

Review

# Current Advancements and Strategies of Biomaterials for Tendon Repair: A Review

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Academic Editors: Jessica Amber Jennings and Josh Bush

Submitted: 13 December 2022 Revised: 27 February 2023 Accepted: 8 March 2023 Published: 6 April 2023

## Abstract

Tendon is a bundle of tissue comprising of a large number of collagen fibers that connects muscle to bone. However, overuse or trauma may cause degeneration and rupture of the tendon tissues, which imposes an enormous health burden on patients. In addition to autogenous and allogeneic transplantation, which is commonly used in the clinic, the current research on tendon repair is focused on developing an appropriate scaffold via biomaterials and fabrication technology. The development of a scaffold that matches the structure and mechanics of the natural tendon is the key to the success of the repair, so the synergistic optimization of the scaffold fabrication technology and biomaterials has always been a concern of researchers. A series of strategies include the preparation of scaffolds by electrospinning and 3D printing, as well as the application of injectable hydrogels and microspheres, which can be used individually or in combination with cells, growth factors for tendon repair. This review introduces the tendon tissue structure, the repair process, the application of scaffolds, and the current challenges facing biomaterials, and gives an outlook on future research directions. With biomaterials and technology continuing to be developed, we envision that the scaffolds could have an important impact on the application of tendon repair.

**Keywords:** tendon repair; scaffolds; biomaterials; electrospinning; 3D printing

## 1. Introduction

Tendon is a bundle of fibrous connective tissues that connects muscle and bone tissues. Tendinous tissues play a pivotal role in musculoskeletal activities as well as help transmit contraction forces from the muscle to the bone [1,2]. Musculoskeletal disorders are a major health burden worldwide. It is estimated that more than 25% of adults suffer from tendon-related musculoskeletal disorders [3,4]. Tendon injuries primarily result from high-axis sports, including skiing, basketball, and soccer [5,6]. Besides, tendon-related injuries mostly occur in the anterior cruciate ligament (ACL), Achilles tendon, rotator cuff, flexor tendon, and patellar tendon, which account for a total of 45% of all musculoskeletal injuries. The probability of re-tear after the repair is about 4.4% for the Achilles tendon, 20% for the rotator cuff, and 30% for the ACL [7,8].

The success of tendon repair may be related to several factors, such as the patient's age, activity level, body mass index (BMI), lifestyle, number of tendon injuries, extent of the tear, and so on. For instance, the risk of rotator cuff tears is 2–3 times higher in elderly people than that in younger

adults. Similarly, a high cholesterol level is also associated with an increased risk of rotator cuff tears. Achilles and patellar tendons are thinner and stiffer in smokers than that in non-smokers. The injury site inflammation may drive tendon fibrosis, which may further hamper the healing process [9,10]. The hypocellularity and hypovascularity of tendons have been shown to be responsible for the spontaneous healing failures following an injury, which lead to the production of disordered extracellular matrix (ECM) as well as weak biomechanical properties of the regenerated tendon tissues [11].

Biofabrication refers to the production of complex biological and non-biological products from live cells, molecules, ECM components, and biological materials [12]. Biomaterials are one of the key factors in tendon tissue engineering (TE). A series of materials, including natural and synthetic polymers as well as therapeutics and cells, in combination with fabrication technology, have been used for tendon tissue repair. Tissue-engineered scaffolds may not only provide structural and mechanical support to the degenerated tendon tissues but may also induce the re-



pair of tendon tissues. Moreover, the degradation rate of the biomaterials may be further tailored to leverage a conducive microenvironment for tendon tissue repair as well as induce the recruitment of endogenous stem/progenitor cells into the injured tissues and facilitate their differentiation into tenocytes for functional tendon repair [13–15]. Physico-chemical parameters of scaffolds, including stiffness and degradation rate may also influence the behavior of a multitude of cell types, such as the invasion of the scaffolds by stem cells, macrophages, and fibroblasts [16]. Therefore, developing biocompatible and biodegradable scaffolds which can mimic the tendon tissues may be of considerable significance for the repair of injured tendon tissues. In the following sections, we will provide an overview of the tendon structure, its mechanical properties, and the current approaches for tendon repair.

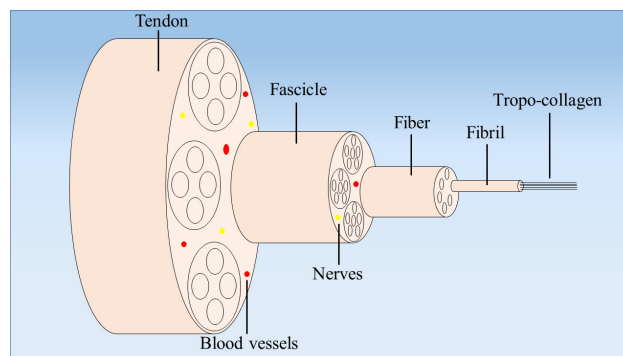
## 2. Tendon Structure and Repair

### 2.1 Tendon Structure

Tendons exhibit a hierarchical structure composed of the bundles of collagen fibers arranged along their longitudinal axis. The fibers of the tendon are organized regularly: the tropo-collagen constitute fibrils, the fibrils constitute fibers, the fibers constitute fascicles, and the tendon matrix is constituted of fascicles (Fig. 1) [17]. In addition, tendon tissues also have horizontal fibers, which can prevent damage and fracture under the action of longitudinal, transverse and rotational forces [18]. The endotendon is a thin membrane composed of lymphatic vessels, blood vessels, and nerves that occupies the spaces between fiber bundles. The epitendon wraps the surface of the tendon and prevents its adhesions to the adjacent tissues [19]. Tendon is mostly composed of the collagen type I (COL I), which accounts for 60% of the dry weight of the tissue and 95% of the total collagen content in the tendon tissues. The other types of collagen components in tendon tissues include collagen type III (COL III), collagen type V (COL V), and collagen type VI (COL VI). At the cellular level, tendon is mainly composed of tenoblasts and tenocytes, which account for about 90–95% of the cellular components and play an important role in mechanical stimulation. In addition to the tenocytes, tendon tissues also exhibit synovial cells, chondrocytes and vascular cells [20,21]. While the intrinsic compartment of tendon tissues is mainly comprised of tenocytes and collagen, the extrinsic compartment of tendon tissues connects the synovial-like tissues of the immune, vascular, and nervous systems, which also play an important role in musculoskeletal activity [22].

### 2.2 The Effect of Mechanics on Tendon

The structure of tendon determines its ability to bear the force. Tendon tissues are subjected to a large number of tensile stresses in a hierarchical manner. The macroscopic tensile strength (TS) and elastic modulus ( $E$ ) of the supraspinatus tendon are 4.1–22.1 MPa and 217.7–592.4



**Fig. 1. Schematic diagram illustrating the tendon structure.** The tendon is composed of tropo-collagen, fibrils, fibers, fascicles, nerves, and blood vessels.

MPa, respectively [23]. The  $E$  of the ACL and Achilles tendon has been shown to be  $113 \pm 45$  MPa and  $822 \pm 211$  MPa, respectively [24]. The tensile forces exerted on the tendon tissues affect their service life. As shown in Fig. 2, when the strain of the tendon is less than 2%, the fibers are in a curled state, and this range is called the “Toe region”. When the stress is further increased, the strain is in the range of 2%–4%, the fibers undergo a stretched state from the curling state and this range is called the “Linear region”. With a further increase in the force and the strain value beyond 4%, there may be a slight tearing of the fibers, which is called the “Plastic region”. If the plastic region is continuously stressed, tendon tissues are likely to develop tendinopathy. When minor injuries repeatedly occur or the strain exceeds 8%, the fibers are easy to tear, and then the tendon ruptures, which is called the “Failure region” [25].

### 2.3 Tendon Repair Process

Tendon injuries can develop from chronic tendinopathy to acute tendon rupture. Chronic tendinopathy is usually associated with histological changes, such as increased proteoglycans (PGs) and glycosaminoglycans (GAGs) and disorganized collagen arrangement, but without obvious tissue tearing. However, acute tendon rupture is often associated with direct contusion or tear [26].

There are two modes of repair after tendon injury about intrinsic and extrinsic healing. The former is the self-healing of injured tendon tissues from the parenchyma as well as the inner tendon, which may provide better mechanical properties and reduce complications. Extrinsic healing is mainly caused by adventitial injury, and there are many problems after injury [27,28]. Since extrinsic healing has more problems than intrinsic healing, a lot of attention has been paid to the process of external healing, and it is divided into three parts, which are the inflammation phase, proliferative phase, and remodeling phase [29] (Fig. 3). The inflammation phase occurs 1–2 weeks following tendon injury. The blood vessels at the injury site first form blood clots and release growth factors (GFs) [30],

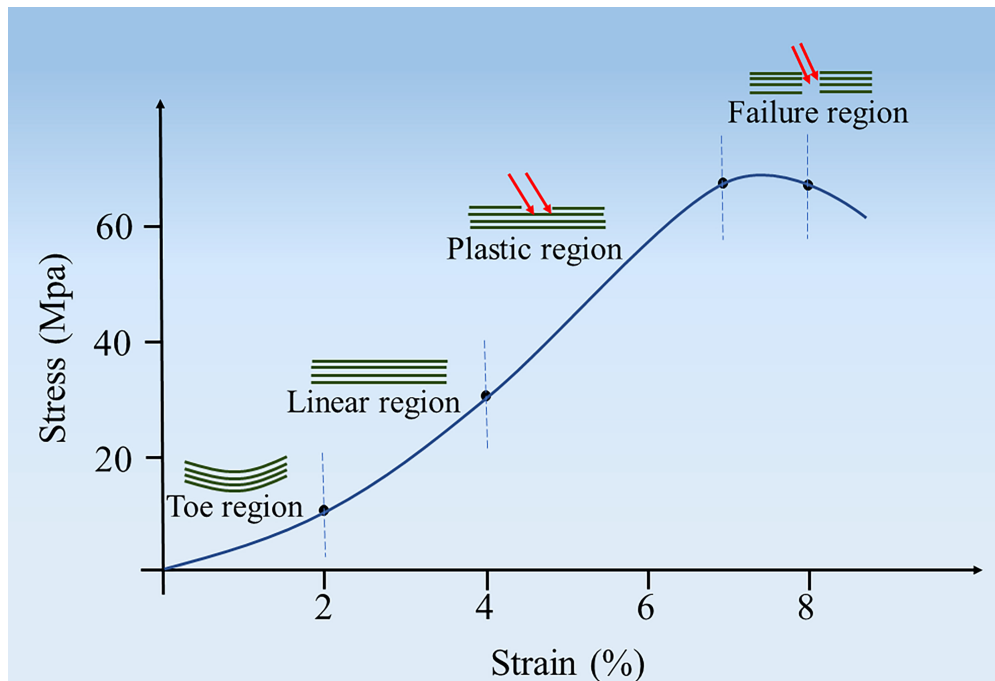


Fig. 2. Schematic diagram illustrating a typical stress-strain curve of tendon tissue.

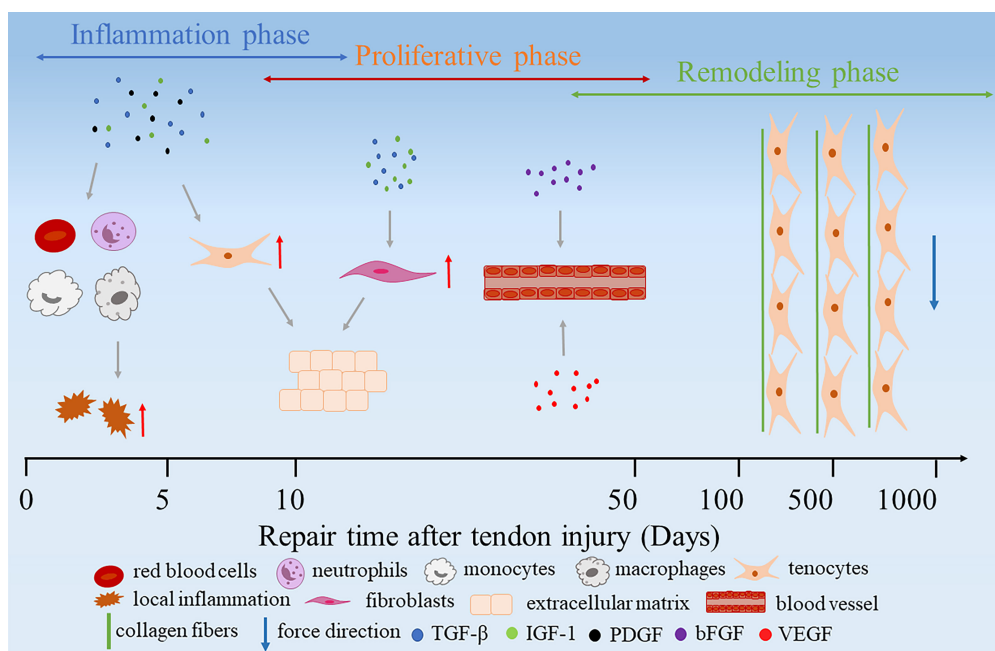
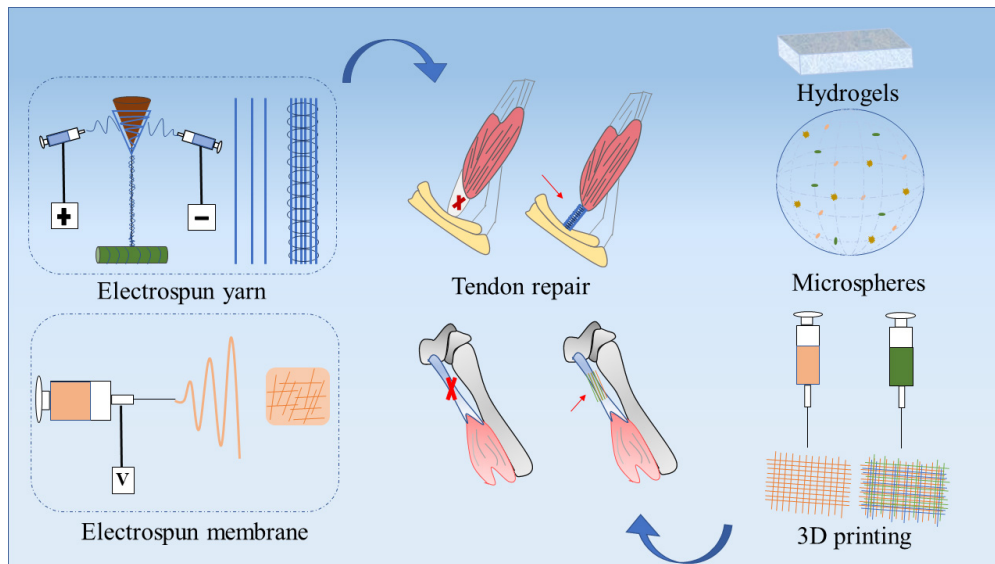


Fig. 3. Extrinsic healing of the injured tendon tissues.

such as transforming growth factor- $\beta$  (TGF- $\beta$ ), insulin-like growth factor-1 (IGF-1), and platelet-derived growth factor (PDGF), which ultimately increase neovascularization as well as stimulate the proliferation of tenocytes and the recruitment of different types of inflammatory cells. There is an increase in red blood cells and neutrophils, followed by an increase in monocytes and macrophages, which induce local inflammation. In the subsequent proliferative phase, which lasts for up to several weeks, a large number

of fibroblasts will be recruited due to the high expression of TGF- $\beta$  and IGF-1. With fibroblasts proliferate, they and tenocytes synthesize different types of ECM components, including COL III, PG, and GAGs [26]. Furthermore, tenocytes, fibroblasts, and inflammatory cells release basic fibroblast growth factor (bFGF), which synergizes with vascular endothelial growth factor (VEGF) to promote angiogenesis. After about 6 weeks, the remodeling period begins, which is manifested with the lower numbers of cells,



**Fig. 4. Schematic illustration of the application of different strategies for tendon repair.**

while the higher content of COL I. The collagen and tenocytes align in the direction of the stress [31]. Beyond 10 weeks, both the metabolism of tenocytes and the numbers of blood vessels decrease. However, the crosslinking of collagen fibers increases and the tendon-like tissues form, which may last for up to 1–2 years or even longer.

#### 2.4 Problems after Tendon Injury

After tendon injury, newly generated tissues and the original tendon tissues display varying biomechanical properties due to the different content of COL I and COL III [32]. Consequently, owing to these subtle structural and compositional changes, it is likely to occur several types of problems, which may perturb normal tendon healing. For instance, the degenerative tendinopathy may lead to a lower content of COL I as well as inferior tensile strength and a poor ability to withstand the mechanical load, which may reduce the quality of the tendon tissues as well as compromise their strength. The degenerated tendon tissues display a higher content of COL III, which is smaller and thinner than the COL I, it exhibits insufficient mechanical strength, and may also be prone to the secondary rupture or scarring during the repair process [33].

Peri-tendonious adhesions also pose a major problem after tendon injury within the healing area [34]. The adjacent cells and tissues may stick to the injured tendon. If the repair effect is not ideal, it may lead to loss of tendon structure and failure of tendon repair [35]. However, current treatment modalities do not fully restore the integrity and mechanical functionality of tendon tissues, which are often associated with different types of problems, such as low strength, joint stiffness and poor healing [36]. Tendinopathy may also lead to inflammation of the joint, which causes the occurrence of arthritis [37]. Rotator cuff tears are a common cause of shoulder dysfunction, whose main typical

clinical symptom is pain or poor mobility due to inflammation of the synovium [38].

The gold standard treatment option for the injured tendon tissues is reattachment of the tendon to the bone by surgery, but it often leads to the formation of narrowed fibrovascular scar tissues [39]. Autologous tendon transplantation will occur many problems, such as donor-site associated infection, hematoma and local pain [40]. In addition, the poor blood supply to the Achilles tendon may restrict the transportation of nutrients to reach the injured tissue, which may cause several types of problems, such as re-rupture or adhesion of tendon tissues. The induction of neo-capillaries at the injury site as well as improved blood circulation may be beneficial for the recovery of the injured tendon tissues [41]. Various problems will be encountered after tendon injury. Therefore, external interventions are required to promote tendon repair. For example, tendon-replaceable scaffolds have good mechanical properties, local repair materials can prevent tendon adhesion, and scaffolds with optimized properties can promote cell proliferation and differentiation.

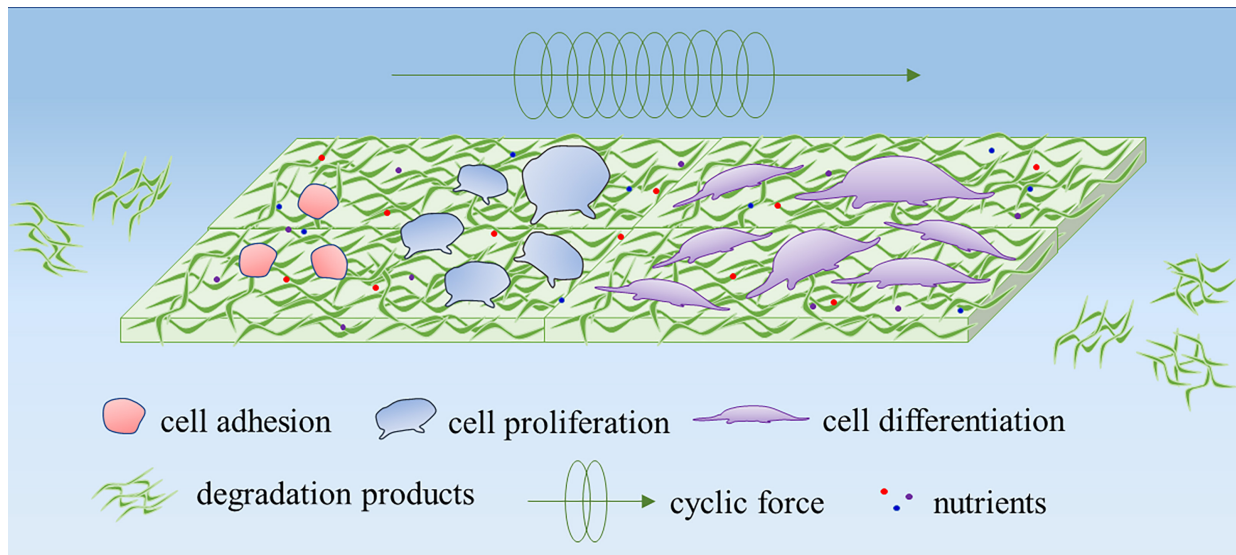
### 3. Current Strategies of Tendon Repair

While autologous, allogeneic and xenogeneic tendon tissues are often employed to replace the injured tendon tissues, these modalities are limited due to a series of problems, such as the lack of appropriate numbers of donors as well as donor-site associated infection and immunogenicity risks [42,43]. Recently, a myriad of strategies have been used to promote the repair of injured tendon tissues (Table 1, Ref. [44–67]). There are many ways to fabricate scaffolds, such as electrospinning and 3D printing, and there are some injectable hydrogels and microspheres, which can be used as GFs and cell carriers, either alone or in combination with other methods for tendon repair [68] (Fig. 4).

**Table 1. The application of different types of strategies for tendon repair.**

Approaches	Materials	Advantages	Application	[Ref]
Electrospinning	PCL, Hydroxyapatite, ZnO NPs	Cell compatibility, Tendon regeneration, Osteogenesis, Antibacterial	Bone-tendon interface repair	[44]
	HA, PCL, Polyethylene glycol, Silver nitrate, Ibuprofen,	Anti-inflammation, Antibacterial, Prevent fibroblast penetration, Nutrients transport	Peri-tendinous anti-adhesion	[45]
	Poly (ethylene oxide)	Cell proliferation, Tenogenic differentiation, Collagen fiber remodeling	Tendon injury repair	[46]
	SF, PLCL, PCL, PCL microfibers	Chondrogenic and tenogenic differentiation of rat bone marrow stromal cells, Improve the biomechanical properties	Rotator cuff tendon–bone healing	[47]
	PCL, Kartogenin	Increased cell viability, Tenogenesis-related marker expression	Tendon regeneration	[48]
3D printing	Growth differentiation factor 5, ADSCs sheets, SF, PLCL	Mimics multiple tissue structures and phenotypes, Improve the mechanical strength, Fibrocartilage formation between supraspinatus tendon and bone	Rotator cuff regeneration	[49]
	Tendon-derived decellularized ECM, Bone-derived decellularized ECM, BM-MSCs, Polyurethane, PCL	Biocompatibility, Nontoxic, Reduce tissue adhesion, Collagen deposition	Tendon repair and prevent tendon adhesion	[50]
	Polydopamine NPs, TGF- $\beta$ 1 gene silencing plasmid, Gelatin, HA, Sodium alginate, PCL	Cell proliferation, Thick and ordered muscle fiber, Tendon tissue remodeling, Improve mechanical strength	Tendon growth	[51]
	Ti-6Al-4V powder	Improve collagen organization, Increase fibrocartilage	Rotator cuff tendon–bone healing	[52]
	PLGA, BM-MSCs, Bone morphogenic protein 12	Biomimetic recapitulation of native enthesis structures, Improve collagen organization, Support cell communication and infiltration, Show better histological score	Rotator cuff tears	[53]
Hydrogel	PCL, Sodium alginate, Melatonin	Promote cell proliferation and viability, Promote the expression of tendon markers, Anti-oxidative	Tendon repair	[54]
	HA, Rhynchophylline	Increase the expression of COL I/COL III, Cell proliferation, Inhibiting the phosphorylation of Smad2	Tendon healing and prevented adhesion	[55]
	Chitosan, PLLA	Higher tensile strength, Cell proliferation, Reduce protein adsorption	Tendon regeneration	[56]
	Alginate, Polyacrylamide, Mesoporous silica	A hierarchically anisotropic structure, Superior mechanical properties	Tendon engineering or replacement	[57]
Microspheres	Curcumin, PLGA	Anti-inflammatory, Increase the tensile strength	Achilles tendinopathy	[58]
	Periodontal ligament stem cells, Gingival MSCs, Alginate	Expression for gene markers related to tendon regeneration	Tendon tissue regeneration	[59]
	Heparin, PDGF	Anti-inflammatory, Gene expression of tendon markers, Increase the collagen content, Improve stiffness and tensile strength	Rotator cuff tendinitis	[60]
	PRP, Gelatin sponge	Promote BM-MSCs proliferation, Have fibrocartilaginous transition region, High maximum failure load and stiffness	Tendon-to-bone healing	[61]
Other strategies	MSCs, PRP	Enhance production of growth factors, Tissue regeneration, Enhance the biomechanical property	Rotator cuff injuries	[62]
	PRP, Graphene oxide	Good biocompatibility, BM-MSCs proliferation, Improve mechanical strength	Supraspinatus tendon reconstruction	[63]
	VEGF	Regulate the Hippo signaling pathway, Induces angiogenesis	Rotator cuff reconstruction	[64]
	bFGF, VEGF-A, PLGA, NPs/plasmid complexes	Produce more COL I, New fibrocartilage formation, Improve mechanical strength	Tendon-to-bone healing	[65]
	Hydroxyapatite/COL I paste	Cell proliferation, Osteogenic gene expression, New bone formation, Sharpey fibers attached to the bone	Tendon-to-bone healing	[66]
	PET, Calcium phosphate	MC3T3-E1 cells proliferation, Osteogenic differentiation, Improve UTS and stiffness	Anterior cruciate Ligament reconstruction	[67]

PCL, Polycaprolactone; NPs, nanoparticles; HA, Hyaluronic acid; SF, Silk fibroin; PLCL, Poly(L-lactic acid-co- $\epsilon$ -caprolactone); ADSCs, adipose derived stem cells; BM-MSCs, bone marrow derived mesenchymal stem cells; PLGA, Poly(L-lactide-co-glycolic acid); PLLA, Poly(L lactic acid); MSCs, mesenchymal stem cells; PRP, Platelet-rich plasma; PET, Polyethylene terephthalate.



**Fig. 5. Schematic representation of an ideal scaffold for tendon repair.** An ideal scaffold should encourage different cellular behavior, such as cell adhesion, cell migration, and cell proliferation. Besides, the scaffold should exhibit sufficient mechanical properties to withstand the load or reinforce the injured tissues. The degradation products should not induce inflammation at the injury site.

The ideal scaffolds for tendon tissue repair should meet the following requirements (Fig. 5): (1) cells can adhesion, grow and migrate on scaffolds [69]; (2) provides nutrients needed for cell adhesion, proliferation and differentiation [70]; (3) no toxicity to cells [71]; (4) materials can degradable [72]; (5) display good mechanical properties to fulfill the requirements of tissue repair: the uniaxial tensile strength should be equivalent to or even higher than that of the strength of the autologous tendon; withstand high-intensity cyclic loads and resist long-term creep deformation, and permit frictionless movement in an efficient sliding to minimize the wear [73].

### 3.1 Different Derived Stem Cells

The ideal cell therapy is that cells can refill injured tissues and/or enhance the ability of resident cells. The ultimate goal is to promote tissue reconstruction and functional recovery [74]. It is noteworthy to mention here that several important parameters need to be carefully considered, which may affect cell therapy for tendon repair applications, such as cell type, quantity, and delivery method. Moreover, the choice of the biomaterial may also have a substantial effect on the differentiation of transplanted stem/progenitor cells into tenocytes, including surface morphology, hydrophilicity/hydrophobicity, mechanical strength, and so on [75]. Therefore, the selection of the appropriate cell types with an appropriate biomaterial may lead to better repair of tendon tissues.

At present, cells from various sources are being explored for tendon tissue repair. Among them, mesenchymal stem cells (MSCs) are widely used cell types, which can be obtained from the bone marrow (BM), adipose tissues, and tendon. Additionally, BM-MSCs are multipotent stem

cells, which have been shown to differentiate into tenocytes [76]. While mechanisms governing cell-mediated tendon healing yet remain to be explored, it has been reported that the transplanted cells can promote tissue repair through multiple pathways. The transplanted cells may either differentiate into target lineage cells or secrete paracrine factors. The latter can indirectly promote tissue repair, which is manifested by regulating inflammatory reactions and avoiding immunosuppressive treatment after allograft transplantation, and these factors can activate residual receptor cells to play a role in tissue repair [77,78]. Yu *et al.* [79] exploited BM-MSCs-derived exosomes for tendon regeneration and increased proliferation and migration of endogenous tendon stem/progenitor cells. Zhang *et al.* [80] also leveraged tendon stem cell-derived exosomes and observed an enhanced proliferation and migration of tenocytes in a dose-dependent manner. Moreover, the transplantation of exosomes suppressed inflammatory response and promoted the high-quality healing of injured tendons.

Similarly, ADSCs have been shown to promote tendon repair either by differentiating into the tenocytes or by promoting the paracrine effect [81]. From a clinical point of view, ADSCs are easier to be harvested, less invasive and more abundant than that of MSCs [82]. Norelli *et al.* [83] incorporated ADSCs into hydrogel of collagen and alginate for the subsequent transplantation into the defective Achilles tendon tissues in rats. The cell transplantation led to higher strength and toughness as well as a higher expression of ECM proteins, such as COL I and COL III. It was further revealed that ADSCs injected into tendon defects can survive *in vivo* even for up to 4–5 weeks after transplantation.

Tendon-derived stem cells (TDSCs) have also been shown to promote an earlier and better recovery of tendon injury. The transplantation of TDSCs led to increasing collagen content, improved alignment of tenocytes and collagen fibers, formation of collagen birefringence, and improved biomechanical properties of regenerated tissues compared to the fibrin glue-only controls [84]. Xu *et al.* [85] fabricated PLCL/collagen scaffolds using an electrostatic spinning dynamic water flow system, and then implanted TDSCs on the scaffolds. The mechanical stimulation of the cell-seeded construct was shown to improve tendon tissue formation. The expression levels of COL I, COL III and tenascin C in the cell-seeded constructs were significantly higher on day 14 after mechanical stimulation. In addition, the higher deposition of collagen at weeks 4 and 8 after the implantation of scaffolds significantly improved the maturity and mechanical properties of the regenerated tendon tissues. Similarly, Chen *et al.* [86] fabricated chitosan scaffolds that by self-deposition and then seeded TDSCs on the scaffolds. The cell-seeded groups exhibited a higher expression of tendon-specific genes as well as COL I production, while a lower deposition of COL III. The organization of COL I, cell density, maximum load and E of the TDSCs-seeded groups were all closer to those of the native group. Consequently, the healing of the Achilles tendon was improved while the adhesion around the Achilles tendon tissues was reduced (Fig. 6, Ref. [86]). TDSCs, as native cells of the tendon tissue, are better adapted to the tendon microenvironment and preferentially differentiate into tenocytes, however, the number of cells in tendon tissue is very small, and the process is more complicated and costly than other cell extractions to obtain a large number of high-quality cells.

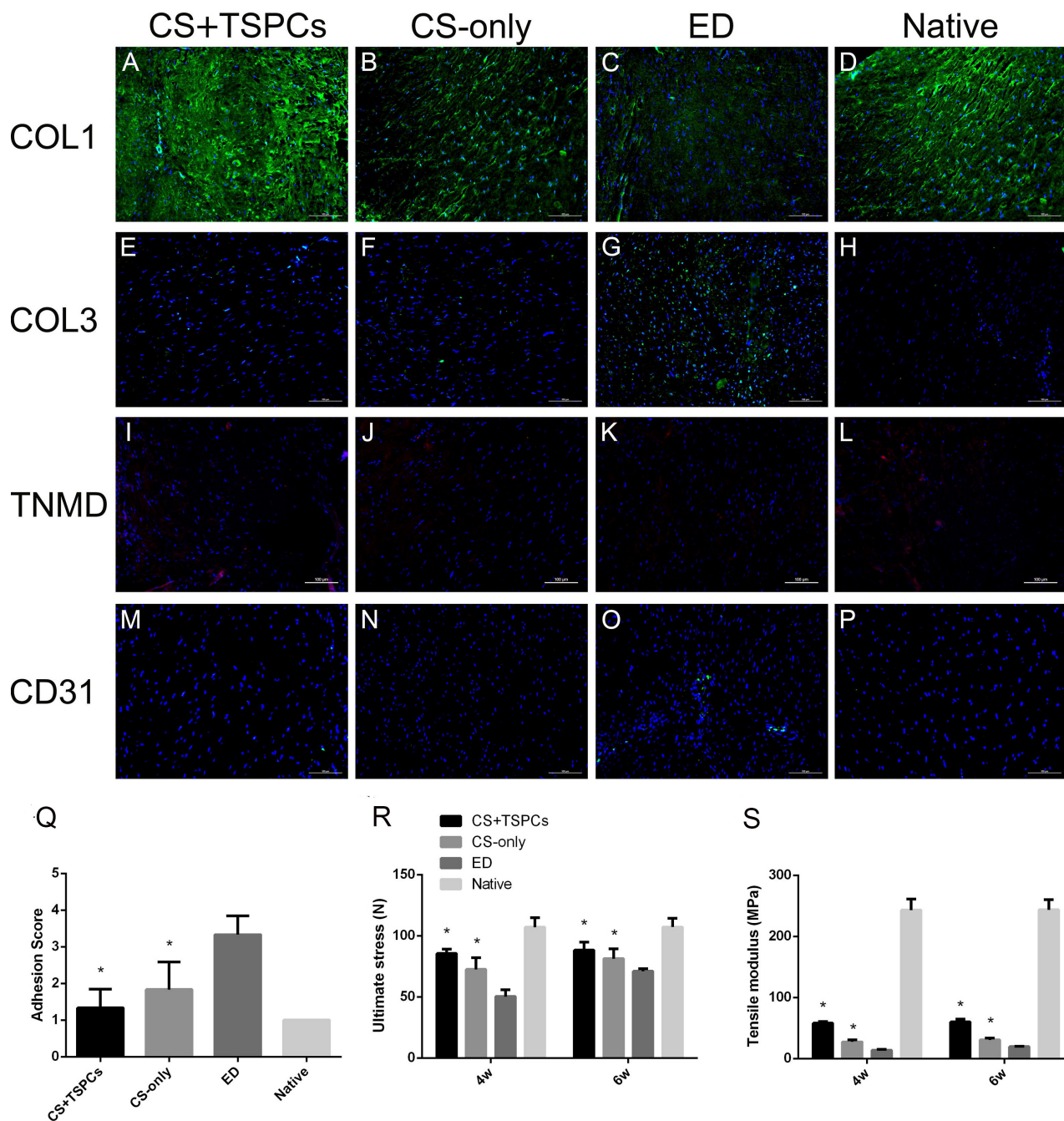
### 3.2 Electrospinning

Electrospinning refers to the jet spinning of a polymer solution or melts in a strong electric field. Under an electric field, the droplet at the tip of the needle changes from a ball to a cone, known as a Taylor cone, and expands into a fibrous filament from the tip of the cone. Electrospinning is a simple, fast, sustainable, size-controllable, and an easy approach, which has already been exploited for the fabrication of different types of scaffolds [87,88]. Nanofibers resemble the fibrous structure of natural ECM, which may positively influence different cellular behavior, such as cell adhesion, cell migration, and cell proliferation [89,90]. Electrospinning technology can combine most spinnable natural materials such as chitosan, collagen, SF, gelatin and synthetic polymers such as PLGA, PCL, PLCL, PET, polylactic acid (PLA), polyglycolic acid (PGA) and can load cells and GFs such as BM-MSCs, TDSCs, VEGF to make scaffolds for tendon repair. Electrospun nanofibers can be designed into different shapes and structures, such as nanofiber membranes and nano-yarns, which can also be used in combination with 3D printing technology and hydrogels to meet the

needs of tendon repair such as tendon regeneration, tendon-bone healing, and anti-adhesion.

Tendon tissues are composed of coiled nanofibers, however, it is still challenging to fabricate scaffolds that may accurately mimic the microstructure and mechanical properties of human tendon tissues as well as promote the infiltration of endogenous stem/progenitor cells into the implanted grafts [91]. With the advancement in technology, electrospinning can afford the design of scaffolds mimicking the structure of collagen fibrils of tendon tissues, such as three-dimensional scaffolds containing nano-yarns or nanofiber bundles to simulate the multi-layered structure of tendons [92]. Guner *et al.* [93] fabricated a biphasic scaffold with a randomly oriented core and an oriented shell structure produced by rotary jet spinning and electrospinning. While the shell layer was conducive to cell elongation and orientation, the core layer structure provided a supportive environment for cell infiltration. These scaffolds significantly improved cell adhesion and viability. Sensini *et al.* [94] exploited high-level nylon 6,6 electrospinning assemblies with single-bundle and hierarchical combinations of nanofibers, which resembled the morphology and orientation of tendon tissues. Moreover, these scaffolds displayed strength and stiffness values comparable to tendons as well as significantly promoted tendon regeneration. Yu *et al.* [95] fabricated gradient nanofiber scaffolds for photothermal mineralization using an electrospinning setup, which underwent structural change and graded mineralization via the photothermal effect of the indocyanine green. The mineral content increased gradiently in the same direction. The TDSCs were differentiated into tenocytes and osteogenic cells in this scaffold. These gradient nanofiber scaffolds may have potential implications for tendon-bone healing applications. The Angle of simulating tendon structure to promote the repair of injured tendon tissue is one of the hot spots of current research. Although many studies have developed such scaffolds, how to make the whole scaffold oriented is still a difficult problem. For example, the combination of electrostatic spinning and yarns is common. Generally, yarns are oriented, and oriented fiber films can also be obtained by electrostatic spinning. However, how to tightly wrap oriented yarns with oriented fiber films without affecting each other's structure is a difficult problem. Secondly, if spinning on the surface of an oriented yarn, it is difficult to determine whether the spun fiber is oriented, which is an unstable factor. Future technologies need to do a lot of research to overcome this problem.

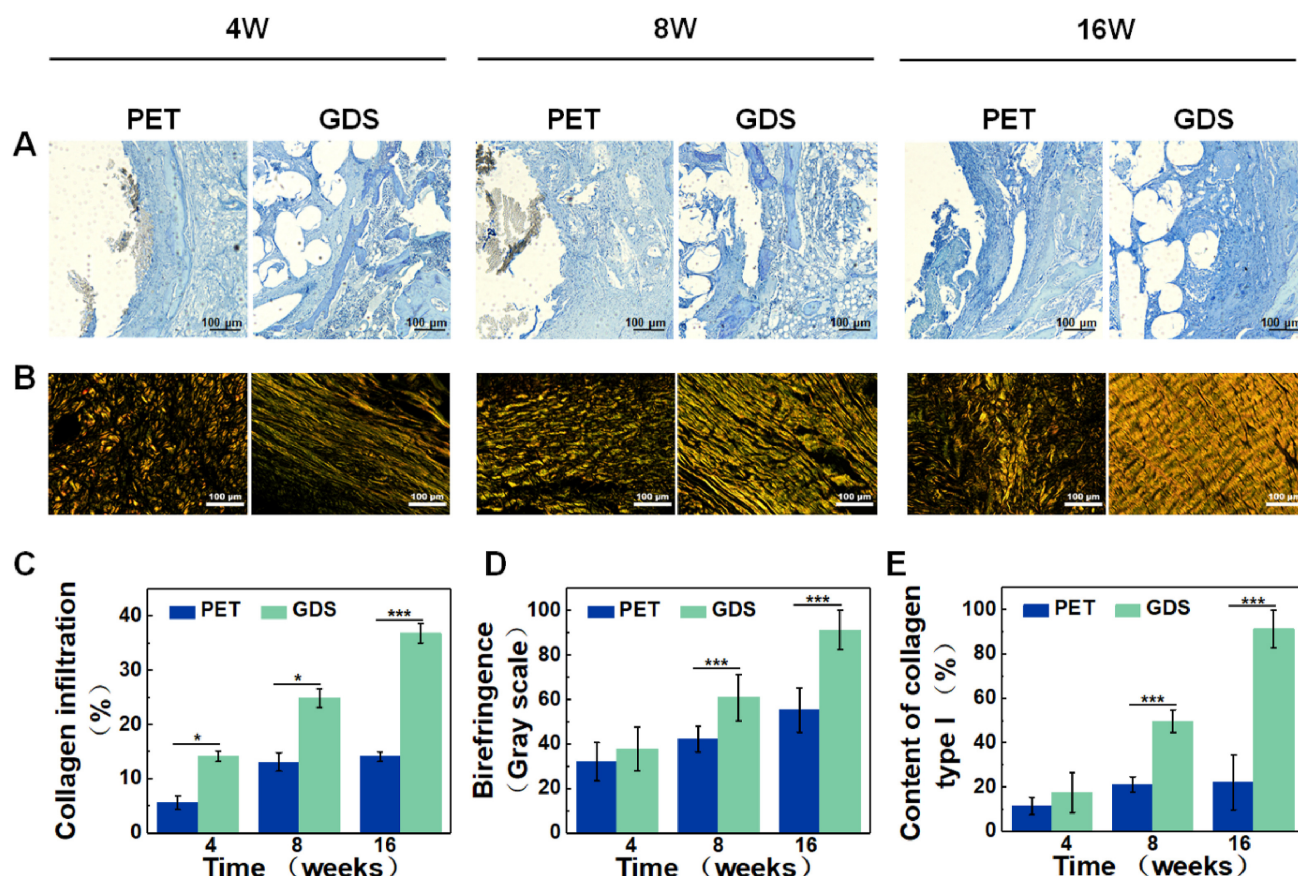
The combination of braiding technology and electrospinning technology makes the mechanical properties of the scaffolds superior to those of fibrous membranes, and the adjustable braiding parameters can further help to design customized scaffolds to meet the needs of different tendon tissues, the porous structure of the braided scaffolds is conducive to the infiltration of cells and the transport of nutrients [96]. Barber *et al.* [97] leveraged PLLA



**Fig. 6. Analysis of tendon tissue by immunofluorescence staining 4 weeks after the implantation of cell-seeded constructs.** (A–D) The production of COL1. (E–H) The production of COL3. (I–L) The production of tenomodulin (TNMD). (M–P) the production of CD31. Blue: DAPI (cell nuclei); Green: COL1/COL3/CD31; Red: TNMD. Scale bar = 100  $\mu$ m. Adhesion score and biomechanical analysis on a tendon defect model. (Q) Adhesion score in each group at 4 weeks after repair surgery. (R) Maximum Load and (S) tensile modulus in each group at 4 and 6 weeks after repair surgery. Data were mean  $\pm$  S.D. \* $p$  < 0.05 vs. ED group. ED: empty defect group. Reproduced with permission from [86].

braided nanofibrous scaffolds for tendon regeneration. The mechanical properties of the scaffold mimicked the three-phase mechanical behavior of native tendon under loading. Human mesenchymal stem cells (hMSCs) can adhere, proliferate, and elongate in a dynamic culture in an *in vitro* bioreactor. Zhao *et al.* [98] fabricated MSCs and bFGF-

loaded PLGA braided scaffolds. Once implanted into the injured tendon tissues, these scaffolds induced the high expression of tendon-related gene markers. Besides, the structural and biomechanical properties of the regenerated tendon were improved. Similarly, Xie and coworkers [99] developed a braided scaffold exhibiting dynamic mechanical



**Fig. 7. Collagen regeneration evaluation.** (A) Masson staining images, scale = 100  $\mu\text{m}$ . (B) PSR staining images, scale = 100  $\mu\text{m}$ . (C) Quantification of collagen infiltration. (D) The birefringence of collagen fibers. (E) Quantification of COL I. PET: control group. GDS: experimental group. \* $p < 0.05$ , \*\*\* $p < 0.001$ . Reproduced with permission from [99].

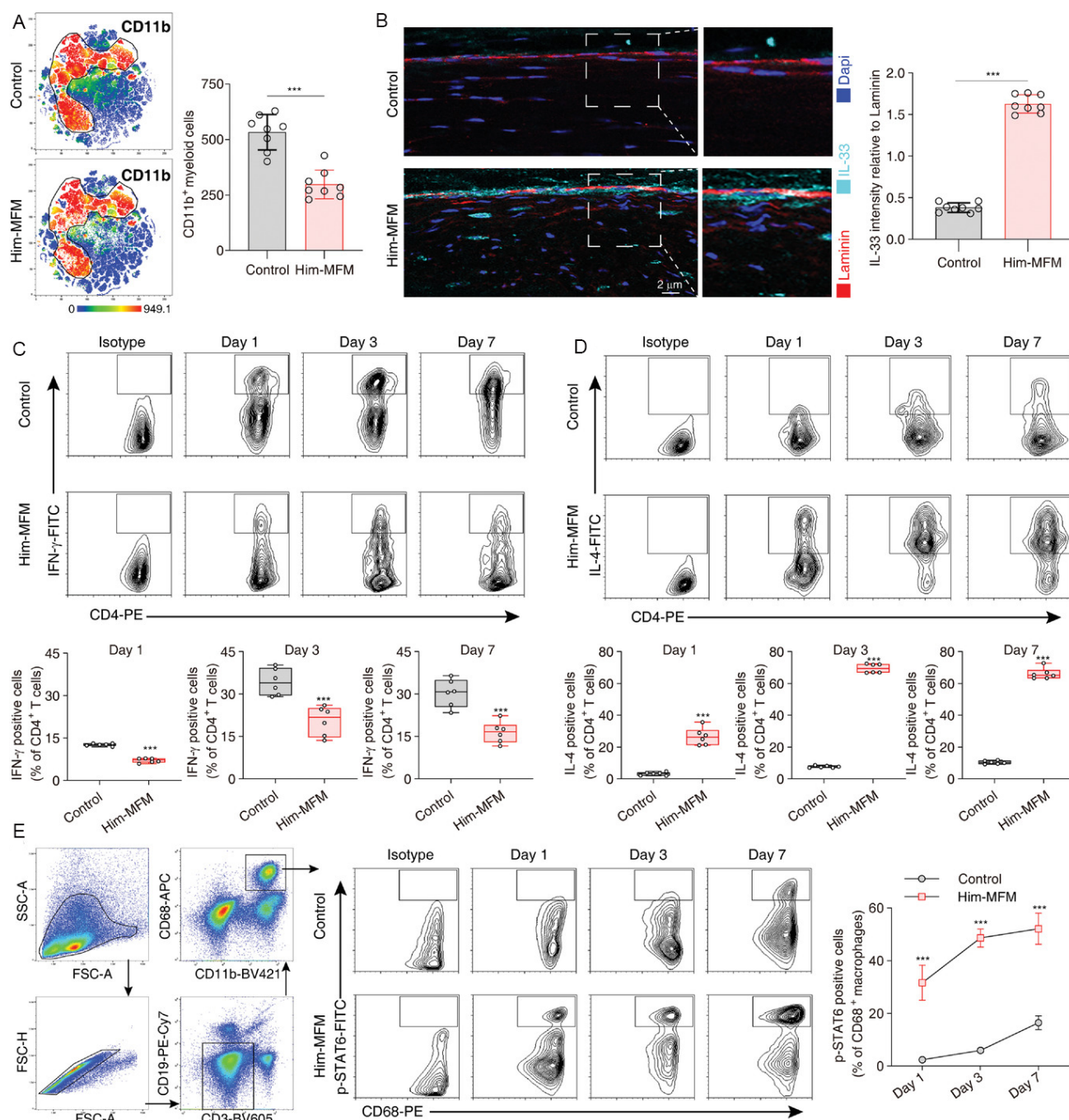
properties as well as spatial adaptability which improved collagen infiltration and remodeling. The regenerated collagen fibers showed curved-like morphology. Moreover, the maturity and structure of the deposited collagen gradually improved with the implantation time. At 16 weeks, the content of COL I was 91.35%, which was similar to that of the native ligament tissues (Fig. 7, Ref. [99]). But it is worth noting that, whether it is hand braiding or machine braiding, it is necessary to consider whether the spun fibers will fall off because of braiding, resulting in uneven distribution of fibers. Secondly, it is necessary to consider whether the braided scaffolds can be cut according to different needs, and whether they will be loose and deformed after cutting. If the scaffold is easy to lose in the process of cutting, then the utilization value is not high.

Since adhesion is a common problem after surgery, many researchers have exploited electrospun scaffolds to reduce tissue adhesion by inhibiting inflammation for tendon repair. Mao and coworkers [100] prepared a sandwich-type electrospun scaffold containing ibuprofen and reported suppressed proliferation of fibroblasts, reduced adhesion of macrophages and lower gene expression of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Wang *et al.* [101] designed a hedge-immune strategy-based microfibrillar mem-

brane namely “Him-MFM”, by electrostatically incorporating distearoyl phosphoethanolamine (DSPE)-phospholipid layer-supported electrospun PLGA nanofibers, which promoted the specific recognition of CD11b+/CD68+ from the injury-derived immune system (Fig. 8, Ref. [101]). The implantation of these scaffolds in flexor tendon injury model mice suppressed the apoptosis of tenocytes. These types of immunomodulatory scaffolds may suppress inflammatory response as well as help realize functional regeneration of the tendon tissues.

### 3.3 3D Printing

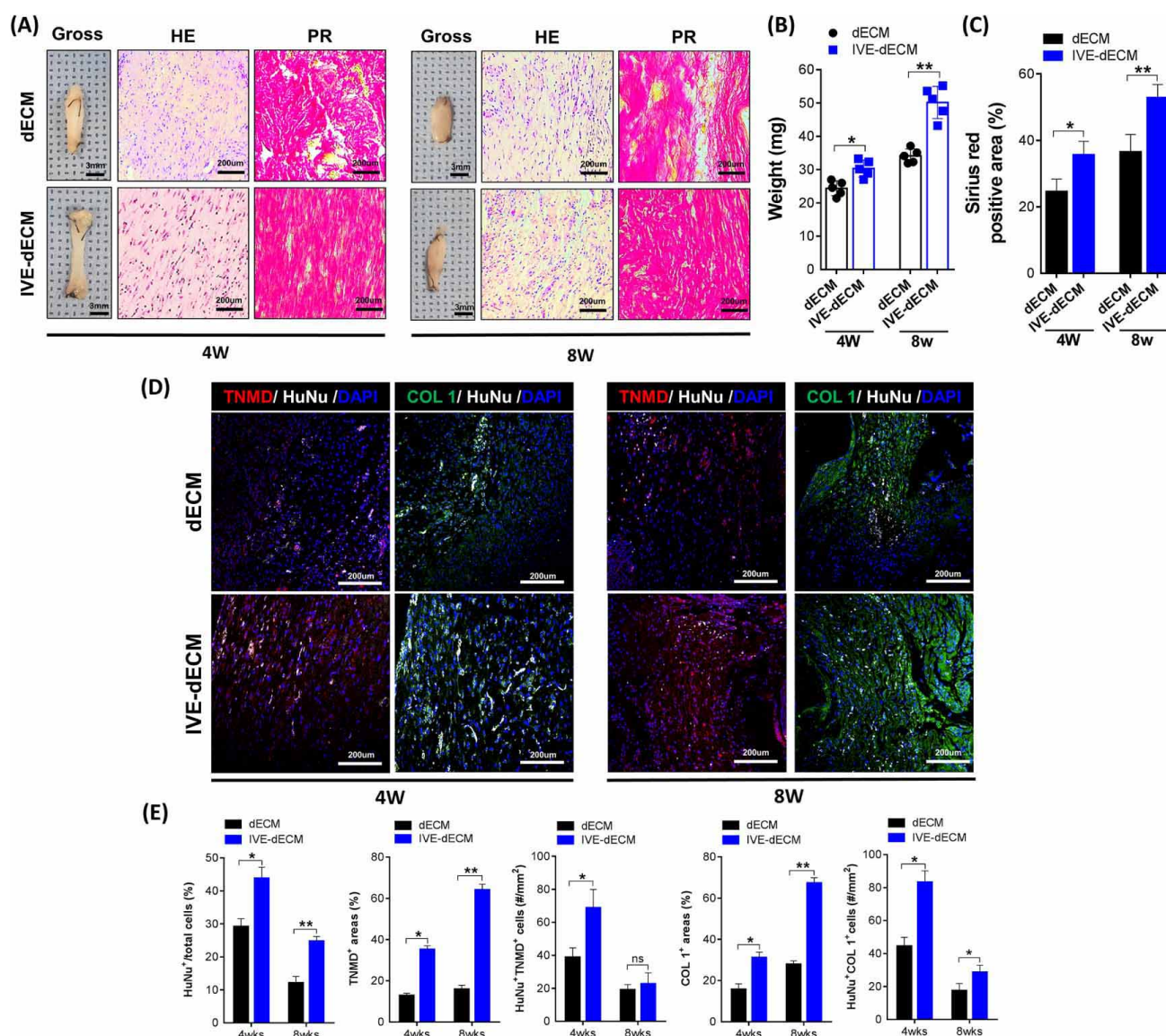
3D printing, a type of rapid prototyping technology, is also known as additive manufacturing and has emerged as an alternative method for the fabrication of tissue-engineered scaffolds [102]. 3D printing can create different types of scaffolds with precise geometrical features and pore size [103]. It can better simulate the 3D structure of the ECM and achieve high mechanical properties, and the added GFs and living cells can improve the performance of the scaffold [104,105]. Consequently, a myriad of approaches have been leveraged to fabricate 3D printed scaffolds and exploit them for tendon repair.



**Fig. 8. Him-MFM implantation activated mucous-IL-33-Th2 axis for regeneration.** (A) CD11b<sup>+</sup> immune cells in control and Him-MFM implantation mice at 3 days post-injury. (B) Representative fluorescence images of a cross-section of mouse tendon sheath at 3 day-post-injury in control or Him-MFM group. Scale bars: 2 μm. Mean fluorescence intensities of at least three independent experiments (n = 8). \*\*\*p < 0.001. (C, D) Representative images and quantification of IFN-γ positive cells (C) or IL-4 positive cells (D) from CD4<sup>+</sup> T cells in control and Him-MFM implantation mice post-injury (n = 6). \*\*\*p < 0.001. (E) Flow cytometry of CD68<sup>+</sup> macrophage (gating at left). Representative flow cytometric plots and quantification of p-STAT6 positive cells tendon tissues from control and Him-MFM implantation mice (middle and left panels), (n = 6). \*\*\*p < 0.001. Data are presented as mean ± SD. Reproduced with permission from [101].

3D printing can be combined with cells to print cell-containing scaffolds for tendon repair [106,107]. Chen *et al.* [108] fabricated 3D printed PLGA scaffolds and then seeded BM-MSCs onto them, which exhibited good bio-

compatibility, promoted collagen formation and increased collagen diameter at the tendon-bone interface, and improved the mechanical properties of regenerated tendons as well as promoted tendon-bone healing. Chae and cowork-



**Fig. 9. In vivo T/L formation following subcutaneous implantation of scaffolds in nude mice.** (A) Histological analysis using hematoxylin and eosin (H&E) and Picrosirius red (PR) staining of regenerated tendon tissues at 4 and 8 weeks postoperatively. (B) Weight of regenerated tendon tissues. (C) Quantification of PR positive area. (D,E) Immunofluorescence staining and quantitative analysis results of neo-tendon formation in regenerated tissues at 4 and 8 weeks postoperatively (scale bar = 200 μm) (ns: no significance, \* $p < 0.05$  and \*\* $p < 0.01$ ). dECM group: 3D cell-printed dECM constructs without *in vitro* preconditioning as a control. IVE-dECM group: 3D cell-printed dECM constructs with *in vitro* preconditioning for 28 days. Reproduced with permission from [109].

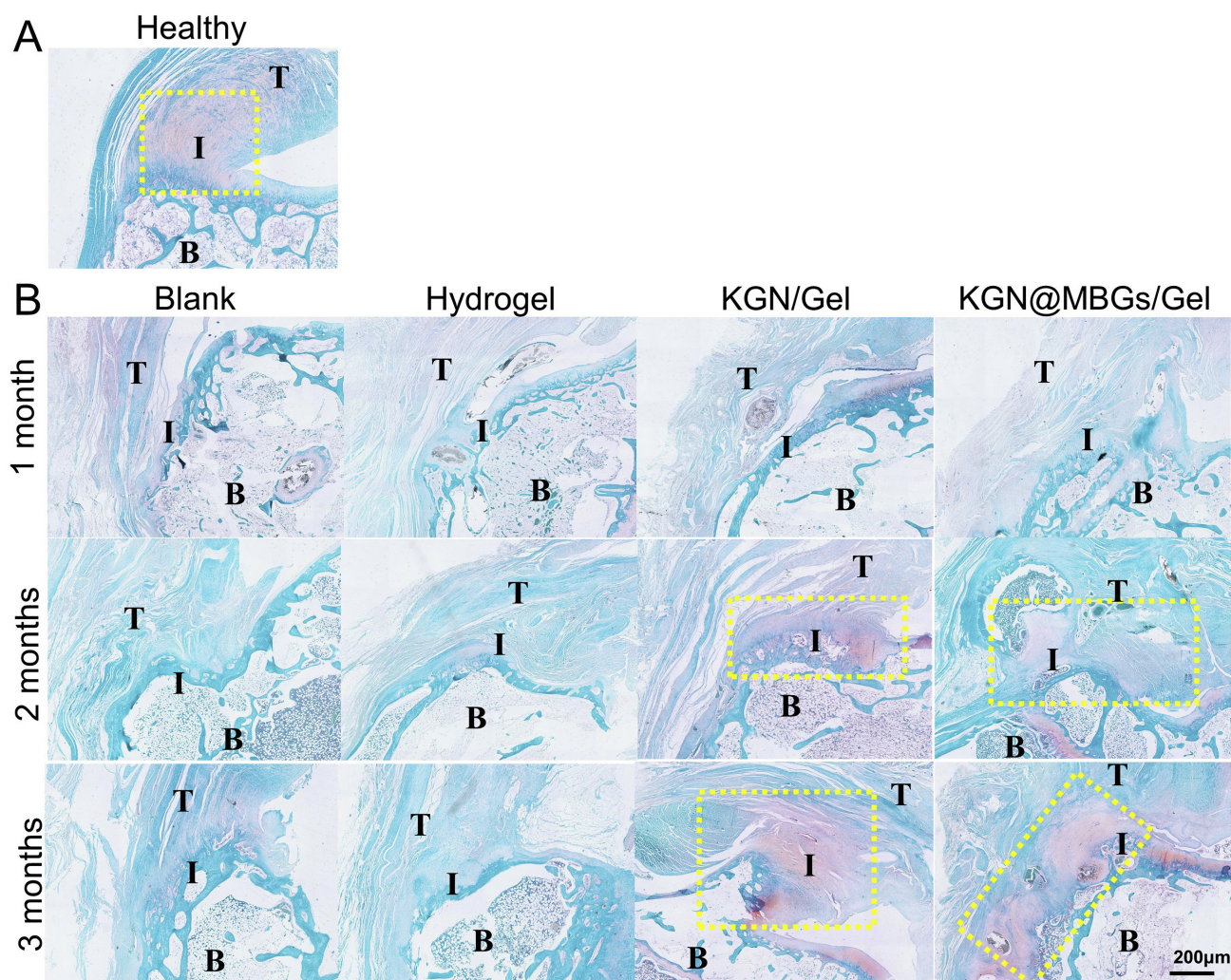
ers [109] used tissue-specific tendon or ligament-derived decellularized extracellular matrix (dECM) components and human BM-MSCs made into bioinks to fabricate 3D printed scaffolds. The pre-treatment of the scaffolds induced the formation of pre-oriented cells and structures 28 days after culture. This *in vitro* matured 3D tissue structure exhibited better regenerative capacity, promoted the formation of the new tendon as well as led to higher mechanical properties after the ectopic implantation in nude mice (Fig. 9, Ref. [109]). Although 3D printing research has become mature, it is very challenging to meet the requirements of high cell density, high cell vitality and high

resolution at the same time. Secondly, a lot of 3D printing on the market is now limited to the realization of macro printing, and the fine control of microstructure is still a difficult point. For cell-carrying printing, it is very important to establish a connection between cells by adjusting the microstructure.

### 3.4 Injectable System

#### 3.4.1 Hydrogel

Tendons are reported to be comprised of about 70% of water content. The weight-bearing collagen fibers are surrounded by a hydrated soft tissue matrix containing PG.

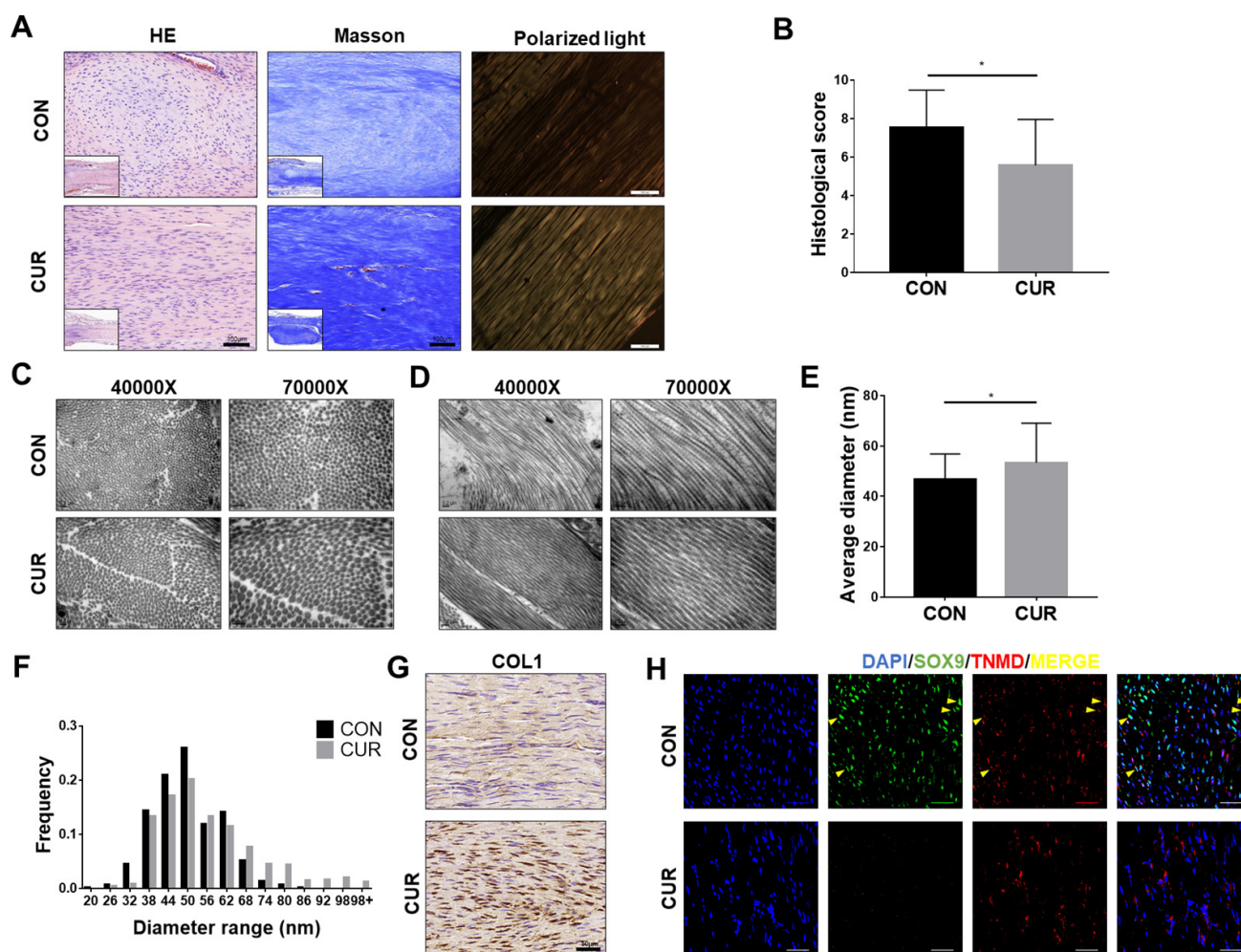


**Fig. 10. Safranin O-fast green staining results of the interface of tendon-to-bone.** (A) Healthy interface presented abundant cartilage layer (red) between tendon and bone. (B) Regeneration of cartilage layer after repair without hydrogel, or with simple hydrogel, KGN/Gel and KGN@MBGs/Gel for 1, 2 and 3 months (T = tendon; B = bone; I = interface; the yellow box labeled the fibrocartilage area). KGN, kartogenin; MBG, mesoporous bioactive glass NPs. Reproduced with permission from [117].

In addition, the soft tissue matrix allows collagen fibers to slide relative to each other further avoiding wear-related damage [110]. While hydrogels may contain a large amount of water and resemble biological tissues, they lack sufficient mechanical strength and toughness. However, tendon tissues exhibit high strength as well as excellent toughness. Consequently, to apply hydrogels for tendon tissue repair, it is necessary to remarkably tailor their production methods to improve their biomechanical properties [111,112]. Nonetheless, hydrogels, especially injectable hydrogels, can be used as drug delivery carriers due to their porous structure as well as high water content and biocompatibility, which can encapsulate bioactive molecules *in situ* and may be exploited to fill irregular defects [113]. Besides, hydrogels also possess other characteristics, such as easy production and handling, high controllability and operability [114,115]. Therefore, the improved drug-loaded and cell-loaded hydrogels are widely used in tendon tissue

repair applications.

Kim *et al.* [116] developed an injectable hydrogel containing celecoxib-loaded NPs with an obvious anti-inflammatory effect, which was shown to relieve excessive inflammation during the early stage of tissue injury, promote collagen regeneration, as well as help restore injured tendon tissues. Huang and coworkers [117] developed injectable thermosensitive hydrogels containing kartogenin and mesoporous bioactive glass NPs. These hydrogels were shown to fill tiny fissures after tendon-bone repair, which may also have good application prospects in chronic rotator cuff tears healing (Fig. 10, Ref. [117]). Xu and coworkers [118] developed an injectable fibromodulin-releasing granular hydrogel, which promoted the migration of tenocytes as well as increased the expression level of LOX in tenocytes and accelerated collagen deposition. The implantation of these hydrogels led to functional recovery in the Achilles tendon injury model in rats.



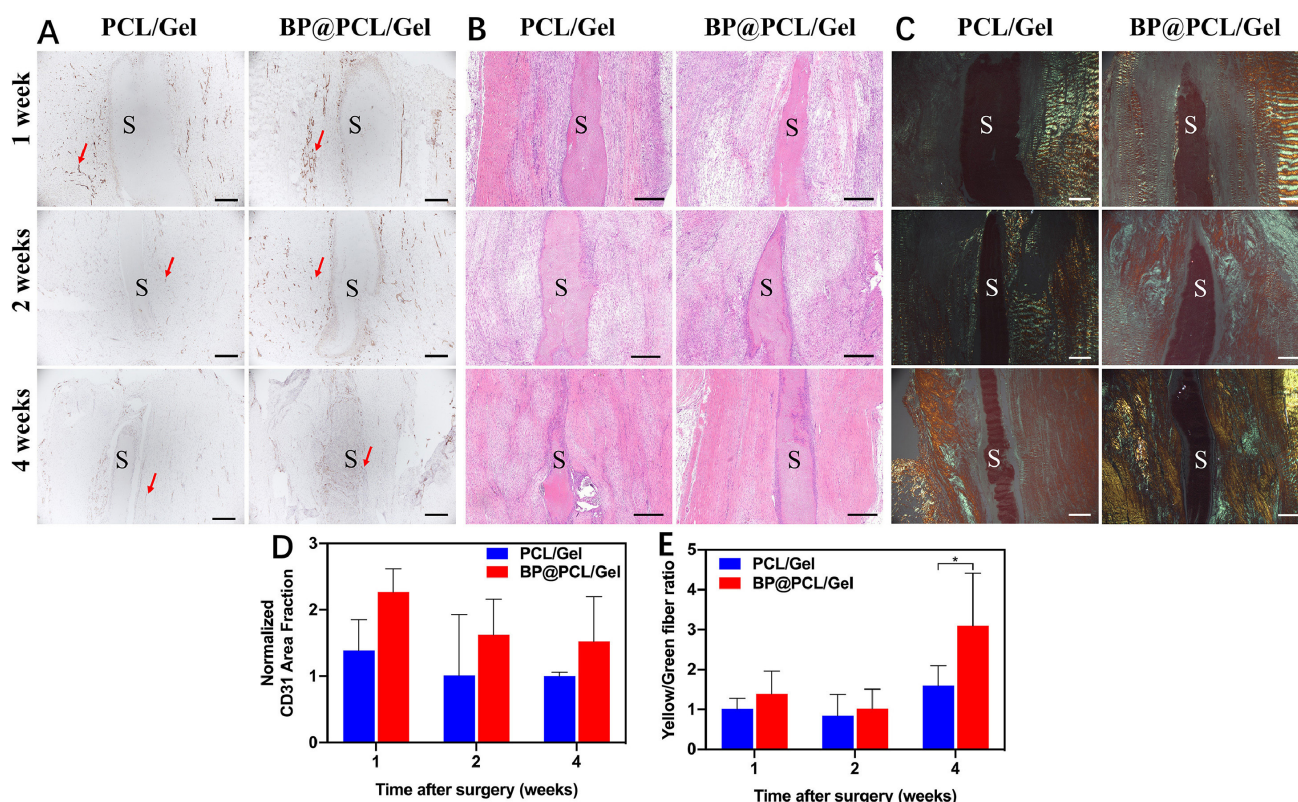
**Fig. 11. Curcumin contributes to tendon regeneration in rat tendon calcification after treatment for up to four weeks.** (A) H&E, Masson's trichrome staining, and polarized light examination of the repaired tissue in the control and curcumin groups. (B) Histological score of the repaired tendon ( $n = 5$ ),  $*p < 0.05$ . (C–F) TEM of the cross (C) and longitudinal (D) sections of collagen fibers from the repaired tendons. The average diameter (E) and diameter range distribution (F) of collagen fibers from the repaired tendons. (G) Immunohistochemical staining of COL1. Scale bar:  $50 \mu\text{m}$ . (H) Immunofluorescence of SOX9 and TNMD. Scale bar:  $50 \mu\text{m}$ . Reproduced with permission from [123].

### 3.4.2 Microspheres

Microspheres are another type of injectable system that has a good clinical prospect, especially those with interconnected pores, which may also be good delivery vehicles for drugs, proteins and cells and may also enable the sustained and long-term delivery of bioactive molecules, thus providing a minimally invasive and convenient method for delivering bioactive factors to tendon injuries [119]. The diameter of the microspheres may be further tailored in the micrometer range, which may improve drug loading rate and encapsulation efficiency, and may also prolong the retention of drugs or other cytokines at the implantation site. Consequently, microspheres are often exploited for the repair of small-scale injuries, including tendon-bone healing and tendon inflammation [120]. Microspheres can be assembled from natural polymers, such as chitosan, alginate, and gelatin, or synthetic polymers, such as PLGA

[121,122]. Chen *et al.* [123] designed curcumin-loaded chitosan microspheres, which promoted the differentiation of tendon stem/progenitor cells into tenocytes, reduced the progression of tendon ectopic calcification, and enhanced tendon regeneration (Fig. 11, Ref. [123]). Choi and coworkers [124] exploited injectable dexamethasone-loaded PLGA microspheres for Achilles tendinitis healing, which could significantly inhibit the expression of COX-2, IL-1 $\beta$ , IL-6, and TNF- $\alpha$ , and increase levels of anti-inflammatory cytokines IL-4 and IL-10. So, it can significantly reduce inflammation in the Achilles tendinitis model.

Injectable systems are currently used to fill small defects or in combination with other methods. Due to their limited mechanical properties, it is almost impossible to replace the entire tendon as a scaffold. Another issue worth noting is their limited drug encapsulation rate and the problem of drug sudden release needs to be solved.



**Fig. 12. Histopathological analysis of the regenerated patellar ligament 1, 2, and 4 weeks after the implantation of scaffolds.** Representative images of CD31 staining (A), H&E staining (B), and PSR staining (C). Quantitative analysis of CD31-positive stained area (D). Quantitative analysis of the PSR staining for the ratio of yellow fibers to green fibers (n = 3) (E). S = Scaffold. The red arrows point toward new blood vessels. \* $p < 0.05$ . Scale bar, 300  $\mu\text{m}$ . Reproduced with permission from [137].

### 3.5 Other Strategies

Besides the strategies described above, a series of bioactive cues has been leveraged for tendon healing. Platelet-rich plasma (PRP) is the plasma fraction of autologous blood that contains high concentrations of platelets and GFs, and upon activation, the PRP may release different types of GFs at the injury site, including PDGF, TGF- $\beta$ , VEGF, IGF-1, FGF, epidermal growth factor (EGF) and hepatocyte growth factor (HGF). In tendon repair, platelets are the first cells that are accumulated at the injury site and initiate tendon repair by secreting various types of cytokines and GFs. Therefore, PRP has been widely used for tendon repair applications [125,126]. The PRP increases wound healing by promoting cell proliferation and collagen production and by reducing the inflammatory response and cell apoptosis [127]. Kobayashi *et al.* [128] exploited PRP to treat patellar tendon injury in mice, and reported higher angiogenesis and collagen production. Niazi *et al.* [129] injected PRP into 30 patients for the treatment of rotator cuff tendinopathy. Finally, the Shoulder Pain and Disability Index (SPADI) were decreased, and the patients had no adverse reactions after injection. However, the application of PRP may also pose some adverse effects. Redler [130] found a patient who was diagnosed with acute patellar tendon rupture with severe tendon tissue degeneration

less than one year after continuous PRP therapy in a clinical trial. Therefore, he raised questions about the actual efficacy and safety of PRP injections in the setting of serious illness. It can be seen from this that not every materials can completely cure the injured tendon, and the possibility of subsequent problems or re-rupture exists. At present, PRP is mainly used as adjuvant therapy for surgery. In the future, researchers will need more research and discussion on PRP.

Since PRP treatment is mainly due to the contribution of GFs, the latter may also be directly combined with the biomaterials for tendon repair. Some of the typical examples of the GFs-loaded scaffolds include FGF-2 combined with hydrogel for tendon repair in chronic tears in rats [131], connective tissue-derived growth factor (CTGF)-loaded sutures to induce cell infiltration, promote angiogenesis and collagen deposition [132]. The co-culture of HGF promoted the proliferation and migration of TDSCs and inhibited osteogenic differentiation [133]. The PDGF-B improved the viability of BM-MSCs, increased the ultimate tensile strength and stiffness of tendon tissue, and promoted the expression of tendon-bone healing-related genes and proteins [134]. The TGF- $\beta$  superfamily coordinates multiple cellular behaviors, including cell adhesion, cell proliferation, cell differentiation, and collagen deposition. Of

these, TGF- $\beta$  is involved in collagen synthesis, fibrosis and scarring during tendon healing [135]. VEGF may play a crucial role in blood vessel formation in the early stages of tendon healing. The VEGF may also play an important role in low perfusion areas, such as the Achilles tendon [136]. Yuan *et al.* [137] designed nanofibrous scaffolds containing prominin-1-binding peptide by electrostatic spinning, which can promote *in situ* binding of the VEGF at the injury site. These scaffolds were shown to promote the regeneration of ligament tissue as well as the production of mature collagen fibers (Fig. 12, Ref. [137]). At present, a series of GFs are being incorporated into biomaterials to exploit the synergistic effect for tendon repair. Biomaterials are being used as carriers for GFs delivery to afford their sustained presentation at the injury site as well as preserve their bioactivity. GFs are now at a hot spot in experimental research, which can repair cell damage and accelerate tissue healing, and are often used to treat major diseases. However, it can also react on cells, control the abnormal growth of cells, lead to cell dysfunction and affect health, so the use of growth factors should be comprehensively considered in many aspects.

#### 4. Conclusions and Future Outlook

This review introduces tendon structure, biomechanical properties, repair process, and the application of scaffolds prepared by various techniques for tendon repair. Tendon is a bundle of tissue that transmit the mechanical forces from muscle to the bone without sacrificing its ability to withstand significant amounts of tension. The tendon can repair itself after a minor injury, but when it suffers a major injury, surgical transplantation has to be performed. However, no matter whether it is autologous, allogeneic transplantation, or artificial tendon transplantation, it cannot well meet the clinical needs currently. Tendon repair is a complex process, so the fabrication of scaffolds needs to fully consider all aspects, and it is crucial to mimic the tendon structure and match the mechanics of the original tendon. At present, a series of strategies such as electrospinning scaffolds, 3D printed scaffolds, hydrogels, and microspheres can be used alone or in combination with cells and GFs for tendon repair.

By summarizing the current research, we found that there are still some problems in the application of scaffolds in tendon repair. For example, most scaffolds are limited to characterization in animal experiments and cannot be used in the clinic. As we all know, the characteristics of tendons require scaffolds to have ultra-high mechanical properties, the scaffolds can be stressed without deformation, or the deformation is small and can rebound after deformation, and the loss in this process is extremely small. However, most of the scaffolds with high mechanical properties are non-degradable materials, and the mechanical properties of degradable materials are poor. Therefore, it is an urgent problem to develop degradable materials that can meet the

demands of tendon mechanics. The content of cells and blood vessels in tendon tissue is low, and scar tissue will be generated during the repair process. The process of tendon healing is accelerated along with increased angiogenesis. Therefore, promoting angiogenesis is also an important issue in tendon repair. The repair of the tendon takes a long time. After implanting the scaffold, it will be one of the key development directions that the mutual status between the scaffold and the tendon, and the regeneration of the tendon can be observed in real-time. This needs to involve many cross-cutting fields such as chemistry, materials, biology and medicine, and it is difficult to achieve this.

In the future, we believe that researchers need to pay more attention to two aspects. On the one hand, the materials and technology of scaffolds need to be comprehensively considered, to provide mechanical properties, biocompatibility, and implant safety. On the other hand, *In vivo* tendon repair involves multiple reactions, multiple mechanisms, multiple factors, and the treatment mechanism of scaffolds needs further research to ensure its effectiveness for tendon injury. It is believed that there will be ideal scaffolds for clinical application in the near future.

#### Author Contributions

Study design—XY, XM, MS, BS; Literature search and data collection—XY, JC, YS, WG, ME-N, YM; Data analysis—XY, PC, YC, ZY, ML, HE-H; Writing and original draft—XY, JC, YS; Writing and review & editing—BS, MS, XM; Funding acquisition—XM, MS, ME-N, HE-H, YM. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

#### Ethics Approval and Consent to Participate

Not applicable.

#### Acknowledgment

Not applicable.

#### Funding

This work was supported by National Natural Science Foundation of China (project # 81501606, 32050410286, and 81771951), Science and Technology Commission of Shanghai Municipality (No. 20S31900900, 20DZ2254900), Sino German Science Foundation Research Exchange Center (M-0263), and Grant-in-Aid for JSPS Fellows (Grant # JP21F21353). This project was also supported by Researchers Supporting Project Number (RSP2023R65), King Saud University, Riyadh, Saudi Arabia. MS is an international Research Fellow of the Japan Society for the Promotion of Science (Postdoctoral Fellowships for Research in Japan (Standard)).

#### Conflict of Interest

The authors declare no conflict of interest.

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