Nanoparticles Reconstruct the Osteoporotic Microenvironment to Promote New Bone Formation Postprint

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Date: 2024-05-10T00:00:00+00:00

Abstract

Osteoporosis (OP) is a systemic bone disease characterized by reduced bone mineral density and altered bone microarchitecture, which increases susceptibility to fractures throughout the body. Although diverse therapeutic regimens exist for OP, their efficacy is strongly associated with patient compliance when long-term treatment safety is considered. Current clinical approaches for OP primarily target osteoclasts and osteoblasts, while overlooking the contributions of immune cells, cytokines, and inorganic components in establishing the aberrant osteoporotic microenvironment. Nanotechnology has revolutionized the paradigm for treating various diseases and exerted profound influence on drug and gene delivery. Presently, pharmacological interventions for OP are accompanied by corresponding adverse effects; consequently, novel therapeutic strategies are urgently needed. Therapeutic modalities employing nanoparticles to modulate osteoclast activity, differentiation, and apoptosis, as well as to intervene in osteoblast function, have recently emerged. Nanoparticles exert their therapeutic effects by loading anti-resorptive agents or incorporating osteoclast gene regulatory molecules. This review summarizes how various nanoparticles influence osteoblast- and osteoclast-related gene expression, reconstruct the osteoporotic microenvironment, and ameliorate bone microarchitecture, with the objective of providing innovative therapeutic approaches for osteoporosis management.

Full Text

1. Effects of Synthetic Nanoparticles on the Osteoporotic Microenvironment

In addition to anti-resorptive agents, bioactive nanomaterials offer an effective and potential approach for osteoporosis treatment and bone regeneration stimu-

lation [8-9]. First, as efficient therapeutic delivery vehicles, nanoparticles demonstrate enhanced intracellular delivery and improved bioavailability of therapeutics [10-11]. Furthermore, for bone tissue regeneration, nanomaterials feature large surface areas and surface roughness, which facilitate their interaction with adjacent proteins, cells, and inorganic components in the bone microenvironment [12]. For instance, mineral-based therapies using calcium-based materials [such as calcium phosphate, hydroxyapatite (HAP), or bisphosphonates] can induce osteoblast differentiation and promote bone tissue regeneration [13-14].

Synthetic nanoparticles are typically classified into organic nanoparticles composed of polymers, lipids, or proteins, and inorganic nanoparticles composed of ceramics or metals [15]. By combining with molecules that exhibit high affinity for bone extracellular matrix, such as bisphosphonates and tetracycline, these nanoparticles achieve bone-specific accumulation. Research has demonstrated that acidic amino acid oligopeptides or serine-containing repeat sequences promote bone resorption and formation, indicating specificity for different hydroxyapatite crystalline phases [16]. HAP, as an inorganic nanoparticle, exhibits remarkable similarity to bone extracellular matrix in mineral structure and possesses excellent osteoinductive properties, attracting significant attention. Implantation of HAP nanoparticles into glucocorticoid-induced osteoporotic rats with fractures resulted in superior bone formation compared to untreated osteoporotic rats after 24 weeks [17]. Additionally, silica nanoparticles can induce osteogenic differentiation of stem cells [18]. Mesoporous silica nanoparticles synthesized via modified Stöber methods have been utilized for small interfering RNA (siRNA) delivery targeting the Wnt/β-catenin signaling pathway, primarily by loading anti-SOST siRNA to silence the SOST gene. SOST encodes sclerostin, a bone formation inhibitor that enhances osteoclast number and activation state [19]. Implantation of 50 L nanoparticle dispersion into the bone marrow of ovariectomy-induced osteoporotic rats increased osteoblast markers after 5 days [20]. On the other hand, leveraging tetracycline' s high affinity for bone ECM, poly(lactic-co-glycolic acid) (PLGA) was employed to develop simvastatin-loaded tetracycline nanoparticles. Intravenous administration of 0.5 mg/kg every 2 days for 2 months in ovariectomy-induced osteoporotic rats promoted increased bone density and improved bone microarchitecture [21]. Hybrid lipid-PLGA nanoparticles were screened as carriers for oligonucleotides to silence sfrp1 expression, which is associated with inhibiting the osteogenic effects of bone morphogenetic protein 2 (BMP-2). Therefore, its silencing enhances the osteogenic action of growth factors. To evaluate the osteoinductive effects of these nanoparticles, they were intravenously injected into ovariectomy-induced osteoporotic mice (3 mg per dose, once monthly) for 3 months, with data demonstrating improved bone microarchitecture and increased bone density [22].

2. Synthetic Nanoparticles Regulating Osteoclasts for Osteoporosis Treatment

Osteoclasts play a crucial regulatory role in bone microstructure improvement. Targeted delivery of nanoparticle-based drugs through nanoparticle systems for osteoclast targeting or osteoclast activity modulation represents a promising strategy for OP prevention and treatment. Metal nanoparticles (GNP) are commonly employed for targeted drug delivery to osteoclasts, with studies confirming that inhibiting RANKL signaling pathway expression exerts intrinsic suppressive effects on osteoclast differentiation [23].

HEO et al. [24] implanted β-cyclodextrin-curcumin complex GNPs into bone marrow mononuclear cells in vitro, finding effective inhibition of osteoclast differentiation. In an ovariectomy (OVX)-induced osteoporotic mouse model, intragastric administration of 50 or 500 mol/L curcumin-loaded GNPs for 9 weeks weakened osteoclast activity, increased bone density, and avoided toxicity-related risks. LEE et al. [25] prepared alendronate-conjugated GNPs to enhance bone-targeted delivery, demonstrating synergistic effects between alendronate and gold nanoparticles. In vitro experiments showed inhibition of bone marrow macrophages (BMMs) and osteoclast differentiation, while oral administration of GNPs in OVX-induced osteoporotic mice exhibited superior bone resorption inhibition compared to single-drug treatments. Beyond metal nanoparticles, other nanoparticle systems have been utilized to target osteoclasts. CHEN et al. [26] applied fullerenol nanoparticles in lipopolysaccharide (LPS)-induced bone erosion mouse models and OVX-induced OP rat models. By altering osteoclast podosome patterns, both osteoclast activity and BMM differentiation into osteoclasts were inhibited without affecting osteoblast activity or observing toxicity, indicating promising anti-osteoporotic effects.

Recent studies reveal that most therapeutic molecules traditionally used for OP treatment have been incorporated into variable nanoparticle systems, with significantly enhanced therapeutic effects and no reported toxicities. This may be attributed to minimal accumulation in target tissues or short treatment durations with nanoparticles.

3. The Role of Extracellular Vesicles (EV) in Bone Reconstruction Microenvironment

EVs are complex phospholipid structures secreted by various cells, classifiable into microvesicles, apoptotic bodies, and exosomes based on size. Due to their lipid bilayer structure, low immunogenicity, excellent plasma stability, and high penetration capacity in cells and tissues, EVs possess tremendous potential as natural nanoparticles for drug delivery [27]. EVs are released by diverse cell types, including immune cells, mesenchymal stem cells, platelets, and tumor cells [28], playing active roles in intercellular communication, homeostasis, immune responses, programmed cell death, and even tumor progression [29]. Known to encapsulate active cargo that modifies cell surface activity, EVs serve as medi-

ators in intercellular communication and represent an essential communication mechanism in bone remodeling [30]. The specific cargo carried by EVs in the bone remodeling microenvironment includes microRNAs (e.g., miR-143-3p or miR-218), mRNAs involved in transcriptional regulation or kinase activity (e.g., BDP1 or ZEB2), proteins involved in osteoclast differentiation (e.g., RANK or RANKL), non-collagenous matrix proteins (e.g., osteocalcin), and osteogenic proteins (e.g., bone morphogenetic proteins or BMP), facilitating interactions among bone remodeling cells [31].

3.1 Communication Between Osteoblasts, Mesenchymal Stem Cells, and Surrounding Cells

During bone reconstruction, EVs play a vital role in inter-osteoblast communication. Osteoblast-generated extracellular vesicles containing miR-143-3p can inhibit osteoblast differentiation by suppressing Runt-related transcription factor activity, thereby reducing bone formation [32]. Research also demonstrates that EVs mediate communication between osteocytes and osteoblasts, with myostatin-treated osteocytes downregulating Wnt signaling pathways and reducing osteoblast differentiation through exosomes targeting osteoblast precursors [33]. EVs also facilitate communication between mesenchymal stem cells and osteoblasts. Exosomes released by osteoblasts can regulate Wnt signaling pathway activation to trigger BMSC differentiation into osteoblasts [34]. However, contrasting findings show that osteoblast-derived EVs obtained from OP patients alter cellular metabolism and negatively impact BMSC osteogenic differentiation [35].

Communication between mesenchymal stem cells is also regulated by EVs. Studies confirm that BMSC-derived EVs containing miR-22-3p enhance MSC osteogenic differentiation and increase bone formation by inactivating the MYC/PI3K/AKT signaling pathway [36]. Other research reveals that EVs acquired by MSCs during mid-to-late osteoblast differentiation stages can also promote BMSC osteogenic differentiation and bone formation [37]. It has been reported that exosomes secreted by osteogenic mesenchymal stem cells can induce osteogenic differentiation of other mesenchymal stem cells both in vitro and in vivo, suggesting that MSC-derived extracellular vesicles effectively regulate the osteogenic differentiation capacity of undifferentiated MSCs [38]. Additionally, mesenchymal stem cells can secrete EVs that regulate immune cell behavior.

3.2 Effects of Extracellular Vesicles on Osteoblast and Osteoclast Activity

Osteoblasts and osteoclasts play crucial roles in bone remodeling and can be combined with nanoparticles to regulate bone mass balance [30]. Table 1 below summarizes literature on the effects of EVs secreted by various cells on osteoclast differentiation and activity and their impact on skeletal status.

Table 1 Effects of EV Secreted by Multiple Cells on Osteoclast and Osteoblast Differentiation and Activity

Bioactive Factor	Cell Source	Effect on Osteoclasts	Effect on Osteoblasts	Skeletal Impact	Reference
miR-27a-5p	Epimedium-treated MSCs	-	Promotes osteogenic differentiation	Improves bone mass and microstructure	[39]
circRNA-0008542	Osteoblasts/prostate cancer cells	Promotes osteoclast differentiation	-	Promotes bone resorption	[40]
miR-92a-1-5p	Osteosarcoma cells	Promotes osteoclast differentiation	-	Promotes bone resorption, reduces bone formation	[41]
miR-19a-3p	Osteosarcoma cells	Promotes osteoclast differentiation	-	Promotes bone resorption, reduces bone formation	[28]
miR-125-b	M2-like macrophages	Inhibits osteoclast differentiation	-	Inhibits bone resorption	[42]
IL-10 mRNA	Mesenchymal stem cells	Inhibits osteoclastogenesis	-	Reduces bone resorption	[43]
miR-27a	Mesenchymal stem cells	Inhibits osteoclastogenesis	-	Improves bone density/structure	[44]

According to relevant studies, preconditioning cells (such as mesenchymal stem cells) with compounds like Epimedium (a traditional Chinese medicine known to improve bone remodeling) can generate exosomes with therapeutic properties. In this manner, intravenous injection of exosomes extracted from Epimedium-treated MSCs containing miR-27a-5p at a dose of 100 ng/mL for 12 weeks improved bone mass and microstructure in an ovariectomy OP rat model by promoting osteogenic differentiation [39]. Osteoblast-secreted EVs can effectively regulate osteoclast activity. For example, osteoblast matrix vesicles containing miR-125b inhibit osteoclast formation in vitro, and mice treated with

these matrix vesicles show reduced osteoclastogenesis [42]. Similarly, exosomes containing miR-503-3p hinder osteoclast differentiation in vitro by downregulating heparanase gene expression [45]. However, other studies have found that osteoblast-derived EVs containing RANKL exhibit pro-osteoclast effects [46].

Likewise, exosomes transporting circular RNA enhance osteoclast differentiation by promoting RANK gene expression via circRNA-0008542, thereby increasing bone resorption in vivo [40]. It has also been reported that osteoblasts can regulate their own behavior; during differentiation, weekly intravenous administration of 3 mg EV/kg for four weeks demonstrated potential for OP prevention by promoting osteoblast differentiation in an OVX osteoporotic mouse model [37].

Furthermore, endothelial cells can influence osteoclast and osteoblast differentiation. EVs obtained from bone marrow-derived endothelial progenitor cells have been found to help reduce corticosteroid-induced osteoblast damage by inhibiting the ferritin pathway, thereby alleviating steroid-induced osteoporosis in mice [47]. Weekly intravenous injection of 50 g EV once per month for 1 month reduced femoral head necrotic tissue formation while improving trabecular thickness and connectivity [47]. It is well-established that osteoclasts can regulate their own behavior, as exosomal EVs containing RANK isolated from osteoclasts administered at a dose of $5\$\times10^{7}EVs/mLondays1,4,and6havebeenfoundtohinderosteoclastogenesisin1\ \$$,25-dihydroxyvitamin D3-treated bone marrow [48]. On the other hand, mesenchymal stem cells can also modulate osteoclast activity. Additionally, EVs derived from cancer cells have been reported to play a role in bone resorption. For instance, osteosarcoma cell-derived EVs containing microRNA miR-19a-3p or miR-148a and miR-21-5p have been found to enhance osteoclastogenesis and bone resorption in vitro when administered to Raw264.7 cells at 15 g/mL for 4 days and at 25 g/mL for 6 days [28]. Moreover, the higher presence of miR-19a-3p-loaded EVs may account for the bone destruction and osteopenia observed in an osteosarcoma mouse model [28]. Therefore, EVs obtained from various cell types and sources constitute a promising tool for improving the management of bone-related diseases such as OP by effectively regulating osteoclast and osteoblast functions. However, recent studies indicate that clinical translation of EVs has been hindered by issues related to their isolation and purification. Furthermore, considering their heterogeneous composition and various effects they can trigger, some authors argue that further research is needed before clinical EV use in OP [49].

This review has identified several nanoparticles from the literature that have been screened for OP prevention and treatment. Similar to conventional OP therapies, they primarily focus on inhibiting bone resorption or promoting bone formation. To this end, nanoparticles mainly aim to demonstrate therapeutic effects on osteoclasts or osteoblasts. Therefore, targeting osteoclasts with natural or synthetic nanoparticles is considered an alternative approach to control osteoclast behavior for OP prevention and treatment. Nanoparticles exert their ther-

apeutic effects primarily by loading anti-resorptive molecules or incorporating genes that regulate osteoclasts, without displaying the adverse effects observed with conventional anti-resorptive drugs. Thus, controlling osteoclasts indeed helps manage bone resorption and OP-related bone quality decline. Moreover, the use of natural nanoparticles holds tremendous potential in bone remodeling and offers excellent prospects for OP prevention and treatment. However, research in this field remains in its initial stages, though EVs demonstrate critical roles in bone homeostasis. Future studies should further investigate nanoparticle utilization and OP prevention strategies to provide novel therapeutic approaches for osteoporosis management.

Author Contributions: MA Binxiang conceived and designed the article and drafted the manuscript; DENG Qiang, ZHANG Yanjun, PENG Randong, YAO Pengcheng, and CHANG Bin conducted feasibility analysis and revised the manuscript; PENG Randong, YAO Pengcheng, and CHANG Bin collected and organized literature/materials; MA Binxiang and DENG Qiang were responsible for quality control and final review, with overall responsibility and supervision.

Conflict of Interest: The authors declare no conflict of interest.

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(Received: November 16, 2023; Revised: February 20, 2024) (Editor: JIA Mengmeng)

Note: Figure translations are in progress. See original paper for figures.