

Current and Novel Therapeutics for Articular Cartilage Repair and Regeneration

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Abstract: Articular cartilage repair is a sophisticated process that has is being recently investigated. There are several different approaches that are currently reported to promote cartilage repair, like cell-based therapies, biologics, and physical therapy. Cell-based therapies involve the using stem cells or chondrocytes, which make up cartilage, to promote the growth of new cartilage. Biologics, like growth factors, are also being applied to enhance cartilage repair. Physical therapy, like exercise and weight-bearing activities, can also be used to promote cartilage repair by inducing new cartilage growth and improving joint function. Additionally, surgical options like osteochondral autograft, autologous chondrocyte implantation, microfracture, and others are also reported for cartilage regeneration. In the current literature review, we aim to provide an up-to-date discussion about these approaches and discuss the current research status.

Keywords: chondrogenesis, osteoarthritis, tissue engineering, mesenchymal stem cells, surgical repair

Introduction

Articular cartilage, a form of connective tissue, covers the surface of bodily joints like the hip and knee. It is a smooth and durable tissue that provides a low-friction surface for bones to move against each other. This is due to its unique structure and composition. The collagen fibers in the cartilage give it strength and elasticity, while the high-water content helps to lubricate the joint and absorb shock. Chondrocytes, which are the cells that produce and maintain cartilage, also have a vital role in maintaining its integrity and health.¹

However, when this tissue is damaged, it can lead to significant pain and mobility issues since it is difficult to regenerate because it is avascular.² Articular cartilage damage might develop due to various factors, such as injury, overuse, or degenerative diseases such as osteoarthritis. Younger individuals may experience cartilage damage because of sports injuries, while older individuals may experience it because of natural wear and tear on the joints. Risk factors for cartilage damage include being overweight, having a history of joint injuries, and having certain genetic conditions. The commonest cartilage damage is associated with osteoarthritis, a degenerative condition resulting in the cartilage breakdown in a joint.³ Osteoarthritis is marked by cartilage degeneration, and bone spurs formation, leading to significant pain and limited mobility. Moreover, cartilage damage can lead to joint degeneration and even disability in severe cases, greatly impacting a person's quality of life.^{4,5}

Current practices used for cartilage damage and repair include a range of options like medications, rest, physical therapy, and surgical procedures.^{6,7} The intensity of inflammation and pain can be decreased by medications like non-steroidal anti-inflammatory drugs (NSAIDs). Improving strength and flexibility of affected joint might also be achieved by physical therapy. Surgical approaches, like osteochondral autograft transplantation system (OATS), autologous chondrocyte implantation (ACI), and microfracture may be necessary in some cases, particularly when there is severe joint degeneration or a lack of response to other treatments. Moreover, cellular therapy has been introduced in this field to promote cartilage repair and regeneration with promising results.⁸ Mesenchymal stromal cells (MSCs) differentiations into chondrocytes have been studied, leading to the formation of cartilaginous materials. In laboratory studies, MSCs

were able to form cartilage-like tissue when cultured with the proper growth factors and scaffolds.⁹ Additionally, MSCs have been shown to produce molecules that promote the growth and maintenance of cartilage, such as collagen and proteoglycans.^{6,8} In the current literature review, we aim to discuss the current practices used for articular cartilage repair.

Methods

A comprehensive search was run through academic databases such as PubMed, Scopus, and Web of Science to find relevant articles. No limitations were applied to the search whether by country, date, or language of publication to retrieve as much evidence. However, we mainly focused on studies published within the last ten years to make the current discussion up-to-date. The search was performed using different keywords related to the field of this literature review, such as “articular cartilage”, “cartilage repair”, “cartilage regeneration”, and “chondrocyte transplantation”. Our evidence was generated from original investigations mainly and reviews were considered and reviewed to extract any relevant information or articles.

Microfracture Technique

Microfracture is a surgical modality that can be applied for cartilage damage with standard arthroscopy portals drill holes.¹⁰ The procedure involves making small fractures in the bone beneath the damaged cartilage, which stimulates the growth of new cartilage. The technique is usually conducted on patients with small to medium size cartilage defects. It involves using a sharp instrument to create multiple small fractures in the underlying bone, which bleeds and forms a clot. The clot, in turn, leads to forming of a fibrocartilage repair tissue. A literature review of microfracture for treating articular cartilage damage found that the procedure can significantly enhance function and pain within a short period.¹¹ Nevertheless, Kreuz et al demonstrated that repaired tissues gradually deteriorate within 18–24 months following knee surgery because of increased susceptibility to mechanical forces. Overall, it was reported that microfracture surgery increases the production of fibrocartilage, which is biomechanically and chemically not as effective as hyaline cartilage.

In terms of the specific outcomes of microfracture, studies have found that the procedure can lead to enhancements in knee function and pain, together with an increase in the amount of cartilage in the knee.¹² In a meta-analysis of five trials assessing the effectiveness of microfracture of the knee, Negrin et al¹³ indicated that the modality is associated with a significant postoperative clinical improvement. However, various limitations and significant heterogeneity among the included trials were reported by the authors. In 2022, Fortier et al¹⁴ published another meta-analysis to assess the clinical and MRI findings of microfracture of knee focal chondral lesions conducted with and without augmentation. After analyzing the results of 14 studies that recruited 744 patients, the authors found that microfracture combined with augmentation was associated with a remarkable enhancement in different scores compared to the other group. Besides, it is vital to consider that microfracture is most suitable in cases with small to medium-sized cartilage defects and may not be suitable for larger defects.^{15–19} Additionally, the success of the procedure may be influenced by the patient’s age and overall health, together with the specific type and location of the cartilage damage.

Nano-fracture, on the other hand, is a more novel surgical approach that enhances cartilage surfacing characteristics and increases bone marrow access by developing deeper cell channels in a more reproducible way.²⁰ Another alternative approach is subarachnoid abrasions or drillings, done by K wires or drill bits within cartilage defects and up to the subchondral bone.²¹ A motorized burr usually does debride chondral defects. However, it has been shown that cyst formation, hypertrophy, and thermal necrosis might complicate this approach.²² Accordingly, evidence indicates that microfracture should be considered superior to this technique.²³ In addition, a 43-month follow-up study showed that improvements in clinical outcomes of small-to-medium-sized osteochondral lesions were similar between microfracture and subchondral drilling techniques.²⁴

Osteochondral Grafting

Osteochondral grafting is a surgical procedure that aim to transplant healthy cartilage and bone from one body region to an injured one. The goal of the procedure is to repair or replace the damaged tissue and restore normal joint function.^{25–27} One of the most used techniques for osteochondral grafting is ACI. This procedure involves harvesting healthy cartilage cells from the patient’s own body, growing them in a lab, and then transplanting them back into the damaged area.²⁸ Studies have shown that ACI can effectively repair cartilage defects and improve joint function. Nevertheless, the process requires a lot of technical skill and requires specialized equipment and expertise.^{29–31} Another technique that has been

used for osteochondral grafting is the use of allografts, which are transplantations of tissue from a donor. This technique has the advantage of being readily available, but it is related to an elevated risk of rejection and infection.^{6,7,26,27}

Mosaicplasty and OATS are the two types of osteochondral grafting. Both techniques involve transplanting healthy bone and cartilage from one body area to an impacted one. Mosaicplasty is a surgical technique that involves the transplanting small plugs of sound bone and cartilage from a non-weight-distributed joint area to a damaged one. The plugs are typically taken from the patient's own body and are carefully matched to the size and shape of the defect. The plugs are then placed into the defects using small drilling instruments. The aim of this technique is to repair the defect and normalize joint function. Mosaicplasty has been shown to be effective for treating small to medium-sized defects. However, it is not recommended for larger defects or for patients with significant joint degeneration.³²⁻³⁵

OATS is a surgical modality that is done by transplanting cylindrical plugs of sound bone and cartilage from a non-weight-distributing joint region to a damaged one. OATS procedure is similar to mosaicplasty, but the plugs are cylindrical and are typically taken from the patient's body. The plugs are then placed within defects using a special drill, and it targets repairing the damage and regain sound joint functions. OATS has been shown to be effective for treating small to medium-sized defects, and it is recommended for larger defects or for patients with significant joint degeneration.^{6,7,33} Both Mosaicplasty and OATS have been extensively studied and were deemed safe and effective for treating knee defects. These procedures were reportedly related to improved patient outcomes, including reduced pain and improved function. However, it is essential to consider the need for long-term follow-up studies to fully understand the long-term effectiveness and safety of these procedures.⁷ Table 1 presents the advantages and disadvantages of all surgical techniques that might be used for cartilage repair. It should be noted that the appropriateness of a certain technique relies on the individual patient's case and should be discussed with a specialist. Not all techniques are available in every location, and some are still considered experimental.

Cellular Therapy Overview

MSCs are a type of adult stem cell investigated for their potential in repairing cartilage damage. MSCs can differentiate into various cell types, including cartilage cells, and have been shown to have anti-inflammatory and regenerative

Table 1 Advantages and Disadvantages of the Different Surgical Techniques Reported for Cartilage Repair

Technique	Advantages	Disadvantages
Microfracture	Minimally invasive procedure- Cost-effective- Can be performed arthroscopically- Low risk of complications- Can be used for small to medium-sized cartilage defects	May not be suitable for large cartilage defects - Limited long-term success rates - May not be as durable as other techniques - Recovery time can be longer
Osteochondral Autograft Transfer System (OATS)	Considered the gold standard for cartilage repair - Can be applied for large cartilage defects - Provides long-term success rates - Durable and provides good mechanical strength	Invasive procedure - Requires a second surgical site for donor tissue - Risk of adverse events related to the donor site - Long recovery time
Autologous Chondrocyte Implantation (ACI)	Can be applied for large cartilage injuries - Provides long-term success rates - Durable and provides good mechanical strength - No need for a second surgical site	Invasive procedure - Requires laboratory cultivation of chondrocytes - Risk of complications associated with the implantation process - Long recovery time
Allograft Cartilage Implantation	Can be applied for large cartilage defects - No need for a second surgical site	Risk of disease dissemination with allograft tissue - Risk of immune response to the allograft tissue - Limited long-term success rates
Matrix-induced Autologous Chondrocyte Implantation (MACI)	Good repair potential, normal hyaline cartilage formed, less invasive than traditional ACI	High cost, long recovery time, risk of complications

characteristics. In terms of regenerating cartilage damage, MSCs differentiations into chondrocytes have been studied, leading to the formation of cartilaginous materials. In laboratory studies, MSCs were able to form cartilage-like tissue when cultured with the proper growth factors and scaffolds.⁹ Additionally, MSCs have been shown to produce molecules that promote the growth and maintenance of cartilage, such as collagen and proteoglycans.^{6,8}

MSCs have also been studied for their ability to modulate the immune response in conditions such as osteoarthritis. MSCs have been shown to reduce inflammation and promote healing in animal models of osteoarthritis. This is thought to be owing to the capability of MSCs to suppress the actions of pro-inflammatory cells and promote the activity of anti-inflammatory cells. Another area of research for MSCs in cartilage repair is their potential use in cell-based therapies. In these therapies, MSCs are isolated from a patient's own tissue and then expanded in the laboratory before being re-injected into the affected joint.³⁶ This approach avoids the need for invasive surgery and the use of foreign materials, such as artificial implants. Additionally, the use of a patient's own cells reduces the risk of rejection or immune response. In clinical trials, MSCs have been shown to be safe and well tolerated in humans, with minimal side effects reported. However, the results of these studies are still preliminary, and more research is warranted to determine the long-term safety and efficacy of MSC-based therapies for cartilage repair.

Overall, MSCs have shown promise in the treatment of cartilage damage and repair. Their ability to differentiate into cartilage cells and modulate the immune response make them an attractive option for cell-based therapies. However, more research is needed to fully understand the mechanisms of MSCs action and to optimize the conditions for their use in clinical practice.^{37–39} It is important to mention that MSCs are not a panacea for the cartilage repair, there are still many challenges to overcome before these cells can be used in a clinical setting. There is a need for more research to understand the optimal conditions for MSC proliferation, survival, and differentiation *in vivo*, as well as the optimal routes of administration and cell dosages. Additionally, more studies are warranted to assess the prolonged effectiveness and safety of MSC-based therapies for cartilage repair. Despite these challenges, treating damaged cartilages by MSC is promising, and further research in this area could lead to new and effective treatments for this debilitating condition.^{8,40,41}

Among the challenges that might hinder using MSC is their long-term effectiveness and safety, which has been investigated by some studies. All indicators of cartilage regeneration were steady throughout a seven-year follow-up period, as reported by Park et al,⁴² which provides cause for optimism. Moreover, high tibial osteotomies with and without BMSCs were compared for their long-term (over 10 years) efficacy by Yamasaki et al.⁴³ There was no statistically significant change in Hospital for Special Surgery Knee-Rating Scale ratings between both groups at any time throughout the study's follow-up period. Seven patients out of a total of 12 in the initial cohorts have accessible follow-up data. Another long-term (follow-up for ten years) cohort study also compared the safety and efficacy of BMSCs and ACI in 36 patients and found that both modalities had comparable outcomes at the end of the follow-up period, providing evidence for the safe and efficacious administration of BMSCs for cartilage repair.⁴⁴ Favorable findings were also reported in a 5-year follow-up report, which demonstrated that the outcomes of BMSCs for osteoarthritis were favorable, although the reported outcomes were for only three patients. Other 2-year follow-up studies can also be found in the literature.^{45,46} However, the results of these studies might be biased due to remarkable heterogeneities between the study groups, and long-term outcomes cannot be ruled out due to the inadequate follow-up period.

The risk of tumor formation after cellular therapy represents the major challenge when it comes to assessing the long-term safety of these modalities. The possibility of malignant transformation after *in vitro* growth was first observed in early studies.^{47,48} However, it was later discovered that the discrepancies may have resulted from cell line cross-contamination,⁴⁹ and subsequent evaluations have tended to back up the safety of BMSCs.^{50,51} Wakitani et al⁵² conducted a clinical investigation with 41 patients who had intra-articular BMSC implantation and found no evidence of tumor development up to 137 months postoperatively. In line with the positive safety data presented in these studies, Teo et al⁴⁴ indicated that no clinical indications of tumor development in their BMSC group was noticed at up to 10 years of follow-up.

MSCs can be obtained from different sources, like adipose tissue, peripheral blood, and bone marrow (Figure 1A).^{9,53} Although the efficacy of these modalities has been indicated, various issues, like *in vitro* premature differentiation, and stem cell heterogeneity remain unsolved.^{8,54} In contrast to the bone marrow, which is the traditional source of MSCs, adipose tissue-derived MSCs (AMSCs) are gaining popularity because of their accessibility, purportedly increased proliferative ability, and anti-inflammatory characteristics. In addition to being given as a culture expanded MSC

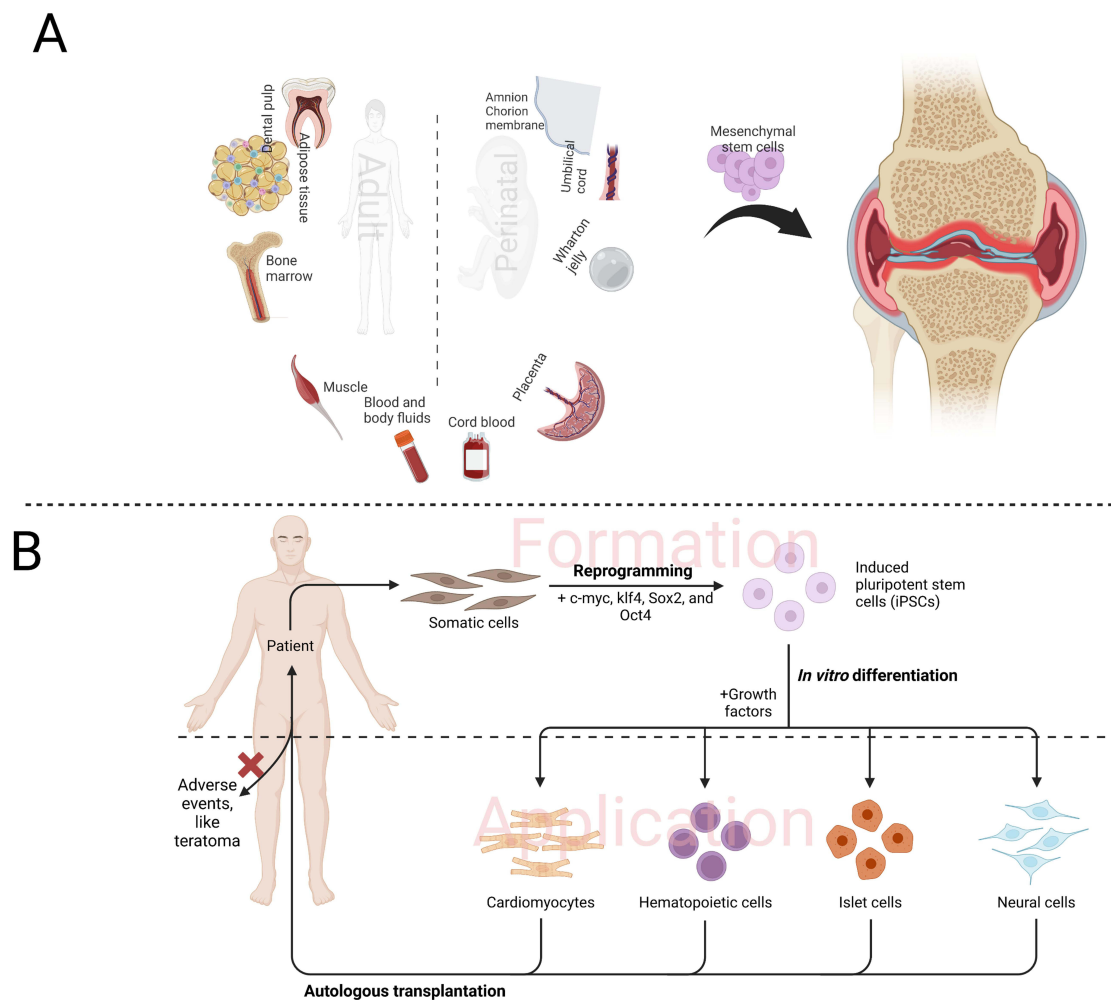


Figure 1 Sources and application of mesenchymal stem cells (A) and induced pluripotent cells (B) for articular cartilage repair.

population, AMSCs may also be given as a part of a combination of heterogeneous cells called Stromal Vascular Fraction (SVF),⁵⁵ which includes AMSCs along with other cell types such as pericytes, endothelial cells, smooth muscle cells, fibroblasts, and so on. Although AMSCs are present in SVF, they cannot be considered MSCs according to the precise definition since they express various cell markers and have different features.⁵⁶

Clinical results for patients with cartilage injuries may be improved by MSC-based treatments due to their ability to stimulate the regeneration of hyaline-like cartilage. This disease-modifying strategy is quite unlike the standard palliative care approach. Immunohistological staining of type II collagen or expression of glycosaminoglycan in the regenerated tissue reminiscent of hyaline cartilage has been used in previous *in vitro* investigations to demonstrate the chondrogenic differentiation potential of AMSCs.^{57–59} The safety of administering MSCs has also been assessed in animal experiments,^{60,61} lending support to the *in vitro* findings. Histological findings concerning type II collagen production and integration, as well as biochemical findings, such as an increase in the glycosaminoglycans content, indicate the ability of MSCs isolated from bone marrow and synovium to cause hyaline-like cartilage regeneration. Administration of AMSCs to human knees has been linked to possible cartilage repair in early investigations.⁶² Biomarker analyses, imaging findings, and histology findings all point to the existence of hyaline-like cartilage regeneration.⁶³ Histological staining performed by Koh et al⁶⁴ showed that patients who received microfracture in conjunction with AMSC administration showed a higher degree of staining for safranin O and type II collagen, indicating the presence of hyaline cartilage regeneration. The Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) software compares the shape and signal intensity of the imaged regenerated cartilage to that of the surrounding natural hyaline cartilage. Because of this, it may be inferred that the regenerated cartilage has hyaline-like features from the increased MOCART score after AMSC

delivery.⁶³ The quality of the regenerated cartilage was evaluated by Freitag et al using T2-weighted imaging in addition to MOCART, and they discovered that the cartilage gradually matured over time.^{65,66} These findings support the hypothesis that AMSCs may give rise to human cartilage with properties similar to hyaline. However, the long-term effects of AMSC treatment on cartilage healing are uncertain, with the average follow-up duration being just 18.3 months.⁶³ After two years post-treatment, cartilage degeneration was found by Jo et al.⁶⁷ This may have been owing to the knee joint being desensitized to AMSC therapy or simply the necessity for another AMSC injection.

Promising findings in cartilage repair were also found with the application of induced pluripotent stem cells (iPSCs) (Figure 1B).⁶⁸ These modalities might surpass the above limitations. However, genomic modifications remain a controversial issue that intervenes against their clinical application. Genetically modified cells were also reported as effective candidates for tissue regeneration since they can induce the synthesis of hyaline matrix, chondrogenic differentiation, together with production of pro-inflammatory mediators.⁶⁹

Paracrine factors are released by cells in the form of EVs, such as exosomes. Exosomes are prevalent in all body fluids, including saliva, blood, urine, and milk,^{70–73} and serve a role in cell-cell communication. Their payload is cell-specific.⁷⁴ Repair of injured cartilage may be aided by exosomes.^{75,76} Stem cell differentiation is boosted by exosomes.^{77,78} Injured cartilage additionally benefits from their ability to dampen inflammation.⁷⁹ In order to reduce immune rejection during cartilage healing, exosomes are used.⁸⁰ Hyaline cartilage development is also a potential outcome of exosome therapy. The use of EVs in treatment may reduce inflammation. Exosomes generated from MSCs have been shown to inhibit IL-1 production.⁸¹ Inflammatory responses during disc degeneration are also associated with IL-1, the most prominent proinflammatory mediator.^{82,83} By inhibiting inflammatory mediators and NLRP3 inflammasome activation, exosomes generated from mesenchymal stem cells were shown to decrease the course of intervertebral disc (IVD) degeneration in separate research.⁸⁴ Pyroptosis is a kind of programmed cell death induced by proinflammatory signals, although it may be avoided by inhibiting the NLRP3 pathway. Regulation of pyroptosis and inhibition of the NLRP3 pathway by exosomal miR-410 from MSCs. Macrophage polarization has recently been the subject of therapy for osteoarthritis. Macrophages are immune cells that may be either proinflammatory (M1) or anti-inflammatory (M2).⁸⁵ They are located in the synovial lining. Exosomes extracted from BMSCs have been shown to decrease inflammation by modulating macrophage polarization, namely by preventing the development of M1 macrophages and encouraging the creation of M2 macrophages.⁸⁶

Various in vivo and animal studies investigated the administration of EVs for cartilage repair. In an animal model of osteoarthritis, He et al found that exosomes produced from BMSCs increased collagen type II synthesis and decreased MMP13 protein expression.⁸⁷ In vitro research on degenerated nucleus pulposus cells demonstrated that BMSC-derived exosomes stimulated ECM synthesis.⁸⁸ Therefore, it seems that EVs have distinct functions in restoring cartilage ECM. Although chondrocyte numbers are modest in normal cartilage, these cells play an important role in cartilage regeneration by synthesizing extracellular matrix. Since chondrocyte numbers decrease after cartilage damage, some therapeutic intervention is necessary to keep them at a stable level. Stem cell differentiation into chondrocytes is one method for keeping the chondrocyte population stable. By blocking the Notch1 pathway, EVs from nucleus pulposus cells direct MSC to develop into cells similar to those seen in the nucleus pulposus.⁸⁹ Chondrogenic differentiation may also be targeted by miRNA, a component of EVs. In their study, Li et al⁹⁰ found that miR-8485 from exosomal chondrocytes stimulated differentiation of BMSCs into chondrocytes by activating the Wnt/-catenin pathways. Improving cartilage regeneration requires not only the differentiation of stem cells into chondrocytes but also the proliferation of these cells at the site of damage. MiRNA is one example of EV cargo that has been proven to stimulate chondrocyte proliferation in research settings.^{91–93} EV treatment may prevent further chondrocyte depletion from apoptosis and autophagy. It was shown by Cheng et al⁹⁴ that miR-21 in exosomes produced from mesenchymal stem cells inhibited apoptosis in cells of the nucleus pulposus. Similarly, EVs have been demonstrated to be useful in preventing IVD degeneration due to apoptosis triggered by the endoplasmic reticulum.^{95,96} The number of chondrocytes may be kept constant throughout cartilage healing by preventing apoptosis and promoting cell growth.

Tissue Engineering

Tissue engineering is a captivating and cutting-edge method for regenerating the tissue found in joints.⁹⁷ The technique involves the utilization of growth factors (GF), scaffolds, and cells to replicate the intricate three-dimensional micro-environment present in joints, which necessitates the collaboration between these various elements. However,

reproducing this complexity is essential and there are still many challenges that need to be addressed, such as determining the optimal cell population, the suitable scaffold materials, and the appropriate GF applications.^{98,99} Two categories have been suggested for cartilage repair by tissue engineering, including scaffold-based and independent methods.

Scaffolds

Scaffold-dependent approaches use synthetic or natural biomaterials to create an environment that supports cell growth and interactions, while independent methods do not rely on scaffolds.¹⁰⁰ Various natural materials have been reported in the literature for cartilage repair and regeneration (Table 2). Hydrogel-based scaffolds have become a popular treatment strategy for cartilage defects. They can be injected to fill irregular shaped defects, mimic the natural environment and be minimally invasive. Recently, sol-gel phase transition-generated thermogels have also been applied for cartilage regeneration. One example is a PLGA-PEG-PLGA thermogel that solidifies at body temperature and has demonstrated

Table 2 Advantages, Disadvantages, and Sources of Common Natural Products for Cartilage Regeneration and Repair

Material	Advantages	Disadvantages	Sources
Collagen	It is a natural and biocompatible material, promotes cell growth and differentiation	Not very stable	Animal sources such as bones, tendons, skin, and cartilage
Chitosan	Biocompatible, non-toxic, promotes cell growth and differentiation	Poor mechanical properties	Shells of crustaceans such as shrimp, crab, and lobster
Hyaluronan	Lubricates joints, promotes cell growth and differentiation	Expensive to produce	Rooster comb, umbilical cord, and synovial fluid
Alginate	Non-toxic, biocompatible, can be used in hydrogels	Poor mechanical properties	Brown seaweed
Fibrin	Promotes cell growth and differentiation, forms a strong clot	Limited degradation	Blood plasma
Poly(lactic acid) (PLA)	Biocompatible, can be used in 3D printing	Poor mechanical properties	Renewable resources such as corn starch and sugarcane
Poly(ethylene glycol) (PEG)	Biocompatible, can be used in hydrogels	Expensive to produce	Petroleum-based or biosynthetic
Poly(ε-caprolactone) (PCL)	Biocompatible, can be used in 3D printing	Poor mechanical properties	Renewable resources such as castor oil and sugarcane
Silk fibroin	Biocompatible, strong and flexible	Expensive to produce	Silkworm cocoons
Gelatin	Biocompatible, can be used in hydrogels	Poor mechanical properties	Animal by-products such as bones and skin
Poly(vinyl alcohol) (PVA)	Biocompatible, can be used in hydrogels	Poor mechanical properties	Petroleum-based or biosynthetic
Agarose	Biocompatible, can be used in hydrogels	Expensive to produce	Red seaweed
Cellulose	Biocompatible, abundant, and renewable	Poor mechanical properties	Plant sources such as wood and cotton
Gellan gum	Biocompatible, can be used in hydrogels	Expensive to produce	Bacteria
Chondroitin sulfate	Promotes cell growth and differentiation	Expensive to produce	Animal sources such as cartilage and bones
Hydrogel-based scaffolds	Biocompatible, can mimic the extracellular matrix	Poor mechanical properties	Natural or synthetic polymers, like chitosan, collagen, and hyaluronan, alginate

encouraging outcomes in repairing a full-thickness cartilage defect of a rabbit model. Although initial mechanical stability is a major characteristic of scaffolds, they have numerous drawbacks such as toxicity associated with degradation, hindrance to remodeling, stress shielding, and alteration of cell characteristics.¹⁰⁰ Therefore, researchers have focused on innovating scaffold-free approaches. For instance, cohesive tissue microarchitecture can be successfully produced by 3D bioprinting, which entails maintains a production with characteristics like in vivo conditions.¹⁰¹ Hydrogels are frequently employed as the printing medium, a method known as bio-ink dependent hybrid bioprinting.^{101,102} The selection of bioink is vital as it can impact cell-matrix interactions and cell spreading, and the chondrocyte phenotype can differ in hyaline cartilage and fibrocartilage.¹⁰³

Another scaffold-free technique is cell-sheet engineering, where transplantable hyaline-like cartilage tissue can be deployed through 3D MSC sheets, which has demonstrated encouraging results in chondrogenic differentiation.¹⁰⁴ Currently, in vitro investigations are the main source of evidence regarding the function of tissue microenvironment in regulating articular cartilage and chondrocyte phenotype, indicating the need for future in vivo investigations. Having more insight into how MSCs and chondrocytes are impacted by microenvironment might aid in developing novel therapeutic approaches. For example, the application of scaffolds with chondrogenic GFs might enhance implantation parameters and boost cartilage synthesis.¹⁰⁵

Moreover, scaffolds serve as time-controlled means of distribution for EVs by sequestering them at the damaged area and distributing them at regular intervals. Diffusion, polymer breakdown and degradation, and swelling are among mechanisms that might lead to the release of medicines or EVs from a scaffold.¹⁰⁶ Scaffolds, either solid or hydrogel, are required to capture EVs and sustain their release. One of the most popular hydrophilic polymers utilized in cartilage tissue engineering is hydrogel. It may be used as a cartilage replacement due to its favorable mechanical properties.¹⁰⁷ Hydrogel, which may be made from either natural or synthetic polymers to resemble the ECM, will regulate the release of EVs that are encapsulated inside it. Exosomes produced from stem cells may be trapped within a photo-induced crosslinking hydrogel to speed up cartilage healing.¹⁰⁸ ECM and gelatin methacrylate hydrogel scaffolds impregnated with embryonic stem cells related EVs were shown to stimulate cartilage regeneration by Chen et al.¹⁰⁹ Thus, research suggests that the transport of EVs for cartilage healing relies heavily on biomaterial. Research into the potential uses of different biomaterials for EV delivery in cartilage regeneration is warranted.

Growth Factors and Platelet-Rich Plasma

Natural GFs and anti-inflammatory agents are becoming a prevalent treatment for various musculoskeletal disorders. These biologic compounds can accelerate tissue healing and regeneration through various mechanisms, such as modulation of metalloproteinases and inflammatory markers, cell recruitment, and matrix remodeling and synthesis. Additionally, GF can control stem cell differentiation and protein synthesis, influencing cellular interactions. Specific GF, such as BMP-2 (Bone Morphogenetic Protein 2), VEGF (Vascular endothelial growth factor), and TGF- β 1 (Transforming growth factor beta 1), regulate osteogenesis, angiogenesis, and chondrogenesis, respectively.¹¹⁰ The potential role of GF in regenerating tissues and reducing pain has sparked attention in their application as therapeutics for musculoskeletal injuries.

Recent advancements in understanding the role and importance of GF in tissue engineering have led to deeper discoveries and research in this field. GF promote and facilitate new tissue regeneration through regulation of cellular protein synthesis and interaction with defined transmembrane receptors. GF binding to these receptors stimulates cell signal transduction pathways, which in turn triggers cell differentiation, growth, proliferation, adhesion, survival, and migration. While a great therapeutic potential has been reported with GF application for cartilage repair and regeneration, healthcare authorities have not approved the clinical use.

Obtaining physiological proportions of GFs is feasible through an economic source, that is platelet-rich plasma (PRP). The efficacy and safety of this modality has been widely approved since it was applied for tissue regeneration in different medical fields. PRP is mainly composed of highly concentrated platelets within a blood derivative product, where regeneration characteristics can be observed in these platelets since they contain effective GFs. For instance, it has been reported that various GFs were included in α platelet granules, like IGF-1 (Insulin-like Growth Factor 1), FGF (Fibroblast growth factor), EGF (Epidermal growth factor), VEGF, TGF- β 1, and PDGF (Platelet-derived growth factor) (Table 3). Clinically, the application of PRP was evidenced to be effective, safe, and feasible because it can be easily

Table 3 A Summary to Most Common Growth Factors Used for Cartilage Repair and Regeneration

Growth Factor	Mechanism of Action	Delivery System	Time of Delivery	Dose*
Platelet-derived growth factor (PDGF)	Stimulate chondrocyte proliferation and matrix production	Hydrogel	Immediate	10–100 ng/mL
Fibroblast growth factor (FGF)		Nanoparticle	Immediate	10–100 ng/mL
Insulin-like growth factor (IGF)		Hydrogel	Immediate	10–100 ng/mL
Vascular endothelial growth factor (VEGF)		Hydrogel	Immediate	10–100 ng/mL
Bone morphogenetic protein (BMP)		Microsphere	Immediate	2–20 ng/mL
Epidermal growth factor (EGF)		Hydrogel	Immediate	10–100 ng/mL
Transforming growth factor-beta (TGF-beta)		Microsphere	Immediate	2–20 ng/mL
Interleukin-1 (IL-1)		Hydrogel	Immediate	10–100 ng/mL
Platelet-rich plasma (PRP)	Contains various growth factors that promote tissue repair	Injected	Immediate	Varies

Note: *Doses are remarkably variable and are usually determined by different factors, including patient's status, severity of damage, and type of therapy used.

prepared. Moreover, it has been successfully applied together with scaffolds and microfracture surgical techniques for cartilage repair and regeneration. Intra-articular application of PRP has been widely evidenced for managing osteoarthritis, affecting the knee particularly. However, specifying the most suitable PRP remains controversial since different types with various characteristics and compositions are available due to different preparation techniques.

Small Molecules

Small molecules are widely studied for their potential in cartilage repair and regeneration. The main goal of these studies is to find new ways to stimulate the cartilage regeneration and to promote the growth of new cartilage tissue. The main targets of these small molecules are the signaling pathways, enzymes, and receptors involved in cartilage formation and maintenance.^{111,112} One of the main ways that small molecules can promote cartilage repair and regeneration is by stimulating chondrogenesis, inducing cartilage formation. Studies have shown that promoting stem cell differentiation into chondrocytes can be done by small molecules such as BMP-7, BMP-2, and TGF-beta. Furthermore, they can promote the synthesis of collagen, and proteoglycans, which mainly form the extracellular matrix (ECM) of cartilage.¹¹³

Another way that small molecules can promote cartilage repair and regeneration is by modulating ECM. Some studies have shown that small molecules such as PEG (Polyethylene glycol)-hydrogels and hyaluronic acid can promote the formation of new ECM and aid in cartilage repair and regeneration.^{114–116} Additionally, other small molecules can target enzymes such as MMPs (Matrix Metalloproteinases) and aggrecanases that degrade cartilage, helping to preserve the cartilage matrix. Inhibiting inflammation is also an important aspect for promoting cartilage repair and regeneration. Inflammation can cause damage to cartilage and inhibit the repair process. Studies have shown that small molecules such as celecoxib and curcumin can reduce inflammation and promote cartilage repair and regeneration by inhibiting the production of inflammatory mediators such as prostaglandins and TNF (tumor necrosis factor)-alpha.¹¹⁷

Examples of small molecules include Kartogenin, compound TD-198946, molecule [i,2], Salidroside, BNTA, and berberine chloride, which have been reported to stimulate chondrocyte differentiation and proliferation through different pathways, including regulation of CBF β -RUNX1 signaling, upregulation of Runx1 expression, improving the transcription of chondrogenic markers including aggrecan and SOX9, and induction of superoxide anion elimination.^{111,113,116,118–124} Moreover, promoting angiogenesis is also essential for cartilage repair and regeneration. Blood vessels supply oxygen and nutrients to the cartilage, and without them, the repair process is hindered. Studies have shown that small molecules such as VEGF and FGF can promote the growth of new blood vessels and aid in cartilage repair and regeneration^{125,126} (Table 3). It is important to note that while small molecules have shown promising results in promoting cartilage repair and regeneration

in preclinical studies, more clinical research is needed to confirm their safety and efficacy in humans. Additionally, it is important to consider the potential side effects and toxicity of these molecules, and to evaluate their long-term effectiveness.¹²⁷

Pharmaco-Therapy

Various pharmacological modalities have been proposed for the management of articular cartilage injuries. However, the evidence supporting these treatments is limited and inconsistent. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most used pharmacological treatment for articular cartilage injuries. These drugs reduce inflammation and pain, but their long-term use may have negative effects on cartilage repair. Studies have shown that NSAIDs inhibit the proliferation and differentiation of chondrocytes, the cells responsible for cartilage repair, and may delay healing. Therefore, the use of NSAIDs should be limited to the acute phase of injury and used with caution in chronic injuries.^{128–130} Glucocorticoids, another commonly used class of drugs based on their local anti-inflammatory action,^{131,132} have been shown to have long-term negative effects on cartilage repair. These drugs inhibit chondrocyte proliferation and matrix synthesis and may lead to chondrocyte death, in addition to having other adverse events.^{133–135} Therefore, the use of glucocorticoids for the treatment of articular cartilage injuries should also be limited.

Hyaluronic acid (HA) is a naturally occurring substance found in the synovial fluid of joints and were suggested to treat injured articular cartilages. Studies have indicated that HA can improve the functions of affected joints and decrease painful sensations in individuals with osteoarthritis by reducing oxygen free radicals-induced damage, decreasing inflammation mediated by reducing the production and release of arachnoid acid and prostaglandin E₂, stimulating endogenous production of hyaluronic acid, and enhancing joint viscoelasticity.^{136,137} The favorable advantages were reported among various trials and reviews among patients with knee osteoarthritis.¹³⁸ However, some limitations regarding intra-articular injection of such viscosupplements should be considered.^{139–143}

Prolotherapy (or regenerative injection therapy) is a treatment that involves the injection of a solution (usually a mixture of dextrose and lidocaine) into the affected joint to stimulate the biological healing processes of the body. The theory behind prolotherapy is that the injection of the solution induces a controlled inflammatory response, leading to the recruitment of cells responsible for tissue repair and regeneration, such as mesenchymal stem cells, to the injury site.^{144,145} The evidence on the effectiveness of prolotherapy for the treatment of articular cartilage injuries is mixed. Evidence from animal studies indicates the cartilage-specific anabolic growth, and biopsies show the remarkable ability to form fibrocartilage, and hyaline-like cartilage mixtures.¹⁴⁴ A meta-analysis of four randomized controlled trials, revealed that prolotherapy is remarkably superior to exercise for treating knee osteoarthritis. The authors of the review also pointed out that the studies included in the review had limitations related to the methodology, like inadequate population size, and that larger and more rigorous trials are warranted to establish the safety and efficacy of prolotherapy for the treatment of articular cartilage injuries.¹⁴⁵ More recently, Wang et al¹⁴⁶ published a meta-analysis of five studies that recruited 319 individuals and indicated the efficacy of hypertonic dextrose prolotherapy with a favorable safety profile. However, they also suggested that further investigations are warranted to evaluate the prolonged outcomes of these modalities and better understand the underlying mechanism.

Glucosamine and chondroitin sulfate are dietary supplements that are commonly used to treat osteoarthritis and other types of joint pain. Glucosamine is a naturally occurring compound that is believed to stimulate the production of proteoglycans that are vital components of cartilage. Chondroitin sulfate is a component of proteoglycans and is believed to protect cartilage from damage.^{147,148} The effectiveness of glucosamine and chondroitin sulfate for the treatment of articular cartilage injuries is mixed.¹⁴⁹ Some studies have shown that these supplements can enhance the functions of the joints and decreases pain in individuals with osteoarthritis. However, other studies have failed to find significant benefits from the treatment. A meta-analysis, which included 29 randomized controlled trials, found that glucosamine and chondroitin sulfate alone, but not in combination, significantly reduce pain (as measured by VAS) in patients with knee osteoarthritis. However, the authors of the meta-analysis also noted that the included investigations had limitations related to the methodology, and that larger and more methodologically-enhanced investigations are warranted to establish the safety and efficacy of these supplements for treating injuries of articular cartilages.¹⁵⁰ A more recent meta-analysis of randomized studies found the impact of chondroitin sulfate on pain to be moderate, with a significant impact on

functional status. However, various limitations to these findings were reported, indicating the need for additional future studies.¹⁵¹

Miscellaneous Approaches

Several interventions have been studied to understand their effectiveness in treating cartilage damage, including exercise, physical therapy, braces, and weight loss. Exercise, specifically weight-bearing and muscle strengthening exercises, have been found to be beneficial in improving joint function and reducing pain in individuals with cartilage damage. Weight-bearing exercises such as walking, running, and hiking, help to promote the growth and repair of cartilage by providing the necessary mechanical stimulus.^{152–154} Moreover, muscle-strengthening exercises, such as resistance training and weightlifting, not only improve muscle strength but also help to take pressure off the affected joint, reducing pain and improving function. However, it has been previously demonstrated that combining dry needling with exercises is not very effective in reducing disability or pain.¹⁵⁵ On the other hand, Tai Chi, a form of low-impact exercise, can also be effective in improving knee function and reducing pain in individuals with knee osteoarthritis.¹⁵⁴ Favorable effects of muscle strengthening exercises were also reported for postmenopausal women with osteoarthritis in a systematic review by Alonso Pérez et al.¹⁵⁶ Moreover, in cases with carpometacarpal joint osteoarthritis, a proprioceptive exercise program may enhance force sensing accuracy.¹⁵⁷ Physical therapy can also be a highly effective intervention for cartilage damage. Physical therapists can provide manual therapy to reduce pain and inflammation,¹⁵⁸ and education on how to properly move and protect the affected joint.¹⁵⁹ Additionally, physical therapists can provide exercises that target the affected joint, including range of motion exercises and strength training, which can help to improve joint function and reduce pain.¹⁶⁰ However, it has been shown that other approaches, like interferential therapy, therapeutic ultrasound, and transcutaneous nerve stimulation have negligible benefits on cartilage damage.¹⁶¹

Braces, such as knee or ankle braces, can provide support and reduce stress on the affected joint. These braces can help to reduce pain and improve function by redistributing the load on the joint and can also be helpful in individuals who have difficulty maintaining proper posture or alignment during movement.^{162,163} Weight loss is another important intervention for cartilage damage, as obesity is a risk factor for cartilage damage. Excess weight puts added stress on the joints, which can accelerate cartilage damage. By losing weight, the pressure on the joints is reduced, and the risk of cartilage damage progression is decreased.^{164,165}

Limitations and Implications

Various techniques have been developed and tested for articular cartilage generation and repair. While these techniques have shown promising therapeutic potentials, various limitations still need to be addressed. For example, the long-term outcomes of these modalities are not yet fully understood, and there is a need for more research to better understand the mechanisms of cartilage repair and regeneration. The long-term safety of MSCs was reported in some studies. There is still a need for further evidence with larger randomized studies because of the biased designs of the currently available reports. However, clinicians are encouraged to start considering these promising modalities because of their favorable advantages and enhanced outcomes over other therapeutics with limited clinical capacities and favorable outcomes of regeneration and repair.

Another limitation is the difficulty in achieving adequate cell survival and integration into the host tissue with cell-based therapies. This is a significant challenge that needs to be addressed to enhance the outcomes of these therapies. Using synthetic and natural scaffolds in scaffold-based therapies is also limited by the difficulty in achieving optimal properties for cell growth and differentiation, as well as being able to interact with the host tissues. Additionally, the ability to compare and evaluate the results of different studies is limited by the shortage of using standardized methods and techniques among these studies, making it difficult to evaluate the effectiveness of these techniques and determine which methods are most effective for a given patient population. Future clinical studies are encouraged to strengthen the current evidence of human clinical applicability and safety of these approaches.

When researching EVs, it is crucial to have proper identification and potency requirements to assure quality control and consistency. Although there is compelling data supporting the utilization of EVs for cartilage healing, certain considerations are needed beforehand. Before using EVs in clinical practice, larger animal models ought to be

researched. Large animal models allow for the study of partial- and full-thickness chondral, in addition to osteochondral repair.¹¹⁴ Due to the variable nature of EV content, further research on the selection and upkeep of EV parental cells is required. Targeted treatment is significant since no panacea exists. Given the difficulty of isolating EVs of high purity in big quantities, it is also important to find ways to maximize output from EV manufacturing on a massive scale. The most popular approach to EV isolation, ultracentrifugation, has drawbacks including poor purity and EV aggregation.¹¹⁵ Alternative methods, such as tangential flow filtering, exist for achieving repeatable manufacturing on a massive scale.¹¹⁶ There has to be uniformity in the procedures used to mass manufacture EVs for use as a therapeutic agent in cartilage repair. Additional investigations are needed to ensure the effectiveness and safety of engineered EVs for targeted cartilage treatment.

The right amount of EVs and how to administer them are also crucial. EVs are rapidly eliminated by the body's circulatory system, requiring a greater dosage, or trapping in biomaterial to maintain their effectiveness. Hydrogel scaffolds have a promising potential as a transport medium. Despite the popularity of live cell transplantation, the lack of cells in EV-based treatment gives it a better possibility for healing. Current surgical procedures for repairing cartilage defects may be modified to include the implantation of EV-loaded scaffolds at the location of the lesion. It is envisaged that by optimizing the EV dose in the scaffold, this method may reduce the need for further procedures and improve postoperative patient comfort. Hyaline cartilage may be regenerated when EVs are employed therapeutically, such as in the case of an articular cartilage damage. The pharmacokinetics of EVs is another important factor in drug discovery. In addition, the product quality of EVs has to be standardized, including storage conditions (such as temperature and expiry date). The research on the role of EVs in repairing cartilage damage is encouraging, however there are several obstacles to the practical use of EVs for cartilage regeneration. Healthcare expenditures may be greatly reduced if the therapeutic potential of EVs was better understood and if more people had access to them.

Conclusion

Articular cartilage repair and regeneration is a complex field that has been the focus of numerous studies in recent years. Various treatment modalities have been reported, including interventional and conservative techniques. The main limitation of interventional techniques is the lack of long-term data supporting their feasibility in the clinical settings. Cellular therapies ACI seem to be the most favorable approaches with favorable outcomes and enhanced safety profiles. EVs may be designed and loaded with biomaterials to regulate their release, increasing their potential as a therapeutic tool. With the right plans in place, EV treatment for cartilage regeneration will become more widely available and efficient. If EV products are to be used in clinical settings, they will need to be standardized to assure their safety.

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