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Review Article

Therapeutic potential of stem cell-derived exosomes for bone tissue regeneration around prostheses

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ABSTRACT

Artificial joint replacement is a widely recognized treatment for arthritis and other severe joint conditions. However, one of the primary causes of failure in joint replacements is the loosening of the prosthesis. After implantation, wear particles between the implant and the adjacent bone tissue are the principal contributors to this loosening. Recently, exosomes have garnered significant interest due to their low immunogenicity and effective membrane binding. They have shown potential in promoting bone regeneration via the paracrine pathway. This review examines the role and mechanisms of exosomes derived from mesenchymal stem cells (MSCs) in bone regeneration, their impact on the integration of various implants into surrounding bone tissue and current challenges and future directions for the clinical application of exosomes.

The Translational Potential of this Article: Emerging evidence suggests that mesenchymal stem cell-derived exosomes may offer a promising therapeutic strategy for aseptic prosthesis loosening, potentially mediated through mechanisms such as modulation of inflammatory responses, suppression of osteoclastogenesis, enhancement of osteogenic differentiation and facilitation of bone regeneration. Preclinical studies further indicate that the therapeutic potential of these extracellular vesicles could be optimized through bioengineering strategies, including surface modification and cargo-loading techniques, warranting further investigation to advance their clinical translation.

1. Introduction

Currently, artificial joint replacement stands as an effective treatment for end-stage joint injury. It offers pain relief, restoration of normal joint function, extended joint lifespan, and improved quality of life, significantly enhancing patient prognosis [1]. However, despite proven clinical efficacy, some patients experience prosthesis loosening post-joint replacement, diminishing the success rate of implantation [2,3]. Revision surgery, commonly employed in clinics to address loosening, bears several disadvantages. It not only prolongs treatment time but also inflicts secondary harm on patients. Hence, there is a pressing need for a new therapeutic method to resolve the issue of aseptic prosthetic loosening.

Numerous scholars have conducted extensive studies on prosthesis loosening, revealing that the implanted prosthesis can not only generate biologically active wear particles through friction with the surrounding bone tissue, but also produce biologically active wear particles through friction between prosthetic components themselves [4,5]. Su et al. found that in patients undergoing total hip arthroplasty, wear particles generated between the artificial femoral head and the acetabular liner are phagocytosed by macrophages, leading to the production of a large number of cytokines. These cytokines activate osteoclasts, causing

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osteolysis around the prosthesis, which in turn leads to prosthesis loosening [4]. Furthermore, Liu et al. discovered that stress shielding (SS) is considered the primary mechanical cause of femoral stem loosening after total hip arthroplasty (THA). Replacing a part of the femur with a hip implant disrupts the natural load transfer along the shaft and introduces a new interface between the implant and the bone, through which the load must be transferred. A stiffer femoral stem bears a greater load than the surrounding bone, leading to a reduction in pressure transmitted to the proximal femur, which is known as SS [5]. Additionally, clinical data confirm a link between the size of wear particles and osteolysis:a decrease in wear particle size may increase their bioactivity and local concentration, thereby increasing the degree of osteolysis [6].

These wear particles can interact with osteoclasts in bone tissue, promoting osteoclast differentiation and ultimately leading to osteolysis around the prosthesis, resulting in loosening [3,7]. Additionally, research suggests that macrophages can engulf wear particles, triggering inflammation and subsequent osteolysis [8,9]. Furthermore, a model for prosthesis loosening has been developed, indicating that inadequate initial integration with surrounding bone tissue can lead to implant integration failure [10]. However, the mechanisms behind this phenomenon are still not fully understood and further research is needed. At present, in addition to aseptic loosening caused by wear particles generated from the friction between the implant and the surrounding bone tissue, studies have shown that the mechanism behind aseptic loosening may also be due to bone resorption and bone dissolution caused by stress shielding and wear particles [7].

2. Exosomes of mesenchymal stem cell

Mesenchymal stem cells (MSCs) are pluripotent stem cells capable of self-renewal and differentiation into various cell types, including osteoblasts and chondrocytes [11,12]. MSCs are ubiquitously found throughout the body and can be isolated from bone marrow, adipose tissue, synovial membranes, and umbilical cords, among other sources [13–16]. Owing to their ease of isolation, ability to be expanded in vitro, and pluripotent properties, MSCs have become one of the most frequently utilized stem cells in cell therapy [17–22]. Research has demonstrated that MSCs can significantly enhance the treatment outcomes for conditions such as bone defects and osteonecrosis [23]. Mesenchymal stem cells (MSCs) participate in the treatment of bone defects and osteonecrosis through various mechanisms. For instance, MSCs can directly differentiate into osteoblasts, chondrocytes and other cell types, directly participating in the repair and reconstruction of bone tissue [24]. Additionally, MSCs are capable of secreting a variety of growth factors and cytokines, such as bone morphogenetic proteins (BMPs) and vascular endothelial growth factor (VEGF). These factors can promote angiogenesis, cell proliferation and differentiation, thereby facilitating the repair of bone tissue [25]. The combined action of these mechanisms promotes the repair and regeneration of bone tissue.

However, the high costs associated with MSC production and storage, among other factors, limit their clinical application [26]. Recent studies have highlighted that MSCs primarily exert their therapeutic effects through a paracrine mechanism, with exosomes playing a pivotal role [27,28]. Therefore, exosomes represent a promising new approach for treating conditions such as bone regeneration in the future.

Exosomes are secreted by nearly all cell types and are found throughout the body in various fluids such as breast milk, semen, saliva, urine, sputum, cerebrospinal fluid, and serum. They are bilayer lipid extracellular vesicles originating from cells or tissues, typically ranging in size from 30 to 150 nm [29,30]. As lipid vesicles secreted by cells, exosomes exhibit low immunogenicity and exceptional membrane-binding properties, which enhance their functionality within the body. Exosomes contain a diverse array of bioactive molecules, including nucleic acids, proteins, and lipids. These components enable them to participate in and regulate a variety of biological processes through paracrine pathways [31]. Exosomes derived from mesenchymal stem cells (MSC-exos) mimic some physiological functions of the stem cells themselves. They carry soluble molecules such as VEGF which are involved in the regulation of angiogenesis and immune responses [32]. Exosomes were first discovered in 1983 and were initially thought to be merely cellular waste products [33]. With the deepening of research on exosomes, it has been confirmed that exosomes can stimulate the regeneration of tissues and organs, including the heart, lung, endometrium, liver and kidney [34–38]. This ability makes exosomes a very promising treatment for bone regeneration.

3. Bioactive substances exosomes that promote bone regeneration

Exosomes contain an array of bioactive substances, including nucleic acids, proteins, lipids, and various soluble metabolites. The composition of exosomes varies depending on the parental cells from which they are derived, which in turn affects their therapeutic potential. To address this variability, some researchers have modified the contents of exosomes by pre-treating the parental cells. Exosome can be engineered through surface modification, endogenous loading and exogenous loading. Surface modification involves displaying targeting ligands, such as specific antibodies or peptides, on the surface of exosomes through genetic engineering or chemical modification techniques to enhance their targeting ability. Endogenous loading involves genetically engineering the cells that secrete exosomes to produce exosomes carrying target molecules. Exogenous loading,on the other hand, involves loading specific molecules into exosomes through methods such as electroporation, sonication, lipid chemical reactions or membrane protein chemical reactions. For example, some researchers have found that exosomes obtained from mesenchymal stem cells (MSCs) after hypoxic preconditioning can enhance angiogenic responses, thereby better promoting bone regeneration [39]. This approach tailors the exosomes to meet specific therapeutic needs in different environments (Fig. 1).

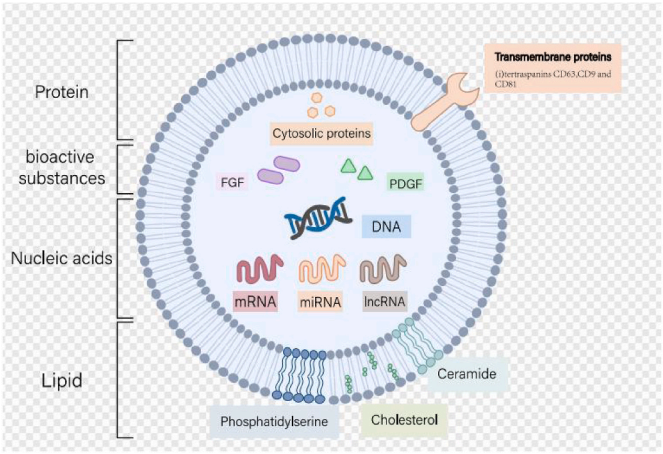

Fig. 1. Components of exosomes and their role in repairing bone damage. This figure introduces the basic structure of exosomes, including proteins, nucleic acids, lipids and bioactive substances. Proteins include transmembrane proteins, cytoplasmic proteins and others. Nucleic acids consist of DNA and RNA, RNA can be further divided into lncRNA, miRNA and mRNA, where miRNA and mRNA are hot topics in exosome research promoting bone regeneration. Lipids are important components of the exosome membrane, commonly divided into phosphatidylserine, cholesterol and ceramide. Bioactive substances are diverse and typically participate in various biological reactions, playing different biological functions. Here, only two substances related to bone regeneration, FGF and PDGF, are mentioned.

3.1. Nucleic acid

Exosomes are carriers of both RNA and DNA, allowing these nucleic acids to be transported to other cells, where they can regulate gene expression and protein synthesis [40]. While DNA is known to be transmitted through exosomes, its specific functions remain largely undefined. RNA within exosomes includes various forms such as mRNA, lncRNA, and miRNA [40]. mRNA acts as an intermediary in transcription, carrying the information needed for protein synthesis. Previous research has demonstrated that MSCs can influence the gene expression of target cells through the mRNA contained in their exosomes [41]. lncRNA, or long non-coding RNA, is involved in regulating gene expression, chromatin remodeling, and other biological processes [42]. For instance, studies have shown that the lncRNA H19 in MSC-exos can enhance the healing of diabetic foot ulcers by promoting the upregulation of phosphatase and tensin homolog (PTEN) via microRNA-152-3p [43]. Despite these findings, research on lncRNA within MSC-exos is still in its early stages, and our understanding of the variety and functions of lncRNA they contain remains limited.

miRNA has gained significant attention in recent years due to its potential to promote bone regeneration. Numerous in vitro studies have validated the osteogenic capabilities of specific miRNAs. In Table 1, we have summarized some of the sources and effects of the RNAs on bone regeneration. For instance, exosomes that overexpress miR-381 have been shown to enhance the chondrogenesis of MSCs [44]. Similarly, miRNA-196a has been identified as a critical regulator in the bone regeneration process [45]. Currently, many studies focus on modifying the genetic content of parent cells using viral vectors and plasmids to produce exosomes with specific properties. For example, research involving the treatment of bone marrow mesenchymal stem cells (BMSCs) with lentivirus to overexpress miR-140-3p has yielded exosomes that effectively promote the remodeling of bone defects [46]. These advancements highlight the therapeutic potential of engineered exosomes in regenerative medicine. Through the release of exosomes, nucleic acids contained within MSC-exos can be delivered to other cells, influencing the function and gene expression of these target cells. The presence of these nucleic acids enables exosomes to play a crucial role in bone regeneration. Some research has successfully engineered MSC-exos to be rich in various types of nucleic acids, thereby enhancing their therapeutic efficacy [41]. Only a few specific types of miRNA have been identified to directly or indirectly affect the expression of key osteogenic and angiogenic molecules in the bone repair process, showing a dual role in promoting osteogenesis and angiogenesis. miR-29a is one of them [47].

Table 1
Bone regeneration-related RNAs and their functions.

RNAs	Function	Reference
miR-381	Exosomes overexpressing miR-381 promote chondrogenesis of mesenchymal stem cells in vitro.	[47]
miRNA-196a	As a critical regulator in the bone regeneration process	[48]
miR-140-3p	Exosomes overexpressing miR-140-3p were found to promote the remodeling of bone defects.	[49]
miR-29a	Exhibiting a dual role in promoting osteogenesis and angiogenesis.	[50]
miR-128-3p	Elevated levels of miR-128-3p can decrease therapeutic efficacy and inhibit fracture healing by suppressing Smad5 expression	[51]
miR-29a	inhibit the expression of noggin, a natural antagonist of bone morphogenetic proteins, thus activating the BMP/Smad signaling pathway and enhancing the osteogenic properties of BMSC-exos	[52]
miR-31a-5p	suppresses osteogenesis but also promotes osteoclast differentiation, leading to bone loss	[53]
miR-21-5p	suppresses osteoclast differentiation and decreased the expression of genes associated with bone resorption	[54]
let-7b-5p	suppresses osteoclast differentiation and decreased the expression of genes associated with bone resorption	[54]
miR-27a-3p	modulate macrophage behavior	[55]
miR-3470b	Macrophage-derived exosomes(M-exos)modulate osteolysis by targeting the TAB3/NF-κB pathway through miR-3470b,directly regulating inflammatory bone resorption in aseptic prosthetic loosening.	[56]
lncRNA H19	lncRNA H19 in MSC-exos can enhance the healing of diabetic foot ulcers by promoting the upregulation of phosphatase and tensin homolog (PTEN) via microRNA-152-3p	[43]
LncRNA MALAT1	BMSCs-derived exosomal MALAT1 enhances osteoblast activity in osteoporotic mice by mediating the miR-34c/SATB2 axis	[57]
lncRNA NEAT1	HUVECs-derived exosomes enable transmitting NEAT1 to alleviate inflammation by inducing M2 polarization of macrophages	[58]
lncRNA HOTTIP	lncRNA HOTTIP accelerated osteogenic differentiation and angiogenesis by interaction with TAF15	[59]
lncRNA TUG1	lncTUG1 from BMSCs may be transported into osteoblasts via exosomes, and increased lncTUG1 in osteoblasts may upregulate Anxa8 expression via reducing the inhibiting action of miR-22-5p on Anxa8, which ultimately leads to enhanced osteoblast differentiation and activity.	[60]

This table lists some of the RNAs related to bone regeneration mentioned in this article, and also reveals the pathways through which they affect bone regeneration. The table includes both RNAs that promote bone regeneration and those that inhibit it.

3.2. Protein

The MSC-exos encompass a diverse array of proteins. These proteins are capable of being transferred to other cells through the release of exosomes, thereby fulfilling a spectrum of biological functions. Notably, proteins belonging to the tetraspanin superfamily, including CD9, CD63, and CD81, are prominently displayed on the surface of exosomes and serve as specific markers thereof [48]. Furthermore, exosomes harbor various annexins, primarily involved in the formation of the exosomal membrane and intraluminal structures, as well as in mediating interactions and signal transduction between exosomes and target cells [49]. Heat shock proteins (HSPs), a category of protective proteins induced during cellular stress conditions, are widely acknowledged as pivotal factors in managing cellular stress and preserving cellular homeostasis. Several studies have identified the presence of HSP70 and HSP90 within exosomes, underscoring their role in the aforementioned functions [50,61]. Additionally, MSC-derived exosomes contain bioactive molecules such as fibroblast growth factor (FGF) [62–64] and platelet-derived growth factor (PDGF) [65,66], which facilitate cell proliferation, differentiation, and repair processes. Moreover, tumor necrosis factor (TNF) has been implicated in modulating immune responses within MSC-derived exosomes [67]. The proteins encapsulated within MSC-derived exosomes exhibit multifaceted capabilities in regulating various biological processes, encompassing cell proliferation, differentiation, migration, inflammatory responses, and immune modulation.

The protein composition of MSC-exos varies depending on cell type, state, and the microenvironment. Consequently, some studies have engineered exosomes enriched with specific proteins to enhance the efficacy of MSC-exos [68].

3.4. Lipid

MSC-exosomes are rich in various lipid components, which are crucial for their formation, function, and interactions. Among these lipids, phospholipids such as phosphatidylcholine and phosphatidylserine are key constituents of the exosomal membrane. These phospholipids contribute to the structural integrity and stability of the exosomes [69]. Cholesterol, another significant lipid, is prevalent within exosomes and plays a vital role in regulating and maintaining the

structure of their membranes. It influences the fluidity and permeability of the membranes, thereby affecting how exosomes interact with target cells [70]. Additionally, fatty acids, both saturated and unsaturated, are involved in the biosynthesis and functional expression of exosomes. These acids may also influence the interactions between exosomes and target cells [71]. Furthermore, sphingolipids, which are known for their roles in signal transduction and cell recognition, are present in exosomes and likely participate in the signaling and interaction processes between exosomes and target cells [72].

The lipid composition of exosomes can differ based on the type of cell, its state, and the surrounding environment. Despite being among the least studied elements, lipids are critical to the structural and functional integrity of exosome membranes. Many aspects of their roles and mechanisms remain to be uncovered.

3.5. Others

Exosomes can be sourced from a variety of tissues, including bone marrow, adipose tissue, synovial membrane, and umbilical cord [13–16]. The composition of MSC-exos varies depending on their source, which in turn affects their therapeutic efficacy. Research has indicated that MSC-exos can enhance fracture healing, whereas exosomes derived from HOS, an osteosarcoma cell line, do not exhibit this capability [73]. Moreover, the effectiveness of exosomes can also vary with the age of the individual. Studies have noted a diminished therapeutic function in exosomes from aged rats in models of femoral fracture (Table 1) [74]. Additional research identified an increase in miR-128-3p levels in MSC-exos associated with cellular aging. Elevated levels of miR-128-3p can decrease therapeutic efficacy and inhibit fracture healing by suppressing Smad5 expression [74]. This suggests that future research could focus on characterizing and selecting exosomes based on their contents and therapeutic potential from various sources.

4. Effects of exosomes on bone regeneration related cells and bioactive substances

Bone regeneration is a multifaceted biological process involving a range of cells and molecules. Initially, MSCs differentiate into osteoblasts and chondrocytes, which then collaborate with osteoclasts to regulate bone formation [75]. Concurrently, angiogenesis plays a crucial role as new blood vessels supply oxygen and nutrients essential for bone growth, while also removing metabolites that facilitate bone regeneration. Thus, stimulating the growth and proliferation of vascular endothelial cells is pivotal for enhancing bone regeneration [76]. Moreover, since the body's immune system responds to exogenous implants, the involvement of immune cells is also critical in the osteogenic process [51] (Fig. 2).

The coordinated involvement of osteoblasts, osteoclasts,vascular endothelial cells, immune cells, and MSCs ensures the smooth progression of bone regeneration. The addition of exosomes that can modulate the functions of these cells can enhance the therapeutic effects of bone regeneration. The various osteogenic factors contained within exosomes can directly act on osteoblasts to promote their proliferation and differentiation. Components such as miRNAs and proteins within exosomes can regulate signaling pathways within osteoblasts and osteoclasts, thereby enhancing the osteogenic activity of osteoblasts and inhibiting the formation and function of osteoclasts. In addition, exosomes can carry factors that directly act on osteoclasts, inhibiting their differentiation and activity and reducing bone resorption. For vascular endothelial cells, the growth factors carried by exosomes can promote the proliferation and migration of vascular endothelial cells, accelerating the formation of new blood vessels and providing adequate blood supply and nutritional support to the bone defect area, thereby promoting angiogenesis. Regarding immune cells, some anti-inflammatory factors carried by exosomes can inhibit the proliferation of inflammatory cells and the release of inflammatory factors, reducing the inflammatory

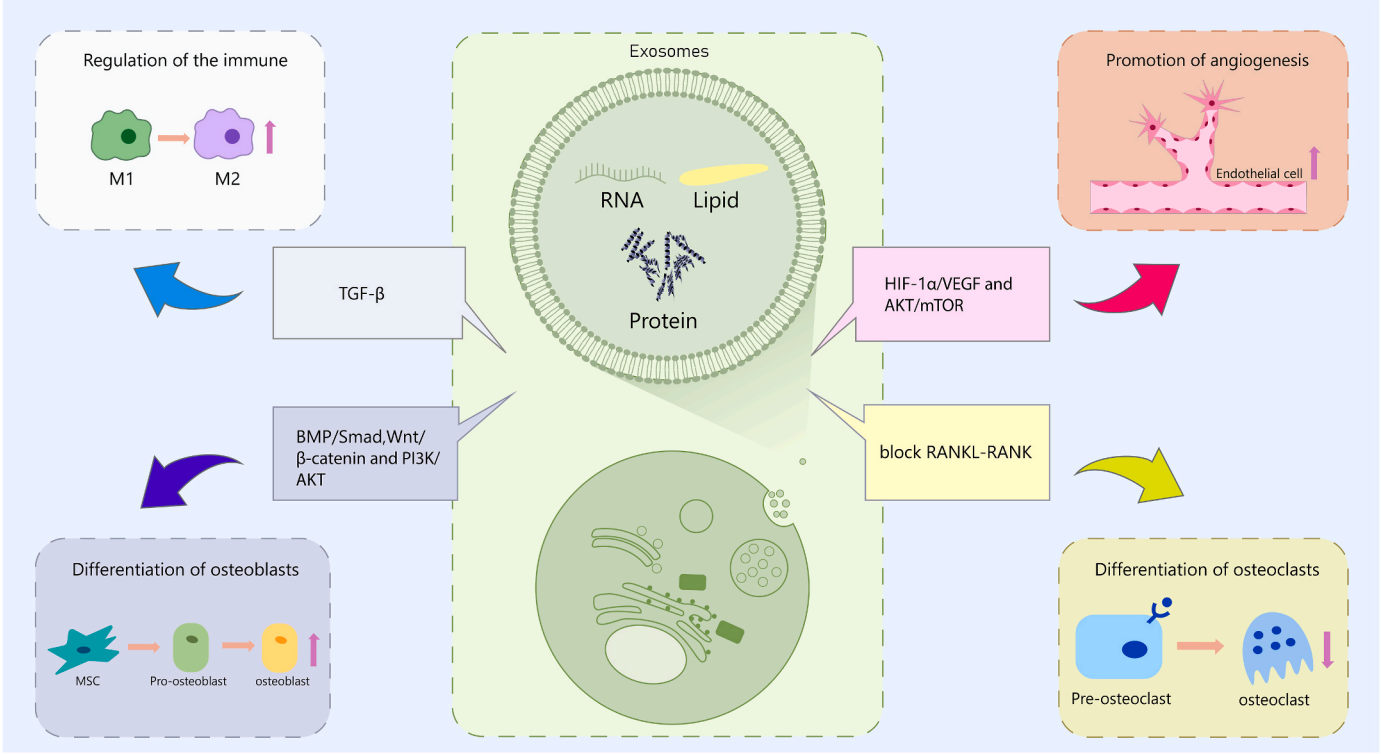

Fig. 2. The function of exosomes.
Exosomes regulate immunity, promote angiogenesis, and promote differentiation of osteoblasts and osteoclasts in bone regeneration. The upward purple arrow represents the promotion of proliferation differentiation of immune cells, osteoblasts and vascular endothelial cells, and the downward purple arrow represents the inhibition of osteoclast differentiation.

response at the bone defect site and creating a favorable microenvironment for bone repair. Moreover, exosomes can also regulate the polarization state of macrophages, promoting their transformation into M2 type (anti-inflammatory) macrophages and inhibiting the activity of M1 type (pro-inflammatory) macrophages, thus exerting an anti-inflammatory effect. Finally, components such as miRNAs and proteins within exosomes can also promote the migration and recruitment of bone marrow MSCs, providing more stem cell sources for bone repair [77].

4.1. Exosomes and osteoblasts

For bone formation, osteoblasts, which originate from bone marrow mesenchymal stem cells, are critical [78]. Alkaline phosphatase (ALP) is a bone-specific enzyme, and its expression level is directly proportional to the differentiation level of osteoblasts. Consequently, ALP is often used as an early marker of bone formation. Osteocalcin (OCN) is another bone-specific protein primarily deposited in the bone matrix by osteoblasts, typically serving as a marker of late bone formation [79]. Furthermore, Runt-related transcription factor 2 (Runx2) and Osterix (Osx) are important markers for osteogenic differentiation. For bone repair, MSC-exos promote the proliferation, differentiation and mineralization of osteoblasts [80]. Researchers have used exosomes to deliver signals to osteoblasts and activate various signaling pathways, including BMP/Smad, Wnt/-catenin, and PI3K/AKT, to enhance osteoblast proliferation and differentiation [81]. For instance, research involving bone marrow mesenchymal stem cell-derived exosomes (BMSC-exos) transplanted at femoral nonunion fracture sites in rats showed increased levels of BMP-2, Smad1, RUNX2, and OCN, facilitating the healing process. Conversely, the addition of BMP inhibitors resulted in decreased levels of these factors and impaired fracture healing, indicating that BMSC-exos promote osteogenesis and fracture healing through the BMP-2/Smad1/RUNX2 signaling pathway [82]. However, not all miRNAs enhance bone formation. For example, down-regulation of miR-29a can inhibit the expression of noggin, a natural antagonist of bone morphogenetic proteins, thus activating the BMP/Smad signaling pathway and enhancing the osteogenic properties of BMSC-exos (Table 1) [83]. Conversely, overexpression of miR-31a-5p derived from senescent BMSC-exos not only suppresses osteogenesis but also promotes osteoclast differentiation, leading to bone loss (Table 1) [84]. Furthermore, studies involving the injection of BMSC-exos into the tail vein of a rat model have shown that these exosomes can promote β-catenin expression in MSCs, reducing bone loss compared to controls without exosome treatment. This suggests that BMSC-exos might also promote bone regeneration by activating the Wnt/β-catenin signaling pathway [52]. However, evidence also indicates that Wnt/β-catenin might inhibit osteogenesis, suggesting that further research is needed to clarify this pathway's role [53]. Further, gene expression profiling and bioinformatic analysis have shown that human bone marrow stem cells (hBMSCs) respond to exosome-induced osteogenesis through the PI3K/AKT signaling pathway [85].

4.2. Exosomes and osteoclasts

Bone formation is a coordinated process that involves not only osteoblasts but also osteoclasts. Osteoclast differentiation is induced by the binding of the receptor activator of nuclear factor-κB ligand (RANKL) to its receptor RANK, and these activated osteoclasts then secrete proteolytic enzymes and acids to fulfill their roles [54]. Research involving exosomes derived from adipose stem cells (ASC-exos) has demonstrated their potential in modulating bone dynamics. When ASC-exos were injected intravenously into a mouse model of osteoporosis, they were found to inhibit osteoclast differentiation. Further analysis revealed that osteoprotegerin (OPG) present in ASC-exos played a significant role in this inhibition by blocking the RANKL-RANK interaction. Additionally, miR-21-5p and let-7b-5p within ASC-exos contributed to the suppression of osteoclast differentiation and decreased the expression of genes associated with bone resorption (Table 1) [54]. Currently, there are limited studies focusing on the mechanisms through which exosomes influence osteoclasts.

4.3. Exosomes and vascular endothelial cells

Bone regeneration is intricately linked with vascular regeneration, as the newly formed blood vessels provide essential nutrients, oxygen, hormones, and growth factors that are crucial for bone healing [86]. HIF-1α/VEGF pathway is well recognized for its role in angiogenesis [87], suggesting that HIF-1α and VEGF could be key angiogenic regulators within MSC-exos. Research involving exosomes derived from human umbilical cord mesenchymal stem cells (HUMSC-exos) demonstrated that when these exosomes were introduced at the site of femoral fractures in rats, there was an observable enhancement in angiogenesis and accelerated fracture healing [88]. Further investigations into this mechanism revealed that angiogenesis was significantly reduced when HIF-1α was inhibited using specific siRNA, indicating the pivotal role of HIF-1α in the angiogenic capability of the exosomes. Additionally, studies have shown that activating HIF-1α in exosomes through hypoxia preconditioning can promote vascular regeneration in vivo [89]. Another pathway implicated in the promotion of angiogenesis by exosomes is the AKT/mTOR pathway. Studies involving BMSC-exos that were pretreated with a low dose of dimethoxyglycine (DMOG) and then transplanted into a rat model with a skull defect showed a significant enhancement in angiogenic activity. In vitro experiments further confirmed that DMOG-stimulated BMSC-exos promote angiogenesis and osteogenesis primarily by targeting the AKT/mTOR pathway [90].

At present, it has been found that mitochondria in bone cells can promote angiogenesis in bone tissue [91]. At the same time, some scholars have found that mitochondria can be transferred into target cells through transient cell connection, extracellular vesicle encapsulation, and free exosome capture [92]. Therefore, it is possible to improve the angiogenesis capacity in bone tissue by loading the mitochondria of bone cells into the exosomes of mesenchymal stem cells.

4.4. Exosomes and immune cells

After prosthesis implantation, one of the factors contributing to implant failure is the reaction of immune cells to wear particles. Previous research has shown that exosomes derived from degenerated nucleus pulposus cells, which carry miR-27a-3p, can modulate macrophage behavior (Table 1) [55]. Consequently, the manipulation of immune cells through exosomes represents a promising strategy to mitigate prosthesis implantation failures.

Macrophages are pivotal in regulating the bone immune microenvironment and play distinct roles at different stages of fracture healing. In the inflammatory phase, M1 macrophages become activated, exhibiting phagocytic activity and releasing pro-inflammatory cytokines including TNF, IL-1β, IL-6, and IL-12. These cytokines are crucial for early and middle-stage osteogenesis. In later stages of healing, M2 macrophages release pro-regenerative cytokines to create an anti-inflammatory environment that promotes tissue differentiation and blood vessel growth [93]. The presence of M2 macrophages is therefore more favorable for bone regeneration. Research has demonstrated that in a mouse model of bronchopulmonary dysplasia, the administration of BMSC-Exos reduced the levels of pro-inflammatory factors such as TNF-α, IL-6, and CCL5 secreted by M1 macrophages and increased the expression of anti-inflammatory factors like arginase-1 (Arg-1), indicative of a shift from M1 to M2 macrophages [94]. Research has reported similar findings using exosomes from human adipose stem cells, which are also capable of promoting the transformation of M1 macrophages into M2 macrophages [95]. A 2023 study has found that exosomes derived from bone marrow mesenchymal stem cells (BMSC-Exos) promote the M2 polarization of macrophages and inhibit M1 polarization

[96].

4.5. Exogenous exosomes and endogenous bone marrow mesenchymal stem cells

MSCs have the capacity to differentiate into osteoblasts, making the exploration of exosomal effects on MSCs crucial. It has been observed that when MSCs from the jaw bone (BMSC-J) are co-cultured with MSCs from the iliac bone (BMSC-I), the exosomes secreted by BMSC-J enhance the ALP activity, osteogenic gene expression, and new bone formation in BMSC-I in vivo. Conversely, when siRNA is used to inhibit exosome secretion, these osteogenic effects are diminished [97]. Additionally, while studies have begun to analyze the interactions between exosomes and MSCs [98], the specific mechanisms underlying these interactions remain insufficiently understood and warrant further investigation.

Some researchers have injected Wharton's jelly derived from the umbilical cord, which contains exosomes, into patients to explore the safety and effectiveness of umbilical cord-derived Wharton's jelly in treating osteoarthritis [99]. Additionally, there have been studies on the intradiscal injection of platelet-rich plasma enriched with exosomes for the treatment of chronic lower back pain. Although there are some clinical trials investigating the therapeutic effect of exosomes on bone-related inflammation, the related research on the treatment of bone regeneration by exosomes needs to be conducted.

5. Biological modification of MSC exosomes for bone repair

5.1. Engineered MSC exosomes

Given that the contents of exosomes secreted by different MSCs vary and that different diseases require specific therapeutic agents, there is a demand for the production of diverse types of exosomes. This necessity has led to the concept of engineering exosomes. By manipulating the contents of exosomes, it is possible to create exosomes enriched with specific components tailored to meet varied therapeutic needs. Several studies have successfully generated exosomes rich in various miRNAs that enhance bone formation, thereby improving the therapeutic potential of exosomes. For example, some research has combined exosomes from ATDC5 cells with plasmids encapsulating VEGF genes to produce engineered exosomes. These engineered exosomes not only induced osteogenic differentiation of MSCs but also facilitated the release of VEGF genes, contributing to vascular remodeling [100]. Furthermore, other studies have shown that exosomes from human gingival mesenchymal stem cells, pretreated with TNFα, can enhance M2 macrophage polarization and inhibit periodontal bone loss [101]. It was also found that TNF-α pretreatment significantly increased the secretion of exosomes from IPFP-MSCs compared to untreated BMSCS. The underlying mechanism involves the activation of the PI3K/AKT signaling pathway in IPFP-MSCs by TNF-α pretreatment, leading to the upregulation of autophagy-related protein 16-like 1 (ATG16L1), which subsequently promotes exosome secretion. Additionally, engineered exosomes loaded with bone morphogenetic protein 2 (BMP-2) from BMSCs have been shown to induce bone regeneration both in vitro and in vivo [102]. Current research on exosomes is still evolving, and the detailed composition and mechanisms of action of exosomes have not been fully elucidated. Therefore, further exploration of the contents of exosomes will enhance our understanding of their functions and roles, potentially leading to more effective therapeutic applications [103].

5.2. Hydrogel-packed exosomes

While the effectiveness of exosomes in enhancing bone regeneration is well-established, the challenge of achieving a sufficient therapeutic concentration of exosomes at the target site remains a significant barrier to their clinical application. It has been demonstrated that hydrogels can effectively deliver the active components they contain to therapeutic targets, thereby facilitating bone regeneration and addressing bone defects [104].

Researchers have incorporated BMSC-exos into chitosan/β-glycerophosphate hydrogels for bone regeneration in rat models with skull defects. These exosome-loaded hydrogels have demonstrated biocompatibility and exceptional efficacy in promoting bone tissue regeneration [105]. Additionally, other studies have successfully combined exosomes derived from human adipose stem cells (hASCs) with gelatin nanoparticle (GNP) hydrogel scaffolds. This integration allowed for precise delivery of exosomes to the target site, enhancing bone repair capabilities [106]. However, the inherent mechanical and chemical limitations of hydrogels pose challenges in their standalone use. To address these issues, a novel self-healing hydrogel composed of coralline hydroxyapatite (CHA), silk fibroin (SF), glycol chitosan (GCS), and difunctionalized polyethylene glycol (DF-PEG) was developed. Human umbilical cord mesenchymal stem cell-derived exosomes (hucMSC-exos) were incorporated into this new hydrogel formulation. When implanted into SD rats with femoral condylar defects, this complex significantly enhanced bone defect healing [107].

Hydrogels can be effectively combined not only with exosomes but also with other biological materials to enhance the efficacy of exosomes. Research has shown that hydrogels incorporating hADSCs-exos, Mg^{2+}, and gallic acid (GA) to create a composite scaffold, specifically a PLGA/Exo-Mg-GA MOF, significantly promote bone formation and angiogenesis, and improve anti-inflammatory capabilities both in vitro and in vivo [108]. Consequently, exploring diverse hydrogels could represent promising research avenues in future studies.

6. The application of exosomes in the treatment of prosthesis loosening caused by different artificial prosthesis materials

The primary cause of joint replacement failure is the generation of wear particles due to friction between the prosthesis and surrounding bone tissue. These particles interact with osteoclasts and macrophages in the bone, resulting in osteolysis around the implant and ultimately leading to prosthesis loosening. In response to this issue, some studies have explored the use of exosomes to block this deleterious mechanism. By leveraging exosomes, researchers aim to reduce the incidence of prosthesis loosening and enhance the integration of the implant with the adjacent bone tissue.

6.1. Experimental findings

6.1.1. Exosomes and metallic prostheses

Due to their outstanding properties, titanium (Ti) and its alloys are extensively used in bone tissue engineering. These properties include biocompatibility, high mechanical strength, and corrosion resistance [109]. Studies have shown that the injection of titanium particles can induce osteolysis and attract a significant influx of macrophages in mouse skulls. However, the local administration of human umbilical cord mesenchymal stem cells (HUCMSCs) and their derived exosomes can mitigate this osteolysis and macrophage migration. The use of the exosome inhibitor GW4869 was found to increase both the osteolytic area and the number of migrating macrophages in a mouse craniolysis model [110]. Further research indicated that HUCMSCs and HUCMSC-derived exosomes prevent wear particle-induced aseptic loosening by suppressing the activity of chemokine (C–C motif) ligand 2 (CCL2) and chemokine (C–C motif) ligand 3 (CCL3) [104]. Additional studies have demonstrated that exosomes derived from macrophages (M-exos) modulate osteolysis by targeting the TAB3/NF-κB signaling pathway through miR-3470b, directly affecting inflammatory osteolysis in aseptic prosthodontic loosening. This finding opens new potential therapeutic avenues for managing osteolysis (Table 1) [56]. In another application, human mesenchymal stem cell exosomes (hMSC-exos) were incorporated into 3D-printed titanium alloy scaffolds, which were shown to induce bone tissue regeneration in vivo [111]. Similarly, a

composite scaffold composed of titanium (Ti), graphene (Gr), and adipose stem cell-derived exosomes (ADSC-exos) was developed. In a rabbit mandibular defect model, Gr-Ti scaffolds showed low toxicity and high biocompatibility, enhancing both adhesion and osteogenic differentiation of ADSCs. RUNX2, ALP, and Osterix mRNA levels were significantly higher in the Gr-Ti/Exos group compared to the Gr-Ti group, implicating the Wnt signaling pathway. Furthermore, the Gr-Ti scaffold with ADSCs and ADSC-exos effectively repaired mandibular defects in rabbits, and the bone mineral density and bending strength were significantly improved in the Gr-Ti/Exos group compared to the Gr-Ti group [112]. Although exosomes have demonstrated efficacy in treating osteolysis around prostheses, targeting exosomes to the osteolytic areas remains a challenge. To address this, recent research has explored the use of macrophage membrane-encapsulated human urine-derived stem cell exosomes (MM-exos), which can specifically target osteolytic regions and enhance the therapeutic efficacy of exosomes in periprosthetic osteolysis [113].

Porous tantalum (pTa) has garnered significant interest due to its exceptional biocompatibility and robust mechanical strength. Research indicates that pTa can stimulate the overexpression of osteogenic genes such as OSX, Col I, OSN, and OCN by activating the MAPK/ERK signaling pathway, thereby enhancing the osteogenic differentiation of BMSCs in vitro [114]. Additional studies have explored combining pTa with exosomes derived from BMSCs (BMSC-exos) and implementing this composite in a rat model of femoral supracondylar defect. In these studies, pTa served as a primary scaffold for cell adhesion and demonstrated excellent biocompatibility. Further investigations using micro-CT scans and histological examinations revealed that pTa significantly promoted osteogenesis. Moreover, the integration of exosomes into the pTa scaffold further enhanced the regeneration and repair of bone tissue [115].

6.1.2. Exosomes and polymer prostheses

Polyether ether ketone (PEEK) is a high-performance thermoplastic polymer material. In the field of orthopedic clinical practice, it is widely used in the manufacturing of implantable devices, such as spinal fusion cages, artificial joint replacement components and others. Compared to traditional metallic implants, PEEK has emerged as a preferred alternative for orthopedic implants due to its biomimetic mechanical properties (elastic modulus closely matching that of natural bone tissue), excellent medical imaging compatibility (artifact-free X-ray transparency), and customizable processing advantages [116]. It is particularly suitable for complex clinical scenarios requiring long-term in vivo retention, dynamic postoperative imaging evaluation, or precise biomechanical adaptation [116]. MSC-exos were also integrated into sulfonated polyether ether ketone (SPEEK) that had been modified with tannic acid (TA). This MSC-exos-loaded SPEEK was found to promote M2 macrophage polarization via the NF-κB pathway and enhance the integration of implants into bone [117].

6.1.3. Exosomes and bioactive ceramic prostheses

Bioceramics are extensively employed in clinical settings due to their exceptional mechanical strength, microporosity, biocompatibility, and biodegradability. Among various bioceramics, β-tricalcium phosphate (β-TCP) is particularly valued as a bone graft substitute because of its superior absorbability, bone conductivity, and bone inductivity. Research has demonstrated that scaffolds combining β-TCP with exosomes derived from human-induced pluripotent stem cell-derived mesenchymal stem cells (hiPS-MSC-exos) have enhanced osteogenic activity compared to scaffolds composed solely of β-TCP. This combination has been successfully used to repair critical-sized skull defects, showing improved bone regeneration [101]. To further enhance the osteogenic potential of exosomes, β-TCP scaffolds integrated with pretreated exosomes enriched in HIF1α (MSC-exos-HIF1α) were implanted into a rat model with critical-sized skull bone defects. It was observed that MSC-exos-HIF1α stimulated both the proliferation and osteogenic differentiation of BMSCs, displaying superior osteogenic capabilities compared to the standard MSC-exos group [118]. Additionally, hiPS-MSC-exos combined with β-TCP scaffolds were implanted in rats with critical skull defects following ovary resection. This intervention significantly promoted bone regeneration and angiogenesis, and it was noted that the effectiveness of the exosomes increased with higher exosome concentrations [119]. Contrastingly, hydroxyapatite, another type of bioceramic, is known for its biological activity. Studies incorporating MSC-exos with hydroxyapatite scaffolds have also demonstrated promising results in promoting bone regeneration [120].

6.1.4. Other material prostheses

Currently, a diverse range of bone replacement materials is available, and research has indicated that adding specific coatings to these materials can enhance bone regeneration. For instance, a bionic bone scaffold composed of SF-CS-nHA (SCN) was developed and functionally modified by applying a polydopamine (PDA) coating that was loaded with BMSC-exos. Studies found that this SCN/PDA-exos functionalized composite scaffold not only promoted the proliferation and osteogenic differentiation of BMSCs in vitro but also significantly improved bone regeneration efficiency in vivo [121]. Therefore, exploring different coatings for various materials could be a promising direction for future research.

6.2. Clinical findings

As of January 9,2025, there are 245 studies on exosomes listed on clinicaltrials.gov (https://clinicaltrials.gov/). These studies explore the role and mechanisms of exosomes in various diseases such as cancer, inflammation, wound healing and neurological disorders from different perspectives. The methods of exosome isolation and the types of donor cells are also hot topics in current research. By studying the methods of exosome isolation, a unified standard for exosome preparation can be established, which is beneficial for determining a unified dosage standard for exosome therapy in future clinical applications. Research on the types of donor cells for exosomes can identify which cells secrete the most effective and highest concentration of exosomes. This makes the clinical translation of exosomes possible. Currently, only six studies are related to bone-related inflammation and exosomes, and clinical research on exosome treatment for periprosthetic loosening is still in its infancy. In addition, experiments on large animals are also very scarce. Therefore, exosome treatment for periprosthetic loosening may become a hot topic for future clinical trials.

7. Exosomes promote bone tissue regeneration around prosthesis loosening osteolysis

When a prosthesis is implanted, it rubs against the surrounding bone tissue, generating biologically active wear particles. These particles can activate osteoclasts and macrophages, leading to bone resorption, and inhibit the functional expression of osteoblasts [122]. Research has demonstrated that exosomes can enhance the proliferation and differentiation of osteoblasts while inhibiting the formation of osteoclasts through the BMP/Smad, Wnt/β-catenin, and PI3K/AKT signaling pathways [79,80,83,52]. Consequently, exosomes play a significant role in promoting bone regeneration.

Successful bone regeneration entails not only the restoration of bone tissue but also the regeneration of blood vessels. Regenerated blood vessels provide essential nutrients, oxygen, hormones, and growth factors to the bone tissue. Additionally, they facilitate the removal of wear particles, thereby minimizing damage from these particles. Research has shown that wear particles can inhibit both bone and blood vessel regeneration [123]. Engineered exosomes enriched with miR-3470b help to inhibit osteolysis. A microenvironment enriched with miR-3470b can suppress wear particle-induced osteolysis by inhibiting TAB3/NF-κB in vivo [56]. Studies have demonstrated that exosomes derived from umbilical mesenchymal stem cells (UMSC-exos) can

enhance the expression of VEGF and hypoxia-inducing factor-1α (HIF-1α) in human umbilical vein endothelial cells (HUVECs). This leads to accelerated proliferation, migration, and tube formation of HUVECs, thereby promoting angiogenesis [124].

Aseptic inflammation triggered by wear particles is a primary cause of aseptic loosening of prostheses after joint replacement surgeries. Consequently, mitigating the inflammatory response presents a viable strategy for treating prosthesis loosening. Macrophages can differentiate into two types: M1 and M2. M1 macrophages produce inflammatory factors that are detrimental to bone regeneration, whereas M2 macrophages produce pro-regenerative factors that facilitate bone healing. Research has indicated that exosomes derived from BMSC-exos can induce the polarization of macrophages towards the M2 type through miR-223, thereby exerting anti-inflammatory effects [125]. Further studies have shown that in a mouse model of bronchopulmonary dysplasia, the exogenous addition of BMSC-exos can promote the transition of macrophages from the M1 to the M2 type, enhancing their pro-regenerative capabilities [112]. A study found that in preclinical models of rheumatoid arthritis (RA), matrix-bound nanovesicles (MBV) which contain exosomes can modulate macrophage phenotypes and prevent adverse bone remodeling [126]. Some scholars have found that MBV can weaken osteoclast differentiation and activity by inhibiting the NF-κB signaling pathway and the expression of downstream NFATc1, DC-STAMP, c-Src and cathepsin K.In vivo, they discovered that local administration of MBV alleviated bone dissolution, bone reconstruction and periosteal inflammation induced by ultra-high molecular weight polyethylene particles. Therefore, MBV containing exosomes might be a therapeutic option for preventing periprosthetic loosening [127].

In conclusion, exosomes have shown potential in treating aseptic loosening of prostheses by promoting osteoblast generation, inhibiting osteoclast formation, enhancing blood vessel regeneration, and facilitating the transformation of macrophages into the M2 type. These findings suggest that exosomes could represent a novel approach to managing aseptic loosening of prostheses in future treatments.

8. Limitations and prospect

While the effectiveness of exosomes in promoting bone regeneration is recognized, several limitations hinder their clinical application [128]. First, the large-scale production of high-quality exosomes is fraught with challenges [129]. Second, the heterogeneity of exosomes complicates their clinical translation. Variations in the composition and content of exosomes from different sources make it difficult to establish standardized treatment protocols, thereby limiting their clinical implementation [130]. Third, although pretreatment of engineered exosomes has been shown to enhance their effectiveness, there is no clear standard regarding the optimal concentration of exosomes for maximum efficacy [131]. Fourth, the delivery of exosomes to targeted cellular sites presents another challenge. The body can rapidly eliminate exosomes; hence, targeted delivery can enhance the concentration of exosomes at specific sites, potentially increasing therapeutic effectiveness—a current area of intense research [132]. Fifth, the use of scaffolds to transport exosomes to targeted cells is being explored to improve outcomes. However, the most effective scaffold type is yet to be determined [131]. Sixth, most existing studies are limited to small animal models, with large animal models and clinical trials still relatively scarce [132]. Finally, the mechanisms by which exosomes lose effectiveness post-implantation have not been fully elucidated. Addressing these issues may open new avenues for future research in this field.

Despite some current drawbacks, the various advantages of exosomes make them promising for treating periprosthetic loosening. Exosomes offer similar benefits in a safer and more stable extracellular vesicle form, overcoming the limitations of cell-based therapies. They appear to possess inherent immunomodulatory properties and do not carry risks such as ectopic tissue formation. Exosomes can be isolated from various mesenchymal stem cell sources, such as bone marrow, adipose tissue and synovial fluid. Their cargo can also be engineered to enhance regenerative bioactivity. These advantages make it possible for exosomes to become a standardized clinical treatment and for large-scale biological production in the future, making them a potential solution for the clinical treatment of aseptic periprosthetic loosening [133].

Availability of data and materials

The data presented in this study are available from the corresponding author on reasonable request.

Author contributions

Conceptualization, QL, ZD, YM and JZ; methodology, SW; validation, BW, SG, YL,GL and FL; resources, BW and YP; writing—original draft preparation, BW; writing—revision and editing, QL, ZD and FL; supervision, ZD and QL; project administration, QL; funding acquisition, QL. All authors have read and agreed to the published version of the manuscript.

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Competing interests

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