The Application and Transformation Challenges of Stem Cell Technology in the Repair of Articular Cartilage Injuries

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Abstract. The articular cartilage lacks blood vessels, nerves and lymphatic vessels. If damaged, it is difficult to achieve effective endogenous repair. Focal defects often progress to osteoarthritis. Traditional treatments such as microfracture surgery and autologous chondrocyte transplantation can alleviate related symptoms, but the repaired tissues are mostly fibrocartilage, which has a gap in mechanical performance compared to natural transparent cartilage. Moreover, they may face issues such as secondary surgeries, donor site damage, and insufficient long-term durability. Stem cells, due to their proliferative potential, multi-directional differentiation ability and microenvironmental regulatory function, are currently an important research direction for cartilage regeneration. This article systematically reviews the research progress of different stem cells in joint cartilage repair and summarizes related mechanisms such as directed differentiation, paracrine regulation, immune regulation and anti-apoptosis protection. In terms of clinical evidence-based application, data on mesenchymal stem cells (MSCs) is the most sufficient, which can improve pain, function and cartilage volume; iPSCs-derived cartilage shows advantages in long-term matrix synthesis and anti-hypertrophic apoptosis. However, heterogeneity of efficacy, lack of efficacy indicators, uncertain regulatory pathways, bottlenecks in manufacturing scale-up and problems of graft integration and durability still restrict clinical translation. Further exploration is still needed in the future.

Keywords: Stem Cell Technology, Articular Cartilage Injuries, Repair.

1. Introduction

Articular cartilage is a highly specialized type of connective tissue, composed of sparsely distributed chondrocytes and a dense extracellular matrix. The main components of the matrix are type II collagen and proteoglycans. Cartilage tissue lacks blood vessels, nerves, and lymphatic vessels. The proliferation and migration capabilities of mature chondrocytes are very limited, resulting in almost no effective endogenous repair after cartilage damage, which gradually leads to osteoarthritis (OA). The latest research and survey in 2026 show that the global burden of osteoarthritis is continuously increasing, and the occurrence of the disease is closely related to obesity, population aging, and gender differences [1]. An analysis based on GBD 2021 data predicts that the lifetime risk of developing osteoarthritis for individuals worldwide was 14.21% in 2021, with knee osteoarthritis having the highest risk (9.31%), and the pain, functional impairment, and medical burden caused by the disease constitute a major public health challenge [2].

The traditional treatments include conservative therapy, microfracture surgery, autologous chondrocyte transplantation, and osteochondral transplantation. Although these methods can alleviate symptoms or promote the repair of defects to some extent, the repaired tissues formed by microfractures are mostly fibrocartilage, and their type II collagen content, tissue structure, and mechanical properties differ from those of natural transparent cartilage; autologous chondrocyte transplantation involves repeated surgeries and has issues such as cell expansion, cell phenotype alteration, and damage to the donor site. Additionally, the existing products also face limitations such as insufficient tissue maturity and long-term durability.

Stem cells possess strong proliferative potential, multi-directional differentiation ability, and the ability to regulate the local tissue microenvironment, and also have considerable potential for cartilage regeneration. This article aims to systematically review the research progress of stem cell technology in joint cartilage repair and focuses on analyzing the core obstacles faced at each stage

from cell source selection, clinical practice application to clinical transformation, in order to provide references for its further clinical application.

2. Main Types of Stem Cells in Joint Cartilage Repair

The stem cells currently applied in joint cartilage repair mainly include three types: mesenchymal stem cells (MSCs), pluripotent stem cells, and peripheral blood stem cells. Each type of cell has its own characteristics in terms of source, differentiation ability, and clinical transformation stage.

Mesenchymal stem cells (MSCs) are the most deeply studied and widely used type. Depending on the tissue source, MSCs can be classified into subtypes such as bone marrow, adipose, umbilical cord, and synovial. Bone marrow mesenchymal stem cells (BMSCs) have a clear chondrogenic differentiation ability, but the acquisition process is invasive and the cell yield decreases with age. Adipose mesenchymal stem cells (ADSCs) have attracted attention due to their abundant sources and convenient isolation, and their exosomes carrying RNA and proteins can regulate immune responses and promote chondrocyte proliferation [3]. Umbilical cord mesenchymal stem cells (UCMSCs) demonstrate advantages due to non-invasive collection and stronger proliferation ability. The exosomes from their source have been proven to inhibit the Wnt/β-catenin pathway and enhance autophagy to alleviate cartilage pathological damage [4].

PSCs include ESCs and iPSCs. The core advantage lies in unlimited proliferation and stable chondrogenic differentiation ability. iPSCs can be induced to differentiate into chondrocytes, and their small extracellular vesicles (sEVs) can be extracted to show potential in promoting cartilage regeneration and extracellular matrix deposition in mouse models of osteoarthritis. Chondrocytes derived from ESCs, after optimized culture, can reach the same glycosaminoglycan and type II collagen deposition level as natural chondrocytes, and the increased PD-L1 expression suggests their immunomodulatory properties, providing a possibility for allogeneic transplantation [5, 6].

Peripheral blood stem cells (PBSCs) are a recently emerging type of source. A sheep model study showed that post-drilling of subchondral bone combined with intra-articular injection of autologous PBSCs and hyaluronic acid resulted in significantly better ICRS II histological scores than the hyaluronic acid alone group, suggesting that PBSCs can enhance the histological quality of cartilage repair [7]. The collection of peripheral blood stem cells is relatively convenient, but the specific mechanism and optimal protocol of their use in cartilage repair still need to be further clarified.

3. Main Mechanism of Stem Cell Repair of Articular Cartilage

Articular cartilage lacks blood vessels and nerve innervation, resulting in extremely limited self-repair ability. Stem cell therapy provides a new approach for cartilage regeneration. Its repair mechanism is not a single pathway but involves the synergistic effects of directed differentiation, paracrine regulation, and immune regulation.

Differential differentiation and the cartilage matrix synthesis are the classic mechanisms of stem cell repair. MSCs possess multi-directional differentiation potential and can differentiate into chondrocytes under specific induction conditions, expressing cartilage-specific matrix components such as the type II collagen and the aggrecan. Studies have confirmed that umbilical cord-derived MSCs can significantly upregulate the expression of the Sox9, Col2 and aggrecan in damaged chondrocytes, promoting cartilage matrix reconstruction [8]. However, recent research has revealed that the direct differentiation efficiency of MSCs in vivo is limited, and their therapeutic effects are more dependent on the regulation of paracrine signals.

Paracrine and nutrient factor secretion are the core pathways through which stem cells exert their effects. MSCs can secrete various bioactive molecules such as transforming growth factor-β (TGF-β), hepatocyte growth factor (HGF), and fibroblast growth factors (FGFs), which directly act on articular chondrocytes, promoting matrix synthesis and inhibiting degradation [9]. More importantly, stem cells transfer miRNAs and proteins through extracellular carriers such as exosomes and

microvesicles to regulate the proliferation and matrix metabolism of target cells [10]. Studies have shown that IL-10 and TGF-β1 secreted by MSCs play a key role in inhibiting joint cavity inflammation and protecting chondrocytes, and their protective effects significantly weaken after the removal of these factors [8].

Immune regulation and anti-inflammatory effects are also crucial aspects of stem cell repair. The pathological process of osteoarthritis is accompanied by persistent synovial inflammation and elevated pro-inflammatory factors (such as IL-1β, TNF-α), which induce degradation of the cartilage matrix by activating signaling pathways such as NF-κB. MSCs can inhibit T cell proliferation, regulate macrophage polarization, and secrete immunosuppressive molecules such as indoleamine 2,3-dioxygenase (IDO) and PGE2, thereby reshaping the local immune microenvironment of the joint. Umbilical cord MSCs transplantation can significantly reduce the levels of IL-1β, TNF-α, and MMP13 in joint fluid, and at the same time alleviate chondrocyte apoptosis [8,9].

Inhibiting chondrocyte apoptosis and fibrosis is also one of its protective mechanisms. Stem cells directly inhibit chondrocyte apoptosis by up-regulating anti-apoptotic protein Bcl-2 and down-regulating pro-apoptotic proteins Bax and Bad. In addition, stem cells can also down-regulate osteogenic transcription factors such as Runx-2 and up-regulate Sox-9, inhibit abnormal ossification tendencies in damaged cartilage, and promote the maintenance of chondrocyte phenotype [8,11].

In summary, stem cell repair of joint cartilage is an integrated process involving multiple mechanisms such as differentiation replacement, paracrine regulation, immune regulation, and anti-apoptotic protection. Among these, paracrine and immune regulation are considered the dominant mechanisms, while different sources of stem cells (bone marrow, fat, synovium, umbilical cord) have differences in mechanism emphasis. A deeper understanding of these mechanisms is of great significance for optimizing stem cell treatment protocols and promoting clinical translation.

4. Application

4.1. MSCs

MSCs are the most widely used cell type in current clinical research for cartilage repair. Their advantages lie in the diverse sources (bone marrow, umbilical cord, fat, synovium), clear immunomodulatory activity, and the fact that allogeneic use does not trigger severe immune rejection reactions.

A meta-analysis included 24 randomized controlled trials involving 1,389 patients to evaluate the efficacy and safety of MSC treatment for osteoarthritis. The results showed that c ompared with the control group, MSC treatment significantly improved pain (SMD = -1.31, 95% CI: -1.82 to -0.81), WOMAC score (SMD = -0.78, 95% CI: -1.09 to -0.47), cartilage volume (SMD = 0.91, 95% CI: 0.28 to 1.53), and each sub-scale of KOOS, and there was no significant difference in the incidence of adverse events (OR = 1.58, 95% CI: 0.72 to 3.47). Subgroup analysis suggested that autologous MSCs, bone marrow sources, and no scaffold injection might have better effects, but the heterogeneity was large [12].

Another II-stage randomized controlled study included 28 patients with knee joint cartilage damage, randomly assigned to the umbilical cord-derived MSCs combined with hyaluronic acid group (Arm A, 17 cases) or bone marrow aspiration concentrate combined with hyaluronic acid scaffold group (Arm B, 11 cases). The results showed that Arm A showed significant pain relief at 3 months, with the visual analogue scale (VAS) score from baseline 6.83±0.98 to 4.83±0.98 ($p < 0.01$), while Arm B only showed significant VAS improvement after 3 months. After adjusting for baseline age and VAS, the pain scores of Arm A at 6 months (2.56±1.41 vs 3.09±1.22, p=0.015) and 12 months (2.27±1.49 vs 2.50±1.35, p = 0.043) were significantly lower than those of Arm B. The KOOS scores showed a similar trend, with Arm A's corrected KOOS being significantly better than Arm B at 6 months and 12 months (p = 0.009 and p = 0.037). This data suggests that umbilical cord-derived MSCs may have better pain relief speed and persistence than the traditional bone marrow aspiration concentrate protocol [13].

4.2. iPSCs

A study published in 2025 in "NPJ Regen Med" systematically compared the performance of iPSC-derived chondrocytes and MSC-derived chondrocytes in long-term cartilage formation. During the 56-day in vitro cartilage differentiation process, the expression of COL2A1 and ACAN in the MSC group peaked on the 28th day, while in the iPSC group, it reached the highest level on the 56th day, suggesting that iPSC-derived chondrocytes have a more persistent ability to synthesize cartilage matrix. What is more noteworthy are the differences in hypertrophy and apoptosis indicators: the expression of COL10A1 and BGLAP in MSC-derived cartilage continuously increased throughout the culture period and was significantly higher than that in the iPSC group; on the 56th day, the number of apoptotic cells in the MSC-derived cartilage was significantly higher than that in the iPSC-derived cartilage. This finding has direct clinical implications - hypertrophy and apoptosis are the key risk factors leading to the degeneration and calcification of regenerated cartilage, and the advantage of iPSC-derived cartilage in this dimension may translate into a more durable repair effect [14].

A systematic review in 2021 included 8 animal studies of xenotransplantation, showing that iPSC-derived chondrocyte progenitor cells can successfully repair osteochondral defects in the knee joint, without tumor formation, and is considered a promising cell therapy [15].

5. Challenges

5.1. Heterogeneity of Efficacy and Patient Stratification

The most perplexing phenomenon in clinical trials is that the efficacy of the same product varies greatly among different patients. The sources of this heterogeneity include at least three levels: the "tolerance" differences in the joint microenvironment of patients (determined by inflammatory factor profiles, synovial fluid components, and mechanical environment); the heterogeneity of the product itself (sources, donor age, expansion generations, lack of unified standards for potency markers); and the differences in defect characteristics (size, location, accompanying force line abnormalities).

The lack of standardized potency indicators is a key bottleneck. Current clinical trials often report "MSC" uniformly, but in reality, different preparation batches and different sources of MSCs may differ by several times in their chondrogenic potential and immune regulatory ability. Before treatment, the joint microenvironment of patients can be evaluated to determine whether it is conducive to cartilage formation, thereby avoiding ineffective intervention for patients with an "unfavorable environment" [16,17].

5.2. Uncertainty in Regulatory Pathways

Cell-based cartilage repair products face multiple regulatory classifications - may be classified as biological products, devices, or combination products. In the United States, the FDA's CBER is responsible for cell therapy products, and typically requires an IND application and ultimately obtains marketing authorization through the BLA or PMA pathway. The non-clinical and clinical requirements of this process are highly dependent on the specific classification of the product, and the classification boundaries for cartilage repair products are not always clear.

The more fundamental challenge lies in the selection of clinical endpoints. How is the "success" of cartilage repair defined? Pain relief, functional improvement, MRI-documented filling of the defect, or histological confirmation of transparent cartilage formation? Early trials often rely on PROMs (patient-reported outcomes), but these indicators have limited sensitivity to structural changes and are significantly influenced by the placebo effect. The FDA's approval of cartilage repair products tends to require evidence of structural endpoints, but obtaining such evidence requires a longer follow-up period and more rigorous imaging assessment, significantly increasing research and development costs and time [18,19].

5.3. Manufacturing and Scaling Barriers

The manufacturing complexity of iPSC-derived products is much higher than that of MSCs. From iPSC cell line establishment, expansion, directed differentiation to the final product release, it involves dozens of key steps. Even a minor variation at each step can be magnified in the final product. 3D bioprinting offers the potential for process control, but the development of bioink requires a balance between printing compatibility and biological functionality. For allogeneic products, issues such as immune rejection and immunosuppression protocols also need to be addressed [20]. MSCs products also face scaling challenges. Autologous MSCs require individualized preparation and cannot achieve economies of scale; allogeneic MSCs can be batch-produced, but donor screening, aging and functional decline after expansion, as well as cold chain transportation requirements all increase costs. The current model of the ACI - two surgeries and 4 weeks of in vitro expansion - has already demonstrated the inherent difficulties of cell therapy in logistics and costs [18].

5.4. Integration and Persistence Issues

Even if the cells successfully survive and differentiate into chondrocytes, the integration of the new tissue with the host cartilage remains an unsolved problem. Cartilage has no blood vessels, and integration depends on the migration of the transplanted cells to the interface and the deposition of matrix. However, the anti-adhesion properties of mature cartilage and its low metabolic state hinder this process. The consequence of poor integration is micro-motion and stress concentration at the interface, which eventually leads to the degradation of the repaired tissue. Current strategies include enzymatic treatment (such as chondroitinase ABC) to expose binding sites, gradient scaffold design, and local release of migration-promoting factors, but none of these have been proven reliable in clinical settings [21].

6. Conclusion

Stem cell technology offers the possibility of joint cartilage repair ranging from symptom relief to structural regeneration. Current evidence-based research indicates that MSCs have relatively sufficient clinical data support in terms of short-term pain relief and functional recovery, while iPSCs demonstrate potential advantages in long-term repair quality due to the unlimited proliferation and more persistent cartilage matrix synthesis capabilities, as well as lower tendencies towards hypertrophy and apoptosis. However, more clinical verification is still needed. Future research should focus on the following directions: establishing a standardized evaluation system, combined with the assessment of the patient's joint microenvironment tolerance, to achieve the precise patient stratification and individualized treatment; optimizing the source and preparation process of stem cells, promoting the development of allogeneic, ready-to-use products, and reducing manufacturing complexity and costs; exploring combined strategies, such as the collaborative application of stem cells with exosomes, biomaterial scaffolds, gene editing, and integrin-promoting factors, to enhance the integration strength and long-term stability of the new cartilage and the host tissue; promoting international coordination of regulatory frameworks and the improvement of conditional approval pathways, to accelerate the accessibility of innovative products while ensuring long-term safety monitoring. With the deepening of mechanism research, the advancement of manufacturing technology, and the increasingly standardized clinical design, stem cell cartilage regeneration is expected to gradually move from alternative treatment to functional repair, providing a more long-term solution for osteoarthritis patients.

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