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THE USE OF STEM CELLS IN THE TREATMENT OF ARTICULAR CARTILAGE INJURIES: A COMPREHENSIVE REVIEW OF CURRENT STRATEGIES AND CLINICAL OUTCOMES

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ABSTRACT

Introduction and purpose: Articular cartilage lesions represent a major clinical problem because of the cartilage's limited self-healing capability. In this regard, current regenerative medicine approaches emphasize stem cell-based strategies, especially those that employ MSCs, as a hopeful approach toward the repair of cartilage lesions. This review aims to provide an updated synthesis of current strategies, including cellular mechanisms, delivery techniques, and clinical outcomes, with a focus on optimizing MSC-based interventions.

A brief description of the state of knowledge: MSCs from different tissues, such as bone marrow, adipose tissue, synovium, and umbilical cord, manifest dissimilar biological behaviours, which influence their therapeutic performances. They promote the repair of damaged cartilage by direct differentiation, immunomodulatory effects, and paracrine signalling. Delivery systems, like intra-articular injections and scaffold-based methods, are being refined to enhance MSC retention, viability, and integration. Preclinical models confirm their regenerative capacity, while early clinical trials have shown safety and functional improvement. However, cell heterogeneity, hypertrophic differentiation, and inflammatory environments in joints are some issues yet to be overcome.

Conclusions: Stem cell therapies, with MSCs in particular, hold immense potential for the regeneration of articular cartilage. Although present results are encouraging, additional studies should be conducted to standardize treatment protocols, improve cell sources and delivery systems, and establish long-term clinical efficacy.

KEYWORDS

Articular Cartilage, Mesenchymal Stem Cells, Cartilage Regeneration, Stem Cell Therapy, Scaffold-Based Delivery

CITATION

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Introduction and purpose

Articular cartilage injuries are a major clinical problem, given the limited self-repairing capability of the involved tissues. These injuries can result from trauma, degenerative diseases such as osteoarthritis, or the natural ageing process, causing debilitating pain, reduced functionality of joints, and decreased patient quality of life if left untreated [1, 2]. Recently, breakthroughs in regenerative medical technology have increasingly attracted attention to stem cell-based therapy, representing an innovative, alternative solution for repairing injured articular cartilage. Among the approaches developed, the application of mesenchymal stem cells (MSCs) stands out for their chondrogenic potency, their immunosuppressive role, as well as their ability to produce trophic factors that contribute to their role in repairing damaged tissues [2]. Despite the increasingly supportive literature on stem cell therapy, their application in clinical practice remains poorly developed. Concerns about inconsistency in study methodologies, variability in therapeutic preparation, or uncertain standardization remain important challenges to overcoming the hurdles of translation from research development to clinical application. This paper seeks to compile recent progress in the utilization of stem cell therapy for repairing articular cartilage injuries with emphasis on improving chondrogenic potency of mesenchymal stem cells, improving delivery systems, as well as investigating applications for clinical practice. Toward understanding methodologies used for repair results achieved, efforts seek to ensure more effective regenerative approaches for repairing injuries of the articular cartilage.

Material and Methods

This narrative review is carried out through the analysis of 33 research articles that were peer-reviewed, focusing on the application of stem cell therapy in the treatment of injuries of articular cartilage. These papers were selected through targeted search carried out on biomedical literature databases such as PubMed and Google Scholar search engines.

A broad range of publications including various study designs, such as in vitro studies, preclinical trials on animal models, as well as studies on human subjects, are reviewed. Both research publications and systematic reviews were considered for better understanding of the biological concepts, treatment modalities, or translation possibilities of cell-based therapeutic approaches.

Criteria for selection of studies were the inclusion of research that involved mesenchymal stem cells derived from multiple sources, approaches for cell delivery, use of scaffolding technology, and outcome studies more relevant to the clinical setting. Some publications were related to cutting-edge bioengineering techniques, such as scaffolding with nanotechnology or gene-modified stem cells. Others involved human clinical trials.

A qualitative thematic analysis was adopted that explored the inherent challenges, novel approaches, and broader clinical prospect of stem cell therapy for the regeneration of articular cartilage.

Description of the state of knowledge

Structure and Function of Articular Cartilage

Articular cartilage is a highly specialized connective tissue covering the surfaces of bones in synovial joints. It plays an essential biomechanical role, as it minimizes friction and distributes mechanical loads while resisting compressive forces during joint movement. These properties are supported by a biphasic composition: a fluid phase-primarily water-and a solid phase formed by a rich-in-collagen fibres and proteoglycans ECM.

From a structural standpoint, articular cartilage is separated into four zones: the superficial, middle, deep, and calcified zones. The superficial zone consists of flat, tangentially oriented chondrocytes that secrete lubricin (PRG4), which is a molecule crucial for minimizing friction. Collagen fibres in this zone are densely packed and parallel to the articular surface, providing resistance against shear stress [6]. In the middle zone, the oval or spherical chondrocytes are embedded in a matrix rich in proteoglycans with obliquely oriented collagen fibres, allowing for good absorption of compressive forces [4]. Large chondrocytes in the deep zone are orientated in vertical columns, while collagen fibres are orientated perpendicular to the surface, adding to the tissue's ability to support high compressive loads [4]. Underlying the former is the calcified zone, anchoring the cartilage to the subchondral bone and containing hypertrophic chondrocytes embedded in a mineralized matrix [6, 7].

By its structure, the ECM represents an intricately organized network of macromolecules that ensures both the structural integrity and biomechanical performance of cartilage. The major components of ECM are water, type II collagen, proteoglycans, GAGs, and several glycoproteins. Type II collagen predominates in the composition of the fibrillar matrix while types IX, XI, and VI collagens play an important role in the stabilization of the network and the modulation of the immediate pericellular environment. Type X collagen, present only in the calcified zone, is associated with hypertrophic chondrocytes and the mineralization process [4].

Among the non-collagenous components, the most abundant proteoglycan is aggrecan. It forms large aggregates with hyaluronic acid and is stabilized by link proteins, enabling the ECM to retain water and resist compressive stress. Other smaller proteoglycans, including biglycan, decorin, and fibromodulin, together with glycoproteins, like COMP, matrilins, fibronectin, and tenascin-C, further contribute to ECM architecture and facilitate interactions between cells and matrix [4, 8].

Types of Stem Cells Used in Cartilage Repair

Several stem cell sources have been investigated for cartilage repair, with mesenchymal stem cells (MSCs) being the predominantly investigated source. These multipotent stem cells can be isolated from various tissues such as bone marrow (BM-MSCs), fat (AD-MSCs), synovium (SDSCs), or umbilical cord (UC-MSCs). Originating tissue plays a crucial role in defining their biological properties such as proliferation rates, immune modulatory properties, or chondrogenic differentiation [9, 10].

BM-MSCs are viewed as the traditional cell type for cartilage repair, given their established chondrogenic properties [11]. Nevertheless, isolating BM-MSCs is a more intrusive procedure, with their regenerative property gradually lost with advancing age or diseases [10]. Notably, it was found that AD-MSCs could potentially migrate into scaffolding better than BM-MSCs, promoting enhanced integration of engineered constructs [12]. AD-MSCs are easier to obtain, with active proliferation rates but reduced chondrogenic abilities by a slight margin [11]. SDSCs were found to possess enhanced chondrogenic

differentiation properties in numerous research studies, ensuring their position as a significant candidate for cartilage tissue engineering [11]. UC-MSCs, especially those isolated from Wharton's jelly, are distinctive for their minimal immunogenic properties and the retained ability for effective cell differentiation, ensuring their utility for allogeneic transplantation applications [9].

Immunological properties constitute important factors in defining the practicability of MSCs in clinical applications, particularly allogeneic transplantations. HLA-DR, as well as costimulation molecules are low in UC-MSCs, conferring low risk of immune rejection [9].

MSCs display their immune system modulation properties through both cell interactions and the secretion of bioactive factors. MSCs are shown to modulate immune cells such as T cells, B cells, macrophages, NK cells, and dendritic cells [10]. The major bioactive factors secreted by MSCs that modulate the immune system are transforming growth factor-beta (TGF-β), interleukin-10 (IL-10), prostaglandin E2 (PGE2), and indoleamine 2,3-dioxygenase (IDO) [9].

Although MSCs were once thought to be "immune privileged," it is more accurate to classify them as "immune evasive." Indeed, MSCs were initially evasive of the immune system, but prolonged allogeneic use could potentially activate the host immune response [10].

Of the numerous factors that affect the potency of MSCs for regeneration, the age of the donor is one of the most important. Younger cells possess enhanced proliferation ability, better immunomodulation properties, and better chondrogenic differentiation capacities than cells from older individuals [10]. BM-MSCs or AD-MSCs from older donors tend to display an increased doubling time, decreased colony-forming efficiency, and higher levels of gene expression of senescence markers such as CHEK1 or ink4a [10].

Apart from age, other variables such as sex, obesity, or presence of comorbid conditions could also influence the functionality of MSCs. For example, it has been observed that the M SCs of obese patients could potentially exhibit decreased proliferative ability with more immunosuppressive effects [10].

Not only mesenchymal stem cells, but also iPSCs have recently appeared as a promising source for cartilage regeneration. Recent reports demonstrate that allogeneic transplantation of iPSC-derived cartilage organoids into chondral defects in a primate model resulted in graft survival and tissue integration in the absence of an immune response. Of note, the grafted cells expressed PRG4-a key molecule responsible for joint lubrication-revealing functional adaptation of iPSC-derived chondrocytes to the articular environment [13].

Recently, a specific type of stem cell - immunity-and-matrix-regulatory cells (IMRCs) - was developed from clinical-grade human embryonic stem cells. IMRCs are similar to typical mesenchymal stem cells in many respects, with the capability of tri-lineage differentiation and expression of typical MSC surface markers; however, they also possess enhanced immunomodulatory and matrix-regulatory properties. Large-scale production under GMP conditions can be achieved with stable quality for providing consistent and potent sources for regenerative therapies [14].

TSPCs are also an attractive cell source for cartilage repair, especially for those patients under ligament reconstruction, in whom autologous TSPCs can be provided from surplus graft tissues. This cell type exhibits high proliferative activity and undergoes chondrogenic differentiation when cultured on decellularized cartilage matrix even without exogenous growth factor supplementation, indicating its potential in combined strategies of cartilage–ligament repair.

In all, different types of stem cells, including MSCs from different tissues, iPSCs, IMRCs, and TSPCs, present various biological benefits for cartilage regeneration. Their therapeutic functionalities relate to cell source, donor features, immunomodulatory properties, and the capacity for differentiation, all features that need consideration for optimization of the regenerative effect.

Mechanisms of Action

Mesenchymal stem cells (MSCs) were shown to support cartilage repair in several ways: by direct differentiation into chondrocytes, by immunomodulation, or by paracrine effects. While their differentiation potential is important, there is an increasingly great body of evidence that the therapeutic properties of MSCs are achieved through their secretome—their vast resource of trophic factors that affect other cells and tissues [1, 16].

Paracrine secretion by MSCs involves the release of various growth factors such as Transforming growth Factor Beta (TGF-β), Insulin-Like Growth Factor 1 (IGF-1), Fibroblast Growth Factor 2 (FGF-2), and Hepatocyte Growth Factor (HGF). These factors work by promoting the proliferation of endogenous chondrocytes, improving the secretion of the extracellular matrix, as well as protecting the integrity of the cartilage tissue [9]. Moreover, these factors secrete extracellular vesicles that carry factors such as cytokines, chemokines, and microRNAs that are involved in remodeling the extracellular matrix as well as inhibiting inflammation [9, 17].

Apart from their paracrine properties, MSCs also possess robust immunomodulatory properties in the joint microenvironment. Inflammatory cell infiltration by immune cells such as macrophages, T-lymphocytes, and B-lymphocytes is one of the major contributing factors in the progression of osteoarthritis. This can be overridden by MSCs through the secretion of various bioactive factors such as cytokines, which work to reduce inflammation and repair tissues [18].

A major mechanism is related to the polarization of macrophages from the pro-inflammatory M1 type to the anti-inflammatory M2 type. MSC-derived exosomes that are miR-135b-enriched, especially those that were TGF-β1-mediated, were found to suppress the expression of iNOS and support the expression of Arg-1, which are characteristic of the M2 type. This polarization is linked with decreased cartilage damage with beneficial repair of OA in experimental models [18].

MSCs also have the ability to differentiate into chondrocytes under certain biochemical and physical conditions. This occurs as a multistep process that follows the pathway of endochondral ossification. Cellular condensation and matrix production proceed with chondrogenic commitment and maturation, and terminate with tissue remodeling [11].

Multiple signaling cascades regulate chondrogenic differentiation, but the TGF-β and Smad pathways stand out for their central roles. Activated Smad2/3, in complex with Smad4, translocates to the nucleus and activates the expression of important genes such as SOX9 and COL2A1 [11]. Other pathways-RhoA/ROCK and MAPK (p38 and ERK-further refine these outcomes: p38 promotes chondrogenesis, whereas ERK inhibits it [11].

Other genes are also an critical part, and stimulation of these genes might promise some effective results. In vivo studies have suggested that BMP2 stimulation in combination with VEGF inhibition can drive endogenous stem cells toward cartilage regeneration in degenerative lesions, forming a stable, mature cartilage tissue [19].

Another gene that because of its protective properties, represents a promising target for therapeutic application is TNFAIP3. Overexpression of TNFAIP3 increases the functional properties of ACSCs toward better repair of the subchondral bony structure in arthritic conditions due to their local inhibitory effect on osteoclastic activity at places of pathological bone resorption.

It has been shown that external factors may influence the results of MSC chondrogenesis, such as growth factor gradients, scaffold composition, and coculture with chondrocytes. Over the last few decades, MSCs have been widely used to establish cartilage-like tissues; however, how to maintain a stable chondrogenic phenotype and avoid hypertrophic differentiation remains a major challenge for long-term cartilage repair [11].

Taken together, these mechanisms point out the complexity of the role played by MSCs in cartilage regeneration, underlining their therapeutic potential as cellular building blocks and as active joint microenvironment regulators.

Delivery Methods

The MAS cell delivery technique to the areas of damaged cartilage is one of the major factors that influence the effectiveness of therapy. Some widely used techniques for MAS cell delivery include intra-articular injection and implantation with scaffolds, which have their merits depending on the situation [21, 22].

IA injection is a minimally invasive procedure that is widely used both in clinical practice and research. This procedure makes it possible to directly implant MSCs into the joints, which would potentially provide relief from pain, reduce or modify the inflammation process, or even partly suppress the progression of the disease. It was shown in clinical trials that one IA injection of allogeneic bone marrow-derived MSCs could result in pain relief and improve joint functioning in patients with knee osteoarthritis without any severe side effects [21].

Scaffold-based delivery, on the other hand, offers structural support that can potentially enhance MSC retention, survival, and integration into the area of damage. Three-dimensional scaffolds support cell transplantation by allowing cell interactions with the extrinsic matrix surrounding the cell, as well as host cell migration into the area of damage [22].

Of the various scaffolds developed, injectable hydrogels are especially of great interest, as they can fill irregularly shaped defects, promoting the regeneration of cartilage in situ. It can provide a biocompatible setting that is rich in growth factors [23]. It is low in strength, such that it would not be able to resist mechanical stresses. This could be resolved by using a combination of hydrogels with biodegradable polymers such as poly(lactic-co-glycolic) acid or PLGA scaffolds. These scaffolds provide better strength with controlled degradation without inhibiting cell viability [23].

Currently, there has also been great emphasis on improving the functionality of stem cells using techniques such as surface modification of scaffolds with bioactive factors. Coating the scaffolds with

hydrophilic molecules such as hyaluronic acid (HA), collagen, or chondroitin sulfate (CS) helps in improving MSC cell adhesion, proliferation, and chondrogenic differentiation [24].

For instance, HA-modified PLGA or PLLA scaffolds showed considerable stimulation of chondrogenesis in AD-MSCs, whereas CS-grafted PLLA fibers enhanced cartilage repair in vivo. These scaffolds are designed to mimic the components of the natural extracellular matrix for better cell-matrix interactions [24]. Moreover, composite scaffolds with multiple layers of anti-inflammatory cytokines such as IL-4 or IL-13 or chemotactic factors such as CXCL12 support spatial and temporal loading for enhanced MSC homing and regulation of the immune microenvironment [24].

Electrospun scaffolds of both Polycaprolactone (PCL) and PLGA with a ratio of 80:20 were also found to possess good characteristics for use in cartilage tissue engineering. These scaffolds were observed to support cell adhesion, migration, chondrogenic differentiation when seeded with mesenchymal stem cells of the dental follicle (DFMSCs), as well as achieve complete repair of the defects with integration with the surrounding cartilage tissue upon implantation into the body [25].

Within the novel delivery systems, injectable porous microspheres are a promising, minimally invasive, and versatile approach for the promotion of cartilage regeneration. Recently, aldehyde-modified PLGA-based microspheres that were functionalized with platelet-derived growth factor-AB (PDGF-AB), kartogenin, and metformin were explored. This approach allowed for the simultaneous harnessing of host-derived MSCs with the reprogramming of the immune microenvironment through macrophage polarization. These microspheres induced chondrogenic differentiation for enhanced host tissue integration, thereby promoting significant cartilage repair in a rat osteoarthritis model [26].

A delivery system would also encompass the transplantation of MSCs along with particulate allogenic cartilage matrix. This delivery system has been observed in clinical practice to retain cells effectively and improve integration with the host cartilage, resulting in better outcomes than using MSCs alone. This particulate allogenic matrix works as a scaffolding material and contains chondrogenic growth factors that help in regeneration [27].

Taken together, the selection of delivery strategies for MSCs, ranging from simple intra-articular injection to bioengineered scaffolds, is crucial to unlock the full therapeutic potential of stem cell therapy for cartilage repair.

Preclinical and Clinical Evidence

Preclinical studies involving large animal models have considerably aided in understanding the safety and therapeutic efficacy of MSCs in the repair of cartilage. In a porcine model of osteochondral defect, autologous bone marrow-derived MSCs were immobilized in a polyglycolic acid–hyaluronan scaffold using a plasma-based hydrogel and implanted into knee joint lesions.

The histological evaluation on post-injury day 90 demonstrated significant creation of hyaline-like cartilage in MSC-loaded scaffold-treated defects, while untreated controls mainly developed fibrous tissue. No systemic inflammatory response or local adverse effects were noted, further supporting the safety of the approach. Combining MSCs with a biocompatible scaffold has been shown to enhance functional tissue regeneration in a clinically relevant large animal model.

Small animal models have also played a crucial role in evaluating the regenerative potential of MSC-derived therapies in osteoarthritis. In a rat OA model, induced by anterior cruciate ligament transection with partial medial meniscectomy, exosomes derived from human umbilical cord MSCs significantly attenuated cartilage degradation and promoted the tissue repair [28].

Therefore, hUC-MSC-derived exosomes, through twice-weekly intra-articular administration for four continuous weeks, protected cartilage structure and significantly decreased histological damage scores. Treatment promoted the proliferation and migration of chondrocytes and inhibited IL-1β-mediated apoptosis and matrix degradation, reflected by maintained COL2A1, SOX9, and aggrecan expression and lowered levels of MMP-13 and ADAMTS5 [28]. The findings indicate the therapeutic potential for MSC-derived exosomes in treating inflammatory and degenerative joint diseases.

More recently, preclinical data suggest that even a clinically feasible dose of 3×10^7 MSCs is capable of significantly reducing cartilage degradation and alleviating joint pain in posttraumatic osteoarthritis models, although the higher the dose, the stronger the protective effects [29].

Comparative preclinical studies have established that the regenerative performance of MSCs depends on the tissue from which they were derived. BM-MSCs, which have shown chondrogenic capacity, represent the ones that are most commonly used. AD-MSCs are also used because of their high proliferative potential

and ease of harvest. On the other hand, several animal models have shown that SM-MSCs have the highest chondrogenic potential of the three [9, 10].

In one rabbit model of cartilage injury, intra-articular injection of SM-MSCs resulted in better repair compared to both BM-MSCs and AD-MSCs, characterized by higher expression of cartilage markers and more complete restoration of the structural integrity of cartilage. The SM-MSCs were also less affected by donor age and had more immunomodulatory capabilities, such as suppression of pro-inflammatory cytokines including TNF-α and IL-17A [9]. Given these characteristics, SM-MSCs may represent especially promising cells for cartilage regeneration in preclinical and perhaps clinical applications.

Early clinical trials so far have shown that IA injection of MSCs is a safe and effective treatment for knee osteoarthritis. Patients involved in the randomized, double-blind, placebo-controlled trial received a single IA injection of allogeneic BM-MSCs or saline. Over 12 months of follow-up, MSC-treated patients showed significant improvement in pain and function as measured by WOMAC and KOOS scores compared to the control group [21].

MRI findings of quantitative T2 cartilage mapping also showed that MSC treatment slowed cartilage degeneration and thus is potentially disease-modifying. No serious adverse events were recorded, and mild local reactions resolved spontaneously without any intervention. This series of results provides supporting evidence for the feasibility of the MSC therapy as minimally invasive and well-tolerated intervention in OA.

Due to their high proliferative ability and accessibility, adipose-derived MSCs have also been clinically explored. A total of 40 patients with moderate knee OA were treated in a randomized, double-blind, placebo-controlled phase I/IIa clinical trial with a single intra-articular injection of an allogeneic AD-MSC preparation, MAG200, at ascending doses from 10 to 100 million cells, or placebo.

Over 12 months, the treatment was well tolerated and associated with a higher proportion of clinical responders compared to placebo. The changes in pain and functional scores reached statistical significance in the lower and intermediate dose cohorts. MRI assessment also demonstrated a perceived trend for the treated groups toward cartilage volume preservation, where disease progression was demonstrated in the placebo group. These findings point toward the therapeutic potential of allogeneic AD-MSCs as a scalable and effective strategy in OA treatment [30].

Despite these promising clinical outcomes, there are numerous disadvantages that hamper the wider application and long-term verification of MSC-based therapies. Of note, one important obstacle is the disparity in therapeutic approaches among investigations. The source of the MSCs, cell dose, mode of delivery, and use of adjuvant therapies all vary and do not allow comparability among clinical trials, making the development of standard treatment recommendations burdensome to construct [3].

Besides, there is a continuing concern about long-term follow-up availability. In contrast to already established methods of treatment like ACI, most trials with MSCs lack extended observation periods, thus further limiting our knowledge about their efficacy and safety for a very long period. While some theoretical risks include the formation of tumors or growth of ectopic tissues, none of these have surfaced in the clinical scenarios. Larger randomized trials with longer follow-up are, however, needed to fully assess durability and risk profile of these MSC-based interventions.

Preclinical and clinical studies have demonstrated that MSC-based therapies may have great promise for cartilage repair, but these approaches need further research to overcome limitations in current studies and to establish standardized treatment protocols for long-term use.

Challenges and Limitations

In one rabbit model of cartilage injury, the intra-articular injection of SM-MSCs achieved better repair compared to both BM-MSCs and AD-MSCs, with higher expression of cartilage markers and more complete restoration of structural integrity in the cartilage. It was less affected by donor age and also possessed more immunomodulatory capabilities, such as suppression of pro-inflammatory cytokines including TNF-α and IL-17A [9]. With these characteristics, SM-MSCs could represent especially promising cells in cartilage regeneration for preclinical and perhaps clinical applications.

The early clinical trials so far have demonstrated that IA injection of MSCs is safe and effective in treating knee osteoarthritis. Patients involved in the randomized, double-blind, placebo-controlled trial received a single IA injection of allogeneic BM-MSCs or saline. Follow-up over 12 months demonstrated significant improvement in pain and function, as measured by WOMAC and KOOS scores, in MSC-treated patients compared to the control group.

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Despite these promising clinical outcomes, there are several disadvantages that impede the broader applicability and long-term validation of MSC-based therapies. Specifically, one major barrier is the variability in therapeutic strategies among studies. The origin of the MSCs, cell dose, route of administration, and administration of adjuvant therapies all differ and preclude comparison across clinical trials, which creates a challenge for establishing consensus treatment guidelines [3].

Moreover, there is a continued concern about the availability of long-term follow-up. In contrast to most of the other currently established treatment modalities, such as ACI, trials involving MSCs generally lack extended periods of observation, thus even further limiting our knowledge about their efficacy and safety for very long periods. Whereas some theoretical risks include tumor formation or growth of ectopic tissues, none of these have come to the front in clinical scenarios. Larger randomized trials with longer follow-up are, however, needed to fully assess durability and risk profile of these MSC-based interventions.

Preclinical and clinical trials have given promise to the fact that MSC-based therapies might have tremendous potential for cartilage repair; however, these approaches need further research to overcome limitations in present studies and to establish standardized treatment protocols for long-term use. Recent studies have focused on biomaterial-based strategies to improve MSC retention and interface integration. For instance, the incorporation of RGD peptides into HA hydrogels used to modify defect sites enhanced MSC adhesion, induced focal contact formation, and facilitated mechanosensing. These events favor nuclear translocation of YAP/TAZ-transcriptional coactivators that drive matrix production and chondrogenic signaling-which ultimately improves cell performance at the repair site [5]. Such biofunctional scaffolds represent a promising means of overcoming the structural obstacles to long-term integration.

Another point of concern is that the inflammatory milieu in osteoarthritic joints creates an adversity for effective MSC-based therapy. Exposure to pro-inflammatory cytokines, like IFN-γ, IL-1β, and IL-17A, impacts MSC viability and modulates their immunological profile. Nonetheless, MSCs possess a unique capacity to respond to inflammatory cues by activating counter-regulatory, anti-inflammatory mechanisms [10].

As such, it has been demonstrated that IFN-γ upregulates the expression of indoleamine 2,3-dioxygenase (IDO) in MSCs through the JAK-STAT1 pathway. This further enhances their T cell suppression ability and orients the macrophages toward the anti-inflammatory M2 phenotype. Similarly, the presence of IL-17A enhances the secretion of prostaglandin E2 and promotes the expansion of Tregs, thereby contributing to immune tolerance within the joint environment. While an advantage of these adaptive responses is clear, sustained inflammation may still compromise the long-term effectiveness of MSC-based interventions.

It has also been demonstrated that patient-specific factors, such as age, sex, and body mass index, can significantly impact the results of the cartilage repair procedures. Higher BMI was found moderately associated with a higher risk of graft hypertrophy, while higher age correlated with poorer functional results. These findings again emphasize careful selection and individualization of treatment strategies in regenerative cartilage therapies [31].

In all, this essentially means that surmounting biological, technical, and environmental challenges of MSC-based cartilage repair is necessary for tapping their full therapeutic potential as far as durable, reproducible clinical outcomes are concerned.

Conclusions

In this regard, stem cell-based therapies, especially with MSCs, represent a promising frontier in the treatment of articular cartilage injuries. The multi-faceted mechanisms of MSCs involve the capability for chondrogenic differentiation, immunomodulation, and paracrine signalling that enable both structural and functional support for cartilage regeneration. The enhancements in delivery methodologies, especially scaffold-based implantations and intra-articular injections, have further enhanced the therapeutic functionality of MSCs by bringing improvement in cell retention, viability, and integration.

Preclinical and clinical data appear to support the safety and efficacy of MSC-based therapies. Different tissues, including bone marrow, adipose tissue, synovium, and umbilical cord, represent various advantageous sources. However, many factors have prevented standardization of these therapies for long-term clinical outcomes: biological heterogeneity among the MSC populations, instability in the chondrogenic phenotype, limited integration with host tissue, and modulation by the inflammatory environment of the joint.

To fully realize the potential of MSC-based cartilage repair, future research must be focused on cell source optimization, delivery strategy, and biofunctional scaffolds. Moreover, harmonization of clinical protocols, including long-term follow-up in trials, is badly needed to translate such regenerative techniques into consistent and durable clinical outcomes.

Disclosure

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