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REVIEW ARTICLE

Three-dimensional bioprinting in tendon/ligament–bone interface regeneration: From design innovations to performance enhancement

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Abstract

The tendon/ligament–bone (T/L–B) interface represents a critical junction where tendons and ligaments anchor to bone and is characterized by a complex, graded structure. Pathological conditions caused by aging, lifestyle factors, or trauma can severely impair this interface, leading to functional deficits and a significant decline in quality of life. However, replicating the intricate structural and biological features of the native T/L–B interface remains a major challenge with conventional fabrication methods. In this context, three-dimensional (3D) bioprinting has emerged as a promising approach for tissue repair and regeneration. This review aims to summarize the application of 3D bioprinting technologies in the reconstruction of the T/L–B interface. The review first provides a brief overview of the biology of the T/L–B interface. It then examines recent innovations in 3D printing technologies, biomaterials, and gradient structure design applied to interface regeneration. The review also explores strategies for optimizing the mechanical performance and bioactivity of 3D-bioprinted scaffolds for T/L–B interface regeneration. Finally, it highlights current challenges and future directions for advancing 3D bioprinting in this field. This review provides new insights into the clinical translation of 3D-bioprinted T/L–B interface constructs and may inform the future development of next-generation orthopedic implants.

Keywords: Gradient scaffold design; Tendon/ligament–bone interface; Three-dimensional bioprinting; Tissue engineering

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1. Introduction

The tendon/ligament–bone (T/L–B) interface is a critical junction where tendons and ligaments connect to bone tissue, enabling the efficient transmission of muscle-generated forces to the skeleton.[1,2] It has a four-layered gradient structure comprising tendon/ligament, nonmineralized fibrocartilage, mineralized fibrocartilage, and bone tissue.[3,4]

This hierarchical architecture not only exhibits remarkable biomechanical complexity but also reflects a finely tuned gradation of tissue function and mechanical performance. The interface is composed of multiple cell populations and extracellular matrix (ECM) components arranged in a spatially graded manner.[5,6] In addition, tendons and ligaments connect to bone through a fibrocartilaginous transition zone, in which the progressive increase in mineral content and stiffness across layers creates a seamless mechanical and structural continuum.[7] Such a gradation effectively dissipates stress concentrations and enables the interface to withstand substantial external loading. Importantly, each layer is distinguished by specific cell types and ECM compositions, ensuring the structural integrity and biomechanical functionality of the T/L–B interface.[8]

Numerous clinical scenarios, such as common tendon/ligament injuries, rotator cuff tears, and ligament damage, place substantial demands on tissue repair and regeneration. Rotator cuff tears are among the most common sports-related injuries, especially in middle-aged and elderly individuals, and are often accompanied by extensive tendon damage.[9,10] Ligament injuries are common in the knee joint, with anterior cruciate ligament (ACL) ruptures particularly prevalent in competitive sports and high-intensity physical activities.[11,12] These injuries are often associated with severe disruption of the T/L–B interface, compromising joint stability and overall function.[13,14] Suture anchors, ligament reconstruction, and tendon transposition are commonly used clinically to treat T/L–B interface damage. However, the repaired tissue typically exhibits fibrotic scar formation rather than regeneration of the native gradational structure of the interface. As a result, the reconstructed interface frequently suffers from insufficient mechanical performance, suboptimal functional recovery, and a high risk of reinjury.[15–17] Moreover, reestablishing the intrinsic gradient architecture of the T/L–B interface after injury is difficult, as the complex anisotropy and zonal organization do not readily regenerate spontaneously.[18] Therefore, strategies that can replicate the natural anisotropic characteristics of the T/L–B interface and provide cells with appropriate mechanical and biochemical cues are crucial for successful tissue regeneration and functional restoration.[19]

Three-dimensional (3D) bioprinting has attracted considerable attention because of its ability to precisely deposit biomaterials, living cells, and biochemical components to fabricate complex tissue structures.[20,21] Using computer-aided design (CAD), 3D bioprinting enables the layer-by-layer deposition of multiple biomaterials in a spatially and temporally controlled manner, thereby generating engineered constructs with customizable architectures.[22,23] This approach helps overcome many of the limitations associated with conventional repair strategies and has been shown to significantly improve regeneration outcomes.[24,25] Importantly, 3D bioprinting offers the potential to better mimic the biological and mechanical characteristics of the native T/L–B interface. By integrating specific biochemical cues within printed scaffolds, it is possible to recreate a favorable microenvironment that promotes cell survival, differentiation, and tissue integration.[26] Through precise biomimetic design, 3D bioprinting not only allows for the optimization of scaffold mechanical properties and the enhancement of biological activity but also provides a novel and promising solution for T/L–B interface repair.[27–29] Consequently, this technology is emerging as a valuable therapeutic strategy for conditions, such as rotator cuff tears and ligament injuries.[30]

This review provides a comprehensive overview of 3D bioprinting in the repair of the T/L–B interface, with a particular emphasis on performance enhancement. Specifically, we discuss innovations in 3D printing technology, biomaterials, and gradient structure design applied to T/L–B interface regeneration. Furthermore, we also examine the strategies for optimizing the mechanical performance and bioactivity of 3D-bioprinted scaffolds for T/L–B interface regeneration. Finally, we highlight current challenges and future directions for 3D bioprinting in T/L–B interface regeneration. Unlike previous reviews that primarily provide general overviews of bioprinting applications in musculoskeletal tissue engineering, this work focuses on how to improve the mechanical strength, biological activity, and degradation behavior of bioprinted scaffolds for T/L–B interface regeneration. These optimizations help bridge the gap between laboratory experiments and clinical applications. The key topics discussed in this review are summarized in Figure 1.

2. Overview of 3D bioprinting technology and its application at the tendon/ligament–bone interface

2.1. Principles of 3D bioprinting

3D bioprinting is an advanced manufacturing technology that enables the construction of 3D biological structures by precisely depositing biomaterials in a spatially controlled manner.[31,32] The core principle relies on the use of bioinks containing living cells, biomaterials, and bioactive cues, which are deposited layer by layer under CAD guidance to fabricate constructs with predefined geometries and microenvironmental features.[33–35] This method not only enables the creation of scaffolds with highly controlled geometry, porosity, and mechanical

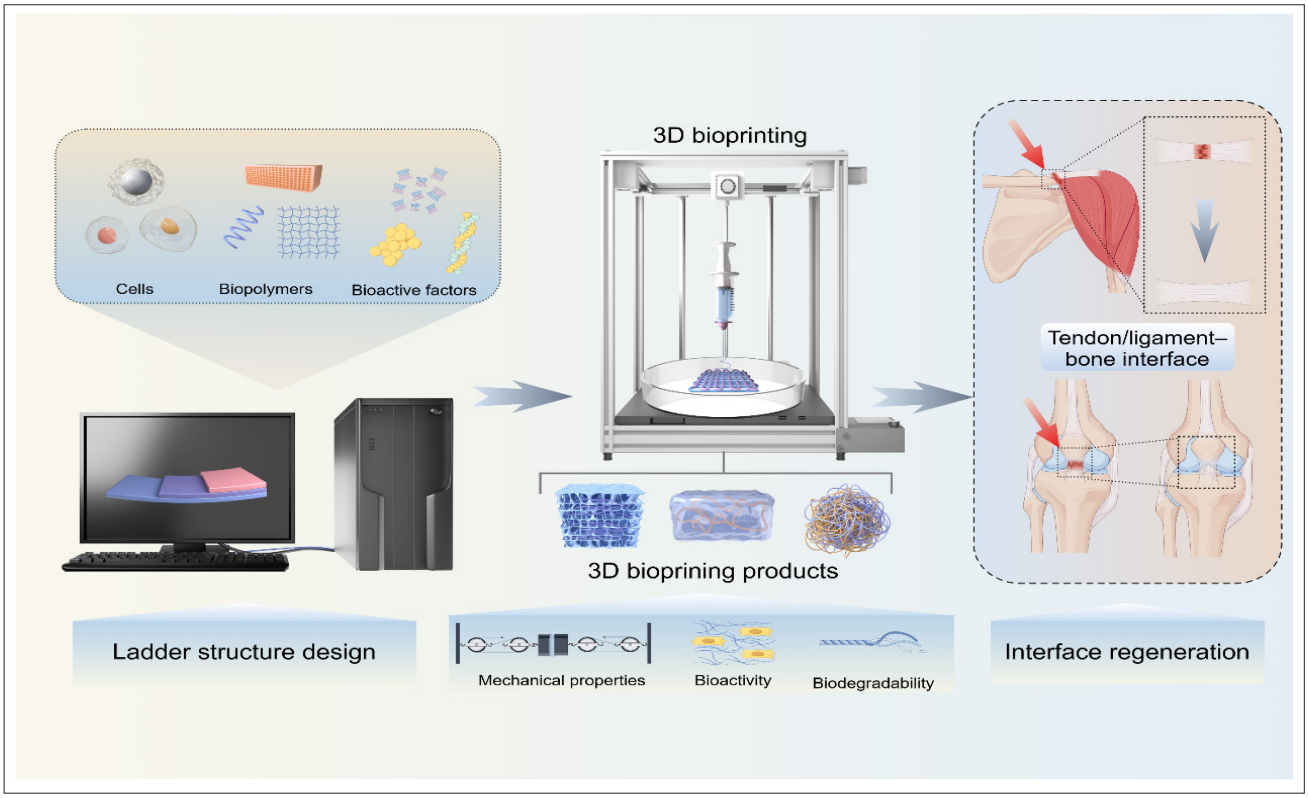

Figure 1. Schematic representation of three-dimensional (3D) bioprinting materials applied to the tendon/ligament–bone interface. Image created using Figdraw.

properties but also facilitates the construction of biomimetic scaffolds incorporating living cells and growth factors.[36,37] Compared with conventional two-dimensional approaches, 3D bioprinting offers greater design flexibility and high spatial resolution. It can more effectively mimic the complex compartmentalization, mechanical gradients, and biochemical environments of natural tissues.[38–41] As such, it opens new avenues in tissue engineering and regenerative medicine.

2.2. Major strategies for 3D bioprinting

Currently, various bioprinting strategies are based on the fundamental principles for fabricating different functional tissue structures. The main modalities are inkjet printing, extrusion bioprinting, stereolithography (SLA), and laser-assisted bioprinting.[42] For example, researchers utilized an extrusion-based 3D bioprinter to print hydrogels containing predifferentiated autologous adipose-derived mesenchymal stem cells (ADMSCs) into region-specific structures, thereby mimicking the architecture of the tendon–bone (T-B) interface.[43] Ker *et al.*[44] used an inkjet-based bioprinter to pattern geometric and biochemical cues that directed musculoskeletal cell alignment and differentiation *in vitro*, in line with fiber orientation and the printed patterns. Additionally, researchers have developed an SLA-based bioprinting platform for the multimaterial fabrication of multiphase hydrogel structures.[45] They validated the system's biocompatibility by introducing gelatin methacryloyl with encapsulated cells into a microfluidic device to fabricate cellular constructs.

2.3. Applications of 3D bioprinting in tendon/ligament–bone interface regeneration

2.3.1. Structural design and gradient material printing

Given the functional complexity of the T/L–B interface, reproducing its hierarchical and gradated structure is critical for successful repair and regeneration.[46] 3D bioprinting enables the fabrication of scaffolds with graded compositions and structures to mimic the natural transitional interface. For instance, Du *et al.*[47] successfully developed a biomimetic gradient scaffold by combining tendon/bone-associated cells with a molybdenum silicate bioceramic to mimic the hierarchical structure and cellular composition of the T-B interface. The scaffold induced tendinogenic and osteogenic differentiation of tendon/bone-related cells *in vitro* and promoted regeneration of the T-B interface *in vivo* (Figure 2A–2D). By integrating 3D cell printing with tailored bioinks, a

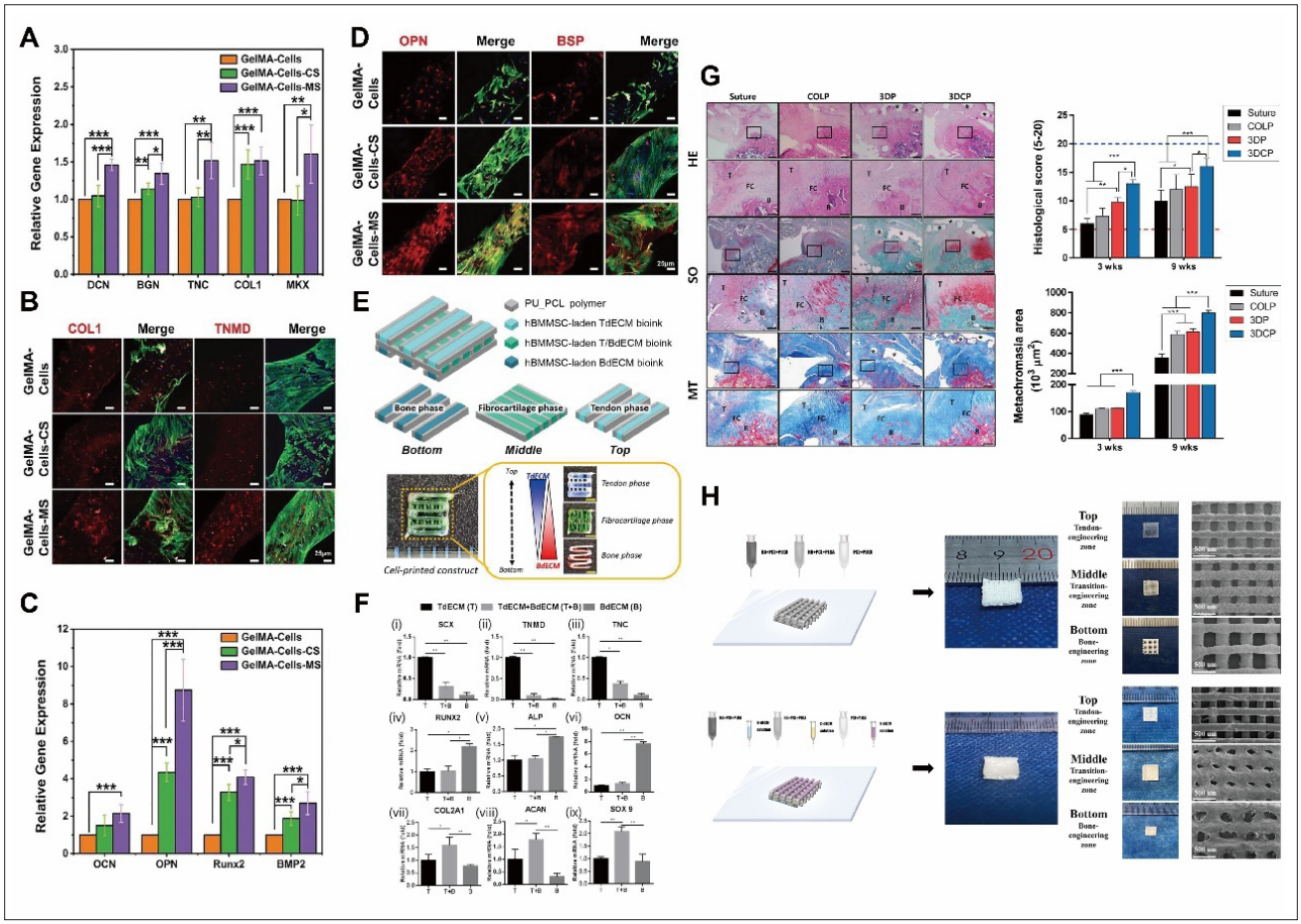

Figure 2. Gradient 3D-bioprinted scaffolds enabling spatial control of tendon-, cartilage-, and bone-lineage differentiation. (A and B) TSPC tenogenic differentiation in biomimetic multicellular scaffolds. Scale bar: 25 μm. Reprinted from.[47] (C and D) BMMSC osteogenic differentiation in biomimetic multicellular scaffolds. Scale bar: 25 μm. Reprinted with permission.[47] (E) Design and fabrication of 3D cell-printed T–B interface patches. Reprinted with permission.[48] Copyright © 2021, IOP Publishing. (F) T–B interface patches induced human BMMSCs to differentiate into tendon, cartilage, and bone at the interface. Reprinted with permission.[48] Copyright © 2021, IOP Publishing. (G) Patches promoted healing at the T–B interface *in vivo* studies. Scale bar: 500 and 200 μm. Reprinted with permission.[48] Copyright © 2021, IOP Publishing. (H) Design, manufacture, and observation of the graded biomimetic scaffold. Reprinted with permission.[51] Copyright © 2023, American Chemical Society. Abbreviations: 3D, Three-dimensional; 3DCP, Three-dimensional printed composite; 3DP, Three-dimensional printing; BdECM, Bone-derived extracellular matrix; BSP, Bone sialoprotein; COL1, Collagen type 1; COLP, Collagen peptide; CS, Cartilage sheets; GelMA, Gelatin methacryloyl; BMMSCs, Bone marrow mesenchymal stem cells; HE, Hematoxylin and eosin; MS, Muscle sheets; MT, Masson's trichrome; OPN, Osteopontin; PU_PCL, Polyurethane–polycaprolactone composite; SO, Safranin O; T–B, Tendon–bone; T/BdECM, Tendon/bone-derived extracellular matrix; TdECM, Tendon-derived extracellular matrix; TNMD, Tenomodulin; TSPC, Tendon stem/progenitor cells.

new therapeutic system has been designed to replicate the spatially graded physiological environment of the T-B interface and promote its functional regeneration.[48] The novel spatially graded T-B interface patch induced region-specific differentiation of encapsulated human bone marrow mesenchymal stem cells (BMMSCs) *in vitro*. *In vivo*, the intervention enhanced T-B interface healing, including regeneration of the transitional zone, improved collagen alignment, and increased biomechanical strength (Figure 2E–2G). Additionally, scaffold pore size and overall porosity play essential roles, as they regulate oxygen and nutrient diffusion, which is essential for cell viability.[49] Moreover, researchers have observed changes in cellular behavior as a function of pore size.[50] Zhang *et al.*[51] fabricated a graded biomimetic scaffold (GBS-E) with structural, compositional, and mechanical hierarchies using 3D bioprinting. The GBS-E scaffold demonstrated zone-specific surface topographies, each approximating the ideal pore dimensions known to promote tenogenic, chondrogenic, or osteogenic differentiation (Figure 2H). Researchers also proposed a multitissue construct with a cell-loading gradient.[52] Using 3D bioprinting technology, an inverse gradient containing T-B interface-specific bioink and stem cells was constructed to simulate the

multitissue structure and phenotype of the T-B interface, providing guidance for complex interface regeneration in animal rotator cuff models.

2.3.2. Integration of cells and bioactive factors

In addition to structural features, 3D bioprinting allows the direct incorporation of cells and bioactive molecules into scaffolds. Mesenchymal stem cells (MSCs), chondrocytes, and osteoblasts can be embedded within printed scaffolds to support proliferation, migration, and lineage-specific differentiation during regeneration.[53–55] For example, a heterogeneous T-B interface was engineered using a 3D-printed multiphasic scaffold, with tendon fibroblasts, BMMSCs, and osteoblasts seeded onto distinct scaffold phases to regenerate tenogenic, fibrocartilaginous, and osteogenic tissues, respectively (Figure 3A).[56] In addition,

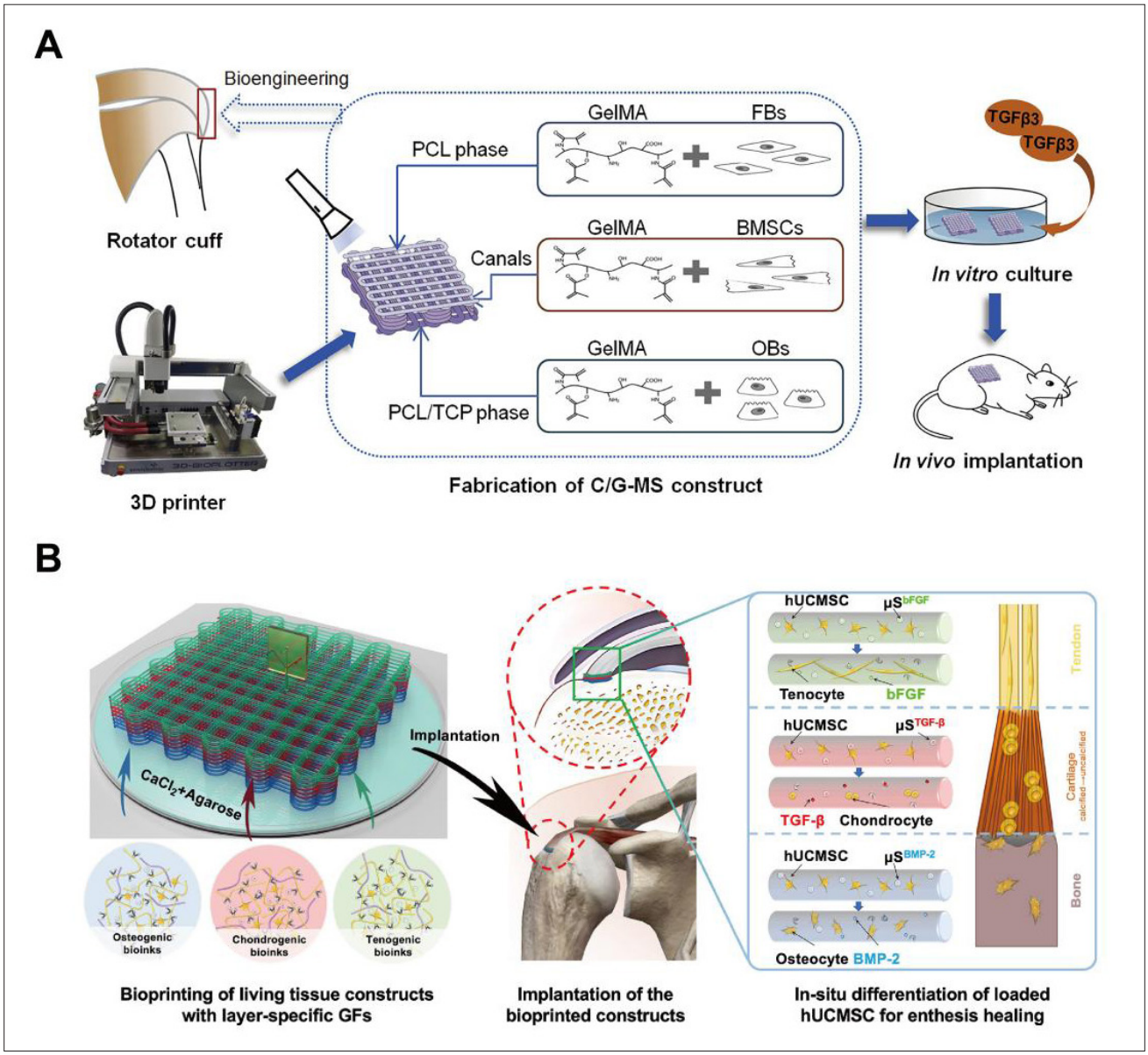

Figure 3. 3D-bioprinted constructs integrating cells, biomaterials, and cues to induce tendon-, cartilage-, and bone-like tissues. (A) Illustration of the use of 3D-printed multiphasic scaffolds to construct heterogeneous tendon-to-bone interfaces. Reprinted with permission.[56] Copyright © 2020, Elsevier. (B) Implantation of bioprinted living tissue constructs with layer-specific GF-loaded μS to facilitate zonal tenogenesis, chondrogenesis, and osteogenesis during the rotator cuff healing process. Reprinted with permission.[58] Copyright © 2022, Elsevier. Abbreviations: 3D, Three-dimensional; bFGF, Basic fibroblast growth factor; BMSC, Bone marrow mesenchymal stem cells; C/G-MS, Collagen/gelatin microspheres; FB, Fibroblast; GelMA, Gelatin methacryloyl; GF, Growth factor; hUCMSC, Human umbilical cord mesenchymal stem cells; OB, Osteoblast; PCL, Polycaprolactone; TCP, Tricalcium phosphate; TGF, Transforming growth factor.

signaling factors, such as bone morphogenetic protein-2 (BMP-2), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and transforming growth factor (TGF), can be spatially loaded or hierarchically distributed to achieve spatiotemporally controlled release, thereby regulating osteogenesis, chondrogenesis, and angiogenesis in specific regions.[57] One bioprinted construct incorporated layer-specific growth factors that directed localized differentiation of embedded stem cells into tendon-, cartilage-, and bone-like cells, significantly improving enthesis healing in a rabbit rotator cuff injury model (Figure 3B).[58] Through this synergistic integration of cells, biomaterials, and signaling molecules, 3D-bioprinted scaffolds can optimize both biofunctionality and mechanical performance during tissue repair. Table 1 summarizes the primary 3D bioprinting approaches, the associated biomaterials and bioactive molecules, and their outcomes.

3. Application of performance-optimized 3D bioprinting strategies in tendon/ligament–bone interface repair

An ideal 3D-bioprinted scaffold for T/L–B interface regeneration should not only mimic the hierarchical, graded architecture of the native interface but also optimize mechanical strength, biological activity, and degradation kinetics, thereby supporting the tissue regeneration process.

3.1. Mechanical performance optimization

The T/L–B interface, as a region subjected to complex biomechanical loads, requires repair scaffolds with robust mechanical properties to ensure that the repaired area can withstand movement and external forces during the healing process.[62–64] By tailoring fiber alignment, porosity, and compositional gradients, 3D-bioprinted scaffolds can reproduce the natural transition from soft tissue to hard tissue, thereby restoring mechanical functionality. To evaluate the mechanical performance of 3D-bioprinted scaffolds, various mechanical testing protocols have been employed. *In vitro* tensile, compressive, and cyclic loading tests are typically used to assess the elastic modulus, ultimate tensile strength, and fatigue resistance of scaffolds under conditions that simulate the physiological mechanical stress at the T/L–B interface. For example, Zhang *et al.*[65] fabricated a mechanically robust, slow-degrading polythiourethane (PHT) elastomer scaffold via a simple and rapid 3D printing method for tendon repair. The 3D-printed PHT scaffold exhibited mechanical properties comparable to those of the human supraspinatus tendon and maintained integrity after undergoing 10 000 cycles of physiological tensile loading (Figure 4A–4E). In another study, polycaprolactone (PCL), poly(lactic-

Table 1. Summary of 3D bioprinting approaches, biomaterials, bioactive molecules, and their principal outcomes

3D printing strategy	Biomaterials	Cells/Bioactive factors	Key findings	References
Extrusion	PCL	hMSCs, CTGF, TGF-β3, BMP-2	Enabled microprecise, spatiotemporal delivery of multiple growth factors.	[59]
	mPCL	Cell sheets, BMP2	Provided scompartmentalization and guided fiber alignment.	[60]
	PCL, hydrogels	ADMSCs	Supported host-cell infiltration into the multilayered scaffold and interaction with implanted autologous ADMSCs.	[43]
	Mo-containing silicate bioceramics, GelMA	TSPCs, BMMSCs	Exhibited bidirectional bioactivity, promoting both tenogenic and osteogenic differentiation.	[47]
Inkjet	Agarose hydrogel	H9C2, HUVEC	Printed heterogeneous constructs with different components.	[61]
	Polystyrene STEP fibers	FGF-2, BMP-2	Controlled stem cell orientation and directed differentiation toward multiple phenotypes.	[44]
SLA	GelMA	MSCs, fibroblasts, osteoblasts	Demonstrated efficient fabrication with noticeable improvement in speed.	[45]

Abbreviations: 3D: Three-dimensional; ADMSCs: Autologous adipose-derived mesenchymal stem cells; BMMSCs: Bone marrow mesenchymal stem cells; BMP-2: Bone morphogenetic protein-2; CTGF: Connective tissue growth factor; FGF: Fibroblast growth factor; GelMA: Gelatin methacryloyl; hMSCs: Human mesenchymal stem cells; HUVEC: Human umbilical vein endothelial cells; mPCL: Methacrylated polycaprolactone; MSCs: Mesenchymal stem cells; PCL: Polycaprolactone; SLA: Stereolithography; STEP fibers: Shear-templated electrospun fibers; TGF: Transforming growth factor; TSPC: Tendon stem/progenitor cells.

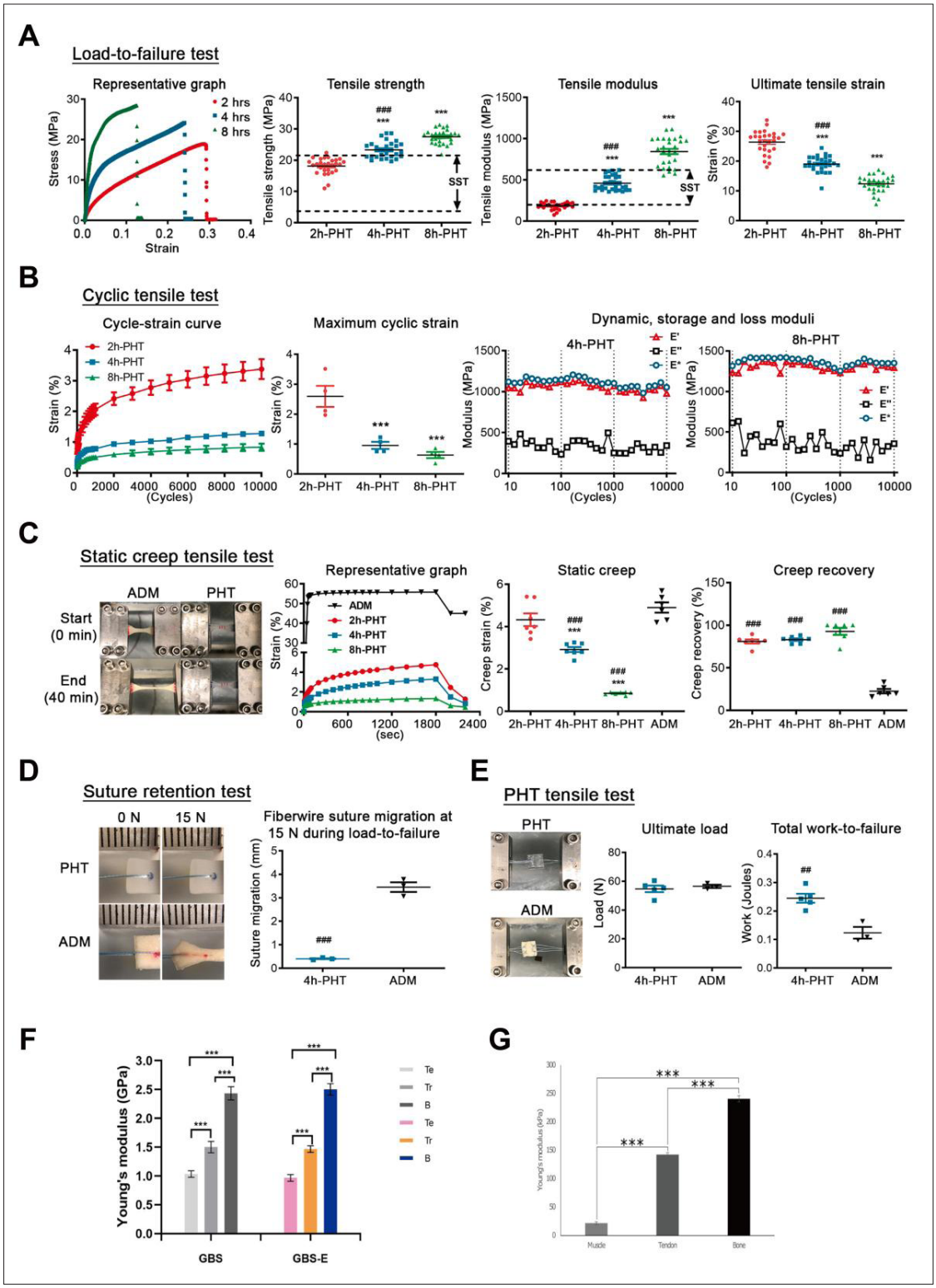

Figure 4. 3D-bioprinted scaffolds with tendon-like mechanics and a continuous stiffness gradient toward bone. (A–E) PHT polymers and 3D-printed PHT scaffolds exhibited mechanically robust, tendon-like properties. Reprinted with permission.[65] Copyright © 2024, Elsevier. (F) Young's modulus increased from the tendon-engineering zone to the bone-engineering zone along with increasing mineral content. Reprinted with permission.[51] Copyright © 2023, American Chemical Society. (G) A stiffness gradient was obtained as the Young's modulus increased. Reprinted from.[71] Abbreviations: 3D, Three-dimensional; ADM, Acellular dermal matrix; PHT, Polyhexahydrotriazine.

co-glycolic acid) (PLGA), and hydroxyapatite (HA) were combined in different ratios to fabricate triphasic scaffolds representing tendon (1:1:0), transition (1:1:2), and bone (1:1:4) regions.[51] The results indicated that the Young's modulus progressively increased from the tendon region to the bone-mimetic region as the mineral content increased (Figure 4F). *In vivo* experiments demonstrated that this scaffold exhibited favorable biomechanical properties, enhancing tendon-to-bone repair. The use of composite materials (such as bioceramic–polymer composites) can enhance the overall mechanical properties of the scaffold.[66,67] HA increases compressive strength and stiffness, whereas polymers, such as polylactic acid (PLA) and PCL, provide flexibility suitable for tendon/ligament regions.[68–70] One study developed a 3D *in vitro* model using collagen and agarose matrices with varying concentrations of HA to simulate a stiffness gradient across muscle, tendon, and bone.[71] The engineered constructs exhibited Young's moduli of 20, 140, and 240 kPa, respectively, successfully mimicking the mechanical transition from soft to mineralized tissues (Figure 4G).

3.2. Biological activity optimization

Beyond mechanical support, scaffolds must also serve as bioactive microenvironments that regulate cell behavior and drive tissue regeneration. The biological activity of 3D-bioprinted scaffolds is typically assessed through both *in vitro* cell-based assays and *in vivo* regeneration models. *In vivo* animal models, such as rabbit rotator cuff tear repair, rat Achilles tendon reconstruction, and ACL replacement, are widely used to assess osteointegration, collagen organization, fibrocartilage regeneration, and vascularization, thereby validating the regenerative efficacy of the scaffold in a physiologically relevant environment. Microchannels or porous architectures within the scaffold provide pathways for neovascularization, facilitate the distribution of angiogenic factors, and thereby improve the blood supply to the repair site.[72–74] For instance, Kim *et al.*[75] developed an innovative bioprinting method utilizing tendon- and bone-specific decellularized ECM-based bioinks supplemented with HA and TGF-β/poly(vinyl alcohol) to enhance construct functionality. The resulting complex construct induced angiogenesis, enhanced ECM formation, and supported functional restoration of full-thickness tendon-to-bone defects, with robust interface integration and improved mechanical function (Figure 5A–5C). Controlled delivery of bioactive factors represents another key strategy for enhancing scaffold bioactivity.[76] For example, osteogenic (e.g., BMP-2) and angiogenic (e.g., VEGF) factors can be loaded onto the bone side, chondrogenic factors (e.g., TGF-β) can be introduced into the cartilage or transition zone, and factors promoting fibroblast activity (e.g., FGF) can be applied to the ligament region.[77–79] Spatially patterned or temporally controlled release systems can recapitulate native biochemical gradients, enabling coordinated multitissue regeneration. One study reported that sustained, spatially regulated release of tenogenic, chondrogenic, and osteogenic growth factors was achieved through microsphere-based delivery systems incorporated into thin, membrane-like scaffolds.[59] *In vitro*, scaffolds incorporating growth factors effectively directed the spatial differentiation of mesenchymal progenitor cells, resulting in the formation of multiphasic tissues resembling tendon, cartilage, and bone regions. *In vivo*, these scaffolds promoted the integrative healing of tendon and bone via the reformation of a strong fibrocartilaginous interface (Figure 5D).

Furthermore, integrating cells with scaffolds is crucial for achieving functional repair. Cells seeded within scaffolds not only deposit ECM components but also modulate the immune microenvironment via paracrine signaling, enhancing both early stabilization and long-term integration at the repair site.[80–82] For example, researchers designed and fabricated two types of scaffolds by combining a 3D-printed PLGA scaffold with cell-laden collagen-fibrin hydrogels.[83] The findings indicated that the printed scaffolds effectively promoted the adhesion, proliferation, and tenogenic differentiation of human ADMSCs. Another study investigated 3D-bioprinted scaffold sleeves seeded with MSCs.[84] These MSC-seeded sleeves significantly enhanced osteointegration between the tendon graft and tunnel bone in a rabbit model. In general, the combined use of cells and growth factors can further augment scaffold bioactivity. A recent study designed a 3D-printed PCL scaffold loaded with basic FGF and BMMSCs (PCLMF) to restore the T–B interface and regulate the local inflammatory microenvironment.[85] This construct not only promoted osteogenesis and inhibited adipogenesis but also regulated macrophage polarization and inflammatory responses in both *in vitro* and *in vivo* settings (Figure 6A–6C).

3.3. Degradation performance optimization

In T/L–B interface repair, the degradation rate of scaffolds must be synchronized with the regeneration rate of newly formed tissues. Excessively rapid degradation may result in insufficient mechanical support, whereas overly slow degradation can trigger chronic inflammatory responses or hinder tissue integration.[86,87] The degradation kinetics can be fine-tuned by adjusting the material composition, molecular weight, and crosslinking density.[88] For example, polyester-based materials, such as PLA and PCL, exhibit predictable degradation profiles, allowing degradation time frames to be tuned by adjusting their compositional ratios.[89] Ni *et al.* analyzed the degradation of composite

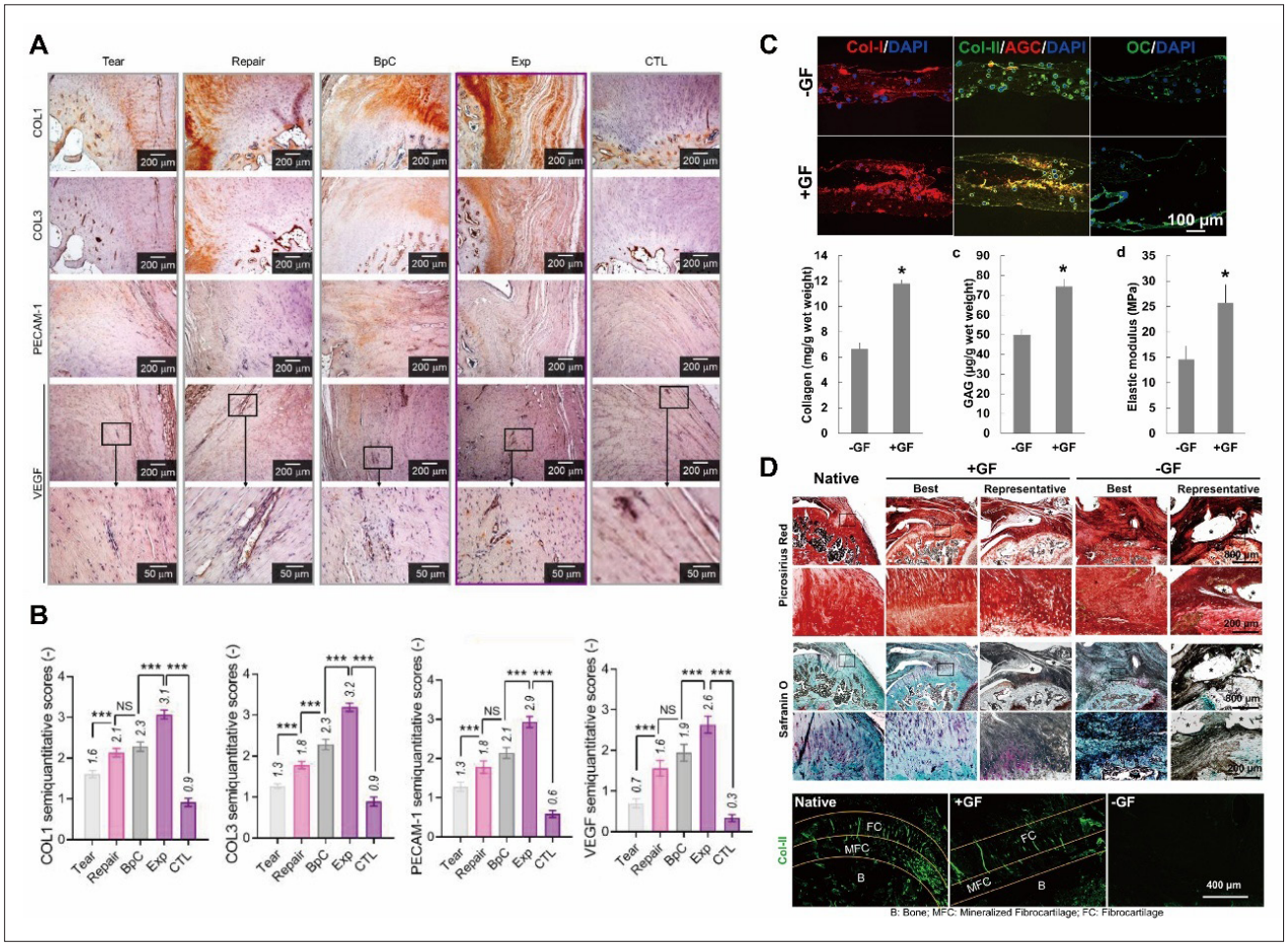

Figure 5. Bioactive 3D-bioprinted constructs enhancing vascularization and tendon–bone interface healing. (A–B) The complex construct promoted regenerative capacity, including tendon-to-bone tissue integration and vascular formation. Scale bar: 200 and 50 μm. Reprinted with permission.[75] Copyright © 2024, Elsevier. (C) Scaffolds embedded in a spatiotemporal delivery system guided the differentiation of hMSCs to form a gradient fibrocartilaginous matrix tissue. Scale bar: 100 μm. Reprinted with permission.[59] Copyright © 2019, IOP Publishing. (D) Spatiotemporal delivery of GFs via 3D-printed scaffolds improved the healing of the tendon-to-bone fibrocartilaginous interface. Scale bar: 800, 200, and 400 μm. Reprinted with permission.[59] Copyright © 2019, IOP Publishing. Abbreviations: 3D, Three-dimensional; BpC, Bone progenitor cells; COL, Collagen; CTL, Control; FC, Fibrocartilage; GAG, Glycosaminoglycan; GF, Growth factor; hMSCs, Human mesenchymal stem cells; MFC, Mineralized fibrocartilage; PECAM-1, Platelet endothelial cell adhesion molecule-1; VEGF, Vascular endothelial growth factor.

scaffolds and reported that degradation was most rapid during the first 2 weeks in both *in vitro* and *in vivo* settings, consistent with the inflammatory period following surgery.[85] Complete degradation occurred at approximately 4 weeks. Furthermore, as the scaffold degraded, its microstructure was disrupted, leading to the gradual release of loaded cytokines (Figure 6D). By the fourth week, nearly all cytokines had been released, which facilitated subsequent tissue repair. Composite scaffold design can also enable region-specific degradation. In another study, novel structural designs integrating biomaterials and stem cells were used to fabricate multilayered scaffolds with *in vivo* degradability via 3D printing.[83] Experimental findings revealed that the solid ends were partially degraded when the scaffolds were harvested. In the middle part, more than 60% of the scaffolds were degraded by the time of harvest. Table 2 summarizes the mechanical, biological, and degradation performance of 3D-bioprinted constructs used in T/L–B interface repair.

4. Conclusion and future perspectives

Although T–B and ligament–bone interfaces differ in their origins and functions, they share striking similarities in histological structure, biomechanical properties, injury repair mechanisms, and tissue-engineering strategies.[94,95] The T/L–B interface is highly specialized transitional tissues characterized by unique gradients in composition,

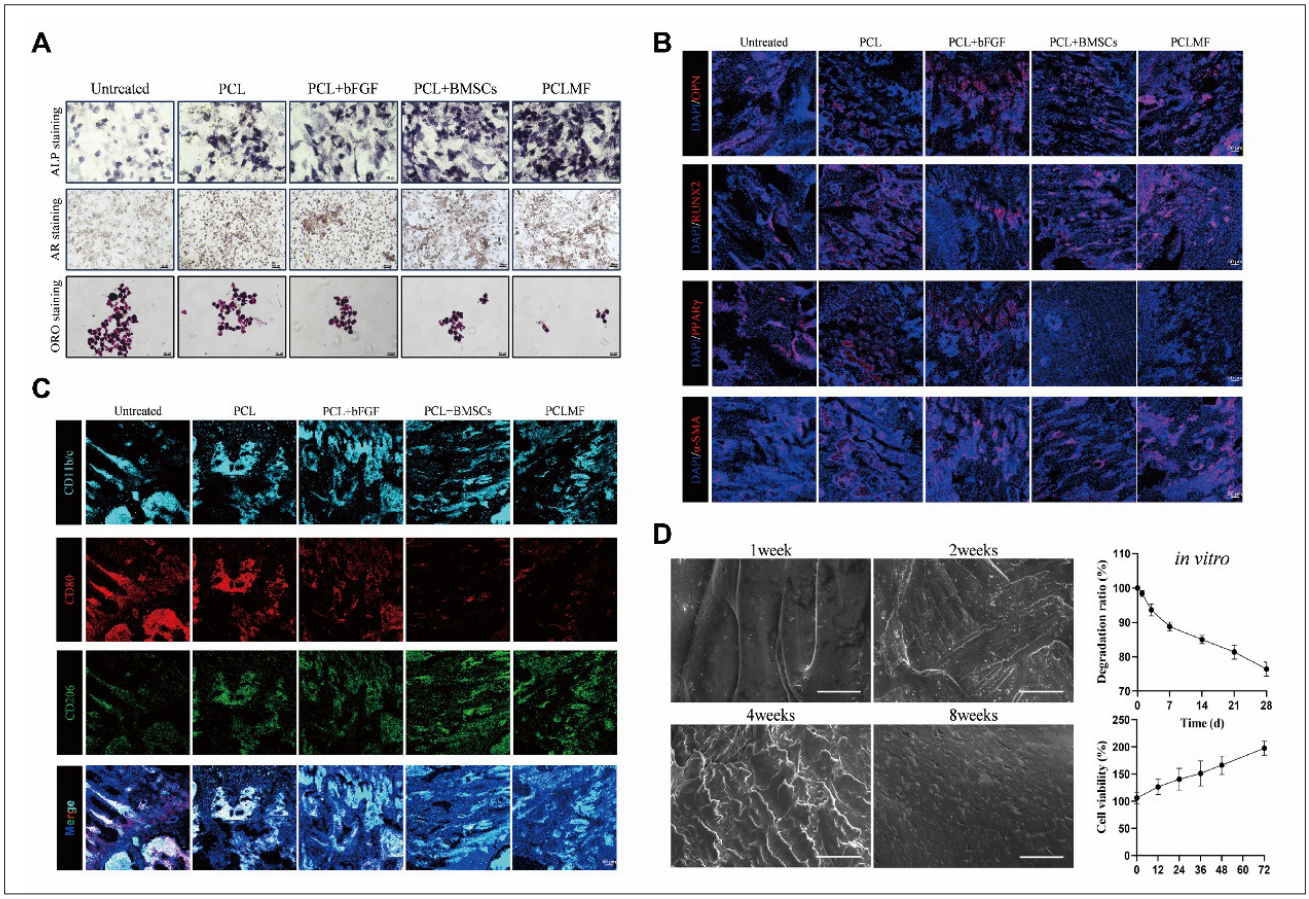

Figure 6. 3D-bioprinted scaffolds promoting osteogenesis, modulating immunity, and allowing controlled biodegradation. (A–B) 3D-printed PCLMF scaffolds promoted osteogenesis and inhibited adipogenesis both *in vitro* and *in vivo*. Scale bar: 100 and 50 μm. Reprinted with permission.[85] Copyright © 2025, American Chemical Society. (C) Modulation of macrophage polarization by 3D-printed PCLMF scaffolds *in vivo*. Scale bar: 50 μm. Reprinted with permission.[85] Copyright © 2025, American Chemical Society. (D) The PCLMF scaffold degradation rate was fastest at 2 weeks. Reprinted with permission.[85] Copyright © 2025, American Chemical Society. Abbreviations: 3D, Three-dimensional; ALP, Alkaline phosphatase; AR, Alizarin red; bFGF, Basic fibroblast growth factor; BMSCs, Bone marrow mesenchymal stem cells; ORO, Oil red O; PCL, Polycaprolactone; PCLMF, Polycaprolactone scaffold loaded with basic fibroblast growth factor and bone marrow mesenchymal stem cells.

structure, and mechanical properties.[96] Understanding the mechanobiological principles underlying these interfaces is essential for guiding effective repair strategies.[97] Current repair strategies include direct repair and graft-based reconstruction. The rapid advancement of tissue engineering has spurred the development of multiple strategies to promote graft repair and regeneration.[98–100] In this context, 3D bioprinting has emerged as a promising technology, offering spatial precision and the ability to integrate cells, bioactive molecules, and biomaterials in a highly controlled manner.[27] By enabling the fabrication of scaffolds with distinct biomechanical properties and hierarchical architectures, 3D bioprinting provides a novel pathway to recapitulate the native structure and function of the T/L–B interface.[101,102] Although the application of biological 3D printing in interface tissue engineering is rare, recent advances are still worth discussing. By emphasizing performance enhancement as the central theme, this work bridges the gap between structural design and functional outcomes, aiming to guide future translational research in T/L–B interface regeneration.

Nevertheless, significant challenges remain before clinical translation can be achieved, and these can be broadly categorized into three domains: (i) design and fabrication challenges, (ii) material challenges, and (iii) biological and translational challenges. In terms of design and fabrication, multifunctional gradient scaffolds remain technically demanding. At present, the generation of physiologically relevant heterogeneous interfaces with functionally graded spatial variations remains constrained by technical limitations.[103] Achieving scaffolds that both accurately mimic the native attachment site and maintain spatial

Table 2. Summary of the performance and outcomes of 3D bioprinted constructs used for tendon/ligament–bone interface repair.

Category	Mechanical properties	Biological activity	Degradation performance	*In vitro*/*in vivo* results	References
Tendon–bone interface	Tensile modulus: 42.94 ± 6.04 kPa; tensile strength: 159.75 ± 1.31 kPa	Increased number of spreading cells from day 4 to day 7	Lost original shape within 12–18 days	Promoted Col-I remodeling, fibrocartilage reconstruction, and osteointegration	[58]
	Tensile toughness: 3 MPa; ultimate load: 54.69 ± 2.26 N; suture migration: 0.4 ± 0.03 mm	Maintained high cell viability	Exhibited little to no mass loss under acidic/oxidizing conditions and 69% mass loss under alkaline conditions	Restored tendon biomechanical function to native levels; regenerated 1 cm of rotator cuff tendon tissue	[65]
	Ultimate load comparable to other patch types	Enhanced proliferation, migration, and tenogenic differentiation of BMMSCs	Scaffold remained only partially degraded at 8 weeks	Promoted BMMSCs' tenogenic differentiation and induced regeneration of tendon tissue	[90]
	Young's modulus increased gradually from the tendon to the bone zones	Demonstrated good cytocompatibility	Biodegradable	Improved tendon-to-bone healing by promoting zone-specific cellular differentiation	[51]
	Tri-layered scaffolds exhibited higher elastic stiffness compared with individually printed single-layer scaffolds	Increased cell proliferation rate within scaffolds	PLGA partially degraded during culture; the collagen–fibrin hydrogel became thinner after 14 days	Supported human ADMSC viability and tenogenic differentiation; showed excellent biocompatibility and *in vivo* degradability	[83]
	Provided reliable mechanical properties	Enabled efficient cell proliferation and adhesion on scaffold fibers	Displayed an appropriate degradation rate	Promoted stratified cell seeding and chondrogenesis	[56]
	Significantly increased strength of regenerated tendon	Showed no cytotoxicity and no adverse effect on rabbit BMMSC proliferation	PLGA mass loss: 25% (4 weeks), 43.3% (8 weeks), 75.7% (12 weeks)	Improved collagen organization and fibrocartilage deposition	[91]
Ligament–bone interface	Linear stiffness: 130.6 ± 12.54 N mm^{-1}; compressive modulus: 29.03 ± 3.35 MPa	Maintained cell viability	Not described	Promoted rapid tissue infiltration, vascularization, and compartmentalization	[60]
	Increased tensile toughness, modulus, and yield stress	Improved cell attachment and homogeneous cell distribution	Supported bone regeneration with simultaneous scaffold degradation	Induced MSC differentiation toward the osteoblast lineage; coordinated bone and periodontal regeneration	[92]
	Facilitated improved integration and enhanced mechanical properties	Demonstrated optimal cellular affinity and osteogenic potential for BMMSC differentiation	Not described	Promoted stem cell differentiation into tendon and bone cells; enhanced ACL repair and healing	[93]

Abbreviations: ACL: Anterior cruciate ligament; ADMSCs: Autologous adipose-derived mesenchymal stem cells; BMMSCs: Bone marrow mesenchymal stem cells; MSC: Mesenchymal stem cell; PLGA: poly(lactic-*co*-glycolic acid).

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continuity with biologically specific gradient distributions will require innovations in material systems and printing strategies. Moreover, reproducing the anisotropic collagen fiber orientation and progressive mineralization patterns of the native interface remains a critical hurdle.[104,105] From a materials standpoint, the native tendons and ligaments endure complex tensile, compressive, and shear forces, demanding scaffolds with high load-bearing capacity, fatigue resistance, and dynamic adaptability.[106,107] Existing biomaterials often struggle to strike a balance between printability and long-term mechanical stability, highlighting the urgent need to develop novel composite or hybrid materials.[108] In addition, integrating diverse biological cues and cell sources is indispensable for engineering optimal multitissue interfaces.[52,109] Scaffolds must not only support cell adhesion, proliferation, and differentiation but also actively coordinate osteogenesis, chondrogenesis, and tenogenesis in a spatially regulated manner.[110] From biological and translational perspectives, several key obstacles continue to impede the clinical application of 3D-bioprinted constructs. The precise spatiotemporal delivery of bioactive signals, such as growth factors, peptides, and extracellular vesicles, remains an area requiring substantial refinement. Additionally, limitations in printing resolution, bioink properties, and immunocompatibility must be addressed to ensure reproducibility and safety.[111,112] Beyond the technical aspects, tissue integration and regulatory approval represent crucial bottlenecks in translating laboratory-scale constructs into clinical-grade therapeutic products. Overcoming these multifaceted challenges is essential for advancing 3D bioprinting from experimental innovation to practical orthopedic applications.

Future progress will depend on continuous innovations in scaffold design, functional materials, and biomanufacturing technologies to engineer musculoskeletal interfaces with native-like gradient mechanics. Future research should place greater emphasis on the role of mechanobiological principles in interfacial regeneration. By integrating materials science, tissue engineering, biomechanics, and computational modeling, it will be possible to better elucidate the dynamic interactions among cells, biomaterials, and their mechanical environment.[113] The development of next-generation multifunctional biomaterials represents another promising direction.[114] These dynamic, stimuli-responsive materials can direct cell growth, alter degradation rates, or release bioactive molecules in response to mechanical stress or inflammatory cues.[115,116] Ideally, such materials should have mechanical strength, bioactivity, and immunomodulatory capacity while offering antibacterial or anti-inflammatory properties to minimize postoperative complications. Beyond this, integrating 3D printing with nanomedicine and synthetic biology aids in optimizing scaffold structures to better mimic the native tissue environment. Just as importantly, establishing specialized regulatory frameworks tailored to bioprinted medical products—including safety, immunogenicity, and standardization guidelines—will be essential to accelerate clinical translation. If these challenges can be addressed, 3D bioprinting may provide transformative therapeutic solutions for common injuries, such as rotator cuff tears and ACL ruptures.

In summary, 3D bioprinting holds tremendous potential for regenerating T/L–B interfaces, with its core strength in precisely reconstructing their complex hierarchical architecture and biological characteristics. The future of this technology relies on interdisciplinary innovations spanning biomaterials science, biomechanics, tissue engineering, and biomanufacturing. By overcoming current barriers in scaffold design, bioactivity, and translational manufacturing, 3D bioprinting could evolve from a conceptual strategy into a clinically viable solution, ultimately enabling functional regeneration of the T/L–B interface.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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