Treatment and application of stem cells from different sources for cartilage injury: a literature review

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Background and Objective: Cartilage defects and degeneration have a major impact on daily mobility and quality of life for millions of people worldwide. As the most effective seed cells for tissue engineering applications in regenerative medicine, mesenchymal stem cells (MSCs) are pluripotent cells with mesoderm and neural crest origin. The combination of biomaterial scaffolds with stem cells and drugs for cartilage damage repair has brought much hope to the medical field.

Methods: We searched and compared the literature on cartilage damage repaired by stem cells through PubMed and Web of Science method, this review summarizes the research progress of mesenchymal stem cells from various tissue sources in repairing articular cartilage injury.

Key Content and Findings: We found that peripheral blood, bone marrow, umbilical cord blood, adipose tissue, and umbilical cord are classic stem cell sources. Stem cells can be stimulated by various growth factors, recombinant proteins, or important monomers to generate cartilage in vitro. At the same time, MSCs obtained from various sources can secrete different growth factors to further regulate their own cartilage formation. These stem cells may promote the cartilage damage repair by promoting differentiation and fighting inflammation.

Conclusions: This review summarizes and discusses the advantages and disadvantages of the ability of MSCs from different sources to treat cartilage injury, and provides help and identification for the subsequent in-depth research and preclinical application of various MSCs.

Keywords: Cartilage defects; scaffolds; mesenchymal stem cells (MSCs)

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Introduction

In view of the lack of vascularization and the insufficient number of cartilage cells, articular cartilage has extremely poor repair and self-healing capabilities (1). In this case, the first choice is the treatment of focal cartilage lesions. Otherwise, full-scale joint defects may occur. At the same time, if conservative treatment fails, joint replacement surgery may eventually be required. This review aims to describe in detail the latest advances in the repair of cartilage damage by stem cells derived from various tissues and explore its clinical efficacy and theoretical research.

Traditional cartilage repair treatment methods mainly refer to bone marrow stimulation techniques. Common

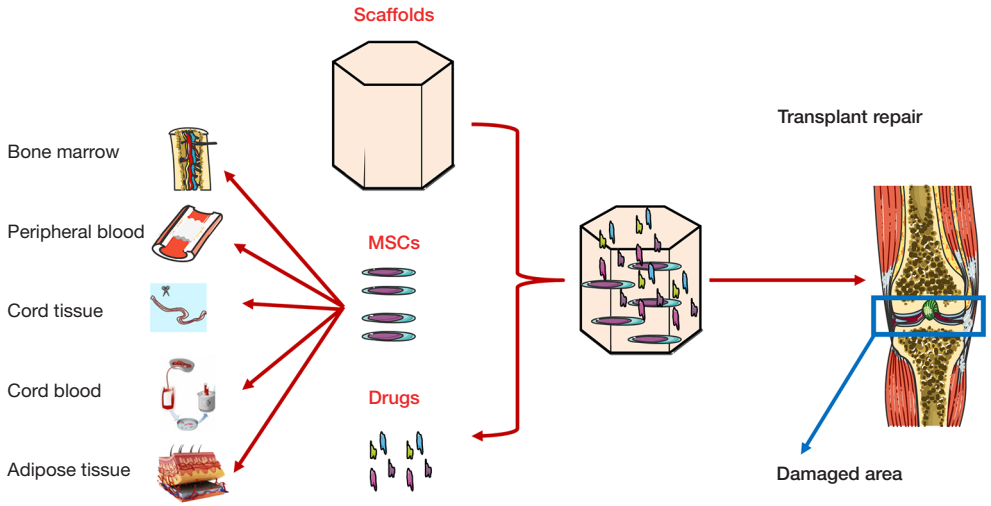

Figure 1 Multiple sources and applications of MSCs in tissue engineering. MSCs are derived from a variety of tissues, such as the umbilical cord, adipose tissue, umbilical cord blood, bone marrow, and peripheral blood. They can form complexes with scaffolds and cytokines for cartilage regeneration. MSCs, mesenchymal stem cells.

methods include microfractures, subchondral drilling, cartilage angioplasty, and nanofractures (2). The unified goal of these technologies is to enable pluripotent bone marrow mesenchymal stem cells (BM-MSCs) to migrate to the damaged area and undergo subsequent cartilage differentiation. However, regenerated tissues are usually unable to resist the continuous stress imposed on them because they do not have the biomechanical and biochemical properties of natural cartilage (3). In recent decades, with the development of new treatment options, the treatment of articular cartilage lesions has become more and more realistic.

Regenerating damaged tissues into joints with biological and biomechanical characteristics is the most important aim of tissue engineering (4). Tissue engineering requires three elements (*Figure 1*). Firstly, it requires cells that can differentiate into specific phenotypes under specific conditions, and research in this field constitutes most of the content and framework of this review. Growth factors, cytokines, hormones and monomers of Traditional Chinese Medicine (TCM), etc., affect the growth and differentiation of stem cells, which were called the second element of tissue engineering, in addition, scaffolds for providing a sufficiently stable three-dimensional environment are necessary (5,6).

Cells expressing CD73, CD105 and CD90 but not CD34, CD79, CD14, CD45 or HLA-DR are defined as stem cells by the International Society for Cell Therapy (ISCT) Mesenchymal and Tissue Stem Cell Committee (7). MSCs are pluripotent stem cells with multi-directional differentiation and self-renewal ability, which can be used to treat various diseases (8). Mesenchymal stem cells can be used to treat autoimmune diseases due to the immunomodulatory properties of stem cells (9). MSCs can also be used in the repair of articular cartilage damage (10), bone formation (11), cartilage regeneration (12), prevention of myocardial infarction (13), MSCs repair various tissues and organs mainly by promoting the proliferation of organ cells and inhibiting the inflammatory response and apoptosis of tissue-derived cells (14).

Mesenchymal stem cells have different phenotypes and functions, and this heterogeneity is determined by different cell populations, donors and tissues (15). There are studies reporting that donor variation, such as age (16), sex (17), and physiological status (18), could result in functional differences in MSCs. It was also reported that chemotaxis-related gene expression differences exist between human adipose-derived MSCs (hAD-MSCs) and human bone marrow mesenchymal stem cells (hBM-MSCs) (19). It was suggested that BM-MSCs were more immunomodulatory than placenta-derived MSCs (PD-MSCs) in commercial regenerative or transplantation medicine (20).

Growth factors, which are molecular peptides with biological activities originating from cells and tissues of the body, regulate cell division, growth, and differentiation. Growth factors also regulate and balance articular

Table 1 The search strategy summary

Items	Specification
Date of Search (specified to date, month and year)	Jan 1st, 2022
Databases and other sources searched	PubMed, Web of Science
Search terms used (including MeSH and free text search terms and filters)	"Bone marrow mesenchymal stem cells", "adipose mesenchymal stem cells", "umbilical cord blood mesenchymal stem cells", "peripheral blood mesenchymal stem cells", and "cartilage damage repair"
Timeframe	From Jan 1st, 1994 to Dec 1st, 2021
Inclusion and exclusion criteria (study type, language restrictions, etc.)	All references were SCI indexed articles written in English
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Two independent reviewers screened the titles and abstracts to assess eligibility
Any additional considerations, if applicable	None

cartilage development and homeostasis (21). It was shown that insulin-like growth factor 1 (IGF-1) was used for maintaining a coherent and intact articular cartilage surface in rats (22). As a proliferation-related gene, bFGF plays a role in promoting MSC proliferation and the synthesis of hepatocyte growth factor (HGF), and can promote the maintenance of the differentiation potential and immune properties of MSCs (23). TGF-β1, derived from the TGF-β superfamily, can stimulate bone marrow-derived MSCs to generate cartilage and participate in and regulate early chondrogenesis in the inner synovial layer (24,25). It has also been reported in the literature that TGF-β2 plays a significant role in enhancing the repair of cartilage defects in rabbits (26). In mouse articular cartilage defects, BMP-7 was shown to be beneficial for symptomatic relief of osteochondral or focal cartilage defects (27).

In fact, there are no standardized procedures for the isolation, culture, and expansion of stromal cell populations and the induction of late differentiation due to the difference between the source of the laboratory and the donor tissue. Normally, under aseptic conditions, tissue samples are collected and the cells are separated by enzymatic digestion, tissue culture and density gradient centrifugation. Next, the cells are seeded and induced in a dish for different purposes (28). Culture media including dexamethasone, insulin, sodium pyruvate, ascorbic acid, and growth factors (such as TGF-β, BMP, or TCM monomers) can successfully and classically induce stem cells to generate cartilage (29). Alcian blue and safranin staining and molecular detection methods are generally used to confirm cartilage aggrecan (AGG) production (30).

The 3D microspace is beneficial for the division, proliferation, and directed differentiation of stem cells (31). The microspace is constructed by scaffold material that can maintain a certain concentration of growth factors and oxygen and provide space for cell growth. The scaffold material and its properties such as porosity (32), stiffness, mechanical force, and biodegradability (33) will affect the regeneration of cartilage tissue. Therefore, in tissue engineering, growth factors and scaffolds usually combine cells to form a 3D complex for tissue regeneration. For cartilage repair, a variety of cell sources are currently available, and new cell sources may appear in the future. The following content aims at following the latest progress and application of stem cells in cartilage damage treatment. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1715/rc).

Methods

We conducted a literature search for published manuscripts on stem cells/cartilage damage repair to December 2021 in the PubMed and Web of Science. We used the following search words and terms: "Bone marrow mesenchymal stem cells", "adipose mesenchymal stem cells", "umbilical cord blood mesenchymal stem cells", "peripheral blood mesenchymal stem cells", and "cartilage damage repair". Useful data were extracted by carefully reading and taking notes and summarizing each paper to avoid missing potentially valuable data (*Table 1*).

Discussion

Multipotent cells for cartilage repair

As previous seed cells, articular chondrocytes have been commonly used in autologous chondrocyte transplantation (34). Unfortunately, *in vivo* treatment of articular chondrocytes cultured *in vitro* is often limited by certain characteristics. One is that the viability of chondrocytes is limited, and the other is that the chondrocytes need to be expanded in a dedifferentiated state *in vitro* (35). In a report by Brittberg and colleagues, 14 of 16 patients with femoral condyle lesions were symptomatic in a 2-year survey after autologous chondrocyte implantation (ACI) surgery in 1994 (36). Confirming the safety of the procedure, changes in various clinical scores were increased by the 2-year survey and follow-up (37,38). However, it has been reported that the structure of the graft site changes after ACI, and the cartilage injury site presents repaired tissue composed of fibrocartilage with no biological properties (39). Continuous clinical follow-up experiments show that due to the shortcomings of ACI, it may not be the most effective treatment for articular cartilage damage.

MSCs are easy to culture and expand *in vitro* and have the potential to generate cartilage. Therefore, they are considered as the preferred seed cells for cartilage tissue engineering. Numerous studies have reported that MSCs can be expertly and efficiently isolated, identified, expanded, and characterized from various sources such as adipose tissue (40), synovium (41), bone marrow (42), periosteum (43), umbilical cord (44), and peripheral blood (45). The abundance of stem cell sources has been well explored and studied by researchers. Below, we will individually describe, compare, and analyze the strengths and weaknesses of different tissue sources of stem cells in detail. Compared with previous research, our study also summarizes the characteristics of stem cells from various sources and their application in articular cartilage injury, the regulatory role of various growth factors and some active monomers of TCM in stem cell tissue engineering, and At the same time, the role of some scaffolds such as hyaluronic acid (HA) and demineralized cancelous bone (DCB) in the prevention and treatment of articular cartilage damage by tissue engineering has also been discussed in this study.

Bone marrow

BM-MSCs have the advantages of strong proliferation ability, little damage, good chondrogenesis potential, and easy collection, and have become the preferred seed cells for cartilage regeneration (46). It is reported in the literature that bFGF encapsulated in a biodegradable 3D scaffold loaded with BM-MSCs regulated a-SMA expression and promoted nascent cartilage stretch and spreading in tissue engineering (47). BM-MSC-engineered tissue can promote cartilage formation and provide a reference standard for the improvement of the shape and mechanical properties of engineered cartilage. It is reported that 3D bioprinted scaffolds of hydrogel-PCL complexes encapsulating GDF-5 and BM-MSCs can significantly promote cartilage repair (48). This indicates that the BM-MSC loaded scaffold combined with GDF-5 implanted in the cartilage damage area can be used for cartilage repair by 3D printing. As a commonly used large animal preclinical model, BM-MSCs have shown promise in the repair of articular cartilage damage in sheep. It has been reported and confirmed that the characterization of BM-MSCs loaded on alginate-foams facilitates *in vivo* use for repair and regeneration of cartilage tissue using three-dimensional tissue engineering method (49). As reported in the literature, BM-MSC-loaded scaffold complex transplantation can effectively promote osteochondral defect repair in rats by inhibiting the PLCγ1 pathway (50). It was reported that polyethersulfone (PES) scaffolds could promote the increased activity and differentiation of BM-MSCs and could significantly increase the chondrogenic differentiation potential of BM-MSCs (51).

BM-MSCs have the advantages of non-tumorigenicity, non-immunity, convenient storage and transportation, etc., so, BM-MSCs are the preferred recommendation for promoting articular cartilage damage in mice. BM-MSC-derived exosomes have also been reported to repair articular cartilage damage, and compared with classical MSC therapy, MSC-derived exosomes are coated on scaffolds for transplantation (52). It has been reported in the literature that BM-MSC-derived exosomes are significantly beneficial for chondrocyte extracellular matrix (ECM) secretion and articular cartilage damage repair, and at the same time, BM-MSC-derived exosomes could relieve cartilage defect-induced knee joint pain in OA rats (53).

Currently, the core concern regarding the use of BM-MSCs loaded on scaffolds for cartilage damage repair is the risk of tumorigenesis, especially in the isolation and expansion of BM-MSCs in vitro. On the one hand, BM-MSCs have strong expansion and differentiation potential *in vitro*, while on the other hand, they may not form tumors or develop inflammatory responses because BM-MSCs

have antitumor and anti-inflammatory properties (54). A clinical follow-up trial (10 years) showed that treatment of articular cartilage lesions with BM-MSCs and ACI had essentially the same clinical outcome, with a very low risk of tumorigenesis (55). In addition, the relatively easy isolation of BM-MSCs can effectively avoid unnecessary second surgical procedures and the onset of donor site infections. In the future, more clinical follow-up experiments need to be carried out, which are expected to prove the superiority of BM-MSCs in repairing cartilage damage.

Adipose tissue

Compared with BM-MSCs, AD-MSCs have a broader and more abundant source. In fact, the viability and number of AD-MSCs are not affected by the donor, thereby having significant advantages in cell-based therapy and tissue damage repair and regeneration, such as for articular cartilage defects (56,57). AD-MSCs have similar characteristics to BM-MSCs, including growth characteristics, secreted protein profile, differentiation ability, and low immunogenicity, and AD-MSCs are considered to be the preferred seed cells for cartilage defect repair (58). AD-MSCs have been used for transplantation into osteoporosis-induced osteoarticular cartilage lesions due to their osteoblastic differentiation, which was ultimately proven to be an effective protocol (59,60). It was demonstrated that there were no adverse events at 6-month follow-up for patients with knee OA who underwent intra-articular injection of autologous AD-MSCs, showing significantly reduced wear and improved cartilage function in a clinical study. This clinical outcome requires long-term follow-up and larger a sample size for confirmation (61).

It has been reported that the combination use of insulin-like growth factor 1 (IGF-1) and TGF-β1 improved the chondrogenic differentiation of AD-MSCs (62). It was suggested that allogeneic AD-MSCs transplanted into osteochondral defects in a rabbit model achieved good repair results (63), and a method of using molds to prepare MSC scaffold complexes has been successfully proposed (64). By implanting the scaffolded AD-MSC constructs produced from a "mold" into articular cartilage lesions in both small and large animals for repair, the end result is the simultaneous regeneration and reformation of subchondral bone and superficial articular cartilage under the treatment of the graft (64). Furthermore, MSCs implanted in osteochondral defects were loaded on scaffolds that adhered to the defect and regenerated subchondral bone and articular cartilage *in vivo* (63). Although immune rejection caused by allogeneic MSCs is unavoidable, it was confirmed that AD-MSCs and their vesicle secretions can increase cellular immune tolerance (65). Responses from allogeneic MSC transplantation to donor antigens were not enhanced (66).

Peripheral blood (PB)

According to recent reports, PB mesenchymal stem cells (PB-MSCs) are a preferred replacement for BM-MSCs. PB-MSCs have chondrogenic differentiation potential similar to BM-MSCs, which has been gradually confirmed through *in vivo* and *in vitro* research (67,68).

Demineralized cancellous bone (DCB) is used as a classic 3D bioactive scaffold for cartilage tissue engineering. It has been reported in the literature that DCB can benefit PB-MSCs in cartilage formation. In a previous study, rabbit PB-MSCs were seeded on porcine DCB scaffolds and cartilage damage repair was achieved (69). It has been reported in the literature that the repair complex is constructed from chitosan sustained-release microspheres/DBM scaffolds, PB-MSCs, BMP-2, and TGF-β3, and the complex cartilage has a good repair effect on porcine cartilage defects (70). To date, the optimal cell seeding densities involved in the transplantation of scaffold-encapsulated MSCs have remained unconvincing. An authoritative review showed that in human clinical study, the density of MSCs used for cartilage repair varied from 2×10^6–8×10^7 cells/mL (71). Constrained by the knee joint space, excessive cell densities can trigger hypoxia and subsequent cell death (72). Considering the lack of evidence for the clinical implementation and application of PB-MSCs in cartilage regeneration and repair, the optimal concentration of PB-MSCs remains to be explored. In general, unlike other tissue-derived MSCs, PB-MSCs are more difficult to culture *in vitro*, which is also why there are less reports on their clinical application. However, because PB-MSCs have the characteristics of repeatable sampling, conforming to clinical ethics, and easy sample collection, they still have broad application prospects (73).

Umbilical cord blood

Compared with MSCs of various origins, human umbilical cord blood-derived MSCs (hUCB-MSCs) showed powerful cartilage regeneration potential and repair ability, and this repair was not accompanied by cartilage degradation or bone formation after repair (74-76). hUCB-MSCs have additional innate advantages due to their excellent *in vitro* passaging and

expansion levels, non-tumorigenicity, and ultra-low immune response. In addition, hUCB-MSCs can generally be produced as a commercial product and provide a very high-purity stem cell population for cartilage injury (77-79).

It has been reported in the literature that after implanting the UCB-MSC-hydroxyapatite (HA) scaffold complex into a patient with joint injury, the results of arthroscopy showed that the cartilage injury was improved and pain disappeared. UCB-MSC-HA is clearly the best choice for the prevention and treatment of knee cartilage defects and wear in patients with OA (80). The researchers cross-linked HA hydrogel (4%) with hUCB-MSCs (0.5×10^7–3×10^7 cells/mL) to obtain a complex, and transplanted the complex into minipigs with articular cartilage damage. The pigs were sacrificed 12 weeks after surgery. Samples were obtained and histological analysis revealed that the hyaline cartilage from the grafted joint was intact and coherent compared to the control knee. hUCB-MSCs have strong proliferation and chondrogenic differentiation ability, leading to their great cartilage regeneration potential. In the future, the composites of hUCB-MSCs and HA hydrogels will likely be applied in large animal models to further verify their superior reparative effects, and theoretical evidence from these basic models will provide evidence and reference for human clinical trials (81).

Umbilical cord

Umbilical cord mesenchymal stem cells (UC-MSCs) have gradually sprung up in the past decade. According to the report, UC-MSCs should be able to differentiate into osteogenic, adipogenic and chondrogenic lineages. Using umbilical cord stem cells to regenerate cartilage would be an extremely powerful alternative for allografting. Compared with traditional autologous chondrocytes for the prevention and treatment of articular cartilage wear and trauma, the use of UC-MSCs encapsulated on the scaffold is inexpensive, ethical, has better mechanical properties and biological activity, and has no risk of immune rejection (82).

Specialized in cartilage repair and regeneration, UC-MSCs have increasingly evolved into alternative seed cells with significant advantages. A large number of experiments demonstrated that Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) are potential to differentiate into chondrocytes under appropriate stimulation and induction. Once this effect is aided by biologically active scaffolds, WJ-MSCs will be able to significantly promote the repair of articular cartilage damage in model animals (83), and this differentiation effect of WJ-MSCs is more durable and can significantly protect articular cartilage from being damaged for a long time (84,85). In addition, it was demonstrated that WJ-MSCs have superior cartilage regeneration ability compared with BM-MSCs. When both WJ-MSCs and BM-MSCs were encapsulated on PGA scaffolds, UC-MSCs could produce a higher amount of total collagen (86). When WJ-MSCs were seeded on collagen/PCL scaffolds coated with basic fibroblast growth factor-transferrin-selenium and insulin, WJ-MSCs could more significantly promote cartilage regeneration compared with BM-MSCs (87). In addition, according to the report, large amounts of cartilage oligomeric matrix protein and collagen type II (COL II) accumulated around WJ-MSCs seeded on collagen type I hydrogels, and at the same time, the expression of SOX9 was significantly promoted (88). However, compared with BMP-6-treated AD-MSCs, it was found that WJ-MSCs produced more GAGs and more chondrogenic genes. Therefore, although BMP-6 is a potent cartilage growth factor for AD-MSCs, it may not be involved in WJ-MSC chondrogenesis *in vitro* and *in vivo* (89). Therefore, the regulatory mechanisms of various active factors on WJ-MSC cartilage regeneration still require further investigation.

Regeneration and repair signaling mechanism of MSCs in damaged cartilage

It was confirmed that in repairing and protecting damaged cartilage, MSCs can be loaded on the scaffold to successfully generate cartilage (90). MSCs mainly improve cartilage function and repair cartilage damage from two aspects. On the one hand, MSCs can resist and prevent cartilage degeneration by synthesizing and secreting bioactive factors or accepting foreign growth factors or TCM monomers. At the same time, the potential of MSCs to differentiate into chondrocytes is also stimulated by various factors (91,92). Tumor necrosis factor (TNF)-α, interleukin (IL)-17, IL-1β, and IL-6, as classical inflammatory cytokines, play a decisive role in the occurrence and development of cartilage injuries (93). High expression of matrix metalloproteinases (MMPs) including MMP-13, MMP-9, and MMP-2 was associated with arthritis-induced cartilage defects in patients (94). MMP-2 and MMP-9 are generally responsible for the degradation of extrachondral matrix at the site of bone and joint injury, however, tissue inhibitor of metalloproteinases (TIMP) including TIMP1 and TIMP2 secreted from various MSCs

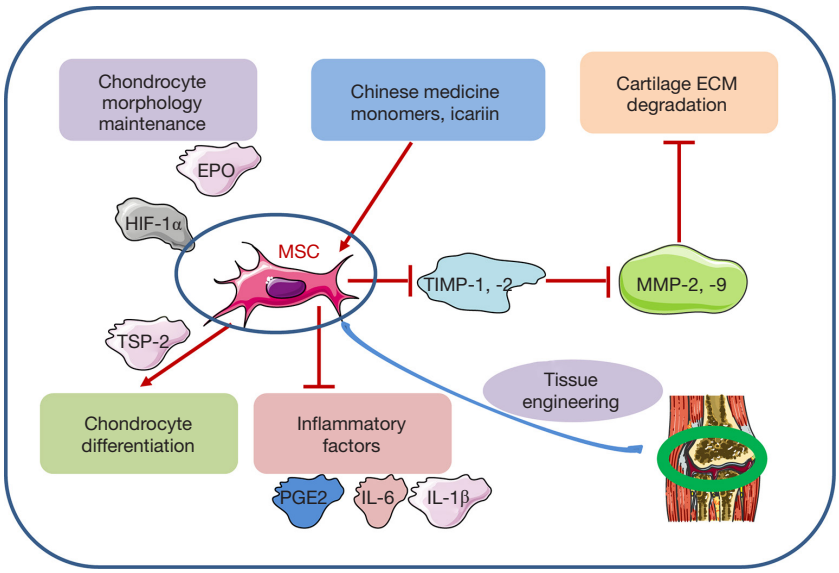

Figure 2 Mechanism of MSC chondrogenesis. MSCs generate cartilage by inducing chondrogenesis or by inhibiting inflammatory responses or cartilage degradation. ECM, extracellular matrix; EPO, erythropoietin; HIF-1α, hypoxia-inducible factor 1-α; MSC, mesenchymal stem cell; TSP-2, thrombospondin-2; TIMP-1, tissue inhibitor of metalloproteinases-1; TIMP-2, tissue inhibitor of metalloproteinases-2; MMP-2, metalloproteinases-2; MMP-9, metalloproteinases-9; PGE2, prostaglandin E2; IL-6, interleukin-6; IL-1β, interleukin-1β.

can inhibit MMPs. MMP-2 and MMP-9 expression in turn inhibit the degradation of cartilage ECM (94). The classical functions of MSCs are to inhibit T lymphocyte proliferation and prostaglandin E2 (PGE2) synthesis and secrete proinflammatory cytokines (95,96).

Basic fibroblast growth factor (bFGF), secreted by MSCs, can significantly promote chondrocyte activity, growth, and ECM synthesis, while inhibiting subchondral apoptosis (97,98). It has been suggested in the literature that extracellular vesicles (EVs) produced by MSCs can promote articular cartilage damage repair by increasing regulatory B cell-mediated IL-10 secretion (99). Exosomes derived from MSCs can inhibit early OA-induced cartilage damage by significantly inhibiting the expression of inflammatory genes, especially IL-1β (100,101). However, the repair mechanism of EVs or exosomes derived from MSCs on cartilage damage is not fully understood, and more research is needed in the future Another experiment demonstrated that BM-MSCs-exosomes could promote cartilage damage repair by promoting COL II synthesis and inhibiting catabolic markers including ADAMTS5 and MMP-13, while inhibiting IL-1β-induced senescence and apoptosis (102).

Due to hypoxia and lack of blood vessels in cartilage tissue, hypoxia-inducible factor 1-α (HIF-1α) is mainly responsible for the regulation of the survival and differentiation of chondrocytes. The author's previous study confirmed that icariin (ICA) can significantly promote the HIF-1α/SOX9 signaling pathway and promote BM-MSCs and cartilage progenitor cells to form cartilage to relieve articular cartilage damage (29). In the latest article, the authors constructed scaffolds loaded with rBM-MSCs and two drugs including TGF-β and stromal cell-derived factor 1α (SDF-1α), and remarkable repair of damaged articular cartilage was achieved by the rBM-MSC scaffold complexes (103). However, the mechanism by which SDF-1α promotes chondrogenic transformation is still unclear. It has been reported that CXC chemokine receptor 4 (CXCR4) in MSCs plays an important role in chondrogenic transformation (104-107). It has also been reported that MSCs homed to cartilage defects to develop new cartilage via the SDF-1α/CXCR4 axis (108).

Various cytokines, growth factors, and signaling molecules regulate the chondrogenesis and differentiation of MSCs (*Figure 2*). Among them, TGF-β members classically regulate chondrogenesis (109). TGF-β1, TGF-β2, and TGF-β3 induce MSCs to produce proteoglycans (AGG) and COL II, with the aim of contributing to chondrogenesis in MSCs (110). Activation and phosphorylation of Smad2/3 have been reported to be significant in the regulation of chondrogenesis by TGF-β signaling, and the expression

of the transcription factor SOX9 and its target genes such as AGG and COL II is mainly regulated by the nuclear transcription of Smad 2/3 (111,112). It was suggested that the Wnt/β-catenin pathway family is also involved in influencing MSC differentiation and chondrogenesis (113,114). As a protein factor with therapeutic value, thrombospondin-2 (TSP-2) is secreted by MSCs. TSP-2 mainly participates in the development and formation of animal cartilage and bone (115). The extracellular signal-regulated kinase (ERK), Notch cross-linking, and p38/MAPK pathways are involved in the chondrogenesis of MSCs (115,116). In addition, some nutritional factors such as erythropoietin, fibroblast growth factor-2 (FGF-2), and Chinese herbal monomer (icariin) can also regulate the chondrogenesis of MSCs (29,117,118).

Conclusions

A preliminary conclusion is drawn from the source analysis of stem cells in this paper. At present, tissue engineering using BM-MSCs as seed cells is more suitable for the repair of human cartilage according to the content of this study. Injuries and defects of articular cartilage are important causes of disability and pain. Meanwhile, additional clinical trials of various stem cells were conducted to evaluate their suitability for the repair of human articular cartilage. A clinical trial demonstrated that the use of BM-MSCs in cartilage repair reduced costs, minimized morbidity at the donor site, and most importantly, achieved the same effect as chondrocytes used for articular cartilage repair (119). The researchers confirmed that four patients who received low-dose AD-MSCs topically experienced significant improvements in knee function. After a 6-month follow-up, the treatment was found to be safe and effective (120). Saw *et al.* demonstrated that intra-articular injection of autologous PB-MSCs combined with hyaluronic acid improved the articular cartilage repair level compared to the treatment with hyaluronic acid alone (121). However, as a degenerative disease, there is currently no clear treatment, and almost all current treatments are limited to relieving symptoms. Treatment with MSCs has been used as a novel and effective therapeutic strategy to improve the efficacy and level of cartilage damage repair. The repair and regeneration of articular cartilage is still a challenging problem in the current field of regenerative medicine research.

After years of research, a variety of techniques including osteochondral transplantation, bone marrow stimulation, and chondrocyte transplantation have been widely studied, applied, and improved. However, the highly anticipated continuous progress of cartilage tissue engineering still faces many development bottlenecks. For example, in cartilage tissue engineering, it is necessary to optimize the cell culture conditions *in vitro*, to discover new seed cells and the application of new discoveries and new combinations of various novel natural or synthetic materials. Based on the current theoretical research foundation and technology, the existing tissue engineering production process and final products are continuously optimized using 3D cell culture *in vitro* expansion technology and 3D bioprinting technology, among others, to obtain cartilage tissue with more ideal performance. More research and clinical trials are still needed to confirm its actual effect. Additionally, more stem cell chondrogenesis mechanisms need to be explored. In the future, it is necessary to explore the mechanism of strong regeneration of articular cartilage and the endogenous repair mechanism of various stem cells into cartilage, and to deeply study the interaction between the disease microenvironment and cell molecules. This article provides a simple summary of stem cell therapy for articular cartilage injury to help researchers quickly understand the current development status.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1715/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1715/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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