

Healing beyond tradition: Advanced regenerative therapies for joint-related sports injuries

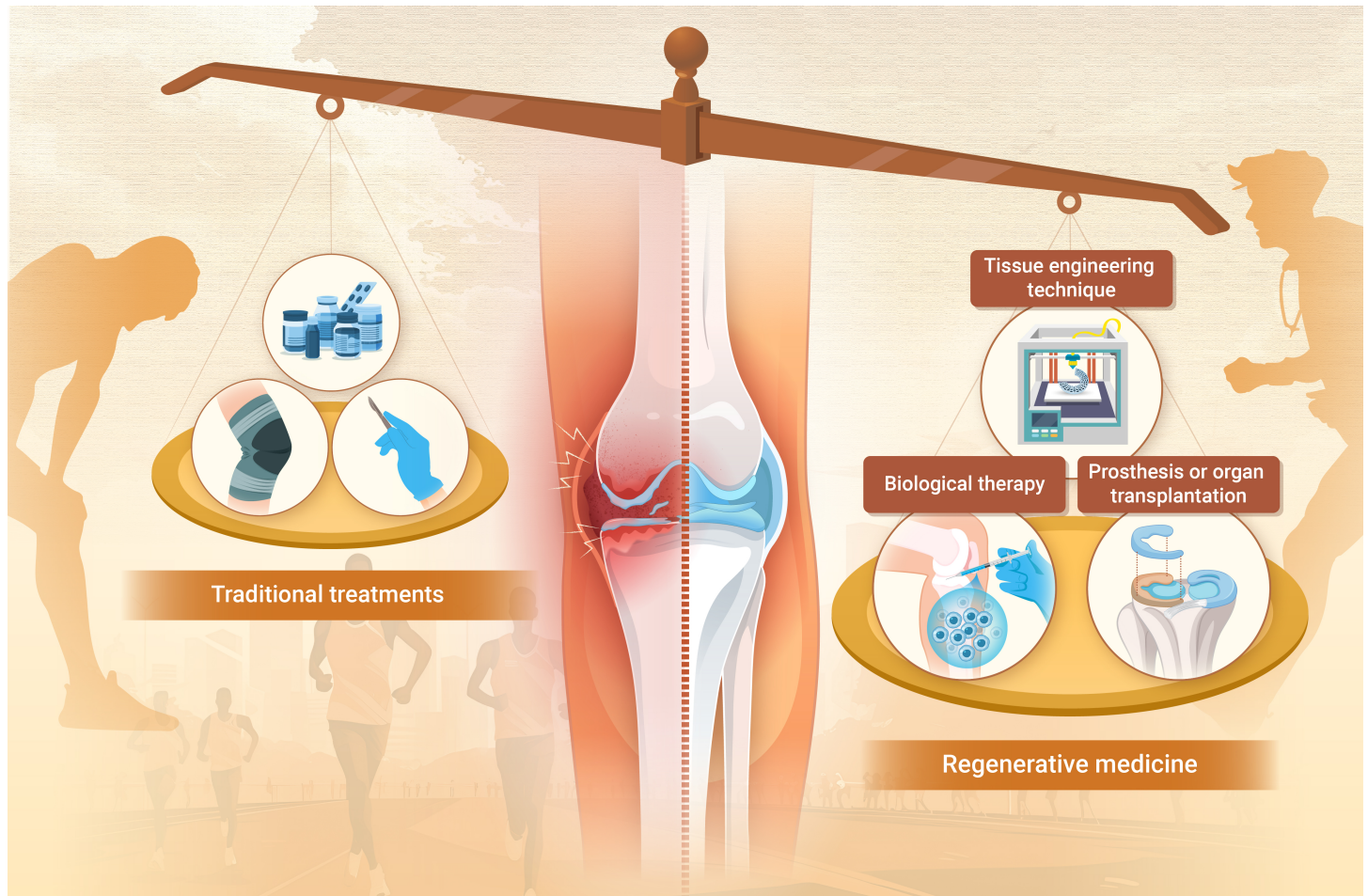
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Received: February 2, 2025; Accepted: April 30, 2025; Published Online: May 7, 2025; <https://doi.org/10.59717/j.xinn-med.2025.100132>

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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Regenerative therapies promote soft tissue repair in sports injuries beyond symptom relief.
- Biological therapies reduce inflammation and promote cell differentiation, facilitating tissue regeneration.
- Tissue engineering and organoids offer structural and functional reconstruction of tissues.
- Clinical translation requires standardization, long-term validation, and personalized treatment strategies.

Healing beyond tradition: Advanced regenerative therapies for joint-related sports injuries

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Citation: Du M., Gu Y., Xu T., et al. (2025). Healing beyond tradition: Advanced regenerative therapies for joint-related sports injuries. *The Innovation Medicine* 3:100132.

Sports injuries are one of the most common diseases, and the repair and regeneration of joint soft tissues (ligaments, tendons, cartilage, etc.) involved in them are challenging. Traditional treatment strategies, such as drugs, physical therapy, and surgery, are difficult to achieve tissue regeneration and reconstruction of natural physiological functions. Regenerative medicine offers promising solutions, including biotherapy, tissue engineering, prosthesis or organ transplantation. These approaches aim to regenerate damaged tissues, reduce recovery time, and improve functional outcomes. Stem cells from different sources and their constructed organoids, novel biomaterials, 3D printing and other innovative technologies have been used. Individual variability, uncertain long-term efficacy, and high costs remain obstacles for clinical application. Further research is needed to explore the molecular mechanisms underlying regenerative therapies and orchestrate biological, physical and chemical factors.

INTRODUCTION

Regenerative medicine, as a cutting-edge field, has provided innovative solutions for the treatment of joint sports injuries.¹⁻³ Sports injuries represent a significant public health concern, with millions of athletes experiencing injuries at different levels every year.^{4,5} Epidemiological studies have shown that sports related injuries account for a significant proportion of all injuries treated in emergency departments and outpatient clinics, and sports injuries among teenagers and adults result in approximately 3.5 million medical visits annually in the United States.^{6,7} Common injuries include cartilage injury, tendon/ligament injury and meniscus injury, which are often caused by high-intensity activities, repetitive movements, or accidents.^{8,9} The increasing participation in competitive sports and the global rise in aging populations further exacerbates the prevalence of these injuries, necessitating effective and innovative treatment strategies.¹⁰ Current clinical treatments for sports injuries include protection, rest, ice, compression, elevation (PRICE), physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs),^{3,11-14} and surgical intervention in more severe cases.^{3,15-17} Although these traditional methods may be effective in relieving symptoms and restoring function, they often fail to promote complete recovery and prevent further injury.^{18,19} In addition, traditional surgical techniques may involve longer recovery times, resulting in significant impacts on athletes' training and competition schedules. Therefore, more effective strategies are required in the treatment of sports injury.

Regenerative medicine includes a range of biological and pharmaceutical treatments, tissue engineering techniques, and organ and prosthesis transplantation strategies^{20,21} (Figure 1). These methods are not only aimed at relieving pain and restoring function, but also at promoting the regeneration of damaged tissues and enhancing the body's natural healing process. Biological and pharmaceutical therapy, including the use of cytokine, stem cells, exosomes, platelet rich plasma (PRP), and macromolecular medicine has shown significant potential in enhancing tissue repair and regeneration.^{1,22} Studies have shown that PRP can stimulate the healing of tendon, cartilage and meniscus injuries, and also promote angiogenesis and

collagen synthesis by directly delivering concentrated growth factors to the site of injury.²³⁻²⁵ Similarly, stem cell therapy offers the possibility of regenerating damaged joint soft tissues, providing a more holistic recovery approach.^{26,27} These biological therapies utilize the body's inherent self-healing ability, which may result in faster recovery times and better long-term outcomes than traditional methods. Besides, tissue engineering technology further supplements the field of regenerative medicine by integrating biological scaffolds and biomaterials to support the repair and regeneration of damaged tissues. These scaffolds can provide a temporary structure for cells to adhere and proliferate, promoting the regeneration of complex tissues.^{3,28} For example, engineered ligaments or tendons developed using biodegradable materials can simulate the mechanical properties of natural tissues, promoting better integration and functional recovery.^{29,30} In addition, the progress of organ and prosthesis transplantation is beginning to have an impact on the field of sports medicine, especially for athletes facing serious injuries that may hinder their athletic abilities.³¹⁻³³ The innovation of transplantation technology and materials makes it possible to develop bioengineered organoids and prostheses that can meet the unique needs of athletes, providing feasible solutions for athletes who require extensive repair or replacement.³⁴

In summary, the application of regenerative medicine in the treatment of sports injuries presents a transformative shift in the management approach in this field. By not only focusing on symptoms but also addressing the underlying biological and structural disorders, regenerative methods present the potential to enhance recovery outcomes, reduce the risk of recurrence, and ultimately improve the quality of life for athletes or sports enthusiasts. This review will introduce the common types of sports injuries, traditional clinical strategies and explore the current application status of regenerative medicine in sports injuries, highlighting the latest research findings and clinical significance, and discuss the future directions of this constantly evolving field.

COMMON TYPES OF JOINT SPORTS INJURIES

Cartilage injury

Articular cartilage is a layer of connective tissue with unique viscoelastic property that lubricates joint surfaces, reduces friction and facilitates load transfer. Cartilage injuries are common, especially among athletes, with an overall prevalence of 36% in the knee alone.^{35,36} Due to the lack of blood vessels and low cell density in cartilage tissue, damage from trauma or degenerative pathology frequently results in tissue deterioration and impaired healing.³ Different types of cartilage injury include chondral fissure, chondral fracture, chondral delamination and chondral defect.³⁷ Impact/shear forces cause collagen network fragmentation and proteoglycan loss, resulting in surface fibrillation, fissures, and eventual exposure of subchondral bone.³⁸

Ligament/Tendon injuries

Ligament injuries are one of the most common sports injuries, particularly affecting the knee, ankle, and shoulder joints.^{39,40} Research shows that among 18890 hospitalized patients, 11% were diagnosed with ligament/tendon

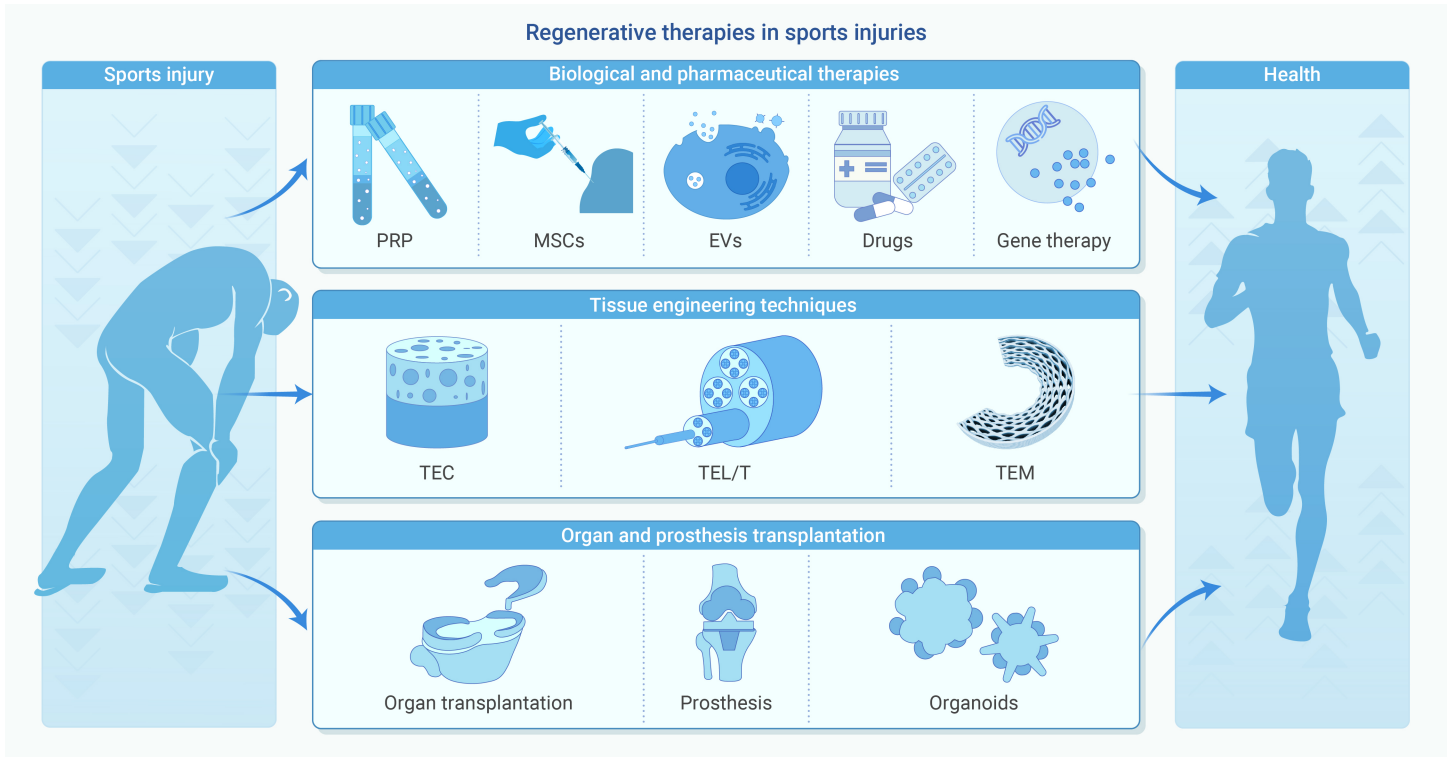


Figure 1. Application of regenerative therapies in joint-related sports injuries (PRP, platelet rich plasma; MSCs, mesenchymal stem cells; EVs, Extracellular vesicles; TEC, tissue engineering cartilage; TEL/T, tissue engineering ligament/tendon; TEM, tissue engineering meniscus.)

injuries.⁴¹ The anterior cruciate ligament (ACL) is particularly susceptible to injury in the knee, often occurring in the context of a sharp turn in direction, landing from a jump, or a direct impact. The lateral collateral ligament (LCL) of the ankle accounts for the majority of ankle sprains, with a particularly high prevalence in athletes.⁴²⁻⁴⁴ Complete ruptures induce collagen fiber disarray, while partial tears show incomplete healing with disorganized scar tissue. Chronic instability promotes abnormal neoangiogenesis and ectopic calcification.^{45,46} These injuries affect the quality of life of a large number of patients each year and incur significant medical costs.

Meniscus injury

The meniscus is a crucial structure in the knee joint, performing a range of functions including load transfer, shock absorption, maintenance of joint stability, and lubrication. Medial meniscus tears are more prevalent and frequently occur concurrently with ligament injuries, particularly ACL injury. Meniscus tears can be divided into vertical, horizontal, complex, and so on. Meniscal tears occur in about 12% to 14% of the population, with an incidence rate of approximately 61 cases per 100,000 people.⁴⁷ Traumatic tears are usually caused by combination of axial loading and rotational forces, which occur in young, athletically active individuals. In older patients, degeneration renders the meniscus particularly susceptible to injury.⁴⁸ Tears disrupt collagen fiber alignment, impairing load distribution and shock absorption. Progressive degeneration leads to fibrillation and altered biomechanics, accelerating osteoarthritis (OA).^{49,50}

TRADITIONAL CLINICAL THERAPIES FOR JOINT SPORTS INJURIES

There are various treatment methods for sports injuries, and conventional clinical treatment methods mainly include non-surgical treatment and surgical treatment (Figure 2). The conventional treatment methods for sports injuries and further challenges they currently face will be introduced as follows.

NON-SURGICAL TREATMENT

Acute phase treatment

Rapid and appropriate medical intervention within the first 24 hours after sports injuries is crucial for improving patient prognosis.⁵¹ The early treatment principles for acute sports injuries have evolved from "RICE" to "PRICE"

and then to "POLICE". Recently, some scholars have proposed the "PEACE and LOVE" principle, which has received widespread attention.⁵²

The "PRICE" principle, widely applied in the early stages, includes Protection (P), Rest (R), Ice (I), Compression (C), and Elevation (E).^{53,54} On this basis, the "POLICE" principle adds the concept of Optimal Loading to "PRICE", suggesting early resumption of exercise when pain is tolerable to promote recovery. With the development of modern sports medicine and rehabilitation therapy, Dubois B proposed the "PEACE and LOVE" principles, where LOVE represents Load, Optimism, Vascularization, and Exercise respectively, with a greater emphasis on rehabilitation therapy in the subacute and recovery phases. In addition, the proposal of avoiding anti-inflammatory modalities is also a revolution in traditional concepts, which will be elaborated in the drug treatment section below.

Pharmacological treatment

Oral or topical NSAIDs can reduce pain and inflammation through inhibition of cyclooxygenase (COX) activity. Currently, selective COX-2 inhibitors are more commonly used in clinical settings to minimize gastrointestinal side effects while retaining their anti-inflammatory efficacy. However, some controversies indicating that the indiscriminate use of anti-inflammatory medications during the inflammatory phase of injury may inhibit soft tissue healing.¹⁴ Additionally, these medications carry a range of side effects if used for a long time, including exacerbation of asthma, gastrointestinal and renal issues, hypertension, and other cardiovascular diseases.⁵⁵

Local injection therapy

Local injection therapy, also known as local blockade, involves injecting medication directly into the injury site, including corticosteroids, local anesthetics, and joint lubricants. Various medications can be mixed to suppress inflammation, reduce pain and swelling, and eliminate edema. However, this approach may also inhibit fibroblast activity and collagen deposition, delaying tissue healing, and can significantly reduce blood supply to the tendon, leading to ischemic necrosis and increased risk of tissue rupture.⁵⁶ Therefore, direct injections into tendon tissue should be avoided in clinical practice. Other adverse effects of corticosteroid injections include tibial stress fractures, multifocal avascular necrosis, as well as local skin thinning, fat atrophy, and infection.⁵⁷

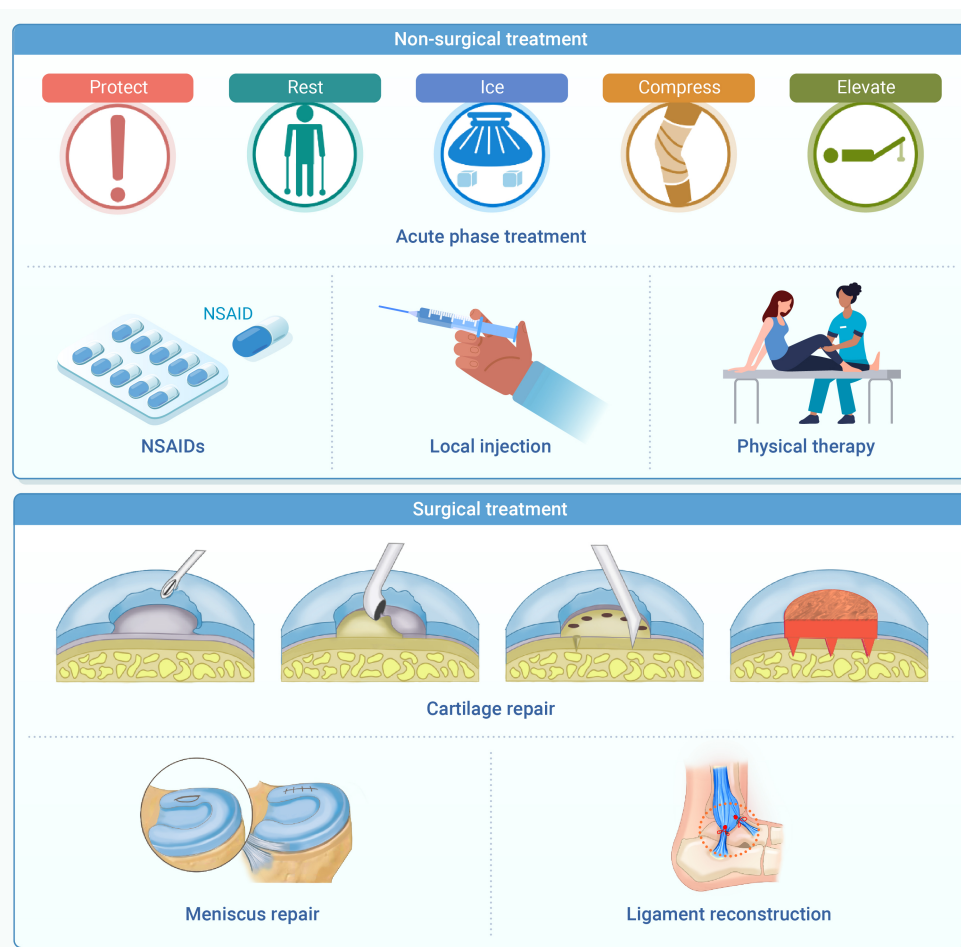


Figure 2. Traditional clinical therapies for joint sports injuries.

cal approaches for meniscal injuries. However, research indicates that meniscal repair is becoming increasingly common compared to partial meniscectomy.⁶⁵ Meniscal repair is typically performed by suturing the tear, and studies have shown that, due to lack of blood supply in the inner rim of the meniscus and the insufficient nutritional supply from synovial fluid, repairing red-red and red-white zone tears can achieve a 76% patient satisfaction rate,⁶⁶ while white-white zone repairs remain a significant challenge. Besides, based on observational data, the evolving consensus suggests that meniscectomy is associated with an increased risk of knee OA progression.⁶⁷ Postoperative sports rehabilitation for meniscal injuries requires tailored protocols based on tear type/surgery, initiating immediate pain/swelling control, joint mobility restoration, and progressive strength/proprioceptive training with sport-specific return timelines.⁶⁸ In terms of complications, recent research shows that complications are associated with medical comorbidities, smoking, and longer operating times.⁶⁹

Surgical treatment for tendon and ligament injuries

Patients with tendinopathy who do not show improvement after 6 to 9 months of

Physical therapy

After the acute phase of a sports injury, physical therapy can be employed, including extracorporeal shock wave therapy, laser therapy, electrical stimulation, and manual therapy to promote recovery. Extracorporeal shock wave therapy is effective for treating tendon insertions and tendon pathologies, such as calcification and fatty degeneration, facilitating tendon stem cell regeneration and participation in the repair process.⁶⁸ Research indicates that high-intensity laser therapy (HILT) can reduce pro-inflammatory mediator concentrations and enhance capillary permeability, thus alleviating inflammation.⁶⁹ Manual therapy can enhance blood circulation, soften scar tissue, improve joint mobility, relieve muscle fatigue, and relax muscles. Electrical stimulation can activate motor units and enhance muscle contraction, although its role in facilitating muscle injury recovery remains debated.⁶⁰

SURGICAL TREATMENT

Surgical treatment for articular cartilage injuries

Common surgical methods have evolved from simple arthroscopic lavage and debridement to microfracture techniques.⁶¹ Microfracture is a marrow stimulation technique that creates multiple perforations in the subchondral bone, allowing marrow and its mesenchymal stem cells (MSCs) to migrate to the cartilage defect site, thereby promoting cartilage regeneration. However, studies have shown that microfracture produces predominantly fibrous cartilage rather than hyaline cartilage, leading to poor long-term outcomes.⁶² Besides, osteochondral autograft transplantation (OAT) and autologous chondrocyte implantation (ACI) strategies have also been used clinically for better recovery.⁶³ Postoperative cartilage rehabilitation requires preoperative physical/psychological/behavioral assessments, multidisciplinary collaboration, and real-time protocol adjustments via smart monitoring to ensure compliance and optimize functional recovery.⁶⁴

Surgical treatment for meniscus injuries

Partial meniscectomy and meniscal repair are the two conventional surgi-

conservative treatment may consider surgical intervention, which includes removal of pathological tissue, repair of tendon defects, tendon decompression, and so on. However, surgical outcomes vary among individuals and are significantly related to postoperative rehabilitation training. There are notable differences in the healing capacity of various ligaments. For instance, medial collateral ligament (MCL) injuries are often treated non-surgically, while ACL injuries typically require surgical repair. Currently, there are various techniques for ACL reconstruction, ranging from isometric reconstruction to double-bundle reconstruction, anatomical reconstruction, and triple-bundle reconstruction.⁷⁰ Postoperative rehabilitation and return-to-sport require criterion-guided progression, prioritizing biomechanical markers (ROM/strength/power) and functional capacity after anatomic joint stabilization, with staged advancement based on quantitative performance thresholds.⁷¹ Quadriceps strengthening is critical for complication prevention and functional restoration.⁷²

Overall, traditional clinical treatment methods for sports injuries still face some limitations, particularly regarding limited functional recovery and long-term efficacy. The application of biochemical therapies, tissue engineering techniques, organ transplantation, and organoids in regenerative medicine provides insights and solutions to overcome the shortcomings of traditional treatments.

REGENERATIVE MEDICINE FOR JOINT SPORTS INJURIES

The treatment methods for sports injuries have undergone significant changes. Traditional treatment methods mainly rely on physical therapy, surgical intervention, and medication. Although these methods can alleviate pain and promote recovery to a certain extent, they often cannot effectively solve the primary cause of injury, which also along with long recovery time and high recurrence rate. In recent years, with the rapid development of regenerative medicine, the treatment of sports injuries has gradually shifted towards more innovative and efficient regenerative therapies. These advancements in medicine will also accelerate existing medical and

commercial processes to address people's ever-changing health demands.⁷³ The core concept of regenerative medicine is to promote tissue regeneration and functional recovery by stimulating the body's own repair mechanisms. The application of biological therapy, tissue engineering techniques and organ transplantation provides new possibilities for tissue regeneration. By integrating research results from multiple disciplines, future regenerative medicine is expected to open up new perspectives for the treatment of sports injuries, promote the development of sports medicine, bring more ideal treatment effects and improve life quality of patients.

BIOLOGICAL AND PHARMACEUTICAL THERAPIES

In the realm of regenerative medicine, biological and pharmaceutical therapies encompass a diverse array of advanced treatment modalities designed to restore, replace, or regenerate damaged or diseased tissues and organs.⁷⁴ These therapies harness the body's intrinsic reparative capabilities by employing biologics, cellular agents, and pharmacological compounds, either independently or in synergy, to optimize and accelerate tissue repair and functional recovery. The key therapeutic domains within regenerative medicine including PRP, stem cells, cytokines, biological macromolecules, and gene therapies.

PRP

PRP therapy offers the advantage of quick, autologous transplantation with relatively low immune risk and cost, making it an appealing choice for certain sports injuries and regenerative needs.⁷⁵ PRP is renowned for its ability to release growth factors from platelets, which significantly aid in tissue regeneration and healing processes.⁷⁶ Specifically, factors such as platelet-derived growth factor (PDGF), transforming growth factor β (TGF- β), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF) work together to promote the inflammatory phase, proliferative phase, and remodeling phase of tissue healing processes.^{77,78} The applications of PRP are extensive, particularly in sports medicine, where it has been shown to effectively aid in the repair of musculoskeletal systems.⁷⁹ However, PRP's therapeutic efficacy is constrained by intrinsic biological variability, including inconsistent platelet/leukocyte concentrations and undefined growth factor ratios, which limit its reproducibility compared to standardized pharmacologic agents (e.g., corticosteroids, hyaluronic acid).

PRP for meniscus injuries. Current evidence suggests that PRP is a promising nonoperative treatment for meniscus injury, particularly for degenerative meniscal tears. A recently comprehensive review of ten selected studies, encompassing a total of 686 patients, has revealed that PRP injections can lead to significant improvements in pain and function. Although the data is somewhat limited and heterogeneous, the overall evidence suggests that PRP therapy holds great potential in the regenerative treatment of sports-related meniscal injuries.⁸⁰ Due to the limited clinical studies on PRP for meniscus injuries, the effects of different doses of PRP with different frequencies for meniscus injuries are still unclear and need to be further studied.

PRP for cartilage injuries. PRP has shown efficacy in improving pain relief and functional outcomes in cartilage injuries, particularly for knee OA. PRP therapy has demonstrated significant improvement in pain relief and joint function at follow-up periods of up to 12 months compared to corticosteroids or hyaluronic acid injections.⁸¹ In addition, there is evidence that larger platelet doses may produce better clinical outcomes.⁸² The review analyzed 29 studies and found that, at 6 months, the mean platelet dose in studies with positive outcomes was $5,500 \pm 474 \times 10^6$, while those without positive differences had a mean platelet dose of $2,302 \pm 437 \times 10^6$ ($P < 0.01$). This suggests that the platelet dose administered during PRP injection may play a crucial role in determining the clinical efficacy of the treatment for knee OA.⁸² A recent network meta-analysis of 10 RCTs ($n = 719$ knee OA patients) demonstrates significantly greater pain reduction (VAS) and functional improvement (WOMAC score) with higher-dose (3 times) regimens versus PRP1 at 1-, 3-, and 6-month follow-ups, with no significant difference between 2 and 3 times, suggesting therapeutic efficacy correlates more with total dose than injection frequency.⁸³

PRP for tendon and ligament injuries. Current evidence supports PRP as an effective treatment for tendon repair, particularly in rotator cuff injuries, by

providing sustained pain relief and long-term functional improvement. PRP has shown superior outcomes compared to corticosteroids and hyaluronic acid (HA) injections in long-term follow-ups, despite less pronounced short-term benefits. Specifically, in functional improvement assessed by the Constant score, PRP had an MD of 11.11 (95% CI: 0.53, 21.68), corticosteroids had an MD of 5.01 (-7.43, 17.44), and HA had an MD of 5.15 (-4.58, 14.89).⁸⁴ Additionally, PRP demonstrates consistent efficacy in treating rotator cuff tears, irrespective of the injection site, and the combination of PRP and HA offers the most effective short-term (≤ 6 months) relief for partial rotator cuff tears, though this benefit diminishes over time.^{85,86} A systematic review of 20 studies on PRP treatment for lateral epicondylitis revealed that both high and low platelet concentrations significantly reduce pain, with no significant difference in efficacy between the two.⁸⁷ Additionally, for chronic patellar tendinopathy, multiple PRP injections led to superior long-term outcomes.⁸⁸ This suggests that frequency may contribute more to the efficacy of tendinopathy than concentration. Evidence for PRP use in ligament healing, such as ACL reconstruction, is mixed, with no significant improvement in graft maturation or clinical outcomes.⁸⁹ In contrast, PRP has shown promise in the non-operative management of partial ulnar collateral ligament (UCL) tears, enhancing return-to-sport rates when combined with rehabilitation, although its success varies based on PRP composition and tear severity.⁹⁰

Mesenchymal stem cells

Stem cell therapy offers the unique advantage of differentiating into multiple tissue types, enabling the regeneration of structures,⁹¹ which provides a more comprehensive healing solution than PRP, exosomes, or cytokines. In addition, MSCs can also play a variety of functions such as resisting inflammation, regulating immunity, and promoting regeneration through paracrine effects,^{92,93} making them a more versatile and practical option in sports medicine compared to gene therapies or other biologic treatments. Despite their potential, MSCs therapies face critical limitations: inconsistent cell survival, source-dependent efficacy, and a lack of standardized protocols. Transient functional gains in cartilage and meniscus repair, coupled with variable tendon/ligament outcomes, highlight unresolved biological and technical barriers.

MSCs for meniscus injury. Current studies suggest that MSCs therapy holds potential in meniscus repair due to their ability to differentiate and secrete bioactive molecules that promote tissue regeneration. Clinical studies with 3–24 month follow-ups report enhanced imaging outcomes (e.g., increased meniscal volume on MRI) and clinical improvements (e.g., pain reduction, functional gains) without severe adverse effects, underscoring short-term safety and efficacy.⁹⁴ However, clinical efficacy remains inconsistent compared to preclinical models, likely due to disparities in injury complexity, biological responses, and rehabilitation protocols between animal studies and human patients. Variability in stem cell sources, delivery methods, and treatment timing further limit sustained functional benefits. While BMSCs demonstrate robust chondrogenic differentiation and osteoarthritis mitigation, synovial-derived MSCs (SMSCs) show comparable efficacy in select studies. Adipose tissue-derived mesenchymal stem cells (ADSCs) and meniscus-derived stem cells (MMSCs) exhibit regenerative potential but require further validation.⁹⁴ Notably, functional gains, including pain relief and MRI-detected healing, often diminish over time, with secondary meniscectomy rates of 15–24% highlighting incomplete meniscal restoration.⁹⁵ This may be due to the fact that the underlying factors of meniscal injury are not corrected, and treatment with MSCs alone, although it may improve symptoms and healing to some extent, makes it difficult to reverse the degenerative process in the long term.

MSCs for cartilage injury. Current studies indicate that MSCs show promise in cartilage repair, especially for knee OA, by providing short-term clinical improvement and satisfactory cartilage restoration. MSCs injections have shown superior efficacy compared to HA in reducing pain and improving function in patients with knee osteoarthritis, with comparable safety profiles and benefits lasting up to 12 months. The WOMAC total score (MD = -10.22, $P < 0.0001$) and WOMS scores (MD = -26.01, $P < 0.001$) in the MSCs group significant decrease at 12 months.⁹⁶ Another systematic review found that MSCs implantation in knee osteoarthritis provides short-term clinical improvement and satisfactory cartilage restoration, although evidence

remains limited due to high variability and insufficient long-term data.⁹⁷ Study have also found that bone BMSCs provided the most significant improvements in pain relief and knee ROM, while ADSCs were most effective for improving the WOMAC scores, and umbilical cord-derived mesenchymal stem cells (UC-MSCs) showed the highest efficacy in enhancing WORMS outcomes.⁹⁸

MSCs for tendon and ligament injury. Current evidence suggests that stem cell therapy, particularly with BMSCs and ADSCs, shows promise in tendon repair by enhancing tissue quality and reducing re-tear rates, especially in rotator cuff injuries. Clinically, At the 28-month follow-up, the re-tear rate in the ADSC-augmented group was found to be significantly lower (14.3%) compared to that of the control repair group (28.5%) ($P < 0.001$).⁹⁹ However, other studies have found no significant differences in pain relief or shoulder function between stem cell injections and control treatments for supraspinatus tears.^{100,101} In acute tendon injuries, ADSCs have shown significant short-term (12 weeks) improvements in pain and function in Achilles tendon ruptures, although long-term outcomes remain unclear. In the AOFAS score, Group 3 (rupture + ADSCs) had a significantly higher score (98.40 ± 0.75) compared to Group 1 (83.60 ± 4.23).¹⁰² For ACL repair, MSCs show promise in animal models but yield mixed results in humans, with concentrated bone marrow and adipose tissue therapies proving less effective than marrow stimulation combined with allograft cultured cells, likely due to higher cell concentrations and reduced preparation damage.^{103,104}

Extracellular vesicles

Extracellular vesicles (EVs) are membrane-bound particles released by cells that facilitate intercellular communication by transporting biomolecules, with exosomes being a specific subtype (30-150 nm) derived from the endosomal pathway.^{105,106} Exosome therapy may outperform PRP and stem cells by delivering a broader range of growth factors and bioactive molecules.¹⁰⁷ Additionally, their small size and natural role in cell communication make them highly efficient in penetrating tissues and promoting healing at a cellular level.¹⁰⁸ EVs therapy facilitates motor system repair through a coordinated mechanism involving the suppression of inflammation via delivery of anti-inflammatory mediators like miR-146a and IL-10, alongside polarization of macrophages towards an M2 regenerative phenotype.¹⁰⁹ These properties position exosomes as a promising therapeutic option in sports medicine. However, the lack of standardized protocols for isolation, dosage, and delivery remains a significant obstacle.

Extracellular vesicles for meniscus injury. EVs and exosomes derived from MSCs show promising potential for the treatment of meniscus injuries. These vesicles enhance cell migration, growth, and tissue regeneration through specific signaling pathways, as in cartilage repair. Kawata et al. demonstrated that MSCs-EVs mediate meniscus repair by upregulating CXCL5 and CXCL6 and acting through the CXCR2 axis, which promotes chondrocyte and synovial MSCs growth and migration. Scientists further reported that stem cell-derived exosomes significantly promote healing in the avascular regions of meniscus tears, preventing secondary osteoarthritis by modulating inflammation and enhancing extracellular matrix secretion.^{110,111}

Extracellular vesicles for cartilage injury. Current research on EVs, particularly exosomes, for cartilage repair shows promising potential, mainly due to their ability to promote tissue regeneration, reduce inflammation, and provide protective effects in OA and post-traumatic cartilage injuries. A review highlights that while exosomes derived from MSCs have the ability to modulate several key processes in OA cells. Specifically, they have been shown to enhance anabolic activities, as evidenced by increased expression of genes and proteins related to cartilage matrix synthesis. Additionally, chondroprotective effects have been observed, with exosomes potentially inhibiting cartilage degradation by downregulating the expression of matrix-degrading enzymes like MMP-13.¹¹² However, there remains a high degree of heterogeneity in current protocols, necessitating standardized methodologies for future research. Another systematic review shows that exosome-laden scaffolds can halt and even reverse the progression of cartilage injury in animal models, yet challenges like rapid clearance and variability in preparation methods limit clinical translation.¹¹³

Extracellular vesicles for tendon and ligament injury. Current research on EVs, particularly exosomes, in tendon repair demonstrates their potential

to promote tendon healing through mechanisms such as modulating inflammation, regulating macrophage polarization, and enhancing collagen synthesis. A review highlighted that exosomes promoted tendon and tendon-bone healing by suppressing inflammatory responses and regulating the extracellular matrix, but the lack of standardization in exosome concentration, delivery methods, and limited data from large animal models restricts their clinical translation.¹¹⁴ Another systematic review of studies on Achilles tendon repair found that exosomes significantly improved tendon regeneration, restored tendon morphology, and enhanced biomechanical properties in animal models, but there are still challenges in optimizing isolation methods and delivery protocols.¹¹⁵ Similarly, in preclinical studies, MSCs-derived exosomes have also been proved to be effective in reducing inflammatory response and accelerating ligament matrix regeneration, resulting in improved structural and functional results.¹¹⁶

Cytokines and biopharmaceutical macromolecular drugs

In regenerative medicine, drugs refer to biologically active substances that are designed or discovered to promote tissue repair, regeneration, and functional recovery after injury or disease. Unlike traditional pharmaceuticals, which are often used to alleviate symptoms or manage chronic conditions, regenerative medicine drugs aim to stimulate the body's natural healing mechanisms and regenerate damaged tissues. Cytokine and biomacromolecule therapies offer precise modulation of inflammation and tissue repair, without the risks or logistical challenges of cell-based therapies.¹¹⁷ However, poor tissue penetration in dense ECM-rich tissues (e.g., meniscus, tendon) reduces efficacy without advanced delivery systems.

Cytokines and biopharmaceutical macromolecular drugs for meniscus injury. Several drugs have been investigated for treating meniscal injuries. In a rat model, intra-articular injection of stromal-cell-derived factor-1 α (SDF-1) enhances meniscal healing by recruiting macrophages and mesenchymal stem cells through the SDF-1-CXCR4 pathway.¹¹⁸ Mohawk (MKX), a transcription factor regulating meniscus cell phenotype, shows promise for meniscus repair and osteoarthritis prevention when combined with TGF- β 3. MKX is the second most meniscus enriched (ME) transcription factor (TF), with higher expression in the meniscus than in all tissues in Genotype-Tissue Expression (GTEx) and articular cartilage (Figure 3A). The expression of MKX in the damaged OA meniscus is lower than that in the normal meniscus, and the expression of MKX in the normal vascular area is higher than that in the avascular area (Figure 3A). The combination of Ad MKX and TGF- β 3 induced MSCs differentiation into the phenotype closest to mature meniscus cells (Figure 3B). The combination of Ad MKX and TGF- β 3 increased meniscus specific markers (Figure 3C). On TGF- β 3-conjugated DMS, the Ad-MKX transduced MSCs group observed the highest Safranin-O staining intensity and the most DAPI positive cells in decellularized meniscus scaffolds (DMS) (Figure 3D). In joints with destabilization of medial meniscus (DMM) surgery, MKX expression was observed throughout the entire meniscus. The anterior meniscus degeneration of male mice was more severe than that of female mice (Figure 3E).¹¹⁹ Additionally, thrombospondin-2 (TSP-2) promotes chondrogenesis in bone marrow mesenchymal stem cells under mechanical pressure via NF- κ B signaling, highlighting its role in cartilage formation.¹²⁰ However, research on drugs specifically promoting meniscal regeneration remains limited, necessitating further exploration and screening.

Cytokines and biopharmaceutical macromolecular drugs for cartilage injury. Recent studies have explored cytokine-based and biopharmaceutical macromolecular drugs for treating cartilage injuries and OA, focusing on targeting inflammatory pathways and growth factors to regulate disease progression and support cartilage regeneration. Proinflammatory cytokines such as IL-1 α , IL-1 β , IL-6, and TNF- α contribute to joint destruction, making them prime targets for anti-cytokine therapies.¹²¹ IL-1 inhibitors (Anakinra),¹²² TNF- α inhibitors (Infliximab and Etanercept),^{123,124} IL-6 inhibitors (Tocilizumab),¹²⁵ COX-2 inhibitors and IL-17 inhibitors (Secukinumab) have been explored to treat cartilage injury and osteoarthritis.^{126,127} Among these, IL-1 inhibitors are the most extensively studied. Anti-IL-1 therapeutics overall relieved OA pain (SMD = -0.38) and improved function (SMD = -1.11). IL-1 antibodies and the inhibitor had better pain relief and function improvement than placebo, with IL-1 antibodies showing stronger effects, while IL-1Ra had inconsistent results. Both IL-1 antibodies and IL-1Ra showing favorable

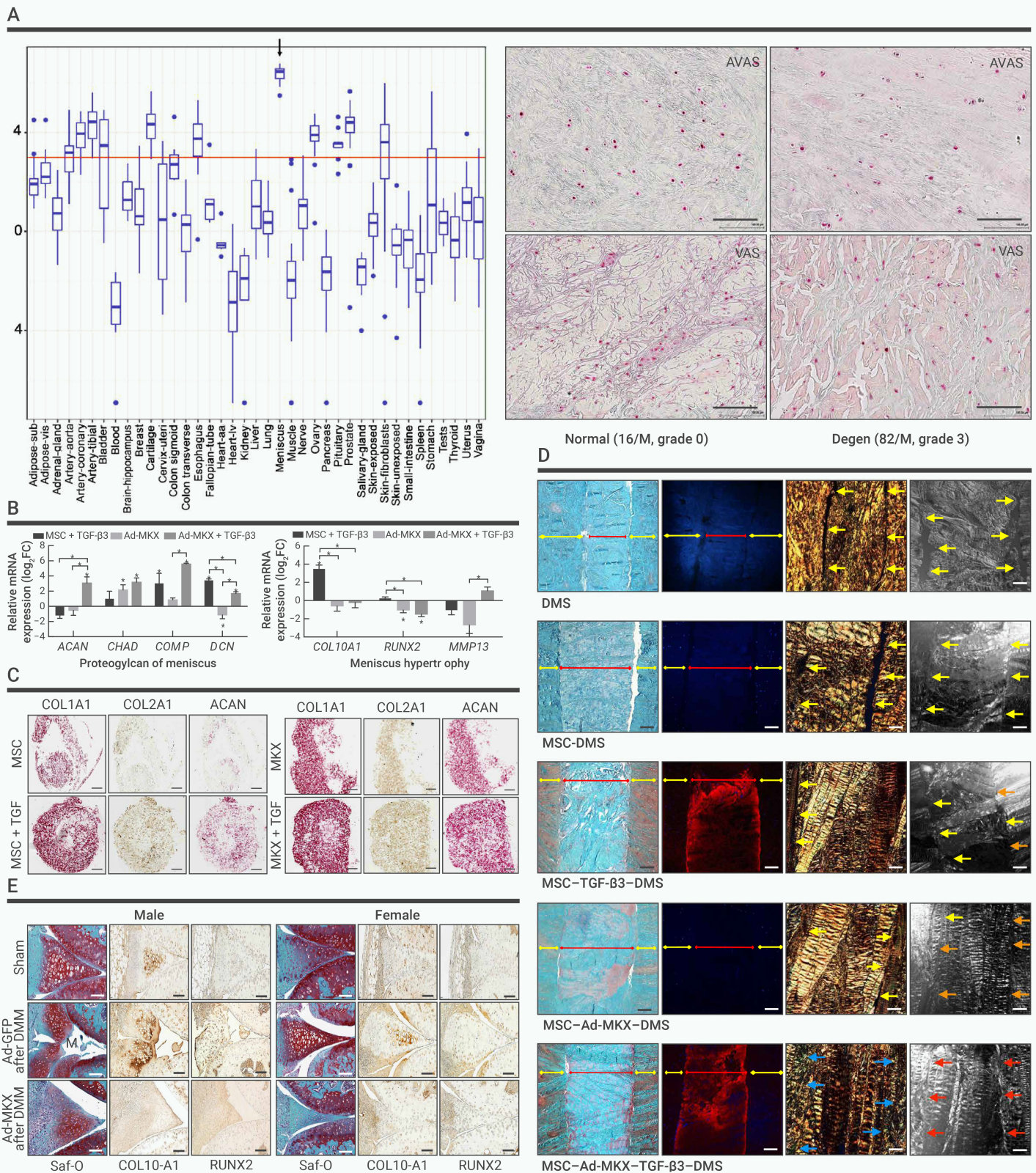


Figure 3. Impact of mohawk on meniscus repair (A) Left: Comparison of MKX expression levels in meniscus and articular cartilage tissues from GTEx and RNA-seq data. Right: Immunohistochemical analysis of MKX in the avascular (AVAS) and vascular (VAS) regions of both healthy and degenerated human meniscus tissue. (B) Gene expression analysis showing (left) MKX and genes associated with fibrogenic differentiation, and (right) genes linked to chondrogenic differentiation. (C) Left: BM-MSC pellets cultured in basal media and in TGF- β 3 media; Right: BM-MSC pellets transduced with Ad-MKX and cultured in basal media or in TGF- β 3 media. (D) Tissue sections stained with Safranin-O, DAPI, picrosirius red under polarized light, and observed with differential interference contrast (DIC) microscopy. (E) Safranin-O staining and immunohistochemical analysis of mouse knee joints from sham surgery, Ad-GFP-injected knees with DMM surgery, and Ad-MKX-injected knees with DMM surgery after 4 weeks.¹¹⁹ Copyright © 2020, The American Association for the Advancement of Science.

safety profiles, while IL-1 inhibitors are linked to higher adverse events.¹²⁸ In addition, drugs targeting other growth factors and cytokines (such as NGF,¹²⁹

TGF- β ¹³⁰) or cartilage degrading enzymes (such as MMPs and ADAMTS) have also been explored.^{131,132} The EGFR signaling pathway has been identi-

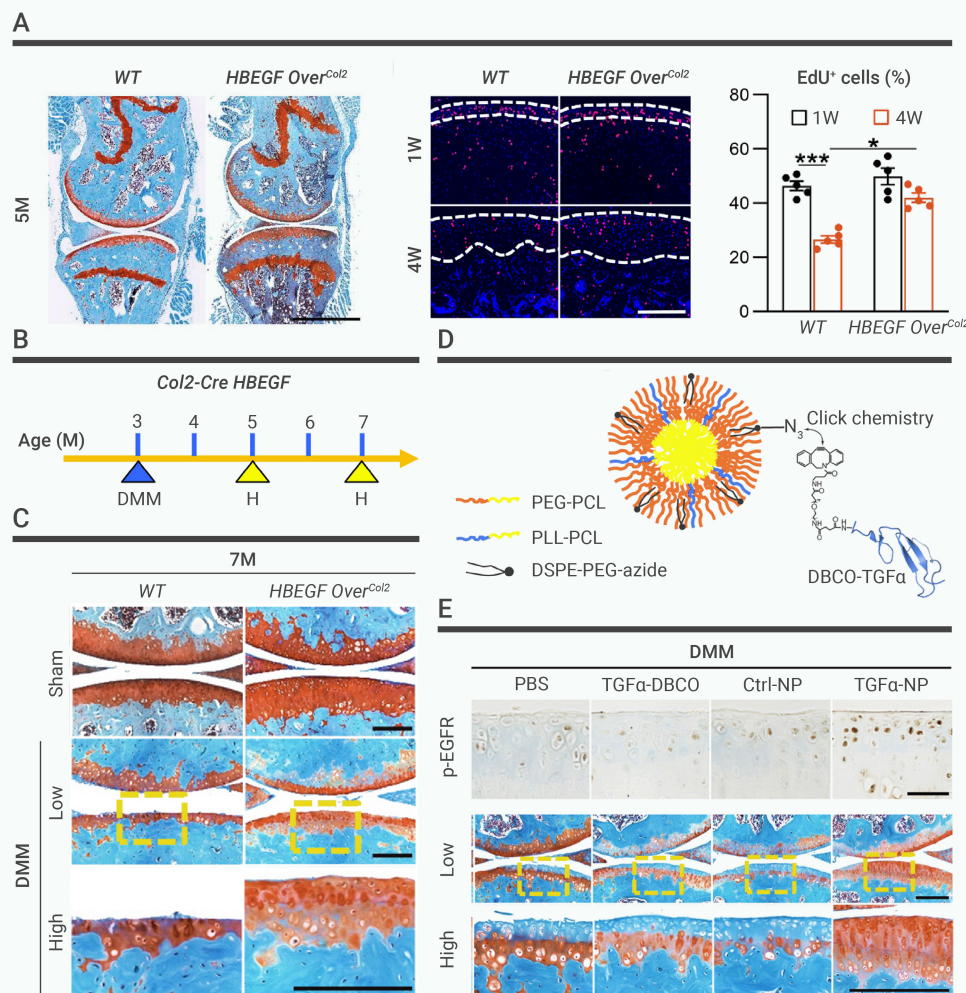


Figure 4. Impact of EGFR on cartilage Repair (A) Left: Safranin O/Alcian blue staining of knee joints from 5-month-old HBEGF OverCol2 mice and their control littermates (WT). Middle and Right: Long-term EdU labeling to track slow-cycling cells in the articular cartilage. (B-C) Experimental protocol and Safranin O/Alcian blue staining of DMM and sham-treated joints at the medial region from 7-month-old WT and HBEGF OverCol2 mice. (D-E) Schematic illustration, along with immunostaining and Safranin O/Alcian blue staining of p-EGFR in knee cartilage of mice 1 month post-sham or DMM surgery.¹³³ Copyright © 2021, The American Association for the Advancement of Science.

their ability to induce tenogenic differentiation, stimulate cellular proliferation, and enhance extracellular matrix synthesis, all of which are crucial for tendon regeneration.¹³⁷⁻¹³⁹ Furthermore, granulocyte-colony stimulating factor (G-CSF), traditionally used to treat neutropenia, has been found to improve rotator cuff healing in animal models.¹⁴⁰ Other biomolecules, such as secretory leucocyte protease inhibitor (SLPI),¹⁴¹ rhFGF-18,¹⁴² and runt related transcription factor 1 (RUNX1) have also shown potential in promoting tendon-bone healing in various studies.¹⁴³

Gene therapy

Gene therapy is a medical approach that involves modifying or manipulating genes within a patient's cells to treat or prevent disease, often by introducing healthy copies of genes or correcting defective ones.¹⁴⁴ Unlike therapies such as PRP, stem cells, or exosomes that rely on augmenting the natural repair processes, gene therapy can introduce

as a potential target for OA treatment. To investigate its role in cartilage, Col2-Cre Rosa-DTR mice [Col2-Cre Rosa-HBEGF (HBEGF OverCol2) mice] were created. At 5 months of age, HBEGF OverCol2 mice exhibited normal knee joint morphology. These mice showed increased labeling of proliferative, slow-cycling chondrocytes (i.e., chondroprogenitors) (Figure 4A). Wild-type (WT) knees began to lose proteoglycan and displayed fibrillation on the cartilage surface following DMM surgery (Figures 4B-C). The EGFR activator, TGF α , was shown to reduce OA-related cartilage degeneration post-DMM surgery (Figures 4D-E).¹³³ Monoclonal nerve growth factor (NGF) antibodies have demonstrated superior pain relief and functional improvement in OA compared to NSAIDs and opioids, though they carry a risk of sensory abnormalities. Regarding functional improvement, they outperformed NSAIDs (SMD = 2.03, 95% CI: 0.97 to 3.09), potent opioids (SMD = 1.20, 95% CI: -0.81 to 3.21), and were not significantly different from selective COX-2 inhibitors (SMD = 2.34, 95% CI: -0.38 to 4.29) and weak opioids (SMD = 2.48, 95% CI: -0.93 to 5.89).¹²⁹ Whereas the ADAMTS-5 inhibitor S201086/GLPG1972 showed no significant improvement in reducing cartilage loss or modifying symptoms in knee OA patients compared to placebo.¹³¹ Besides, in terms of rheumatoid arthritis (RA), Huang et al. construct engineered lastingly IL-10 expressed macrophages (Elite M Φ s) through CRISPRa system. The Elite M Φ s possessed powerful anti-inflammatory capability and relieved inflammation, synovial hyperplasia and joint destruction in RA mouse models.¹³⁴

Cytokines and biopharmaceutical macromolecular drugs for tendon and ligament Injury. Inflammatory factor inhibitors, such as Tocilizumab, an IL-6 receptor inhibitor, have demonstrated clinical potential in reducing tendon inflammation and promoting healing in arthritis-related tendon damage, presenting new therapeutic options for tendon repair.¹³⁵ Additionally, Bevacizumab, an anti-VEGF antibody, supports tendon healing by maintaining a balance between blood supply and cell differentiation, optimizing the repair process.¹³⁶ In parallel, cytokines like TGF- β and GDF-5 are recognized for

or silence specific genes to modulate protein expression directly, offering targeted and potentially long-lasting effects.¹⁴⁵ Additionally, it can be tailored for complex conditions where other treatments may fall short, such as inherited disorders or conditions requiring sustained therapeutic protein production.¹⁴⁶

Gene therapies have emerged as promising strategies in sports medicine for the treatment of cartilage-related disorders and tendon or ligament injuries. In OA, gene therapies like FGF18 delivered via adeno-associated virus (AAV) have shown potential by enhancing chondrocyte proliferation and promoting the expression of hyaline cartilage-specific genes,^{147,148} while MMP13-selective siRNA conjugates mitigate cartilage degradation and reduce inflammation by targeting MMP13 expression.¹⁴⁹ Additionally, non-coding RNAs like circIRAK3, circCREBBP,^{150,151} and lncRNAs such as XIST influence chondrocyte metabolism and differentiation,^{152,153} showcasing the potential of precision medicine in managing degenerative joint diseases. Similarly, gene therapies for tendon and ligament injuries focus on modulating the differentiation and function of tendon-derived stem cells. For instance, lncRNA MALAT1 promotes TDSC differentiation through the miR-378a-3p/MAPK1 axis,¹⁵⁴ while circRNA PVT1 inhibits TDSC aging by suppressing miR-199a-5p and enhancing SIRT1 expression.¹⁵⁵ Furthermore, lncRNA H19 accelerates tenogenic differentiation and tendon-bone healing through the H19/miR-140-5p/VEGFA axis, suggesting new therapeutic strategies for tendon repair.¹⁵⁶ Despite its potential, gene therapy faces challenges distinct from other regenerative approaches. Viral vectors risk immunogenicity and insertional mutagenesis, while non-viral delivery systems often suffer from low transfection efficiency.¹⁵⁷

Limitations and challenges

The application of biological and pharmaceutical therapies in regenerative medicine to sports medicine faces numerous challenges, including variability

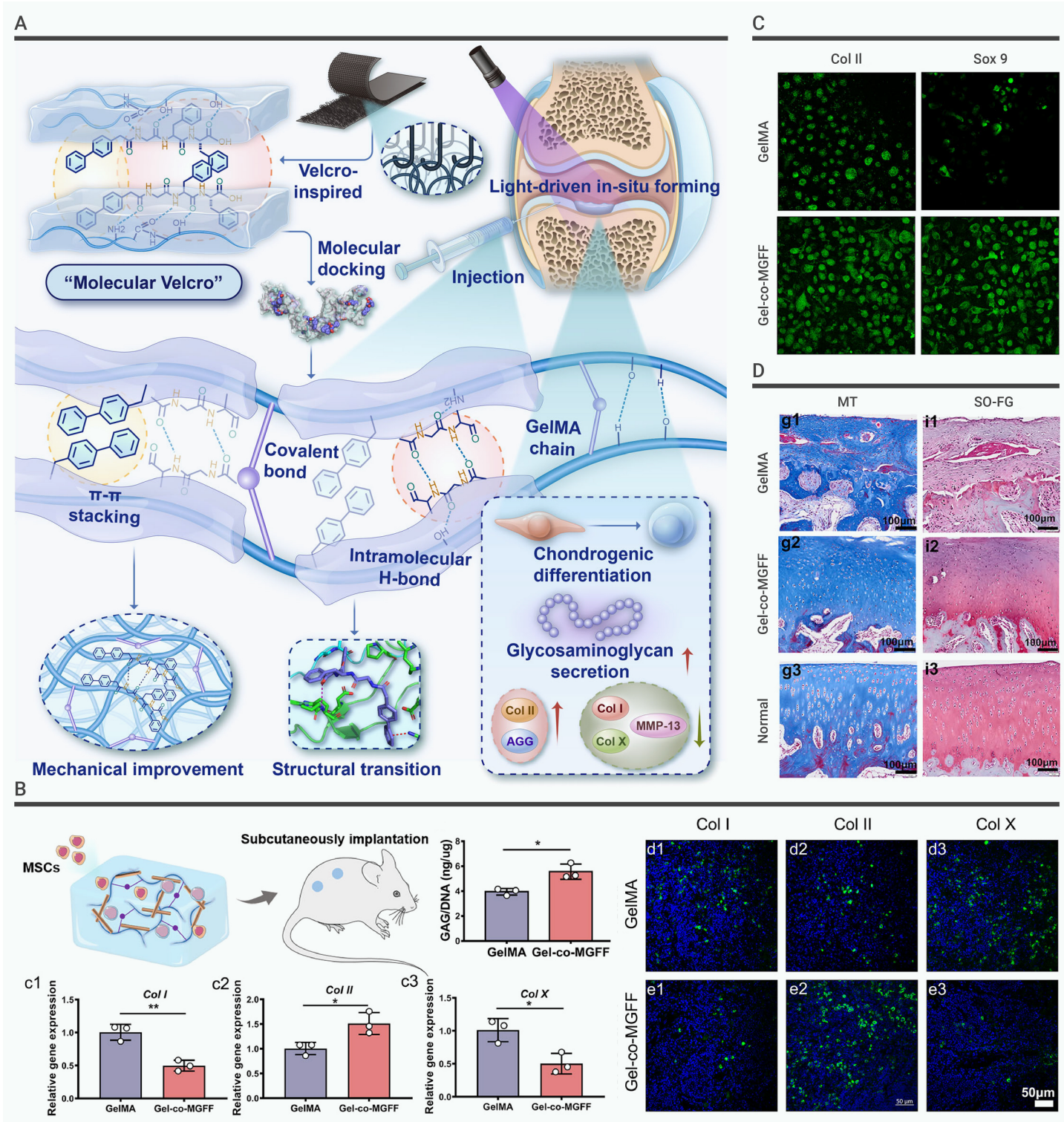


Figure 5. A molecular co-assembly approach to modulate protein conformation for cartilage repair (A) Schematic representation of a velcro-inspired protein-peptide co-assembly method used to create injectable fibrillar protein hydrogels that promote cartilage regeneration. (B) BMSCs-loaded co-assembled hydrogels were transplanted subcutaneously into nude mice and showed good chondrogenic effect. (C) In vitro staining for Col II and Sox9. (D) Histological images showing that BMSCs-loaded Gel-co-MGFF regenerated hyaline cartilage in a rabbit model.¹⁷⁴ Copyright © 2024, Springer Nature.

in preparation methods, inconsistent delivery protocols, and lack of standardization in dosages, which lead to heterogeneous clinical outcomes. While therapies such as stem cells, EVs, biological macromolecules and gene therapy have shown potential in enhancing tissue regeneration, reducing inflammation, and improving pain relief, their long-term safety and efficacy remain uncertain due to limited clinical evidence and inconsistent results. Additionally, the high cost, potential adverse events, and regulatory hurdles further restrict their widespread clinical adoption. Future directions in this field

should focus on optimizing therapeutic protocols through rigorous clinical trials, developing standardized guidelines for biologic use, and exploring combination therapies to enhance regenerative outcomes, ultimately paving the way for more reliable and personalized treatments in sports-related injuries and degenerative conditions.

TISSUE ENGINEERING TECHNIQUES

Tissue engineering (TE) is a multidisciplinary approach to induce the repair

Table 1. Commercial products for tissue engineering in sports injury.

	Seed Cells	Scaffold	Applications
BioCart II	Autologous Chondrocytes	fibrin, hyaluronic acid	osteoarthritis
MACI	Autologous Chondrocytes	Porcine collagen	Cartilage regeneration
CAIS	Autologous Chondrocytes	Polycaprolactone, polyglycolic acid, polydioxanone	Cartilage regeneration
BioSeed-C	Autologous Chondrocytes	Fibrin-polymer matrix	Cartilage regeneration
BST-CarGel	Stem cells by marrow stimulation	Chitosan gel, glycerophosphate, and autologous blood	Cartilage regeneration
Novocart 3D	Chondrocytes	Collagen	Cartilage regeneration
Cartipatch	Autologous Chondrocytes	Agarose-alginate hydrogel	Cartilage regeneration
N-TEC	Autologous nasal chondrocytes	type I/III collagen membranes	osteoarthritis
Hyalograft-C	Autologous Chondrocytes	esterified derivative of hyaluronic acid (Hyafl 11)	Cartilage regeneration
MegaCarti	Stem cells by marrow stimulation	decellularized allogeneic cartilage	Cartilage regeneration
OrthoACI	Autologous Chondrocytes	collagen	Cartilage regeneration
Cell Bandage	Bone marrow stem cells	collagen	Meniscal cartilage tears

and replacement or regeneration of tissue. TE has been a promising technique for repair and regeneration of sports injuries in the past few decades.¹⁵⁸ TE combines seed cells, scaffolds, and active factors (chemical growth factors and cytokines) to create a suitable regeneration environment.¹⁵⁹ Seed cells are usually donor tissue cells and stem cells. The donor tissue cells are often limited, whereas stem cells with proliferative ability and feasible sources can be the most promising sources in TE.¹⁶⁰ Scaffolds can carry seed cells, have good histocompatibility, and be suitable for cell adhesion, proliferation, and differentiation,¹⁶¹ which can be produced through multiple techniques, like freeze-drying, electrospinning, gas foaming, etc. At the same time, the active factors are directly compounded on the scaffold or secreted by seed cells.¹⁶²

Tissue-engineered cartilage

Cartilage in sports injury mainly refers to hyaline cartilage on the articular surface, which lacks blood vessels and lymphatic vessels and relies on joint fluid to nourish chondrocytes.¹⁶³ Articular cartilage can be divided into four layers: superficial layer (fibers parallel to the cartilage surface, chondrocytes functioning as reservoir), middle layer (fiber randomly distributed, chondrocytes flattened into organized columns), deep layer (fibers perpendicular to the surface, chondrocytes entering hypertrophic differentiation), and calcified layer (transition between cartilage and the underlying subchondral bone).^{164,165} The unique properties (multilayered cell structure, different extracellular matrix composition, and fibril orientation) make it hard to repair. Therefore, for tissue-engineered cartilage, the critical approach involves constructing zonally stratified scaffolds with depth-dependent stiffness gradients and immobilized bioactive factors to restore articular surface integrity while suppressing inflammation-mediated degeneration.¹⁶⁶

Arthroscopic surgery, bone marrow stimulation, osteochondral autografts and allografts, and autologous chondrocyte implantation can partly solve cartilage injury. Novel TE approaches amid of clinical trials and laboratory studies may offer better treatment in the near future.¹⁶⁷ Seed cells are chondrocytes and stem cells. Chondrocytes are often harvested from a healthy joint area and enzymatically released and implanted on the scaffolds. Different from the limited source of chondrocytes, MSCs from bone marrow, periosteum, synovium, and adipose are attractive due to the ease of harvesting and proliferation ability.¹⁶⁸ Certainly, cytokines-like TGF- β , insulin-like growth factor 1 (IGF-1), bone morphogenetic proteins (BMPs), fibroblast growth factors (FGFs), and epidermal growth factor (EGF), would benefit the anabolism and catabolism of chondrocytes.¹⁶⁹ So far, many scaffolds like natural, synthetic, and composite materials are multifarious.^{170,171} Recently, advanced researches have provided innovative insight into cartilage TE.

Anisotropic bicellular living hydrogels (ABLHs) were bio-printed, promoting osteochondral regeneration by fulfilling osteogenesis and chondrogenesis.¹⁷² The ARTICAR, a combination of polymeric nanofibrous bone wound dressing and bone marrow-derived mesenchymal stem cells, promotes subchondral bone and cartilage regeneration through the preclinical safety trail.¹⁷³ BMSCs-laden Gel-co-MGFF (Figure 5A) could fill the cartilage defect in rabbits after three months. The cartilage thickness and collagen fiber direction were similar to the normal group (Figures 5B-D).¹⁷⁴ Other researches also combine mechanical stimulation to enhance regeneration. Humphreys et al. indicated that the blue light could activate BMP signaling mechanisms and upregulate a chondrogenic phenotype for TE.¹⁷⁵ There are several products under development for articular cartilage repair, such as BioCart II, BioSeed-C, and BST-CarGel, etc (Table 1).¹⁷⁶ Although TE technology still has a long way to go, more licensed products will eventually come to the bedside.

Tissue-engineered meniscus

The meniscus is a fibrocartilage tissue in the knee joint, withstanding many forces like shear, tension, and compression for load-bearing, load transmission, shock absorption, lubrication, and nutrition.¹⁷⁷ The meniscus injury can lead to osteoarthritis due to the destruction of physical biomechanics. The structure can be divided into the red-red zone (collagen I approximately 80%), red-white zone, and white-white zone (collagen II 42%, collagen I 28%).^{178,179} Besides, proteoglycans are major components of the meniscus ECM, enabling the meniscus to absorb water to support compression.¹³

The injury can hardly heal without surgery because of the inadequate blood supply to the inner two-thirds of the meniscus. TE provides a promising treatment for meniscus repair. Seed cells are usually chondrocytes (autologous, allogeneic, and xenogeneic) and stem cells. For tissue engineering meniscus, the key is to mimic the anisotropic fiber arrangement of natural collagen network to achieve physiological load distribution, while promoting fibrocartilage regeneration through biomechanical and biological clues.³ Scaffolds range from synthetic polymers, hydrogels, and ECM components to tissue-derived materials.¹⁸⁰ Due to the falcate structure of the meniscus, traditional surgical intervention could not solve the structural and biomechanical challenge. Researches are focusing on TE advancement. A tissue-engineered meniscus seeded with MSCs under biomechanical and biochemical dual stimuli in vitro could promote functional anisotropy and support a long-term chondroprotective effect in a rabbit model.¹⁸¹ Zong et al. used silk fibroin (SF), polycaprolactone (PCL), and a SMSCs-specific affinity peptide to realize better autologous MSC recruitment, differentiation, meniscus regeneration, and chondroprotection.¹⁸²

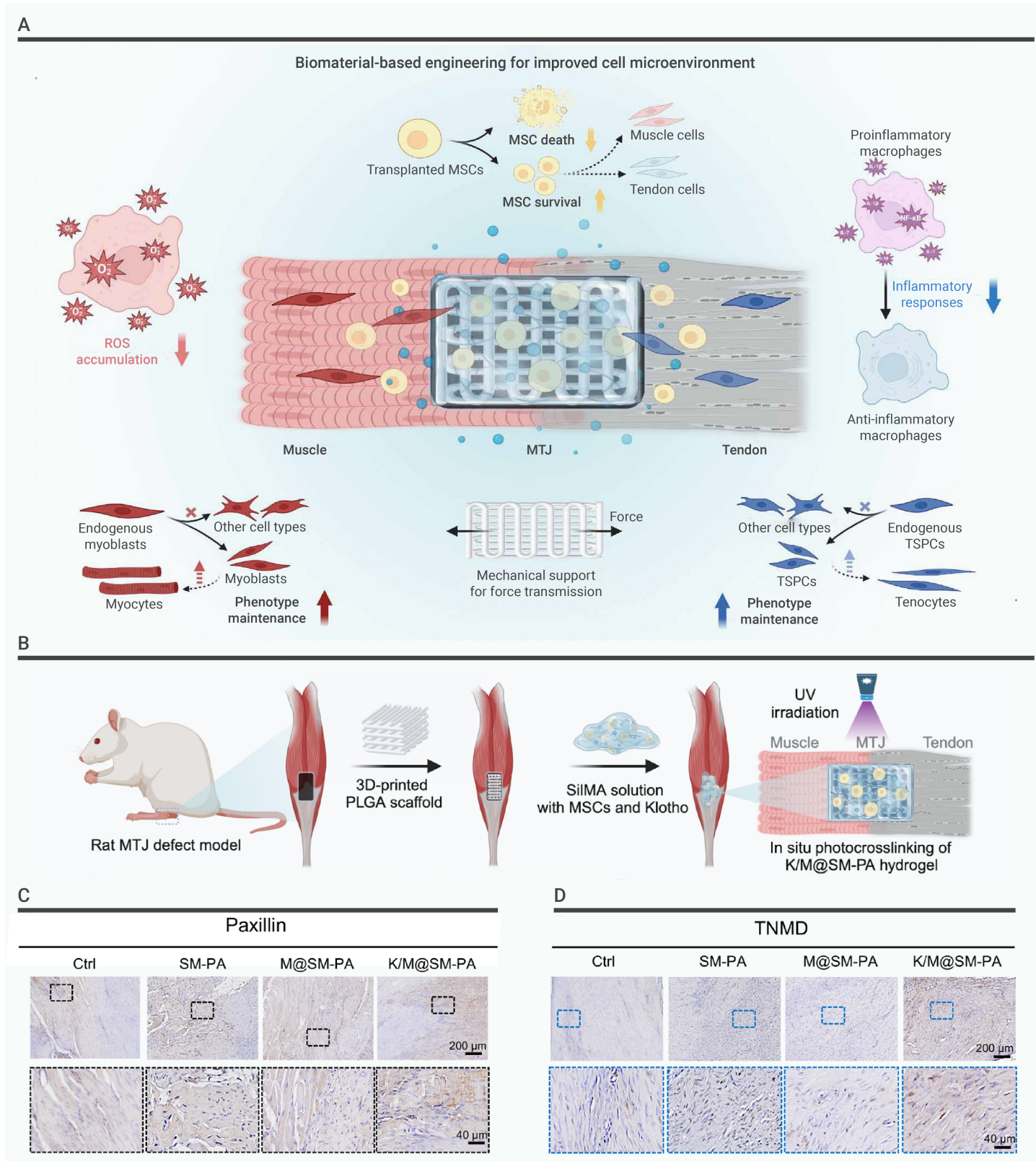


Figure 6. Bioactive fiber reinforced hydrogel can customize the cell microenvironment for the structural and functional regeneration of myotendinous junction (A) Schematic of bioactive fiber reinforced hydrogel promoting MTJ regeneration. (B-D) Schematic of K/M @ SM-PA hydrogel implanted into MTJ defect of rats in situ. IHC staining of Paxillin (MTJ marker) and TNMD (tendon marker).¹⁹¹ Copyright © 2024, The American Association for the Advancement of Science.

Tissue-engineered ligament and tendon

Ligaments and tendons are fibrous compositions that enable the transmission of mechanical force between different parts of the musculoskeletal system.¹⁸³ Ligaments are dense bony attachments for joint stability, which contain approximately two-thirds water and one-third solid (principally colla-

gen, type I collagen accounting for 85% and the rest made up of types III, VI, V, XI, and XIV).¹⁸⁴ Tendon connects muscles and bones for force transition and motion production, where collagen I account for approximately 90%–95%.¹⁸⁵ Both tendons and ligaments have poor regeneration capacity with low cell density.¹⁸⁶ For tissue-engineered ligaments, the key lies in developing

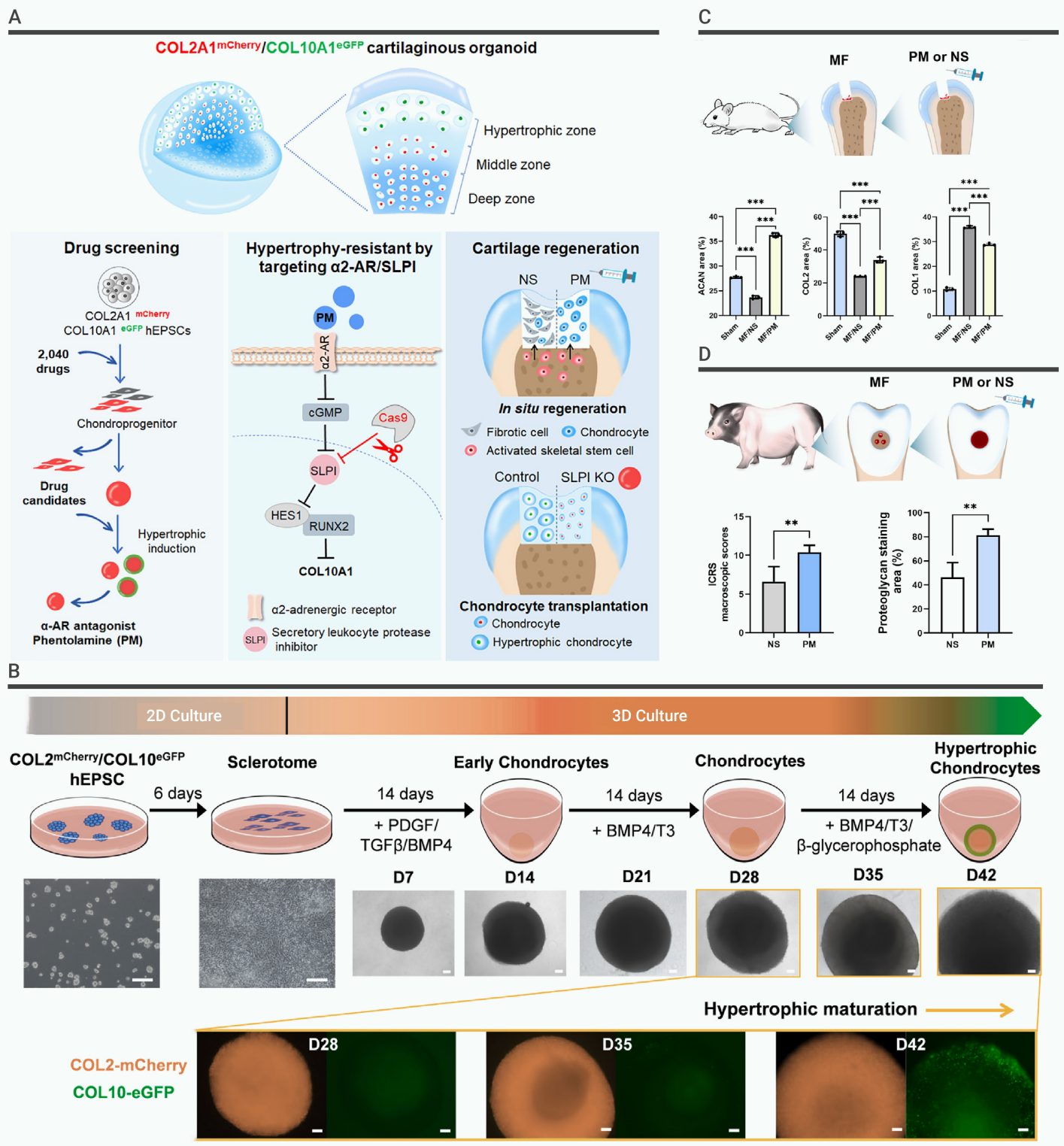


Figure 7. A human organoid drug screen identifies α_2 -adrenergic receptor signaling as a therapeutic target for cartilage regeneration (A) Schematic of cartilage organoid construction and its application in drug screening and cartilage regeneration. (B) Hypertrophic cartilaginous organoids construction. (C-D) The effects of phentolamine on promoting cartilage regeneration in situ in mouse and minipigs.²⁵⁵ Copyright © 2024 Elsevier.

helically structured, strain-responsive scaffolds that recapitulate non-linear biomechanics and drive tenocyte differentiation through topography-activated mechano-transduction pathways.¹¹

Traditional physical modalities (heat, cold, ultrasound, extracorporeal shock wave therapy, etc), mechanical loading, cytokines, and growth factors can only solve part of the problems.^{187,188} For instance, the gradient in collagen fiber organization and mineral content is reversal across the rotator cuff enthesis. The structural gradient turns into a gradation in mechanical proper-

ties to ensure smooth stress distribution across the insertion and decreases the risk of fracture.¹⁸⁹ Therefore, cell and co-culture strategies in a scaffold for the generation of a tendon/ligament-bone construct are reasonable. However, to date, there is no tissue-engineered substitute that has been successfully implanted in humans. Nonetheless, studies have shown the promising effect of these substitutes in animals. Hierarchically organized collagen scaffolds loaded with recombinant periostin (POSTN) promoted endogenous tendon stem/progenitor cell (TSPC) recruitment for tendon

regeneration and repair.¹⁹⁰ A three-dimensional-printed bioactive fiber-reinforced hydrogel containing mesenchymal stem cells (MSCs) and Klotho for myotendinous junction regeneration. Meanwhile, the system could also repolarize macrophages from proinflammatory M1 to anti-inflammatory M2 phenotype (Figure 6A), and the bioactive fiber-reinforced hydrogel was proved to improve structural regeneration of MTJ in rats (Figures 6B-D).¹⁹¹ Du et al. suggested that the multicellular scaffolds containing manganese silicate (MS) nanoparticles could induce fibrocartilage regeneration, improve collagen deposition, and achieve the integrated repair of tendon-to-bone injury in animal model.¹⁹² Other stimulation referring to the modern bioreactor and mechanical stimulation could benefit the tendon/ligament engineering.¹⁹³

Limitations and challenges

TE, as an interdisciplinary field, has great potential in sports injury intervention, but it still faces some limitations and challenges. As one major component of TE, the seed cells are crucial. The autologous cells have good biocompatibility, but the sources are limited, and the harvesting procedure can do harm to patients. Besides, the allogeneic cells and stem cells may face immune rejection and ethical problems. Innovative technology, such as gene editing for seed cells, should be further investigated and monitored for clinical application. The biocompatibility and degradability of biological scaffolds should be ensured. The integration of artificial intelligence (AI)-empowered additive manufacturing methods will also bring prospects for precision and specialized tissue-engineered organ manufacturing.¹⁹⁴ As a form of AI, finite element analysis can simulate the properties and implementation of materials for optimizing and reducing complications, while neglecting injection location, solidification, and over-simplification.¹⁹⁵ New approaches combining image analysis and machine learning for osteocyte growth modeling, or using 3D convolutional neural networks for innovative scaffold design provide possibilities for transformative TE.¹⁹⁶ Moreover, the organized engineering industry is still in the preliminary stage in our country compared with foreign countries. More appropriate TE options for different tissues will come in the future.

ORGAN AND PROSTHESIS TRANSPLANTATION

When conventional methods like conservative treatment or minor surgical repairs are insufficient to restore function, organ transplantation and prosthesis implantation become critical considerations in sports medicine.²¹⁹⁷ Both them are essential in treating severe sports injuries, with the choice of method depending on factors like the extent of damage, availability of biological tissues, and desired functional outcomes.

Allogeneic and heterologous organ transplantation

Organ transplantation in sports medicine involves surgically transferring tissues or organs, such as ligaments, tendons, or cartilage, to replace or repair damaged structures. This includes allografts, which are grafts from a donor of the same species, offering better compatibility and functionality,¹⁹⁸ and xenografts, which use tissue from a different species and are less common due to risks like immune rejection.¹⁹⁹ While allografts are preferred in reconstructive surgeries for their natural compatibility, xenografts remain an option when human donor tissue is unavailable.

Allogeneic and heterologous organ transplantation for meniscus injury.

A meta-analysis of 35 studies involving 1658 patients showed that MAT led to significant improvements in IKDC (mean improvement 22.245, exceeding MCID of 16.7 and MAT-specific 9.9), Lysholm (mean improvement 23.125, above MCID of 10.1 and MAT-specific 12.3), and VAS pain (mean improvement 3.618, surpassing MCID of 2.7), with postoperative improvements exceeding the minimal clinically important difference (MCID) threshold.²⁰⁰ Another systematic review showed that MAT could improve knee joint function and pain in the follow-up period of more than 5 years.³² A recent follow-up study shows that this effect can last for 10 years, although the clinical results are still getting worse during the follow-up observation. The Lysholm score improved from 46.4 ± 17.2 at preoperative assessment to 77.7 ± 20.4 at the 5-year follow-up (P<0.001), but then decreased to 71 ± 23.3 at the final follow-up (P=0.018). The VAS for pain decreased from 72.5 ± 22.6 at baseline to 29.9 ± 29.5 at 5 years (P<0.001), and then worsened to 47.2 ± 30.7 at

the final follow-up (P<0.001), yet still remained better than the baseline.²⁰¹ In addition, BMAC and bone marrow stem cells have been explored to enhance the therapeutic effect of allograft.^{202,203} Heterogeneous meniscal transplantation has shown promising chondroprotective effects in animal experiments, with studies demonstrating that it can promote tissue regeneration and reduce cartilage degeneration in rabbits, making it a potential alternative to traditional allografts.²⁰⁴ Gene editing represents a sophisticated approach with substantial promise, as triple knockout porcine meniscal tissue exhibits reduced immune cell infiltration and effectively suppresses human T-cell activation by targeting specific xenoreactive antigen genes, potentially offering a more targeted and comprehensive solution compared to the other methods.²⁰⁵ However, the method remains in the experimental stage, and issues like immunogenicity and graft strength need further investigation before clinical application in humans can be considered.²⁰⁶

Allogeneic and heterologous organ transplantation for cartilage injury.

Allogeneic cartilage transplantation, such as osteochondral allograft transplantation (OCA), has shown good long-term efficacy in treating large cartilage defects, with survival rates of 80% at 10 years and 73% at 15 years, particularly for knee injuries.²⁰⁷ Particulated juvenile cartilage allograft (PJCA) demonstrates moderate short-term clinical benefits in treating talar lesions but carries a high complication (25.2%) and failure rate (12.4%), raising concerns about its long-term effectiveness.²⁰⁸ Compared to autografts, allografts are associated with higher graft failure and revision rates due to immunogenicity and limited donor availability, although both methods achieve similar pain relief and functional improvement.^{209,210} Autografts are preferred for lower complication rates and reduced disease transmission risk, but donor site morbidity and limited availability make allografts a valuable alternative in certain cases. However, xenotransplantation utilizing acellular technologies has demonstrated significant potential for future therapeutic applications, offering promising outcomes in terms of reducing immunogenic responses and enhancing tissue integration.^{211,212} Multiplex-edited porcine chondrocytes (GGTA1/CMAH knockout with transgenic human complement inhibitors and anti-apoptotic/anti-inflammatory factors) enhanced resistance to complement-mediated damage, supporting their preclinical potential for xenogeneic cartilage transplantation.²¹³

Allogeneic and heterologous organ transplantation for tendon and ligament injury.

A meta-analysis of 25 studies (980 patients) on large/massive rotator cuff tears found autograft and allograft had similar retear rates (27.0% and 20.9% respectively) and functional improvements (e.g., Constant score +28.8/+38.4 points) at 18.4 ± 7.8 months mean follow-up, suggesting both grafts are viable options.²¹⁴ However, challenges like graft quality variability, immune responses, and higher revision rates compared to autografts highlight the need for further research to improve long-term outcomes.²¹⁵ Similarly, allogeneic transplantation has been increasingly used for ligament injuries, including ACL,²¹⁶ PCL,²¹⁷ and medial ulnar collateral ligament (MUCL) reconstructions,²¹⁸ demonstrating high return-to-play rates (e.g., 95.3% for MUCL) and satisfactory short-term results.²¹⁹ For PCL and ACL reconstructions, allografts have shown comparable short-term functional results to autografts, but some studies indicate higher retear rates and lower return-to-sport rates for allografts compared to autografts, particularly in revision surgeries.^{216,217} Xenotransplantation for tendon and ligament repair is still experimental, with promising short-term results in animal models and early human trials.²²⁰⁻²²² However, complications such as inflammatory reactions and poor integration present significant barriers to clinical application.

Prosthesis implantation

In sports medicine, a prosthesis is an artificial device used to replace or support damaged body parts like joints or ligaments.²²³ Modern prostheses are increasingly integrated with regenerative medicine, using bioactive materials and tissue-engineering techniques to promote cellular growth and improve integration with host tissue, enhancing recovery and long-term outcomes.²²⁴

Prosthesis implantation for meniscus injury. Current artificial meniscus products include the NUsurface® Meniscus Implant, Actifit® Meniscus Scaffold, and Collagen Meniscus Implant (CMI®), each utilizing different base materials to provide mechanical support and promote tissue regeneration.²²⁵⁻²²⁷ NUsurface® uses polycarbonate-urethane to mimic natural meniscus proper-

ties,²²⁸ while Actifit® employs a polyurethane scaffold that encourages tissue ingrowth and improves knee function.²²⁹ CMI®, made of type I collagen, supports new tissue formation in meniscus-deficient areas post-meniscectomy.²³⁰ A systematic review comparing MAT and meniscal scaffold implantation (MSI) found that both improved patient-reported outcome measures, with MSI having a higher 10-year survival rate (80.37% vs 66.57%, $P=0.034$), lower complication rate (9.64% vs 17.52%, $P<0.001$),²³¹ suggesting both procedures have benefits and drawbacks in treating meniscal defects.

Prosthesis implantation for cartilage injury. Current cell-free cartilage repair products use various materials to support tissue regeneration and integration. Agili-C™ utilizes aragonite-based scaffolds to promote cell infiltration and tissue formation,²³² while BioCartilage® employs a micronized cartilage matrix to replicate the extracellular environment.²³³ Cartiva® SCI uses polyvinyl alcohol (PVA) cryogels for mechanical stability,²³⁴ and collagen-based scaffolds (e.g., Chondro-Gide®, ChondroMimetic®) combined with polyglycolic acid (PGA) and hyaluronic acid (e.g., Chondrotissue®) are favored for their biocompatibility and cell proliferation support. Additional materials like chitosan (JOINTREP™)²³⁵ and multi-layered collagen-hydroxyapatite (MaioRegen®)²³⁶ address different repair needs.²³⁷⁻²³⁹ Clinical studies suggest that cell-free scaffolds in knee chondral lesion treatment show significant pain reduction (e.g., mean VAS improvement of 37.6 at 1-year, 39.1 at 2-year, and 40.0 at ≥3-year follow-up) and joint function improvement (e.g., mean Lysholm score improvement of 35.0 at 1-year, 36.7 at 2-year, and 33.8 at ≥3-year follow-up), with certain products like AMIC demonstrating comparable results to cell-based therapies at short-/mid-term follow-up, yet current literature has limitations including low evidence level and short mean follow-up.²⁴⁰

Prosthesis implantation for tendon and ligament injury. Current artificial ligament and tendon products include the Gore-Tex® PTFE Ligament, CoNexions TR, Teno Fix Tendon Repair System, Achillon System, OrthoCoupler, and Bridge-Enhanced ACL Repair (BEAR) Implant, each providing mechanical support and promoting tendon or ligament repair.^{223,241} The Gore-Tex® PTFE Ligament has shown good initial outcomes but faces high long-term complication rates.²⁴² CoNexions TR and OrthoCoupler,²⁴³ made from polyethylene terephthalate fibers, offer strength and durability but have challenges with poor biological integration. The Teno Fix system, composed of stainless steel multifilament cables, provides high tensile strength but may cause local inflammation and reduced flexibility.²⁴³ The Achillon System, using polycarbonate and stainless steel, is effective for suture management but lacks versatility for complex repairs.²⁴⁴ The newer BEAR Implant has shown promise in ACL reconstruction with re-rupture rates of 0 - 14%, mean side-to-side differences of 1.6 - 1.9mm and comparable improvements in IKDC, Tegner, Lysholm and KOOS scores at 2 - 5 years' follow-up, yet it requires further long-term studies to confirm its safety and efficacy.²⁴⁵ Although these products support early healing and mechanical stability, issues like implant degradation, limited integration, and variable long-term outcomes highlight the need for continued research and optimization.

Limitations and challenges

Organ and prosthesis transplantation in sports medicine face challenges like immune rejection, infection risks, and limited long-term success due to poor integration and mechanical complications. Organ transplants such as allografts and xenografts are prone to rejection and infection, while prostheses can suffer from issues like loosening, wear, and implant failure under heavy loads. Regenerative medicine offers promising solutions by using stem cells, bioactive scaffolds, and growth factors to improve compatibility and integration of both tissues and prostheses. Future advancements could lead to "living" prostheses that support cellular growth, reduce immune reactions, and adapt to the body's needs, ultimately improving long-term outcomes and making these treatments more effective and reliable. Regenerative medicine techniques, such as the use of growth factors, stem cells, and bioengineered scaffolds, are increasingly integrated into organ transplantation.

ORGANOIDS

Organoids refers to 3D multicellular structures generated in vitro that recapitulate the cellular architecture, functionality, and spatial organization of native organs,²⁴⁶ often created through stem cells or bioengineering approaches to mimic the physiological and pathological conditions of actual

organs.²⁴⁷ Compared with traditional 2D culture systems, 3D organoids better resemble the native organ in terms of gene and protein expression, metabolic function and microscale tissue architecture, providing a promising tool to replicate the function of organs of origin.²⁴⁸ The microenvironment of musculoskeletal system is a unique, highly dynamic compartment composed of heterogeneous cells, extracellular matrix, soluble growth factors, and cytokines. Therefore, organoids are more capable of maintaining aspects of molecular and cellular heterogeneity and the original functions.²⁴⁹ The application of organ-like structures in sports medicine holds significant potential for disease modeling, personalized drug testing, and regenerative therapies, such as studying tissue repair mechanisms, assessing treatment efficacy, and developing innovative solutions for sports-related injuries and musculoskeletal disorders.^{250,251} Unlike tissue engineering, which often relies on scaffolds, organoids self-organize into functional structures, enhancing tissue replacement precision.²⁵² They also circumvent some risks of gene therapy by providing functional tissues without genetic alteration, making them promising for patient-specific therapies and reducing reliance on donor organs for transplantation.²⁵³

Applications in sports injuries

Due to low healing capacities and tissue integration properties of cartilage, a major scientific and clinical challenge remains to achieve simultaneous structural and functional repair of cartilage in sports injuries.²⁵⁴ Cartilage organoids have shown promising potential in cartilage injury repair by mimicking the structure and function of native cartilage, promoting tissue regeneration, and enabling personalized treatment approaches. Bai et al. constructed a human cartilage model for real-time monitoring of cartilage generation and hypertrophy differentiation, they found that phentolamine targets α -AR to stimulate chondrogenesis, but inhibits hypertrophy by suppressing the production of secretory leukocyte protease inhibitor (SLPI) (Figures 7A-B). Phentolamine injection or SLPI deficient chondrocyte implantation provides a clinically feasible strategy for the regeneration of transparent cartilage (Figures 7C-D).²⁵⁵ Organoids can replicate complex cell interactions within cartilage and subchondral bone, making them effective models for studying disease mechanisms and drug responses. A recent study demonstrated that allogeneic iPSC-derived cartilage organoids transplanted into chondral defects in a primate model successfully survived, integrated with native cartilage, and contributed to tissue repair without eliciting immune reactions, indicating their potential for clinical application in treating articular cartilage defects. It is worth noting that the organoids had integrated with the surrounding native cartilage by 17weeks. The immature tissue bridging the cyiPS-Cart and native cartilage was mainly composed of type II collagen, which is characteristic of articular cartilage.²⁵⁶ To boost chondrocyte expansion while preserving their chondrogenic phenotype, Crispin et al. cultured bovine chondrocytes in a suspension culture, using spinner flasks, and notochordal cell derived matrix as a supplement.²⁵⁷ The constructs had an interconnected matrix similar to native cartilage in composition and organization, expressing enhanced cartilage formation compared with standard approach, as it leads to the formation of more matrix with higher quality. In order to construct an organoid with hierarchical structure, Yang et al. developed an in situ self-assembled organoid for osteochondral regeneration without reliance on a bulk scaffold or use of growth factors.²⁵⁴ MSCs in the microcryogels achieved directional chondrogenic and osteogenic differentiation in the microcryogels. Sequential injection of microcryogels into osteochondral defects in beagle dogs achieved in situ self-assembly into osteochondral organoids and substantial in vivo tissue repair, suggesting the usefulness of this approach as a simplistic, injectable solution for the regeneration of cartilage defects. Shen et al. integrated self-assembly with photopolymerization through microfluidic system to develop innovative RSD-MSs for cartilage organoid precursors construction, which demonstrated promoted in vivo cartilage repair capacity in a rat femoral cartilage defect model. Tendon/ligament organoids have been prepared,^{258,259} but there is still a lack of research on their application in injury repair.

Limitations and challenges

Although there are promising potential applications of cartilage organoids, some challenges remain to be addressed. Firstly, as cartilage is widely

distributed throughout the body, different kinds of cartilage show distinct characteristics, which require targeted researches and design. For example, meniscus, a special kind of cartilage in knee joint, plays important role in stress dispersion, joint stabilization, lubrication and nutrient supplement. Its critical functions predestine the unique heterogeneous structure, which requires more refined exploration of organoid construction. Besides, for cartilage is originally lack of blood supply, the natural regeneration is restricted. Therefore, researches on vascularizing the cartilage organoids are essential in facilitating regenerative efficiency. Even though the development of bone organoid is still in its infancy, the researches and applications have shown prospective results. With further exploration, the organoid technology as a novel tool, may achieve potential application in regeneration of sports injuries and bring possibilities for personalized treatments in musculoskeletal system.

CONCLUSION

As mentioned above, the application of regenerative medicine in the treatment of sports injuries has shown great potential, providing new solutions for sports injuries that cannot be completely cured by traditional therapies. Biological therapies, including PRP, stem cell injection, cytokines, etc., can not only accelerate tissue healing processes, but also reduce local inflammation, improve tissue function, and thus enhance the efficiency of sports recovery. The tissue engineering technology utilizing biomaterials, physical and chemical stimuli, and seed cells has also shown great potential, such as tissue engineering cartilage, ligaments, meniscus, etc., which can promote tissue regeneration and functional recovery, and is expected to fill the huge gap in the origin of transplants. Prostheses and organ transplants also provide new treatment strategies for severe tissue defects, especially for athletes who need to return to high-level competitive competitions.

Although regenerative medicine has shown promising prospects in the treatment of sports injuries, there are still limitations and challenges in its practical clinical application, such as individual differences, long-term efficacy and high cost. Therefore, in order to promote the wider application of regenerative medicine in the field of sports injury treatment, future research should pay more attention to the following aspects. Firstly, the mechanism of regenerative medicine still needs further exploration and clarification: a deeper understanding of the specific roles and mechanisms of stem cells, PRP, and cytokines in tissue repair processes, and how to better control inflammation and rejection reactions during tissue repair can promote smoother tissue repair and optimize treatment plans. In addition, the biocompatibility, mechanical strength, and degradation rate of tissue engineering scaffold materials still need to be further optimized: developing intelligent materials that can better simulate the structure of natural tissues, so that regenerated tissues have physiological functions that mimic those of natural tissues, which may be optimized through the introduction of AI; Orchestrate biological, physical and chemical factors, and optimize 3D printing technology to precisely customize patient specific scaffolds, promoting personalized tissue regeneration and functional recovery. Moreover, precise and personalized regenerative therapy is one of the important directions for future medical development: combining transcriptomics, proteomics and other technologies to characterize genes and proteins and accurately formulate personalized treatment plans. Finally, the long-term effectiveness and stability of regenerative medicine therapy still need to be further studied: long-term follow-up and clinical trials are one of the core areas for the future development of regenerative medicine. The clinical application scale of regenerative therapy should be further expanded, and long-term effectiveness, safety, and stability evaluations should be conducted to ensure that it can maintain sports function in the long term and reduce recurrence.

To sum up, regenerative medicine demonstrates transformative potential in joint sports injury rehabilitation through advanced biotherapies (e.g., PRP, stem cells), precision tissue engineering (3D-bioprinted scaffolds, smart biomaterials), and prostheses. However, clinical translation faces multifaceted challenges: (1) incomplete understanding of cellular crosstalk and immune microenvironment modulation during regeneration; (2) patient-specific variability in treatment responses influenced by genetic profiles and injury heterogeneity; (3) insufficient long-term efficacy data from multicenter trials. Future priorities include elucidating mechanobiological signaling

networks, optimizing combinatorial delivery of growth factors and physico-chemical stimuli, and establishing standardized protocols. Integration with AI-driven predictive models and multi-omics profiling will enable patient-tailored regenerative strategies, positioning these therapies as cornerstone interventions for restoring functional tissue homeostasis in athletes. The regenerative medicine therapy will play a more important role in the field of sports injuries as an efficient and accurate treatment strategy.

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FUNDING AND ACKNOWLEDGMENTS

This work was supported by grants from the National Natural Science Foundation of China No. 82441025 (D.J.), 82472428 (D.J.), 82172508 (W.F.), 82372490 (W.F.), National Key R&D Program of China (2024YFA0919200) (G.L.), Shenzhen Science and Technology Program (JCYJ20241202124908012) (G.L.), Research Grants Council of University Grants Committee Hong Kong (14119124, 14113723, N_CUHK472/22) (S.L.), and Natural Science Foundation of Sichuan Province (25QNJJ3423) (T.X.). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

Gang Li, Dong Jiang, Weili Fu and Sien Lin offered directions on this manuscript. Mingze Du, Tianhao Xu and Yingluo Gu drafted the manuscript. Mingze Du, Tuo Wu, Yuwei Wang and Jiajun Liu made the figures and table. Mingze Du, Tianhao Xu and Yingluo Gu reviewed the literature. Dong Jiang, Gang Li, Weili Fu and Sien Lin reviewed the manuscript and gave comments. All authors have read and agreed to the published version of the manuscript.

DECLARATION OF INTERESTS

Dong Jiang is an Editorial Board member of The Innovation Medicine. He was blinded from reviewing or making final decisions on the manuscript. The article was subject to the journal's standard procedures, with peer review handled independently of this Editorial Board member and their research groups. The other authors declare no competing interests.

DATA AND CODE AVAILABILITY

Not applicable.