Proceedings of ICMMGH 2027 Symposium: Transforming Nutrition for Public Health Across the Life Course
DOI: 10.54254/2753-8818/2027.KL39069

Application of Mesenchymal Stem Cells in Bone and Joint Remodeling

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Abstract. Osteochondral defects are difficult to repair due to the absence of blood vessels and poor self-healing ability of cartilage. Although mesenchymal stem cells (MSCs) have multipotent differentiation potential, their directional differentiation is uncontrollable and survival rates after injection are low. This paper aims to clarify the mechanisms and material strategies of MSCs in bone and joint remodeling, reviewing the signaling pathways and transcription factor regulation of osteogenic and chondrogenic differentiation, as well as research progress on genetically modified stem cells combined with hydrogel scaffolds for bone defect repair. The results show that osteogenic differentiation converges on core transcription factors such as RUNX2; Gene modification can enhance the directed differentiation and paracrine effects of stem cells; hydrogels achieve three-dimensional support and fixed-site residence through in situ gelation; biomimetic scaffolds combine mechanical support with osteogenic-angiogenic coupling. This collaborative strategy of "signal regulation—gene modification—material delivery" offers feasible ideas for bone and joint repair, but matching material degradation and regeneration rhythms, as well as the long-term safety of gene modification, still need to be verified. Future focus can be on intelligent response stents and clinical translation.

Keywords: Mesenchymal stem cells, Bone and joint remodeling, Hydrogels

1. Introduction

Osteochondral tissue defects (such as temporomandibular joint osteoarthritis and traumatic bone defects) have extremely limited self-repair capacity due to the avascular nature of articular cartilage, and large bone defects are difficult to heal spontaneously. Traditional therapies such as autologous/allogeneic bone grafts, artificial joint replacement, and microfracture procedures are often constrained by limitations such as insufficient donor sources, immune rejection, and numerous complications. Therefore, regenerative medicine has become an important breakthrough. Mesenchymal stem cells (MSCs), with their multipotent differentiation potential and immunomodulatory properties, are regarded as the most promising seed cells in osteochondral tissue engineering. These mixtures of different stem cells can differentiate into skeletal tissues, such as bone and cartilage, as well as adipose tissue, muscle, connective tissue, and blood vessels; they can also be driven by special methods to accelerate bone regeneration. However, their directed

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DOI: 10.54254/2753-8818/2027.KL39069

differentiation is not a spontaneous event, but is precisely regulated by cascades of signaling pathway activation in the microenvironment (such as Wnt/β-catenin) and the balanced expression of key transcription factors (such as RUNX2 and SOX9) [1, 2]. Nevertheless, simple stem cell injections face challenges of low survival rates, uncontrollable differentiation, and difficulty in precise retention. In this regard, gene modification techniques (such as the introduction of therapeutic genes like BMP-2, TGF-β1, or HGF) can enhance the directed differentiation capacity or paracrine effects of stem cells, while hydrogels, as injectable scaffolds, not only provide three-dimensional physical support and immune isolation, but also allow in situ cell fixation and sustained functional output. At the same time, various biological scaffolds can effectively cooperate with MSCs to repair bone defects by simulating different structures of natural bone (such as porous structures).

This article, centered on the aforementioned technical route, elaborates respectively on the molecular mechanisms of MSC osteogenic and chondrogenic differentiation, the application of gene-modified stem cells combined with thermosensitive hydrogels in joint and bone remodeling, as well as the application and frontier progress of different biological scaffolds combined with MSCs in bone defect repair, with the aim of providing reference for related research and clinical translation.

2. MSCs molecular regulatory mechanisms of bone formation

Osteogenic differentiation of MSCs is driven synergistically by a series of signaling pathways, ultimately activating core transcription factors and initiating the expression of osteogenesis-related genes. The Wnt/β-catenin pathway is a key signaling pathway regulating MSC osteogenic differentiation. In the resting state, the destruction complex in the cytoplasm, composed of Axin, APC, GSK-3β, and CK1, continuously phosphorylates β-catenin, marking it for ubiquitination and degradation by the 26S proteasome, thereby keeping nuclear TCF/LEF transcription factors in an inhibited state. When Wnt ligands bind to Frizzled receptors and LRP5/6 co-receptors, the destruction complex disassembles, β-catenin accumulates stably in the cytoplasm and translocates into the nucleus, where it binds TCF/LEF to initiate downstream target gene transcription.

In osteogenic differentiation, this pathway promotes the determination of osteoblast fate and inhibits lipogenesis and chondrogenic differentiation; On the other hand, it induces key transcription factors such as Runx2 and Osterix, increasing the levels of osteogenic markers like alkaline phosphatase, type I collagen, and osteocalcin, and inhibits osteoclast activity by modulating OPG/RANKL. Among these, functional loss or acquired mutations in the LRP5 gene can significantly reduce or increase bone mass, further confirming the core role of this pathway in regulating bone metabolism and making it an important intervention target for osteoporosis treatment.

RUNX2 is considered a key transcription factor for osteogenic differentiation. This gene is a member of the RUNX family of Transcription Factors and encodes a nuclear protein with an Runt DNA-binding domain. This protein is essential for osteoblastic differentiation and skeletal morphogenesis in mesenchymal stem cells and acts as a scaffold for nucleic acids and regulatory factors involved in skeletal gene expression. The protein can bind DNA both as a monomer or, with more affinity, as a subunit of a heterodimeric complex. Two regions of potential trinucleotide repeat expansions are present in the N-terminal region of the encoded protein, and these and other mutations in this gene have been associated with the bone development disorder cleidocranial

DOI: 10.54254/2753-8818/2027.KL39069

dysplasia (CCD). Transcript variants that encode different protein isoforms result from the use of alternate promoters as well as alternate splicing.

3. Molecular regulatory mechanisms of chondrogenic differentiation and application directions

3.1. Molecular regulatory mechanisms of MSC chondrogenic differentiation

Unlike osteogenic differentiation, chondrogenic differentiation relies on a sophisticated regulatory network, with the TGF-β/BMP/Smad pathway playing a central role. This pathway belongs to the TGF-β superfamily and mainly transduces signals via receptor-mediated Smad-dependent pathways: TGF-β or BMP ligands first bind to type II receptors and phosphorylate them, thereby activating type I receptors (BMP via ALK2/3/6, TGF-β via ALK5). The latter is a phosphorylated receptor-regulated Smad—BMP activates Smad1/5/8, TGF-β activates Smad2/3. Phosphorylated R-Smad and co-mediated Smad4 translocation into the nucleus and regulation of target gene transcription, inhibitory Smad6/7 negative feedback regulation.

Among the signaling pathways that govern chondrogenesis, BMPs act as the most potent chondroinductive factors, driving the commitment of mesenchymal stem cells (MSCs) toward the chondrocyte lineage. In concert with this, TGF-β promotes chondrocyte proliferation and sustains the differentiated phenotype, and the two signals synergistically induce the master transcription factor Sox9, which in turn drives the expression of cartilage matrix genes such as type II collagen and aggrecan. At a later stage, this pathway also participates in the regulation of chondrocyte hypertrophic differentiation by upregulating Runx2 and type X collagen. Consequently, aberrant signaling through this pathway is closely associated with the pathogenesis of diseases such as osteoarthritis and chondrodysplasia.

SOX9 is a decisive transcription factor for chondrogenic differentiation: it is encoded by the SOX9 gene and belongs to the SRY-related high-mobility-group (HMG) box protein family.

During the chondrogenic differentiation of mesenchymal stem cells (MSCs), SOX9 acts as a core transcriptional regulator that binds, via its highly conserved HMG-box domain, directly to the promoter regions of cartilage-specific target genes such as COL2A1 and ACAN, thereby initiating their transcription. Its expression is regulated by the TGF-β/BMP signaling pathway through Smad2/3 and is markedly upregulated during differentiation; consequently, SOX9 is widely used as a key molecular marker of MSCs entering the chondrogenic differentiation program.

Therefore, the synergistic mechanism by which MSCs promote osteochondral defect repair lies in directed differentiation to restore the defect, such that their intrinsic differentiation potential acts in concert with the local microenvironment, including biomaterial scaffolds..

3.2. Microenvironment-driven MSC differentiation and its application in osteochondral defect repair

Synergistic Mechanisms of MSCs in Promoting Osteochondral Defect Repair and Their Application At bone defects, the local hypoxic microenvironment can induce paracrine effects in MSCs, regulating angiogenesis via pathways such as JAK1/STAT1/MMP-10, providing essential nutrients and oxygen for the osteogenesis process, known as the "osteogenic-angiogenesis coupling".

At the same time, the differentiation direction of MSCs is strongly influenced by the microenvironment. For example, a functionalized decalcified bone matrix (FDBM) scaffold can

DOI: 10.54254/2753-8818/2027.KL39069

mimic natural joint tissue, providing a microenvironment for cartilage and osteogenesis, thereby inducing the supported BMSCs to differentiate into chondrocytes or participate in bone formation in the corresponding region, thereby achieving repair of composite osteochondral defects.

In the non-cartilage microenvironment, cartilage tissue regenerated from MSCs can further transform into bone tissue through endochondral osteogenesis, which is an important model for bone development and fracture healing.

For example, temporomandibular disorders (TMD) are diseases caused by the interplay of multiple factors. Among them, temporomandibular osteoarthropathy is a common type of TMD. After onset, organic changes in joint cartilage occur, causing irreversible defect damage and lowering the patient's quality of life.

Human amniotic mesenchymal cells (h AMSCs) possess the characteristics of MSCs, multipotent differentiation potential, and low immunogenicity. Under appropriate conditions, they can be induced to differentiate into chondrocytes, providing a new therapeutic approach for TMJ osteoarticular disease. Traditional therapies have hit bottlenecks due to the lack of blood vessels in joint cartilage, poor self-repair ability, and frequent surgical complications, whereas hAMSCs happen to possess the key characteristics of ideal seed cells—they are derived from abandoned placenta, are abundant and non-invasive, do not express major immune rejection molecules such as HLA-DR, thus reducing transplantation risk, have a stronger proliferative capacity than bone marrow MSCs, and have been confirmed by multiple experiments to successfully induce differentiation into chondrocytes expressing type II collagen in vitro. Animal studies have also shown that stem cell therapy is feasible.

Therefore, hAMSCs can fill the gap that traditional therapies cannot achieve in repairing cartilage defects, providing a new pathway for regenerative repair of the temporomandibular joint [3].

Additionally, some studies have shown that potent bioactive metabolites can be used to stimulate osteogenesis and differentiation in mesenchymal stem cells. By stimulating with nano vibrations, specific bioactive metabolites can be identified, thereby inducing highly specific osteogenesis differentiation in MSCs [4].

4. Combined application of hydrogels and stem cells in bone and joint remodeling

In bone and joint remodeling therapy, the combination strategy of MSCs (such as genetically modified stem cells) and hydrogels (such as thermosensitive hydrogels) aims to address core issues of uncontrolled differentiation, low survival rates, and difficulty in precise delivery of traditional cell therapies

4.1. Advantages of hydrogel scaffolds in binding to genetically modified stem cells

The extracellular matrix consists of a three-dimensional (3D) network that promotes cell adhesion, migration, and proliferation, as well as oxygen and nutrient exchange, playing an indispensable role in bone repair. Additionally, bone substitute biomaterials must have good intraoperative processing performance. Therefore, significant attention has been paid to injectable composite biomaterials for bone regeneration. The three-dimensional hydrophilic network and high water content distinguish hydrogels from different scaffold materials. This composition is very similar to normal stromal cells. For example, sodium alginate (SA) hydrogels have been approved by the U. S. Food and Drug Administration (FDA) due to their excellent biocompatibility. Moreover, the effective combination

DOI: 10.54254/2753-8818/2027.KL39069

and synergistic therapeutic effects of genetically modified stem cells and hydrogels are further due to their complementary functions and physical properties

The advantages of combining hydrogels with gene-modified stem cells are mainly reflected in three aspects: First, hydrogels provide physical support and protection for genetically modified stem cells, simulating the extracellular matrix microenvironment and isolating transplanted cells from the host's immune system, improving their survival rate in inflammatory microenvironments and avoiding cell loss and premature death caused by simple cell suspension injections; Second, genetically modified stem cells provide continuous therapeutic output to the hydrogel system, allowing long-term local survival and stable secretion of therapeutic proteins or peptide factors, forming an "in-situ drug factory" to achieve local sustained release and continuous supply, avoiding side effects and concentration fluctuations of systemic administration; Third, the reversible transformation of the hydrogel's physical state (such as thermosensitive hydrogels being liquid outside the body and gelling in vivo) enhances delivery operability and adaptability, making cell delivery both minimally invasive and precise, and can be filled in situ and fitted to irregular defect shapes.

4.2. Gene-modified stem cells combined with thermosensitive hydrogels

The combination of the two first uses genetic engineering techniques (transfection of viral or non-viral vectors, CRISPR gene editing) to introduce therapeutic genes such as TGF-β1, hepatocyte growth factor, or BMP2 into stem cells, enhancing their chondrogenic and osteogenic differentiation or immune regulatory abilities; Next, gene-modified stem cells are uniformly mixed with thermosensitive hydrogels in a low-temperature sol state, injected into target sites via minimally invasive injection, and a three-dimensional porous scaffold is formed in situ at the injury site by sol-gel phase transformation induced by body temperature (about 37°C), precisely fixing stem cells at the defect site to achieve targeted cell retention.

For example, adenovirus-mediated transfection of hepatocyte growth factor (HGF) into adipose stem cells, combined with thermosensitive injectable hydrogels, and implanted into the joint cavity of rabbit TMJ models can significantly improve cartilage lesions, normalize the expression of key enzymes in cartilage matrix metabolism (MMP-13) and its inhibitor (TIMP-1), and achieve better repair outcomes than treatments with pure stem cell injections or untransfected composite materials [5].

Some studies have employed a stem cell–homing biomimetic hydrogel to promote the repair of osteoporotic bone defects by coupling osteogenesis with angiogenesis. This hydrogel construct can effectively promote the formation of both bone tissue and neovasculature, and it additionally exerts immunomodulatory functions. Accordingly, it may constitute an effective strategy for accelerating the healing of osteoporotic bone defects in the future [6].

In related experiments, synthetic hydrogels functionalized with integrin-specific peptides enhanced the survival, persistence, and bone-repair function of human bone marrow–derived mesenchymal stem cells (hMSCs) transplanted into bone defects in mice [7]. In particular, integrin-specific hydrogels effectively regulate hMSC adhesion, paracrine signaling, and osteoblastic differentiation in vitro. Hydrogels presenting GFOGER, a peptide targeting integrin α2β1, further prolong hMSC survival when implanted into segmental bone defects, resulting in superior bone repair compared with other peptides. In addition, integrin-specific hydrogels exert multiple pleiotropic effects on the reparative activity of hMSCs, such as modulating cytokine secretion in vitro and regulating the in vivo expression of genes associated with inflammation, angiogenesis, and

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bone formation. Collectively, these results indicate that integrin-specific hydrogels can promote tissue healing by directing the survival, engraftment, and reparative activity of hMSCs.

5. Biological scaffolds are used in bone tissue engineering to help repair bone defects with MSCs

Biostents are an important branch of biomaterials, and their application in bone defect repair has become one of the key research directions in regenerative medicine.

For example, porous biological scaffolds represent a core technology for bone defect repair; in essence, they mimic the honeycomb-like porous architecture of native bone tissue to provide three-dimensional spatial support for cell adhesion, proliferation, and the ingrowth of new bone. Through techniques such as 3D printing, scaffolds can be precisely and individually tailored in terms of porosity (60%–90%), pore size (300–900 μm), and external shape, thereby ensuring the ingrowth of blood vessels and nutrients while maintaining sufficient mechanical support. The design philosophy of porous biological scaffolds emphasizes "osteogenesis–angiogenesis coupling," that is, loading bioactive molecules such as growth factors to achieve temporally controlled release, so as to synergistically promote angiogenesis and bone regeneration. Concurrently, surface modification strategies are utilized to endow the scaffolds with multiple functions, including antibacterial and immunomodulatory properties.

A few studies have adapted the concept of stent guided bone regeneration to the dentistry field. regeneration (SGBR) from the desktop to bedside jobs with an emphasis on 3D. Biodegradable composite stents, which are printed, have been developed [8].

To address stent angiogenesis, various methods have been studied, including pre-vascular angiogenesis before grafting, axial vascular angiography at the vascular base (arteriovenous ring and related variants), and flap-based axial angiogenesis (muscle flaps, periosteal flaps, etc.). Among these, vascularized cortical bone marrow tissue has greater regenerative capacity, while corticospinal bone flaps (CPF) provide ample blood supply and offer many donor sites for distant transplantation. For rapid and uniform stent angiogenesis, axial medial methods are considered key and have been successfully achieved through vascular methods (arteriovenous rings). In the research by David S. Sparks' team, a method combining intrinsic axial angiogenesis strategies with flap-matched tissue regeneration was defined as regenerative matching axial angiodilation (RMAV) [8]. In this method, CPF is used not only for intravascularization of stents but also for releasing large amounts of mesenchymal precursor cells within the stent structure, thereby stimulating bone regeneration

To address the challenge of balancing mechanical support and osteogenic activity with a single material in large bone defect repairs, a study has developed a BMP2@Gel@PLGA composite scaffold [9]. Based on phthalmaldehyde-terminated 4-arm polyethylene glycol cross-linking with gelatin, a low-concentration (2%) hydrogel system was prepared to load bone morphogenetic protein 2 (BMP2), achieving a controlled release rate of 72.44% within 3 weeks, continuously recruiting MSCs and inducing osteogenic differentiation in the early stages of bone repair; At the same time, PLGA75/25 porous scaffolding (pore size about 380μm, porosity about 57%, compression modulus 0.68GPa, comparable to cancellous bone) was prepared using fused deposition 3D printing, and hydrogel was filled into the scaffold pores by negative pressure suction [9]. Animal experiments (models of rat cranial bone defects and rabbit femoral condyle defects) confirmed that this composite scaffold combines favorable biocompatibility, an appropriate degradation profile (approximately 3 weeks for the hydrogel and 4–6 months for PLGA), and sustained, stable osteogenic activity. While providing long-term mechanical support to the bone defect region, it

DOI: 10.54254/2753-8818/2027.KL39069

achieves a synergy between the early sustained release of growth factors and the later ingrowth of bone tissue. Thus, it offers a novel strategy for the treatment of large segmental bone defects that reconciles mechanical performance with biological activity.

Other related studies have also described cytoskeletal regulation on polycaprolactone (PCL)/graphene porous scaffolds in bone tissue engineering. In the work by Hendrik Setia Budi and colleagues, the scaffolds were shown to play a key role in promoting cell motility by stimulating the dynamic formation of filopodia and lamellipodia. In particular, the test specimen containing 3 wt% G significantly enhanced toughness, yield strength, and strain, thereby improving cell motility while promoting the development of longer filopodia and larger lamellipodia in MG-63 cells [10].

6. Conclusion

This review has examined the application of mesenchymal stem cells (MSCs) in bone and joint remodeling at three levels: molecular mechanisms, cell–material composite strategies, and biological scaffolds. At the mechanistic level, osteogenic differentiation is driven by signaling pathways such as Wnt/β-catenin and ultimately converges on core transcription factors including RUNX2, whereas chondrogenic differentiation follows a distinct regulatory network; this indicates that the directed differentiation of MSCs is the outcome of a delicate balance between signaling pathways and transcription factors rather than a spontaneous event. At the application level, genetic modification can enhance the directed differentiation capacity and paracrine effects of stem cells; injectable scaffolds, such as thermosensitive hydrogels, provide three-dimensional support, immune isolation, and in situ retention; and porous biological scaffolds, by virtue of their biomimetic architecture, simultaneously achieve mechanical support and osteogenesis–angiogenesis coupling. It is evident that the trinity approach of "signal regulation—gene modification—material delivery" addresses the bottlenecks of traditional cell therapies such as low survival rates, uncontrollable differentiation, and difficulty in precise retention, and also confirms the conclusion in the introduction: materials are not just cell carriers, but also microenvironmental elements involved in regulating cell fate. Of course, most existing evidence comes from small animal models and short-term observations; the alignment of material degradation with bone regeneration rhythms and the long-term safety of gene modifications still need to be verified. If future chronological release and individualized scaffold designs can be combined and tested in large animals and clinical settings, this strategy is expected to provide more practical solutions for regeneration and repair of bone and joint defects.

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