation of BMMs, and facilitate osseointegration of dental implants in OVX rat; gold NPs mediated PPARγ gene on implants improves osseointegration in diabetes mellitus rat model	88 and 89
	Gold nanorods	Gold nanorods mediated BMP-2 peptide delivery enhanced chondrogenesis	90
	IONPs	IONPs enhanced transfection efficiency of miR-21 into BMSCs and HUVECs, promoted osteogenic differentiation of MSCs and angiogenesis of HUVECs	91
Cell labeling	fNPs	fNPs labeled MSCs on the periosteal side of tibial defects promoted tibial defect repair and increased vascular maturity in mice by NIR-II live imaging	94
	SPIO@SiO_2–NH_2	The proliferation, migration, and differentiation potentials of BMSCs could be tracked by SPIO@SiO2–NH2 *via* MRI imaging	95
	SPIONs	SPIONs serve as good MRI contrast agents to track MSCs biodistribution in the whole body	93, 96 and 97
	UCNPs	UCNPs could be labeled and tracked the osteogenic differentiation and chondrogenic differentiation of BMSCs *in vitro*	99
	Magnetic NPs	The migratory activity of hBMSCs labelled with 1.0 μg μL^{-1} silica-coated magnetic NPs incorporating rhodamine B isothiocyanate was reduced	100
	Gold NPs	Gold NPs-labeled stem cells could be monitored and tracked therapeutic processes *in vivo* by ultrasound-guided photoacoustic imaging	101

Table 2 (*Contd.*)

Application	Type of NP	Outcome	Ref.
	Au NPs	PDL-FITC AuNPs could identify M1 macrophages in different cell populations by labeling RAW 264.7 cells and BMDMs	102
	QDs	QDs could label hASCs and tracked osteogenic differentiation of labeled stem cells	103 and 104

and inhibited OVX-induced reduction of bone density and mechanical properties in mice.[81] In conclusion, nanoparticle bone-targeted drug delivery systems have good prospects for application.

Gene delivery

Gene delivery is a promising application of nanoparticles due to the long-term expression and longer therapeutic effect. It can use the viral or the plasmid vehicles for the delivery of genetic material, and so that it does not degrade once internalized by cells. Nanoparticles emerged as a strategic tool for gene delivery, mainly due to their size and simple functionalization. Such as the application of liposomes, gold nanoparticles and silica nanoparticles, and so on. Nanoparticles are used as gene delivery carriers to absorb DNA, RNA, dsRNA(double-stranded), oligonucleotides, and other bioactive molecules on the surface of nanoparticles or wrapped inside by electrostatic action. The specific ligands modified on the surface of nanoparticles interact with the receptors on the cell surface targeting specific tissue cells. When the nanoparticles absorbed by the cells through endocytosis, these active molecules were released through a series of complex processes according to the changes in the microenvironment of the organism, thus playing the role of gene delivery and increasing the expression of genes at the target location.[82]

Kim *et al.*[83] prepared a complex of mesoporous silica nanoparticles with BMP2 plasmid DNA (pDNA) to tested its transfection efficiency in MSCs. The results showed significant intracellular uptake of the complex BMP2 pDNA/MSN-NH2 and increased transfection efficiency, and the osteogenic differentiation of the MSCs was promoted. Bioactive glass nanoparticles (BGN) surface aminated by adding 15% calcium silica could be loaded with BMP2 plasmid DNA and internalized into MSCs to increased osteogenic differentiation, and bone regeneration at the rat calvarium critical-sized defect model was promoted.[84] Novel ionizable lipid nucleic acid nanoparticles for systemic BMP-9 gene delivery to BMSCs to promote osteogenic differentiation of BMSCs and increase bone density in OVX mice.[85] Lipopolysaccharide amine nanovesicles loaded with the gene pBMP-2-green fluorescent protein complex could significantly induce osteogenic differentiation of BMSCs.[86] Lipopolysaccharide-amine nanopolymersomes mediated Noggin small interfering (si)RNA (siNoggin) and pBMP-2 to transfect MC3T3-E1 cells, respectively. The results showed that osteoblast differentiation was promoted *in vitro*.[87] Chitosan gold nanoparticles mediated gene delivery of c-myb promote osteogenic differentiation of MC3T3-E1 cells, inhibit osteoclast differentiation of bone marrow macrophages (BMMs), and facilitate implant osseointegration of dental implants in ovariectomized rat.[88] Gold nanoparticle-mediated PPARγ gene on implants improves osseointegration in diabetes mellitus rat model.[89] Hyaluronic acid-encapsulated gold nanorods mediated BMP-2 peptide delivery could enhance chondrogenesis.[90] In addition, the gene delivery mediated by IONPs can achieve better tissues targeting and reduce free diffusion of particles under the external magnetic field. Electromagnetic field and IONPs enhanced transfection efficiency of miR-21 into BMSCs and human umbilical endothelial cells (HUVECs), and osteogenic differentiation of MSCs and angiogenesis of HUVECs were promote.[91] In conclusion, nanoparticles can minimize toxicity and improve *in vivo* stability due to their good biosafety, surface modifiability and degradability. Nanoparticle-based gene delivery can effectively deliver target genes into the specific cells and affect cell proliferation and differentiation, thus promoting bone regeneration. Currently, it has good prospects for application in the field of bone tissue engineering.

Cell labeling

Due to their regenerative potential, stem cells are used in the field of bone tissue engineering or regenerative therapies. Nanoparticles provide visualization and tracking opportunities for stem cell labeling and imaging, and guide stem cells to different target locations, thus assessing the fate and involvement of the transplanted cells in tissue regeneration. Fluorescent nanoparticles are organic fluorescent dyes (including fluorescein and rhodamine dyes) adsorbed on the surface of nanoparticles or wrapped inside by chemical or physical methods, which improves the stability of the dye molecules in the biological environment and prevents the diffusion of organic dye molecules in biological tissues. The connectivity proteins or biomolecules modified on the surface of nanoparticles bind to the specific receptors on the cell surface to enter the cell, which realizes the specific biomarkers and fluorescence imaging diagnosis of cells and living tissues, thus enabling dynamic tracking of the cell status.[92] For example, nanoparticles for labeling MSCs have SPIONs, fluorescently labeled mesoporous silica nanoparticles, gold nanoparticles, or quantum dots *et al.*[6,14,93]

It has been shown that local implantation of fluorescent nanoparticles (fNPs)-labeled MSCs on the periosteal side of tibial defects could promote tibial defect repair and increase the number of stem cell and vascular maturity in mice by NIR-II live

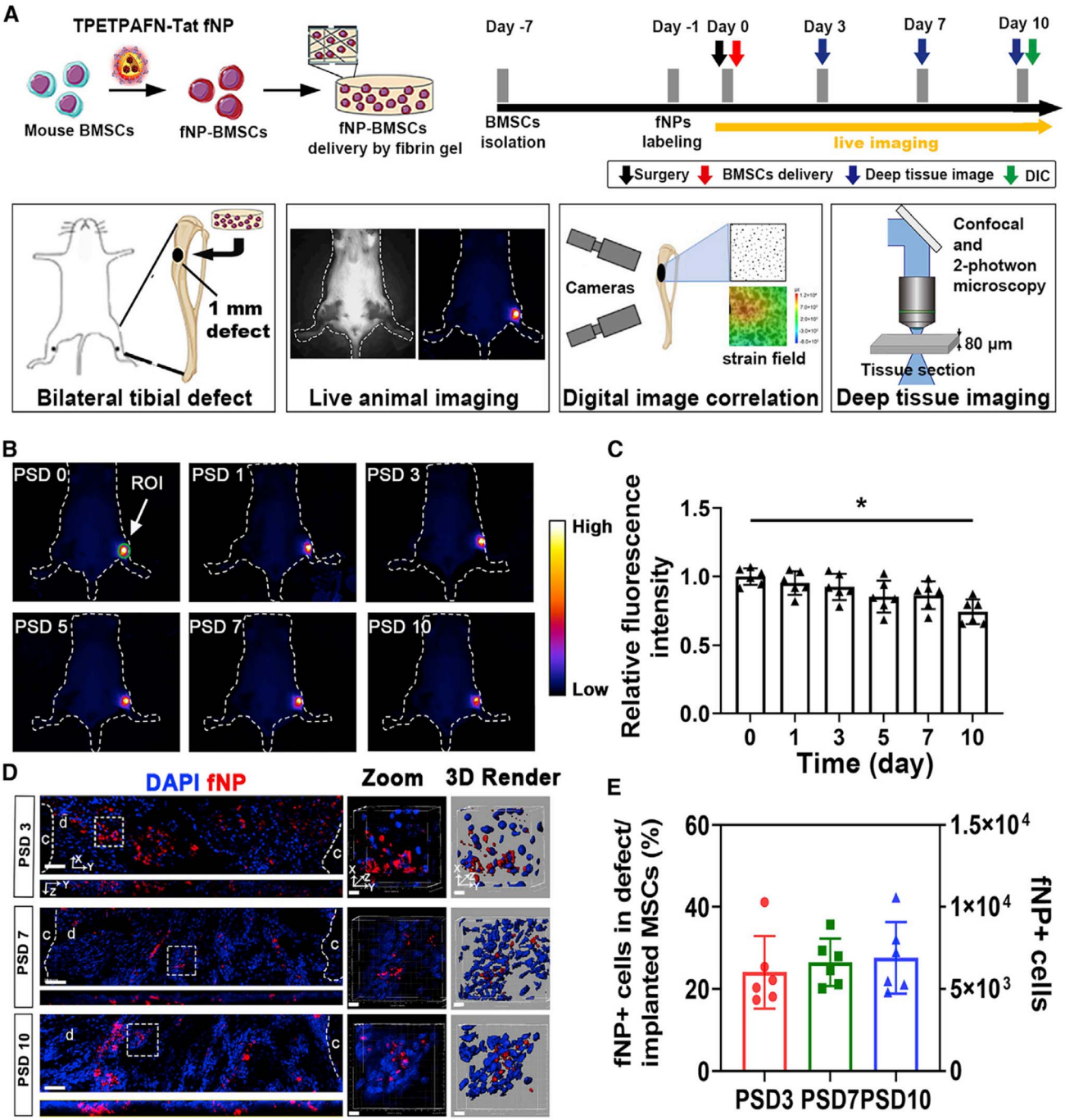

Fig. 2 Long-term tracking of implanted MSCs labeled by NPs in tibial bone defect during bone repair. (A) Schematic of NPs labeling and MSC transplantation, (B) quantitative analysis of areas of interest, (C) fluorescence intensity analysis of defect area, (D) implanted cells (fNP in the defect) on PSD 3, 7, and 10 were observed by confocal microscopy, and (E) the number of MSCs from (C) at each time point.[94] Reprinted with permission from ref. 94. Copyright 2022, *Stem Cell Reports*.

imaging[94] (Fig. 2). Silica-coating and amine-modified SPIONs (SPIO@S–N) increased migration capacity while retained proliferation and differentiation potential of BMSCs. As an ideal tracking marker, the P/T scaffold facilitated homing of MSCs in rabbit bone defect model, and this process could be traced by SPIO@SiO_2–NH_2 *via* MRI imaging.[95] In addition, MSCs-labeled with SPIONs serve as good MRI contrast agents to track their biodistribution in the whole body.[93,96,97] Dextran-coated doped with Yb^{3+}/Ho^{3+} fluorapatite crystals for labeling and tracking chondrogenic differentiation of BMSCs process *in vitro* and *in vivo*.[98] Polyacrylic acid (PAA) and polyallylamine hydrochloride (PAH) modified upconverted fluorescent nanoparticles (UCNPs) could be well labeled and tracked the osteogenic differentiation of rabbit BMSCs *in vitro*.[99] However, the migratory activity of hBMSCs labelled with 1.0 μg μL^{-1} silica-coated magnetic nanoparticles incorporating rhodamine B isothiocyanate was

reduced by reducing membrane fluidity and altering the cytoskeleton. This study suggested that optimal nanoparticle concentrations are critical for stem cell labeling and migration.[100]

In addition, ultrasound-guided photoacoustic imaging of gold nanoparticle-labeled stem cells could monitor and track therapeutic processes *in vivo*. It was shown that function and imaging properties of AuNP-labeled MSCs were retained after freezing and storage.[101] Hernandez *et al.*[102] prepared a fluorescein isothiocyanate-conjugated poly D-lysine (PDL-FITC)-modified reactive oxygen species (ROS)-sensitive AuNP. PDL-FITC AuNPs were loaded into RAW264.7 macrophages and primary BMDMs for labeling helped to identify M1 macrophages in different cell populations. Histidine conjugated β-cyclodextrin loaded with Dex attached to QDs nanoparticle could effectively label human adipose stem cells (hASCs). And osteogenic differentiation of labeled stem cells was promoted by monitoring in temperature-sensitive chitosan hydrogel scaffolds.[103,104] In conclusion, the application of nanoparticles in stem cell labeling and tracking supports the prognostic monitoring and tracking of stem cell therapies in clinical. In the field of bone tissue engineering, this technology has great potential.

Research progress on the interaction of nanoparticles with bone cells

During bone regeneration, normal bone remodeling is maintained through the coupling of bone formation by osteoblasts and bone resorption by osteoclasts. With the development of biotechnology, the application of nanoparticles in bone regeneration is becoming more and more widespread. However, the possible particle uptake and potential effects of nanoparticles on bone cells activity and functions, such as differentiation potential of MSC, mineralization by osteoblasts or regulation of resorptive activity by osteoclasts, are required to investigate before any nanoparticles applied in the field of bone research. Therefore, this section reviews the experimental study on the interaction of nanoparticles with bone cells.

Bone marrow mesenchymal stem cells

BMSCs are multifunctional differentiation cells derived from bone marrow, which can be differentiated into osteoblasts, adipocytes, and chondrocytes during the special environment of bone regeneration, and are widely used in tissue engineering and biomedical fields.[105]

Studies have shown the absorption behavior of BMSCs for nanoparticles primarily depended on the shape of the nanoparticles, charge, cell type, microenvironment, as well as the chemical properties.[106] Thereby, it is generally difficult to predict exactly the uptake rules of nanoparticles. In the aspect of shape and size, Li *et al.*[107] prepared bovine serum albumin (BSA)-coated Au nanospheres, Au nanostars and Au nanorods with diameters of 40, 70 and 110 nm. The results found that sphere-40, sphere-70, and rod-70 significantly promoted osteogenic differentiation ALP activity and calcium deposition of hBMSC, while rod-40 reduced osteogenic differentiation, which may be related to the activation of Yes-associated protein (YAP). With regard to charge, mesoporous silica microspheres (MSNs) uptake by hMSCs could be modulated by positive surface charge.[108] Positively charged polymers promote internalization of genetic material with high transfection efficiency, suggesting that positive charged particles polymer interact with negative charge of BMSCs membranes by bind to each other, and promoting uptake of nanoparticle.[109] Positively charged AuNPs promoted higher uptake by hMSCs.[110] However, there are also negatively charged polymeric nanoparticles, such as carboxyl-or phosphate-functionalized particles were also susceptible internalized by MSC.[111] Moreover, Yan *et al.* found that positively charged CQDs were more cytotoxic and lower photoluminescence (PL) but they have higher uptake and labeling efficiency compared to negative CQDs. The relatively weak positive surface charge gives CQDs good biocompatibility and labeling efficiency in hUCMSCs.[112]

In regards to the uptake mechanisms of nanoparticles, they can enter cells rely on diverse endocytosis pathways. Such as pinocytosis, micropinocytosis, receptor-mediated endocytosis and clathrin. PLGA-PEI PCS NPs was transported to the lysosomes of MSCs through clathrin-mediated endocytosis.[113] Ag-NP particles were internalized to hMSC in a concentration-dependent manner with clathrin-dependent endocytosis and macropinocytosis.[114] Hydroxyapatite nanoparticles of different sizes could be uptake by hWJ-MSCs through clathrin and caveolin-mediated endocytosis and macropinocytosis.[115]

After illuminate the mechanism of nanoparticles into cells, further research for the BMSCs differentiation potential is crucial. The process of osteogenic differentiation of BMSCs is a complex and involves the activation of several signaling pathways as the BMP/Smad, PI3K/Akt/mTOR, MAPK, Wnt/β-catenin.[116] Exosomal miR-1260a and miR-21-5p derived from BMSCs preconditioned with Fe_3O_4 nanoparticles and SMF could improve osteogenic differentiation of BMSCs and enhance wound healing.[117,118] Exosomes derived from BMSCs inhibited mitochondrial dysfunction-induced apoptosis of chondrocytes through p38, ERK, and Akt pathways.[119] *In vitro* research shows that IOPNs promoted osteogenic differentiation of BMSCs by activating MAPK pathway, increased the expression of ALP, BMP2 and Runx2.[120] Electromagnetic feld (EMF) and IONPs enhanced magnetofection efficiency of miR-21 into BMSCs and HUVECs, which improved the osteogenesis and angiogenesis and contributes to the intervertebral fusion.[91] The osteogenic differentiation of BMSCs was facilitated by HA NPs and wedelolactone with increased formation of ALP and mineralization and upregulation of osteogenic related genes.[121] Tantalum NPs could promote osteogenic differentiation of BMSCs and induce bone regeneration by activating the BMP2/Smad4/Runx2 signaling pathway.[122] In addition, BGN inhibited osteoclast differentiation and osteoporotic bone loss by activating lncRNA NRON expression derived from BMSCs.[123] And it has been proved zinc silicate/nano-hydroxyapatite/collagen scaffolds could promote angiogenesis of aortic endothelial cells and bone regeneration of BMSCs *via* the p38 MAPK pathway in activated monocytes.[124] Au NPs promoted osteogenic

differentiation of BMSCs through activation p38 MAPK pathway, and increased the expression of Runx2, ALP and OCN.[125] In addition, a polydopamine-mediated graphene oxide (PGO) and hydroxyapatite nanoparticle (PHA)-incorporated conductive alginate/gelatin (AG) scaffold increased the cell adhesion *via* RhoA/ROCK signaling pathways and improved osteogenic differentiation of BMSCs.[126] Mesoporous silica nanoparticle (MSN)-incorporated PDLLA (poly (DL-lactide))-PEG-PDLLA (PPP) thermosensitive hydrogel markedly enhanced the migration and osteogenic capacities of rBMSCs under high glucose conditions *in vitro* and significantly promote periodontal bone regeneration under type 2 DM *in vivo*.[127] 3D-printed bio-scaffolds composed of Sr-containing mesoporous bioactive glass nanoparticles (Sr-MBGNs) and gelatin methacrylate (GelMA) promoted the osteoblast differentiation of BMSCs harvested from type II diabetic rats *via* the Kindlin-2/PTH1R/OCN axis.[128] Chen *et al.*[129] constructed a nano platform by modifying BMSCs-derived EXOs using the bone-targeting peptide SDSSD and encapsulated capreomycin (CAP) within a shell. And the results showed the constructed NPs induced ferroptosis in osteosarcoma cells by activate Keap1/Nrf2/GPX4 signaling pathway.

In general, different shapes, sizes and charges affect the absorption mechanism of BMSCs, meanwhile greatly affect the differentiation potential of BMSCs. These *in vitro* studies indicate NPs, NPs-loaded scaffolds accelerate osteogenic differentiation of BMSCs through the BMP-2/Smad, PI3K-Akt, and MAPK signaling pathways (Fig. 3a). Therefore, it is necessary to continue deeply research nanoparticles to ensure safer and more effectively targeting to objective sites without affecting the differentiation potential of BMSCs.

Osteoblast

Osteoblasts are derived from marrow mesenchymal stem cells and are primarily responsible for bone formation. Osteoblast play a key role in the reconstruction and maintenance of bones.[130] The effect of nanoparticles on osteoblasts is like BMSCs, such as hydroxyapatite, polymers, and calcium phosphate particles. Shape, size and charge will affect the uptake mechanism and potential function of osteoblasts.[6]

With respect to the shape and size, Steckiewicz *et al.*[131] examined the cytotoxicity of AuNPs stars (≈215 nm), AuNPs rods (≈39 nm length, 18 nm width) and AuNPs spheres (≈6.3

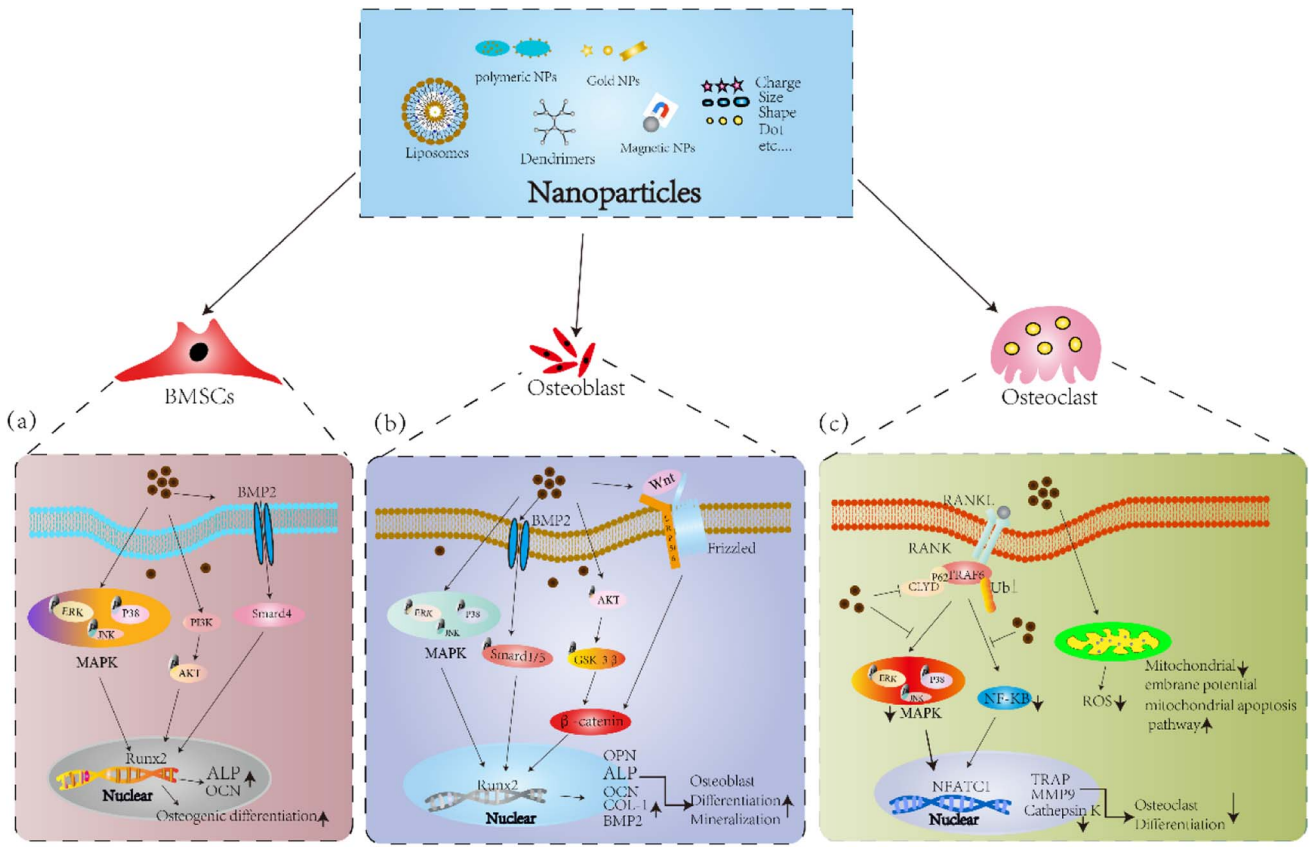

Fig. 3 Potential mechanism of the effects of NPs on bone cell. (a and b) Schematic illustration of NPs facilitated osteogenic differentiation in BMSCs and osteoblasts. Classical MAPK, BMP-2/Smad, PI3K-Akt-GSK-3β-β-catenin, and Wnt/β-catenin signaling pathways are activated by NPs. Therefore, transcription of downstream osteogenesis-related gene is significantly promoted, resulting in enhanced osteogenic differentiation. (c) Schematic illustration of NPs attenuated osteoclastic differentiation in osteoclast. NPs upregulated p62 expression which result in recruitment of CYLD and increased deubiquitination of TRAF6, and suppression the activation of RANKL-induced downstream signaling pathway as MAPK and NF-κB. Thus, transcription of downstream osteoclastogenesis-related genes was markedly inhibited, resulting in reduced osteoclastic differentiation.

nm) on human osteoblast(hFOB1.19) and osteosarcoma cells (143B, MG63). The results have proven that AuNPs stars were the most cytotoxic against osteosarcoma cells and had a good anti-cancer potential. AuNPs spheres were the least toxic and safest. Previous studies have proved that 20 nm HANPs have a good effects on promotion of cell growth and inhibition of cell apoptosis of human osteoblast-like MG-63 cells.[132] Juhl *et al.*[133] found that compared with 200 nm and 900 nm carbonated hydroxyapatite (CHA), 500 nm CHA were more conducive to inducing the differentiation of human osteoblasts hFOB 1.19 and did not affect cell viability. About the particle charge, HANPs with positive charge were more easily internalized and promoted cell proliferation activity of MC3T3-E1 cells compared to negative charge. The underlying mechanism may be attributed to the interaction of positively charged nanoparticles with negatively charged cell membranes.[134]

Apart from particle uptake and potential effects on proliferation activity, different nanoparticles simultaneously affect the mineralization and differentiation of osteoblast cells. The expression of ALP and deposition of calcium salts were increased, and the expression of osteoblast marker BMP-2, OCN, Col-1 and Runx-2 were upregulated by AuNPs through ERK/MAPK signaling pathway.[135] HANPs facilitated the expression of osteoblast related genes and proteins, and the BV/TV, BMD were improved in a zebrafish and within sagittal suture during expansion in rats.[136,137] In addition, HANPs modulated osteoblast cell line MC3T3-E1 differentiation through autophagy induction *via* mTOR signaling pathway.[138] Moreover, bioactive silica nanoparticles promoted osteoblast differentiation and mineralization through stimulation of autophagy and direct association with LC3 and p62, and enhanced BMD of young rats.[139] Sun *et al.*[140] designed ROS scavenging and responsive prolonged oxygen-generating hydrogels (CPPL/GelMA, an antioxidant enzyme catalase (CAT) and ROS-responsive oxygen-releasing nanoparticles (PFC@PLGA/PPS) co-loaded liposome (CCP-L) and GelMA hydrogels), which founded the osteogenic differentiation of MC3T3-E1 cell was promoted and showed excellent bone regeneration effect in a mice skull defect model *via* the Nrf2-BMAL1-autophagy pathway. Novel PEEK scaffolds modified with molybdenum disulfide (MoS_2) nanosheets and hydroxyapatite (HA) nanoparticles significantly reduced the viability of MG63 osteosarcoma cells and increased the mineralization of MC3T3-E1 cells, and promoted the osteogenesis capacity in bone defect repair.[141] At present, the application of magnetic nanoparticles in bone remodeling has received more attention due to good biosafety. Research have shown the MNPs coated with citric acid (MG@CA) have a good biocompatibility for ECs and MC3T3-E1 cells.[142] Tran *et al.*[143,144] Showed HA-coated Fe_3O_4 magnetic nanoparticles enhanced ALP activity, collagen synthesis and calcium deposition of osteoblast cells through increased amounts of fibronectin, a protein known to increase osteoblast functions. In addition, IONPs calcium phosphate improved osteogenic behavior of hDPSCs by activating the WNT/β-catenin signaling.[145] Yu *et al.*[146] developed a novel polysaccharide-based iron oxide nanoparticle (Fe_2O_3@PSC), which showed the ability to scavenge ROS and promote osteogenic differentiation of MC3T3-E1 cells through activating Akt-GSK-3β-β-catenin signaling. Study have shown that IONPs could be rapidly magnetized under exposed to an SMF, and the combination of IOPNs and SMF have a synergistically enhance or inhibit effect on the differentiation of osteoblasts and osteoclasts.[147] Marycz *et al.*[148] showed α-Fe_2O_3/γ-Fe_2O_3 nanocomposite (IOs) combined with 0.2 T SMF enhance the expression of osteogenic marker OPN, OCN, and Coll-1 in MC3T3 osteoblasts by activating integrin alpha-3 (INTa-3). IONPs-loaded bovine serum albumin (Fe_3O_4/BSA) particles exposed to 1 T SMF enhanced ALP activity and the expressions of COL-1 and OCN, and increased the osteogenic differentiation of MSCs.[149] However, 50 nm silver NPs exhibited strong cytotoxic effects on osteoblasts, but weak cytotoxic effects were observed for silver microparticles (3 μm). Such adverse effects may have deleterious effects on the biocompatibility of orthopedic implants and requires detailed evaluation prior to clinical use of orthopedic implants with silver nanoparticle coatings.[150] In summary, these results *in vitro* and *in vivo* suggest that NPs and NPs-loaded scaffolds promote osteogenic differentiation *via* the BMP-2/Smad, MAPK, Akt-GSK-3β-β-catenin, and Wnt/β-catenin signaling pathways (Fig. 3b).

To date, studies on the interaction between nanoparticles and osteoblasts are limited. Therefore, it is necessary to further evaluate the properties of nanoparticles to find more ways for bone-related diseases to achieve a positive balance in the process of bone remodeling.

Osteoclast

Osteoclasts are differentiated from mononuclear macrophages under the induction of macrophage colony-stimulating factor(M-CSF) and receptor activator of nuclear factor-κB ligand (RANKL), and are the component of bone tissue and mainly perform bone resorption.[151] Studies have shown that high expression of osteoclasts has a negative impact on bone tissue. Compared with osteoblasts and BMSCs, there are fewer research on the effects of nanoparticles on osteoclasts, and the underlying mechanism needs to be further clarified.

Studies have shown that AuNPs decreased the expression of osteoclast differentiation marker NFATC1, c-Fos and TRAP, inhibited osteoclast formation by suppression RANKL-induced signaling pathway, and prevented OVX-induced bone loss. Moreover, bisphosphonate-conjugated AuNPs showed more significant inhibition.[152,153] Silica nanoparticles restrained bone resorption through inhibiting NF-κB signaling pathway and phosphorylation of MAPK signaling pathway, osteoblasts activity and bone mineral density (BMD) were enhanced *in vivo* and prevented osteoporosis and fracture.[154–156] Yang *et al.*[123] shown BGN induced the expression of extracellular vesicles secreted by BMSCs, which could suppress osteoclast differentiation *in vitro* and alleviated osteoporotic bone loss *in vivo*. Moreover, studies have shown that Ferucarbotran and Feraheme inhibited the differentiation of osteoclast and OVX induced bone loss by regulating TRAF6-p62-CYLD signaling complex. Then, they showed hydroxyapatite coated SPIO (SPIO@HA) significantly prevented the bone loss of OVX mice

and increased BMD though activating MSC osteogenic differentiation *via* TGF-β, PI3K-AKT and calcium signaling pathway regulation.[157,158] Similarly, Fe_2O_3@PSC resisted osteoclast differentiation of Raw264.7 cells by scavenging ROS and blocking the MAPK and NF-κB pathways *in vitro* and prevent iron accumulation (IA)-related osteoporosis *in vivo*.[146] Zheng *et al.*[80] prepared Fe_2O_3@PSC loaded with alendronate, a new bone targeting IONP(BTNPs), which verified BTNPs revised bone loss caused by OVX, and the effects of BTNPs were more pronounced than alendronate alone. Marycz *et al.*[148] found α-Fe_2O_3/γ-Fe_2O_3 combined with SMF inhibited osteoclasts activity, and diminished the mRNA expression levels of MMP9. Moreover, α-Fe_2O_3/γ-Fe_2O_3 combined with SMF increased the expression of BAX, p21, Casp-3 in osteoclasts and decreased mitochondrial membrane potential, which revealed mitochondrial dysfunction was associated with osteoclast apoptosis. In addition, our previous studies showed that 1–2 T SMF and Ferumoxytol prevented the damage to bone microstructure in HLU mice. And the osteoclast differentiation was suppressed by decreasing the levels of ROS and blocking NF-κB and MAPK signaling pathways.[159] Chen *et al.*[160] designed a novel nanofluorescent carbon quantum dots (N-CDs), the results showed the osteoclastogenesis and bone resorption was attenuated *via* downregulating ROS level by impaired the activation of NF-κB and MAPK pathways. Therefore, NPs can inhibit osteoclast differentiation *via* the inhibition of MAPK and NF-κB signaling pathways, and decrease the levels of ROS (Fig. 3c).

In short, the differentiation process and potential mechanism of osteoclasts induced by different nanoparticles need to further study, so that to choose suitable and effective nanoparticles to provide a theoretical basis for the treatment of osteoporosis and other bone-related diseases.

Conclusion and future clinical prospects of NPs

In summary, this review discusses the different types of nanoparticles and application in the bone tissue engineering and the potential effects bone cells applications (Fig. 3). Currently, nanoparticles are at the forefront of nanotechnology. Some studies have shown that nanoparticles affected the activity of bone tissue-related cells such as BMSCs, osteoblasts and osteoclasts, and it will affect bone growth, resorption, and repair. However, the potential effects of nanoparticles on cells are different, depending on the different materials and properties. For example, magnetic nanoparticles can be targeted under an external magnetic field, reducing damage to normal tissue, and improving the precise delivery and treatment of drugs. In addition, SMF as a non-invasive physical therapy, some medical devices based on SMF have been used in the treatment of orthopedic related diseases, such as osteoporosis, fracture and *et al.* The combination of magnetic nanoparticles and SMF is a non-invasive, convenient, and inexpensive form of therapy for preventing osteoporosis and enhancing bone regeneration, which has the potential value for clinical application in the future.

Overall, nanoparticles have shown great potential as enhanced bone regeneration and tissue engineering. However, previous researches have mainly focused on animal and cell experiments, and few clinical studies have been conducted. The toxicity detection and safety evaluation are the primary evaluation criteria in clinical therapy. At present, most of the applications of nanoparticles in bone tissue have mainly focused on the study of biological effect, and the toxic dose *in vivo* have not been studied in more detail. Therefore, further research on the absorption, distribution, and metabolic pathways of nanoparticles are needed to understand their optimal use. Further explore the potential risks of nanoparticles to bone-associated cells to assess the impact of these risks on bone health and discover the underlying mechanisms, thereby providing a better theoretical basis for clinical translation application.

Author contributions

PS and GZ defined the focus of the review. GZ and CZ summarized studies. GZ drafted the manuscript. JY and JW participated in some parts of the final manuscript. GZ, SW, and PS revised the manuscript. All authors reviewed the final version of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest for this work.

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