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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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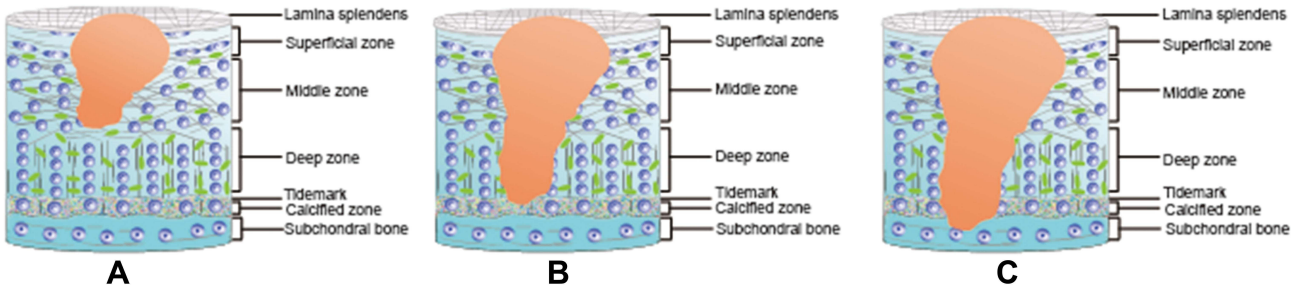


**Figure 1** Schematic diagram of different degrees of cartilage injury. (**A**) Partial-thickness cartilage injury (defect depth does not exceed the deep cartilage layer); (**B**) Full-thickness cartilage defect (defect depth reaches below the tidemark); (**C**) Osteochondral injury (defect depth exceeds 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).

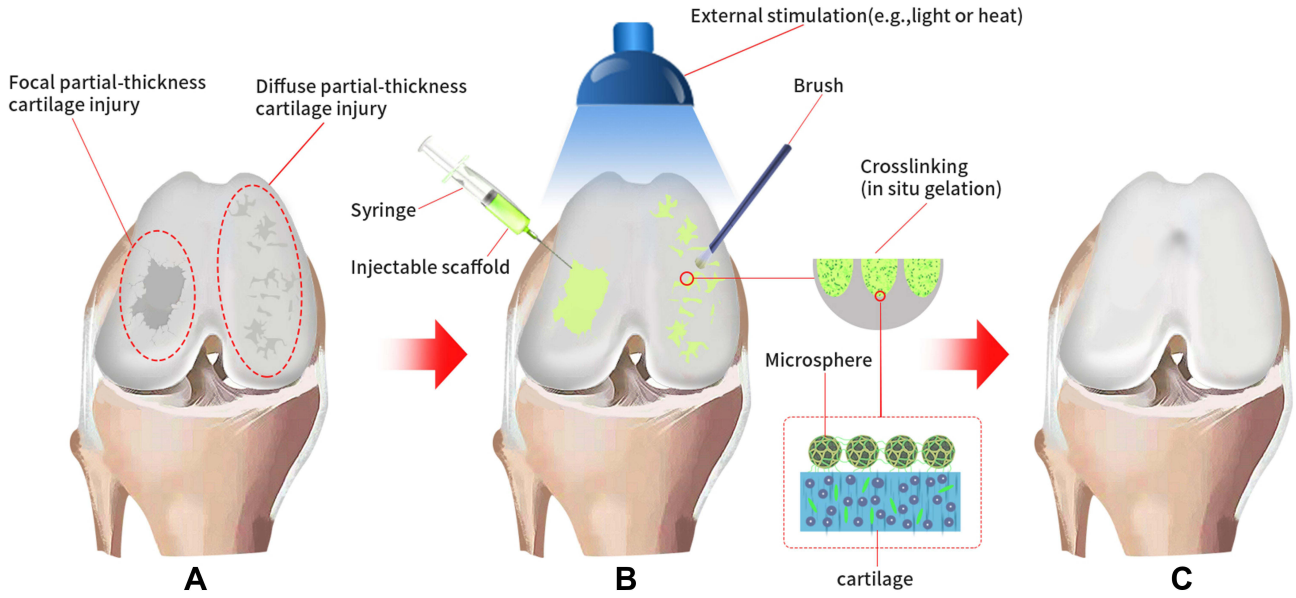


**Figure 2** Schematic diagram of the bottom-up cartilage repair process. (**A**) Cartilage lesion/damage, the cartilage surface can be seen as rhagadia, shrinkage, cracks or even some areas of superficial damage, the cartilage surface is uneven; (**B**) The cartilage injury is filled with microgel, 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.

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## Disclosure

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

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