ACCSCIENCE PUBLISHING

International Journal of Bioprinting

REVIEW ARTICLE

Bioprinted biomaterials for tendon repair and regeneration: Material systems and functional strategies

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Abstract

Tendon injuries often heal slowly because of the limited vascularity, low cellularity, and low metabolic activity of native tendon tissue. Newly formed tendon tissue is frequently characterized by disorganized collagen alignment, reduced mechanical performance, and scar-like remodeling, making it difficult to restore the structure and function of native tendon. Bioprinting enables precise control over material composition, spatial architecture, fiber orientation, and the distribution of cells and bioactive components, thereby providing a promising strategy for functional tendon regeneration. However, tendon is a highly load-bearing and anisotropic tissue, whereas most hydrogel-based bioinks, despite their favorable cytocompatibility and cell-loading capacity, often remain biomechanically weak, with insufficient tensile strength, limited fatigue stability, and inadequate long-term shape fidelity, making them insufficient to independently meet the biomechanical requirements of tendon repair. This review summarizes natural and modified natural bioinks, synthetic reinforcing materials, printed load-bearing frameworks, and inorganic or ion-releasing functional components for tendon bioprinting, with emphasis on printability, biocompatibility, mechanical reinforcement, degradation behavior, and structural stability. We further discuss functional strategies involving structural and topographical modulation, bioactive molecule delivery, immunomodulatory regulation, physical stimulation, and smart responsiveness. Future studies should prioritize multi-material cooperative printing, tendon–bone interface gradient construction, responsive bioink development, long-term *in vivo* functional evaluation, and translational validation to advance tendon bioprinting materials toward functional regenerative applications.

Keywords: Bioprinting; Tendon repair; Bioink; Functionalized scaffolds; Immunomodulation

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Citation: Gao L, Zhang J, Zhao X, *et al*. Bioprinted biomaterials for tendon repair and regeneration: Material systems and functional strategies. *Int J Bioprint*. 2026;12(4):026200189.
doi: 10.36922/IJB026200189

Received: May 13, 2026

Revised: June 21, 2026

Accepted: July 1, 2026

Published online: July 2, 2026

1. Introduction

Tendons are dense connective tissues that connect muscles to bones and play essential roles in force transmission, joint stability, and coordinated movement.[1] Acute trauma, excessive exercise, chronic overuse, and age-related degeneration can all lead to tendon injuries, resulting in pain, restricted mobility, and functional impairment.[2] Current

treatments, including conservative management, suture repair, autograft or allograft reconstruction, and artificial material-assisted repair, remain unable to simultaneously address large-defect regeneration, restoration of mechanical function, donor-site morbidity, immune rejection, and insufficient long-term integration.[3] This limitation is closely related to the unique structural and biological characteristics of native tendon. Native tendons rely on highly aligned type I collagen fibers and hierarchical architectures to achieve efficient stress transmission. After injury, however, newly formed tissue is mainly characterized by rapid deposition of type III collagen, accompanied by disorganized alignment, insufficient crosslinking, and reduced mechanical performance. In addition, the limited vascularity, low cellularity, and low metabolic activity of tendon tissue further restrict cell recruitment and matrix reconstruction, making the repair process more prone to scar-like remodeling rather than functional regeneration.[4,5] Therefore, materials for tendon repair need not only to fill tissue defects but also to provide regulatory conditions closer to those of native tendon in terms of structural alignment, mechanical support, cellular microenvironment, and matrix reconstruction, which provides an important rationale for introducing bioprinting material design into tendon repair.

Tendon repair is not merely a process of defect filling, but rather a coordinated continuum involving inflammatory initiation, cell recruitment, matrix deposition, and collagen remodeling.[6] Early inflammation contributes to the clearance of necrotic tissue. However, if the classically activated pro-inflammatory M1 macrophage response persists, sustained elevation of pro-inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) may exacerbate matrix degradation, adhesion formation, and scar remodeling. In contrast, a timely alternatively activated reparative M2 macrophage response can promote the resolution of inflammation, angiogenesis, and collagen reconstruction through factors such as interleukin-10 (IL-10), vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), and insulin-like growth factor-1 (IGF-1).[7,8] However, excessive or persistent M2 polarization may also promote fibrotic matrix deposition and scar-like remodeling, indicating that immunomodulatory materials should regulate macrophage responses in a time-dependent manner rather than simply enhancing M2 polarization. During the proliferative and remodeling phases, tenocytes, tendon stem/progenitor cells (TSPCs), and mesenchymal stem cells (MSCs) participate in cell migration, tenogenic differentiation, and matrix deposition.[9-11] Therefore, ideal materials should be designed according to stage-specific repair requirements, with the capacity to regulate inflammation, support directional cell alignment, promote organized type I collagen deposition, and guide the repair tissue toward a mechanically organized structure resembling native tendon.[12] For bioprinting materials, this means that material composition, spatial architecture, cell distribution, and bioactive component delivery need to be co-designed rather than merely serving as passive defect-filling scaffolds.

Against this background, bioprinting provides a designable approach for constructing materials for tendon repair.[13] Compared with conventional scaffolds, bioprinting enables precise control over material composition, pore architecture, fiber orientation, mechanical gradients, and the spatial distribution of cells and bioactive components, making it particularly suitable for recapitulating the anisotropic and hierarchical structures of native tendon.[14] Natural or modified natural materials, such as collagen, gelatin methacryloyl (GelMA), alginate, hyaluronic acid (HA), silk fibroin, and tendon-derived decellularized extracellular matrix (dECM), can serve as cell-laden bioinks or printable hydrogel matrices, providing microenvironments for cell adhesion, bioactive delivery, and local matrix mimicry. Synthetic materials, including polycaprolactone (PCL), poly(lactic-co-glycolic acid) (PLGA), poly(lactide-co-caprolactone) (PLCL), and polyethylene glycol (PEG) diacrylate (PEGDA), are more suitable as printed load-bearing frameworks, structural reinforcing phases, or tunable crosslinked networks, thereby compensating for the insufficient mechanical support and long-term shape retention of single hydrogel-based bioinks. Bioactive glass, molybdenum-containing silicate bioceramics, and related ion-releasing functional components can further act as functional additives in printable composite systems or post-printing regulatory modules, contributing to immunomodulation, angiogenesis, interfacial mineralization, and stage-specific responsive regulation.[15-17] Accordingly, the value of bioprinting materials is no longer limited to defect filling, but lies in integrating structural design, bioactive delivery, immunomodulatory and inflammatory regulation, physical stimulation, and smart responsiveness into a comprehensive platform for functional tendon regeneration.[18] Based on this perspective, this review summarizes the tendon repair process, the fundamental requirements of bioprinting materials, major material systems, and functionalization strategies for tendon repair.

This article is a narrative review that aims to provide a thematic integration of bioprinted material systems and functionalization strategies for tendon repair and regeneration. Relevant studies were mainly identified through searches of PubMed, Web of Science, and Scopus,

supplemented by checking the reference lists of included articles. The search terms included "tendon repair," "tendon regeneration," "tendon injury," "bioprinting," "3D bioprinting," "bioink," "hydrogel," "tendon-derived extracellular matrix," "polycaprolactone," "tendon–bone interface," "immunomodulation," "mechanical stimulation," and "smart responsive biomaterials." The literature selection focused on representative bioprinting-related studies relevant to tendon or tendon–bone interface repair, including bioinks, printed scaffold architectures, cell-laden printed constructs, and post-printing functionalization strategies. Studies not directly using bioprinting were discussed only when they were closely related to tendon repair material design and provided clear design-relevant evidence for printable material systems, such as rheological regulation, mechanical reinforcement, degradation control, immunomodulatory microenvironment regulation, bioactive molecule delivery, physical stimulation responsiveness, or interfacial functionalization. Studies with limited relevance to tendon repair or printable material design, reports lacking key experimental information, and conference abstracts without sufficient methodological details were not emphasized in this review.

Unlike previous reviews that mainly focused on tendon tissue engineering scaffolds, general bioink development, or broad applications of three-dimensional (3D) bioprinting, this review emphasizes a stage-specific, function-oriented framework for tendon bioprinting. The main contribution of this review is to integrate the stage-specific requirements of tendon repair, the functional roles of different material systems, and major functionalization strategies within a unified bioprinting design framework. Rather than simply listing materials according to their source or isolated biological effects, we discuss how natural and modified natural bioinks, synthetic reinforcing materials, printed load-bearing frameworks, and ion-releasing functional components can serve as bioink matrices, mechanical-supporting phases, functional additives, delivery modules, or regulatory units for tendon and tendon–bone interface repair. By linking material selection to printability, mechanical evaluation, phase-specific regulation, and translational challenges, this review aims to provide a practical design reference for selecting, combining, and functionally optimizing bioprinted materials for tendon repair.

2. Tendon repair process

Tendon injuries are commonly caused by acute mechanical stress, direct trauma, or chronic overload, which can disrupt collagen fiber continuity, alignment, and local mechanical transmission.[19,20] Native tendon is hierarchically assembled from collagen fibrils, collagen fibers, fascicles, and the whole tendon, and its highly aligned and hierarchical structure provides the basis for tensile strength and stress transmission (Figure 1A), also serving as an important biomimetic reference for aligned architecture construction, hierarchical pore design, and mechanical reinforcement in bioprinted scaffolds. After injury, tendon repair can be divided into intrinsic and extrinsic healing: the former mainly depends on cells from the tendon substance and endotenon and is associated with relatively better tissue integration and mechanical recovery; the latter relies more on cells from the tendon sheath and circulation and may accelerate defect filling, but is more likely to be accompanied by persistent inflammation, adhesion formation, and scar-like remodeling.[21,22] Regardless of the healing mode, tendon repair usually involves three interconnected and partially overlapping phases: inflammation, proliferation, and remodeling.[23] The inflammatory phase is mainly characterized by neutrophil and macrophage recruitment and the clearance of necrotic tissue and matrix debris, suggesting that early printed constructs should not only stabilize the defect area but also support cell protection and local immune microenvironment regulation; the proliferative phase is accompanied by gradual inflammation resolution, during which macrophages release anti-inflammatory factors and growth factors to promote the proliferation and differentiation of tendon-resident TSPCs and tendon-related cells as well as new ECM deposition, thereby requiring bioinks to provide cell-loading capacity, pore interconnectivity, bioactive component delivery, and early matrix-guiding functions; during the remodeling phase, inflammatory cells gradually decrease, collagen fibers become rearranged and progressively mature, and the repair tissue transitions toward a more organized mechanical structure, which further requires printed scaffolds to maintain aligned architecture and mechanical support during degradation and to promote collagen reorganization along the loading direction (Figure 1B). Therefore, clarifying the main tasks of each phase helps shift bioprinting material design from simple defect filling toward multidimensional goals, including printability, shape retention, structural support, immunomodulation, bioactive delivery, spatial cell distribution, and functional recovery.[24,25]

2.1. Inflammatory phase

Chisari *et al.*[7] noted that the inflammatory phase is the earliest phase initiated after tendon injury, with the central task of clearing necrotic tissue and establishing an early microenvironment required for subsequent regeneration. After injury, platelets release factors such as platelet-derived growth factor (PDGF), TGF-β, and VEGF, thereby

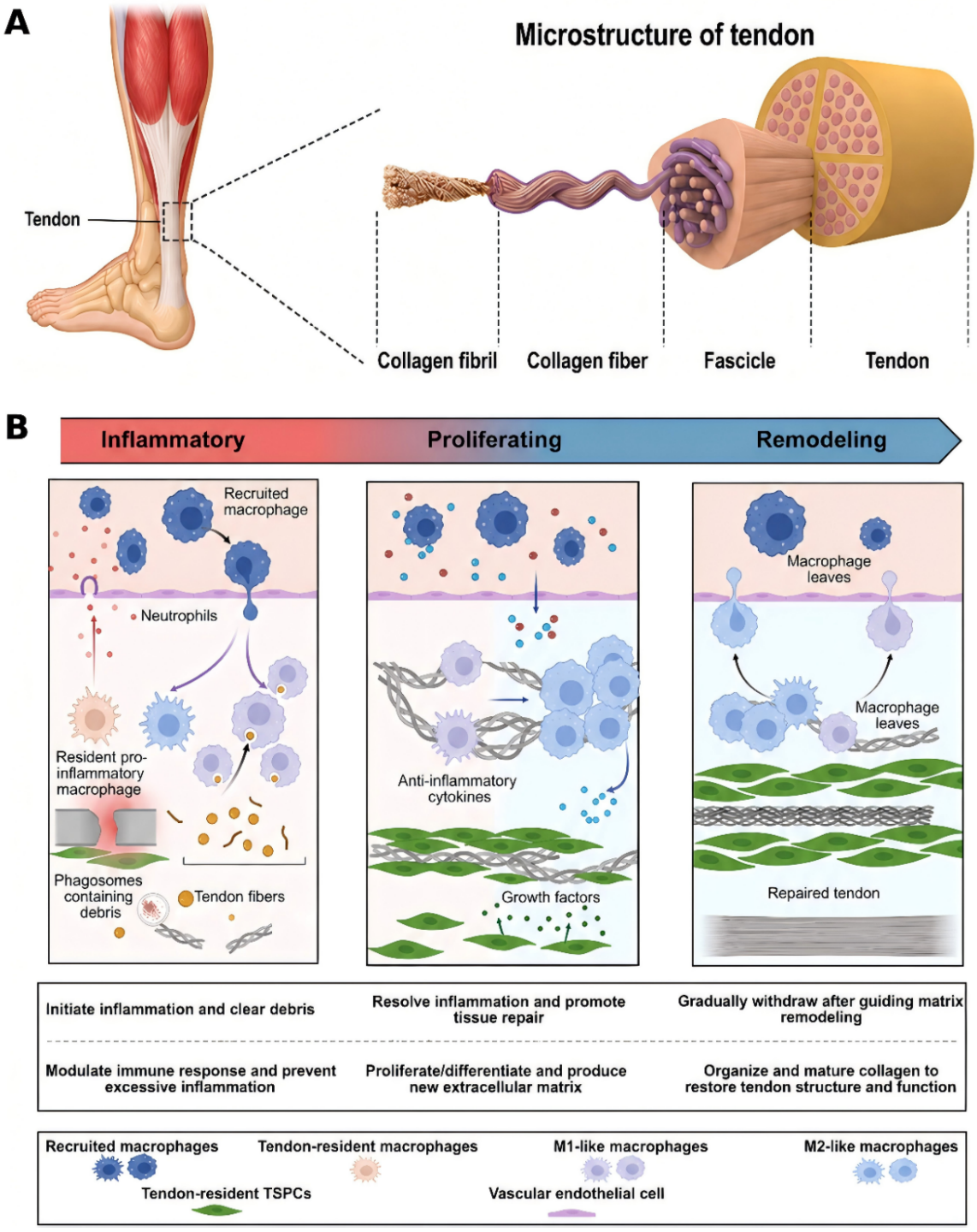

Figure 1. Hierarchical structure of tendon and repair process after injury. (A) Tendon is hierarchically assembled from collagen fibrils, collagen fibers, and fascicles to the whole tendon, forming a highly ordered hierarchical structure. (B) After injury, tendon repair sequentially proceeds through the inflammatory, proliferative, and remodeling phases. The inflammatory phase is mainly characterized by immune cell recruitment, transendothelial migration across vascular endothelial cells, and debris clearance; the proliferative phase is characterized by inflammation resolution, repair-associated macrophage activity, proliferation/differentiation of tendon-resident tendon stem/progenitor cells (TSPCs), and increased extracellular matrix (ECM) production; and during the remodeling phase, macrophage infiltration gradually decreases, while the collagen matrix becomes aligned and mature, contributing to the restoration of tendon structure and function. Created in BioRender. Qing, H. (2026) https://BioRender.com/9h0lbvd

increasing vascular permeability, promoting immune cell recruitment, and initiating the repair response.[26,27] Damage-associated molecular patterns released from injured tissues further amplify inflammation.[28] Darrieutort-Laffite *et al.*[5] reported that IL-1β and IL-6 are markedly elevated at the early stage, during which neutrophils and macrophages participate in tissue clearance. Wang *et al.*[8] emphasized that a persistent and excessive M1 response may increase TNF-α, IL-1β, IL-6, and matrix metalloproteinases, thereby inducing matrix degradation and fibrosis.[8,29] In contrast, an M2 response established within an appropriate time window is conducive to the resolution of inflammation, angiogenesis, and matrix reconstruction,[30] although excessive or persistent M2 polarization may also promote fibrotic matrix deposition and scar-like remodeling. Therefore, the inflammatory phase does not imply that material design should simply pursue anti-inflammatory effects; rather, it requires bioprinting materials to balance early defect stabilization, cell protection, and regulation of the local immune microenvironment. By modulating bioink composition, interfacial architecture, degradation behavior, and local release of immunomodulatory ions or factors, printed constructs may provide early structural support while limiting excessive pro-inflammatory responses and guiding the immune response from clearance toward repair.[31]

2.2. Proliferative phase

As inflammation is controlled, tendon repair enters the proliferative phase, which is characterized primarily by cell proliferation, angiogenesis, and matrix deposition.[23,24] Darrieutort-Laffite *et al.*[5] noted that TGF-β, basic fibroblast growth factor (bFGF), PDGF, VEGF, and IGF-1 collectively contribute to the migration of fibroblasts and tendon-related cells, vascular formation, and ECM deposition. Wang *et al.*[26] and Docheva *et al.*[32] also considered these factors to constitute a key growth factor network in tendon repair. Maffulli *et al.*[33] reported that tenocytes from ruptured and tendinopathic Achilles tendons produce greater quantities of type III collagen than those from normal Achilles tendons, suggesting that type III collagen is involved in tendon injury- and repair-related matrix remodeling. Lu *et al.*[10] and Huang *et al.*[34] further emphasized that TSPCs participate in cell proliferation, migration, and collagen production. These features suggest that materials designed for the proliferative phase should not merely fill defects but should also provide a suitable spatial microenvironment for cell migration, vascular ingrowth, early matrix deposition, and tenogenic induction. Therefore, in tendon bioprinting, scaffolds designed for the proliferative phase need to integrate cell-friendly bioinks, interconnected pore architectures, aligned printed strands, and region-specific bioactive signal delivery, thereby promoting directional cell alignment, vascular support, and formation of a tenogenic microenvironment through both structural guidance and signals such as PDGF, bFGF, VEGF, and IGF-1.[26,32]

2.3. Remodeling phase

The remodeling phase is a critical stage during which tendon repair shifts from early tissue restoration toward long-term functional recovery.[19,23] Maffulli *et al.*[33] also showed increased type III collagen production by tenocytes from ruptured and tendinopathic Achilles tendons, indicating that repair-associated collagen remodeling differs from the organized collagen matrix of normal tendon. Darrieutort-Laffite *et al.*[5] suggested that the remodeling phase usually begins approximately four weeks after injury and continues until repair is completed, with ECM reorganization and optimization of collagen alignment as its core processes. Previous studies have shown that mechanical loading influences tendon repair throughout the healing process. Appropriate tensile loading facilitates collagen reorganization along the direction of force, whereas insufficient or abnormal loading may lead to structural disorder.[35,36] Therefore, material design during the remodeling phase should not remain limited to early defect filling or initial strength, but should maintain appropriate structural continuity and load transmission as the newly formed matrix gradually matures. For bioprinted scaffolds, aligned printing paths, anisotropic pore architectures, and mechanically reinforced frameworks can provide structural guidance for collagen reorganization along the loading direction; meanwhile, material degradation should be coordinated with new tissue formation to avoid premature loss of support or prolonged interference with matrix remodeling, thereby supporting organized type I collagen reconstruction and functional recovery.[25,35]

Taken together, tendon repair involves overlapping inflammatory, proliferative, and remodeling phases, each of which imposes distinct requirements on the design of bioprinting materials. Early printed constructs should stabilize the defect microenvironment and regulate excessive inflammatory responses; proliferative-stage printed constructs should support cell loading, migration, angiogenesis, and early tenogenic matrix formation; and remodeling-stage printed constructs should maintain structural continuity, match material degradation to tissue maturation, and promote collagen alignment and mechanical functional recovery. The phase-specific design goals, material strategies, functional cues, and evaluation indicators for tendon bioprinting are summarized in Table 1.

Table 1. Phase-specific bioprinting design framework for tendon repair

Repair phase	Design goal	Material strategy	Functional cues	Evaluation indicators	References
Inflammatory phase	Stabilize the early defect microenvironment, protect cells, limit excessive pro-inflammatory responses, and guide the transition from inflammatory clearance to reparative remodeling rather than simply suppressing inflammation	Immunomodulatory hydrogels; hyaluronic acid-, decellularized extracellular matrix (dECM)-, gelatin methacryloyl (GelMA)-, or alginate-based composite bioinks; reactive oxygen species (ROS)- or pH-responsive delivery systems; ion-releasing or anti-inflammatory functional components	Interleukin-10 (IL-10) and other anti-inflammatory signals; regulation of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and ROS; macrophage phenotype modulation from excessive M1 activation toward a balanced reparative response	TNF-α, IL-1β, IL-6, and ROS levels; CD86 or inducible nitric oxide synthase; CD206 or arginase-1; macrophage infiltration; early matrix degradation; local inflammatory microenvironment	[5,7,8,24,25,28-31]
Proliferative phase	Support cell loading, migration, proliferation, angiogenesis, early extracellular matrix deposition, and tenogenic induction while maintaining printed construct stability	Cell-friendly bioinks, including collagen, GelMA, alginate, and tendon-derived dECM; interconnected pores; aligned strands; polycaprolactone (PCL) or poly(lactic-co-glycolic acid) (PLGA) frameworks; and region-specific delivery systems	Platelet-derived growth factor, basic fibroblast growth factor, vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), growth differentiation factor-7, and exosome-related bioactive signals; structural guidance for directional cell alignment and vascular support	Cell viability and proliferation; TSPCs/MSCs migration; tenogenic marker expression (SCX, TNMD, COL1, and COL3); angiogenic indicators (CD31 or VEGF); collagen deposition, cell alignment, and early tenogenic matrix formation	[5,10,23,24,26,32-34]
Remodeling phase	Maintain long-term structural continuity and load transfer, match material degradation with tissue maturation, promote collagen alignment and type I collagen-dominant matrix remodeling, and support functional recovery	Aligned printing paths; anisotropic pore structures; multi-material cooperative printing; PCL-, PLGA-, or poly(lactide-co-caprolactone)-based load-bearing frameworks; dECM-containing composite systems; mechanically responsive or multi-stimuli-responsive materials	Mechanical loading or mechanoresponsive cues; structural anisotropy; degradation-matched support; physical stimulation or responsive regulation to promote collagen organization and matrix maturation	Tensile strength, elastic modulus, ultimate load, fatigue resistance, and suture retention strength; type I collagen to type III collagen ratio; collagen alignment; gliding resistance; adhesion score; mechanical recovery and functional outcome	[5,19,23,25,33,35,36]

Abbreviations: COL1: Type I collagen; COL3: Type III collagen; MSCs: Mesenchymal stem cells; SCX: Scleraxis; TNMD: Tenomodulin; TSPCs: Tendon stem/progenitor cells.

3. Fundamental requirements of bioprinting materials for tendon repair

Bioprinting materials for tendon repair must not only meet the requirements for printability and shape formation but also adapt to the tendon's tissue environment, which is characterized by high alignment, long-term mechanical loading, and limited regenerative capacity.[37,38] Therefore, material evaluation should not be restricted to formability alone, but should also consider printability,

biocompatibility, mechanical matching, degradation behavior, and structural stability.[39] Ideally, these materials should enable controllable fabrication while supporting directional cell alignment, matrix deposition, and tissue integration.[12,25]

3.1. Printability

Printability is a fundamental requirement for bioprinting materials.[40] For extrusion-based printing, materials should exhibit appropriate viscosity, shear-thinning behavior, yield stress, and elastic recovery, allowing them to flow smoothly through the nozzle and rapidly recover after extrusion to maintain the printed structure.[41,42] Hull *et al.*[43] summarized the key rheological characteristics of cell-laden hydrogel bioinks, including shear storage/loss moduli (G'/G"), yield stress, shear-thinning behavior, and post-shear structural recovery. Together, these parameters determine the printability and shape fidelity of extrusion-based bioprinting (Figure 2A).[43] Excessively low viscosity can lead to scaffold collapse and blurred boundaries, whereas excessively high viscosity increases extrusion pressure and may damage encapsulated cells.[44] For tendon scaffolds, materials should also possess adequate layer-by-layer stacking ability and shape retention, as unstable construct formation may compromise subsequent cell alignment and matrix reconstruction.[45]

3.2. Biocompatibility

Materials should support cell survival, adhesion, migration, proliferation, and differentiation while minimizing cytotoxicity, adverse or excessive foreign-body responses, and excessive inflammation.[46,47] For cell-laden printing systems, extrusion pressure, nozzle-induced shear stress, tensile/extensional stress, crosslinking conditions, and light intensity should also be carefully controlled to reduce the adverse effects of the printing process on cell membrane integrity and cellular function, thereby maintaining cell viability during printing.[48,49] Hull *et al.*[43] further noted that appropriate yield stress helps maintain a homogeneous cell suspension and reduce cell sedimentation, whereas shear-thinning behavior and plug-like flow can decrease shear and tensile damage to cells during extrusion, thereby improving the printing safety of cell-laden bioinks (Figure 2B). For tendon repair, materials should not only support cell growth, but also facilitate host cell recruitment, local inflammatory regulation, and integration of newly formed tissue.

3.3. Mechanical matching

Tendons are subjected to long-term tensile loading. Zhu *et al.*[50] divided the stress–strain response of the Achilles tendon during tensile loading into the toe region, linear region, yield region, and failure region, reflecting the progressive mechanical response of the tendon matrix, including collagen fiber uncrimping, fiber alignment, interfibrillar sliding, disruption of matrix or fibril interactions, and eventual tissue-level failure (Figure 2C). Therefore, materials that are too soft may fail to provide sufficient support for the defect area, whereas excessively stiff materials may impair tissue compliance and cellular mechanosensing.[35,36] An ideal scaffold should maintain mechanical continuity during the early repair stage and gradually transfer load as the newly formed matrix develops.[25,51] Jiang *et al.*[52] constructed 3D-printed multilayered PLGA scaffolds combined with collagen–fibrin hydrogels. In their study, tensile properties were evaluated by uniaxial tensile testing and force–strain curve analysis. Compared with single-layered PLGA scaffolds, the multilayered printed structures showed higher elastic stiffness and ultimate force, indicating enhanced tensile stiffness and load-bearing capacity. These findings suggest that layered structural design may improve the compatibility between the scaffold and the tensile loading environment of tendon repair by enhancing tensile support, ultimate load-bearing capacity, structural stability, and load transfer, rather than simply increasing material strength.[52] For oriented tendon scaffolds, materials should not only possess sufficient strength and fatigue stability, but also support cell alignment along the loading direction and promote organized collagen deposition.

3.4. Degradation behavior and structural stability

Material degradation should match the temporal progression of tendon repair. Excessively rapid degradation may cause the scaffold to lose support before newly formed tissue matures, whereas excessively slow degradation may hinder tissue integration and induce persistent inflammation.[53,54] After printing, materials usually require further crosslinking or solidification to maintain shape and enhance structural stability. Common strategies include thermally induced crosslinking, spray crosslinking, crosslinking baths, pre-crosslinking, and photocrosslinking.[48,55] Ionic crosslinking, photocrosslinking, and chemical crosslinking each have distinct advantages and limitations; therefore, practical material design should balance cell safety, shape maintenance, mechanical support, and degradation rate.

3.5. Mechanical evaluation and functional outcome assessment

Because tendon is a mechanically loaded and anisotropic tissue, evaluation of tendon bioprinting scaffolds should extend beyond cell viability, tenogenic marker expression, and histological appearance. Mechanical testing is needed to determine whether printed constructs can provide early

support, maintain structural continuity, and transfer load during matrix remodeling. Commonly used parameters include tensile strength, elastic modulus, ultimate load or failure load, failure strain, fatigue resistance, and failure mode, which together reflect load-bearing capacity, deformation behavior, and structural stability under repeated loading.[50,52,56]

For surgically implanted scaffolds, suture retention strength is also important because it reflects fixation stability and resistance to early postoperative loading. For flexor tendons and other adhesion-prone sites, gliding resistance, tendon excursion, adhesion score, and range of motion should be considered, as excessive friction or adhesion may impair tendon sliding despite favorable histological repair. *In vivo* studies should further combine explant mechanical testing with functional assessments, including gait analysis, weight-bearing behavior, grip strength, joint range of motion, and gross motor recovery. These outcome measures help connect scaffold architecture, degradation behavior, and mechanical performance with clinically meaningful tendon repair.[25,35,56]

Overall, the fundamental requirements of bioprinting materials for tendon repair do not lie in maximizing any single property, but rather in achieving a coordinated balance among printability, biocompatibility, mechanical matching, degradation behavior, and structural stability.[38,39] Only when this foundation is established can subsequent functionalization strategies, including structural optimization, bioactive delivery, immunomodulation, physical stimulation, and smart responsiveness, become practically meaningful.[12,24]

4. Bioprinting material systems for tendon repair

Tendon tissue is highly aligned, mechanically anisotropic, and limited in regenerative capacity. Therefore, bioprinting materials should simultaneously provide biomimetic properties, mechanical support, cytocompatibility, and repair-regulating capability.[16,56] Natural biomaterials are better suited to providing cell-adhesive sites and biological signals, whereas synthetic biomaterials are more commonly used as load-bearing frameworks and structural platforms. Inorganic ions are mainly incorporated to enhance functions such as immunomodulation, angiogenesis, interfacial integration, and matrix maturation.[14,56] Accordingly, the focus of material design has shifted from the use of single materials toward multi-material synergy.[14,16]

4.1. Natural biomaterials for bioprinting

Natural biomaterials generally more closely resemble the ECM and can provide cell-adhesive sites, a supportive spatial microenvironment, and biological cues. These properties have important effects on the alignment, maintenance of phenotype, and collagen reconstruction of tenocytes and TSPCs.[57,58] However, in tendon bioprinting, the applicability of natural biomaterials is determined not only by their biological activity, but also by their rheological properties, cell-loading capacity, shape stability, and post-printing structural fidelity.[40,41] Commonly used natural

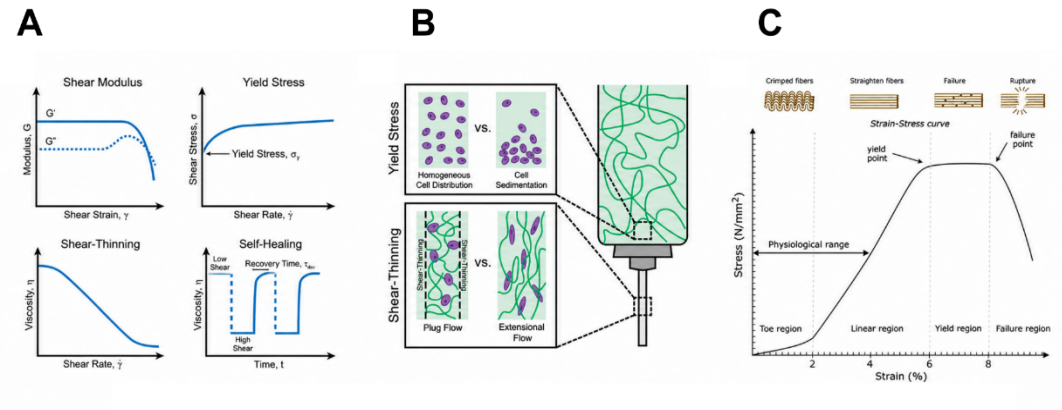

Figure 2. Schematic illustration of the fundamental performance requirements of bioprinting materials for tendon repair. (A) Schematic illustration of key rheological parameters related to bioink printability, including shear modulus, yield stress, shear-thinning behavior, and self-healing properties. Reprinted with permission from Hull *et al.*[43] Copyright © 2021, Wiley-VCH GmbH. (B) Schematic illustration showing the effects of bioink rheological properties on cell distribution and cell damage during extrusion. Appropriate yield stress and shear-thinning behavior help reduce cell sedimentation and decrease mechanical damage caused by extensional flow. Reprinted with permission from Hull *et al.*[43] Copyright © 2021, Wiley-VCH GmbH. (C) Schematic illustration of a typical tendon stress–strain curve, showing the mechanical response of the tendon from the physiological deformation range to the yield and failure regions. Reprinted from Zhu *et al.*[50]

biomaterials include collagen, alginate, HA, and silk fibroin, while tissue-specific dECM is also emerging as a promising direction for enhancing biomimicry.[59]

4.1.1. Collagen

Collagen is the major structural protein of the ECM in native tendon. It provides cell-adhesive sites and supports 3D cell adhesion, spreading, maintenance of a tendon-like phenotype, and matrix deposition, making it an important component in constructing biomimetic hydrogels.[57,60] However, collagen gels usually exhibit weak mechanical properties, limited shape retention, and relatively rapid degradation, making them insufficient to independently provide early tensile support for tendon repair.[61] In addition, collagen-based bioinks are also limited by low-pH preparation and gelation-related conditions. Collagen solutions usually need to be prepared and stored under acidic conditions to maintain solubility; before cell-laden printing or gel formation, they should be neutralized to near-physiological pH. This neutralization process is not merely a procedural step, because pH adjustment, together with temperature, ionic strength, and gelation time, can influence collagen fibrillogenesis, gelation kinetics, final gel microstructure, viscosity evolution, extrusion stability, cell encapsulation performance, post-printing construct stability, and cell viability. Inadequate neutralization or poorly controlled processing conditions may further compromise the viability and function of encapsulated cells.[62] Therefore, in tendon bioprinting, collagen is more suitable as a biomimetic matrix component in composite bioinks rather than as an independent load-bearing bioink, and it is often combined with GelMA, alginate, PCL, or dECM to improve printing stability and mechanical performance while preserving cytocompatibility.[16,61]

4.1.2. Alginate

Alginate has mild gelling conditions and good printing compatibility. It can rapidly crosslink through divalent cations such as Ca^{2+} to form an ionically crosslinked network and maintain 3D structures, making it suitable for live-cell encapsulation, extrusion-based printing, and improving shape fidelity.[63,64] Its major limitation is the lack of cell-adhesive sites, and its long-term mechanical support capacity is also limited. When used alone, alginate is therefore insufficient to support the adhesion, spreading, and directional behavior of tendon-related cells.[65] For example, RGD-modified alginate can be mixed with human adipose-derived stem cells (ASCs) to form a cell-laden bioink, which can be printed onto a calcium-containing substrate, where Ca^{2+}-mediated ionic crosslinking forms a hydrogel. This strategy takes advantage of the rapid gelation and shape-retention properties of alginate, while the RGD peptide provides cell-adhesive sites to improve cell adhesion and spreading within the printed hydrogel constructs (Figure 3A).[63] In addition, the long-term structural stability and degradation behavior of alginate are jointly affected by ionic crosslinking stability, ion exchange, swelling, and chemical modification. Because mammalian tissues lack alginase or alginate lyase capable of efficiently degrading the alginate backbone, unmodified alginate does not primarily undergo enzymatic degradation in the same manner as collagen, gelatin, or dECM. Instead, Ca^{2+}-crosslinked alginate networks may gradually soften because of Ca^{2+} loss, exchange with monovalent ions such as Na^{+}, swelling, and relaxation of the gel network, leading to reduced shape retention and mechanical support.[66] Oxidation, molecular weight, and crosslinking density can further regulate the degradation rate and mechanical retention of alginate hydrogels; oxidation introduces more degradable structures, whereas higher crosslinking density generally delays network loosening but may also restrict cell migration and tissue ingrowth.[67] Accordingly, in tendon bioprinting, alginate is more suitable as a basic printable component or rheology-modulating material and is often combined with collagen, gelatin, GelMA, dECM, or other reinforcing components to take advantage of its rapid gelation, cell encapsulation, and shape-retention properties while compensating for its limited bioactivity, restricted cell adhesion, and insufficient long-term load-bearing support.[64,65]

4.1.3. Hyaluronic acid

Hyaluronic acid is an important polysaccharide in the ECM and plays roles in water retention, lubrication, support for cell migration, and regulation of the inflammatory microenvironment.[68] For tendon tissue, which is poorly vascularized, sparsely cellular, and prone to forming adhesions, HA is more suitable as a microenvironment-modulating component. It can improve hydration, facilitate cell migration, and alleviate inflammatory interference.[69] However, unmodified or weakly crosslinked HA systems generally have low mechanical strength and limited shape stability and may be subject to hyaluronidase-mediated degradation; therefore, HA alone is difficult to use as a stand-alone load-bearing bioink for the long-term maintenance of printed structures. Chen *et al.*[70] summarized that HA and its derivatives often require chemical modification and crosslinking strategies to improve printability, gel stability, and post-printing shape fidelity when used as bioinks. Luo *et al.*[71] further summarized that HA can form more stable and tunable hydrogel networks through methacrylation, thiolation, tyramine modification, aldehyde functionalization, and dynamic covalent crosslinking. For example, methacrylated HA can form

tunable networks through photocrosslinking; thiolated HA and tyramine-modified HA can enhance gel stability through thiol-related reactions or enzymatic oxidative crosslinking, respectively; and aldehyde-functionalized or hydrazone-crosslinked HA can provide design flexibility for shear recovery, injectability, and dynamic structural regulation. It should be noted that although higher crosslinking density can improve shape retention and resistance to degradation, excessive crosslinking may also restrict cell migration, matrix remodeling, and tissue ingrowth. Therefore, in bioprinting, HA is usually combined with other natural or synthetic materials to improve the repair interface, prevent adhesion, and enable bioactive molecule delivery,[69] and in tendon bioprinting, it is more suitable as a microenvironment-modulating and functional component in composite bioinks, with a balance among stability, cytocompatibility, and tissue remodeling capacity.

4.1.4. Silk fibroin

Silk fibroin exhibits good biocompatibility, tunable mechanical properties, processability, and controllable degradation, making it one of the most suitable natural biomaterials for the mechanically loaded environment of tendon.[72] As a bioink or composite printing component, silk fibroin can improve scaffold shape stability, biocompatibility, and tissue engineering applicability through compositional modification and crosslinking strategies.[73] Kim *et al.*[73] developed a methacrylated silk fibroin (Sil–MA) bioink for digital light processing 3D bioprinting. The rheological and mechanical properties of this bioink could be modulated by varying the Sil–MA content, and the system enabled the fabrication of complex 3D constructs with good structural stability and biocompatibility.[73] Ning *et al.*[74] further developed a silk fibroin–hydroxypropyl cellulose–TSPC bioink and fabricated porous Achilles tendon scaffolds using 3D bioprinting. This system showed favorable cytocompatibility, rheological properties, printability, mechanical strength, controlled biodegradability, and suitable porosity, and supported TSPC survival, migration, proliferation, and tenogenic differentiation, providing more direct evidence for the application of silk fibroin-containing composite bioinks in Achilles tendon-related repair scenarios. However, silk fibroin still has several limitations as a bioink. When used alone, it often cannot simultaneously satisfy the requirements for printability, shape fidelity, cytocompatibility, and long-term mechanical retention. Therefore, methacrylation, in combination with cellulose derivatives or other rheology-modulating components, and optimized crosslinking strategies are usually required to broaden the printable window and enhance structural stability.[73,74] In addition, compared with tissue-specific materials such as tendon-derived dECM, silk fibroin does not provide the full composition of the tendon ECM or tenogenic inductive cues.[75-77] Therefore, in tendon bioprinting, silk fibroin is more suitable as a mechanical-reinforcing and structure-stabilizing component in composite bioinks rather than as a stand-alone repair system.[72-74]

4.1.5. Decellularized extracellular matrix

The main advantage of dECM lies in its tissue specificity. Compared with conventional collagen or gelatin, tendon-derived dECM retains structural proteins, glycosaminoglycans, and endogenous biological cues, thereby more effectively mimicking the native tendon microenvironment, maintaining the tenocyte phenotype, and supporting matrix reconstruction.[59,75] However, dECM bioinks still face limitations related to compositional and processing stability. Their major challenges include variability in tissue source, decellularization protocol, degree of digestion, and batch-to-batch composition, all of which may affect compositional stability and reproducibility. In addition, dECM bioinks used alone often exhibit weak mechanical properties, insufficient viscosity, and limited post-printing structural maintenance; therefore, polymer blending, supporting frameworks, or crosslinking strategies are commonly required to improve printability and shape fidelity.[76] Zhao *et al.*[77] systematically compared the effects of different acidic solutions on the preparation of tendon-derived dECM bioinks and found that the acidic digestion system and digestion degree can markedly alter the viscoelasticity, osmolarity, gel stiffness, and post-printing stability of dECM precursors, thereby influencing cell viability, spreading, proliferation, and tenogenic induction. These findings suggest that the function of dECM bioinks is determined not only by tissue origin, but also by preparation parameters and the physical microenvironment (Figure 3B).[77] Therefore, dECM is more suitable as a tissue-specific bioactive component that works synergistically with printable and load-bearing materials to enhance biomimicry while improving printing stability and structural maintenance.[59,76,77]

4.2. Synthetic biomaterials

Synthetic biomaterials offer advantages in mechanical performance, structural stability, manufacturing consistency, and parameter controllability, and are therefore commonly used as load-bearing frameworks in tendon bioprinting.[51,78] Their significance lies not only in supporting the defect area, but also in providing a designable, reproducible, and tunable structural basis for complex repair systems, with controllable degradation

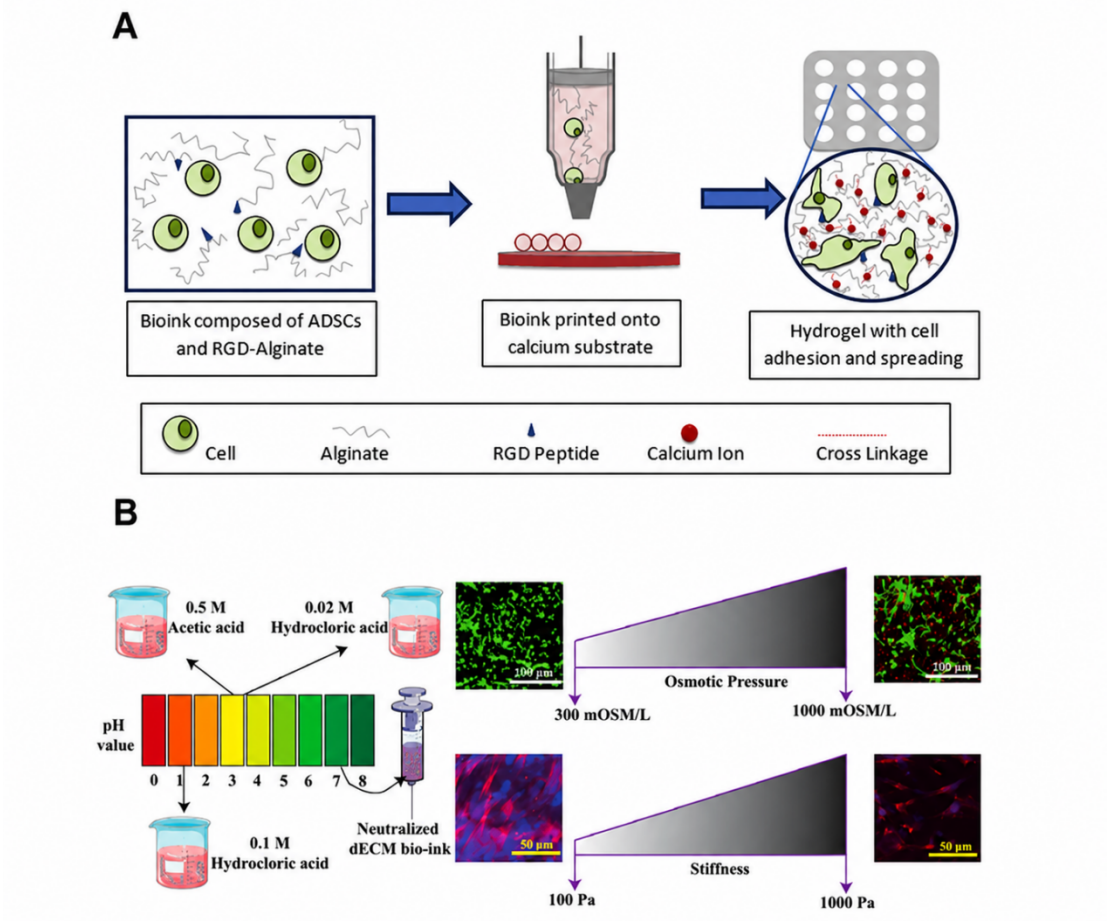

Figure 3. Schematic illustration of natural biomaterials and tissue-specific decellularized extracellular matrix (dECM) bioinks for tendon repair. (A) Schematic illustration of an arginine-glycine-aspartic acid (RGD)-modified alginate bioink. RGD-modified oxidized alginate is mixed with human adipose-derived stem cells (hADSCs) to form a cell-laden bioink, which is printed onto a calcium-containing substrate and ionically crosslinked through Ca^{2+} to form hydrogel constructs. The RGD peptide provides cell-adhesive sites on alginate hydrogels, thereby improving cell adhesion and spreading. Reprinted with permission from Jia *et al.*[63] Copyright © 2014, Acta Materialia Inc. Published by Elsevier Ltd. (B) Schematic illustration of the preparation parameters of tendon-derived dECM bioinks. Different acidic solutions, osmotic pressure, and stiffness can affect the cytocompatibility, cell spreading, and tenogenic induction capacity of dECM bioinks. Scale bars: 50 μm, 100 μm. Reprinted with permission from Zhao *et al.*[77] Copyright © 2021, The Author(s). Published by Elsevier Ltd on behalf of Acta Materialia Inc.

after the maturation of newly formed tissue.[79] However, most synthetic materials lack intrinsic cell-adhesive sites and tendon-specific biological cues. When used alone, they are often insufficient to support cell loading, phenotype maintenance, and the reconstruction of an organized matrix. Some materials may also exhibit hydrophobicity, mismatched degradation rates, degradation products that affect the local microenvironment, or printing conditions that are unfavorable for live-cell encapsulation. Therefore, in tendon bioprinting, synthetic materials are more suitable as load-bearing frameworks, structural reinforcement phases, or degradable supporting systems, and they are often combined with natural hydrogels, dECM, cells, and bioactive factors to balance mechanical stability, printability, and biological function.[51,78,79]

4.2.1. Polycaprolactone

Polycaprolactone exhibits good mechanical properties, pronounced thermoplasticity, mature melt-printing capability, and relatively slow degradation, making it suitable for constructing oriented fibrous frameworks with long-term shape retention. Such frameworks can provide physical guidance for directional cell alignment and organized collagen deposition.[78,79] However, PCL is intrinsically hydrophobic, has low bioactivity and limited cell-adhesive capacity, and its melt-printing process usually requires relatively high temperatures, making it unsuitable as a direct cell-laden bioink.[78] Through surface

modification, aligned structural optimization, post-printing cell seeding, or combination with cytocompatible hydrogels such as collagen, GelMA, and alginate, PCL can help balance mechanical support, structural guidance, and tissue compatibility.[80]

4.2.2. Polylactic acid-based materials and their copolymers

Polylactic acid-based materials and their copolymers, including PLA, PLGA, and PLCL, can provide good structural stability for scaffolds.[51] PLA has relatively high stiffness and good shape retention, but its compliance is limited. PLGA has a tunable degradation rate and can be used not only as a scaffold material, but also in microspheres, nanoparticles, and drug delivery systems. PLCL exhibits better flexibility and is more suitable for dynamically loaded soft tissues such as tendons and ligaments.[81] It should be noted that these materials generally lack cell-adhesive sites and tendon-specific biological cues, and the degradation products of some polyester-based materials may alter the local microenvironment. Therefore, in tendon bioprinting, they are more suitable as degradable load-bearing frameworks, structural reinforcement phases, or drug-delivery carriers rather than as stand-alone cell-laden bioinks. Jiang *et al.*[52] combined a 3D-printed multilayered PLGA framework with a collagen–fibrin hydrogel to construct a composite scaffold consisting of regular porous gaps, solid end structures, and hydrogel-filled regions. In this system, the PLGA scaffold mainly provided shape stability and mechanical support, whereas the hydrogel regions provided space for cell loading, growth, and matrix deposition. Tenomodulin (TNMD) immunofluorescence and the expression of tenogenic genes, including *SCX*, *TNMD*, and *COL3*, further indicated that this system could support stem cell tenogenic differentiation (Figure 4A).[52] This study suggests that integrating a degradable synthetic framework with a cytocompatible hydrogel can help balance structural stability, cell-loading capacity, and a tenogenic microenvironment. Overall, these materials are suitable for providing stable structures and tunable degradation, but they often need to be combined with natural polymers, functional ions, or bioactive molecules to compensate for their limited bioactivity.[51,52]

4.2.3. Polyethylene glycol and its derivatives

Polyethylene glycol and its derivatives, such as PEGDA, are typical synthetic hydrogel systems. Their main advantage lies in the designability of their network structure, which allows the modulation of modulus, degradation behavior, drug-loading capacity, and pore networks by adjusting molecular weight, crosslinking density, and functional group modification.[82] In bioprinting, PEG-based materials are particularly suitable as photocrosslinkable, tunable, and relatively inert bioink platforms for constructing controllable microenvironments, spatially delivering bioactive molecules, and regulating cell behavior; however, they are generally not suitable for providing the high-strength mechanical support required for tendon repair.[83] Because PEG-based materials inherently lack cell-adhesive sites, adhesive peptides are often introduced, or PEG-based systems are combined with natural materials such as collagen, gelatin, or HA to improve cell adhesion, migration, and functional expression.[84] Therefore, in tendon bioprinting, PEG and PEGDA are more suitable as tunable hydrogel matrices, crosslinked networks, or bioactive molecule delivery platforms rather than as stand-alone load-bearing repair materials.

4.3. Inorganic ions

In tendon bioprinting systems, inorganic ions and ion-releasing inorganic functional components are generally better suited as auxiliary functional phases in composite bioinks or printable scaffolds than as primary shape-forming materials. Mg^{2+}, Zn^{2+}, and Cu^{2+} have been used to modulate inflammation, oxidative stress, angiogenesis, and the microenvironment of the tendon–bone interface; however, in this review, they are summarized only briefly as auxiliary functional components rather than as an independent core material category.[85-89] Bioactive glass can also serve as an ion-releasing inorganic component in tendon–bone interface-related composite systems. Liu *et al.*[90] reported that a bioactive glass-containing gradient hydrogel promoted synchronized regeneration of tendon, fibrocartilage, and bone tissues by continuously releasing bioactive ions such as silicon, calcium, and phosphorus and providing gradient cues, while also enhancing interfacial biomechanical strength. This study provides a useful design reference for ion-releasing materials for tendon–bone interface regeneration, although it should be interpreted primarily as evidence for functional materials rather than as direct evidence for tendon bioprinting. Du *et al.*[91] further incorporated molybdenum-containing silicate bioceramics (MS) into GelMA-based multicellular bioinks containing TSPCs and bone marrow MSCs (BMSCs), thereby using MS as an inorganic bioactive component for 3D bioprinting of regionally organized tendon–bone interface scaffolds (Figure 4B). The corresponding cell-staining images showed that TSPCs and BMSCs maintained cell spreading and organized distribution within the GelMA-based printed constructs over 7 and 14 days, suggesting that MS-containing multicellular bioinks can integrate inorganic functional regulation with spatially patterned cellular organization (Figure 4C).[91] Overall, the value of inorganic functional components in

tendon bioprinting should be reflected in their functional supplementation, local release, spatial organization, and interface regulation within printable composite systems, rather than in the isolated biological effects of a single ion.[85,88,91]

Overall, different bioprinting materials play distinct functional roles in tendon repair. Natural biomaterials mainly provide cytocompatibility, cell-adhesive cues, and tissue-specific microenvironmental support, whereas

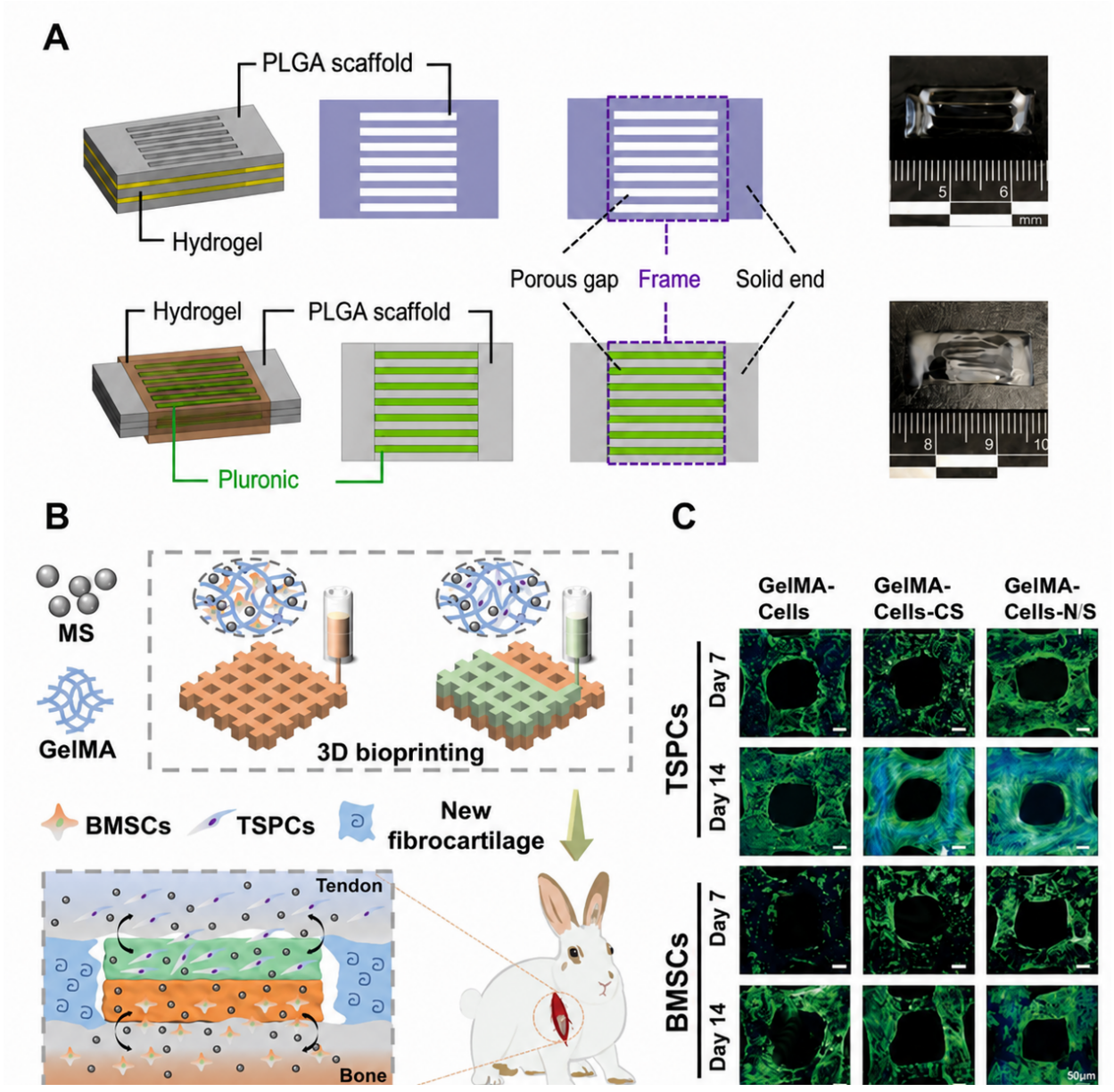

Figure 4. Schematic illustration of synthetic material scaffolds and ion-functionalized multicellular bioprinted scaffolds for tendon and tendon–bone interface repair. (A) Schematic illustration of the structural design of a 3D-printed multilayered poly(lactic-co-glycolic acid) (PLGA) scaffold combined with a collagen-fibrin hydrogel, including a separate layer-by-layer structure and a trilayered structure. This system can be used to construct a rotator cuff tendon repair scaffold that provides both mechanical support and a cell-friendly microenvironment. Reprinted with permission from Jiang *et al.*[52] Copyright © 2020, The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co., Ltd. (B) Gelatin methacryloyl (GelMA)-based multicellular bioprinting strategy incorporating molybdenum-containing silicate bioceramics (MS). MS is integrated into the printable hydrogel matrix as an inorganic bioactive component, while tendon stem/progenitor cells (TSPCs) and bone marrow mesenchymal stem cells (BMSCs) provide region-specific cellular cues for tendon–bone interface repair. Reprinted from Du *et al.*[91] (C) Cell-staining images of MS-containing GelMA-based printed constructs showing the morphology, spreading, and spatial distribution of TSPCs and BMSCs on days 7 and 14. Scale bar: 50 μm. Reprinted from Du *et al.*[91]

synthetic materials are more suitable as load-bearing frameworks or structural reinforcing phases. Inorganic or ion-releasing components primarily serve as functional additives for immunomodulation, angiogenesis, matrix maturation, and tendon–bone interface integration. The major material types and their functional roles in tendon bioprinting are summarized in Table 2.

5. Functionalization strategies of bioprinting materials for tendon repair

Relying solely on material composition and basic mechanical properties is insufficient to meet the stage-

Table 2. Major material types and their functional roles in tendon bioprinting

Bioprinting material type	Printing-related features	Advantages	Limitations	Functional role	References
Collagen	ECM-mimetic protein hydrogel with cell-adhesive motifs. Requires low-pH dissolution, neutralization, and controlled gelation to maintain printability and cell viability	High biological relevance; supports cell adhesion, spreading, tendon-like phenotype maintenance, and early matrix deposition	Weak tensile support, limited shape fidelity, and relatively rapid degradation. Process variables may affect fibrillogenesis, viscosity, construct stability, and cell function	Biomimetic matrix phase for composite bioinks, particularly with GelMA, alginate, PCL, or tendon-derived dECM to improve shape retention and mechanical support	16,57,60-62
Alginate	Natural polysaccharide with rapid Ca^{2+}-mediated ionic crosslinking. Useful for extrusion printability, rheology regulation, cell encapsulation, and initial shape retention	Mild gelation, good extrusion compatibility, and rapid construct stabilization. Helps improve initial shape fidelity in hydrogel blends	Lacks cell-adhesive sites and tendon-specific cues; limited long-term load-bearing capacity. Ca^{2+} loss, Na^{+} exchange, swelling, and gel relaxation may soften the network	Printable base and rheology-modulating phase for extrusion-based composite bioinks, commonly combined with collagen, gelatin, GelMA, dECM, or reinforcing frameworks to improve bioactivity and structural support	63-67
Hyaluronic acid (HA) and methacrylated hyaluronic acid (HAMA)	ECM-associated polysaccharide with hydration, lubrication, anti-adhesion, and microenvironment-modulating functions. HAMA improves crosslinking stability and shape retention	Supports cell migration, interface lubrication, regulation of the inflammatory microenvironment, and adhesion reduction; useful for bioactive delivery	Unmodified or weakly crosslinked HA has low mechanical strength and poor shape stability. Hyaluronidase degradation may reduce retention; excessive crosslinking may restrict tissue ingrowth	Anti-adhesion interfaces, microenvironment-modulating hydrogels, and delivery systems, often combined with GelMA, collagen, PEG-based hydrogels, PCL frameworks, or reinforcing components	68-71
Silk fibroin	Natural protein with tunable mechanics, processability, and controllable degradation. Printability is improved by methacrylation, blending, or optimized crosslinking	Better mechanical potential than many soft natural hydrogels; contributes to shape stability, structural retention, and reinforcement in mechanically loaded tendon constructs.	Limited tendon-specific ECM composition and tenogenic cues. Alone, it may not simultaneously satisfy the requirements of printability, shape fidelity, cytocompatibility, and long-term mechanical retention	Mechanical-reinforcing and structure-stabilizing component in composite bioinks or printed tendon scaffolds, rather than a stand-alone repair system	72-74,77
Tendon-derived decellularized extracellular matrix (dECM)	Tissue-specific decellularized ECM bioink retaining tendon-related proteins, glycosaminoglycans, and endogenous cues. Printing behavior depends on solubilization and digestion	Strong tendon-mimetic biological relevance; supports tendon-like microenvironment reconstruction, phenotype maintenance, and tenogenic induction	Batch variability, tissue-source differences, decellularization protocol, degree of enzymatic digestion, viscosity, gel stiffness, and post-printing stability affect reproducibility. Weak mechanics alone	Tissue-specific bioactive phase in composite bioinks, preferably with GelMA, collagen, alginate, PCL, PEG-based networks, or crosslinking strategies to improve printability and structural maintenance	59,75-77

(*cont'd...*)

Table 2. (*Continued*)

Bioprinting material type	Printing-related features	Advantages	Limitations	Functional role	References
Polycaprolactone (PCL)	Synthetic thermoplastic polymer suitable for melt-based printing. Functions primarily as a printed load-bearing framework, an orientation guide, and long-term structural support	Good shape retention, mechanical stability, and load-transfer capacity; suitable for aligned architectures and hydrogel-reinforced constructs	Hydrophobic and bioinert surface; limited cell adhesion and low intrinsic bioactivity. Slow degradation may interfere with remodeling if not properly matched.	Oriented scaffolds, load-bearing frameworks, and hydrogel-reinforced composite constructs, particularly with natural bioinks, dECM, cells, or bioactive coatings	[51,78-80]
Polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), and poly(lactide-co-caprolactone) (PLCL)	Biodegradable synthetic polyesters with adjustable stiffness, flexibility, degradation rate, and scaffold architecture. Useful as structural frameworks or delivery carriers	Good structural stability and design flexibility. PLGA provides tunable degradation and delivery potential; PLCL offers flexibility for dynamically loaded soft tissues	Limited intrinsic bioactivity and lack of tendon-specific cues. Polyester degradation products and local acidification require attention	Multilayered scaffolds, degradable reinforcing frameworks, tendon-bone interface support systems, and drug-delivery carriers, usually combined with cell-friendly hydrogels or bioactive factors	[51,52,81]
Polyethylene glycol (PEG) and polyethylene glycol diacrylate (PEGDA)	Designable synthetic hydrogel networks with tunable crosslinking, modulus, pore structure, degradation, and delivery behavior	Chemically defined and highly controllable; useful for building tailored microenvironments and controlled-release platforms	Lacks natural cell-adhesive sites and tendon-specific biological cues. Limited high-strength support unless reinforced or functionalized	Tunable hydrogel networks, controlled-delivery platforms, and composite bioink systems, often functionalized with adhesive peptides or combined with collagen, gelatin, HA, dECM, or reinforcing frameworks	[82-84]
Ion-releasing functional additives	Magnesium ions (Mg^{2+}), zinc ions (Zn^{2+}), copper ions (Cu^{2+}), molybdenum-containing silicate bioceramics (MS), and bioactive glass. Serve as auxiliary functional additives or post-printing regulatory modules, not primary bioinks	Provide ion-mediated regulation of immunomodulation, angiogenesis, matrix maturation, interfacial mineralization, and tendon-bone interface integration	Cannot independently serve as the main bioink or load-bearing scaffold. Dose, release kinetics, particle dispersion, rheological effects, cytocompatibility, and long-term safety require optimization	Auxiliary functional additives in composite hydrogels, molybdenum-containing silicate bioceramics (MS)-containing gelatin methacryloyl (GelMA)-based multicellular bioinks, bioactive coatings, and tendon–bone interface gradient constructs, preferably combined with natural bioinks, synthetic frameworks, and regionally organized bioprinting strategies	[85-91]

specific requirements of tendon repair. In the early phase, materials should stabilize the defect, regulate inflammation, and maintain cell viability. In the intermediate phase, they should promote cell migration, angiogenesis, and matrix deposition. In the later phase, greater emphasis should be placed on organized collagen alignment, tissue maturation, and mechanical recovery.[92,93] In tendon bioprinting, the value of scaffolds or bioinks should not be limited to forming visible 3D structures. Instead, they should further enable active intervention across different repair stages through architectural design, bioactive factor delivery, immune regulation, spatial cell distribution, and modulation of the mechanical microenvironment. Therefore, current research has shifted from scaffold construction itself toward active regulation of the repair process, making functionalization strategies a central approach for improving repair outcomes.[94] This section summarizes the major functionalization strategies for tendon bioprinting materials, including structural and topographical regulation, chemical and bioactive modification, immune microenvironment modulation, cell loading, and mechanical stimulation.

Functionalization does not simply mean adding more material components; rather, it involves targeted design around the key challenges of tendon regeneration. Structural and topographical modulation can guide directional cell

alignment; bioactive molecule delivery can supplement stage-specific regenerative signals; immunomodulation can reduce excessive inflammation and scar formation; conductive, piezoelectric, or mechanically responsive materials can mimic physical stimulation; and pH-, reactive oxygen species (ROS)-, or temperature-responsive systems may enable dynamic intervention in response to local microenvironmental changes.[95,96] It should be noted that these functionalization strategies are not independent of one another, but should be co-designed with material printability, cytocompatibility, degradation behavior, and mechanical stability. The core principle is to match material functions with the inflammatory, proliferative, and remodeling phases of tendon repair.

Current bioprinted scaffolds are shifting from single-material constructs toward integrated systems that combine structural design, bioactive delivery, microenvironmental regulation, and stimulus responsiveness.[92,94] The key determinant of scaffold performance is no longer limited to material source or mechanical strength, but rather lies in whether the scaffold can coordinate printability, structural stability, biological activity, and stage-specific regulation to create a regenerative microenvironment that supports cell survival, matrix deposition, collagen alignment, and functional maturation.[93,96]

5.1. Structural and topographical modulation strategies

Tendon exhibits pronounced anisotropy, and its native structure comprises parallel collagen fiber bundles and hierarchical architectures.[1] Beyond defect filling, bioprinted scaffolds should provide directional structural cues for cells through pore architecture, fiber arrangement, surface topography, and the local mechanical microenvironment, thereby guiding cell adhesion and spreading along the loading direction and promoting the secretion of organized ECM.[97] Compared with random structures, aligned scaffolds are more favorable for cell alignment and collagen reconstruction.[79] Therefore, structural and topographical modulation in tendon bioprinting should not be regarded merely as scaffold-shape design, but rather as a core functionalization strategy that regulates cell behavior, matrix deposition, and mechanical maturation through printable structural units.

5.1.1. Pore size and porosity

Pore size and porosity directly influence cell infiltration, nutrient exchange, tissue ingrowth, and mechanical support. Caliari *et al.*[97] compared anisotropic pore structures with pore sizes of 55, 152, and 243 μm and found that pore size affected tenocyte viability, proliferation, metabolic activity, and infiltration into the deeper regions of the scaffold. Among these structures, the 243 μm-aligned pores were more conducive to cell alignment and migration along the pore channels than the smaller pore groups. For 3D-printed porous Ti-6Al-4V titanium alloy scaffolds, Zheng *et al.*[98] compared pore sizes of 657.65, 527.15, 348.68, and 169.20 μm and found that the 527.15 μm group showed more favorable fibroblast adhesion, infiltration, and tendon ingrowth than the 657.65, 348.68, and 169.20 μm groups in a rabbit rotator cuff model. Therefore, pore architecture should not simply aim for larger or smaller pores, nor should findings from conventional porous scaffolds be directly generalized to a universal optimal pore size for tendon bioprinting. In tendon bioprinting, pore architecture should be optimized together with filament spacing, nozzle scale, pore interconnectivity, bioink rheology, cell-loading strategy, post-printing collapse risk, shape fidelity, and mechanical stability.[16,40,41,97,98]

5.1.2. Micropore morphology and alignment direction

Micropore morphology and alignment direction likewise determine the cell-guiding capacity of scaffolds.[97] In anisotropic collagen–glycosaminoglycan scaffolds, oriented elliptical pores can improve tenocyte alignment consistency, deep infiltration, and metabolic activity, indicating that pore channels should not only be interconnected but also possess a defined orientation.[97] Bioprinting can generate continuous parallel microstructures by controlling printing paths, interlayer angles, and fiber deposition directions,[16] and can further translate pore orientation, regional architecture, and cell distribution into programmable spatial parameters, thereby enabling coordinated regulation of cell alignment, material compartmentalization, and the local microenvironment. Yao *et al.*[99] constructed a multiscale biomimetic tendon scaffold with a shell–core structure, in which the outer porous shell mimicked the tendon sheath and provided support, while the inner microscale wavy fibers and nanoscale hybrid structures corresponded to the macro-, micro-, and nanoscale levels of native tendon, respectively. This design enabled biomimetic reconstruction of collagen fibrils, collagen fibers/fascicles, and the overall tendon structure (Figure 5A).[99] Li *et al.*[100] reported that aligned fiber-based composite constructs could increase cell density and alignment consistency. These studies primarily provide design references for multiscale structural biomimicry and aligned-construct fabrication, suggesting that bioprinted scaffolds can be further optimized in hierarchical architecture, orientational continuity, and cell guidance. However, when the repair target extends from the tendon midsubstance to the tendon–bone interface, the structural design goal is no longer limited to restoring

aligned collagen organization on the tendon side but also requires reconstructing stable, continuous interfacial integration capable of load transfer between tendon and bone. The tendon–bone interface generally corresponds to the tendon enthesis and is not a simple contact surface between tendon and bone, but rather a highly hierarchical soft-to-hard tissue transition. Its core function is to gradually transmit tensile loads from tendon to bone while buffering the stiffness mismatch between soft and hard tissues and reducing interfacial stress concentration.[101] A typical fibrocartilaginous tendon enthesis usually consists of a gradual transition from tendon to unmineralized fibrocartilage, mineralized fibrocartilage, and bone, with continuous gradients in collagen fiber orientation, cell phenotype, ECM composition, degree of mineralization, and mechanical stiffness across different regions.[102] After injury or surgical reconstruction, tendon–bone healing often fails to regenerate the organized hierarchical transitional structure and instead forms a fibrous scar-like attachment, resulting in insufficient interfacial mechanical strength, discontinuous load transfer, local stress concentrations, and an increased risk of reinjury. Therefore, tendon–bone interface bioprinting should not be limited to the fabrication of tendon-like scaffolds, but should integrate tenogenic, fibrocartilage-like, and mineralized bone-like microenvironments within a single printed construct through region-specific bioink deposition, gradient material composition, zonal structural design, and spatial organization of multiple cell populations, thereby providing structural and biological support for fibrocartilage formation, interfacial mineralization, and restoration of load transfer. Based on this design rationale, Kim *et al.*[103] used tendon- and bone-derived dECM bioinks to construct a gradient core–shell interface, thereby promoting fibrocartilage formation and regeneration of the tendon–bone interface in a rabbit rotator cuff model. Chae *et al.*[104] further fabricated a gradient multi-tissue interfacial scaffold by 3D cell printing using tendon-derived dECM, bone-derived dECM, and mixed bioinks. In this scaffold, the upper, middle, and lower regions corresponded to tenogenic, fibrocartilage-like, and osteogenic microenvironments, respectively, and were used for rotator cuff tendon–bone interface regeneration. These findings indicate that gradient structural design can integrate spatial partitioning, material composition, and cell induction. These more direct bioprinting studies further indicate that the value of microstructural and gradient design in tendon and tendon–bone interface bioprinting lies not only in reproducing the hierarchical morphology of native tissues, but also in integrating structural biomimicry, material compartmentalization, and tissue induction into printable constructs through region-specific bioink deposition, interface zoning, and spatial cell organization.

5.1.3. Surface topography

Surface topography affects cell adhesion, morphology, and alignment through surface roughness, microgrooves, ridge-like structures, micro- and nanopatterns, and local stiffness.[105,106] Kapoor *et al.*[105] found that regular microgrooves could alter tendon cell morphology and orientation. English *et al.*[106] further reported that groove depths of approximately 317 nm and 1,988 nm both promoted parallel alignment of human tendon cells, indicating that directional topography itself can serve as a cell-alignment cue. Tsiapalis *et al.*[107] reported that bidirectionally aligned electrospun fibers enhanced cell growth and tendon-related matrix deposition. Long *et al.*[108] found that ordered topography could induce ASC alignment and alter their secretome, thereby promoting TSPC proliferation and tenogenic differentiation, enhancing ECM deposition, and regulating local immune responses through pathways related to mitogen-activated protein kinase, G protein-coupled receptor, integrin signaling involving ITGA1, ITGA11, and ITGB1, and complement signaling. These effects contributed to the formation of a repair-associated macrophage microenvironment with increased M2-related features (Figure 5B).[108] These findings indicate that surface topographical modulation not only provides physical guidance, but also reshapes the repair microenvironment through paracrine signaling and immunomodulation.[109] In tendon bioprinting, these topographical and aligned-structure studies should be translated into the design of printed-filament surface roughness, micro- and nanopatterned interfaces, aligned strand deposition, and post-printing surface functionalization, rather than being interpreted simply as direct bioprinting evidence. Their application still needs to be coordinated with bioink rheology, printing resolution, nozzle- or strand-induced microarchitecture, structural fidelity, and cell-loading strategies.[16,40,41,109]

Overall, structural and topographical modulation represents one of the most fundamental functionalization strategies in tendon bioprinting. Its value lies not only in maintaining scaffold morphology and mechanical support but also in providing spatial structural cues for cell alignment, collagen deposition, and neotissue reconstruction through designable pore architectures, printing paths, filament spacing, printed-strand alignment, interlayer angles, surface micro- and nanotopography, and the local mechanical microenvironment.[16,97] On this structural basis, bioactive delivery, immunomodulation, cell loading, and physical stimulation strategies can be spatially coupled with printed scaffold architectures

through region-specific bioink deposition, controlled pore interconnectivity, aligned strand organization, and post-printing surface functionalization, thereby establishing a more controllable stage-specific regenerative microenvironment.[16,100,109] Therefore, future structural and topographical optimization should not merely pursue morphological biomimicry but also be co-designed with bioink rheology, crosslinking kinetics, printing resolution, nozzle scale, shape fidelity, post-printing structural stability, and cell-loading strategies.[40,41]

5.2. Material chemical modulation strategies

In addition to structural factors, the chemical composition and interfacial chemistry of materials also influence

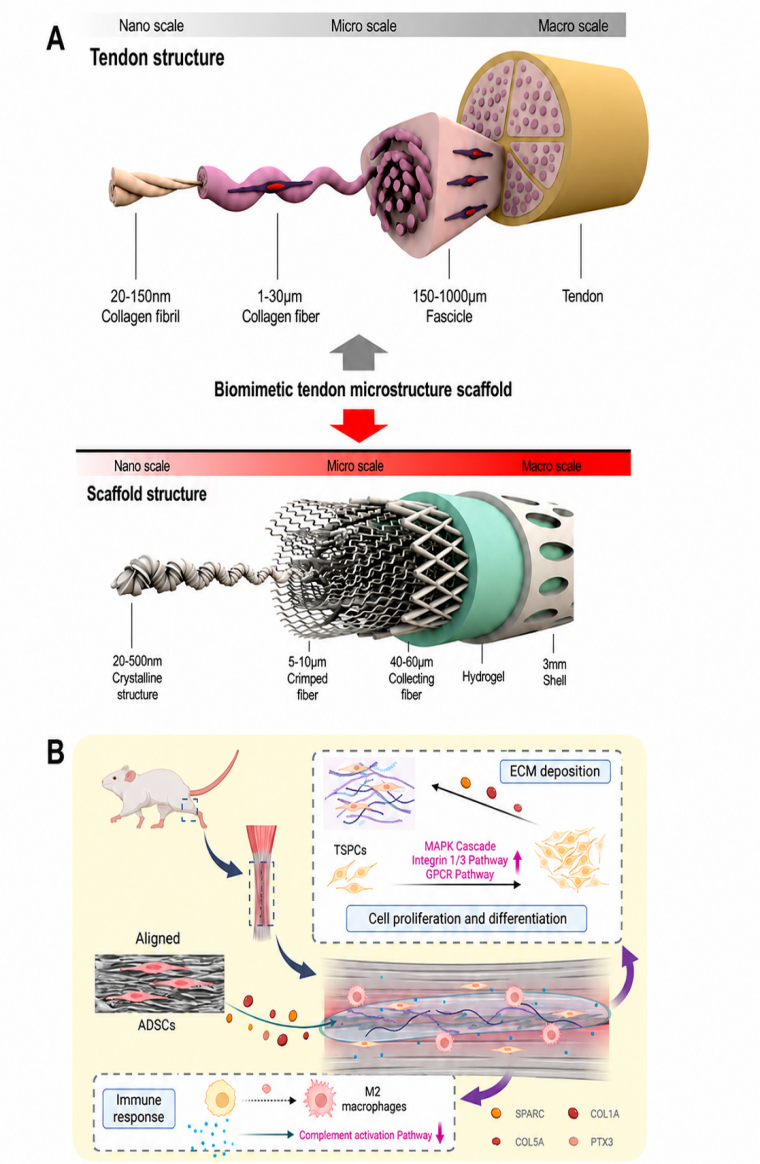

Figure 5. Schematic illustration of multiscale biomimetic scaffolds and aligned topography-regulated adipose-derived stem cell (ADSC) secretome for promoting tendon regeneration. (A) Schematic illustration of the structural design of a multiscale biomimetic tendon scaffold (MBT scaffold). This scaffold mimics the hierarchical structure of native tendon, including collagen fibrils, fibers, and fascicles, at the nanoscale, microscale, and macroscale. Reprinted with permission from Yao *et al.*[99] Copyright © 2024, Wiley-VCH GmbH. (B) Schematic illustration of the mechanism by which aligned topography regulates the ADSC secretome and promotes tendon regeneration. Conditioned medium derived from aligned ADSCs can promote tendon stem/progenitor cell (TSPC) proliferation and tenogenic differentiation, extracellular matrix (ECM) deposition, and M2 macrophage-related reparative polarization, and is associated with the regulation of mitogen-activated protein kinase (MAPK), G protein-coupled receptor (GPCR), integrin, and complement-related pathways. Reprinted from Long *et al.*[108]

cell behavior, oxidative stress, inflammatory responses, and tissue integration during tendon repair. Chemical modulation mainly acts through surface functional groups, chiral molecules, dynamic crosslinking, or the incorporation of functional components, thereby shifting materials from passive structural supports toward active regulators of the local microenvironment.[110]

5.2.1. External chemical modulation

External chemical modulation alters the chemical environment that cells first encounter through surface or interfacial modification, thereby influencing cell adhesion, migration, orientation, differentiation, and immune responses.[110] Unlike surface topographical regulation, this strategy places greater emphasis on the roles of functional groups, chiral molecules, hydrophilicity, charge distribution, and bioactive groups in cell recognition and signal transduction.[111] Wang *et al.*[112] reported that electrospun membranes modified with chiral arginine could alleviate TSPC injury under oxidative stress and improve tendon healing. After these membranes were wrapped around the injured tendon, they promoted cell proliferation, tenogenic differentiation, and collagen deposition through the integrin/vinculin/focal adhesion kinase/Yes-associated protein pathway, while alleviating local oxidative stress injury through L-Arg-mediated nitric oxide (NO) production and ROS scavenging. These findings highlight the regulatory effects of external chemical modification on cell–material interfacial behavior and the local oxidative stress microenvironment (Figure 6A).[112] Further cellular fluorescence results showed that L-Arg treatment enhanced NO-related fluorescence signals and reduced hydrogen peroxide-induced ROS signals, further validating the roles of L-Arg-mediated NO production and ROS scavenging (Figure 6B).[112] Although this study was not based on a directly bioprinted construct, its findings can provide design references for translating external chemical modification into tendon bioprinting systems. For example, similar chiral amino acids, NO-regulating components, or antioxidant functional groups could be incorporated into printable collagen-based bioinks, printed-strand surface chemical modification, or post-printing interfacial functionalization strategies. Their translational application still requires further validation of how these chemical modifications affect bioink rheology, crosslinking kinetics, cell-loading capacity, printing resolution, shape fidelity, stable retention, local release or sustained action of functional components, and post-printing structural stability.[42,49,110,112]

5.2.2. Internal chemical modulation

Internal chemical modulation emphasizes the introduction of sustained functions into constructs through internal material composition and crosslinked networks, such as dynamic covalent/coordination bonds, antibacterial components, tunable degradation networks, and immunomodulatory microenvironments.[49] In tendon bioprinting, internal chemical modulation should not be understood merely as material modification of functional hydrogels or repair patches; rather, it should be translated into the design of internal networks within printable bioinks. Specifically, growth factors, antioxidant components, immunomodulatory units, or dynamic crosslinked networks should be stably incorporated into printed constructs while maintaining suitable rheological properties, shear-thinning behavior, crosslinking kinetics, cytocompatibility, and post-printing structural stability.[40-42,49] Yao *et al.*[113] developed a dual-dynamic crosslinked hydrogel patch with both antibacterial and macrophage-regulating functions. This patch promoted macrophage polarization toward a reparative phenotype, thereby reducing peritendinous adhesion while supporting tissue regeneration. Ouyang *et al.*[114] constructed a one-step Janus hydrogel with an asymmetric structure formed by gradient emulsion droplets and photocrosslinking. One side faced the injured tendon to provide wet adhesion, mechanical support, and *in situ* sealing, whereas the other side faced the surrounding tissue to serve as an anti-adhesion barrier. Its functional components could also scavenge ROS, downregulate inflammation-related signals such as IL-6, IL-1β, TNF-α, and HIF-1α, and promote macrophage polarization from M1 to M2. In this way, the hydrogel achieved temporal regulation of inflammation and spatial anti-adhesion/pro-repair effects (Figure 6C).[114] Gross observation of tendons and 3D reconstruction of adhesion tissue at 14 and 28 days postoperatively further showed that the polyphosphazene -epigallocatechin gallate-ALC Janus hydrogel reduced peritendinous adhesion formation, providing *in vivo* morphological evidence for its unilateral adhesion, physical barrier, and anti-adhesion design (Figure 6D).[114] These findings indicate that internal chemical modulation not only enhances material stability but also helps regulate immune rhythms and suppress adverse repair responses through synergy between dynamic networks and functional chemical components. Overall, the significance of chemical modulation lies in enabling materials to provide structural support while acquiring the capacity to regulate the local microenvironment.[110,113] External chemical modulation mainly focuses on interfacial recognition and cellular responses, whereas internal chemical modulation emphasizes the intrinsic antibacterial, anti-inflammatory, anti-adhesion, and pro-repair functions of the material itself. These two strategies can be combined with structural

design, bioactive delivery, and smart responsiveness.[110,112] The studies by Yao *et al.*[113] and Ouyang *et al.*[114] suggest that dynamic crosslinked networks, ROS-scavenging capability, antibacterial components, unilateral adhesion and anti-adhesion interfaces, and immunomodulatory units may provide important design references for future printable hydrogel networks, post-printing interfacial functionalization, and immunomodulatory bioinks. However, when these strategies are further integrated into cell-laden bioinks or printed constructs, their effects on bioink rheology, crosslinking kinetics, cell-loading capacity, printing resolution, shape fidelity, post-printing structural stability, and post-printing functional durability still need to be systematically evaluated.[40,49,110,113,114]

5.3. Bioactive molecule delivery strategies

Tendon repair depends on local signal regulation, and scaffold support alone is insufficient to reconstruct the complex repair microenvironment.[26,32] Bioactive molecule delivery integrates growth factors, exosomes, or cell-related components into scaffolds, enabling sustained or stage-specific release of regulatory signals after implantation. These signals can influence cell recruitment, proliferation, angiogenesis, matrix deposition, and collagen maturation.[26,32] The value of this strategy lies in providing regenerative signals in a local, controllable, and stage-matched manner. In tendon bioprinting, bioactive molecule delivery should not be understood simply as

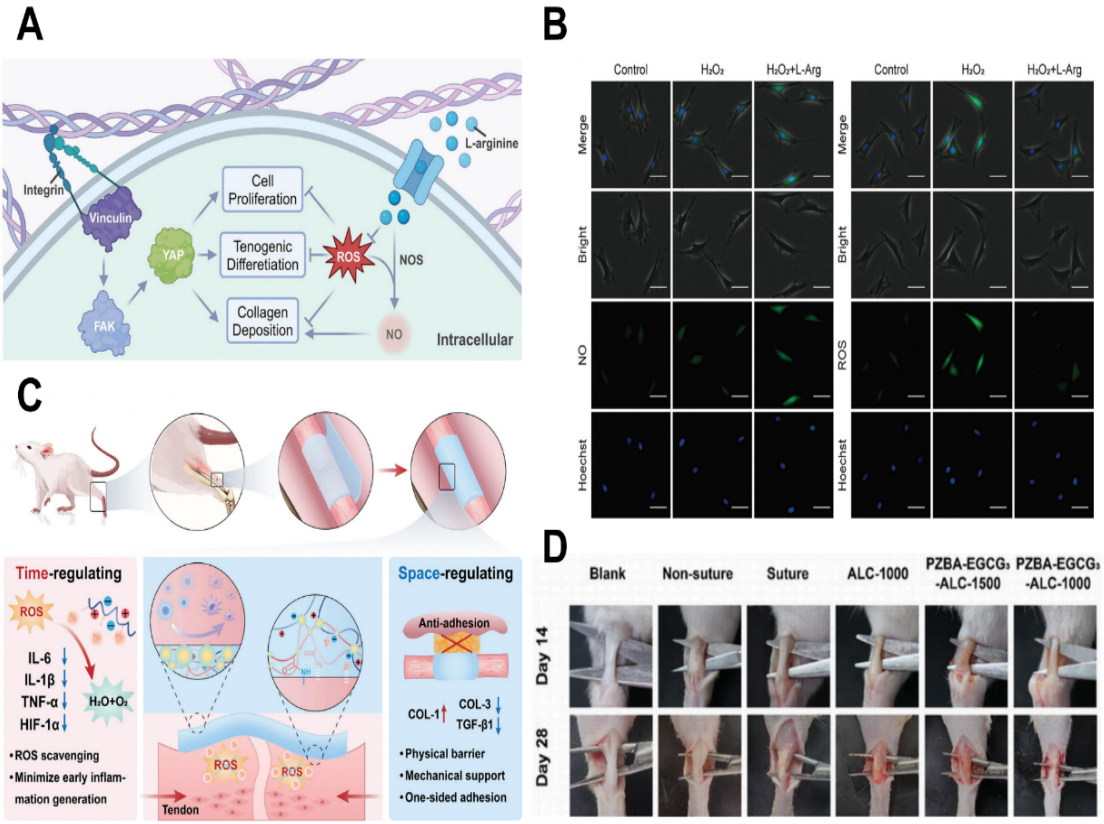

Figure 6. Schematic illustration of external and internal chemical modulation strategies for tendon repair. (A) Schematic illustration of the mechanism by which L-arginine-modified collagen membrane (L-Arg@CM) promotes tendon healing. This membrane regulates cell proliferation, tenogenic differentiation, and collagen deposition through the integrin/vinculin/focal adhesion kinase (FAK)/Yes-associated protein (YAP) pathway and is also involved in nitric oxide (NO) production and reactive oxygen species (ROS) scavenging. Reprinted with permission from Wang *et al.*[112] Copyright © 2024, Wiley-VCH GmbH. (B) Cellular fluorescence validation of L-arginine (L-Arg)-mediated NO production and ROS scavenging, showing changes in NO and ROS signals under different treatment conditions. Scale bar: 50 μm. Reprinted with permission from Wang *et al.*[112] Copyright © 2024, Wiley-VCH GmbH. (C) Schematic illustration of the spatiotemporal regulatory effects of the PZBA-EGCG$_3$-ALC Janus hydrogel. This hydrogel modulates the tendon repair microenvironment through ROS scavenging, inflammatory regulation, unilateral adhesion, mechanical support, and an anti-adhesion barrier effect. Reprinted from Ouyang *et al.*[114] (D) *In vivo* validation of the anti-adhesion effects of the PZBA-EGCG$_3$-ALC Janus hydrogel, showing gross tendon observation and three-dimensional reconstruction of adhesion tissue in different treatment groups at 14 and 28 days postoperatively. Reprinted from Ouyang *et al.*[114]

adding bioactive factors to scaffolds, but rather as an integration with bioink design and printed-structure construction. Specifically, growth factors, exosomes, cytokines, or cell-derived bioactive components can be incorporated into printed constructs through direct mixing into bioinks, microsphere- or nanoparticle-mediated encapsulation, binding within degradable networks, region-specific printing deposition, or post-printing surface loading, thereby enabling local, spatially compartmentalized, or gradient release. At the same time, the delivery system must preserve the stability of bioactive molecules during extrusion shear, photocrosslinking, ionic crosslinking, or enzymatic crosslinking, while avoiding adverse effects on bioink rheology, cytocompatibility, printing resolution, and shape fidelity.[40-42,49] Therefore, the core value of bioactive delivery in tendon bioprinting is not merely to prolong factor release, but to match regenerative signals with printing paths, pore architecture, spatial cell distribution, and stage-specific repair requirements, thereby establishing a more controllable local regenerative microenvironment.[26,32,40,49]

5.3.1. Growth factors

Growth factor delivery mainly supports cell migration, proliferation, angiogenesis, collagen synthesis, and tissue maturation. PDGF, bFGF, VEGF, TGF-β, IGF-1, and connective tissue growth factor are among the most extensively studied factors in tendon repair.[32] PDGF-BB is mainly associated with early cell recruitment and proliferative activation. Evrova *et al.*[115] found that PDGF-BB enhanced rabbit tenocyte proliferation and influenced matrix deposition. bFGF is commonly used to support early cell activation and tenogenic differentiation. Li *et al.*[116] loaded bFGF into bovine serum albumin nanoparticles and incorporated them into aligned PCL electrospun scaffolds, achieving sustained release, promoting tenogenic differentiation of human amniotic MSCs, and improving repair of Achilles tendon defects in rats. VEGF mainly enhances angiogenesis in poorly vascularized environments, whereas connective tissue growth factor and IGF-1 are more closely associated with matrix reconstruction and phenotype maintenance.[26,32] TGF-β can promote collagen synthesis, but excessive activation may also increase the risk of fibrosis.[32] As direct evidence of tendon bioprinting, Ruiz-Alonso *et al.*[117] developed a hydrogel bioink composed of alginate, HA, gelatin, and fibrinogen, and incorporated PDGF-BB and VEGF into the bioink for 3D bioprinting of biomimetic scaffolds for partial tendon injury. This system exhibited favorable rheological behavior and printability, enabled growth factor delivery, and helped maintain tenocyte metabolic activity, phenotype, and tendon ECM-related gene expression, indicating that growth factors can be internally incorporated into bioinks to endow printed constructs with structural support, cell-loading capacity, and bioactive delivery functions.[117] Chen *et al.*[118] constructed a collagen-binding peptide (CBP)-modified growth factor-loaded book-shaped decellularized enthesis matrix (O-BDEM). By delivering CBP-modified bone morphogenetic protein-2 (C-BMP-2), transforming growth factor-β3 (C-TGF-β3), and growth differentiation factor-7 (C-GDF-7) to the bone, fibrocartilage, and tendon regions, respectively, this system achieved region-specific osteogenic, chondrogenic, and tenogenic induction. The CBP-GFs/O-BDEM design visually demonstrated the regional integration of C-GDF-7, C-TGF-β3, and C-BMP-2 within the tendon zone, fibrocartilage zone, and bone zone, respectively (Figure 7A).[118] Further fluorescence tracing showed that differently labeled GDF-7, TGF-β3, and BMP-2 were spatially distributed within their corresponding functional regions and gradually released over time, supporting the rationale of this system for region-specific growth factor delivery at the tendon–bone interface (Figure 7B).[118] In tendon bioprinting systems, the stability of growth factors during extrusion-induced shear, photocrosslinking, ionic crosslinking, or enzymatic crosslinking should also be further considered, together with their effects on bioink rheological properties, cytocompatibility, printing resolution, shape fidelity, and post-printing release behavior.[45,117,118]

5.3.2. Exosomes

Exosomes contain various bioactive components, including proteins, lipids, and microRNAs, and are more suitable than single growth factors for regulating intercellular communication and the repair microenvironment. Kim *et al.*[119] noted that exosomes possess good biocompatibility and intrinsic delivery properties; however, source standardization, loading efficiency, scalable production, *in vivo* stability, and targeted control remain major challenges. In the context of tendon repair, exosomes from different sources have distinct functional emphases. Yu *et al.*[120] found that BMSC-derived exosomes could promote TSPC proliferation and migration and enhance the expression of tenogenic markers. Shen *et al.*[121] reported that extracellular vesicles derived from ASCs could attenuate early inflammation after Achilles tendon injury in mice and improve repair quality. Chen *et al.*[122] showed that dendritic cell-derived exosomes promoted macrophage polarization from M1 to M2 phenotypes via the phosphoinositide 3-kinase/protein kinase B pathway, reduced IL-1β, IL-6, and TNF-α levels, and promoted type I collagen synthesis. Xu *et al.*[123] further suggested that bioactive glass-induced MSC-derived exosomes could promote M2 macrophage-

associated angiogenesis via repair-related microRNAs, thereby improving tendon regeneration and functional recovery. Dou *et al.*[124] reported that human umbilical vein endothelial cell-derived exosome-loaded chitosan hydrogel could serve as a local delivery platform, enabling sustained release of bioactive exosomes at the Achilles tendon injury site, thereby reducing inflammation, decreasing apoptosis of tendon-derived stem cells, and promoting tendon regeneration.

For tendon bioprinting, the key value of exosomes does not lie in simply replacing cell-based therapy, but in serving as cell-free bioactive modules that can be integrated with printable material systems and three-dimensional scaffold architectures. Zhang *et al.*[125] developed a tendon stem cell-derived exosome-loaded scaffold, in which tendon stem cell-derived exosomes and type I collagen were incorporated into a 3D bioprinted PCL-based scaffold to bridge irrepairable massive rotator cuff tears. This system promoted BMSC proliferation, migration, and tenogenic differentiation *in vitro* and enhanced tendon-like tissue regeneration in the bridging region in a rabbit model of unrepairable massive rotator cuff tear, suggesting that exosomes can be combined with 3D bioprinted load-bearing scaffolds to provide both structural support and tenogenic regulatory signals.[125]

Exosomes can be integrated into printed constructs through direct mixing with bioinks, encapsulation in microspheres or nanoparticles, incorporation into degradable hydrogel networks, region-specific bioink deposition, post-printing surface loading, or post-loading onto 3D-printed scaffolds. Future exosome-loaded tendon bioprinting materials should further optimize the retention of exosome bioactivity during mixing, extrusion-induced shear, photocrosslinking, or ionic crosslinking, as well as the uniformity of spatial distribution, release stability, effective dosage, and post-printing functional durability. The effects of exosome incorporation on bioink rheological properties, cytocompatibility, printing resolution, and shape fidelity should also be systematically evaluated.[49,123-125]

5.3.3. Stem cell-related strategies

The significance of stem cell-related strategies lies not only in supplementing cell numbers, but also in improving the repair environment through direct participation in tissue formation and paracrine regulation.[11,34] Commonly used cell types include BMSCs, ASCs, and TSPCs. BMSCs are often used to support tenogenic differentiation and matrix formation. ASCs are abundant and readily accessible; Deng *et al.*[126] demonstrated in a rabbit Achilles tendon defect model that autologous ASC-engineered constructs could promote repair, while Kokubu *et al.*[127] found that ASCs could also reduce early inflammation and promote vascular formation. TSPCs exhibit stronger tissue specificity. Shen *et al.*[128] loaded allogeneic TSPCs onto a knitted silk-collagen sponge scaffold and observed improvements in collagen deposition, tissue structure, and biomechanical properties, suggesting that TSPCs may improve the local environment through anti-inflammatory factors. In tendon bioprinting, these stem cell-related strategies should further shift from conventional cell seeding toward the design of cell-laden bioinks and spatially patterned cell deposition. By encapsulating BMSCs, ASCs, or TSPCs within printable hydrogels, dECM bioinks, or composite bioinks, and combining them with printing paths, region-specific deposition, and gradient architectures, printed constructs can generate cellular spatial distributions and local inductive microenvironments that more closely resemble tendon or the tendon–bone interface. Particularly for tendon–bone interface repair, multicellular or regionally patterned bioprinting can be used to construct tenogenic, fibrocartilage-like, and osteogenic microenvironments, allowing cell source, material composition, and structural compartmentalization to jointly participate in tissue regeneration.[91,104]

Compared with conventional cell seeding, bioprinting enables spatial control of cell distribution in three dimensions, allowing better matching between cells and material composition, pore architecture, and oriented structural design.[15] Zhao *et al.*[77] showed in their study of tendon-derived dECM bioinks that the degree of enzymatic digestion of tendon-derived decellularized ECM during bioink preparation simultaneously affected print shape retention and cell behavior: a lower degree of digestion was beneficial for shape fidelity and stacking accuracy, whereas softer systems were more favorable for stem cell spreading, proliferation, and tenogenic induction. Park *et al.*[15] further demonstrated in their study of tissue-specific dECM bioinks that these bioinks can provide encapsulated cells with a local microenvironment more closely resembling the target tissue. Therefore, cell delivery should be integrated with scaffold architecture, the material microenvironment, and inflammatory regulation, rather than simply increasing the cell-loading density.[15,77]

Overall, bioactive molecule delivery shifts scaffolds from structural support toward sustained signal regulation.[26,32] Future efforts should focus on integrating growth factor, exosome, and cell-based strategies with structural design and material-responsive mechanisms to establish phased and controllable delivery systems that match the signaling requirements of different stages of tendon repair.[26,119]

5.4. Immunomodulatory and inflammatory regulation strategies

Tendon repair is closely associated with local immunoinflammatory responses.[7,8] Inflammation is necessary for the initiation of repair, but the key issue is whether it can smoothly transition from early clearance to later reconstruction.[31] Chisari *et al.*[7] noted that a persistent and excessive M1 macrophage response, accompanied by sustained elevations of pro-inflammatory factors such as IL-1β, TNF-α, and IL-6, can aggravate matrix degradation and functional impairment. Wang *et al.*[8] emphasized that the establishment of M2 macrophages within an appropriate time window is beneficial for the resolution of inflammation, angiogenesis, and matrix reconstruction, whereas excessive or persistent M2 polarization may also contribute to fibrotic ECM deposition and scar-like remodeling. Therefore, the goal of immunomodulation is not simply to suppress inflammation or continuously enhance M2 polarization, but to coordinate macrophage responses within an appropriate time window and promote a dynamic balance among the resolution of inflammation, angiogenesis, and matrix reconstruction. In tendon bioprinting, this immunomodulatory logic should be further translated into the design of printable material systems. Specifically, printed constructs capable of regulating macrophage phenotypic transition and local inflammatory dynamics may be developed through bioink composition, delivery of immunomodulatory ions or factors, exosome or cell loading, region-specific bioink deposition, and post-printing release control.[16,42,49,127]

Materials themselves can also participate in immunoregulation. Scaffold surface roughness, pore architecture, hydrophilicity, stiffness, and degradation behavior can all influence macrophage adhesion, morphology, and secretory profiles.[129] In bioprinting systems, these material-mediated immunomodulatory factors can be further translated into programmable printing parameters and bioink design variables, such as printed-strand surface morphology, pore interconnectivity, local stiffness, degradation rate, release of immunomodulatory components, and region-specific bioink deposition. Wei *et al.*[130] constructed a Wnt3a-modified nanofibrous scaffold that promoted early macrophage recruitment and increased the proportion of M2 macrophages, thereby improving tendon healing outcomes. This finding indicates that structural design and bioactive modification can jointly regulate the local immune rhythm and further affect collagen reconstruction and tissue maturation.[130] Feng *et al.*[131] further developed a macrophage-derived peptide–HA scaffold for rotator cuff tendon–bone interface repair. Through the synergistic action of the M2 macrophage-derived peptide and the HA scaffold, this system regulated the local immune microenvironment and promoted the coupling of immunoregulatory and tissue regenerative signals in the bone, fibrocartilage, and tendon regions (Figure 7C).[131] Immunohistochemical results for CD206 and IL-6 further showed that the macrophage-derived peptide–HA scaffold enhanced reparative immune phenotypes while reducing the expression of inflammatory factors, thereby providing histological evidence for an immunomodulatory tendon–bone interface scaffold (Figure 7D).[131] These studies provide design references for immunomodulatory bioinks, post-printing interfacial functionalization, and multicompartment tendon–bone interface bioprinted constructs by highlighting the roles of Wnt signaling modulation, immunomodulatory peptides, HA matrices, surface architecture, and region-specific interface design. Thus, immunomodulatory bioprinting should focus not only on suppressing inflammation, but also on regulating macrophage phenotypic transition and local inflammatory dynamics to prevent persistent early pro-inflammatory damage and promote later angiogenesis and matrix reconstruction. Future translation should further evaluate the effects of these immunomodulatory components on bioink rheology, crosslinking kinetics, cell-loading capacity, printing resolution, shape fidelity, release stability, and post-printing functional durability.[129,131]

Integrating immunomodulatory bioactive components into bioprinted scaffolds represents an important direction for enhancing local immunomodulation.[24,129] Compared with systemic administration, local delivery is more likely to maintain effective concentrations at the lesion site while reducing systemic exposure and off-target effects. Immunomodulatory multicellular scaffolds targeting the tendon–bone interface have also shown the potential to simultaneously support inflammatory regulation and tissue integration.[91,132] These studies suggest that immunomodulatory bioprinting should integrate bioink composition, region-specific bioactive delivery, interfacial design, spatial cell distribution, and post-printing release control to establish a sustained and temporally regulated local immune microenvironment, rather than relying on a single anti-inflammatory signal.[24,91,129,130]

5.5. Physical stimulation strategies

Tendon development, homeostasis, and injury repair all depend on mechanical loading.[35,36] Native tendons are continuously subjected to tension, recoil, and stress transmission, during which local cells constantly receive physical signals. Therefore, bioprinted scaffolds that provide only static support may be insufficient to fully mimic the physiological environment required for repair.[91,92] Physical stimulation strategies emphasize regulating cell behavior

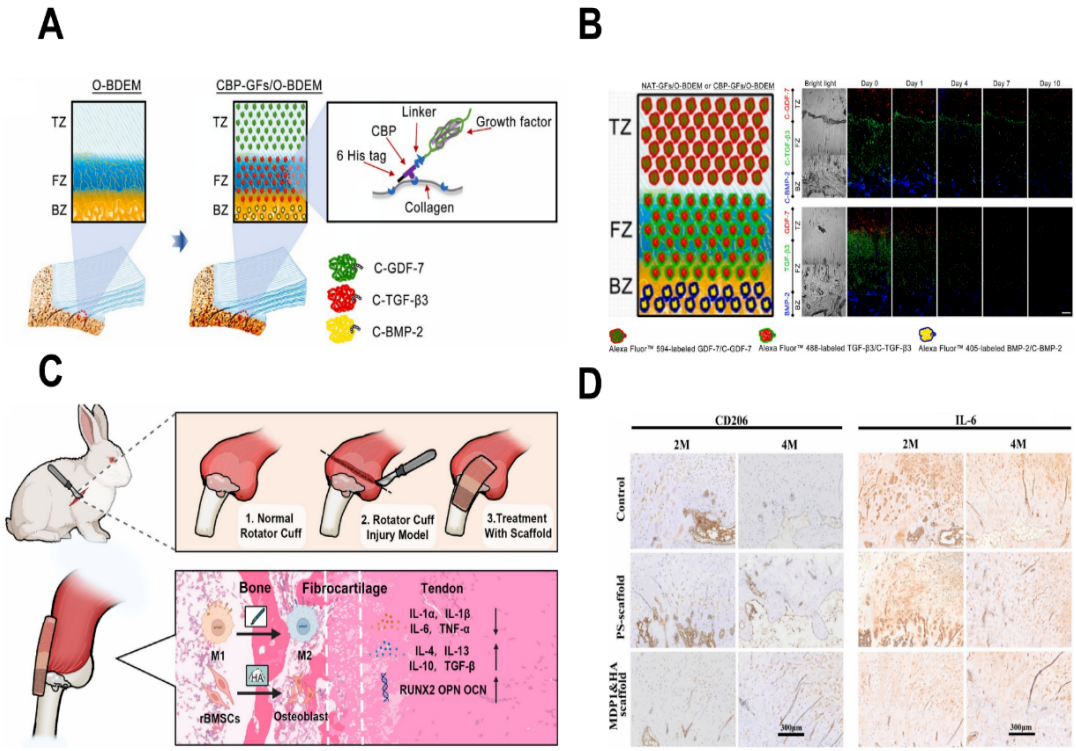

Figure 7. Region-specific growth factor delivery and immunomodulatory scaffolds for promoting tendon–bone interface repair. (A) Schematic illustration of the construction of collagen-binding peptide-modified growth factor-loaded book-shaped decellularized enthesis matrix (CBP-GFs/O-BDEM). This scaffold uses collagen-binding peptide-modified growth factors and regionally integrates collagen-binding peptide-modified growth differentiation factor-7 (C-GDF-7), transforming growth factor-β3 (C-TGF-β3), and bone morphogenetic protein-2 (C-BMP-2) into the tendon zone (TZ), fibrocartilage zone (FZ), and bone zone (BZ), respectively. Reprinted with permission from Chen *et al.*[118] Copyright © 2021, The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd. (B) Validation of region-specific growth factor delivery by CBP-GFs/O-BDEM, showing the spatial distribution and release process of growth differentiation factor-7 (GDF-7), transforming growth factor-β3 (TGF-β3), and bone morphogenetic protein-2 (BMP-2) within different functional regions. Scale bar: 200 μm. Modified and reprinted with permission from Chen *et al.*[118] Copyright © 2021, The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd. (C) Schematic illustration of the mechanism by which the MDP1 and hyaluronic acid (HA) scaffold mediates immunoregulation at the tendon–bone interface, showing its regulatory effects on the immune microenvironment and regenerative signals in the bone, fibrocartilage, and tendon regions in a rabbit rotator cuff injury model. Reprinted with permission from Feng *et al.*[131] Copyright © 2025, The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd. (D) Histological validation of the immunomodulatory effects of the MDP1 and HA scaffold, showing the immunohistochemical staining results of cluster of differentiation 206 (CD206), an M2 macrophage marker, and interleukin-6 (IL-6) at 2 and 4 months postoperatively. Scale bar: 300 μm. Reprinted with permission from Feng *et al.*[131] Copyright © 2025, The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd.

through external or material-derived signals, thereby promoting cell alignment, tenogenic differentiation, collagen remodeling, and functional recovery.[36,91,92] In tendon bioprinting, these strategies should be further integrated with printed structural anisotropy, fiber or printed-strand alignment, local stiffness regulation, deformable materials, conductive or piezoelectric components, and mechanically responsive bioink design, enabling printed constructs to provide not only morphological support but also physical cues that more closely resemble the native tendon microenvironment.

Electrical stimulation strategies are mainly based on cellular responses to local electrophysiological signals. Although tendon is not a typical electroactive tissue, collagen fibers possess piezoelectric properties, and cell migration, changes in membrane potential, and the expression of certain genes can also be influenced by electrical signals.[95] Fernandez-Yague *et al.*[133] developed a self-powered piezoelectric bioelectronic device and showed that electrical signals generated by the piezoelectric scaffold under mechanical stimulation could upregulate tenogenic markers, including the tenogenic transcription factor scleraxis, tenomodulin (TNMD), and collagen type I alpha 1 chain. Luo *et al.*[134] constructed a piezoelectric, injectable anti-adhesion hydrogel that converts mechanical stimulation into local electrical signals under ultrasound

stimulation. Combined with its anti-adhesion barrier effect, this hydrogel reduced extrinsic healing while promoting TSPC-mediated intrinsic tendon repair (Figure 8A). These studies suggest that conductive or piezoelectric components can provide sustained physical regulatory signals for tendon repair through electromechanical coupling and may serve as design references for future conductive or piezoelectric bioinks, functional components in printed scaffolds, and post-printing physical stimulation systems. Their translation into tendon bioprinting still requires further balancing of electrical responsiveness, mechanical stability, bioink rheology, cytocompatibility, printing resolution, and shape fidelity.[49,95,133,134]

Mechanical stimulation more closely resembles the native mechanical microenvironment of tendon. Tenocytes and tendon progenitor cells are sensitive to tensile, compressive, and shear signals, among which cyclic tensile loading is the most representative.[35] Current studies commonly use 3–10% uniaxial cyclic stretching to mimic physiological tensile loading, whereas excessive loading may cause cell damage, increased inflammation, or abnormal differentiation. Xu *et al.*[135] found that cyclic stretching could induce tenogenic differentiation of TSPCs. Park *et al.*[136] further showed that short-term mechanical activation in aligned dense collagen hydrogels increased scleraxis expression and enhanced collagen remodeling. Mechanical stimulation should be matched with loading magnitude, frequency, duration, cell type, and material mechanics, and in tendon bioprinting, this strategy can be translated into the coordinated design of aligned printed strands, anisotropic pore architectures, mechanically responsive bioinks, and post-printing dynamic culture systems to provide both structural guidance and dynamic tendon-like mechanical cues.[35,135,136]

The effects of physical stimulation depend heavily on the intensity, frequency, duration, and timing of application.[35,36] Insufficient stimulation may fail to produce clear biological effects, whereas excessive stimulation may cause cell damage, enhanced inflammation, or secondary injury.[133] In tendon bioprinting, future strategies should integrate printed structural design, conductive or piezoelectric components, mechanically responsive bioinks, and post-printing stimulation systems to establish a sustained, tunable, and tendon-like physical regulatory microenvironment.[95,136]

5.6. Smart responsiveness

Conventional materials often function in a fixed manner after implantation, whereas the degree of inflammation, oxidative stress, pH, temperature, and cellular and matrix states after tendon injury continue to change dynamically.[93,96] Smart responsive materials can dynamically regulate release behavior or material state in response to local microenvironmental changes, and in tendon bioprinting, they can be integrated with responsive bioinks, degradable networks, bioactive delivery, region-specific architectures, and post-printing release control to enable more precise, stage-specific repair regulation.

Currently, widely investigated strategies include pH responsiveness, ROS responsiveness, thermoresponsiveness, and photothermal responsiveness.[96] Li *et al.*[137] developed an HAPP@H-EXO Janus hydrogel that could release exosomes derived from hypoxia-preconditioned TSPCs in response to pH changes and suppress the nuclear factor kappa B pathway to reshape macrophage responses. Meanwhile, this hydrogel combined asymmetric adhesion, antibacterial and anti-inflammatory effects, and stress redistribution, thereby improving the local microenvironment after infected Achilles tendon injury and promoting structural repair (Figure 8B). Wu *et al.*[138] constructed a pH-responsive hydrogel for delayed release of the mitogen-activated protein kinase kinase inhibitor CI1040, enabling localized drug release in response to the inflammatory microenvironment. ROS-responsive systems are more suitable for chronic injury or persistent inflammatory conditions and can alleviate oxidative stress by scavenging excessive ROS.[139] Thermoresponsive materials are suitable for local injection and sustained release, whereas photothermal responsiveness emphasizes externally controllable short-term activation.[140] These studies suggest that pH, ROS, thermal, and photothermal responsiveness may serve as design references for responsive bioinks, temporally controlled bioactive release, region-specific printed architectures, and post-printing controllable interventions. However, their translation into tendon bioprinting still requires further balancing of response sensitivity, release stability, bioink rheology, cytocompatibility, printing resolution, and shape fidelity.[43,49,96,137,139]

For tendon tissue, which has a long repair cycle and a continuously changing microenvironment, the focus of smart responsive design should not be limited to environmental sensing alone. Rather, scaffolds should provide more stage-matched local interventions at different phases of repair.[141] Future studies should integrate responsive mechanisms with responsive bioinks, growth factor or exosome delivery, immunomodulation, anti-adhesion strategies, physical stimulation, region-specific printed architectures, and post-printing release control to establish temporally regulated integrated repair systems.[93,96]

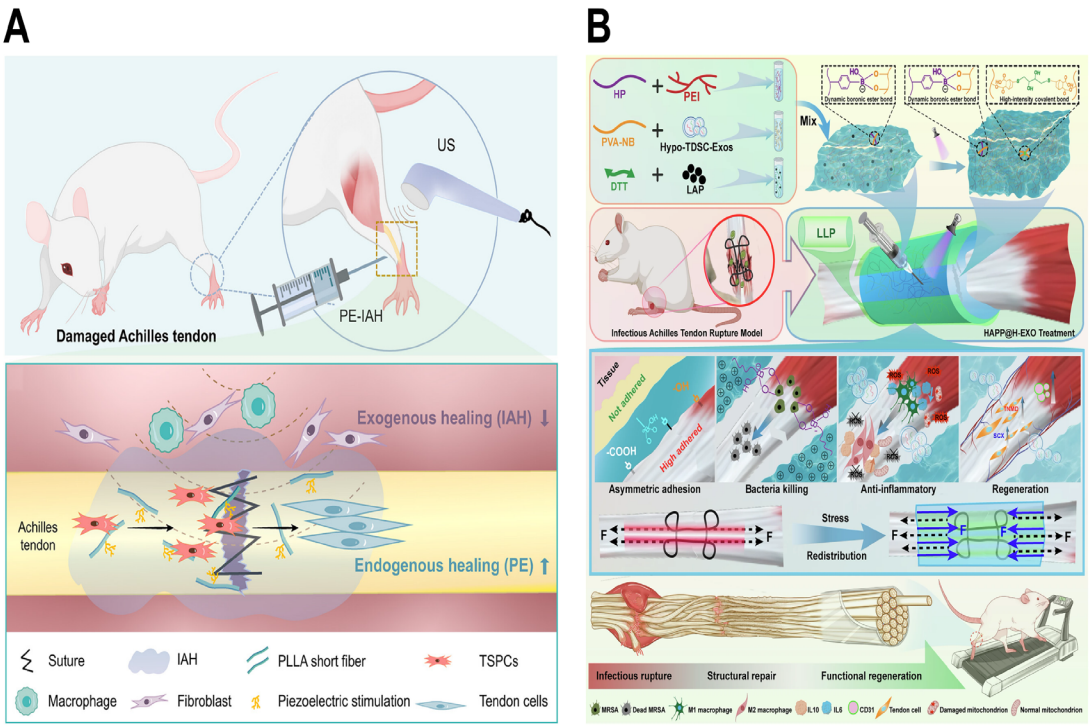

Figure 8. Schematic illustration of piezoelectric stimulation-enhanced intrinsic healing and multifunctional Janus hydrogel-promoted regeneration of infected tendon. (A) Schematic illustration of Achilles tendon repair promoted by a piezoelectric injectable anti-adhesion hydrogel (PE-IAH) combined with ultrasound. This hydrogel reduces extrinsic healing through an anti-adhesion/anti-inflammatory physical barrier and promotes tendon stem/progenitor cell (TSPC)-mediated intrinsic tendon healing via the piezoelectric response of poly-L-lactic acid (PLLA) short fibers. Reprinted with permission from Luo *et al.*[134] Copyright © 2025, Wiley-VCH GmbH. (B) Schematic illustration of the multifunctional HAPP@H-EXO Janus hydrogel, an exosome-loaded multifunctional Janus hydrogel, for the repair of an infected Achilles tendon rupture. This hydrogel promotes structural repair and functional regeneration of infected tendon through asymmetric adhesion, antibacterial and anti-inflammatory effects, exosome delivery, and stress redistribution. Reprinted with permission from Li *et al.*[137] Copyright © 2026, The Author(s).

6. Conclusion

With the development of tissue engineering and bioprinting technologies, tendon repair materials have evolved from providing simple structural support toward actively regulating cell behavior, the inflammatory microenvironment, matrix reconstruction, and tissue maturation. Natural biomaterials offer bioactivity and cytocompatibility, synthetic biomaterials provide mechanical support and structural stability, and inorganic ions and functional components can further enhance immunomodulation, angiogenesis, physical stimulation, and smart responsiveness. Future material design should focus on integrating these advantages into comprehensive systems that are printable, degradable, controllable, and matched to the stages of tendon repair.

Several challenges remain. Most material systems still struggle to simultaneously achieve printability, biocompatibility, mechanical matching, and long-term stability. Current scaffolds remain insufficient in recapitulating the hierarchical structure, interfacial gradients, and long-term mechanical function of native tendon. The release timing, safety, and translational evaluation of bioactive molecules, cells, and functional ions still require further optimization. In addition, many immunomodulatory, physical stimulation, and smart responsive strategies remain limited to *in vitro* studies or small-animal models. Future studies should strengthen the synergistic design of natural biomaterials, synthetic biomaterials, and functional components; integrate anisotropic structures, interfacial gradients, controllable delivery, and responsive regulation; and further conduct large-animal studies, long-term functional evaluations, and clinical translational research. More standardized material evaluation systems and bioprinting process standards should also be established.

Clinical translation remains a major challenge for tendon bioprinting materials. Most current studies are still based on *in vitro* experiments or small-animal models, whereas human tendon injuries often involve larger defects,

higher and more complex mechanical loads, longer healing periods, and substantial patient-to-patient variability. Therefore, results from small-animal models alone are insufficient to predict clinical efficacy, and future studies should incorporate large-animal models and long-term *in vivo* evaluations to assess tissue integration, immune and foreign-body responses, material degradation, adhesion formation, mechanical recovery, and functional outcomes. From a manufacturing and regulatory perspective, scalability, sterilization-compatible processing, aseptic fabrication, batch-to-batch reproducibility, storage and transportation, cost control, and quality control standards must also be considered at an early stage of material design. These issues are particularly important for cell-laden bioinks, exosome delivery systems, and multifunctional responsive materials, for which long-term safety, immunological risk, release stability, and regulatory classification remain insufficiently defined.

Future tendon bioprinting research should focus on several priority directions. First, multi-material cooperative printing should be further developed to integrate cell-friendly hydrogels, bioactive components, and load-bearing frameworks, thereby balancing cell loading, shape fidelity, and mechanical support. Second, gradient tendon–bone interface construction should be strengthened through region-specific control of material composition, cell distribution, degree of mineralization, and mechanical properties to better mimic the continuous transition from tendon to fibrocartilage to bone. Third, immune-responsive bioinks should be designed to regulate the resolution of inflammation, macrophage phenotypic transition, cell recruitment, and matrix remodeling in a phase-specific manner. Fourth, mechanoresponsive and multi-stimuli-responsive systems, including ROS-responsive and pH-responsive bioinks, should be explored to adapt to the dynamic mechanical and inflammatory microenvironment during tendon healing. Fifth, long-term *in vivo* validation and standardized evaluation should be emphasized, with outcome measures extending from short-term cell viability, tenogenic markers, and histological observations to tensile strength, elastic modulus, fatigue resistance, suture retention strength, gliding resistance, adhesion formation, material degradation, immune safety, and functional recovery.

Acknowledgments

None.

Funding

This work was supported by the National Natural Science Foundation of China (grant numbers 82472460, 82272504, and U23A20523), the Jilin Province Health Talent Specialisation Program (grant number 2024WSZX-C12), the Bethune Plan Project of Jilin University (grant number 2024B33), the Lixin Excellent Young Teacher Training Program of Jilin University (grant number 4190805LX119), and the Key Training Plan for Outstanding Youth of Jilin University (grant number 419070623036), and the Research Fund of the First Hospital of Jilin University (grant number JDYYCB-2023010).

Conflict of interest

Jincheng Wang is an Editorial Board Member of this journal, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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