REVIEW

Advances in the Treatment of Partial-Thickness Cartilage Defect

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Video Abstract

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Abstract: Partial-thickness cartilage defects (PTCDs) of the articular surface is the most common problem in cartilage degeneration, and also one of the main pathogenesis of osteoarthritis (OA). Due to the lack of a clear diagnosis, the symptoms are often more severe when full-thickness cartilage defect (FTCDs) is present. In contrast to FTCDs and osteochondral defects (OCDs), PTCDs does not injure the subchondral bone, there is no blood supply and bone marrow exudation, and the nearby microenvironment is unsuitable for stem cells adhesion, which completely loses the ability of self-repair. Some clinical studies have shown that partial-thickness cartilage defects is as harmful as full-thickness cartilage defects. Due to the poor effect of conservative treatment, the destructive surgical treatment is not suitable for the treatment of partial-thickness cartilage defects, and the current tissue engineering strategies are not effective, so it is urgent to develop novel strategies or treatment methods to repair PTCDs. In recent years, with the interdisciplinary development of bioscience, mechanics, material science and engineering, many discoveries have been made in the repair of PTCDs. This article reviews the current status and research progress in the treatment of PTCDs from the aspects of diagnosis and modeling of PTCDs, drug therapy, tissue transplantation repair technology and tissue engineering ("bottom-up").

Keywords: articular cartilage, partial-thickness defect, microenvironment, tissue engineering, treatment progress

Introduction

Articular cartilage is composed of chondrocytes, type II collagen, proteoglycan and water, and has the function of lubrication, shock absorption and pressure relief.[1,2] Once cartilage is damaged, if not treated promptly and appropriately, the damage can continue to increase, resulting in disruption of cartilage anabolism and catabolism, causing FTCDs and osteoarthritis.[3] According to the depth of cartilage damage, it can be divided into the following two types: ① PTCDs, the depth of damage does not exceed the cartilage calcification layer; ② FTCDs, the damage exceeds the cartilage calcification layer (as shown in Figure 1).[4] A previous study showed that more than 60% of knee joints examined by arthroscopy had articular defects,[5] most of which are chronic PTCDs that were difficult to cure.[6] A clinical study also reported that partial- and full-thickness focal cartilage defects equally lead to new cartilage damage in knee osteoarthritis.[7] Therefore, it is very important to repair the superficial cartilage to protect the deeper and surrounding cartilage.

So far, there are various clinical treatments applied to repair articular cartilage injuries.[8–10] Non-surgical treatments mainly includes: ① oral non-steroidal anti-inflammatory drugs, glucosamine hydrochloride, chondroitin sulfate, etc.; ② intra-articular injections: glucocorticoids, sodium glutamate and sodium hyaluronate, etc.; ③ physical therapy: radio-frequency energy (RFE), light therapy (LT) low-intensity pulsed ultrasound (LIPUS) and pulsed electromagnetic field (PEMF), etc. All of these methods can achieve pain relief and delay degeneration, but they cannot fundamentally repair

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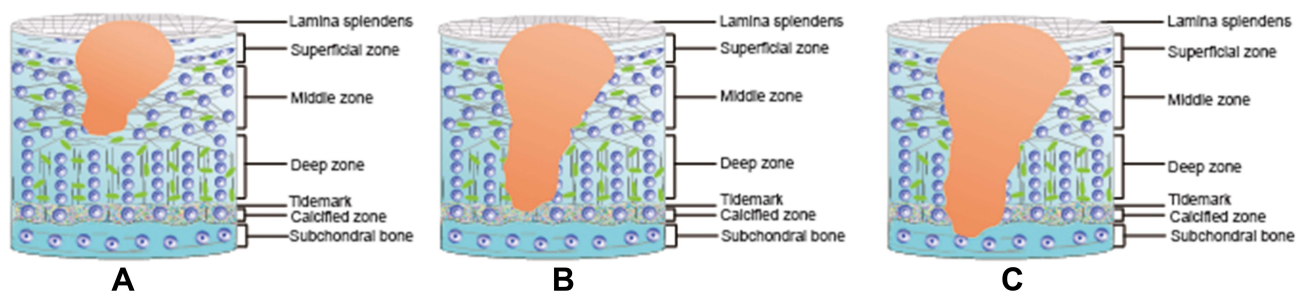
Figure I Schematic diagram of different degrees of cartilage injury. (**A**) Partial-thickness cartilage injury (defect depth does not exceed the deep cartilage layer); (**B**) Full-thickness cartilage defect (defect depth reaches below the tidemark); (**C**) Osteochondral injury (defect depth exceeds the calcified cartilage layer).

the damaged cartilage.[11,12] Common clinical surgical methods for treating cartilage injury include arthroscopic lavage, bone marrow stimulation, chondrocyte transplantation, and osteochondral grafting, which are mainly aimed at FTCDs and have many shortcomings such as the tendency to generate fibrocartilage, trigger lesions at the extraction site, and cause immune rejection.[13,14] In recent years, the main surgical techniques for repairing PTCDs are debridement and ablation, both of which are minimally invasive techniques that also fail to completely restore the structure and function of articular cartilage.[15]

In contrast to FTCDs and osteochondral injuries, the absence of blood supply and bone marrow exudation at the site of PTCDs, as well as the presence of anti-adhesive dermatan sulfate and other proteoglycans on the surface of the injured cartilage, prevent new cell adhesion required for repair,[16] resulting in irreparable cartilage damage. Therefore, these unique features of PTCDs require new therapeutic approaches.

With the development of microtechnology, tissue engineering techniques, especially the "bottom-up" method/strategy, have brought new hope for repairing PTCDs. The key problem of tissue engineering technology is to design scaffold materials that allow therapeutic cells or drugs to specifically adsorb to the injured area and have good tissue integration properties and biocompatibility; the core problem is to solve the problem of fixation/encapsulation and orderly release of cell-inducing factors, which are the current problems encountered in tissue engineering or regenerative medicine. This paper reviews the latest experimental research progress and treatment status of PTCDs in recent years.

PTCDs Diagnosis and Modeling
PTCDs Diagnosis

Early diagnosis or assessment of the effectiveness of PTCDs treatment is currently a medical diagnostic challenge. Arthroscopy can visually evaluate the state of articular cartilage, but it is an invasive examination with associated complications. Among many imaging techniques, magnetic resonance imaging (MRI) is an effective noninvasive diagnostic tool for evaluating articular cartilage and has been widely used to assess cartilage lesions.[17] Early articular cartilage injuries first undergo changes in biochemical components such as water, proteoglycan and collagen components, while there are generally no or only minor morphological changes. Conventional MRI examinations have limited sensitivity to early cartilage injury and do not show the biochemical components and physiological mechanism changes caused by it clearly enough.[18] With the development of technology, some new MRI techniques can quantify the changes in the internal biochemical components of early injured cartilage and are important tools for the early assessment of cartilage injury.[19] Biochemical MRI techniques can achieve a shift from qualitative MRI to quantitative MRI and play an increasingly important role in the early diagnosis of cartilage degeneration.[20] Among them, T1 mapping can reflect the changes of water content in cartilage in the early stages of cartilage injury,[21,22] and T2 mapping and T2*mapping can also provide a reliable basis for early diagnosis of articular cartilage injury.[23,24] These new techniques enhance the diagnostic potential of MRI and provide more and more accurate evidence for the future clinical diagnosis of early cartilage injury.

PTCDs Models

The construction of standardized models is not only a critical step in experimental studies, but also one of the major obstacles to the successful development of cartilage repair therapies. In recent years, scholars at home and abroad have commonly used rats/ mice, rabbits, horses and sheep to make animal PTCDs models. In small animal experiments, rats are the most applied animals, and researchers have used sterile surgical blades from ophthalmology[25–27] or special scalpels modified from ophthalmic knives[28–30] to scratch along the sagittal position in the weight-bearing area of the femoral condyles of rats, respectively, with a length of 5–10 mm and a depth of 100–250 μm, until there is no bleeding. To establish PTCDs in the rabbit knee, some researchers have used a scalpel to scrape away the cartilage surface to expose the mid-deep layer[31,32] or used a dental drill to create a partial cartilage defect (5 mm of diameter, <1 mm of thickness) on the hyaline cartilage layer of the New Zealand White rabbit knee joint.[33] In experiments with large animals, which are rarely studied, some investigators have used special tools to create PTCDs models in the femoral condyles of large animals such as sheep and horses.[26,34,35] Although large animals have limitations such as being expensive and difficult to keep, the anatomical features and mechanical characteristics of the joints in these animals are closer to those of human joints[36] and should also receive due attention. In addition, the existing preparation methods are all controlled by the operator, and the depth and size are difficult to control precisely. Therefore, there is an urgent need to use standardized modeling instruments in order to establish a more ideal joint PTCDs model.

Non-Surgical Treatment

The trauma associated with surgical treatment of superficial cartilage injuries far outweighs the benefits. As a result, conservative treatment is preferred by doctors and patients. Since some drugs work mainly to relieve pain and delay degeneration, they have little effect on the repair of cartilage damage. In recent years, autologous platelet-rich plasma (PRP) and the arthritis drug Sprifermin have attracted wide attention of researchers due to their dual effects of anti-inflammatory and cartilage regeneration.

PRP Therapy

Platelet-rich plasma (PRP) is a biological preparation rich in growth factors and hundreds of other proteins. PRP is more and more widely used in the field of orthopaedics, mainly focusing on the research and application of osteoarthritis and fractures, but less research on the treatment of articular cartilage injury. As a biotherapy to promote cartilage repair, PRP can improve the quality and quantity of cartilage repair tissue by reducing the adverse effects of inflammatory cytokines on gene expression of chondrocytes,[37,38] increasing the content of proteoglycan and collagen II (in vitro),[39] and inhibiting the concentration and gene expression of matrix metalloproteinase-13 and arthritis mediators.[40]

However, the positive effect on chondrogenesis and proliferation of mesenchymal stem cells (MSC) remains highly controversial. The results of some studies showed that PRP did not significantly promote chondrogenesis from adipose and bone marrow mesenchymal stem cells,[41] nor did it improve cartilage damage repair,[38] and even had a significant inhibitory effect on cartilage ECM production.[42] The reason for the discrepancy in the results of these studies may lie in the different composition and concentration in PRP.[43] The lack of standards for PRP in terms of factors such as centrifugation speed and time leads to a wide variation in platelet and leukocyte concentrations, which affects the therapeutic effect.[44]

In sum, more and more studies have shown that PRP can improve clinical cartilage pathology, and some scholars have applied PRP to cartilage tissue engineering,[45–48] but how and why it plays a role in cartilage repair is unclear,[49] which can be used as the next research direction.

Sprifermin Therapy

Sprifermin is a novel recombinant human fibroblast growth factor 18 (rhFGF18), and is currently the only FGF-based drug used in clinical trials (Phase II studies) of osteoarthritis.[50] Fibroblast growth factor (FGF) plays an essential role in regulating the growth, development and homeostasis of joint-related cells.[51,52]

Clinical studies have shown that Sprifermin has a positive effect on cartilage morphological changes and no adverse effects on other joint tissues.[53] Furthermore, Sprifermin favors the maintenance of chondrocyte phenotype and is more

likely to induce hyaline cartilage production than BMP7, IGF1 or IGF2.[54] Experimental studies have found that Sprifermin stimulates chondrocyte proliferation and produces a hyaline ECM,[55] while simultaneously inducing a more physiological chondrocyte phenotype.[56] Recent studies have confirmed that Sprifermin can positively affect cartilage structure by increasing cartilage thickness and decreasing cartilage loss.[57–59]

Therefore, Sprifermin has great potential for repairing damaged articular cartilage. However, the optimal treatment cycle and dosage of Sprifermin remain unclear, and the mechanisms that regulate chondrocyte homeostasis (eg, inflammation, metabolism, differentiation, senescence, and apoptosis) to promote cartilage regeneration still need further research. In addition, it is worth exploring whether Sprifermin has the same restorative effect on PTCDs with or without osteoarthritis.

Tissue Transplantation Repair Techniques

Cartilage transplantation repair is a treatment technique for repairing damaged cartilage by transplanting chondrocytes or cartilage-producing cells, tissues or tissue chimeras. Among them, the most common cartilage repair techniques include chondrocyte grafts, soft tissue grafts (eg, granular cartilage, periosteum, and perichondrium), and undifferentiated cell grafts. In animal experimental studies of PTCDs, there are mainly autologous chondrocyte implantation (ACI) and stem cell transplantation (SCT).

Autologous Chondrocyte Transplantation Techniques

ACI is a technology based on autologous chondrocytes expanded in vitro and then replanted to repair damaged cartilage, which has been developed to the third generation. In the early stage, ACI mainly used chondrocyte sheets and autologous periosteal covering techniques. Experimental results have shown that laminated chondrocyte sheets can attach to damaged cartilage sites and can maintain the chondrocyte phenotype, while also protecting them from catabolic factors in the joint[60,61] and promoting PTCDs healing.[62] In the middle stage, ACI used collagen membrane or matrix membrane assisted technology to repair PTCDs,[63] and these applications were the improvement of the previous technology. Currently, the application of matrix-induced autologous chondrocyte implantation (MACI) for ACI[64] has become the modern gold standard for local cartilage injury repair in North America and parts of Europe.[65,66] However, ACI has drawbacks such as easy to cause morbidity in the donor-site during biopsy, the need for two surgeries, and insufficient donor sources, which limit its clinical application.[67–69]

Stem Cell Transplantation Techniques

The limitations of ACI have limited its further development and application. Meanwhile, stem cells have attracted a lot of attention due to their high proliferative capacity, easy access to materials and low immunogenicity. Among them, intra-articular injection of MSCs has been shown to be effective in reducing patient pain, improving joint function, and having a strong ability to promote hyaline cartilage regeneration.[70,71] Agung et al[72] injected large amounts of MSCs into multiple tissues of the injured knee joint and showed that the transplanted cells moved to the injured area and contributed to tissue regeneration. In experimental animal studies, intra-articular injection of MSCs has been shown to promote PTCDs repair in rats.[26,27]

However, there are many problems to be optimized and solved in the use of MSCs such as ethics, rejection reactions and autologous cell viability, high mortality rate after direct cell injection, limited retention in target tissues, and low cartilage formation rate of MSCs are the main obstacles for their application in cartilage regeneration.[73,74] In recent years, in order to overcome the disadvantages of tissue or cell transplantation, the combination of tissue grafting techniques and cartilage tissue engineering technologies has developed as a research hotspot for cartilage injury repair.

Tissue Engineering Repair Techniques

Tissue engineering (TE) is a discipline of regenerative medicine based on the triad of seed cells, cellular scaffolds and inducing factors, and a continuation of autologous chondrocyte implantation techniques. In addition to the above three key factors of tissue engineering, more and more studies have shown that the cartilage regeneration microenvironment of cartilage regeneration is also crucial for cartilage damage repair. In recent years, tissue engineering techniques have been

a hot topic of research in the treatment of cartilage injuries,[75,76] among which the "bottom-up" approach has great potential to repair PTCDs.

Selection of Seed Cells

Seed cells are a key element of cartilage tissue engineering technology and an important foundation for the technology to achieve clinical application.[77] Depending on the source, they can be divided into exogenous seed cells and endogenous seed cells. Currently, chondrocytes are the most mature and widely used seed cells, and their dedifferentiation and secondary tissue damage after acquisition are still important challenges for clinical transformation.[78,79] Therefore, adult stem cells with multidirectional differentiation potential are the best alternative to chondrocytes and are gradually becoming a hot spot for tissue engineering seed cell research. In terms of mechanistic theory, some researchers support that stem cells can achieve articular cartilage regeneration through directional differentiation into chondrocytes.[80] Among them, bone marrow mesenchymal stem cells (MMSCs), adipose mesenchymal stem cells (ADSCs), synovial mesenchymal stem cells (SDSCs), and induced pluripotent stem cells (IPSCs) are highly favored by researchers. Although exogenous mesenchymal stem cells are rich in sources, they still suffer from problems such as immune rejection and expensive induction of differentiation and proliferation in vitro. Meanwhile, the recruitment of endogenous stem cells to the injured site to promote cartilage repair has also attracted much attention,[81,82] especially the discovery of cartilage stem / progenitor cells with the basic characteristics of stem cells, enabling in situ cartilage tissue regeneration has been research hotspot.

On the other hand, more and more studies have shown that the therapeutic function of transplanted MSCs mainly depends on its paracrine effect.[83] In particular, the secretion of exosomes (Exos) plays an important role in cellular communication, immune response, tissue repair and other biological functions.[84] Among them, MSC-Exos can mediate cartilage repair by promoting cell proliferation, inhibiting apoptosis and regulating immune reactivity.[85] Although Exos has the advantages of non-immune rejection, high penetration and easy storage, it still has limitations such as low recovery rate, short half-life, inability to self-replicate and may require large doses to achieve the desired therapeutic effect.[86] Recently, some researchers used cell nanoporation (CNP) technology to encapsulate specific miRNAs, which not only greatly improved the production of Exos, but also promoted the clinical application of "cell-free" therapy.[87] However, more systematic and in-depth research is still needed if it is to be put into clinical use. However, if it is to be put into clinical use, more systematic and in-depth research is still needed.

Construction of Cartilage Scaffold

A suitable scaffold is the key to constructing tissue-engineered cartilage, providing a temporary "home" for transplanted or resident migrating cells and creating a suitable microenvironment for cell residence, differentiation and new tissue formation. In recent years, a large number of new intelligent biomaterials have emerged, especially especially the injectable hydrogels that can minimally invasively repair damaged and irregular tissues have been a research hotspot.[88,89]

In animal experimental studies, researchers have long used injectable hydrogels to promote the repair of PTCDs, and achieved good results.[90,91] Although hydrogels have many advantages, insufficient mechanical strength has always been an important reason limiting their use in experimental studies of cartilage tissue engineering.[92] To overcome this problem, researchers have tried to increase the mechanical strength of hydrogels by increasing the crosslink density, reducing the gel swelling, introducing fiber reinforcers and preparing interpenetrating networks.[93,94] In addition to the need for enhanced mechanical strength, the development of hydrogel scaffolds that can adhere robustly and durably to the wet-state surfaces of irregular PTCDs remains a challenge. At present, inspired by mussel adhesion, a variety of catechol-functionalized adhesive hydrogels have been developed, bringing hope to overcome the unfavorable wet cartilage environment.[95] Among them, Zhang et al[96] developed an injectable hydrogel with high binding strength to wet cartilage surfaces, which has a higher wet surface adhesive strength than commercially available tissue adhesives and has great potential for repairing PTCDs.

Furthermore, ideal hydrogel materials should provide a favorable biomimetic microenvironment for cell adhesion, orientation, migration, proliferation and chondrogenic differentiation.[97] However, hydrogels are significantly different from natural extracellular matrix, and the spontaneous proliferation, condensation, differentiation as well as matrix

precipitation of cells in hydrogels are restricted.[98] At present, a variety of functional hydrogels that promote cartilage regeneration and repair have been developed.[95,99,100] The development of printable, biocompatible and functional hydrogels is an important future research direction, which is expected to become a promising clinical treatment in the near future.[101,102]

Application of Induction Factors

Repair of articular cartilage damage is an extremely complex process regulated by a variety of complex signaling molecules. The most commonly used inducing factors in cartilage tissue engineering regeneration can be divided into two categories: natural factors and synthetic factors. In recent years, researchers pay more attention to the proliferative effect of a single inducer on chondrocytes and its effect on chondrocyte morphogenesis, but there are few studies on the signaling pathway of single factor and the effect of combined use of multiple factors. If the mechanism of action of inducible factors is to be elucidated in depth and their potential in cartilage repair is to be further explored, the release of inducible factors in a controlled manner, precise targeting of cells and long-term effective retention in target tissues are both the key to its success and the challenge.[103,104]

To solve this problem, researchers commonly use strategies such as surface presentation (non-covalent and covalent binding), encapsulation with pre-programmed delivery (physical encapsulation, particles and nanoparticles), and layer-by-layer assembly.[105] Among them, particles/microcarriers and nanoparticles as carriers for growth factor delivery have emerged as hot directions for cartilage injury repair. Microsphere (microcarrier) drug delivery systems that allow targeted and controlled release of genes, proteins and cytokines and other drugs have been used to reduce pain and stimulate cartilage regeneration.[106,107] In addition, nanoparticle carriers have been widely noted for their high surface area-to-volume ratio, high drug encapsulation efficiency, and rapid response to surrounding environmental stimuli (eg, temperature, pH, magnetic field, or ultrasound).[108]

Recently, in search of a strategy for controlled loading and release of growth factors, Mahmoudi et al[109] used microfluidic chip technology to synthesize uniformly sized sodium alginate nanogels in a microfluidic device, achieving a slow release of growth factors while also achieving a significantly lower release. However, the release rate of microspheres is rarely constant in practice, and problems such as burst release may occur.[110] Nanoparticle carriers also have problems such as fewer toxicological studies on cartilage and short observation time. Therefore, how to control the sustained and controlled release of cytokines while ensuring their activity remains an urgent problem for researchers.

Modification of in-situ Matrix Microenvironment

Cartilage and joint injuries are associated with a variety of microenvironmental changes (mainly including: biophysical and biochemical cues) that are unfavorable for cartilage regeneration occur, eventually leading to the failure of cartilage repair. The ideal microenvironment plays a key role in determining cell adhesion, proliferation and/or differentiation, and is more conducive for regenerating cartilage to present the desired phenotype.[111,112] In addition to the lack of bone marrow mesenchymal stem cell source, the superficial cartilage matrix rich in anti-adhesive proteoglycans, low chondrocyte viability at the defect boundary and dense ECM may be the main reasons why PTCDs is more difficult to repair compared to FTCDs and OCDs.[113,114]

In an animal study, Zhang et al[32] used collagen type I scaffolds containing stromal cell-derived factor-1 (SDF-1) to create an in situ matrix environment conducive to cell migration and adhesion, which improved the self-healing ability of rabbit PTCDs. However, the dense and stiff ECM at the wound interface can hinder endogenous cell migration, and the use of chemoattractant to facilitate cell migration alone is not sufficient without creating an environment with appropriate porosity for cell migration.[115] Therefore, some researchers have tried to improve the injured cartilage microenvironment by using hydrolytic enzymes to digest the cartilage matrix at the injury and its surrounding adhesions. Enzymatic pretreatment releases proteoglycans from the walls of surrounding native cartilage in a controlled manner, thereby creating space for new tissue neo-tissues to firmly anchor and bind to adjacent host cartilage,[116] and has the potential to accelerate cell migration toward cartilage injury, which has great clinical application.[117] Lee et al[118] treated PTCDs in the patellofemoral joints of rabbits with chondroitinase ABC and showed selective degradation of proteoglycans along with increased adhesion of transplanted SDSCs to the cartilage defects.

However, the type, concentration and safety of hydrolase still need more experimental research, and the development of hydrolase products to assist cartilage repair deserves further exploration. In summary, we have been able to manipulate the tissue microenvironment more precisely, but still cannot fully replicate the complex extracellular matrix microenvironment.[119] Seeking key microenvironmental cues affecting cartilage regeneration and creating an ideal microenvironment conducive to the repair of PTCDs will be the direction of future efforts.

"Bottom-Up" Treatment Strategies

In traditional "top-down" approaches to tissue engineering, cells are seeded onto biocompatible and biodegradable scaffolds designed to mimic the physicochemical and biomechanical cues of native ECM.[120] In recent years, the top-down approaches have still dominated experimental studies of macroscopic tissue reconstruction in vitro.[121] However, this strategy suffers from low cell inoculation density and and uneven spatial distribution[122] and usually fails to precisely construct repetitive functional units (modular units) in biological tissues. In contrast, following nature's law of building organisms in a bottom-up manner, building macro-scale tissues with micro-tissues as modular units is a promising tissue engineering repair strategy.[123]

In recent years, in order to overcome the limitations such as porosity and diffusion of traditional bulk hydrogel scaffolds, researchers have successfully prepared microscale (~1–1000μm) hydrogel particles (microgels) with small size and high porosity as modular components using microtechnology.[124,125] Currently, microgels have been increasingly used in cell and drug delivery, scaffold design, and biofabrication.[126] Compared to conventional hydrogel scaffolds, microgels can both be presented/delivered in a minimally invasive manner and provide more space for cell proliferation and migration, thereby promoting cell infiltration and tissue regeneration.[109,127] Zhang et al[128] modified natural silk fibroin particles with small molecule NB (O-nitrobenzene) to make adhesive "joint paint", which can be directly anchored on the surface of PTCDs after being activated by ultraviolet light, which could better promote cartilage repair and restore the smooth surface of joints. This bottom-up tissue engineering repair strategy consists of the following processes: (1) Preparation of particles (microcarriers). Microcarriers can be classified as solid and porous in terms of appearance and morphology, and cargoes such as seed cells, drugs and growth factors can be adhered to their surfaces or loaded inside the pores; (2) Applying the material with a brush to diffuse PTCDs or injecting it minimally invasively into focal PTCDs according to the clinical characteristics of the cartilage injury; (3) In situ gelation by external stimulation (mainly light and temperature control, etc.), so as to achieve the goal of personalized and precise treatment to bring new life to the scarred cartilage (Figure 2).
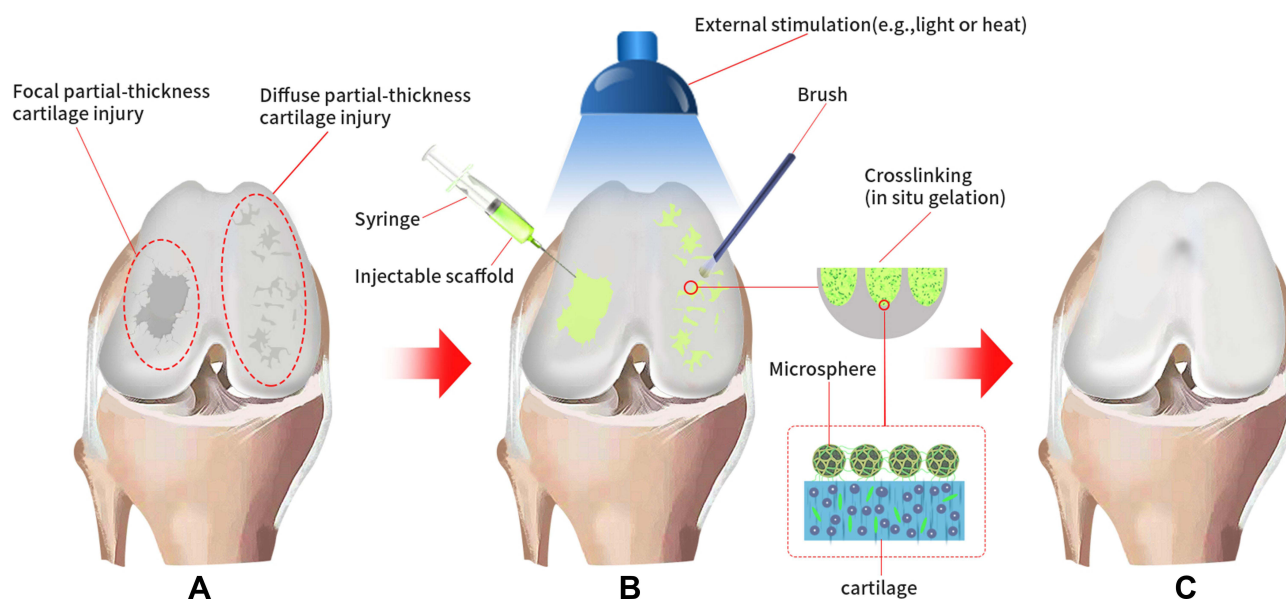
Figure 2 Schematic diagram of the bottom-up cartilage repair process. (**A**) Cartilage lesion/damage, the cartilage surface can be seen as rhagadia, shrinkage, cracks or even some areas of superficial damage, the cartilage surface is uneven; (**B**) The cartilage injury is filled with microgel, and the surface is restored to flatness, but with slightly less smoothness and moistness; (**C**) Smooth and moistened surface of cartilage lesion/damage is restored after the material (drug) works.

In addition, it has been demonstrated that the articular cartilage surface has a layer of approximately 20 μm thick, semi-independent mobile tissue with a synovial surface that is directly affected by frictional and additional shear force.[129,130] (Figure 1) Disruption of this cartilage surface layer may lead to irreversible articular cartilage damage and joint disease.[131,132] However, few studies have focused on the importance of this lamellar tissue for cartilage repair and prognosis, and traditional top-down tissue engineering strategies are usually not suitable for repairing this microscale cartilage injury. Therefore, a bottom-up repair strategy may be the best option for treating PTCDs arising in the early and middle stages of articular cartilage lesions.

Conclusions and Future Perspectives

In order to avoid serious risks, adverse events and off target effects caused by continuous high-dose administration or lack of disease specific targets, it is of great significance to target the diseased cartilage and achieve precise and individualized treatment. In practical applications, in order to improve the adverse matrix microenvironment at the cartilage lesions, we can try to target the removal of collagen and proteoglycan at the interface of cartilage defects to increase the size of matrix pores, reduce matrix stiffness, and promote cell migration.[115] In addition to the unfavorable physical microenvironment, the oxidative environment can also interfere with the chondrogenic differentiation of stem cells.[133] The overexpression of ROS is a challenge for cartilage regeneration, which is considered as an inflammatory mediator regulating chondrocyte apoptosis and can lead to tissue damage.[134] The development of nano antioxidants that can target cartilage tissue is one of the most advanced methods to improve cartilage regeneration and resist oxidative stress.[133,135] In addition, engineered cells are usually unable to colonize cartilage defect sites efficiently, the therapeutic effect is obviously limited. In order to enhance the ability of mesenchymal stem cells to colonize PTCDs, Li et al[136] directly modified MSCs with transglutaminase 2 to achieve targeted treatment of PTCDs, and achieved satisfactory therapeutic results. Therefore, it is promising to develop nanoparticles that can functionally target specific components and/or cells of cartilage for the targeted treatment of cartilage defects.

Currently, most studies have focused on the treatment of FTCDs and OCDs. However, most of the cartilage injuries observed in OA joints are PTCDs, which need to be studied separately due to their different nature and extent from FTCDs.[7,137] There are various approaches to treat PTCDs, each with its own advantages and disadvantages. Conservative treatment is an easily accepted treatment for patients, but there are shortcomings such as long treatment cycles, poor efficacy and drug toxicities, and the development of specific drugs to repair cartilage injuries remains a future endeavor. The rapid and creative progress of next-generation tissue bioengineering will be a great hope for in situ repair of PTCDs. However, tissue engineering still faces many problems, such as inability to precisely control the degree of chondrocyte differentiation, vector safety and regulation of multiple gene expression during multigene therapy, and more in-depth research is still needed for clinical application. The development of PTCDs repair techniques with low cost, high safety, good efficacy and easy operation will will still be the focus of future research.

Disclosure

The authors declare that there are no competing interests associated with the manuscript.

References

1. Sophia Fox AJ, Bedi A, Rodeo SA. The basic science of articular cartilage: structure, composition, and function. *Sports Health*. 2009;1 (6):461–468. doi:10.1177/1941738109350438

2. Huey DJ, Hu JC, Athanasiou KA. Unlike bone, cartilage regeneration remains elusive. *Science*. 2012;338(6109):917–921. doi:10.1126/ science.1222454

3. Hong E, Reddi AH. MicroRNAs in chondrogenesis, articular cartilage, and osteoarthritis: implications for tissue engineering. *Tissue Eng Part B Rev*. 2012;18(6):445–453. doi:10.1089/ten.TEB.2012.0116

4. Menetrey J, Unno-Veith F, Madry H, Van Breuseghem I. Epidemiology and imaging of the subchondral bone in articular cartilage repair. *Knee Surg Sports Traumatol Arthrosc*. 2010;18(4):463–471. doi:10.1007/s00167-010-1053-0

5. Widuchowski W, Widuchowski J, Trzaska T. Articular cartilage defects: study of 25,124 knee arthroscopies. *Knee*. 2007;14(3):177–182. doi:10.1016/j.knee.2007.02.001

6. Ono Y, Akagi R, Mikami Y, et al. Effect of systemic administration of granulocyte colony-stimulating factor on a chronic partial-thickness cartilage defect in a rabbit knee joint. *Cartilage*. 2021;13(2_suppl):175S–184S. doi:10.1177/19476035211021905

7. Guermazi A, Hayashi D, Roemer FW, et al. Brief report: partial- and full-thickness focal cartilage defects contribute equally to development of new cartilage damage in knee osteoarthritis: the multicenter osteoarthritis study. *Arthritis Rheumatol*. 2017;69(3):560–564. doi:10.1002/ art.39970

8. Mundi R, Bedi A, Chow L, et al. Cartilage restoration of the knee: a systematic review and meta-analysis of level 1 studies. *Am J Sports Med*. 2016;44(7):1888–1895. doi:10.1177/0363546515589167

9. Chahla J, Piuzzi NS, Mitchell JJ, et al. Intra-articular cellular therapy for osteoarthritis and focal cartilage defects of the knee: a systematic review of the literature and study quality analysis. *J Bone Joint Surg Am*. 2016;98(18):1511–1521. doi:10.2106/JBJS.15.01495

10. Matsiko A, Levingstone TJ, O'Brien FJ. Advanced strategies for articular cartilage defect repair. *Materials*. 2013;6(2):637–668. doi:10.3390/ ma6020637

11. Muhammad SA, Nordin N, Mehat MZ, Fakurazi S. Comparative efficacy of stem cells and secretome in articular cartilage regeneration: a systematic review and meta-analysis. *Cell Tissue Res*. 2019;375(2):329–344. doi:10.1007/s00441-018-2884-0

12. Liu M, Zeng X, Ma C, et al. Injectable hydrogels for cartilage and bone tissue engineering. *Bone Res*. 2017;5:17014. doi:10.1038/ boneres.2017.14

13. Behery O, Siston RA, Harris JD, Flanigan DC. Treatment of cartilage defects of the knee: expanding on the existing algorithm. *Clin J Sport Med*. 2014;24(1):21–30. doi:10.1097/JSM.0000000000000004

14. Hunziker EB. The elusive path to cartilage regeneration. *Adv Mater*. 2009;21(32–33):3419–3424. doi:10.1002/adma.200801957

15. da Cunha Cavalcanti FM, Doca D, Cohen M, Ferretti M. Updating on diagnosis and treatment of chondral lesion of the knee. *Rev Bras Ortop*. 2015;47(1):12–20. doi:10.1016/S2255-4971(15)30339-6

16. Lewandowska K, Choi HU, Rosenberg LC, Zardi L, Culp LA. Fibronectin-mediated adhesion of fibroblasts: inhibition by dermatan sulfate proteoglycan and evidence for a cryptic glycosaminoglycan-binding domain. *J Cell Biol*. 1987;105(3):1443–1454. doi:10.1083/jcb.105.3.1443

17. Wang N, Badar F, Xia Y. Experimental influences in the accurate measurement of cartilage thickness in MRI. *Cartilage*. 2019;10(3):278–287. doi:10.1177/1947603517749917

18. Kaushik AP, Das A, Cui Q. Osteonecrosis of the femoral head: an update in year 2012. *World J Orthop*. 2012;3(5):49–57. doi:10.5312/wjo.v3. i5.49

19. Argentieri EC, Burge AJ, Potter HG. Magnetic resonance imaging of articular cartilage within the knee. *J Knee Surg*. 2018;31(2):155–165. doi:10.1055/s-0037-1620233

20. Trattnig S, Raudner M, Schreiner M, Roemer F, Bohndorf K. Biochemische Knorpeldiagnostik – update 2019 [Biochemical cartilage imaging-update 2019]. *Radiologe*. 2019;59(8):742–749. doi:10.1007/s00117-019-0558-x

21. Shiguetomi-Medina JM, Gottliebsen M, Kristiansen MS, et al. Water-content calculation in growth plate and cartilage using MR T1-mapping design and validation of a new method in a porcine model. *Skeletal Radiol*. 2013;42(10):1413–1419. doi:10.1007/s00256-013-1674-8

22. Tadimalla S, Momot KI, Norman DG. Effect of partial H2O-D2O replacement on the anisotropy of transverse proton spin relaxation in bovine articular cartilage. *PLoS One*. 2014;9(12):e115288. doi:10.1371/journal.pone.0115288

23. Soellner ST, Goldmann A, Muelheims D, Welsch GH, Pachowsky ML. Intraoperative validation of quantitative T2 mapping in patients with articular cartilage lesions of the knee. *Osteoarthritis Cartilage*. 2017;25(11):1841–1849. doi:10.1016/j.joca.2017.07.021

24. Tsai PH, Wong CC, Chan WP, Lu TW. The value of MR T2* measurements in normal and osteoarthritic knee cartilage: effects of age, sex, and location. *Eur Radiol*. 2019;29(8):4514–4522. doi:10.1007/s00330-018-5826-z

25. Ikegawa N, Sasho T, Yamaguchi S, et al. Identification of genes required for the spontaneous repair of partial-thickness cartilage defects in immature rats. *Connect Tissue Res*. 2016;57(3):190–199. doi:10.3109/03008207.2015.1121250

26. Pei M, He F, Li J, Tidwell JE, Jones AC, McDonough EB. Repair of large animal partial-thickness cartilage defects through intraarticular injection of matrix-rejuvenated synovium-derived stem cells. *Tissue Eng Part A*. 2013;19(9–10):1144–1154. doi:10.1089/ten.TEA.2012.0351

27. Enomoto T, Akagi R, Ogawa Y, et al. Timing of intra-articular injection of synovial mesenchymal stem cells affects cartilage restoration in a partial thickness cartilage defect model in rats. *Cartilage*. 2020;11(1):122–129. doi:10.1177/1947603518786542

28. Yoshioka M, Kubo T, Coutts RD, Hirasawa Y. Differences in the repair process of longitudinal and transverse injuries of cartilage in the rat knee. *Osteoarthritis Cartilage*. 1998;6(1):66–75. doi:10.1053/joca.1997.0093

29. Mukoyama S, Sasho T, Akatsu Y, et al. Spontaneous repair of partial thickness linear cartilage injuries in immature rats. *Cell Tissue Res*. 2015;359(2):513–520. doi:10.1007/s00441-014-2041-3

30. Zhang K, Shi J, Li Y, et al. Chondrogenic cells respond to partial-thickness defects of articular cartilage in adult rats: an in vivo study. *J Mol Histol*. 2016;47(3):249–258. doi:10.1007/s10735-016-9668-1

31. Jansen EJ, Emans PJ, Van Rhijn LW, Bulstra SK, Kuijer R. Development of partial-thickness articular cartilage injury in a rabbit model. *Clin Orthop Relat Res*. 2008;466(2):487–494. doi:10.1007/s11999-007-0050-1

32. Zhang W, Chen J, Tao J, et al. The use of type 1 collagen scaffold containing stromal cell-derived factor-1 to create a matrix environment conducive to partial-thickness cartilage defects repair. *Biomaterials*. 2013;34(3):713–723. doi:10.1016/j.biomaterials.2012.10.027

33. Kim M, Hong B, Lee J, et al. Composite system of PLCL scaffold and heparin-based hydrogel for regeneration of partial-thickness cartilage defects. *Biomacromolecules*. 2012;13(8):2287–2298. doi:10.1021/bm3005353

34. Kääb MJ, Bail HJ, Rotter A, Mainil-Varlet P, apGwynn I, Weiler A. Monopolar radiofrequency treatment of partial-thickness cartilage defects in the sheep knee joint leads to extended cartilage injury. *Am J Sports Med*. 2005;33(10):1472–1478. doi:10.1177/0363546505275013

35. Edwards RB 3rd, Lu Y, Uthamanthil RK, et al. Comparison of mechanical debridement and radiofrequency energy for chondroplasty in an in vivo equine model of partial thickness cartilage injury. *Osteoarthritis Cartilage*. 2007;15(2):169–178. doi:10.1016/j.joca.2006.06.021

36. Ahern BJ, Parvizi J, Boston R, Schaer TP. Preclinical animal models in single site cartilage defect testing: a systematic review. *Osteoarthritis Cartilage*. 2009;17(6):705–713. doi:10.1016/j.joca.2008.11.008

37. Chen WH, Lin CM, Huang CF, et al. Functional recovery in osteoarthritic chondrocytes through hyaluronic acid and platelet-rich plasma-inhibited infrapatellar fat pad adipocytes. *Am J Sports Med*. 2016;44(10):2696–2705. doi:10.1177/0363546516651822

38. Filardo G, Kon E, Roffi A, Di Matteo B, Merli ML, Marcacci M. Platelet-rich plasma: why intra-articular? A systematic review of preclinical studies and clinical evidence on PRP for joint degeneration. *Knee Surg Sports Traumatol Arthrosc*. 2015;23(9):2459–2474. doi:10.1007/s00167-013-2743-1

39. Park SI, Lee HR, Kim S, Ahn MW, Do SH. Time-sequential modulation in expression of growth factors from platelet-rich plasma (PRP) on the chondrocyte cultures. *Mol Cell Biochem*. 2012;361(1–2):9–17. doi:10.1007/s11010-011-1081-1

40. Sundman EA, Cole BJ, Karas V, et al. The anti-inflammatory and matrix restorative mechanisms of platelet-rich plasma in osteoarthritis. *Am J Sports Med*. 2014;42(1):35–41. doi:10.1177/0363546513507766

41. Liou JJ, Rothrauff BB, Alexander PG, Tuan RS. Effect of platelet-rich plasma on chondrogenic differentiation of adipose- and bone marrow-derived mesenchymal stem cells. *Tissue Eng Part A*. 2018;24(19–20):1432–1443. doi:10.1089/ten.tea.2018.0065

42. Rikkers M, Dijkstra K, Terhaard BF, et al. Platelet-rich plasma does not inhibit inflammation or promote regeneration in human osteoarthritic chondrocytes in vitro despite increased proliferation. *Cartilage*. 2020:1947603520961162. doi:10.1177/1947603520961162

43. Do Amaral RJ, Matsiko A, Tomazette MR, et al. Platelet-rich plasma releasate differently stimulates cellular commitment toward the chondrogenic lineage according to concentration. *J Tissue Eng*. 2015;6:2041731415594127. doi:10.1177/2041731415594127

44. Chen CPC, Chen JL, Hsu CC, Pei YC, Chang WH, Lu HC. Injecting autologous platelet rich plasma solely into the knee joint is not adequate in treating geriatric patients with moderate to severe knee osteoarthritis. *Exp Gerontol*. 2019;119:1–6. doi:10.1016/j.exger.2019.01.018

45. Li Z, Zhang X, Yuan T, et al. Addition of platelet-rich plasma to silk fibroin hydrogel bioprinting for cartilage regeneration. *Tissue Eng Part A*. 2020;26(15–16):886–895. doi:10.1089/ten.TEA.2019.0304

46. Liu X, Yang Y, Niu X, et al. An in situ photocrosslinkable platelet rich plasma - complexed hydrogel glue with growth factor controlled release ability to promote cartilage defect repair. *Acta Biomater*. 2017;62:179–187. doi:10.1016/j.actbio.2017.05.023

47. Tang Y, Wang H, Sun Y, et al. Using platelet-rich plasma hydrogel to deliver mesenchymal stem cells into three-dimensional PLGA scaffold for cartilage tissue engineering. *ACS Appl Bio Mater*. 2021;4(12):8607–8614. doi:10.1021/acsabm.1c01160

48. Pan X, Yuan S, Xun X, et al. Long-term recruitment of endogenous M2 macrophages by platelet lysate-rich plasma macroporous hydrogel scaffold for articular cartilage defect repair. *Adv Healthc Mater*. 2022;11(6):e2101661. doi:10.1002/adhm.202101661

49. Paschos NK. Editorial commentary: now is the time to discover how and why platelet-rich plasma works in cartilage. *Arthroscopy*. 2019;35(3):977–978. doi:10.1016/j.arthro.2018.12.028

50. Xie Y, Zinkle A, Chen L, Mohammadi M. Fibroblast growth factor signalling in osteoarthritis and cartilage repair. *Nat Rev Rheumatol*. 2020;16(10):547–564. doi:10.1038/s41584-020-0469-2

51. Chijimatsu R, Saito T. Mechanisms of synovial joint and articular cartilage development. *Cell Mol Life Sci*. 2019;76(20):3939–3952. doi:10.1007/s00018-019-03191-5

52. Ellman MB, Yan D, Ahmadinia K, Chen D, An HS, Im HJ. Fibroblast growth factor control of cartilage homeostasis. *J Cell Biochem*. 2013;114(4):735–742. doi:10.1002/jcb.24418

53. Roemer FW, Kraines J, Aydemir A, et al. Evaluating the structural effects of intra-articular Sprifermin on cartilage and non-cartilaginous tissue alterations, based on sqMRI assessment over 2 years. *Osteoarthritis Cartilage*. 2020;28(9):1229–1234. doi:10.1016/j.joca.2020.05.015

54. Müller S, Lindemann S, Gigout A. Effects of Sprifermin, IGF1, IGF2, BMP7, or CNP on bovine chondrocytes in monolayer and 3D culture. *J Orthop Res*. 2020;38(3):653–662. doi:10.1002/jor.24491

55. Reker D, Kjelgaard-Petersen CF, Siebuhr AS, et al. Sprifermin (rhFGF18) modulates extracellular matrix turnover in cartilage explants ex vivo. *J Transl Med*. 2017;15(1):250. doi:10.1186/s12967-017-1356-8

56. Gigout A, Guehring H, Froemel D, et al. Sprifermin (rhFGF18) enables proliferation of chondrocytes producing a hyaline cartilage matrix. *Osteoarthritis Cartilage*. 2017;25(11):1858–1867. doi:10.1016/j.joca.2017.08.004

57. Hochberg MC, Guermazi A, Guehring H, et al. Effect of intra-articular Sprifermin vs placebo on femorotibial joint cartilage thickness in patients with osteoarthritis: the FORWARD randomized clinical trial. *JAMA*. 2019;322(14):1360–1370. doi:10.1001/jama.2019.14735

58. Eckstein F, Kraines JL, Aydemir A, Wirth W, Maschek S, Hochberg MC. Intra-articular Sprifermin reduces cartilage loss in addition to increasing cartilage gain independent of location in the femorotibial joint: post-hoc analysis of a randomised, placebo-controlled phase II clinical trial. *Ann Rheum Dis*. 2020;79(4):525–528. doi:10.1136/annrheumdis-2019-216453

59. Brett A, Bowes MA, Conaghan PG, et al. Automated MRI assessment confirms cartilage thickness modification in patients with knee osteoarthritis: post-hoc analysis from a phase II Sprifermin study. *Osteoarthritis Cartilage*. 2020;28(11):1432–1436. doi:10.1016/j.joca.2020.08.005

60. Kaneshiro N, Sato M, Ishihara M, Mitani G, Sakai H, Mochida J. Bioengineered chondrocyte sheets may be potentially useful for the treatment of partial thickness defects of articular cartilage. *Biochem Biophys Res Commun*. 2006;349(2):723–731. doi:10.1016/j.bbrc.2006.08.096

61. Kaneshiro N, Sato M, Ishihara M, et al. Cultured articular chondrocytes sheets for partial thickness cartilage defects utilizing temperature-responsive culture dishes. *Eur Cell Mater*. 2007;13:87–92. doi:10.22203/ecm.v013a09

62. Nixon AJ, Begum L, Mohammed HO, Huibregtse B, O'Callaghan MM, Matthews GL. Autologous chondrocyte implantation drives early chondrogenesis and organized repair in extensive full- and partial-thickness cartilage defects in an equine model. *J Orthop Res*. 2011;29(7):1121–1130. doi:10.1002/jor.21366

63. Park DY, Min BH, Lee HJ, Kim YJ, Choi BH. Repair of partial thickness cartilage defects using cartilage extracellular matrix membrane-based chondrocyte delivery system in human ex vivo model. *Tissue Eng Regen Med*. 2016;13(2):182–190. doi:10.1007/s13770-016-9043-z

64. Statham P, Jones E, Jennings LM, Fermor HL. Reproducing the biomechanical environment of the chondrocyte for cartilage tissue engineering. *Tissue Eng Part B Rev*. 2022;28(2):405–420. doi:10.1089/ten.TEB.2020.0373

65. Brittberg M, Recker D, Ilgenfritz J, Saris DBF; SUMMIT Extension Study Group. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: five-year follow-up of a prospective randomized trial. *Am J Sports Med*. 2018;46(6):1343–1351. doi:10.1177/0363546518756976

66. Saris D, Price A, Widuchowski W, et al. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: two-year follow-up of a prospective randomized trial. *Am J Sports Med*. 2014;42(6):1384–1394. doi:10.1177/0363546514528093

67. Aae TF, Randsborg PH, Lurås H, Årøen A, Lian ØB. Microfracture is more cost-effective than autologous chondrocyte implantation: a review of level 1 and level 2 studies with 5 year follow-up. *Knee Surg Sports Traumatol Arthrosc*. 2018;26(4):1044–1052. doi:10.1007/s00167-017-4802-5

68. Makris EA, Gomoll AH, Malizos KN, Hu JC, Athanasiou KA. Repair and tissue engineering techniques for articular cartilage. *Nat Rev Rheumatol*. 2015;11(1):21–34. doi:10.1038/nrrheum.2014.157

69. Wylie JD, Hartley MK, Kapron AL, Aoki SK, Maak TG. Failures and reoperations after matrix-assisted cartilage repair of the knee: a systematic review. *Arthroscopy*. 2016;32(2):386–392. doi:10.1016/j.arthro.2015.07.025

70. Wakitani S, Okabe T, Horibe S, et al. Safety of autologous bone marrow-derived mesenchymal stem cell transplantation for cartilage repair in 41 patients with 45 joints followed for up to 11 years and 5 months. *J Tissue Eng Regen Med*. 2011;5(2):146–150. doi:10.1002/term.299

71. Nejadnik H, Hui JH, Feng Choong EP, Tai BC, Lee EH. Autologous bone marrow-derived mesenchymal stem cells versus autologous chondrocyte implantation: an observational cohort study. *Am J Sports Med*. 2010;38(6):1110–1116. doi:10.1177/0363546509359067

72. Agung M, Ochi M, Yanada S, et al. Mobilization of bone marrow-derived mesenchymal stem cells into the injured tissues after intraarticular injection and their contribution to tissue regeneration. *Knee Surg Sports Traumatol Arthrosc*. 2006;14(12):1307–1314. doi:10.1007/s00167-006-0124-8

73. Ennis WJ, Sui A, Bartholomew A. Stem cells and healing: impact on inflammation. *Adv Wound Care*. 2013;2(7):369–378. doi:10.1089/wound.2013.0449

74. Laflamme MA, Chen KY, Naumova AV, et al. Cardiomyocytes derived from human embryonic stem cells in pro-survival factors enhance function of infarcted rat hearts. *Nat Biotechnol*. 2007;25(9):1015–1024. doi:10.1038/nbt1327

75. Yang J, Zhang YS, Yue K, Khademhosseini A. Cell-laden hydrogels for osteochondral and cartilage tissue engineering. *Acta Biomater*. 2017;57:1–25. doi:10.1016/j.actbio.2017.01.036

76. Nukavarapu SP, Dorcemus DL. Osteochondral tissue engineering: current strategies and challenges. *Biotechnol Adv*. 2013;31(5):706–721. doi:10.1016/j.biotechadv.2012.11.004

77. Vinatier C, Guicheux J. Cartilage tissue engineering: from biomaterials and stem cells to osteoarthritis treatments. *Ann Phys Rehabil Med*. 2016;59(3):139–144. doi:10.1016/j.rehab.2016.03.002

78. Phull AR, Eo SH, Abbas Q, Ahmed M, Kim SJ. Applications of chondrocyte-based cartilage engineering: an overview. *Biomed Res Int*. 2016;2016:1879837. doi:10.1155/2016/1879837

79. Gosset M, Berenbaum F, Thirion S, Jacques C. Primary culture and phenotyping of murine chondrocytes. *Nat Protoc*. 2008;3(8):1253–1260. doi:10.1038/nprot.2008.95

80. Jiang S, Tian G, Li X, et al. Research progress on stem cell therapies for articular cartilage regeneration. *Stem Cells Int*. 2021;2021:8882505. doi:10.1155/2021/8882505

81. Lee CH, Cook JL, Mendelson A, Moioli EK, Yao H, Mao JJ. Regeneration of the articular surface of the rabbit synovial joint by cell homing: a proof of concept study. *Lancet*. 2010;376(9739):440–448. doi:10.1016/S0140-6736(10)60668-X

82. Shi W, Sun M, Hu X, et al. Structurally and functionally optimized silk-fibroin-gelatin scaffold using 3D printing to repair cartilage injury in vitro and in vivo. *Adv Mater*. 2017;29(29):29. doi:10.1002/adma.201701089

83. Zhou Y, Yamamoto Y, Xiao Z, Ochiya T. The immunomodulatory functions of mesenchymal stromal/stem cells mediated via paracrine activity. *J Clin Med*. 2019;8(7):1025. doi:10.3390/jcm8071025

84. Huang J, Xiong J, Yang L, Zhang J, Sun S, Liang Y. Cell-free exosome-laden scaffolds for tissue repair. *Nanoscale*. 2021;13(19):8740–8750. doi:10.1039/d1nr01314a

85. Zhang S, Chuah SJ, Lai RC, Hui JHP, Lim SK, Toh WS. MSC exosomes mediate cartilage repair by enhancing proliferation, attenuating apoptosis and modulating immune reactivity. *Biomaterials*. 2018;156:16–27. doi:10.1016/j.biomaterials.2017.11.028

86. Imai T, Takahashi Y, Nishikawa M, et al. Macrophage-dependent clearance of systemically administered B16BL6-derived exosomes from the blood circulation in mice. *J Extracell Vesicles*. 2015;4(1):26238. doi:10.3402/jev.v4.26238

87. Yang Z, Shi J, Xie J, et al. Large-scale generation of functional mRNA-encapsulating exosomes via cellular nanoporation. *Nat Biomed Eng*. 2020;4(1):69–83. doi:10.1038/s41551-019-0485-1

88. Li S, Dong S, Xu W, et al. Antibacterial hydrogels. *Adv Sci*. 2018;5(5):1700527. doi:10.1002/advs.201700527

89. Radhakrishnan J, Krishnan UM, Sethuraman S. Hydrogel based injectable scaffolds for cardiac tissue regeneration. *Biotechnol Adv*. 2014;32(2):449–461. doi:10.1016/j.biotechadv.2013.12.010

90. Kim M, Kim SE, Kang SS, Kim YH, Tae G. The use of de-differentiated chondrocytes delivered by a heparin-based hydrogel to regenerate cartilage in partial-thickness defects. *Biomaterials*. 2011;32(31):7883–7896. doi:10.1016/j.biomaterials.2011.07.015

91. Choi B, Kim S, Fan J, et al. Covalently conjugated transforming growth factor-β1 in modular chitosan hydrogels for the effective treatment of articular cartilage defects. *Biomater Sci*. 2015;3(5):742–752. doi:10.1039/c4bm00431k

92. Asadi N, Alizadeh E, Salehi R, Khalandi B, Davaran S, Akbarzadeh A. Nanocomposite hydrogels for cartilage tissue engineering: a review. *Artif Cells Nanomed Biotechnol*. 2018;46(3):465–471. doi:10.1080/21691401.2017.1345924

93. Bao W, Li M, Yang Y, et al. Advancements and frontiers in the high performance of natural hydrogels for cartilage tissue engineering. *Front Chem*. 2020;8:53. doi:10.3389/fchem.2020.00053

94. Gan Y, Li P, Wang L, et al. An interpenetrating network-strengthened and toughened hydrogel that supports cell-based nucleus pulposus regeneration. *Biomaterials*. 2017;136:12–28. doi:10.1016/j.biomaterials.2017.05.017

95. Zhang W, Wang R, Sun Z, et al. Catechol-functionalized hydrogels: biomimetic design, adhesion mechanism, and biomedical applications. *Chem Soc Rev*. 2020;49(2):433–464. doi:10.1039/c9cs00285e

96. Zhang FX, Liu P, Ding W, et al. Injectable mussel-inspired highly adhesive hydrogel with exosomes for endogenous cell recruitment and cartilage defect regeneration. *Biomaterials*. 2021;278:121169. doi:10.1016/j.biomaterials.2021.121169

97. Yang Z, Yi P, Liu Z, et al. Stem cell-laden hydrogel-based 3D bioprinting for bone and cartilage tissue engineering. *Front Bioeng Biotechnol*. 2022;10:865770. doi:10.3389/fbioe.2022.865770

98. Teng B, Zhang S, Pan J, et al. A chondrogenesis induction system based on a functionalized hyaluronic acid hydrogel sequentially promoting hMSC proliferation, condensation, differentiation, and matrix deposition. *Acta Biomater*. 2021;122:145–159. doi:10.1016/j.actbio.2020.12.054

99. Zhao N, Coyne J, Abune L, et al. Exogenous signaling molecules released from aptamer-functionalized hydrogels promote the survival of mesenchymal stem cell spheroids. *ACS Appl Mater Interfaces*. 2020;12(22):24599–24610. doi:10.1021/acsami.0c05681

100. Yuan T, Li Z, Zhang Y, et al. Injectable ultrasonication-induced silk fibroin hydrogel for cartilage repair and regeneration. *Tissue Eng Part A*. 2021;27(17–18):1213–1224. doi:10.1089/ten.TEA.2020.0323

101. Liang Q, Ma Y, Yao X, Wei W. Advanced 3D-printing bioinks for articular cartilage repair. *Int J Bioprint*. 2022;8(3):511. doi:10.18063/ijb.v8i3.511

102. Qasim M, Chae DS, Lee NY. Advancements and frontiers in nano-based 3D and 4D scaffolds for bone and cartilage tissue engineering. *Int J Nanomedicine*. 2019;14:4333–4351. doi:10.2147/IJN.S209431

103. Chen J, Li Y, Wang B, et al. TGF-β1 affinity peptides incorporated within a chitosan sponge scaffold can significantly enhance cartilage regeneration. *J Mater Chem B*. 2018;6(4):675–687. doi:10.1039/c7tb02132a

104. Patel JM, Saleh KS, Burdick JA, Mauck RL. Bioactive factors for cartilage repair and regeneration: improving delivery, retention, and activity. *Acta Biomater*. 2019;93:222–238. doi:10.1016/j.actbio.2019.01.061

105. Itokazu M, Wakitani S, Mera H, et al. Transplantation of scaffold-free cartilage-like cell-sheets made from human bone marrow mesenchymal stem cells for cartilage repair: a preclinical study. *Cartilage*. 2016;7(4):361–372. doi:10.1177/1947603515627342

106. Sulaiman SB, Idrus RBH, Hwei NM. Gelatin microsphere for cartilage tissue engineering: current and future strategies. *Polymers*. 2020;12 (10):2404. doi:10.3390/polym12102404

107. Tavassoli H, Alhosseini SN, Tay A, Chan PPY, Weng OSK, Warkiani ME. Large-scale production of stem cells utilizing microcarriers: a biomaterials engineering perspective from academic research to commercialized products. *Biomaterials*. 2018;181:333–346. doi:10.1016/j.biomaterials.2018.07.016

108. Li X, Dai B, Guo J, et al. Nanoparticle-cartilage interaction: pathology-based intra-articular drug delivery for osteoarthritis therapy. *Nanomicro Lett*. 2021;13(1):149. doi:10.1007/s40820-021-00670-y

109. Kulchar RJ, Denzer BR, Chavre BM, Takegami M, Patterson J. A review of the use of microparticles for cartilage tissue engineering. *Int J Mol Sci*. 2021;22(19):10292. doi:10.3390/ijms221910292

110. Mahmoudi Z, Mohammadnejad J, Razavi Bazaz S, et al. Promoted chondrogenesis of hMCSs with controlled release of TGF-β3 via microfluidics synthesized alginate nanogels. *Carbohydr Polym*. 2020;229:115551. doi:10.1016/j.carbpol.2019.115551

111. Dodel M, Hemmati Nejad N, Bahrami SH, Soleimani M, Hanaee-Ahvaz H. Modifying the mechanical properties of silk nanofiber scaffold by knitted orientation for regenerative medicine applications. *Cell Mol Biol*. 2016;62(10):16–25. PMID: 27609469.

112. Puppi D, Chiellini F, Piras AM, Chiellini E. Polymeric materials for bone and cartilage repair. *Prog Polym Sci*. 2010;35(4):403–440. doi:10.1016/j.progpolymsci.2010.01.006

113. Khan IM, Gilbert SJ, Singhrao SK, Duance VC, Archer CW. Cartilage integration: evaluation of the reasons for failure of integration during cartilage repair. A review. *Eur Cell Mater*. 2008;16:26–39. doi:10.22203/ecm.v016a04

114. Correa D, Lietman SA. Articular cartilage repair: current needs, methods and research directions. *Semin Cell Dev Biol*. 2017;62:67–77. doi:10.1016/j.semcdb.2016.07.013

115. Qu F, Holloway JL, Esterhai JL, Burdick JA, Mauck RL. Programmed biomolecule delivery to enable and direct cell migration for connective tissue repair. *Nat Commun*. 2017;8(1):1780. doi:10.1038/s41467-017-01955-w

116. Liebesny PH, Mroszczyk K, Zlotnick H, et al. Enzyme pretreatment plus locally delivered HB-IGF-1 stimulate integrative cartilage repair in vitro. *Tissue Eng Part A*. 2019;25(17–18):1191–1201. doi:10.1089/ten.TEA.2019.0013

117. Seol D, Yu Y, Choe H, et al. Effect of short-term enzymatic treatment on cell migration and cartilage regeneration: in vitro organ culture of bovine articular cartilage. *Tissue Eng Part A*. 2014;20(13–14):1807–1814. doi:10.1089/ten.TEA.2013.0444

118. Lee JC, Min HJ, Lee S, Seong SC, Lee MC. Effect of chondroitinase ABC on adhesion and behavior of synovial membrane-derived mesenchymal stem cells in rabbit partial-thickness chondral defects. *J Orthop Res*. 2013;31(8):1293–1301. doi:10.1002/jor.22353

119. Mills DK, Luo Y, Elumalai A, Esteve S, Karnik S, Yao S. Creating structured hydrogel microenvironments for regulating stem cell differentiation. *Gels*. 2020;6(4):47. doi:10.3390/gels6040047

120. Shtein Z, Shoseyov O. When bottom-up meets top-down. *Proc Natl Acad Sci USA*. 2017;114(3):428–429. doi:10.1073/pnas.1619392114

121. Nie M, Takeuchi S. Bottom-up biofabrication using microfluidic techniques. *Biofabrication*. 2018;10(4):044103. doi:10.1088/1758-5090/aadef9

122. Sobral JM, Caridade SG, Sousa RA, Mano JF, Reis RL. Three-dimensional plotted scaffolds with controlled pore size gradients: effect of scaffold geometry on mechanical performance and cell seeding efficiency. *Acta Biomater*. 2011;7(3):1009–1018. doi:10.1016/j.actbio.2010.11.003

123. Gaspar VM, Lavrador P, Borges J, Oliveira MB, Mano JF. Advanced bottom-up engineering of living architectures. *Adv Mater*. 2020;32(6): e1903975. doi:10.1002/adma.201903975

124. Griffin DR, Weaver WM, Scumpia PO, Di Carlo D, Segura T. Accelerated wound healing by injectable microporous gel scaffolds assembled from annealed building blocks. *Nat Mater*. 2015;14(7):737–744. doi:10.1038/nmat4294

125. Sideris E, Griffin DR, Ding Y, et al. Particle hydrogels based on hyaluronic acid building blocks. *ACS Biomater Sci Eng*. 2016;2 (11):2034–2041. doi:10.1021/acsbiomaterials.6b00444

126. Daly AC, Riley L, Segura T, Burdick JA. Hydrogel microparticles for biomedical applications. *Nat Rev Mater*. 2020;5(1):20–43. doi:10.1038/s41578-019-0148-6

127. Gupta V, Khan Y, Berkland CJ, Laurencin CT, Detamore MS. Microsphere-based scaffolds in regenerative engineering. *Annu Rev Biomed Eng*. 2017;19:135–161. doi:10.1146/annurev-bioeng-071516-044712

128. Zhang J, Zhang X, Hong Y, et al. Tissue-adhesive paint of silk microparticles for articular surface cartilage regeneration. *ACS Appl Mater Interfaces*. 2020;12(20):22467–22478. doi:10.1021/acsami.0c01776

129. Chang DP, Guilak F, Jay GD, Zauscher S. Interaction of lubricin with type II collagen surfaces: adsorption, friction, and normal forces. *J Biomech*. 2014;47(3):659–666. doi:10.1016/j.jbiomech.2013.11.048

130. Boyanich R, Becker T, Chen F, Kirk TB, Allison G, Wu JP. Application of confocal, SHG and atomic force microscopy for characterizing the structure of the most superficial layer of articular cartilage. *J Microsc*. 2019;275(3):159–171. doi:10.1111/jmi.12824

131. Neu CP, Reddi AH, Komvopoulos K, Schmid TM, Di Cesare PE. Increased friction coefficient and superficial zone protein expression in patients with advanced osteoarthritis. *Arthritis Rheum*. 2010;62(9):2680–2687. doi:10.1002/art.27577

132. Waller KA, Zhang LX, Elsaid KA, Fleming BC, Warman ML, Jay GD. Role of lubricin and boundary lubrication in the prevention of chondrocyte apoptosis. *Proc Natl Acad Sci USA*. 2013;110(15):5852–5857. doi:10.1073/pnas.1219289110

133. Liang R, Yang X, Yew PYM, et al. PLA-lignin nanofibers as antioxidant biomaterials for cartilage regeneration and osteoarthritis treatment. *J Nanobiotechnology*. 2022;20(1):327. doi:10.1186/s12951-022-01534-2

134. Bose S, Fielding G, Tarafder S, Bandyopadhyay A. Understanding of dopant-induced osteogenesis and angiogenesis in calcium phosphate ceramics. *Trends Biotechnol*. 2013;31(10):594–605. doi:10.1016/j.tibtech.2013.06.005

135. Khezri K, Maleki Dizaj S, Rahbar Saadat Y, et al. Osteogenic differentiation of mesenchymal stem cells via curcumin-containing nanoscaffolds. *Stem Cells Int*. 2021;2021:1520052. doi:10.1155/2021/1520052

136. Li H, Jin Y, Zhao Y, et al. Targeted cell therapy for partial-thickness cartilage defects using membrane modified mesenchymal stem cells by transglutaminase 2. *Biomaterials*. 2021;275:120994. doi:10.1016/j.biomaterials.2021.120994

137. Men YT, Jiang YL, Chen L, Zhang CQ, Ye JD. On mechanical mechanism of damage evolution in articular cartilage. *Mater Sci Eng C Mater Biol Appl*. 2017;78:79–87. doi:10.1016/j.msec.2017.03.289