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Review

Advanced engineering strategies for biomaterial scaffolds application in tendon–bone interface regeneration

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Abstract

Tendon–bone interface injuries, such as rotator cuff tears and anterior cruciate ligament ruptures, remain challenging due to the enthesis's complex structure and poor healing capacity. Conventional repair often fails to restore the fibrocartilaginous transition, causing mismatched integration and high retear rates. Biomaterial-based scaffolds provide biomechanical support and bioactive regulation, showing great promise for regeneration. Recent advances span natural polymers, synthetic polymers, bioceramics, and composites, with designs evolving from monophasic to multiphasic, gradient-based, and functionalized scaffolds. Emerging strategies emphasize immunomodulation, bio-signal delivery, and physical responsiveness, establishing a structure–signal–function paradigm to guide multi-tissue integration. However, translation faces major barriers, including inadequate animal models, manufacturing and scalability challenges, long-term safety concerns, and regulatory complexity, as well as the need to balance personalization with cost. Future directions point to intelligent biomaterials, AI-driven design, and integrated translational frameworks to bridge preclinical research and clinical application. Overall, advanced scaffold engineering offers transformative potential for functional tendon–bone regeneration, but successful translation will depend on close collaboration among biology, materials science, engineering, and medicine.

Keywords: tendon–bone interface; rotator cuff; biomaterials; clinical translation

Background

With the intensifying trend of global population aging, tendon-to-bone injuries, such as rotator cuff tears and anterior cruciate ligament (ACL) ruptures, are emerging as increasingly critical clinical challenges. It is estimated that more than 4 million new cases of tendon-to-bone injuries are reported annually, accounting for over 30% of all musculoskeletal disorders [1]. The incidence of these conditions appears to correlate positively with age. For instance, the prevalence of rotator cuff tears ranges from 5% to 33% in the general population, whereas it increases to ∼ 25% in individuals over 65 years old and exceeds 50% in those aged over 80 years [2, 3]. Taken together, these epidemiological data underscore an urgent clinical need for more effective tendon–bone repair strategies capable of reducing retear rates and restoring durable mechanical function.

Taking rotator cuff tears as an example, tendon–bone injuries can be classified into different grades according to the extent of tearing: partial-thickness tear, small full-thickness tear, and massive full-thickness tear. However, regardless of the model, surgical reconstruction of the tendon-to-bone interface remains the primary treatment for severe tears [4, 5], with reattachment of the torn tendon to its footprint on bone regarded as the gold standard for repair [6] (Figure 1a). Globally, more than 1.1 million rotator cuff repair procedures are performed each year, including over 600 000 cases annually in the USA alone [7, 8]. However, due to technical limitations, current surgical approaches merely excise degenerated tissue and reattach the tendon to the footprint, without achieving microscale reconstruction of the native tendon-to-bone interface. This lack of biological integration between tendon and bone results in scar-mediated healing and contributes to persistently high retear rates [9, 10]. Reported recurrence rates reach 26% in patients with minor tears and up to 94% in those with massive tears, leading to considerable physical and psychological burdens on patients and the repeated consumption of substantial healthcare resources each year [11, 12]. However, current surgical approaches fail to biologically reconstruct this multiscale hierarchical interface, which explains the limited regenerative capacity and persistent retear risk.

A thorough understanding of the tendon-to-bone interface is a prerequisite for developing effective therapeutic strategies. Based on the mode of connection, the tendon-to-bone

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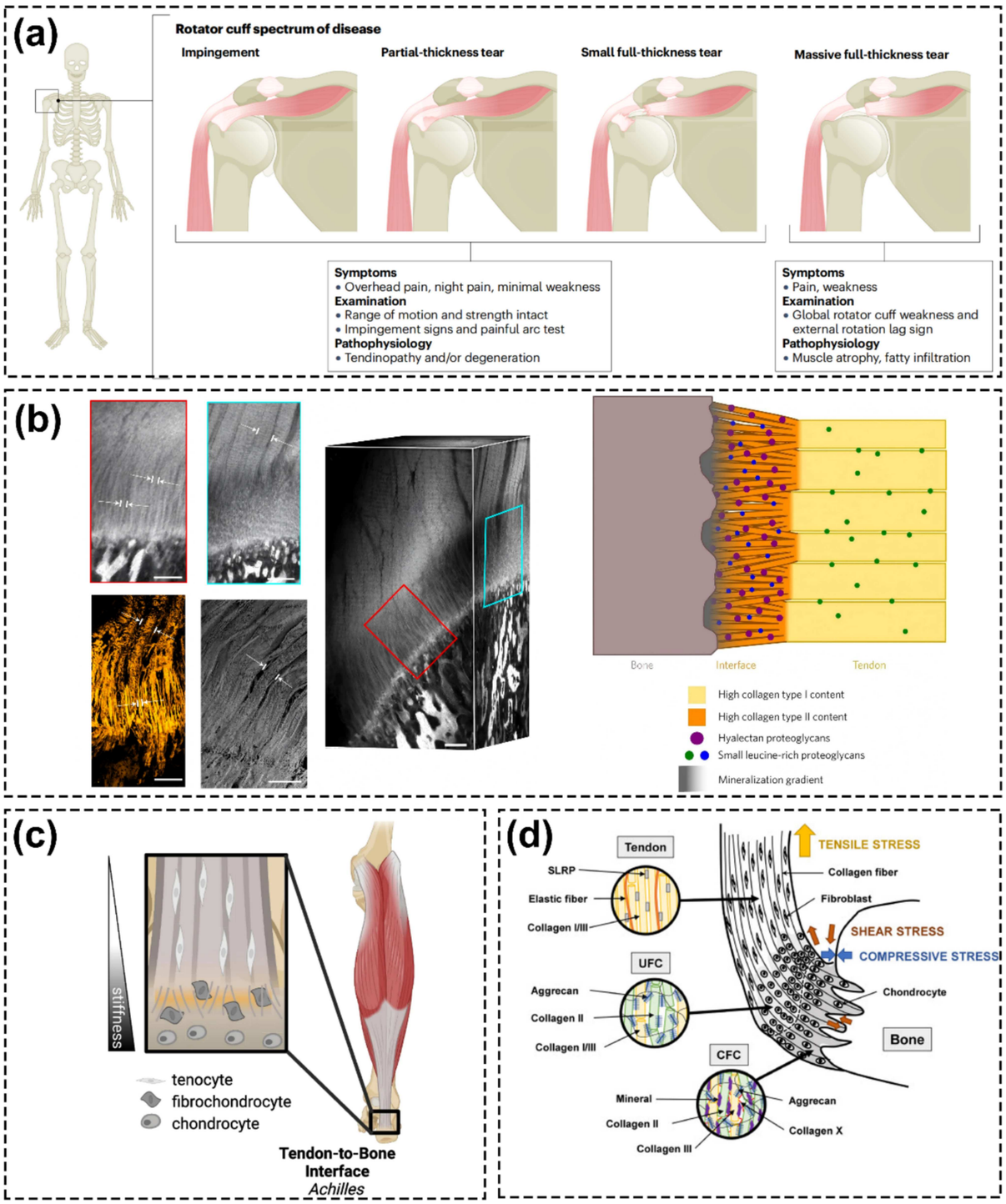

Figure 1. Overview of tendon-to-bone interface structure and pathology. (a) Representative pathology and functional differences in rotator cuff pathology (adapted with permissions [13]. Copyright 2024, Springer Nature). (b) Enthesis high-resolution microcomputed tomography (μCT) and fundamental structural and molecular components, scale bars = 250 μm (adapted with permissions [14]. Copyright 2017, Springer Nature). (c) Tendon-to-bone interface (adapted with permissions [15]. Copyright 2024, Springer Nature). (d) Schematic representation of a fibrocartilaginous enthesis exemplified by the Achilles tendon enthesis (adapted with permissions [16]. Copyright 2021, Elsevier).

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Table 1. Comparative summary of scaffold parameters derived from natural polymers, synthetic polymers, and bioceramics

Material types	Specific category	Animal model	Follow-up	Sample size	Ultimate load-to-failure	Reference
Natural polymer-based materials	COL I, SF	Rabbits, $n = 20$	12 weeks	≈2 cm × 2 cm	\	[38]
	COL I	Rabbits, $n = 40$	8 weeks	20 mm × 3.5 mm × 3 mm	211.56 ± 15.17 N	[39]
	HA	Rabbits	12 weeks	\	109.6 ± 40.2 N	[40]
	Alginate	SD rats, $n = 20$	8 weeks	10 mm × 50 mm × 0.3 mm	105.34 ± 18.14 N	[41]
	ECM	SD rats, $n = 48$	8 weeks	10 mm × 10 mm × 0.2 mm	23.5 ± 0.56 N	[43]
Synthetic polymer-based materials	PET	Rabbits, $n = 16$	12 weeks	20 mm × 4 mm	124.5 ± 5.5 N	[61]
	PLLA	Rabbits, $n = 144$	12 weeks	80 mm × 80 mm × 0.5 mm	181.5 ± 19.0 N	[26]
	PCL	Rabbits, $n = 8$	12 weeks	20 mm × 20 mm × 0.9 mm	16.053 N	[62]
Bioceramics	β-TCP	SD rats, $n = 24$	12 weeks	3 mm × 5 mm	\	[63]
	PCl, SiO_2	SD rats, $n = 12$	8 weeks	10 mm × 10 mm	\	[64]

Abbreviation: collagen type I (COL I).

interface can be classified into fibrous and fibrocartilaginous types, with the tendon–fibrocartilage–bone configuration representing the classical fibrocartilaginous attachment [17]. However, due to its highly complex and heterogeneous architecture, this interface has an extremely limited capacity for spontaneous healing following severe full-thickness tears [18]. Consequently, the repair of such soft-to-hard tissue junctions remains a major challenge in the field. Specifically, the fibrocartilaginous tendon-to-bone interface can be subdivided along the direction of mechanical force transmission into four distinct regions: tendon, uncalcified fibrocartilage, calcified fibrocartilage, and bone [19] (Figure 1d). Each region exhibits unique cellular compositions and extracellular matrix (ECM) characteristics. The tendon region primarily consists of Type I collagen with small amounts of core proteoglycans [20]. The unmineralized fibrocartilage region contains Type II and Type III collagens, as well as aggrecan and core proteoglycans [21]. The mineralized fibrocartilage region is enriched in Type II and Type X collagens together with aggrecan, where mineral deposition and calcification begin to occur. Finally, the bone region comprises a densely mineralized Type I collagen matrix [22–24] (Figure 1b and c). During joint motion, the tendon enthesis must withstand both tensile and compressive forces, and it is the well-integrated transition between these soft and hard tissues that effectively dissipates the high stresses concentrated at the interface [24]. Such structural and compositional heterogeneity fundamentally constrains the intrinsic healing potential of the interface following full-thickness injuries.

Following conventional surgical repair, the healing tendon-to-bone interface often lacks the essential functional gradient transition, resulting in structural mismatch between tendon and bone and consequent stress concentration—one of the primary causes of recurrent injury [25, 26]. In addition, the aberrant microenvironment surrounding the postoperative interface contributes to poor prognosis. An imbalance between anti-inflammatory (M2) and pro-inflammatory (M1) macrophages at the interface drives a sustained inflammatory response [27], while the excessive secretion of inflammatory cytokines not only suppresses fibrocartilage regeneration but also enhances osteoclast activity. As a result, the originally well-organized fibrocartilaginous layer is replaced by disorganized fibrovascular scar tissue, severely impeding the coordinated regeneration of different interface zones [28, 29]. Furthermore, suboptimal bone mineral density [30], fatty infiltration of the muscle [31], and inappropriate postoperative rehabilitation strategies [32] can all negatively impact tendon-to-bone healing to varying degrees. These challenges underscore the urgent need for an efficient, precisely controlled, and temporally orchestrated strategy for tendon-to-bone interface repair. Thus, both biomechanical discontinuity and dysregulated immune microenvironments jointly contribute to the poor prognosis observed after conventional repair.

These converging challenges highlight the necessity of engineered scaffolds capable of recapitulating the structural gradients, modulating the immune microenvironment, and providing spatiotemporally coordinated cues for tendon–bone regeneration. Accordingly, this review focuses on state-of-the-art scaffold design strategies and their potential to overcome current biological and translational barriers.

Review

Scaffold raw materials: categories and characteristics

Despite considerable advances in surgical techniques and biomaterial design, there remains a significant gap between experimental success and clinical translation. Many scaffolds that demonstrate promising biological performance in preclinical studies face challenges in large-scale production, regulatory approval, and cost-effectiveness, thereby hindering their industrialization and widespread clinical adoption. To move toward clinically applicable and commercially viable solutions, it is essential to critically assess scaffold candidates not only from a biological perspective but also in terms of their source materials, manufacturability, and scalability. In the design of implantable scaffolds for tendon–bone repair, it is therefore essential to consider the biocompatibility of all constituent materials, the biomechanical support properties of the scaffold itself, and its potential functional roles. Careful selection of raw materials and advanced processing or modification strategies are of particular importance [33]. The complex and heterogeneous structure of the tendon–bone interface presents significant challenges for scaffold design, including the choice of scaffold type, the selection of material composition, scaffold architecture, the interplay between different phases in multiphasic scaffolds, and the degradation behavior of the scaffold. Collectively, these factors not only determine the extent of tissue regeneration at the tendon–bone interface but also directly influence the feasibility of clinical translation and long-term postoperative outcomes. Biomaterials used in tendon–bone interface regeneration are highly diverse and can be broadly classified into three main categories—natural

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Table 2. Comparative summary of scaffold parameters

Matrix styles	Scaffolds types	Fabrication methods	Composition	Animal model	Follow-up	Ultimate load-to-failure	Reference
Structural architecture	**Monophasic scaffolds**	Freeze-drying	ECM	Human cadaveric, $n = 8$	\	325 ± 74 N	[73]
		Freeze-drying	Collagen	Adult ewes, $n = 8$	24 weeks	894 ± 267 N	[75]
		Electrospinning combined with twisting	PDO	Lewis rats, $n = 36$	20 weeks	\	[82]
		Capillary force lithography	PCL	Rabbits, $n = 24$	12 weeks	\	[79]
	Multiphasic layered scaffolds	Knitting	SF, chondroitin sulfate, HA	Rabbits, $n = 27$	24 weeks	42.7 ± 4.3 N	[93]
		3D printing	Mo-containing silicate	Rabbits, $n = 16$	12 weeks	≈55 N	[96]
	Multiphasic gradient transitional scaffolds	Dual-gradient syringe pumps	Sodium alginate, BG	SD rats, $n = 16$	8 weeks	24.87 ± 1.86 N	[99]
		Template method	Collagen-glycosaminoglycan	\	\	\	[101]
Functionalized scaffolds	**Functional type**	Fabrication methods	Composition	Animal model	Follow-up	Ultimate load-to-failure	
	Immunomodulatory scaffolds	Electrospinning	PEUU, MBG	SD rats, $n = 128$	8 weeks	32.08 ± 2.71 N	[28]
		Electrospinning	Wnt3a protein, PCL	SD rats, $n = 50$	8 weeks	≈4 N	[106]
		Electrospinning	PEFUU, FA	SD rats	8 weeks	48.20 ± 3.22 N	[112]
	Bio-signal-stimulating scaffolds	Electrospinning, non-solvent-induced phase separation	PCL, GelA, nGel-KGN	SD rats	8 weeks	\	[113]
		Electrospinning,	PEEUU, GEL, KGN	SD rats, $n = 72$	8 weeks	$6.9 \text{ N} \pm 1.6$ N	[114]
		Vacuum-induced biomineralization	Fish scale	Rabbits, $n = 20$	12 weeks	146.53 ± 11.2 N	[122]
	Physically responsive scaffolds	Sequential electrospinning	PLLA, ZnO, BTO	SD rats	4 weeks	18.36 ± 1.93 N	[125]
		Electrospinning	PVDF-co-TRIF	SD rats, $n = 105$	8 weeks	\	[126]
		Electrospinning	Gel, PLGA, nHA, BTO	Rabbits, $n = 36$	12 weeks	\	[127]

Abbreviations: FA, ferulic acid; GEL, gelatin; PDO, polydioxanone; PEFUU, poly(ester-ferulic acid-urethane) urea; PEUU, poly(ester urethane urea); PVDF-co-TRIF, poly(vinylidene fluoride-co-trifluoroethylene).

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polymers, synthetic polymers, and bioceramics—either used alone or in combination as composite materials [34–36].

Natural polymer-based materials

Among natural polymers, the most commonly used in tendon–bone repair scaffolds include proteins: collagen, gelatin (GEL), silk fibroin (SF), elastin and polysaccharides, such as chitosan, hyaluronic acid (HA), alginate, and cellulose. Owing to their compositional similarity to native tissues, these materials generally elicit minimal immune responses and provide intrinsic recognition sites that support cell adhesion, migration, and differentiation. Moreover, during degradation, they can release bioactive fragments that modulate cellular behavior and promote tissue regeneration [37]. From an industrial perspective, such biomimetic properties confer a unique advantage: natural polymers are already widely applied in approved medical products (e.g. collagen membranes, HA hydrogels), which lowers translational barriers for scaffold development. Furthermore, their compatibility with composite fabrication strategies allows researchers to combine them with synthetic polymers or ceramics, thereby enhancing mechanical stability and functional tunability.

Several preclinical studies highlight the regenerative potential of natural polymer-based scaffolds. For example, Qian *et al.* developed a novel orthopedic scaffold composed of collagen and SF for tendon–bone interface repair. In a rabbit model, the scaffold facilitated the formation of a new fibrocartilage layer at the interface after 12 weeks, demonstrating its potential to improve tendon–bone healing [38]. Similarly, Meimandi-Parizi *et al.* reported that three-dimensional GEL implants improved both the biomechanical strength and the mobility of rabbits with large tendon defects [39]. HA, already used clinically in visco supplementation, has also demonstrated promising outcomes in tendon–bone repair. Honda *et al.* applied HA to completely transected rabbit infraspinatus tendons and observed significantly higher ultimate failure loads at fourth and eighth weeks post-surgery compared with controls. This demonstrated that HA not only accelerated tendon–bone healing in a rotator cuff repair model but also improved biomechanical strength and promoted fibrocartilage formation and tendon maturation [40]. Likewise, Yoon *et al.* utilized alginate sheet scaffolds incorporated with a small amount of graphene oxide (GO) in a rat rotator cuff model. The GO alginate scaffold markedly increased ultimate failure load, stress, and stiffness, while facilitating collagen fiber bridging and tendon–bone integration [41].

Decellularized ECM, a unique protein–polysaccharide composite, is obtained by removing cellular components from native tissues while preserving their complex three-dimensional architecture [42]. Owing to their high yield, ready availability, and excellent biocompatibility both *in vitro* and *in vivo*, decellularized matrices have been widely applied as substitute biomaterials for tissue regeneration. Li *et al.* designed a bilayer, book-shaped decellularized matrix scaffold for rotator cuff repair. Functionalized with Mg^{2+} and tannic acid, the scaffold exhibited immunomodulatory and reactive oxygen species scavenging properties. In a rat rotator cuff model, scaffold implantation significantly enhanced bone formation, increased maximum load and stiffness, and promoted the development of a more mature fibrocartilage zone [43]. Importantly, the use of ECM scaffolds benefits from relatively abundant raw material sources (e.g. animal tissues), offering scalability advantages compared to some other natural polymers.

Despite these encouraging results, the industrial translation of natural polymer scaffolds remains challenging. Limitations such as poor mechanical strength, unpredictable degradation rates, and batch-to-batch variability due to raw material differences hinder standardization and quality control. Moreover, decellularization processes may leave behind chemical residues, and the bioactive components responsible for therapeutic effects remain insufficiently characterized [44, 45]. In practice, additional crosslinking or blending strategies are often required to ensure reproducible scaffold performance. Taken together, while natural polymers provide an excellent biological foundation and some have existing clinical precedents, their direct large-scale use for tendon–bone scaffold manufacturing faces significant hurdles. Overcoming these barriers will require advances in raw material standardization, scalable processing, and regulatory alignment to enable industrially feasible products.

Synthetic polymer-based materials

Compared with natural polymers, synthetic polymers exhibit superior mechanical properties and flexibility, making them more suitable for applications in tissues where high mechanical demands are required. Their controlled manufacturing processes ensure greater reproducibility, reduced immunogenicity, and improved biosafety, thereby minimizing some of the translational barriers encountered by natural biomaterials. From an industrial perspective, synthetic polymers offer distinct advantages in terms of large-scale production, raw material availability, and quality control, which explains their prominent role in medical devices and tissue engineering. Based on their degradation behavior, synthetic polymers can be categorized into nondegradable and biodegradable polymers, which are selected to match the requirements of different target tissues.

Nondegradable synthetic polymers such as polyethylene terephthalate (PET), polytetrafluoroethylene, and polyethylene have been widely used in tendon–bone interface repair. These materials provide strong and long-lasting mechanical support during tendon–bone healing and demonstrate greater durability compared with degradable polymers. However, their inability to degrade *in vivo* makes them largely biologically inert, meaning that they cannot integrate with host tissues. Prolonged implantation often leads to foreign body reactions and related complications [1, 46]. In the 1980s, three synthetic ligament devices were approved by the US Food and Drug Administration (FDA) for ACL reconstruction: the Gore-Tex cruciate ligament prosthesis (WL Gore and Associates, approved 10 October 1986), the Stryker Dacron ligament prosthesis (Meadox Medicals, Inc., approved 30 December 1988), and the 3 M Kennedy LAD™ ligament augmentation device (3 M, approved 7 May 1987). Although these devices initially demonstrated promising short-term outcomes, long-term follow-up revealed implant degradation, chronic inflammation, and severe synovitis, ultimately leading to regulatory withdrawal [47]. These historical experiences underscore a key industrial lesson: permanent inert implants may succeed in early adoption but face sustainability challenges when adverse long-term outcomes accumulate. More recently, the LARS ligament (Dijon, France), a second-generation nonabsorbable device composed of PET fibers, was introduced and has been approved in multiple

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countries for ACL reconstruction, Achilles tendon repair, and acromioclavicular joint repair. Clinical studies have suggested that the LARS ligament demonstrates improved mechanical strength and biocompatibility compared with earlier synthetic devices, with fewer severe complications. Nonetheless, as a permanent implant, it continues to face concerns regarding chronic inflammation and lack of synchronized remodeling with host tissues, limiting its broader industrial scalability [48–52].

As a result, research and commercial development have shifted toward biodegradable synthetic polymers, which aim to combine early mechanical reinforcement with gradual resorption and tissue regeneration. Biodegradable polymers such as polylactic acid (PLA), polyglycolic acid (PGA), poly (lactic-co-glycolic acid) (PLGA), and polycaprolactone (PCL) are widely used in tendon–bone scaffold design due to their controlled degradability and excellent processability. These polymers contain ester, amide, or anhydride bonds, which are susceptible to hydrolytic and enzymatic cleavage [53]. The degradation products of PLA and PGA are lactic acid and glycolic acid, respectively—both intermediates of the tricarboxylic acid cycle—ensuring excellent biodegradability and biocompatibility without inducing inflammation, immune rejection, or cytotoxicity. Thus, they have been extensively applied in bone, cartilage, vascular, neural, and skin tissue engineering [54]. For example, X-Repair® (Synthasome, USA), a poly (L-lactic acid) (PLLA)-based mesh, has been used as a synthetic patch reinforcement in combination with sutures for large-to-massive rotator cuff tears in 18 patients, achieving favorable outcomes [55]. Wang *et al.* further developed a 3D-printed PCL-based scaffold doped with magnesium ions for rotator cuff repair in rabbits. Both *in vitro* and *in vivo* results demonstrated superior osteogenic capacity, enhanced tissue ingrowth, and improved biocompatibility compared with controls. Biodegradable synthetic polymer scaffolds can provide necessary mechanical support during the early healing phase and are gradually degraded and replaced by regenerating tissues, theoretically eliminating the risk of long-term foreign body reactions associated with nondegradable implants. However, a critical challenge lies in the mismatch between scaffold degradation rates and tissue regeneration rates. To address this, researchers have explored composite strategies, surface modifications, and functionalization approaches to fine-tune degradation profiles and better synchronize scaffold resorption with new tissue formation.

Bioceramics

Bioceramics refer to a class of inorganic ceramic-based materials with excellent biocompatibility, widely used in tissue engineering and implantable medical devices. Commonly studied bioceramics include hydroxyapatite, β-tricalcium phosphate (β-TCP), bioactive glass (BG), zirconia (ZrO_2), and alumina (Al_2O_3) [56, 57]. These materials are characterized by their osteoconductivity, mechanical properties comparable to natural bone, and long-term stability after implantation. Metal ions released from bioceramics can promote osteogenic differentiation and angiogenesis. Moreover, their stiffness is well-matched to bone tissue, enabling adequate compressive strength. Since most bioceramics degrade slowly, they can provide sustained mechanical support during the early postimplantation phase while improving integration with surrounding bone tissue. For example, Bose *et al.* fabricated an interconnected porous β-TCP scaffold via 3D printing. *In vivo* experiments demonstrated that new blood vessels appeared within 8–12 weeks postimplantation, and by 12 weeks, newly formed mineralized bone had fully infiltrated the designed interconnected pores. This finding suggested that the interconnected architecture improved nutrient transport and microenvironmental conditions within the scaffold, thereby enhancing overall bone defect healing [58]. For scaffolds to function effectively in bone repair, their mechanical performance must closely match that of the replaced native tissue. Beyond providing temporary stability, appropriate stiffness is essential for transmitting mechanical forces to the healing site. Insufficient strength results in failure to bear physiological loads, while excessive stiffness leads to stress shielding, depriving surrounding tissues of mechanical stimulation and ultimately causing bone resorption and implant failure.

Despite their osteoconductivity, bioceramics are inherently brittle and lack toughness, making it difficult to fabricate them into structures that conform to the tendon–bone interface or to withstand the complex mechanical loads at this site [59]. In addition, bioceramics preferentially integrate with bone tissue but exhibit limited capacity to bond with fibrocartilage and tendon ends. Therefore, in tendon–bone interface repair, bioceramics are often combined with synthetic polymers or natural macromolecules to construct gradient scaffolds with soft-to-hard transitions, thereby improving both mechanical support and multi-tissue integration [60].

Advanced engineering strategies for scaffold design

The repair of the tendon–bone interface remains one of the major challenges in tissue engineering. Its complexity arises not only from the limited intrinsic regenerative capacity of the damaged tissues but also from the unique anatomical and functional characteristics of this region. Unlike most homogeneous tissues, the tendon–bone interface is composed of four distinct yet continuous zones: tendon, unmineralized fibrocartilage, mineralized fibrocartilage, and bone [14]. These zones exhibit gradual transitions in cell phenotypes, ECM composition, and mechanical properties. Such graded heterogeneity is essential for ensuring stable attachment between tendon and bone under physiological loading. At the same time, this structural complexity poses much higher requirements for scaffold design compared to conventional tissue repair.

In traditional tissue engineering research, material selection has often been the primary focus. Natural polymers are valued for their biocompatibility, synthetic polymers for their tunable mechanical performance, and bioceramics for their osteoconductivity. However, both clinical and experimental studies have shown that single-material scaffolds are insufficient to achieve synchronous regeneration of the tendon–bone interface [65]. On one hand, the mechanical loading environment at the interface is highly complex. Scaffolds with excessively high stiffness may lead to stress-shielding and subsequent bone resorption [63] while insufficiently strong scaffolds fail to provide mechanical stability in the early healing phase, resulting in tendon pull-out and repair failure [66]. On the other hand, functional restoration of the interface requires not only bone integration but also the formation of a fibrocartilaginous transition zone, $\sim$500 μm in thickness

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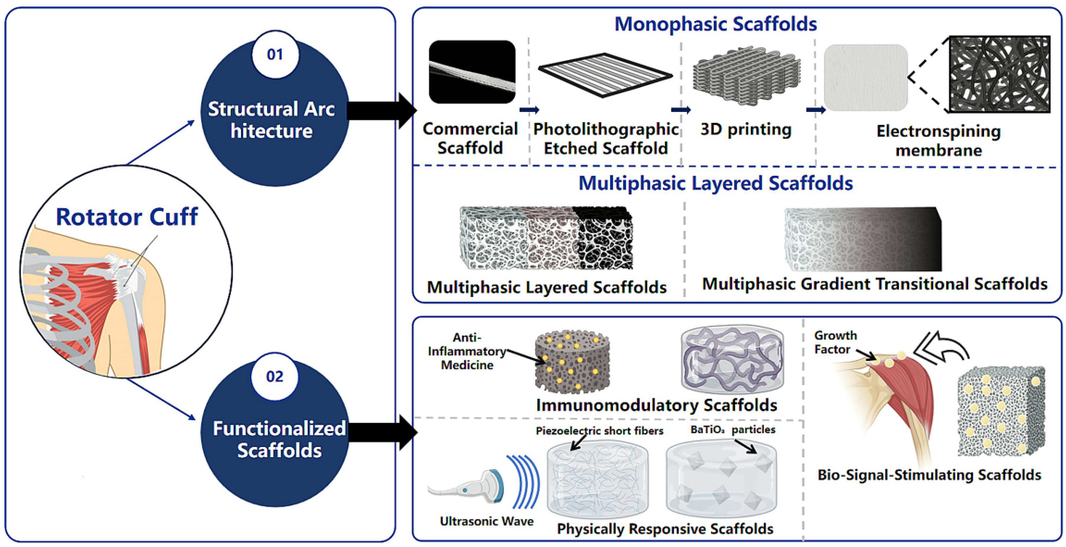

Figure 2. Advanced engineering strategies for scaffold design.

to prevent stress concentration [14]. Single-material scaffolds can usually meet only one of these demands, but rarely achieve comprehensive functional integration.

Therefore, scaffold design for tendon–bone repair must integrate considerations at the levels of materials, structure, and function. First, mechanical matching is the central design goal. Scaffolds should provide sufficient initial stability to withstand physiological loads, while gradually transferring stress to regenerating tissue during degradation [67]. Second, tissue integration is critical to repair outcomes. An ideal scaffold should serve as a structural template for cell infiltration, while simultaneously supporting osteogenic differentiation and vascularization at the bone side, as well as fibroblast adhesion, migration, and ECM deposition at the tendon side [7, 68, 69]. Third, synchronized degradation and regeneration is vital for long-term success. Premature degradation compromises mechanical support, whereas delayed degradation may impede tissue remodeling or even trigger chronic inflammation [70]. Finally, functional modifications—including immunomodulatory strategies, surface engineering, or incorporation of bioactive molecules—have gained increasing attention, as they can modulate cell–material interactions and enhance tissue regeneration at the molecular level (Figure 2) [71, 72].

Despite promising results in animal models, clinical translation still faces significant challenges. First, limitations in material design often lead to discrepancies between scaffold behavior in controlled laboratory conditions and in the complex *in vivo* human environment, where issues such as insufficient mechanical stability or unpredictable degradation emerge. Second, scalability and standardization remain bottlenecks for clinical application, as scaffolds must not only be reproducibly fabricated in bulk but also exhibit stable physicochemical properties and meet stringent biosafety requirements for regulatory approval. Third, long-term efficacy and immune compatibility remain uncertain, as chronic inflammation, fibrotic encapsulation, or structural failure may occur even after successful short-term healing.

Given these challenges, researchers increasingly recognize that relying solely on single-material design is inadequate for addressing the complexity of tendon–bone repair. Accordingly, scaffold development has progressed along two complementary dimensions: structural architecture and functional enhancement.

From the structural perspective, the earliest attempts primarily employed monophasic scaffolds, which gained attention due to their fabrication simplicity and scalability. However, their homogeneous architecture is inherently limited in reproducing the graded soft-to-hard transition of the native interface. To address this mismatch, multiphasic scaffolds—including layered and continuously graded designs—were subsequently developed to integrate distinct regions within a single construct, thereby better mimicking the native interface and improving both load transfer and tissue integration.

In parallel with these structural innovations, researchers have increasingly emphasized scaffold functionalization, recognizing that biological regulation is equally critical for successful healing. These functional strategies—including immunomodulation, bioactive signal delivery, and physical-stimulus responsiveness—can be incorporated into either monophasic or multiphasic scaffolds to actively modulate cellular behaviors and enhance tissue regeneration.

Accordingly, in this review, we adopt a matrix-style framework to organize scaffold strategies for tendon–bone repair. The first tier classifies scaffolds according to structural architecture: monophasic versus multiphasic, with gradient designs considered as a continuum within the multiphasic category. The second tier summarizes functional strategies, which can be orthogonally applied to any structural scaffold. This organization enables a clearer conceptual separation between scaffold form and scaffold function, providing a more systematic overview of current advances in tendon–bone interface engineering (Figure 2).

Structural architecture

Monophasic scaffolds. Research on monophasic scaffolds represents the earliest efforts among scaffold types. As the most

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fundamental form for tendon–bone repair, monophasic scaffolds hold a relative advantage in terms of commercial translation compared with more complex multiphasic or functionalized scaffolds. GraftJacket™, an allogenic graft derived from acellular dermal matrix, retains collagens (Types I, III, IV, and VII), elastin, proteoglycans, and basement membrane structures while removing cells to minimize immune response. Importantly, it preserves vascular channels to promote rapid revascularization [73]. In human cadaveric models, GraftJacket™ demonstrated significant mechanical reinforcement in Achilles tendon and rotator cuff repairs, with improved ultimate load to failure and stiffness compared with untreated repairs, indicating its potential to provide stronger early functional stability [74].

Building on the concept of acellular dermal scaffolds, the Zimmer Collagen Repair Patch (Tissue Science Laboratories, Covington, GA, USA; licensed to Zimmer) is a single-layer porcine dermal xenograft composed of cross-linked, decellularized collagen. In a sheep model, its performance was compared with that of porcine small intestinal submucosa for rotator cuff repair. At 9 weeks, the Zimmer patch group exhibited higher failure loads than controls, and by 24 weeks, it showed favorable tissue integration and vascular infiltration without evidence of foreign-body reaction [75]. In a clinical series, Badhe *et al.* followed 10 patients with massive rotator cuff tears treated with Zimmer collagen patches over 3–5 years. Results showed that constant scores improved from a preoperative mean of 41–62 at final follow-up ($P = .0003$), with significant improvements in pain, range of motion, and strength. Imaging confirmed intact grafts in eight patients, with two cases of detachment, and no adverse reactions were reported.

More recently, the development of REGENETEN™ by Smith Nephew highlights how monophasic scaffolds have progressed toward minimally invasive and resorbable designs. This scaffold, composed of highly purified Type I collagen fibers, can be fixed using a sutureless implantation system and is gradually absorbed within 6 months, being replaced by tendon-like tissue. In a multicenter clinical study across 19 surgical centers in the USA, 227 patients with partial-thickness rotator cuff tears were treated either with REGENETEN™ alone (without surgical repair) or REGENETEN™ combined with conventional repair. Patients receiving REGENETEN™ alone reported significant functional improvement as early as 2 and 6 weeks postoperatively, comparable to outcomes of combined repair. At 1-year follow-up, retear rates were minimal in both groups, and all REGENETEN™-treated patients reported significant reductions in pain and improvements in shoulder function and quality of life compared with baseline [80, 81].

Despite these promising outcomes, most commercial tendon–bone repair patches are simple, planar, and structurally homogeneous. This limits their adaptability to diverse injury patterns. To address this, Mouthuy *et al.* developed a scalable manufacturing process for electrospun nanofiber bundles. Using a specialized guiding device, dense nanofiber meshes were continuously drawn into filament bundles, which could then be twisted into multifilament yarns for tendon–bone scaffolds. *In vivo* implantation studies demonstrated excellent tissue compatibility (only mild foreign-body reaction) and complete degradation within $\sim$ 5 months, fulfilling clinical requirements for a resorbable scaffold [82].

The design of porous scaffolds plays a pivotal role in supporting cell infiltration and tissue ingrowth [83, 84]. Wang *et al.* fabricated a poly (ester urethane urea) scaffold via thermally induced phase separation. The scaffold exhibited an adaptive structure with aligned macropores, enabling cell migration and tissue integration. In a rabbit model of massive rotator cuff tear, this scaffold achieved complete tendon–bone interface regeneration within 3 months, with biomechanical properties approaching those of native rotator cuff tissue, highlighting its potential for clinical application.

From an anatomical perspective, rotator cuff tendons are composed of hierarchically organized, well-aligned fibers that create a unique biomechanical and microenvironmental niche. Studies have shown that aligned fibers, compared with randomly oriented ones, significantly promote cell elongation and migration along the fiber axis [85]. Guo *et al.* fabricated a tendon patch scaffold using a uniaxial cold-drawing technique, producing a structure with highly ordered yet loosely stacked fibers. This scaffold exhibited good biocompatibility, enhanced cell proliferation, and collagen secretion, yielding mechanical properties close to those of native rotator cuff tendons [76] (Figure 3a). Furthermore, scaffolds composed of crimped fibers were shown to better stimulate fibroblasts to deposit ECM with a composition resembling native tendon tissue under dynamic culture conditions [86]. Zhao *et al.* combined electrospinning and hydrogen gas foaming to create a PLLA scaffold with a wavy fiber microstructure and a three-dimensional porous network. Surface modification with decellularized tendon matrix via carbodiimide chemistry endowed the scaffold with both physical guidance and biomimetic bioactivity (Figure 3b). As a result, the scaffold promoted tendon-derived stem cell proliferation, migration, and tenogenic differentiation, while enhancing adhesion to native tendon tissue—demonstrating strong potential for tendon–bone repair applications [77].

In addition to fiber-based strategies, surface micro- and nanotopographical modifications on polymer scaffolds have emerged as an effective approach to mimic tendon ECM cues. By applying techniques such as etching, microcontact printing, or photolithography, regular patterns (e.g. grooves, ridges, or dot arrays) can be introduced to guide cell adhesion, alignment, and proliferation in the absence of exogenous biochemical factors [87–90]. For instance, Gwon *et al.* used capillary force lithography to fabricate highly aligned nanogrooves on FDA-approved PCL membranes, which were seeded with human mesenchymal stem cells (MSCs) to construct tendon nano-constructs (TNCs) (Figure 3c).

These constructs were flexible, suturable, and biomimetic in nanotopography, while simultaneously providing cell delivery and physical guidance. In rabbit and porcine chronic rotator cuff tear models, TNCs significantly improved tendon–bone integration and biomechanical recovery, outperforming conventional sutures and stem cell injection alone [78]. Similarly, Kim *et al.* employed spin-coating and capillary force lithography to generate highly aligned nanotopographical scaffolds on PCL membranes, mimicking native tendon ECM (Figure 3d). These scaffolds demonstrated suitable flexibility and mechanical strength, effectively guided tendon-derived cells in terms of orientation, adhesion, proliferation, and differentiation, and enhanced healing capacity. In both acute and chronic rabbit rotator cuff tear models, the scaffolds promoted tendon regeneration along the nanotopographical axis, leading to

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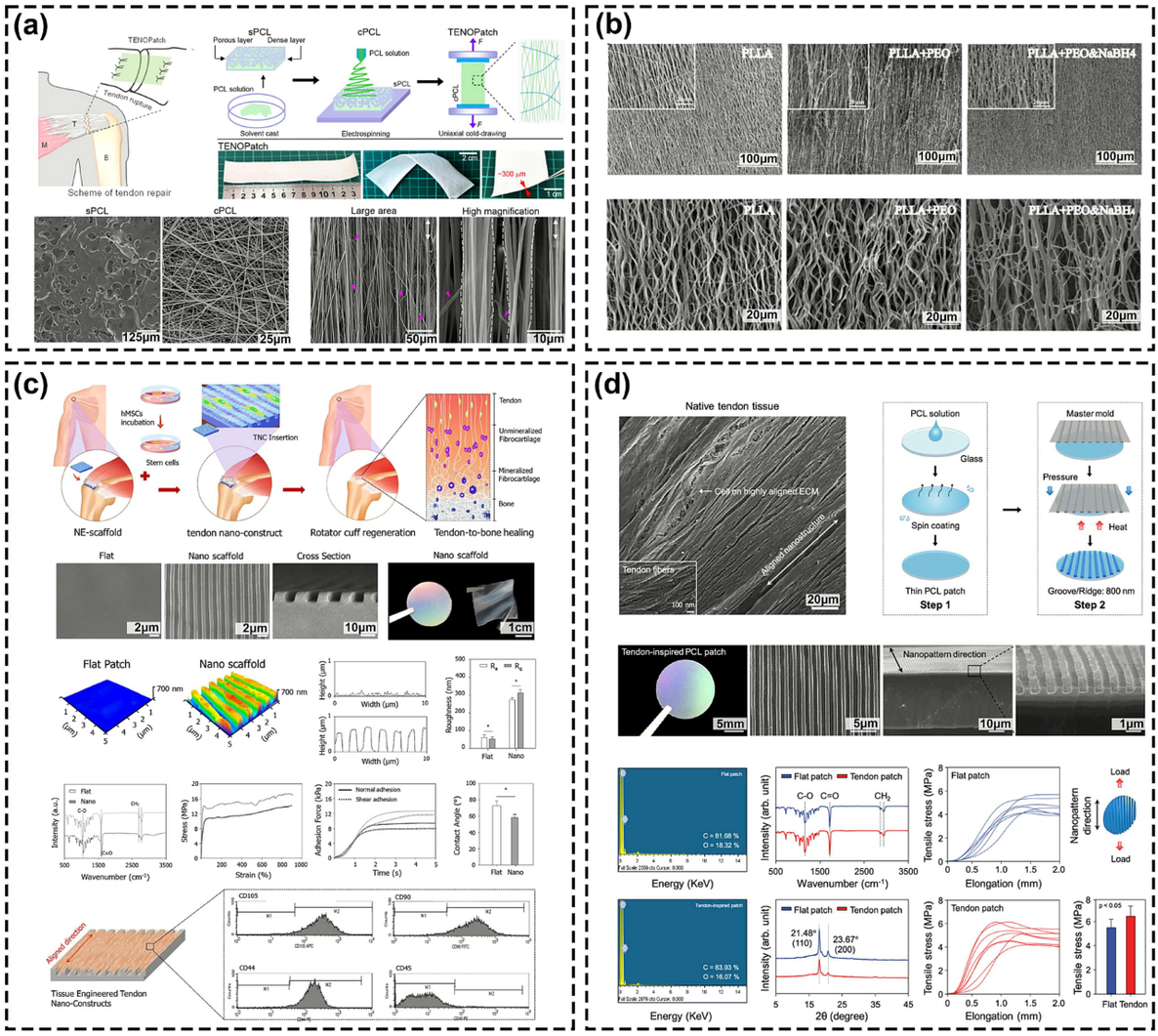

Figure 3. Monophasic scaffolds for tendon tissue engineering and fabrication strategies. (a) Fabrication of mechanically enhanced TENO patch (adapted with permissions [76]. Copyright 2022, Elsevier). (b) Fabrication of 2D crimped nanofiber mats (adapted with permissions [77]. Copyright 2024, American Chemical Society). (c) Rational design of the tissue-engineered tendon nano-constructs for rotator cuff tendon regeneration (adapted with permissions [78]. Copyright 2022, John Wiley and Sons). (d) Design and fabrication of tendon-inspired scaffold (adapted with permissions [79]. Copyright 2020, American Chemical Society).

superior restoration of tendon–bone structure and function [79].

Multiphasic scaffolds. Although monophasic scaffolds, with advantages such as facile fabrication, limited material components, and high biosafety, have demonstrated great potential in clinical translation and commercialization, their intrinsic limitations are becoming increasingly evident. The tendon–bone interface is not a uniform tissue but rather a transitional region where tenocytes, fibrochondrocytes, and osteoblasts display distinct metabolic demands, proliferation characteristics, and microenvironmental dependencies. A scaffold composed of a single material or morphology is unable to simultaneously satisfy the functional requirements of all these cell lineages within one system, thereby restricting spatially coordinated regeneration and biomechanical integration [91, 92]. Consequently, researchers have shifted toward the development of multiphasic or gradient-designed scaffolds. By spatially introducing zonal regulation of material composition, structural morphology, or bioactive cues, these scaffolds more closely resemble the hierarchical features of the native tendon–bone interface, offering the potential for more functional regeneration. Multiphasic scaffolds can be further categorized into layered scaffolds and gradient transitional scaffolds according to their morphology and fabrication strategy, each with distinct advantages and challenges regarding manufacturing and translational application.

Multiphasic layered scaffolds

Multiphasic layered scaffolds are engineered constructs that are deliberately divided into two or more functional zones, each possessing distinct material compositions, structural morphologies, or biological signals, to mimic the discrete

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zonal characteristics of tendon, fibrocartilage, and bone in the native interface. These zones are typically integrated through "layer-by-layer stacking" or "interfacial bonding," resulting in clear structural boundaries. The primary advantages of such scaffolds lie in their relative ease of fabrication, modular assembly, and the ability to tailor materials and signals to specific tissue needs.

To translate this concept into practice, Li *et al.* created a novel triphasic silk scaffold mimicking the ligament–bone insertion, consisting of ligament, fibrocartilage, and bone regions. Each compartment was modified with different coatings: the ligament zone with SF, the fibrocartilage zone with SF/chondroitin sulfate/HA, and the bone zone with SF/hydroxyapatite (Figure 4a). In a rabbit ACL defect model, implantation of this triphasic silk scaffold demonstrated enhanced functional regeneration of the ligament–bone insertion through coordinated interactions with three relevant cell types [93]. Building on this biomimetic rationale, Xie *et al.* developed a scaffold inspired by the spatial mineralization patterns of the native tendon–bone interface, woven from electrospun nanofiber yarns containing different hydroxyapatite contents. This design integrated classical spinning with textile weaving to reproduce the four distinct regions of the interface [94] (Figure 4b).

With the emergence of additive manufacturing, 3D printing technologies have further expanded the design flexibility of layered scaffolds. For example, Jiang *et al.* combined 3D printing technology with collagen–fibrin hydrogels encapsulating stem cells to fabricate two multilayer scaffold models for rotator cuff repair: (i) a "sandwich-type" scaffold, consisting of alternating PLGA sheets and cell-laden hydrogel layers, and (ii) an "integrated-type" scaffold, where PLGA was co-printed with sacrificial materials to form a framework subsequently infiltrated with hydrogel. Both scaffolds showed excellent biocompatibility in a subcutaneous model, validating the feasibility of 3D-printed multilayer scaffolds in tendon repair [95]. In a related study, Du *et al.* developed a 3D-bioprinted scaffold using a molybdenum-doped silicate (MS) bio-ink to vertically stratify tendon stem/progenitor cells and bone marrow-derived mesenchymal stem cells (BMSCs), thereby recapitulating the native tendon–bone interface. Ionic cues released from MS-induced tendonogenic and osteogenic differentiation, promoting fibrocartilage formation and tendon–bone integration in a rabbit rotator cuff injury model [96] (Figure 5a).

In parallel, hybrid designs integrating soft and hard phases have also emerged as a "golden strategy" for scaffold development. Alkaissy *et al.* pioneered a biphasic embedded scaffold that combined an electrospun "soft sleeve" with a 3D-printed "hard block" (Figure 5a). This hybrid scaffold effectively balanced mechanical robustness and cell compatibility, offering a simple, scalable, and clinically translatable soft–hard interfacial construct [97].

Despite these promising advances, layered scaffolds often suffer from mechanical discontinuities and restricted cellular migration across sharp interfacial boundaries. These limitations underscore the need for next-generation designs with more biomimetic transitional regions, enabling smoother structural and biological integration between different tissue phases.

Multiphasic gradient transitional scaffolds

Gradient transitional scaffolds are constructs designed to present continuous, progressive transitions rather than discrete layers. Their material composition, mechanical stiffness, porosity, or biological cues change gradually across regions, mimicking the natural gradation from tendon to fibrocartilage to bone [91]. Unlike layered scaffolds, transitional scaffolds do not emphasize clear boundaries but instead achieve smooth "soft-to-hard" connections through strategies such as compositional gradients, continuous pore size variation, mineralization gradients, or graded bioactive factor distribution. This design more faithfully reproduces the continuity and mechanical synergy of the native interface, directing region-specific cell differentiation and ultimately facilitating more efficient tissue integration. However, the fabrication of gradient scaffolds involves high complexity, challenging quality control, and undefined regulatory pathways, all of which remain major hurdles for clinical translation. Nonetheless, advances in additive manufacturing and biomaterial processing are gradually overcoming these barriers, positioning gradient scaffolds as a promising frontier for next-generation orthopedic implants.

Building on this concept, Liu *et al.* immersed nanofibrous scaffolds into a mineralization solution containing NaCl, KCl, $CaCl_2$, $MgCl_2$, and $NaH_2PO_4{\cdot}H_2O$, with controlled feed supplementation at 36 ml/h. This time-dependent mineralization generated a linear phosphate–calcium coating of varying thickness across fibers located at 1, 2, 3, and 5 cm positions, offering a simple yet feasible approach for gradient scaffold fabrication [98] (Figure 6a). In a subsequent study, another group proposed a more stable, scalable strategy by coextruding BG-containing and BG-free hydrogel solutions using dual syringe pumps with linearly varying flow rates, followed by ultraviolet crosslinking (Figure 6b). The resulting hydrogel scaffolds exhibited a linear BG gradient, enabling sustained release of Ca^{2+} and Si^{4+} ions. In a rat rotator cuff tear model, these scaffolds supported bidirectional osteogenic and chondrogenic differentiation of BMSCs, leading to synchronous regeneration of tendon–fibrocartilage–bone and the highest proportion of mineralized fibrocartilage (~35.7%) within the gradient zone, significantly enhancing biomechanical properties of the repair [99].

Besides, Zhu *et al.* designed and constructed a hierarchically structured biomimetic scaffold to promote functional regeneration of the tendon–bone interface (Figure 6c). The scaffold consisted of three distinct regions: a channel array zone that guided cell migration and collagen deposition; a mineral gradient zone that enabled a smooth mechanical transition between tendon and bone through the progressive increase of inorganic content; and a highly mineralized inverse opal zone that enhanced integration with bone tissue. Experimental results demonstrated that adipose-derived stromal cells could survive well within the scaffold and undergo region-specific differentiation into tenocytes and osteoblasts, thereby establishing a continuous soft-to-hard tissue transition. This study highlights the feasibility of reconstructing the tendon–bone interface through a synergistic design integrating structural, compositional, and mechanical gradients, underscoring the translational potential of hierarchically structured scaffolds [100].

While solution-based mineralization and coextrusion approaches emphasize scalability and continuous gradients, other techniques aim for more localized and physiologically

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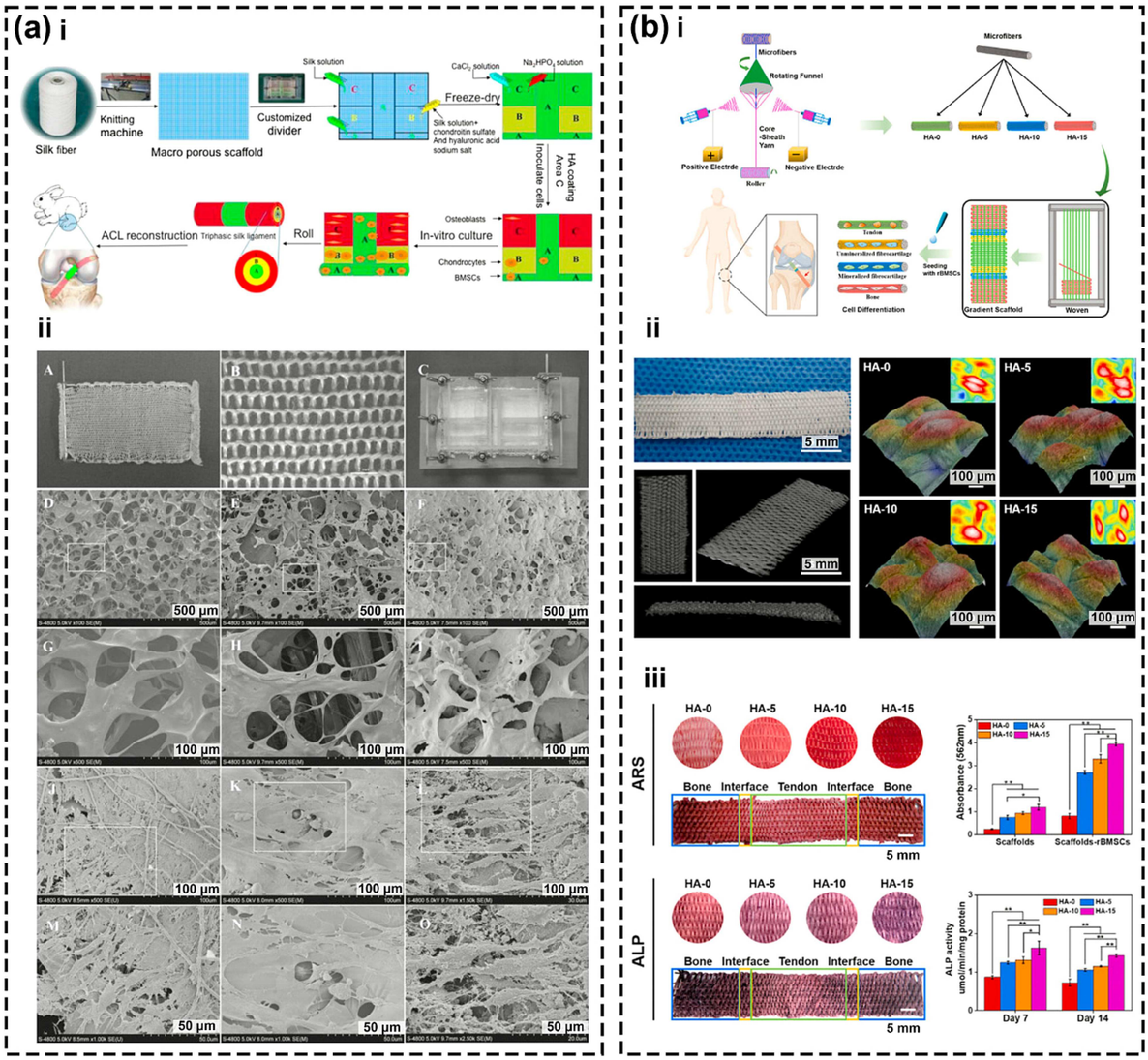

Figure 4. Multiphasic layered scaffolds for fabrication strategies. (a) Triphasic silk-based graft for ligament–bone interface regeneration. (i) The schematic diagram of manufacturing a triphasic silk graft used for restoration of osseointegration in the rabbit ACL-defect model. (ii) The morphology of cell/scaffold (reproduced with permission [93]. Copyright 2016, Elsevier). (b) A woven scaffold with continuous mineral gradients for tendon-to-bone tissue engineering. (i) Schematic illustration of the preparation of the hydroxyapatite (HAP) gradient scaffold. (ii) The macroscopic view and roughness of the HA gradient scaffold. (iii) The osteogenesis-inducing capacity of scaffold segments and HAP gradient scaffold (adapted with permission [94]. Copyright 2021, Elsevier).

relevant transitions. Timmer *et al.* introduced an integrated casting approach using three precursor suspensions—collagen–glycosaminoglycan (Col–GAG), mineralized Col–GAG, and thiolated GEL—loaded into specialized chambers separated by removable partitions and conductive copper plates. Upon partition removal, the suspensions interdiffused and were freeze-dried to form a scaffold with localized linear transitional interfaces. Unlike homogeneous gradients, this design generated region-specific graded zones only at tendon–bone junctions, more closely approximating the physiological architecture [101].

From a structural design perspective, gradient transitional scaffolds currently represent the most ideal model. Compared with monophasic or layered multiphasic scaffolds, gradient constructs better mimic the continuous zonal transitions of the native tendon–bone insertion, with progressive changes in composition, mechanics, porosity, and biological cues. Nevertheless, structural optimization alone may not fully meet the complex requirements of functional repair. To overcome this limitation, the concept of functionalized scaffolds has emerged—an approach that extends gradient structural design by integrating additional biological and physical functions. One representative strategy is the development of immunomodulatory scaffolds, in which surface modifications or controlled-release systems are employed to regulate macrophage polarization and establish a pro-regenerative immune microenvironment. Another approach involves signal-delivering scaffolds, where growth factors, siRNAs, or small molecules are spatially organized to achieve precise, zone-specific control of cellular responses. In

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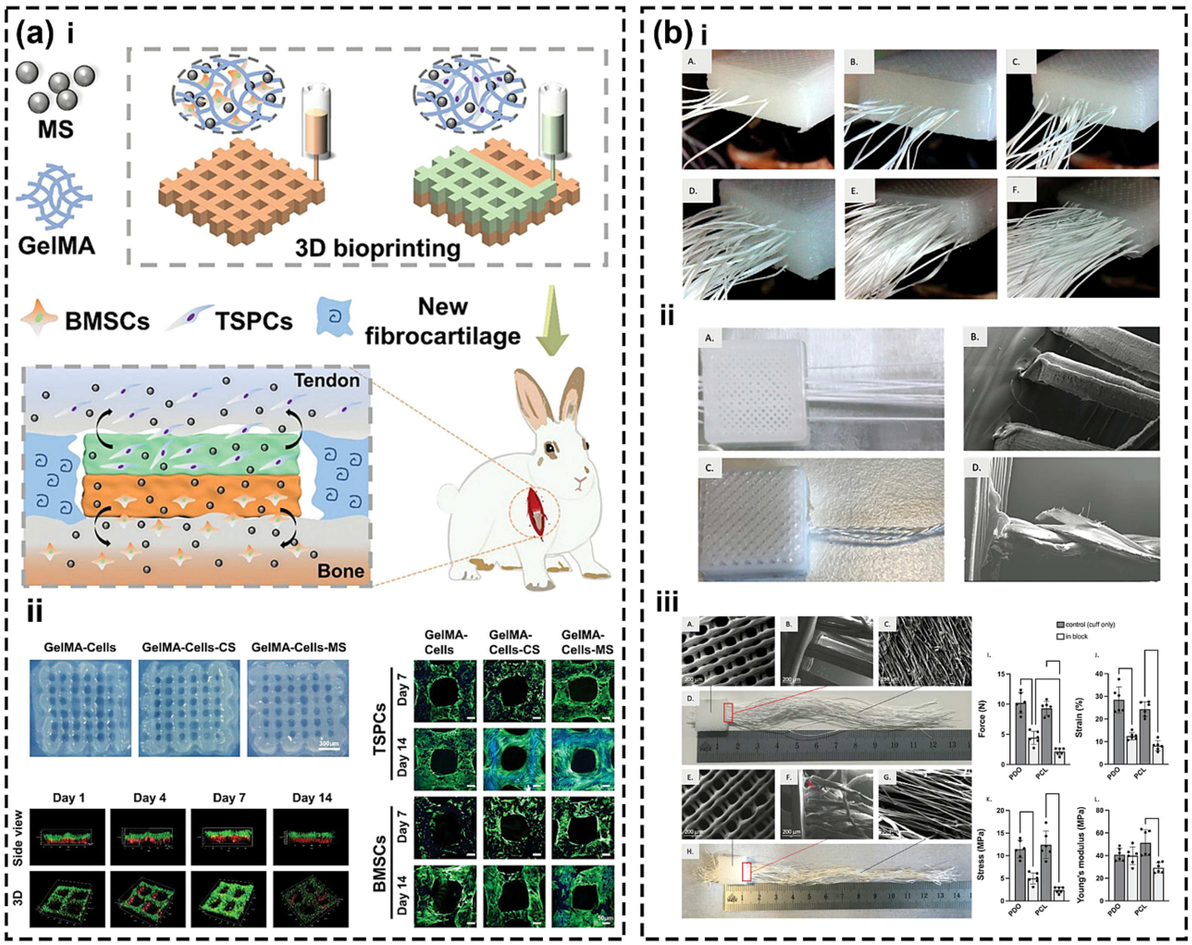

Figure 5. Multiphasic layered scaffolds for tendon tissue engineering. (a) Multicellular bioprinting of biomimetic inks for tendon-to-bone regeneration. (i) A 3D bioprinting scaffold for the regeneration of tendon-to-bone interfaces developed by combining multiple cells and Mo-containing silicate bioceramics. (ii) Characterization of biomimetic multicellular scaffolds (reproduced with permission [96]. Copyright 2023, John Wiley and Sons). (b) Soft-hard implants from electrospun filaments embedded in 3D-printed structures. (i) The scale up potential of scaffolds. (ii) Scanning electron microscopy (SEM) image showing nine parallel filaments in one layer emerging from the block. (iii) Soft-hard scaffolds made of a 3D-printed (3DP) polycaprolactone (PCL) block and either a polydioxanone (PDO) or a PCL electrospun cuff (reproduced with permission [97]. Copyright 2022, John Wiley and Sons).

addition, stimuli-responsive scaffolds incorporate conductive, photosensitive, or magnetoresponsive materials, enabling them to respond dynamically to external cues such as electric fields, light, or magnetic forces. These biophysical signals further modulate osteogenic, tenogenic, or chondrogenic differentiation.

Functionalized scaffolds

By integrating structural, biochemical, and biophysical cues, functionalized gradient scaffolds provide a "structure–signal–function" paradigm, representing a comprehensive strategy for the repair of complex tissue interfaces.

Immunomodulatory scaffolds. Following tendon–bone interface injury, the imbalance between pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages leads to dysregulated chronic inflammation, which is a major cause of impaired fibrocartilage regeneration and periosteal bone loss [102, 103]. In the early phase of injury, M1 macrophages secrete abundant pro-inflammatory cytokines, which not only inhibit fibrocartilage layer regeneration but also enhance osteoclast activity. As the inflammatory response persists, the depletion of M2 macrophages—responsible for resolving inflammation and promoting tissue repair—further compromises the regeneration of fibrocartilage and bone during tendon–bone healing. Therefore, guiding macrophage polarization toward a favorable M2 phenotype has emerged as a promising strategy to correct aberrant inflammation and facilitate tendon–bone interface regeneration [104, 105]. To this end, various immunomodulatory scaffolds have been developed. For example, Gao *et al.* synthesized mesoporous bioactive glass nanoparticles (MBG) and Sr-doped MBG (Sr-MBG) via sol–gel methods, and incorporated them into electrospun fibers through ultrasonication, generating Sr-MBG-loaded fibrous scaffolds with dual inductive and immunomodulatory functions. These scaffolds exhibited excellent biocompatibility and a sustained release of bioactive ions, which enhanced marrow-derived MSCs osteogenic/-chondrogenic differentiation and promoted M2 macrophage polarization. In a rotator cuff tear model, implantation

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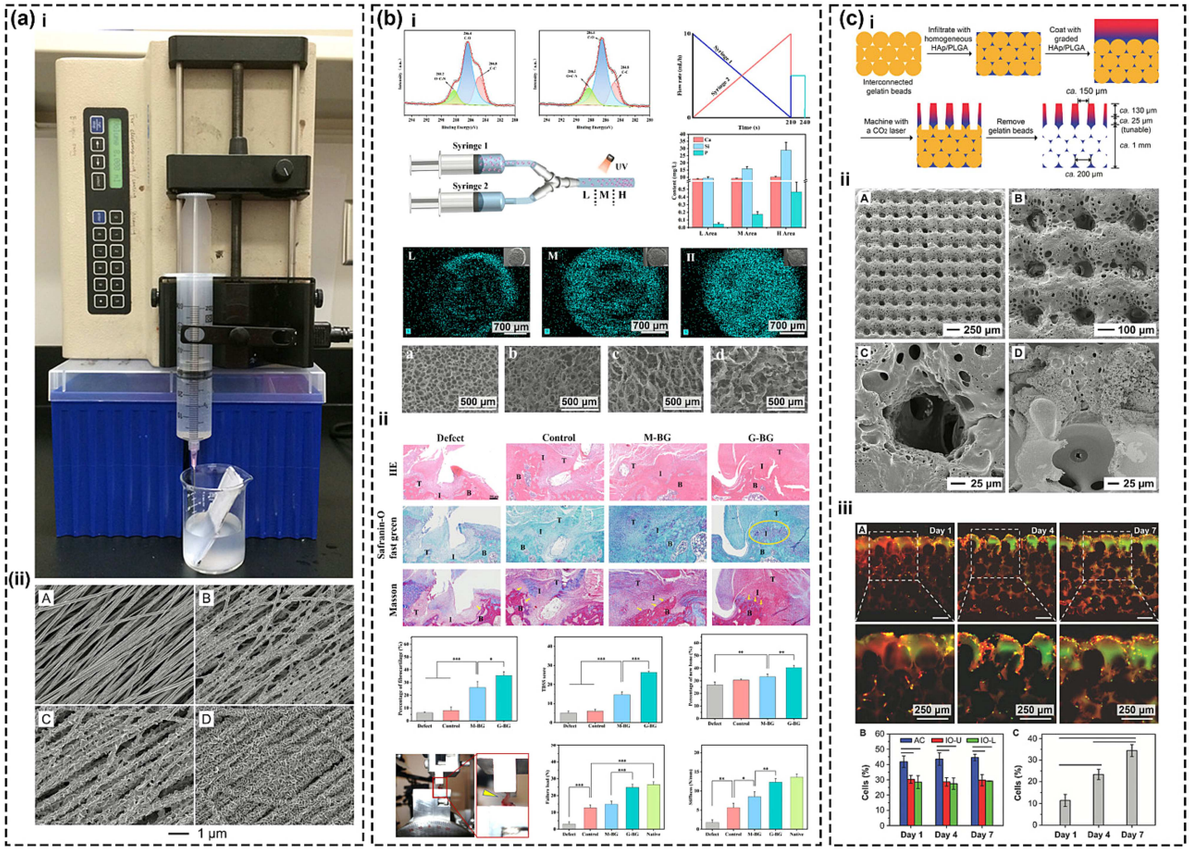

Figure 6. Multiphasic gradient transitional scaffolds. (a) Nanofiber scaffolds with gradients in mineral content. (i) Photograph of the setup used for fabricating a nanofiber scaffold with a gradient in mineral content. (ii) SEM images of calcium phosphate coatings on a plasma-treated nonwoven mat of PLGA nanofibers at 1, 2, 3, and 5 cm from one end of the scaffold (reproduced with permission [98]. Copyright 2014, American Chemical Society). (b) Gradient hydrogel with bioactive glass. (i) Schematic diagram and characterization of gradient hydrogel preparation. (ii) Histopathological and biomechanical analysis (reproduced with permission [99]. Copyright 2025, Elsevier). (c) Hierarchically structured scaffold for tendon-to-bone repair. (i) Schematic illustration showing the fabrication of a hierarchically structured scaffold. (ii) SEM images of a hierarchical scaffold after removal of the template. (iii) Distribution and morphology of ASCs inside the hierarchical scaffolds at days 1, 4, and 7 post cells seeding (adapted with permission [100]. Copyright 2018, John Wiley and Sons).

of the scaffold significantly improved the biomechanical strength of the supraspinatus tendon–humerus complex [28]. Building on this concept, Yu *et al.* developed an electrospun nanofibrous scaffold covalently modified with Wnt3a protein. Compared to control scaffolds, the Wnt3a-modified version effectively modulated early macrophage polarization during tendon repair, enhanced macrophage recruitment, increased the proportion of M2 macrophages, and improved Achilles tendon function and biomechanical outcomes *in vivo* [106]. Moreover, Zhao *et al.* fabricated a functional tendon–bone repair scaffold by modifying decellularized tendon slices with tannic acid. This scaffold demonstrated antioxidative and anti-inflammatory properties *in vitro*, and subcutaneous implantation further confirmed its biocompatibility [107].

Although these strategies highlight the potential of scaffold-mediated immunoregulation, most rely on coatings or physical blending of anti-inflammatory molecules, which often results in accelerated release under dynamic physiological conditions. Such a burst release limits the establishment of a stable anti-inflammatory microenvironment, thereby hindering long-term tissue regeneration [108–111]. To overcome this limitation, Wang *et al.* employed a skeletal copolymerization strategy to construct a hierarchical composite nanofiber patch (HCNP-SC) with enduring immunoregulatory capacity. The scaffold, electrospun from degradable poly (ester-ferulic acid-urethane) urea, exhibited a bipolar fiber architecture, and the random layer was further functionalized with hydrolysates from decellularized Wharton's jelly tissue. *In vitro*, ferulic acid was gradually released in parallel with scaffold degradation, sustaining an anti-inflammatory microenvironment. *In vivo*, the HCNP-SC promoted structural continuity at the tendon–bone interface, induced a triphasic distribution of collagen, and significantly improved interface regeneration outcomes [112].

Bio-signal-stimulating scaffolds. Bio-signal-stimulating scaffolds represent a classic category of functional biomaterials. By integrating bioactive molecules that can be released in a controlled manner or persist within the scaffold, they provide region-specific cues for cellular differentiation, thereby promoting compartmentalized regeneration and functional integration of the interface.

For instance, Zhu *et al.* developed a bilayer composite biomimetic membrane. They first synthesized weakly cationic

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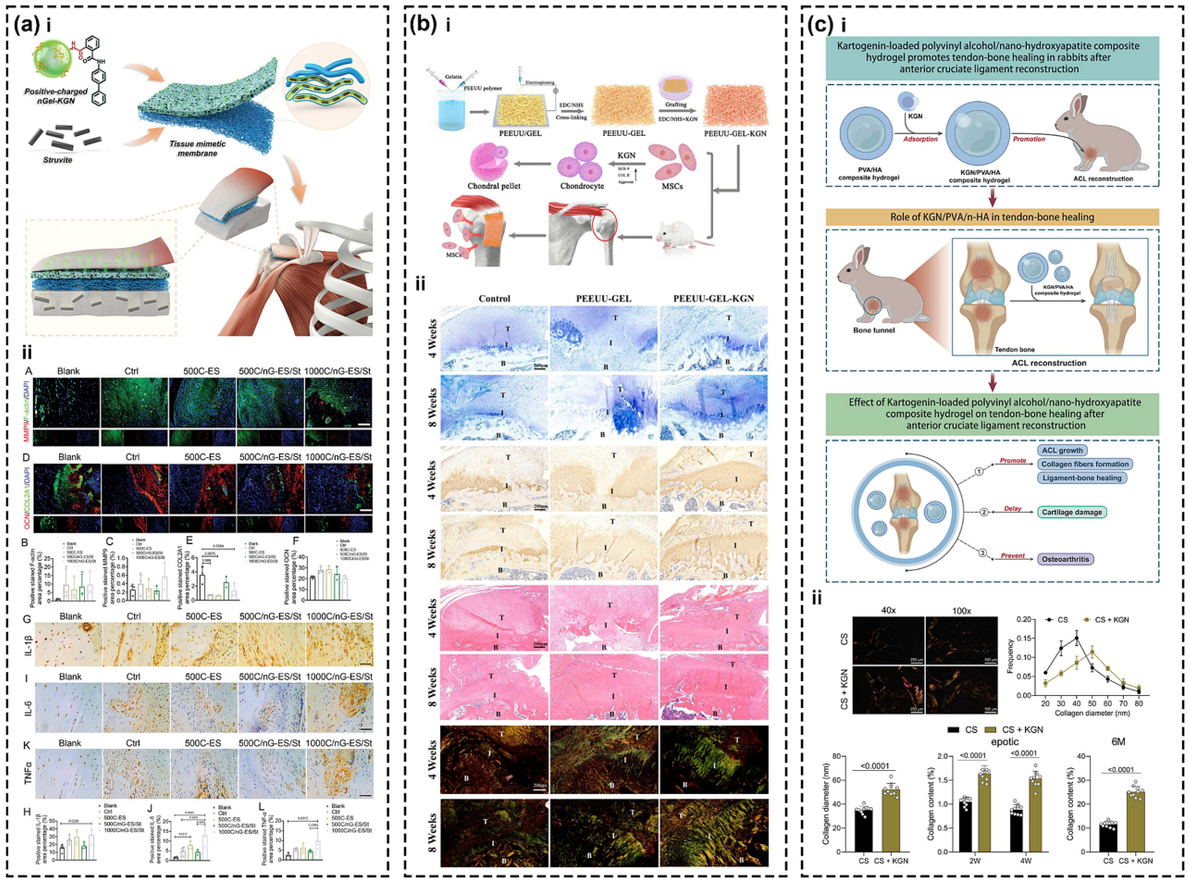

Figure 7. Bio-signal-stimulating scaffolds for enhanced tendon–bone healing and regenerative applications. (a) Tissue mimetic membranes for healing augmentation of tendon–bone interface. (i) schematic illustration of the biphasic structure of the tissue mimetic membrane and its application. (ii) Matrix synthesis and inflammatory responses at tendon–bone interface (adapted with permission [113]. Copyright 2025, John Wiley and Sons). (b) A reinforced nanofibrous patch with chondroinductive effect for rotator cuff. (i) Schematic illustrations of the preparation of the poly(ester-ether urethane urea) (PEEUU)-GEL-KGN patch and its application. (ii) Histological analysis (adapted with permission [114]. Copyright 2022, Elsevier). (c) Kartogenin-loaded polyvinyl alcohol/nano-hydroxyapatite composite hydrogel promotes tendon–bone healing. (i) A schematic illustration of the stimulatory effect of kartogenin-loaded polyvinyl alcohol/nano-hydroxyapatite (KGN/PVA/n-HA) scaffolds in tendon healing following ACL reconstruction in rabbits. (ii) Effect of kartogenin-loaded polyvinyl alcohol/nano-hydroxyapatite (KGN/PVA/n-HA) scaffolds on collagen fiber formation (adapted with permission [115]. Copyright 2023, John Wiley and Sons).

Kartogenin (KGN) conjugated nanogels (nGel-KGN) and incorporated them into a microporous scaffold via non-solvent-induced phase separation. Subsequently, a PCL solution containing whitlockite was coaxially electrospun onto the microporous layer to form a bilayer membrane (Figure 7a). After crosslinking, this membrane was applied to repair rotator cuff tears in SD rats. In addition to acting as a spatiotemporally controlled release platform for nGel-KGN and whitlockite, the membrane also provided region-specific biochemical and topographic cues to guide healing. Both *in vitro* and *in vivo* studies confirmed its effectiveness in enhancing tendon–bone healing, demonstrating synergistic effects of KGN and whitlockite release [113].

Along similar lines, Chen *et al.* advanced this concept by constructing a PEEUU–GEL–KGN nanofibrous patch, in which structural reinforcement and chondroinductive signaling were integrated within a single platform (Figure 7b). By integrating mechanical support, biomimetic flexibility, and chondroinductive capacity into a single construct, the patch not only significantly promoted the directional bioactivity of MSCs *in vitro* but also markedly improved the quality and durability of tendon–bone integration *in vivo*. This design strategy provides a powerful new approach for rotator cuff repair materials and holds considerable potential for clinical translation [114].

Building further on this strategy of combining multiple bioactive factors, Zhou *et al.* fabricated a hydrogel scaffold incorporating KGN, thrombin, and platelet-rich plasma (PRP) for tendon–bone interface repair [116]. KGN is known to induce BMSC chondrogenesis [117], while PRP, enriched in various growth factors (platelet-derived growth factor, transforming growth factor-beta, vascular endothelial growth factor, and hepatocyte growth factor), has been widely used in tendon repair due to its capacity to accelerate healing [118, 119]. Activated PRP forms fibrin gels that serve as scaffolds and release bioactive factors locally, thereby optimizing tendon healing (Figure 7c).

Extending beyond synthetic or hydrogel systems, Han *et al.* proposed an innovative mineralized fish scale scaffold for tendon–bone healing. Natural fish scales exhibit a

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Bouligand microstructure composed of helicoidally arranged collagen lamellae, conferring remarkable toughness and elasticity under tensile load through synergistic deformation mechanisms (collagen sliding, twisting, and stretching) [120, 121]. By inducing *in situ* mineralization with calcium silicate nanoparticles, the authors prepared bioactivated scaffolds. *In vitro*, released calcium and silicate ions promoted tendon, bone, and fibrocartilage regeneration. In rat and rabbit rotator cuff tear models, scaffolds significantly enhanced healing and improved biomechanical performance [122].

Physically responsive scaffolds. Physically responsive scaffolds are designed to sense and transduce external physical stimuli, such as mechanical force, electricity, light, heat, magnetism, or sound—into biological signals recognizable by cells, thereby modulating cell behavior (proliferation, migration, and differentiation) and promoting tissue regeneration. The central concept is to couple external physical cues with the local microenvironment, providing additional nonchemical regulation for tissue healing.

Due to the unique physiology of the tendon–bone interface, electrical stimulation remains the most widely explored physical cue for tendon–bone regeneration. Electrical materials are typically classified into three categories: (i) piezoelectric scaffolds, (ii) conductive scaffolds, and (iii) triboelectric or contact-electrification scaffolds. Electrical stimulation is known to regulate key cellular components, such as ion channels and the cytoskeleton, thereby influencing cell behavior and function. Piezoelectric materials, in particular, are regarded as "smart materials" because they can convert mechanical energy into electrical energy through dipole rearrangements under stress, creating surface charge accumulation and localized electric fields [123]. With technological advancements, piezoelectric composite scaffolds have become the mainstream direction owing to their favorable flexibility, processability, enhanced piezoelectric constants, and electromechanical coupling coefficients [124]. Efforts have been devoted to improving piezoelectric performance through tuning material composition, crystallinity, hierarchical structure (nano to macroscale), and processing conditions.

As a representative example, Zhang *et al.* engineered a Janus nanofibrous scaffold consisting of back-to-back electrospun layers of aligned PLLA/ZnO fibers and randomly oriented PLLA/barium titanate (BTO) fibers. This design endowed the scaffold with both tensile strength and nanotopographic guidance. The piezoelectricity of ZnO and BTO generated exercise-driven electrical cues, which promoted tenogenic and osteogenic differentiation, respectively (Figure 8a). In a rat rotator cuff model, this scaffold significantly improved tendon–bone healing quality, highlighting the potential of exercise-activated piezoelectric scaffolds [125].

Building on the idea of harnessing body movement as a natural stimulus, Fernandez-Yague *et al.* developed a self-powered bioelectronic device using aligned poly (vinylidene fluoride-co-trifluoroethylene) nanofibers (Figure 8b). Driven solely by body movement, the device produced piezoelectric signals that coupled mechanical and bioelectrical cues. This regulated mechanosensitive ion channel activity, enhanced the expression of tendon-specific markers (SCX, TNMD), and suppressed bone morphogenetic protein-driven chondrogenic/osteogenic differentiation, which is often associated with ectopic ossification. *In vivo*, the device promoted tendon-specific regeneration, reduced heterotopic ossification, and improved both structural and mechanical properties at the repair site [126].

More recently, Shi *et al.* combined piezoelectricity with ultrasound stimulation to design a bioinspired piezoelectric patch. Electrospun GEL/PLGA nanofibers were doped with nHA (aligned tendon-side) and BTO (random bone-side) to mimic native gradients. Upon ultrasound activation, the patch generated piezoelectric signals that not only promoted stem cell tenogenic and osteogenic differentiation but also induced M2 macrophage polarization. In a rotator cuff tear model, this approach effectively enhanced tendon–bone interface regeneration and functional recovery, offering proof-of-concept for noninvasive activation strategies.

Despite these advances, translating physically responsive scaffolds into clinical practice remains challenging. First, these scaffolds rely on specialized functional materials (e.g. piezoelectric polymers, conductive fillers, and nano-ceramics), making it difficult to balance mechanical strength, electromechanical performance, and biocompatibility during large-scale fabrication.

Second, tendon–bone repair requires scaffolds with complex architectures and controllable gradients, yet current processing techniques (electrospinning, 3D printing, and composite casting) still face limitations in reproducibility, scalability, and standardization. Third, physically responsive scaffolds often require external stimuli (exercise, ultrasound, and magnetic/electric fields), raising concerns about clinical operability and protocol unification. Therefore, future translation will depend on strategies that preserve bio-functionality while enabling scalable manufacturing, simplifying activation modes, and meeting regulatory requirements for medical devices.

The core challenges and strategies in clinical translation

With the deepening convergence of biology, materials science, chemistry, and medicine, an increasing number of novel scaffold materials have demonstrated remarkable efficacy in preclinical studies [128]. However, the proportion of these materials that ultimately achieve successful clinical translation remains extremely low. The translational challenges for scaffold materials from the laboratory to the clinic are primarily concentrated in three domains: technical challenges, including limitations of preclinical models, manufacturing and process bottlenecks, and long-term safety and functional stability; regulatory challenges, involving unclear product classification, cross-jurisdictional regulatory differences, and inconsistent evidence requirements; and economic challenges, mainly reflected in the tension between personalized therapeutic needs and cost-effectiveness. The core objective of basic research is to explore the scientific boundaries of new materials and technologies, emphasizing mechanistic innovation rather than direct clinical translation, whereas product development focuses on addressing unmet clinical needs by delivering scaffold solutions that comply with regulatory standards and possess market value [129].

Technical challenges

Limitations of preclinical models. The rapid advancement of biomaterials research, while driving scientific breakthroughs, has concurrently given rise to unique ethical challenges propelled by the field's progress. These challenges primarily revolve around three dimensions: the ethics of animal

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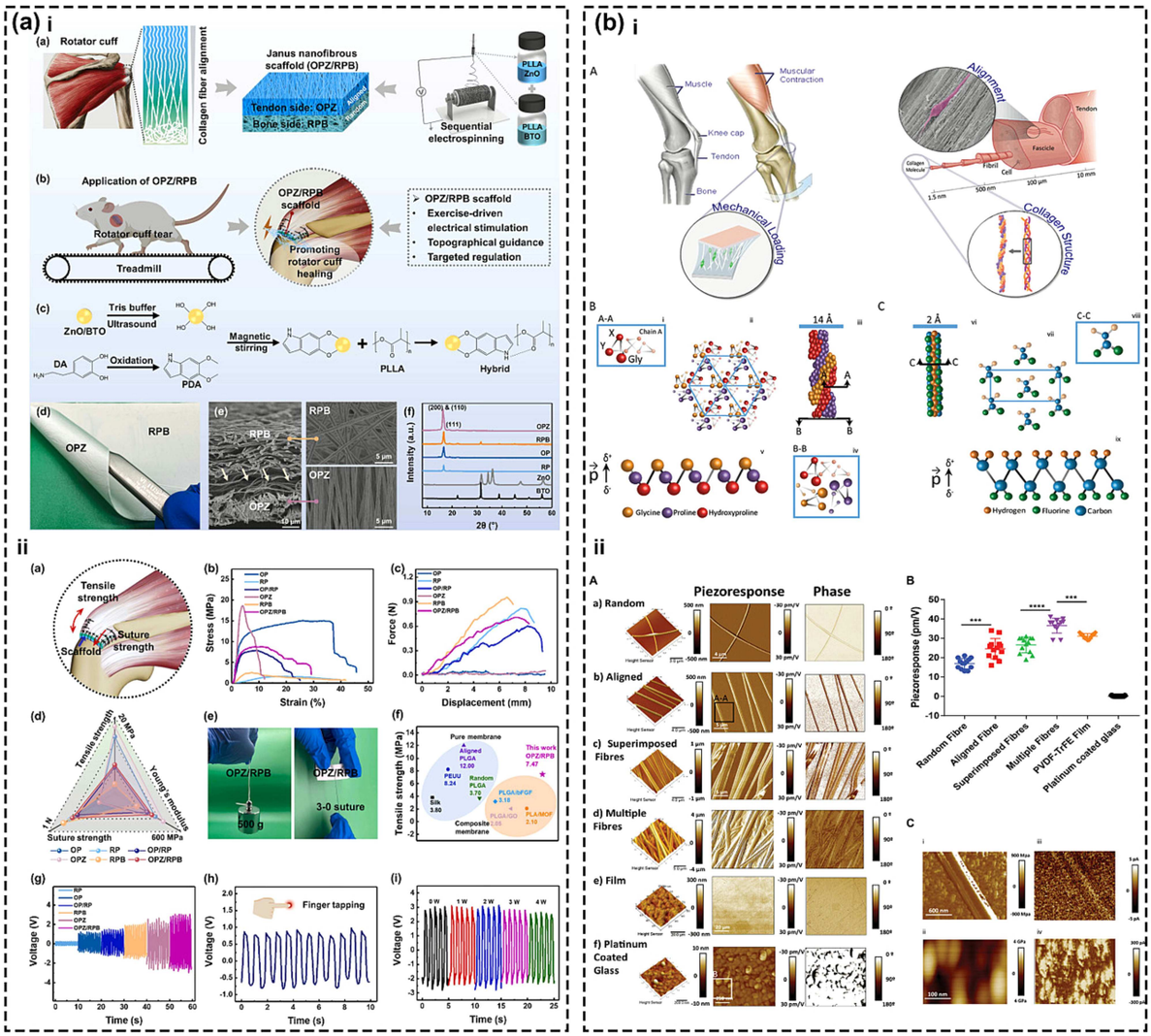

Figure 8. Piezoelectric and electromechanical scaffolds for enhanced tendon-to-bone repair. (a) Janus nanofibrous scaffold integrated with exercise-driven electrical stimulation and nanotopological effect enabling the promotion of tendon-to-bone healing. (i) Preparation and characterization of the scaffolds. (ii) Mechanical property and piezoelectric performance of the scaffolds (adapted with permission [125]. Copyright 2024, Elsevier). (b) Self-powered piezo-bioelectric device regulates tendon repair-associated signaling pathways through modulation of mechanosensitive ion channels. (i) Overview of the tendon electromechanical environment and the piezoelectricity origin analogy of collagen and fibers. (ii) PFM amplitude and phase images for single and multiple fibers (adapted with permission [126]. Copyright 2024, John Wiley and Sons).

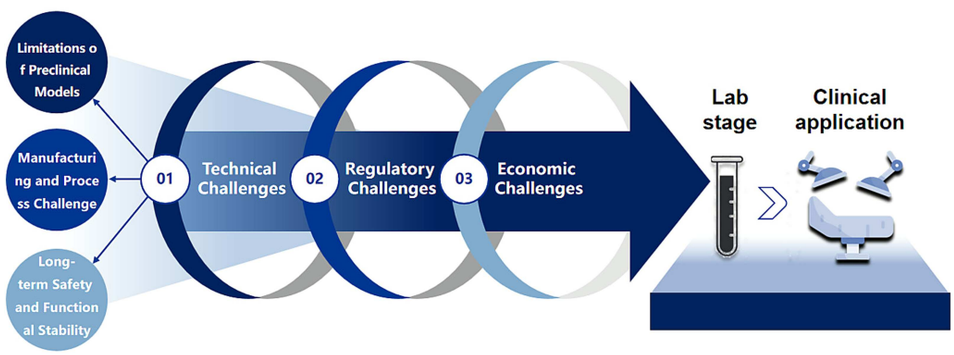

Figure 9. Translation gap between laboratory models and clinical applications.

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experimentation, the protection of human subjects, and the application of emerging and controversial technologies [130]. Effectively addressing these issues relies not only on researchers' ethical awareness but also necessitates robust review mechanisms, such as the Institutional Review Board (IRB) and Institutional Animal Care and Use Committee (IACUC), dynamically updated ethical guidelines, and interdisciplinary dialog [131]. This multifaceted approach is essential to ensure technological innovation consistently serves human well-being. However, the translational process for biomaterials continues to face a critical bottleneck: the high cost and protracted duration of clinical trials. The root cause lies in the preclinical stage's lack of reliable evaluation models capable of accurately predicting biomaterial performance within the human body [132].

The limitations of traditional small-animal models are fully exposed: significant species differences manifest in key dimensions, including anatomical structure, physiological function, and immune response. Combined with their inherent oversimplification and limited lifespan, these models are incapable of accurately predicting long-term behavior, biocompatibility, and efficacy of biomaterials in humans [133, 134].

Moreover, the intrinsic complexity of humans further compounds these challenges. Individual heterogeneity—such as genetic background, age, sex, and comorbidities—dynamic interactions at the immune–microbiome–tissue interface, and the necessity of evaluating long-term effects, including delayed toxicity and chronic inflammation, collectively represent profound barriers to bridging the "bench-to-bedside" gap [135]. This complexity highlights why small-animal models alone are insufficient for translational studies.

To systematically overcome the limitations of traditional preclinical models, a progressive tiered predictive research framework must be established. The primary strategy involves the standardized application of large-animal models, selecting species with anatomical and physiological proximity to humans under stringent operating procedures. For instance, Arun *et al*. leveraged the high similarity between ovine knee joints and human ACL, and a 36-month longitudinal implantation with biomechanical analysis confirmed the osteointegration capacity of citrate-based composites, providing critical validation for tendon repair material translation [136]. Such studies must rigorously adhere to the 3R principles (Replacement, Reduction, and Refinement), incorporating multimodal endpoint assessments (imaging, histopathology, and molecular biology) to authentically simulate human conditions for evaluating biomaterial functional integration, long-term safety, and failure mechanisms [137].

However, even large-animal models cannot fully replicate human physiology. They remain imperfect substitutes for humans due to species-specific anatomical, physiological, and immunological differences. To bridge this gap, emerging organoid and organ-on-a-chip technologies offer more human-relevant preclinical platforms. Bone and cartilage organoids, typically derived from pluripotent or adult stem cells cultured within biomimetic matrices, self-organize into microtissues that recapitulate native tissue architecture, including spatial heterogeneity, zonal cellular composition, and ECM deposition [138, 139]. These organoids allow researchers to assess scaffold effects on cell proliferation, differentiation, and matrix remodeling under physiologically relevant conditions, enable high-throughput screening of biomaterial formulations or bioactive cues, and can incorporate multiple cell types such as osteoblasts, chondrocytes, endothelial cells, and immune cells to study multicellular interactions and immunomodulatory responses within the tendon–bone microenvironment.

Microfluidic bone- or cartilage-on-a-chip systems further enhance predictive modeling by integrating precise mechanical and biochemical cues, including dynamic fluid flow, mechanical loading, and controlled gradients of oxygen and nutrients [140]. These platforms permit real-time monitoring of cell–matrix interactions, vascularization, and early mineralization events, providing mechanistic insights into scaffold performance that are difficult to capture *in vivo*. Importantly, organ-on-a-chip devices can incorporate patient-derived cells, offering personalized predictive models that reflect genetic variability, age, or disease state, which is particularly valuable for tendon-to-bone interface research where tissue heterogeneity and complex mechanical environments significantly influence healing outcomes.

By combining large-animal studies with organoid and organ-on-a-chip platforms, researchers can generate multitiered, human-relevant preclinical data. Such an integrated approach not only complements animal models and reduces reliance on them but also accelerates scaffold optimization and improves the likelihood of successful clinical translation. Following these preclinical evaluations, ethically compliant clinical research under international standards—starting with first-in-human trials, advancing to proof-of-concept studies, and culminating in confirmatory randomized controlled trials with long-term follow-up—remains essential to validate safety and efficacy in target patient populations [141, 142]. Overall, bridging interspecies gaps through combined large-animal and human-relevant platforms constitutes a scientifically essential pathway for safe and effective biomaterial translation that ultimately delivers patient benefits.

Manufacturing and process challenge. The industrial-scale production of scaffolds remains constrained by multiple technical challenges, including material safety, batch-to-batch consistency, sterilization compatibility, and manufacturability of complex structures. Although these biomaterials hold significant potential in tissue regeneration, tendon-to-bone interface healing, and immunomodulation [143, 144], their clinical translation is limited by the need for predictable degradation and biocompatibility, as material toxicity, potential metabolic accumulation, and mismatched degradation and release kinetics directly affect clinical safety [145, 146]. Scaled production requires stable raw material sources and reproducible properties, yet current biodegradable polymers and natural components lack standardized systems, leading to inconsistent performance [147]. Conventional sterilization methods, such as autoclaving or gamma irradiation, can damage protein structures, or compromise scaffold mechanical integrity, for example, through hydrogel fragmentation or deformation of electrospun fibers [148]. Although aseptic processing combined with lyophilization avoids terminal sterilization, its high cost and scale-up complexity impede mass production; therefore, the development and validation of low-damage sterilization approaches, such as supercritical CO_2 or nonthermal plasma, and their integration into scalable processes [149].

The intrinsic trade-off between functional performance and manufacturability further constrains industrialization [150]. Hydrogels often fail to withstand the high loads of deep

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tendon sites, while traditional electrospun scaffolds lack sufficient strength for dynamic regions such as rotator cuffs and ACLs [151, 152]. Moreover, key processes for exosome purification, protein encapsulation, and release control have not yet reached unified industrial standards, resulting in significant batch variability and limited reproducibility in clinical trials [153]. Complex scaffolds designed to mimic the natural tendon gradient structure still rely on artisanal casting or small-scale electrospinning, which are incompatible with high-precision, high-reproducibility mass production [94]. Long-term safety concerns, including potential immunogenicity of nanomaterials, dose–response relationships of exosomes, and *in vivo* metabolic fate, further complicate CMC documentation and terminal sterilization validation [154].

To overcome these barriers, multidimensional innovation is required. Material systems should first achieve tunable mechanics, programmable degradation, and compatibility with low-damage sterilization, supported by standardized raw material systems to minimize batch variability. Advanced manufacturing technologies, including continuous electrospinning, high-throughput hydrogel filling, and modular 3D printing, can overcome the limitations of small-scale artisanal fabrication, improving structural precision and reproducibility. Comprehensive quality control systems grounded in quality by design principles must cover the entire production chain from raw materials to final product release. Finally, early integration of clinical requirements with manufacturability assessments through industry–academic–clinical collaboration can drive scaffold design optimization, process scale-up, and regulatory compliance, thereby facilitating the translation of scaffolds from laboratory prototypes to clinically and industrially viable products.

Long-term safety and functional stability. Implant-associated inflammation and infection remain major obstacles to long-term implant stability, with average infection rates approaching 5% [155]. As any implanted material inevitably triggers an acute immune response, dysregulated inflammation may progress into chronic pathological states characterized by redness, swelling, heat, and pain, ultimately resulting in implant failure or local tissue necrosis [156]. Although all degradable biomaterials induce inflammation, persistent dysregulation is the key risk that must be avoided [157].

A second challenge is the temporal mismatch between material degradation and tissue regeneration. Premature degradation—such as rapid corrosion of magnesium alloy screws—leads to an early loss of mechanical integrity accompanied by an elevated ion concentration or gas evolution that disrupts the healing microenvironment [158]; long-term cytocompatibility and potential immunogenicity remain clinical concerns [30]. Conversely, excessively slow degradation, exemplified by ECM fillers with uncontrolled disintegration, causes progressive volume loss and failure to maintain structural support, necessitating repeated treatment and imposing additional patient burden [159, 160].

A third issue arises from the biological activity of degradation products and their interaction with the immune system. ECM scaffolds may retain immunogenic components that hinder standardization and large-scale clinical use [67]. Metal nanoparticles can trigger toxicity when ion release is uncontrolled or stimulus-responsive [161]. Although many polysaccharides—such as chitosan, HA, alginate, and chondroitin sulfate—exhibit inherent anti-inflammatory properties [162, 163], the variability of natural biopolymers complicates reproducibility. Artelon® Dynamic Matrix™, a PCL-based polyurethane scaffold with optional chondroitin sulfate coating, demonstrates good biocompatibility, dynamic mechanical matching, and infection resistance and is approved for multiple orthopedic applications [164]; however, concerns regarding its long-term efficacy and cost remain.

Finally, long-term functional monitoring of degradable implants is technically demanding. Radiotracers allow *in vivo* tracking, but slow degradation kinetics require repeated imaging, raising cumulative radiation concerns [165].

Effective long-term safety requires minimizing intrinsic material toxicity while incorporating immunomodulatory elements to prevent excessive or chronic inflammation. Matching degradation dynamics with tissue regeneration can be achieved through surface engineering (e.g. coated magnesium alloys) and rational material design that align mechanical decay with biological repair timelines while ensuring degradation products remain safe and low-immunogenic [166, 167]. Reducing immune risks associated with natural or hybrid materials further depends on improved purification, standardized fabrication, and selective biofunctionalization to enhance reproducibility and tissue integration. Clinically validated systems such as Artelon illustrate the value of combining structural biomimicry with controlled degradation and targeted surface modification to enhance biosafety and performance.

Future development should integrate personalized patient conditions into standardized evaluation frameworks and prioritize noninvasive, real-time monitoring technologies capable of tracking material degradation, immune responses, and tissue integration without reliance on repeated radiation-based imaging [165].

Regulatory challenges

As tendon-repair biomaterials shift from single-material scaffolds toward composite systems containing bioactive factors, cells, or gene-editing elements, regulatory ambiguity has become a major barrier. Unlike traditional monolithic products with clear classification pathways, composite systems may be assigned to different regulatory categories depending on the jurisdiction, leading to fragmented development strategies, prolonged timelines, and increased cost.

In the European Economic Area, CE marking requires classification based on the primary mode of action into drugs, medical devices, biologics, or combination products, with the device pathway generally offering faster approval [168, 169]. However, identical materials may fall into different categories depending on intended use. HA exemplifies this divergence: it is considered a medical device for joint lubrication in the USA and as a dermal filler in China, yet its ophthalmic and joint-injection applications in China require drug classification, imposing higher clinical-evidence burdens [129]. Drug–device combination products face even stricter evidence requirements, and China mandates explicit determination of whether the primary action is drug- or device-led.

Scientific evaluation standards also lag behind technological innovation. ISO 10993 biocompatibility standards insufficiently address long-term risks associated with complex or bioactive scaffold components [170]. Moreover, the

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absence of harmonized regulatory frameworks restricts long-term immunometabolism and degradation-related safety assessments across jurisdictions.

To address these challenges, early regulatory engagement through programs such as EMA Scientific Advice and FDA Q-Submission can help developers define classification routes and evidence expectations at the outset, reducing late-stage misalignment [171, 172]. Standardization is being modernized with regenerative-medicine-specific frameworks under ISO/TC 276, providing more appropriate evaluation tools for combination products and filling gaps left by traditional standards [173]. Long-term, real-world evidence collection platforms such as European Database on Medical Devices (EUDAMED) allow systematic monitoring of implant performance, supporting adaptive, life-cycle regulatory management [168]. Managing global regulatory divergence further requires establishing baseline scientific consensus, recognizing that material risk is primarily determined by clinical context. Developers should therefore combine early, front-loaded classification based on combination-product precedents with global evidence harmonization, including IMDRF/MDSAP quality-system certification [174] and utilization of accelerated pathways such as RMAT or PRIME to enable earlier market access with adaptive evidence requirements [175]. Together, this integrated approach transitions regulatory practice from static approval toward dynamic, life-cycle oversight suitable for next-generation tendon-repair biomaterials.

To overcome these limitations, the field is adopting three synergistic strategies: (i) early-stage regulatory engagement: utilizing the European Medicines Agency (EMA) Scientific Advice procedure or FDA's Q-Submission program to predefine classification pathways, thereby preventing late-stage development misalignment; (ii) standard system modernization: developing dedicated standards for regenerative medicine through organizations like ISO/TC 276 on biotechnology, addressing gaps in conventional frameworks; (iii) dynamic evidence generation: establishing adaptive regulatory models using real-world evidence, exemplified by leveraging the EUDAMED implant registry to analyze $\geq$ 10-year follow-up data, for systematic monitoring of long-term immunometabolic effects from bioactive components in combination products.

Economic challenges

Highly personalized scaffolds or cell-based therapies face substantial economic barriers. Patient-specific products require complex *in vitro* expansion, stringent quality assurance/quality control (QC) protocols, and intensive regulatory oversight, resulting in prohibitive costs [176, 177]. Interpatient heterogeneity, including age, injury type, comorbidities, and genetic background—further necessitates individualized regimens, complicating manufacturing and limiting clinical accessibility and payer acceptance, particularly in the absence of robust evidence demonstrating superior cost-effectiveness relative to conventional therapies.

Biomaterials offer a strategic solution by combining personalization with scalable production. They act not only as cell carriers but also as active microenvironment regulators, capable of loading and controlled release of growth factors, nucleic acids, or small molecules to provide patient-specific regenerative signals [178]. Surface functionalization can modulate host immune responses and mitigate adverse microenvironmental effects, while mechanical properties such as stiffness and elasticity can be tuned to match tissue-specific or injury-stage requirements [103, 179, 180]. Platform-based and modular designs further enable standardized base scaffolds to be customized with bioactive modules, reducing production complexity, lowering costs, and simplifying QC [181]. Cell-independent strategies, such as *in vivo* cell recruitment or cell-free therapies, avoid expensive *in vitro* expansion and storage. Enhanced predictability of therapeutic outcomes reduces repeated or ineffective treatments and downstream healthcare costs, such as revision surgeries or prolonged rehabilitation, thereby improving cost-effectiveness and payer acceptance [182].

Within this context, biomaterials demonstrate significant potential as cornerstones of sustainable translational medicine, with their core value residing in resolving the fundamental tension between personalized therapeutic needs and scalable production/cost-effectiveness. In response to individual differences, biomaterials are not only cell carriers but also active regulators of the microenvironment. They can be designed as "bioactive instruction libraries" that load and controlled-release specific growth factors, nucleic acids, or small molecules to provide customized regenerative signals tailored to the pathological conditions of different patients (e.g. inflammation levels, vascularization capacity). Surface functionalization can modulate host immune responses, mitigate the adverse effects of the individual microenvironment, and enhance therapeutic efficacy consistency. Its mechanical properties (stiffness, elasticity) can precisely match the mechanical requirements of different tissues or stages of injury. At the same time, individualized decisions based on imaging or biomarkers ultimately need to be translated into treatment products. Biomaterials (such as 3D-printed patient-matched scaffolds and smart responsive hydrogels) are the ideal physical platform for achieving this transformation.

Future perspectives: integrative innovations in engineering strategies and clinical translation

Tendon–bone regeneration remains fundamentally challenging due to the intrinsic structural heterogeneity of the enthesis, the inability of current surgical techniques to re-establish native gradients, and the dysregulated immune microenvironment after repair. Although substantial progress has been made in scaffold engineering, persistent failure modes—such as mechanical mismatch, interface instability, uncontrolled release kinetics, and inadequate immunomodulation—continue to limit clinical translation. Breakthrough advances in tendon–bone regeneration fundamentally represent a revolutionary process driven by deep integration of engineering strategies and clinical medicine. The integration of intelligent technologies further unlocks the potential of scaffold engineering strategies. At the material design level, artificial intelligence (AI) models are being deployed to integrate multisource heterogeneous data, establishing more universal and interpretable structure–activity relationship models. These models guide the development of next-generation intelligent biomaterials with multifunctional synergy. For instance, AI-driven high-throughput material design utilizes deep generative models to predict the structure–activity relationships between porous scaffold topology and osteogenic activity, thereby accelerating customized solution development [183]. AI-enabled dynamic closed-loop systems (e.g. smart bandages, implantable drug delivery devices) integrate biomaterials with electrical stimulation through "sensing–analysis–intervention" cycles, achieving precise regulation of tissue regeneration [184]. Future research will

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focus on developing miniaturized, low-power implantable sensing and actuation units while ensuring robust protection of patient privacy data [185]. Crucially, these systems dynamically optimize intervention strategies based on longitudinal therapeutic feedback from individual patients, enabling truly personalized and adaptive regenerative medicine [186].

Despite these promising innovations, critical gaps and failure modes persist in current tendon–bone scaffold engineering. Material selection often fails to simultaneously satisfy mechanical matching, tissue integration, and functional restoration. Gradient scaffolds remain difficult to fabricate at clinically relevant scales, and layer interfaces are prone to delamination when improperly designed [187]. Functional limitations, including burst release of bioactive factors [188], inadequate immunomodulation, and asynchronous degradation, can result in fibrotic encapsulation or stress shielding-induced bone resorption [189, 190]. Preclinical evaluation is often limited to small-animal models that poorly replicate human tendon–bone physiology, limiting predictive power for clinical translation. Addressing these gaps requires coordinated strategies across multiple domains.

Future research should prioritize the following directions. (i) Material design and gradient fabrication. The development of multicomponent, gradient-optimized scaffolds guided by AI and computational modeling is expected to enhance mechanical robustness and biological performance while reducing failure risks. Saeed *et al*. developed a machine-learning framework for predicting the quality of 3D-printed scaffolds, in which more than 40 machine-learning and deep-learning algorithms were evaluated and hyperparameters were optimized to uncover hidden patterns and accurately predict cell responses, printability, and scaffold quality. They constructed a fully connected neural network with six hidden layers and optimized it to achieve accurate predictions across 60 biomaterials—including natural and synthetic materials, crosslinkers, and enzymes—as well as 49 cell types, cell densities, and printing conditions. This provides a more reliable basis and evaluation criteria for engineering next-generation tendon–bone interface scaffolds [1]. (ii) Functionalization and immunomodulation. Smart delivery systems should be integrated to dynamically regulate MSC differentiation, ECM deposition, and local immune responses, thereby preventing burst release and fibrotic tissue formation. Moreover, the image-processing and pattern-recognition capabilities of AI can be leveraged to automatically analyze and diagnose wound conditions or pathological regions in patients, guiding the selection of appropriate scaffold compositions and fabrication strategies [191]. (iii) Standardized preclinical modeling: establishment of large-animal models that closely mimic human physiological loading and interface biology to evaluate long-term mechanical stability, tissue integration, and biosafety. (4) Scalable and clinically feasible manufacturing: optimization of advanced 3D printing, electrospinning, and hybrid fabrication techniques to achieve reproducible, degradable, and regulatory-compliant scaffolds suitable for translation. Overall, AI is reshaping the biomaterials field by providing powerful tools for material design, process optimization, performance prediction, and ethical decision-making, thereby accelerating discovery and transforming the development pipeline [192].

Realistic milestones for the next 10 years can be proposed to guide clinical translation. Short-term (1–3 years): refinement of multi-material gradient scaffolds, *in vitro* validation of MSC differentiation and ECM deposition, and establishment of standardized large-animal models. In parallel, develop standardized protocols for scaffold characterization (e.g. mechanical testing, degradation kinetics, and bioactivity assays) and initiate the creation of a centralized, open-access tendon–bone interface material–structure–performance database to facilitate reproducibility and cross-lab comparisons. Begin integrating AI-based predictive modeling to optimize scaffold composition and fiber architecture for targeted mechanical and biological outcomes. Mid-term (3–7 years): demonstration of long-term mechanical stability, tissue integration, and biosafety in preclinical models, alongside scalable and reproducible fabrication processes. Specific measures include implementation of automated fabrication and quality control workflows, integration of high-throughput screening for scaffold properties, and validation of intelligent delivery systems for spatiotemporal regulation of bioactive cues. Expand the TBI database to include multimodal data (e.g. imaging, biomechanical testing, and *in vivo* outcomes) and establish community-wide data-sharing standards. Apply machine learning algorithms to correlate scaffold structure–property–function relationships, enabling predictive design for patient-specific applications. Long-term (7–10 years): initiation of early-phase clinical trials for rotator cuff and other weight-bearing tendon–bone interfaces (e.g. Achilles and patellar tendons), coupled with iterative optimization of scaffold design guided by patient-specific feedback and computational modeling. Conduct comprehensive assessments of functional recovery, patient-reported outcomes, and quality-of-life measures. Establish an integrated clinical–preclinical data-sharing framework to continuously refine scaffold design, incorporate AI-driven predictive models for patient-specific therapy, and facilitate evidence-based regulatory submissions. Explore the use of intelligent materials capable of responsive modulation of inflammation or osteogenesis, guided by real-time patient monitoring and AI-assisted decision-making.

By providing precise biological guidance and dynamic regulation through engineered approaches, sustained functional restoration can ultimately be achieved. The deep integration of engineering principles with clinical needs is expected to reshape the entire translational pathway—from material design and scaffold fabrication to therapeutic implementation and outcome evaluation—while addressing long-standing failure modes that hinder tendon–bone regeneration.

Conclusions

In this review, we summarized the major biomaterial categories used in rotator cuff repair and introduced a dual-matrix framework based on structural architecture and functionalization, offering readers a clearer lens through which to interpret both the pathological complexity of the tendon–bone interface and the shortcomings of current scaffold strategies. Key limitations—such as difficulties in fabricating clinically relevant gradient structures, interface delamination, burst release of bioactive cues, inadequate immunoregulation, and insufficient long-term mechanical and biological integration—were highlighted to define critical future directions. Addressing these challenges will require coordinated strategies that integrate intelligent material design, multiscale structural optimization, and clinically relevant preclinical models, thereby accelerating

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the development of translationally viable scaffolds. Ultimately, by bridging the problems identified in the introduction—high retear rates, poor biological integration, and inadequate mechanical restoration—with targeted engineering and AI-driven solutions, this work provides a coherent roadmap linking fundamental insights to clinical application.

List of abbreviations

Extracellular matrix (ECM), anterior cruciate ligament (ACL), microcomputed tomography (μCT), silk fibroin (SF), hyaluronic acid (HA), graphene oxide (GO), magnesium ion (Mg^{2+}), polyethylene terephthalate (PET), polytetrafluoroethylene (PTFE), polylactic acid (PLA), polyglycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), poly(L-lactic acid) (PLLA), β-tricalcium phosphate (β-TCP), bioactive glass (BG), zirconia (ZrO_2), platelet-rich plasma (PRP), kartogenin (KGN), polyvinyl alcohol (PVA), nano-hydroxyapatite (n-HA), poly(ester-ether urethane urea) (PEEUU), gelatin (GEL), bone marrow-derived mesenchymal stem cells (BMSCs), molybdenum-doped silicate (MS), ferulic acid (FA), mesoporous bioactive glass nanoparticles (MBG), strontium-doped MBG (Sr-MBG), barium titanate (BTO), zinc oxide (ZnO).

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Author contributions

Hao Feng (Conceptualization, Visualization, Writing—original draft, Writing—review & editing [lead]), Xiao Yu (Methodology [equal], Writing—original draft [lead], Writing—review & editing [equal]), Gonghao Zhang (Funding acquisition, Supervision, Visualization [equal]), Zhengchao Yuan (Investigation, Visualization [equal]), Abdullah M. Al-Enizi (Supervision [equal]), Xueqin Cheng (Data curation, Investigation [equal]), Mohamed EL-Newehy (Funding acquisition, Methodology, Supervision [equal]), Xiumei Mo (Funding acquisition, Validation, Visualization [equal])

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Data availability

No new data were created or analyzed in this study.

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