

Advances in extracellular matrix-mimetic hydrogels for muscle repair and regeneration: Biomimetic design, preparation, mechanisms and tissue engineering applications

Hao Wang^{1,§}, Yanan Xu^{2,§}, Feng Luo³, Yihao Long⁴, Fazal ul Nisa⁴, Wan Zhao⁵, Qin Wang⁶, Yuxin Wang¹, Yuanyuan Peng¹, Jiaxin Ding¹, Huan Yan⁷, Liang He⁴, Jianrong Zuo^{1,8}, Feng Wang^{1,8}, Dan Lu^{1,8} (✉)

¹ Department of Otorhinolaryngology, Head & Neck Surgery, West China Hospital, Sichuan University, Chengdu 610041, China

² Department of Scientific Research, The Affiliated Women and Children's Hospital of Ningbo University, Ningbo 315211, China

³ College of Polymer Science and Engineering, State Key Laboratory of Advanced Polymer Materials, Med-X Center for Materials, Sichuan University, Chengdu 610065, China

⁴ School of Mechanical Engineering, State Key Laboratory of Intelligent Construction and Healthy Operation and Maintenance of Deep Underground Engineering, Sichuan University, Chengdu 610065, China

⁵ Department of Otolaryngology-Head and Neck Surgery, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei 230001, China

⁶ Department of Otolaryngology-Head and Neck Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, China

⁷ The First Affiliated Hospital of Traditional Chinese Medical of Chengdu Medical College, XinDu Hospital of Traditional Chinese Medicine, Chengdu 610500, China

⁸ Department of Otorhinolaryngology, Head & Neck Surgery, West China Tian Fu Hospital, Sichuan University, Chengdu 610213, China

[§] Hao Wang and Yanan Xu contributed equally to this work.

Nano Res., **Just Accepted Manuscript** • <https://doi.org/10.26599/NR.2026.94909192>

<https://www.sciopen.com/journal/1998-0124> on Sep. 14, 2026

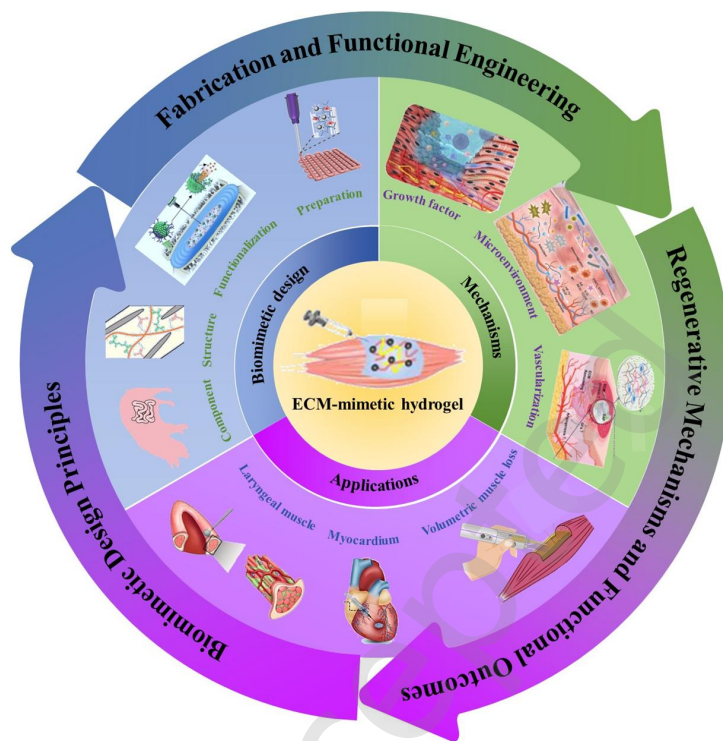
© The Author(s)

Just Accepted

This is a "Just Accepted" manuscript, which has been examined by the peer-review process and has been accepted for publication. A "Just Accepted" manuscript is published online shortly after its acceptance, which is prior to technical editing and formatting and author proofing. Tsinghua University Press (TUP) provides "Just Accepted" as an optional and free service which allows authors to make their results available to the research community as soon as possible after acceptance. After a manuscript has been technically edited and formatted, and the page proofs have been corrected, it will be removed from the "Just Accepted" web site and published officially with volume and article number (e.g., *Nano Research*, **2025**, *18*, 94906990). Please note that technical editing may introduce minor changes to the manuscript text and/or graphics which may affect the content, and all legal disclaimers that apply to the journal pertain. In no event shall TUP be held responsible for errors or consequences arising from the use of any information contained in these "Just Accepted" manuscripts. To cite this manuscript please use its Digital Object Identifier (DOI®), which is identical for all formats of publication.

TABLE OF CONTENTS (TOC)

The graphical abstract presents an integrated framework for ECM-mimetic hydrogels, linking biomimetic design principles and fabrication and functional engineering with regenerative mechanisms and muscle repair applications. It highlights the relationships among ECM-mimetic components, structural design, functionalization, preparation, growth-factor delivery, microenvironment regulation, vascularization, and applications in volumetric muscle loss, myocardium, and laryngeal muscle regeneration.



This review presents an application-oriented framework for ECM-mimetic hydrogels in muscle repair, linking biomimetic design and regenerative mechanisms with disease-specific material selection and translational requirements. It highlights how structural and biochemical cues, dynamic mechanical regulation, immune modulation, and precision therapeutic functions can be comprehensively considered to guide functional muscle regeneration.

Advances in extracellular matrix-mimetic hydrogels for muscle repair and regeneration: Biomimetic design, preparation, mechanisms and tissue engineering applications

Hao Wang ^{1,§}, Yanan Xu ^{2,§}, Feng Luo ³, Yihao Long ⁴, Fazal ul Nisa ⁴, Wan Zhao ⁵, Qin Wang ⁶, Yuxin Wang ¹, Yuanyuan Peng ¹, Jiaxin Ding ¹, Huan Yan ⁷, Liang He ⁴, Jianrong Zuo ^{1,8}, Feng Wang ^{1,8}, and Dan Lu ^{1,8} ✉

¹ Department of Otorhinolaryngology, Head & Neck Surgery, West China Hospital, Sichuan University, Chengdu 610041, China

² Department of Scientific Research, The Affiliated Women and Children's Hospital of Ningbo University, Ningbo 315211, China

³ College of Polymer Science and Engineering, State Key Laboratory of Advanced Polymer Materials, Med-X Center for Materials, Sichuan University, Chengdu 610065, China

⁴ School of Mechanical Engineering, State Key Laboratory of Intelligent Construction and Healthy Operation and Maintenance of Deep Underground Engineering, Sichuan University, Chengdu 610065, China

⁵ Department of Otolaryngology-Head and Neck Surgery, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei 230001, China

⁶ Department of Otolaryngology-Head and Neck Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, China

⁷ The First Affiliated Hospital of Traditional Chinese Medical of Chengdu Medical College, XinDu Hospital of Traditional Chinese Medicine, Chengdu 610500, China

⁸ Department of Otorhinolaryngology, Head & Neck Surgery, West China Tian Fu Hospital, Sichuan University, Chengdu 610213, China

§ Hao Wang and Yanan Xu contributed equally to this work.

Received: 5 July 2026; **Revised:** 14 September 2026; **Accepted:** 14 September 2026

✉ Address correspondence to danlv2008@wchscu.cn

 **Cite this article:** Nano Research, 2026, 19, 94909192 <https://doi.org/10.26599/NR.2026.94909192>

ABSTRACT: Extracellular matrix (ECM)-mimetic hydrogels have attracted increasing attention in muscle tissue engineering because they can partially reproduce the biochemical and biophysical features of native regenerative niches. In contrast to conventional hydrogels that mainly serve as passive structural supports, emerging ECM-mimetic hydrogels are being designed to actively regulate multiple stages of tissue repair, including inflammatory remodeling, stem-cell activation, angiogenesis, and neuromuscular integration. Strategies such as decellularized matrix incorporation, anisotropic structural engineering, electroactive modification, and spatiotemporally controlled factor delivery have all shown great potential for improving regenerative outcomes in skeletal, cardiac, and smooth muscle tissues. Simultaneously, growing evidence suggests that successful regeneration depends not only on biochemical signaling, but also on dynamic interactions between cells and the surrounding matrix, particularly mechanotransduction, immune regulation, and adaptive remodeling processes. In this review, we summarize current advances in ECM-mimetic hydrogels from the perspectives of biomimetic design, regenerative mechanisms, and translational applications. We further discuss several unresolved challenges, including insufficient neurovascular integration, limited long-term matrix adaptability, and the lack of standardized functional evaluation systems. Finally, we highlight emerging directions involving bioelectronics, intelligent responsive biomaterials, and multi-omics-guided design strategies, which will be helpful in advancing the development of next-generation regenerative platforms for functional muscle reconstruction. The revised framework further distinguishes mature and provisional ECM targets, compares application-specific material selection, and maps commercially available or clinically advanced ECM-related products to their translational status.

KEYWORDS: hydrogel, extracellular matrix, muscle regeneration, volumetric muscle loss

1 Introduction

Muscle tissue accounts for approximately 40% of total human body mass and plays indispensable roles in body movement, metabolic regulation, respiration, thermogenesis, and electrophysiological conduction [1]. Severe muscle damage caused by traumatic injury, tumor resection, ischemia, degenerative diseases, or chronic inflammation remains a major clinical challenge because adult muscle tissues possess limited regenerative capacity under pathological conditions [2]. In particular, volumetric muscle loss (VML), muscular dystrophy, and myocardial infarction often lead to irreversible tissue degeneration, fibrosis formation, and permanent functional impairment [3]. Current clinical treatments, including autologous tissue transplantation, synthetic implants, pharmacological anti-inflammatory therapy, and rehabilitation training, frequently fail to restore functional tissue organization and contractile performance [4]. Autologous grafting is limited by donor-site morbidity and insufficient tissue availability, while synthetic scaffolds often lack biological activity and fail to establish dynamic regenerative microenvironments [5]. Therefore, there remains an urgent need for biomaterials capable of simultaneously regulating inflammation, stem cell behavior, angiogenesis, innervation, and mechanical integration.

Hydrogels have attracted widespread attention in regenerative medicine because of their high water content, tunable physicochemical properties, injectability, and

favorable biocompatibility [6]. However, conventional hydrogels primarily function as passive structural matrices and often inadequately reproduce the complex biochemical and biomechanical signaling environment of native extracellular matrix (ECM), thereby limiting their ability to guide functional muscle regeneration [7]. The native muscle ECM is a highly dynamic and anisotropic biological system composed of collagens, laminin, fibronectin, elastin, proteoglycans, and matrix-bound signaling molecules [8-10]. Beyond providing structural support, ECM actively regulates satellite cell activation, mechanotransduction, immune modulation, angiogenesis, and neuromuscular integration during tissue regeneration. Importantly, increasing evidence suggests that the transient provisional ECM formed during endogenous healing differs substantially from mature healthy ECM in composition, stiffness, turnover rate, and signaling activity, and may represent a more appropriate template for regenerative biomaterial design [11].

To address the limitations of conventional hydrogels, ECM-mimetic hydrogels have been developed to reproduce critical structural, mechanical, biochemical, and electrophysiological properties of native regenerative microenvironments [12-15]. These advanced biomaterials can function not only as structural scaffolds, but also as dynamic signaling platforms capable of regulating inflammation, recruiting endogenous progenitor cells, controlling spatiotemporal factor delivery, and promoting vascularized and innervated tissue regeneration [16].

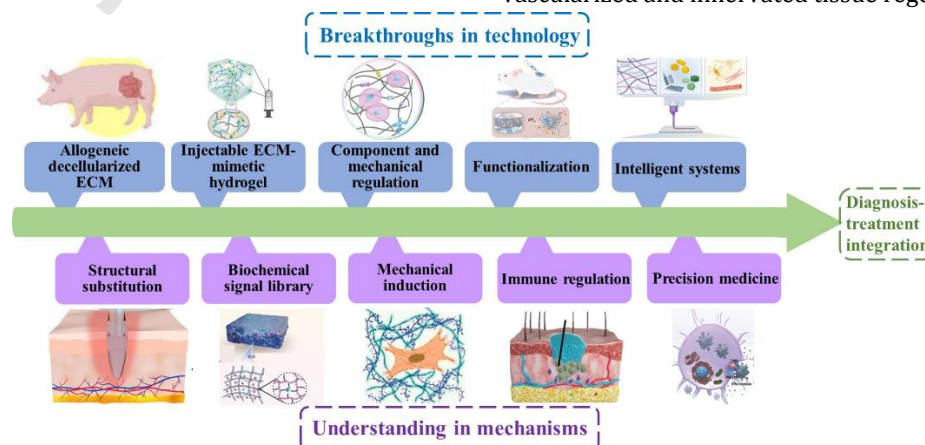


Figure 1 The evolution of ECM-mimetic hydrogels alongside technological breakthroughs and deepening understanding of their mechanisms. Allogeneic decellularized ECM. Reproduced with permission [17]. Copyright 2024, Elsevier. Injectable ECM-mimetic hydrogel. Reproduced with permission [18]. Copyright 2021, Elsevier. Component and mechanical regulation. Reproduced with permission [19]. Copyright 2021, John Wiley and Sons. Functionalization. Reproduced with permission [20]. Copyright 2024, John Wiley and Sons. Intelligent systems. Reproduced with permission [21]. Copyright 2023, Springer Nature. Structural substitution. Reproduced with permission [22]. Copyright 2024, Elsevier. Biochemical signal library. Reproduced with permission [23]. Copyright 2024, Springer Nature. Mechanical induction. Reproduced with permission [24]. Copyright 2025, Elsevier. Immune regulation. Reproduced with permission [25]. Copyright 2022, the American Association for the Advancement of Science. Precision medicine. Reproduced with permission [26]. Copyright 2024, John Wiley and Sons.

However, no existing reviews have systematically summarized the full research chain from biomimetic design to clinical application, while highlighting the paradigm shift from static scaffolds to dynamic intelligent systems. Most published reviews mainly focus on the tissue engineering applications of a single type of hydrogel [27, 28], address specific individual aspects of muscle regeneration [29, 30], or are limited to one specific clinical indication [31, 32]. Herein, we establish a core framework centered on the synergistic integration of compositional, structural, and functional biomimetics.

This review systematically summarizes the latest research advances in the field of ECM-mimetic hydrogels for muscle regeneration. We first provide a concise overview of the historical development of ECM-mimetic hydrogels,

highlighting key technological breakthroughs and the evolving understanding of their underlying mechanisms (Figure 1). On this basis, we then systematically discuss the biomimetic strategies and preparation methodologies for ECM-mimetic hydrogels, with a specific focus on their biomimetic component design, structural biomimicry, and multifunctional design. Furthermore, we critically analyze the advantages and limitations of various preparation techniques, including decellularization, physical crosslinking, chemical crosslinking, and 3D bioprinting, along with their respective applicable scenarios and optimal material selections. This review also elaborates on the multiple core mechanisms of ECM-mimetic hydrogels in muscle repair and regeneration, including biomimetic structural support, mechanical and biochemical signal guidance, controlled bioactive factor release, cell recruitment, immunomodulation, synergistic vascularization and neurogenesis, as well as electrophysiological microenvironment simulation. The subsequent sections detail their applications across a spectrum of muscle pathologies, including acute muscle injury, VML, muscular dystrophy, cardiac muscle regeneration, and other specialized muscle types. In addition, the review critically discusses the key challenges in this field and outlines promising future research directions. Ultimately, this work aims to establish a theoretical foundation and provide innovative insights for developing next-generation, high-efficacy ECM-mimetic hydrogels, thereby accelerating their clinical translation and improving clinical outcomes for patients. A graphical table of contents (TOC) summarizing the review's framework is provided in Figure 2.

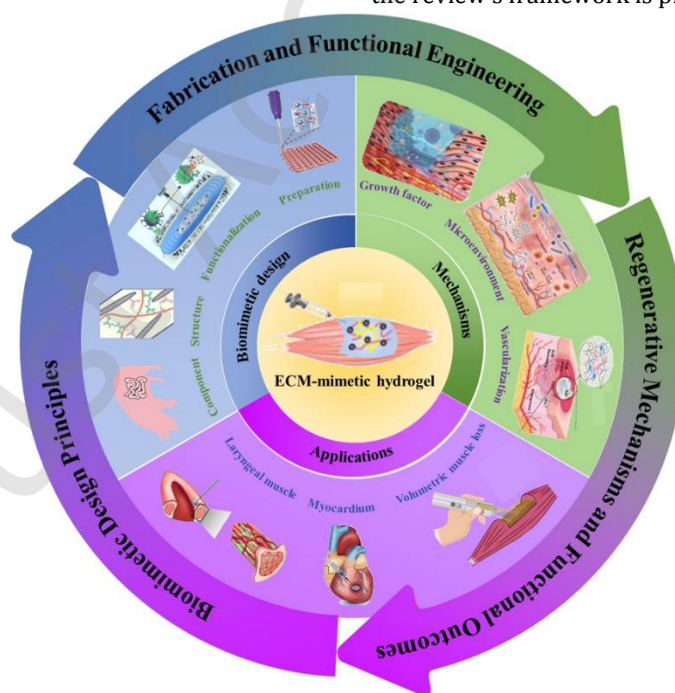


Figure 2 Integrated biomimetic design framework and regenerative mechanisms of ECM-mimetic hydrogels for functional muscle regeneration.

2 ECM-Mimetic Design Principles and Preparation

2.1 Composition and function of the natural muscle ECM

The native muscle ECM is a multi-level, ordered, and dynamic functional network, whose molecular composition and spatial topology collectively determine the mechanical properties and regenerative capacity of muscle tissue. Figure

3 shows the structural features of cardiac muscle, and skeletal muscle. Collagen constitutes the primary structural framework of the ECM. Robust type I collagen assembles into a tensile-resistant network within the epimysium, thus resisting the macroscopic mechanical stresses generated by muscle contraction [33]. Finer type III and V collagen fibers form dense micro-networks in the intramuscular fascia, wrapping individual muscle fibers to maintain the homeostasis of the local microenvironment. In the basement membrane, type IV collagen and laminin work together to

establish cellular anchorage sites, and directly regulate myocyte fate through integrin-mediated mechanical signal transduction [10, 34]. This multi-tiered collagen architecture is highly dynamic, and its functions can be finely tuned via lysyl oxidase-catalyzed cross-linking. Immature cross-links endow the tissue with plasticity to accommodate mechanical deformation, while mature cross-links enhance structural stability. Disruption of this balance will lead to tissue brittleness and progressive functional decline [35].

Elastin and proteoglycans act as key functional regulators within this system, further enhancing the dynamic responsiveness of the ECM network. Elastin enables efficient elastic recovery through its unique cross-linked structure, maintaining mechanical integrity during repeated muscle contraction-relaxation cycles. Proteoglycans serve as biological signaling hubs, sequestering growth factors through electrostatic interactions and precisely regulating their bioavailability [36].

Beyond acting as a passive structural scaffold, the ECM forms a core regulatory network for muscle regeneration through its spatial topology and dynamic signaling

properties. The three-tiered encapsulation system (endomysium-perimysium-epimysium) establishes a hierarchical force transmission chain. The helical arrangement of collagen in the perimysium has been shown to ingeniously redirect mechanical stress to protect muscle fibers, while the nanoscale grid structure of the basement membrane can guide cell migration through physical confinement [37]. At the signaling level, the ECM functions both as a reservoir for growth factors and a core interface for mechanotransduction. The integrin-adhesion complex has been demonstrated to convert external mechanical forces into intracellular chemical signals, activating key myogenic regulatory pathways. Meanwhile, targeted ECM degradation mediated by matrix metalloproteinases (MMPs) triggers the endogenous regenerative program and enables the localized release of bioactive factors [11].

Therefore, through the collaboration of its molecular composition, spatial topology, and dynamic responsiveness, the native ECM operates as an intelligent biological system that delivers structural support, mechanical protection, and biological signaling. This provides an irreplaceable biological blueprint for the rational design of ECM-mimetic hydrogels.

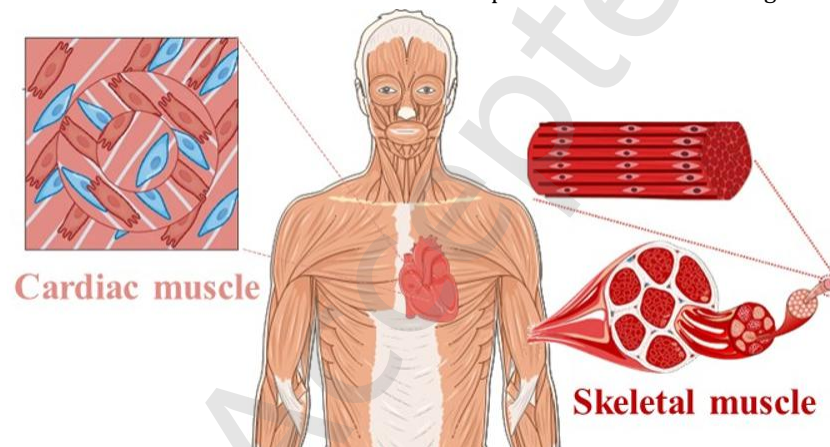


Figure 3 Cardiac muscle [38], and structure of skeletal muscle [39]. Reproduced with permission [38]. Copyright 2025, Springer Nature. Reproduced with permission [39]. Copyright 2025, John Wiley and Sons.

2.2 Compositional Biomimetic

The clinical translation of native ECM materials is constrained by their inherent immunogenicity, interindividual batch variability, limited control over composition, and the inability of many static matrices to be adapted to the evolving injury microenvironment. This distinction is particularly important when selecting the biological template for muscle repair. Mature ECM in healthy muscle is optimized for force transmission and tissue homeostasis, whereas provisional ECM formed after injury is enriched in fibronectin, tenascin-C, hyaluronan, matrix-bound cytokines, and remodeling enzymes that support cell migration, proliferation, and phenotype transition [40-42]. Consequently, the most appropriate biomimetic target depends on the therapeutic stage: mature ECM-like architecture is advantageous when mechanical integration and long-term load transfer are dominant requirements, whereas provisional ECM-like composition and remodeling kinetics are preferable during the early inflammatory and proliferative phases. Rather than reproducing either state in isolation, application-oriented hydrogel design should therefore reproduce the sequence from provisional to mature matrix, and couple this transition to the degradation,

mechanical relaxation, and bioactive-factor presentation of the scaffold [41, 42].

Compositional biomimicry is achieved through multi-scale design strategies that recapitulate the active components and dynamic interaction capabilities of the native ECM. When the therapeutic goal requires maximal recreation of the tissue-specific biochemical microenvironment, decellularized extracellular matrix (dECM) extracted from target tissues is the preferred material choice [43, 44]. The decellularization process removes immunogenic cellular components while preserving the core ECM constituents, including collagen, elastin, and endogenous growth factors [45, 46]. After bio-crosslinking, the resulting dECM hydrogel closely mimics the mechanical and biological properties of the native matrix. For instance, cardiac dECM hydrogels can significantly promote angiogenesis [47, 48], while muscle dECM plays a critical role in maintaining tissue-specific elasticity [49, 50].

When dECM presents issues such as batch-to-batch variability, potential immunological risks, or insufficient mechanical properties, a hybrid material strategy can be adopted. This approach uses precisely tunable synthetic polymers as the backbone scaffold to provide fundamental mechanical structure and processability [51]. Subsequently, bioactive molecules with specific functions are chemically grafted onto the polymer backbone to endow the ECM-

mimetic hydrogel with cell recognition and signaling guidance capabilities [52]. The genetic engineering of recombinant functional proteins can preserve the natural capacity of ECM proteins to regulate stem cell differentiation [53, 54]. Furthermore, the anchoring of biomimetic peptide segments to synthetic polymer networks has been proven to be a feasible approach, which can generate artificial extracellular matrices that are both injectable and biologically programmable [55].

In addition, when the material is required to actively interact with the pathological microenvironment to achieve smart drug delivery or cellular reprogramming, cell-derived components can be selected as the active constituents. These components act as natural mediators of intercellular communication, with exceptional biocompatibility and

targeting capacity. For example, engineered extracellular vesicles loaded with regulatory microRNAs can effectively reprogram the fibrotic pathway in damaged muscle [56].

In summary, the selection of ECM-mimetic materials represents a progressive journey from “complete replication” to “functional mimicry”, and ultimately to “intelligent enhancement”. Researchers should flexibly select and combine the aforementioned strategies based on specific clinical application scenarios, the key biological functions required, and the feasibility of large-scale production, to construct the most suitable ECM-mimetic hydrogels. Table 1 summarizes the performances of ECM-mimetic hydrogels derived from these different materials and their mechanisms for promoting muscle repair and regeneration.

Table 1 The performances of hydrogels made from different materials and their mechanisms for promoting muscle repair and regeneration

Material	Mechanism	Myotube/cell response	Electrical conductivity	Degradation/swelling / pore size	Application	Reference
GelMA	Guide cell alignment, transmit electrical signals, regulate inflammation, and reduce fibrosis	Myotube length: 863±66 µm Myotube maturity index: 92% Cell viability (24 h): >97%	0.26 S/m	Degradability: >8 h Swelling ability: 94% Pore size: 12-20 µm	VML	[57]
	Calcium influx promotes vascular nerve regeneration	Myotube length: - Myotube maturity index: - Cell viability (24 h): Virtually no deaths	3.12±0.03 mS/cm	Degradability: 32 h Swelling ability: - Pore size: 50-150 µm	Diabetic wound	[58]
	Regulate macrophage polarization to suppress excessive inflammation	Myotube length: - Myotube maturity index: - Cell viability (24 h): Virtually no deaths	-	Degradability: >8 days Swelling ability: Approximately 1.2% Pore size: 200-250 µm	VML	[59]
dECM	Structural support and adhesive fixation; Against oxidative stress	Myotube length: - Myotube maturity index: - Cell viability (24 h): -	-	Degradability: Approximately 18% Swelling ability: <3% Pore size: 10-50 µm	Muscle atrophy	[60]
	Recruiting homing cells; Reprogramming macrophages; Promoting angiogenesis	Myotube length: - Myotube maturity index: - Cell viability (24 h): > 95%	-	Degradability: 21 days Swelling ability: Approximately 500% Pore size: 3.6 µm	MI	[61]
	Ensuring MSC survival and function; Promoting host cell migration and differentiation	Myotube length: 200-500 µm Myotube maturity index: High Cell viability (24 h): -	-	Degradability: 28 days Swelling ability: 17.5% Pore size: 8-22 µm	VML	[62]
Gelatin	Inflammation regulation; Vascularization and cell recruitment	Myotube length: - Myotube maturity index: - Cell viability (24 h): >97%	-	Degradability: 21 days Swelling ability: - Pore size: 10-30 µm	VML	[63]
	Adapting to the acidic microenvironment; Programmed regulation and repair	Myotube length: - Myotube maturity index: - Cell viability (24 h): 85%	-	Degradability: 28 days Swelling ability: <10% Pore size: 2-5 µm	Acute urethral injury	[64]
	Provide an electrically active microenvironment; Regulate cellular behavior	Myotube length: - Myotube maturity index: 4.9±0.6% Cell viability (24 h): >95%	0.72±0.02 mS/cm	Degradability: >21 days Swelling ability: Barely swells Pore size: 10-50 µm	VML	[65]
Chitosan	Targeted immunomodulation for anti-inflammation; Silicon ion sustained-release for tissue regeneration	Myotube length: 320 µm Myotube maturity index: 65% Cell viability (24 h): >95%	-	Degradability: 7 days Swelling ability: No excessive swelling Pore size: 11 µm	VML	[66]
Alkylated dipeptide	Topologically guided cell alignment and differentiation; Adaptive mechanical support	Myotube length: 520 µm Myotube maturity index: 17% Cell viability (24 h): >95%	0.45 mS/cm	Degradability: 28 days Swelling ability: No excessive swelling Pore size: 10-20 µm	VML	[39]
Sodium alginate	Clear reactive oxygen species (ROS) to improve the microenvironment; Restore electrical pathways to regain contractility	Myotube length: - Myotube maturity index: - Cell viability (24 h): >95%	2.66×10 ⁻⁴ S/cm	Degradability: 28 days Swelling ability: No excessive swelling Pore size: 80 µm	MI	[67]
Oxidized P-glycoside polysaccharide	Immune modulation alleviates inflammation; Electrical signal transmission reconstruction	Myotube length: 478 µm Myotube maturity index: 65% Cell viability (24 h): >95%	0.8 mS/cm	Degradability: 28 days Swelling ability: 100%-250% Pore size: 11 µm	Diabetes-related muscle repair	[68]
Collagen	SESR transmits extracellular mechanical signals to the nucleus, and regulates chromatin accessibility	Myotube length: 150-250 µm Myotube maturity index: 28-40% Cell viability (24 h): Virtually no deaths	-	Degradability: >7 days Swelling ability: Extremely low Pore size: 2-20 µm	Skeletal muscle regeneration	[69]

vECM	ECM provides regenerative signals; Epithelial-smooth muscle synergistic repair	Myotube length: - Myotube maturity index: - Cell viability (24 h): >90%	-	Degradability: >14 days Swelling ability: No excessive swelling Pore size: 10-50 μm	Vaginal smooth muscle repair	[70]
------	--	---	---	--	------------------------------	------

2.3 Structural Biomimetic

Isolated biomolecules cannot spontaneously form the ordered hierarchical structures required to guide tissue regeneration. Just as bricks require an architectural blueprint to be built into a functional building, biomimetic components rely on precise spatial organization to be transformed into physical instructions that direct cellular behavior. This evolution marks the advancement of biomimetic strategies from molecular design to higher-dimensional structural reconstruction, which is defined as structural biomimetics. The multi-level architecture of native ECM provides a physical blueprint for functional tissue engineering, and its biomimetic reconstruction thus requires consideration across all scales, from macroscopic to nanoscopic [71]. At the macroscale, melt-electrospun fiber scaffolds can replicate the aligned arrangement of native muscle fibers [72]. When infused with dECM hydrogels, they form rigid yet flexible composite materials that deliver integrated mechanical and biological support. Similarly, 4D-printed shape-memory polymers (e.g., polycaprolactone-polyethylene glycol (PCL-PEG)) can self-fold at physiological body temperature into neuroconductive structures that guide axonal regeneration [73]. At the microscopic level, electrospun oriented nanofibers mimic the fiber arrangement of the basement membrane, accelerating myotube fusion through the contact guidance effect [74], while self-assembling peptides form nanoporous networks through β -folding, mimicking the molecular sieve function of the ECM to guide myotube formation [39].

While self-assembling peptides form nanoporous networks through β -folding, mimicking the molecular sieve function of the ECM to guide myotube formation [75]. Such multi-level ordered structures are essential for coordinating mechanical force transmission and cellular crosstalk across heterogeneous tissues. Furthermore, these physical topological cues are actively translated into biological signals by resident cells. Oriented fibers, for instance, not only promote directional cell migration via integrin activation, but also stimulate key mechanosensitive signaling pathways. This process plays a pivotal role in regulating the spatial dynamics of the regenerative process, establishing both a physical framework and a guidance system for functional muscle repair.

2.4 Functional design

2.4.1 Stimulus response

The environmental sensing and feedback execution capabilities of hydrogels are dependent on the incorporation of smart responsive modules. Enzyme-responsive designs utilize matrix metalloproteinase-sensitive peptides as molecular switches, which undergo specific cleavage at inflammatory sites, thus achieving both localized hydrogel degradation and targeted release of anti-inflammatory exosomes [76, 77]. The utilization of motor amphiphiles (MAs) facilitates the preparation of light-actuated artificial muscles characterized by highly oriented supramolecular structures. The integration of these well-aligned artificial muscles with human bone marrow-derived mesenchymal stem cells (hBM-MSCs) enables the function of MA-based light-actuated artificial muscles as an ECM-mimetic scaffold

for mesenchymal stem cells. This novel approach provides a stem cell-based therapeutic strategy for addressing muscle injury, repair, and regeneration (Figure 4a) [78].

Certain hydrogels exhibit excellent temperature sensitivity, remaining in a free-flowing liquid state at room temperature (25 °C) while spontaneously forming stable hydrogels when heated to physiological body temperature (37 °C) (Figure 4b). These hydrogels possess favorable shear-thinning properties and injectability. By modifying their composition and polymer concentration, their storage modulus at body temperature can be tuned across two orders of magnitude [79]. Furthermore, pH responsiveness is a widely used responsive modality in hydrogel stimuli-responsive systems. As illustrated in Figure 4c, researchers have developed hydrogels with excellent injectability, self-healing performance, and tissue adhesion. This hydrogel enables pH- and glucose-responsive release of metformin, achieving intelligent treatment of diabetic wounds [80]. Additionally, incorporating hydrophilic, electrically conductive MXenes into hydrogels enables the fabrication of composite hydrogels and the construction of tissue engineering scaffolds, which can be applied to the treatment of VML (Figure 4d). This hydrogel further enhances muscle fiber maturation and angiogenesis through electrical stimulation, demonstrating the synergistic effect of electrical stimulation and hydrogels on muscle regeneration. It serves as an effective platform for muscle tissue regeneration [65]. It is evident that light, temperature, pH, and electricity act as the “nervous system” for hydrogels, enabling them to adapt dynamically to pathological microenvironments. The distinct stimulus-responsive properties of ECM-mimetic hydrogels allow them to be employed across diverse clinical scenarios, substantially expanding their potential translational applications.

2.4.2 Time- and place-controlled sustained release

The response of the hydrogel to external stimuli remains a passive conditioned reflex. In contrast, native ECM-mediated regeneration fundamentally relies on the ability of the ECM to actively orchestrate the timing of signaling events. Regeneration requires a precise, biologically rhythmic release of growth factors, which guides the evolution of functional design for ECM-mimetic hydrogels. Biomimetic design should therefore accurately replicate this temporal regulatory logic. A core-shell microsphere exemplifies this design principle. One approach encapsulates transforming growth factor- β (TGF- β) inhibitors within the shell for early release post-injury to suppress fibrotic scar formation [81]. Subsequently, insulin-like growth factor-1 (IGF-1) is released from the calcium alginate core during the myoblast activation phase to promote myofibrillar maturation [82]. Another approach employs enzyme-activated cascade release. Enzymatic cleavage of the outer gel layer releases vascular endothelial growth factor (VEGF) to initiate vascularization. The exposed inner gel is subsequently degraded by upregulated esterases in the regenerative niche [27, 83]. Bioactive factors loaded into hydrogels can be released at low doses over extended periods to recruit endogenous stem cells. These recruited stem cells secrete metalloproteinases upon entering the injured tissue, inducing secondary degradation of the gel matrix. This

degradation accelerates the release of encapsulated stem cells and promotes their differentiation, thereby creating a recruitment-activation positive feedback loop [84]. This spatiotemporal sequencing design transcends passive payload delivery, establishing a mechanism for actively regulating cellular behavior throughout the regeneration process.

2.4.3 Bioelectric signal transmission

Once spatiotemporally controlled release of diverse bioactive factors is realized, hydrogels are required to surmount the conduction barriers of electrical signals to decode electrophysiological signals of muscle tissues. Flexible electroactive hydrogels, fabricated by integrating conductive polymers with biological macromolecules, enable real-time monitoring of electromyographic signals for evaluating regeneration progression, and can deliver electrical stimulation to activate calcium channels, thus facilitating myotube maturation [85-87]. As illustrated in Figure 5a, the rationally designed injectable, antioxidant-resistant conductive hydrogel (E-MXene) exhibits a high water content and interconnected porous architecture. These characteristics support the homogeneous dispersion of MXene nanosheets within the ECM matrix and the construction of a continuous conductive network, which strengthens electrical signal propagation in infarcted myocardial tissue. In addition, this hydrogel integrates ROS scavenging capacity with the restoration of electrical integrity in damaged tissues, offering a theoretical framework and innovative strategy for myocardial infarction treatment [88].

Additionally, the homogeneous dispersion of poly(3,4-

ethylenedioxythiophene) (PEDOT) nanoparticles into the hydrogel matrix effectively improves the electrical conductivity of the resulting hydrogel scaffold. Using 3D bioprinting technology, we fabricated conductive scaffolds that encapsulate C2C12 myoblasts. These scaffolds markedly enhanced the myogenic differentiation of C2C12 cells and the formation of mature myotubes *in vitro*, providing a feasible technical route for cell encapsulation and muscle tissue regeneration (Figure 5b) [89]. Meanwhile, polypyrrole-polydopamine (PPy-PDA) nanoparticles can be evenly dispersed and form interconnections within hydrogel networks, establishing a robust conductive network that strengthens electrical coupling between uninjured and damaged muscle tissues. This enables efficient electrical signal transduction at the sites of skeletal muscle defects (Figure 5c). The multifunctional hydrogel-based bioelectronic conductor fabricated through this strategy optimizes the electrophysiological microenvironment at the defect sites, thus accelerating skeletal muscle repair and healing [68].

Through the above biomimetic design strategies, ECM-mimetic hydrogels can not only respond to external environmental stimuli and realize spatiotemporally controlled release of multiple bioactive factors, but also bridge damaged regions with healthy muscle tissues via their electrical signal conduction capacity, thus driving efficient muscle repair and regeneration. This multifunctional integration spanning from biological signal sensing to therapeutic function execution transforms conventional hydrogel scaffolds into intelligent therapeutic systems, which lays a solid technical foundation for the development of precision regenerative medicine.

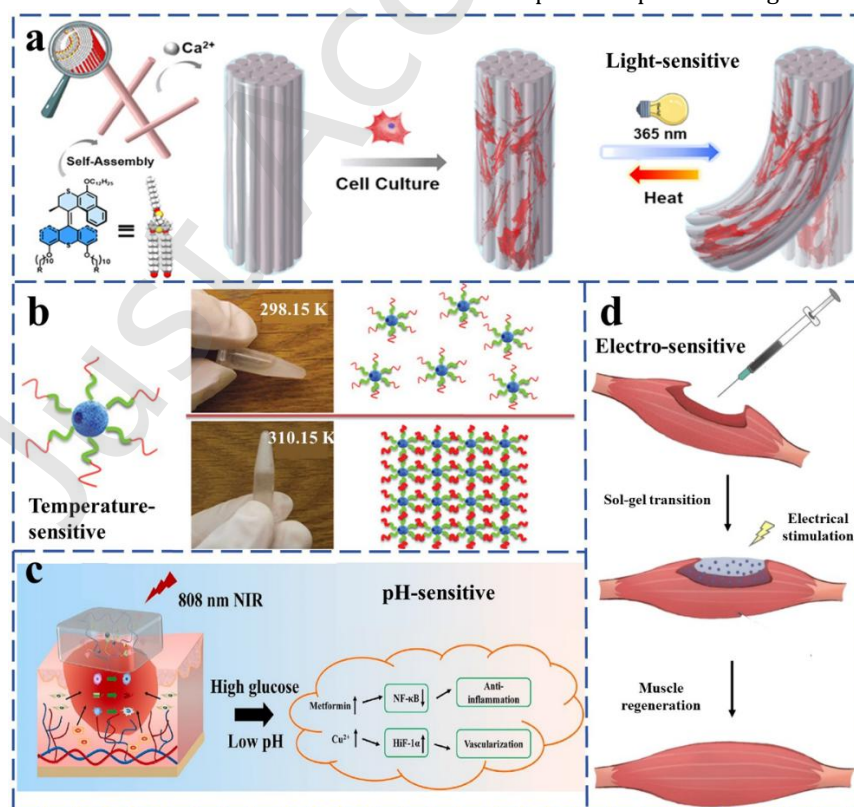


Figure 4 Stimulus-responsive hydrogel strategies for regulating the regenerative microenvironment. a) Light-sensitive hydrogel [78]. b) Temperature-sensitive hydrogel [79]. c) pH-sensitive hydrogel [80]. d) Electro-sensitive hydrogel [65]. Reproduced with permission [78]. Copyright 2022, American Chemical Society. Reproduced with

permission [79]. Copyright 2020, John Wiley and Sons. Reproduced with permission [80]. Copyright 2023, Elsevier. Reproduced with permission [65]. Copyright 2025, Elsevier.

2.5 Preparation and Characterization Methods of the ECM-mimetic hydrogel

2.5.1 Decellularization and enzymatic digestion

Decellularization coupled with enzymatic digestion forms the cornerstone for retaining the inherent biological activity of native ECM. High-quality decellularization, as the fundamental step of this process, requires the complete elimination of cellular and immunogenic components while maximally maintaining the native ultrastructure and bioactivity of the ECM. This process necessitates the rational selection of detergents: ionic detergents exhibit high

decellularization efficiency but carry the risk of protein denaturation, while nonionic detergents can better preserve the intact ultrastructure of the ECM. Following decellularization, controlled enzymatic digestion with pepsin converts the decellularized ECM (dECM) into an injectable and processable hydrogel precursor [59]. Pepsin and α -amylase are the most commonly used digestive enzymes, among which pepsin has gained the most widespread use owing to its superior controllability and excellent biocompatibility.

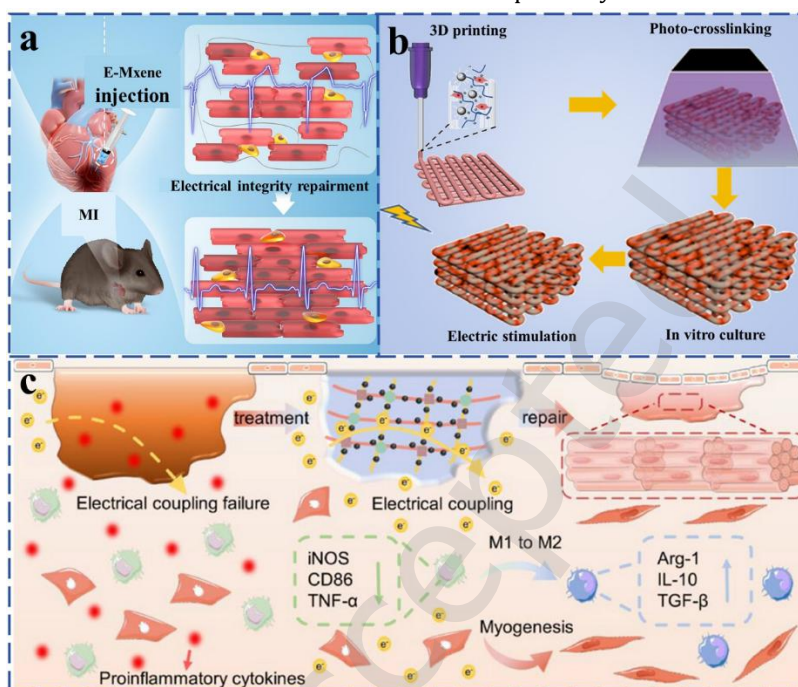


Figure 5 Bioelectric signal transmission and electroactive hydrogel strategies for muscle and cardiac regeneration. a) Application of E-Mxene hydrogel in mice MI [88]. b) 3D printing process of electrically conductive hydrogel scaffolds, as well as *in vitro* cell culture and electrical stimulation process [89]. c) Mechanism of GKP hydrogel in promoting the healing of diabetic skeletal muscle [68]. Reproduced with permission [88]. Copyright 2024, Elsevier. Reproduced with permission [89]. Copyright 2021, Oxford University Press. Reproduced with permission [68]. Copyright 2025, John Wiley and Sons.

2.5.2 Crosslinking strategies

Crosslinking serves as the core approach to endow ECM-mimetic hydrogels with stable network structures and appropriate mechanical properties. For muscle regeneration applications, the primary focus of crosslinking design is to construct a precisely tunable mechanical microenvironment that can facilitate myogenic differentiation [62].

Chemical crosslinking: This strategy relies on the formation of covalent bonds between polymer chains through the use of crosslinking agents or specific chemical reactions. Although conventional chemical crosslinkers can effectively enhance the mechanical strength of hydrogels, they are associated with potential cytotoxicity risks. Recent research strategies have prioritized the use of highly biocompatible crosslinkers, enzyme-catalyzed crosslinking reactions, and click chemistry approaches. Among these, click chemistry has become a leading research hotspot in this field, owing to its high reaction efficiency, mild reaction conditions, and outstanding biocompatibility, which allow for the precise modulation of hydrogel mechanical properties [80].

Photochemical crosslinking: This is defined as a light-

triggered crosslinking process, which generally occurs via the activation of photoinitiators that produce reactive species to drive the formation of covalent bonds between polymer chains. This technology provides exceptional spatiotemporal control and *in situ* forming capabilities. Through the introduction of photosensitive moieties, it can rapidly form three-dimensional (3D) hydrogel networks upon photoirradiation [90]. Novel nonradical photopolymerization mechanisms have further resolved the cytotoxicity limitations of traditional photoinitiators, offering an optimal platform for the 3D fabrication of hydrogel scaffolds that encapsulate highly viable cells.

Physical crosslinking: This refers to the construction of reversible hydrogel networks via non-covalent interactions, including hydrogen bonding, ionic interactions, hydrophobic associations, and molecular chain entanglement. Relying on these non-covalent interactions, physically crosslinked hydrogels present multiple advantages, including the elimination of exogenous chemical reagents, mild gelation conditions, and dynamic reversibility. They can more accurately mimic the dynamic and self-healing properties of native ECM [65]. Thermosensitive ECM-mimetic hydrogels and ionically crosslinked alginate systems are typical examples of this crosslinking strategy, which can provide cells with a more physiologically relevant microenvironment [91].

2.5.3 3D bioprinting

3D bioprinting technology allows for the precise fabrication of complex hierarchical structures, realizing the spatially controlled arrangement of ECM-mimetic hydrogels

and living cells. This capability is of critical importance for the construction of biomimetic layered muscle structures, such as native muscle bundles [92, 93]. The successful application of this technology depends on the development of ECM-based bioinks that satisfy strict rheological properties and biological requirements, including high cytocompatibility and cell viability. This technology can simultaneously reconstruct the 3D architecture, mechanical microenvironment, and biochemical gradients of native tissues, which markedly promotes the functional maturation of engineered muscle tissues [94].

The preparation of ECM-mimetic hydrogels should be selected according to the clinical function that the materials are expected to perform rather than by gelation chemistry alone. Decellularization and enzymatic digestion are most

appropriate when tissue-specific biochemical information is the principal design objective; covalent or photo-induced crosslinking is advantageous when a defined mechanical lifetime and structural stability are required; physical crosslinking is attractive for minimally invasive delivery and dynamic remodeling; and 3D bioprinting becomes more relevant when a large or anatomically organized defect requires spatially controlled architecture. These choices are not interchangeable, because the fabrication route determines the attainable balance among bioactivity, injectability, mechanical stability, degradation, and manufacturing reproducibility. Table 2 therefore provides a preparation-level comparison, while the application-oriented selection framework introduced in Section 4 links these fabrication choices to specific muscle pathologies and translational constraints.

Table 2 Comparison of primary preparation methods for ECM-mimetic hydrogels used in muscle repair and regeneration

Preparation method	Operating steps	Advantages	Disadvantages	Applicable scenarios	Applicable materials	References
Decellularization and enzymatic digestion	Tissue harvesting, decellularization, enzymatic digestion, and gelation	Preserves the natural biological activity of ECM; Promote cellular behavior; High biocompatibility	Residual immunogenic substances; Complex and time-consuming; Significant batch to batch variation	Preserve natural ECM biochemical signatures; Utilize ECM derived from target tissue sources; Investigate the effects of ECM components on myogenesis	Natural skeletal muscle	[59, 95, 96]
					Natural small intestine mucosa	[97, 98]
Chemical crosslinking	ECM solution preparation, addition of crosslinking agent, crosslinking reaction, and washing	Mechanical performance is adjustable; Degradation rate is controllable; Hydrogel exhibits high stability	Cytotoxicity; Masking of ECM bioactive sites	High mechanical load / long-term implantation; Require a slower degradation rate; Maintain specific 3D structure	Collagen	[69, 99]
					Gelatin	[58, 62, 80, 100, 101]
Photo-induced chemical crosslinking	ECM modification, addition of photoinitiators, covalent crosslinking, and post treatment	High controllability and precision molding; Rapid curing; Mechanical performance	Damages biological activity; Require equipment	High-precision structures and patterning; Photopolymerization	GelMA	[90, 102]
Physical crosslinking method (non-covalent bonds)	ECM mixed with polymers, physical stimuli (such as temperature elevation, pH adjustment) induce gelation, and injection	Injectable; Procedures: Rapid and reversible gelation; Typically free of exogenous chemicals, with high biocompatibility	Low mechanical strength; Rapid degradation; Poor stability, susceptible to physiological environmental influences	Minimally invasive therapy and injection fillers: Filling irregular defects; Drug/cell delivery carriers: Serving as temporary controlled-release systems; Short-term temporary scaffolds	Chitosan	[65, 66, 103]
					Collagen/Gelatin	[68, 104]
3D bioprinting	ECM bioink preparation (based on physical/chemical/photo-crosslinking systems), print parameter configuration, layer by layer preparation, and synchronous crosslinking	Highly customizable; High cell viability; Capable of printing multiple materials to construct complex heterogeneous structures	High cost and high technical barriers; Limited print resolution; Challenges in vascularization	Complex structure regeneration: Repairing extensive, structurally complex muscle defects; Personalized medicine: Customized printing based on patient imaging data; Multi-tissue interface construction	Gelatin-based ink	[92, 105-108]
					Collagen-based ink	[93, 94, 109]
					dECM-based ink	[110, 111]

2.5.4 Characterization methods for ECM-mimetic hydrogels

Comprehensive characterization of ECM-mimetic hydrogels is essential because regenerative performance strongly depends on physicochemical, mechanical, and biological properties. Rheological analysis is widely used to evaluate storage modulus (G'), loss modulus (G''), shear-thinning behavior, and viscoelasticity. Storage modulus reflects matrix elasticity sensed by cells and strongly influences myogenic differentiation. Scanning electron microscopy (SEM) and confocal microscopy are commonly employed to characterize pore morphology, anisotropic organization, and fiber alignment. Swelling ratio measurements evaluate hydrogel water absorption capability, which affects nutrient diffusion and mechanical stability. Degradation assays further determine whether

scaffold remodeling kinetics appropriately match tissue regeneration rates. Electrical conductivity measurements are especially important for cardiac and skeletal muscle engineering because conductive hydrogels can improve electrophysiological coupling and synchronized contraction. Mechanical characterization typically includes tensile strength, compressive modulus, stress relaxation, fatigue resistance, and cyclic loading stability. Biological characterization generally involves: Cell viability assays, myotube formation analysis, myogenic marker expression, macrophage polarization, angiogenesis assays, calcium transient analysis, and functional force generation measurements. Future characterization strategies should increasingly integrate multi-scale biomechanical analysis and real-time *in vivo* monitoring technologies. Table 3 shows the quantitative design parameters of ECM-mimetic hydrogels for muscle regeneration. Hydrogel parameters

outside physiological ranges may impair regeneration. Excessively stiff matrices (>25–30 kPa) tend to promote fibroblast activation and fibrosis, whereas overly soft matrices (<3 kPa) fail to support mature myotube formation and effective force transmission. Therefore, quantitative optimization of physicochemical properties is essential for functional muscle regeneration.

3 Mechanisms Underlying ECM-Mimetic Hydrogel-Mediated Muscle Regeneration

Table 3 Quantitative design parameters of ECM-mimetic hydrogels for muscle regeneration

Parameter	Recommended Range	Biological Significance
Matrix stiffness	8–15 kPa	Promotes myogenic differentiation
Pore size	20–150 μm	Facilitates cell infiltration and nutrient transport
Electrical conductivity	10^{-4} – 10^{-1} S/cm	Supports electrophysiological coupling
VEGF release period	3–7 days	Early angiogenesis
IGF-1 release period	1–3 weeks	Myoblast proliferation and maturation
Hydrogel degradation time	2–8 weeks	Matches tissue remodeling
Swelling ratio	100–500%	Maintains nutrient diffusion
Stress relaxation time	Minutes to hours	Enhances mechanotransduction

3.1.1 Topological structure and contact guidance

The micro- and nano-scale topographical features of hydrogels exert a profound regulatory effect on cellular behaviours, a well-documented phenomenon termed the “contact guidance” effect. This effect drives the parallel alignment of newly formed muscle fibers at the tissue level, which establishes the structural basis for the recovery of muscle contractile function [113]. When myogenic cells interact with hydrogel surfaces bearing specific topographical patterns, integrin receptors on the cell membrane can recognize and initiate downstream responses to these physical cues [114–116]. For muscle regeneration applications, mimicking the linear topological structure of parallel myofibril arrangements is of particular importance. Oriented topographical features promote cell elongation and directional migration by guiding the rearrangement of cytoskeletal proteins [29, 117].

Importantly, topographical cues do not function independently; they act synergistically with matrix stiffness and pore architecture to coordinate the regeneration process. For instance, aligned fibers not only drive directional cell migration through integrin activation, but also amplify mechanotransduction via the focal adhesion kinase (FAK) and Rho/ROCK signaling pathways, which in turn increase cellular sensitivity to matrix stiffness cues [118, 119]. Meanwhile, an interconnected porous network guarantees efficient nutrient diffusion and metabolic waste removal, which maintains long-term cell viability within the mechanically dynamic scaffold [62]. This three-pronged synergistic effect, topographical guidance, stiffness-mediated cell differentiation, and porosity-supported cell survival, is indispensable for functional muscle regeneration. The integration of these biophysical signals ultimately results in the upregulation of myogenic differentiation markers in the cell nucleus, promoting the formation and maturation of multinucleated myotubes and driving muscle

3.1 Biomimetic structure support and mechanical signal guidance

Native muscle tissue presents a highly ordered, multilayered architecture, spanning from the parallel arrangement of individual muscle fibers, to the hierarchical organization of muscle bundles, and finally to the macroscopic structure of the whole muscle organ [112]. ECM-mimetic hydrogels should therefore not only replicate the multiscale hierarchical structure of muscle ECM, but also recapitulate its function as a mechanical signal transducer.

regeneration [120, 121]. For example, a liquid crystal (LC) hydrogel scaffold self-assembled from $\text{C}_{15}\text{H}_{31}\text{-CONH-VE-CONH}_2$ was developed to recapitulate the structural and functional characteristics of native skeletal muscle, and was applied in a rat VML model (Figure 6a). This self-assembled scaffold possesses a hierarchical fiber organization that provides contact guidance to boost myoblast alignment and support rapid infiltration of host myoblasts, leading to a marked enhancement of muscle tissue regeneration [39].

3.1.2 Matrix stiffness and mechanotransduction

Tissue stiffness represents one of the most critical mechanical signals that govern cell fate decisions [122]. Through the precise adjustment of preparation parameters, ECM-mimetic hydrogels can be engineered to match the mechanical properties of target muscle tissues, which is a key determinant for their ability to effectively guide muscle regeneration [123]. Tissue-mimetic, functionally programmable hydrogels have been fabricated using a biological membrane hybridization strategy (Figure 6b). These hydrogels feature highly tunable structures and functions, especially adjustable mechanical properties, which broadens the application potential of hydrogels in muscle regeneration [124]. Upon sensing stiffness signals from the surrounding matrix, cells initiate intracellular mechanotransduction cascades via conformational changes in focal adhesion proteins [125, 126]. For this reason, maintaining physiological tissue stiffness is conducive to efficient muscle repair and regeneration. To achieve sustained maintenance of tissue stiffness, a sliding ring structure was integrated into the hydrogel network (Figure 6c). These chiral hydrogel muscles with a transient shape II exhibit contractile work output comparable to that of native muscle, and can be safely injected into damaged muscle tissue. They maintain structural integrity over long periods without rupture even during strenuous muscle contraction, enabling the stable maintenance of tissue stiffness to

support muscle repair and regeneration [127].

In addition, the contractile force produced by actin and myosin is transmitted to the cell nucleus via the cytoskeletal network, which directly modulates chromatin structure and gene expression. The core mechanosensitive signaling pathways involved in this process include the nuclear-cytoplasmic shuttling of YAP/TAZ (the downstream effectors of the Hippo pathway), the activation of the ERK/MAPK pathway, and calcium-dependent signaling cascades [128-130]. When the stiffness of the hydrogel matches that of native muscle tissue, the balance of these signaling pathways

is precisely regulated. Specifically, YAP/TAZ predominantly localizes to the cytoplasm, which promotes myogenic differentiation, while ERK signaling is moderately activated to sustain cell survival and differentiation [131-133]. Moreover, the viscoelastic properties of hydrogels play a vital role, as they allow cells to remodel the surrounding matrix through their endogenous contractile forces. This dynamic mechanical crosstalk between cells and the matrix further amplifies myogenic signaling and promotes the active reorganization of the ECM-mimetic network [10, 134, 135].

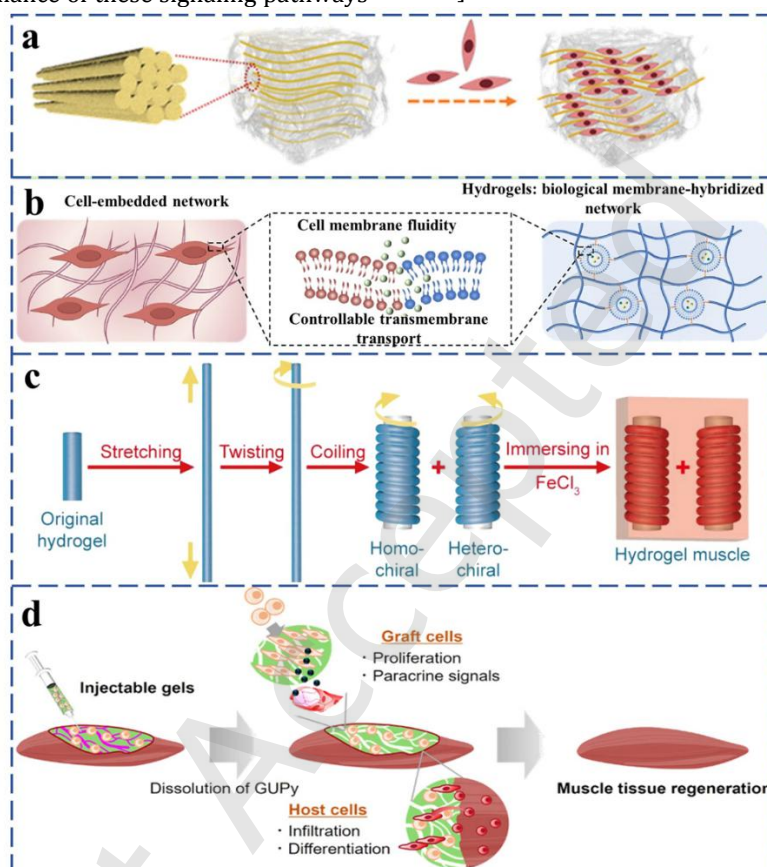


Figure 6 Structural and mechanical design of ECM-mimetic hydrogels for guiding muscle architecture and regeneration. a) Alignment peptide LC hydrogel scaffold for guiding myocyte alignment, promoting muscle regeneration, and facilitating functional recovery [39]. b) Tissue-inspired structurally and functionally programmable hydrogels by a biological membrane-hybridization strategy [124]. c) Shaping process for obtaining homo- and heterochiral hydrogel muscles [127]. d) Schematic of porous hydrogel treatment for VML [62]. Reproduced with permission [39]. Copyright 2025, John Wiley and Sons. Reproduced with permission [124]. Copyright 2025, Springer Nature. Reproduced with permission [127]. Copyright 2021, American Chemical Society. Reproduced with permission [62]. Copyright 2025, John Wiley and Sons.

3.1.3 Pore structure and nutrient transport

The porous characteristics of hydrogels have a profound impact on their biological functions in muscle regeneration. First and foremost, a suitable pore size and high interconnection provide physical channels for cell migration, infiltration, and endogenous tissue ingrowth. In addition, the pore structure directly determines the transport efficiency of nutrients, oxygen, and metabolic waste within the scaffold [117]. The geometric characteristics of the pores further modulate cell morphology and alignment. Studies have demonstrated that the design of gradient pore structures can further guide the spatial organization and orientation of cells, thus recapitulating the complex

hierarchical architecture of native muscle tissue [62, 136].

An injectable hydrogel with tunable microporous structures was developed for stem cell transplantation in VML treatment (Figure 6d). This hydrogel has a precisely controllable internal architecture that promotes the spreading, proliferation, and paracrine signaling of transplanted donor cells, which accelerates the integration of the hydrogel with host tissue and thus facilitates efficient muscle tissue regeneration [62]. Furthermore, the pore architecture modulates the degradation profile of the hydrogel and the deposition pattern of newly formed ECM, with these dynamic changes matching the biological requirements of different stages of the regeneration process [137]. Overall, this type of injectable hydrogel with an interconnected microporous network has great application potential for the regeneration of damaged muscle tissue.

3.2 Spatiotemporal Regulation of Bioactive Signaling

3.2.1 Delivery of bioactive factors

Muscle regeneration is a highly coordinated temporal process involving sequential activation of inflammation, stem cell recruitment, angiogenesis, myogenesis, and tissue remodeling. Therefore, successful regenerative outcomes

require precisely coordinated spatiotemporal signaling. During the early inflammatory phase, transient release of inflammatory cytokines and chemokines promotes debris clearance and immune-cell recruitment. However, prolonged inflammatory signaling often results in fibrosis and regenerative failure. ECM-mimetic hydrogels can modulate this balance by regulating local cytokine retention and release kinetics [138].

Vascular endothelial growth factor (VEGF) is particularly important during the early regenerative stage because rapid vascularization is essential for oxygen and nutrient delivery. Sustained VEGF presentation during approximately the first 3–7 days after injury significantly improves endothelial migration and neovessel formation [139]. Hepatocyte growth factor (HGF) additionally participates in satellite cell activation and migration, while stromal cell-derived factor-1 (SDF-1) promotes endogenous progenitor-cell recruitment [23, 140]. Insulin-like growth factor-1 (IGF-1) mainly regulates satellite cell proliferation and myoblast differentiation during intermediate regenerative stages. Controlled IGF-1 release over 1–3 weeks can significantly enhance myotube maturation and muscle functional recovery [82]. Importantly, uncontrolled supraphysiological growth factor exposure may induce abnormal angiogenesis, inflammation, or fibrosis. Therefore, the biological timing and dosage of factor presentation are equally important as factor selection itself [141]. Recent studies increasingly demonstrate that combinatorial signaling rather than single-factor delivery is required for effective regeneration. Simultaneous coordination of angiogenic, myogenic, neurogenic, and immunomodulatory signaling may more closely reproduce endogenous regenerative cascades [142, 143]. Overall, ECM-mimetic hydrogels function not merely as delivery vehicles, but as dynamic signaling platforms capable of reconstructing temporally coordinated regenerative microenvironments.

An injectable composite material with a dual-release profile, loaded with interleukin-4 (IL-4) and IGF-1, has been developed for VML treatment (Figure 7a). After local injection, it modulates the functional behaviors of macrophages and myogenic cells, and effectively promotes myogenesis, angiogenesis, and neurogenesis [82]. This material shows great promise as a minimally invasive, regeneration-enhancing implant for muscle regeneration applications. Another hydrogel encapsulating nanotechnology-modified curcumin (CNP) and epidermal growth factor (EGF) was designed for wound healing applications. CNPs are released rapidly and continuously in the early stage of wound healing to mitigate inflammation and oxidative stress, while EGF is released in a slower, sustained manner to support cell proliferation and ECM remodeling in the later healing stages (Figure 7b). This hydrogel achieves on-demand release of both small-molecule drugs and biological macromolecules, which markedly improves wound healing efficiency and demonstrates high potential for diabetic wound repair [144].

3.2.2 Presentation of ECM-mimetic bioactive signals

ECM-mimetic hydrogels are endowed with inherent biological activity through the integration of bioactive peptide fragments derived from native ECM proteins. Based on this principle, a cell-free therapeutic strategy has been proposed, in which ECM-mimetic hydrogels are used to reconstruct a muscle-specific regenerative microenvironment that drives the proliferation and

differentiation of endogenous cell populations (Figure 7c). This hydrogel promotes functional skeletal muscle regeneration by maximizing the *in vivo* bioactivity of muscle-specific ECM factors, and simultaneously drives angiogenesis and innervation, thus boosting the intrinsic regenerative capacity of damaged muscle tissue [145]. The modification of Arg-Gly-Asp (RGD) peptides with hyaluronic acid, followed by their incorporation into hydrogels, can significantly enhance cell adhesion and proliferation. This strategy has been applied to optimize the microenvironment after myocardial infarction and promote cardiac repair (Figure 7d). The resulting hydrogel effectively facilitates myocardial tissue repair, reduces myocardial fibrosis, stimulates neovascularization, and improves overall cardiac function [146], demonstrating substantial potential for myocardial infarction treatment and providing an innovative therapeutic strategy for clinical translation.

ECM-mimetic bioactive signals directly modulate cellular behaviors and also influence the deposition and spatial organization of host-derived ECM. When cells interact with these bioactive cues, they secrete their own ECM components and organize them into structures that more closely match the native matrix architecture [147]. By incorporating bioactive fragments to mimic native ECM signals, hydrogels can achieve a markedly enhanced capacity to drive muscle regeneration.

3.2.3 Enzyme-responsive degradation coupled with signaling

The rational design of smart ECM-mimetic hydrogels allows them to dynamically adjust their structure and function in response to cellular activities in the regenerative microenvironment, with enzyme responsiveness being one of the most pivotal design features [148, 149]. This design creates a positive feedback regulatory loop: cellular infiltration into the hydrogel triggers localized degradation and the on-demand release of bioactive factors, while the released factors further drive cell migration and proliferation, thus accelerating the entire regeneration process [150]. In addition, the degradation products of the hydrogel itself may exhibit inherent biological activity to further promote regeneration [151].

3.3 Immunomodulation and regenerative microenvironment remodeling

3.3.1 Recruitment of endogenous stem cells or progenitor cells

ECM-mimetic hydrogels actively recruit multiple endogenous cell populations critical for skeletal muscle regeneration to the site of injury through multiple complementary mechanisms, including satellite cells, mesenchymal stem cells, perivascular cells, and endothelial progenitor cells. First and foremost, the hydrogel serves as a cell migration conduit, with its 3D porous network providing physical channels for cell infiltration and migration. In addition, cytokines produced by the inflammatory response at the hydrogel-host tissue interface also contribute to the recruitment of these progenitor cells [131, 152]. Once cells migrate into the hydrogel, their behaviors are precisely regulated by the physicochemical properties of the hydrogel matrix. Appropriate matrix stiffness signals can maintain the stemness of recruited cells via the YAP/TAZ signaling pathway, while dynamically adjustable mechanical signals can trigger cell differentiation programs at specific time points during regeneration [130, 153, 154].

3.3.2 Precise regulation of cell fate and function

The biophysical and biochemical signals provided by the hydrogel collectively form a sophisticated signaling network that precisely modulates the core signaling pathways controlling cell fate decisions [155, 156]. ECM-mimetic hydrogels can regulate these pathways through multiple design strategies, thus fine-tuning the intensity of downstream signaling events [157]. For example, ECM-mimetic hydrogels loaded with bone morphogenetic protein

(BMP) inhibitors can effectively promote myogenic differentiation [158, 159], while those incorporating TGF- β inhibitors can significantly inhibit fibrotic scar formation [160, 161]. The multi-parameter regulatory capacity of ECM-mimetic hydrogels allows them to simultaneously promote beneficial cellular behaviors and inhibit pathological ones [162], which guides the regeneration process toward functional tissue recovery rather than non-functional pathological repair.

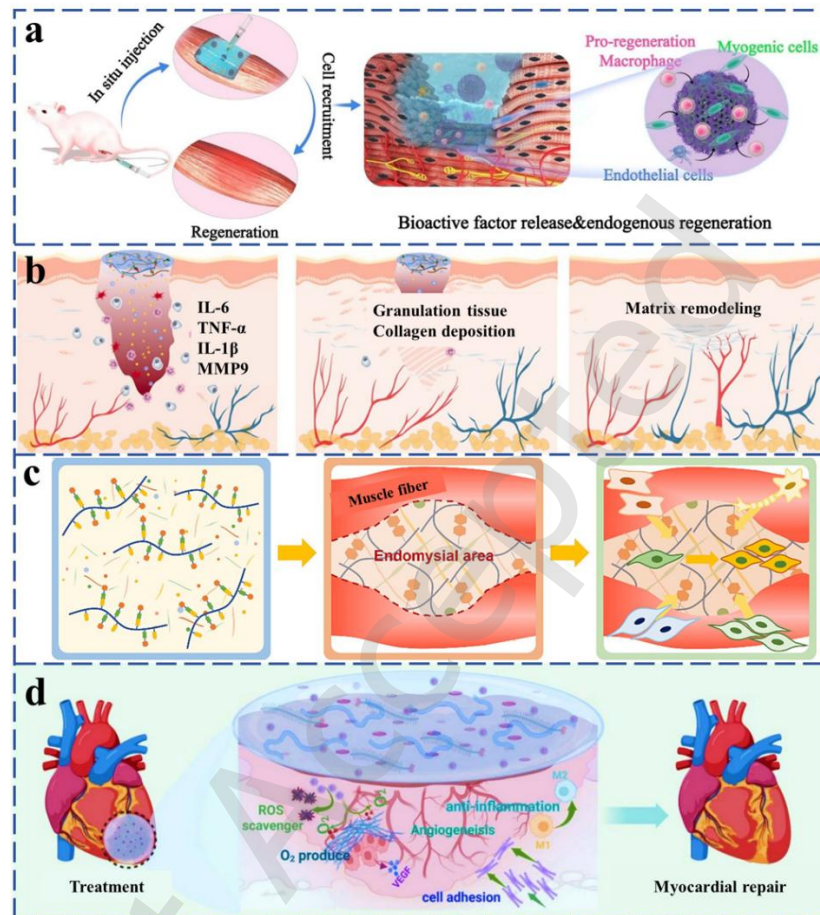


Figure 7 Spatiotemporal delivery and bioactive signal presentation by ECM-mimetic hydrogels for tissue regeneration. a) In situ injection of composites to promote endogenous muscle regeneration [82]. b) Hydrogels deliver drugs through a stepwise release mechanism to address critical issues at different stages of diabetic wound healing [144]. c) Schematic diagram of APM composite hydrogel enabling functional muscle regeneration [145]. d) Schematic diagram of the therapeutic mechanism of hydrogel scaffold-mediated MI treatment [146]. Reproduced with permission [82]. Copyright 2024, Springer Nature. Reproduced with permission [144]. Copyright 2021, Elsevier. Reproduced with permission [145]. Copyright 2024, Elsevier. Reproduced with permission [146]. Copyright 2025, Elsevier.

3.3.3 Modulation of the immune microenvironment and the transition to regenerative inflammation

Immune responses exert a pivotal regulatory role in the muscle regeneration process. First, hyaluronic acid oligosaccharides and collagen-derived peptides can directly modulate the activation state of macrophages through pattern recognition receptors such as TLR and CD44 [153]. In addition, the controlled release of immunomodulatory cytokines, including IL-4 and interleukin-13 (IL-13), from hydrogels has been demonstrated to directly drive the M2 polarization of macrophages [95, 163]. The physical properties of the hydrogel also shape macrophage behavior, with a moderate matrix stiffness being more favorable for

maintaining the anti-inflammatory M2 phenotype [164]. Ultimately, the recruitment of mesenchymal stem cells and other progenitor cells further amplifies M2 macrophage polarization through paracrine signaling mechanisms [165-167]. Beyond macrophage regulation, the recruitment and activation of regulatory T cells represent another important mechanism of hydrogel-mediated immunomodulation. These cells maintain immune homeostasis and directly support satellite cell function through both cell contact-dependent mechanisms and the secretion of immunomodulatory factors such as IL-10 and TGF- β [168, 169].

Hydrogels can modulate the *in vivo* ROS microenvironment by incorporating manganese dioxide, which catalyzes the conversion of hydrogen peroxide into oxygen, thereby improving cell survival and viability (Figure 8a). These hydrogels exhibited improved *in vivo* cell retention and enhanced anti-inflammatory and immunomodulatory properties, demonstrating their high potential for stem cell therapy and immunomodulation in diabetic pathological conditions [170]. An ECM-mimetic hydrogel has been developed to promote VML regeneration by establishing an optimized muscle regenerative microenvironment and enhancing muscle innervation

(Figure 8b). This hydrogel attenuates excessive inflammatory responses while promoting cell proliferation, M2 macrophage polarization, neovascularization, and myofibril formation, thus accelerating skeletal muscle regeneration and restoring motor function in VML models [171].

In addition to immune modulation, hydrogels also regulate metabolic homeostasis through their tunable pore structures, which ensure efficient oxygen and nutrient delivery as well as metabolic waste removal [96, 172]. By

promoting glycolysis in the early regeneration stage and oxidative phosphorylation in the later maturation stage, hydrogels can align cellular energy metabolism with the functional requirements of cell proliferation and tissue maturation. Moreover, by enhancing gap junction intercellular communication (e.g., through the upregulation of Cx43) and paracrine signaling via controlled factor release, hydrogels can coordinate the collective behavior of multiple cell types, guiding their ordered spatial distribution and synchronized differentiation [173, 174].

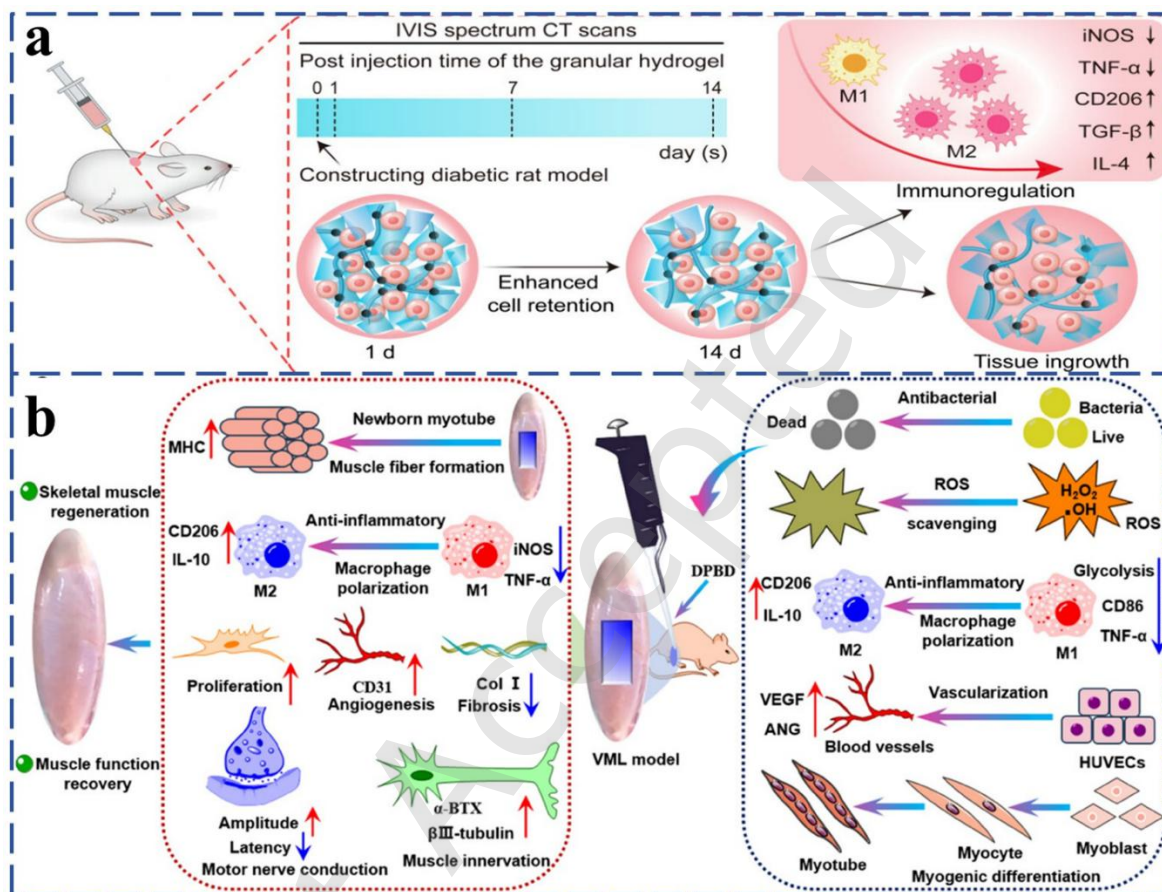


Figure 8 Microenvironmental regulation by ECM-mimetic hydrogels for enhanced muscle regeneration and repair. a) Schematic of hydrogel regulating ROS microenvironment *in vivo* [170]. b) Application of hydrogels in VML repair [171]. Reproduced with permission [170]. Copyright 2025, American Chemical Society. Reproduced with permission [171].

3.4 Synergistic regeneration of vascularization and neurogenesis

The process of functional muscle regeneration requires not only the structural and functional restoration of muscle fibers, but also the synchronized reconstruction of vascular and neural networks. ECM-mimetic hydrogels support the long-term survival and functional maturation of regenerated muscle tissue by simultaneously promoting angiogenesis and neural innervation.

3.4.1 Vascularization

Hydrogel-mediated angiogenesis consists of multiple sequential biological stages, including endothelial cell activation, migration, vascular lumen formation, perivascular cell recruitment, and final vascular maturation. ECM-mimetic hydrogels promote this process through multiple complementary mechanisms [175]. First and foremost, as physical templates for tissue ingrowth, their

porous network provides channels for vascular invasion, while specific topographical patterns can even directly guide directional vascular growth [176]. In addition, through the controlled release of angiogenic factors, hydrogels can activate endothelial cells and guide their directional migration [177]. Furthermore, the mechanical properties of hydrogels also modulate the angiogenic process: moderate matrix stiffness facilitates vascular lumen formation, while appropriate stress relaxation properties allow for cellular contraction and matrix remodeling [178]. The degradation profile of the hydrogel should also be matched to the rate of vascular growth: excessively rapid degradation will lead to scaffold collapse, while overly slow degradation will physically block vascular ingrowth. Finally, the recruitment of mesenchymal stem cells and macrophages further amplifies angiogenic signals via paracrine mechanisms [152, 163, 179, 180].

A hydrogel loaded with adipose-derived mesenchymal stem cells (ADSCs) and polydopamine nanoparticles (PDA NPs) has been developed to promote chronic wound healing (Figure 9a). This ECM-mimetic hydrogel promotes cell proliferation and migration, and possesses excellent antioxidant and antibacterial properties. It accelerates

wound healing by supporting ADSC survival, enhancing angiogenesis and re-epithelialization, and mitigating excessive inflammation [152]. In addition, studies have shown that a Janus peptide-engineered hydrogel has programmable functions driven by the self-assembly of identical α -domains. This hydrogel promotes angiogenesis and vascular functionalization by breaking oxygen diffusion barriers and delivering oxygen in an on-demand manner (Figure 9b). By downregulating YAP to modulate the phenotypes of macrophages and fibroblasts, it alleviates inflammatory responses and accelerates the reconstruction of normal skin structures, demonstrating great potential for the clinical treatment of chronic wounds [181].

Pre-vascularization strategies have also attracted increasing attention in recent years. By pre-establishing microvascular networks through the co-culture of endothelial cells within hydrogels *in vitro*, these preformed vessels can rapidly anastomose with the host vascular system after transplantation, which markedly improves the survival rate of thick engineered tissue grafts [182, 183]. Furthermore, through the design of gradient factor release or gradient physicochemical properties, hydrogels can guide directional vascular growth to achieve efficient functional integration with the host vascular system [184].

3.4.2 Neurotization

Nerve regeneration is also an indispensable component of functional muscle regeneration. The regeneration of the neuromuscular junction (NMJ) is widely recognized as the ultimate marker of functional muscle recovery, as it represents a highly complex biological process that requires precise spatiotemporal coordination between motor neurons and muscle fibers. ECM-mimetic hydrogels promote

this process through multiple regulatory mechanisms [142, 143, 185, 186]. The incorporation of neurotrophic factors is critical, as these factors attract the growth of motor neuron axons toward the regeneration site while providing essential survival and differentiation signals. In addition, the mimicry of basement membrane components provides an optimal microenvironment for axonal growth, and laminin, which contains multiple neuroactive domains, exhibits a strong ability to promote neurite outgrowth and guidance. The controlled release of neurotrophic molecules has also been demonstrated to direct axonal migration. In addition, Schwann cells secrete a variety of neurotrophic factors and ECM molecules to sustain NMJ formation and maintenance [82, 95, 187, 188].

Figure 9c shows a highly oriented anisotropic nanofiber hydrogel engineered to provide the dual effects of structural orientation guidance and pro-angiogenic signaling [184]. This nanofiber hydrogel exhibits excellent fiber alignment and robust multi-cellular regulatory capacity, and can induce angiogenesis of endothelial cells, modulate macrophage phenotypic transition, promote Schwann cell maturation, and enhance ECM deposition by fibroblasts [184]. In addition, electrically conductive hydrogels combine the advantages of water-swelling hydrogels with those of conductive polymers (CPs), providing tissue-matched electrical conductivity and mechanical properties for neurovascular regeneration. At the same time, they promote neurovascular regeneration by increasing intracellular Ca^{2+} concentration, which enhances protein phosphorylation via the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) signaling pathways, leading to a significant acceleration of wound healing (Figure 9d) [58].

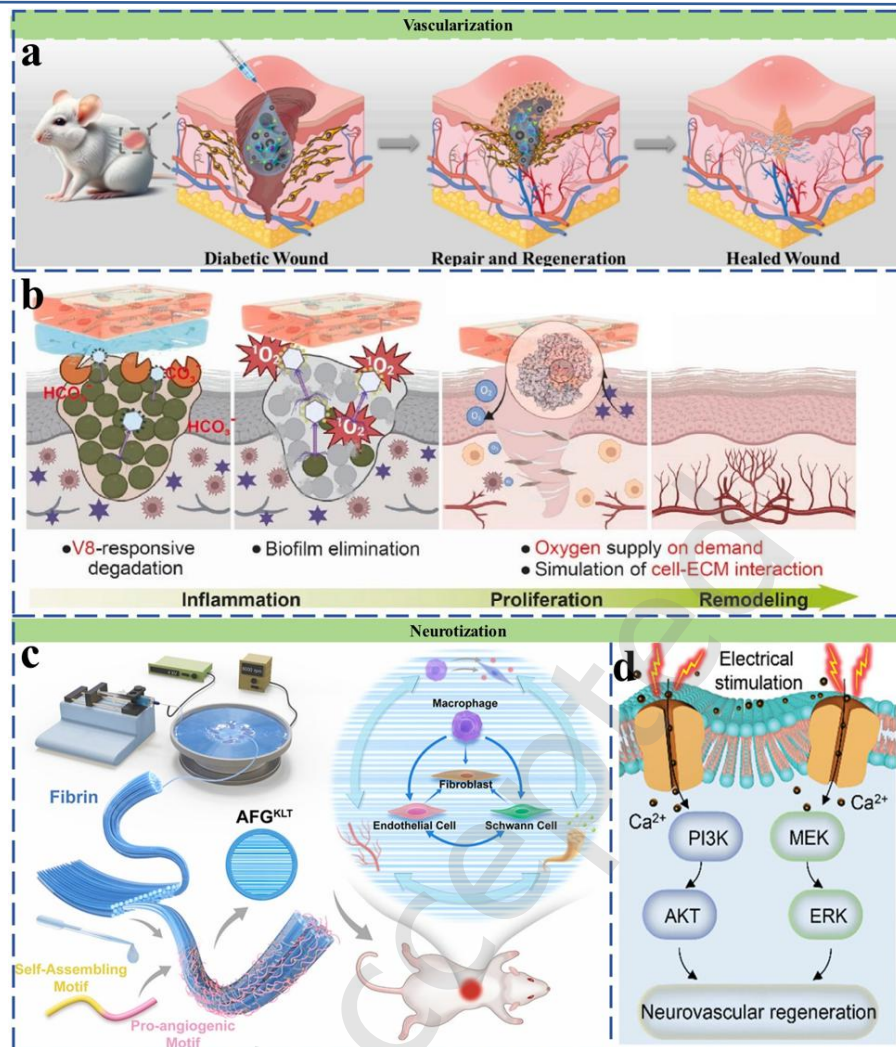


Figure 9 Multifunctional hydrogel platforms integrating structural, biochemical, and electrical cues for tissue repair and neurovascular regeneration. a) Applications of hydrogels in promoting wound healing [152]. b) Schematic diagram illustrating the mechanism by which hydrogels promote wound healing [181]. c) Schematic illustration of electrospinning and self-assembling peptide conjugation during hydrogel preparation, along with its applications [184]. d) Schematic illustration of the mechanism by which electrically conductive hydrogels promote neurovascular regeneration [58]. Reproduced with permission [152]. Copyright 2025, Elsevier. Reproduced with permission [181]. Copyright 2025, Elsevier. Reproduced with permission [184]. Copyright 2025, Elsevier. Reproduced with permission [58]. Copyright 2022, John Wiley and Sons.

Of particular importance is the spatiotemporal coordination between neural and muscle regeneration. Studies have shown that premature innervation can disrupt myotube formation, while delayed innervation will lead to the atrophy of regenerated muscle fibers [145, 171]. ECM-mimetic hydrogels can achieve this precise coordination through the sequential design of factor-controlled release: promoting myogenesis in the early regeneration stage, introducing neurotrophic signals in the middle stage, and enhancing NMJ maturation signals in the late stage [82]. Furthermore, electroactive hydrogels can further promote the functional maturation and integration of the neuromuscular system through the delivery of electrical stimulation [65].

3.5 Electrophysiological microenvironment simulation

As an electrically excitable tissue, the functional recovery of muscle depends not only on biochemical and mechanical

signals, but also critically on the support of a physiological electrophysiological microenvironment. Electrically conductive hydrogels (e.g., those incorporating polyaniline) retain the physical and biochemical regulatory functions of traditional hydrogels, while further recapitulating the electrical conductivity of native muscle tissue, thus driving muscle regeneration through multiple complementary dimensions [189]. These materials not only enhance intercellular electrical coupling to promote the synchronize maturation and alignment of myotubes, but also activate calcium signaling pathways via electrical stimulation, which directly upregulates the expression of myogenic genes [57, 190]. In addition, electrically conductive hydrogels can guide the directional growth of axons and the formation of NMJs, and synergistically promote angiogenesis and immune regulation, leading to a comprehensive acceleration of functional muscle regeneration [191].

In summary, ECM-mimetic hydrogels exert their therapeutic effects in muscle regeneration through multi-level synergistic interactions: they recapitulate the physical structure and biochemical properties of native ECM to establish a supportive microenvironment for normal cellular behaviors; at the same time, they act as a dynamic signaling platform to regulate cell recruitment and fate decisions, and coordinate core regenerative processes including inflammation resolution, angiogenesis, and innervation, ultimately guiding functional tissue restoration. An in-depth understanding of these mechanisms not only elucidates the

therapeutic efficacy of ECM-mimetic hydrogels, but also provides a solid theoretical foundation for the rational design of next-generation smart hydrogels.

4 Application-Oriented Design and Therapeutic Strategies of ECM-Mimetic Hydrogels

4.1 Application-oriented design and material selection

Different muscle injuries and disease conditions expose implanted materials to distinct mechanical, inflammatory, vascular, and neural environments. The design of an ECM-

mimetic hydrogel should therefore begin with the dominant pathological bottleneck and then determine which ECM state, structural cue, fabrication route, and functional module are required. This application-oriented framework also clarifies why a formulation that performs well in a small-animal VML model may not be appropriate for chronic muscular dystrophy or ischemic myocardium, where repeated dosing, electrical coupling, vascular supply, and long-term matrix remodeling become more important than rapid defect filling.

Table 4 Application-oriented selection of ECM-mimetic hydrogel design strategies for different muscle repair scenarios.

Clinical scenario	Dominant bottleneck	ECM-mimetic target	Preferred design/fabrication strategy	Key selection criteria
Acute muscle injury	Excessive inflammation, oxidative stress, early satellite-cell activation	Provisional ECM with transient bioactive signaling	Injectable physical/enzymatic gelation; rapid IL-4/antioxidant presentation; aligned microstructure when laceration is present	Fast in situ formation; moderate stiffness; controlled early degradation; low procedural burden
Volumetric muscle loss	Large tissue deficit with disrupted vascular and neural networks	Hierarchical, anisotropic and remodeling ECM	Pre-structured dECM/synthetic hybrid; 3D printing or aligned fibers; staged angiogenic and neurotrophic delivery	Mechanical integrity under cyclic loading; vascular–neural integration; scalable fabrication
Muscular dystrophy	Chronic inflammation, fibrosis and progressive muscle wasting	Long-lived, adaptive ECM niche	Slowly degrading hydrogel or depot with sustained/repeated therapeutic delivery; antifibrotic and gene/cell combination when appropriate	Long-term safety; repeat-dose compatibility; controlled degradation; disease-stage adaptability
Myocardial infarction	Electrical discontinuity, ischemia, adverse remodeling	Cardiac ECM with electroactive and pro-angiogenic cues	Injectable conductive hydrogel; cardiac dECM or HA-based network; ROS and factor modulation	Electrical conductivity; injectability; mechanical matching; arrhythmia and inflammatory safety
Specialized smooth muscle repair	Tissue-specific ECM composition and coordinated epithelial–muscle regeneration	Tissue-specific biochemical and mechanical cues	Injectable HA/collagen or dECM-based systems with tissue-specific ligands and controlled factor delivery	Biocompatibility; anatomical conformability; tissue-specific signaling; functional contractility

For acute injury, the priority is reproducing a transient provisional ECM and rapidly suppress excessive inflammation while preserving satellite-cell activation. In VML, the design target shifts toward a mechanically persistent and anisotropic regenerative niche capable of supporting vascular and neural ingrowth across a large defect. Muscular dystrophy requires a long-lived depot compatible with repeated or sustained delivery, whereas myocardial repair places a greater emphasis on electrical continuity, wall mechanics, and protection against adverse remodeling. These differences provide practical selection criteria for the materials discussed in Sections 2 and 3 and avoid treating ECM mimicry as a single, universally optimal formulation.

Clinical translation has important advances in ECM-derived matrices and ECM-component hydrogels used in wound and soft-tissue management. This distinction is important when discussing “commercialized ECM-mimetic hydrogels”: several clinically used products reproduce selected ECM functions or use decellularized ECM in non-hydrogel formats, whereas true flowable ECM hydrogels remain uncommon. The current landscape is summarized in Table 5, which distinguishes ECM-derived matrices, synthetic ECM-mimetic hydrogels, and true flowable ECM hydrogels. It is important to note that different muscle injuries and disease conditions present unique microenvironmental challenges, and ECM-mimetic hydrogels must be rationally designed and tailored to address these specific pathological contexts.

Table 5 Commercially available or clinically advanced ECM-related products relevant to the translation of ECM-mimetic hydrogels.

Product/platform	Product type and material/format	Clinical or regulatory status	Reported clinical application / data	Relevance to muscle regeneration
Hyalomatrix® PA	ECM-derived regenerative matrix; HYAFF, an esterified hyaluronic-acid matrix with silicone barrier; hydrates and forms a gel-like wound interface	Commercial clinical device; FDA 510(k) clearance for wound management	FAST multicenter study: 262 patients; ≥10% re-epithelialization in 83% of ulcers at a median of 16 days; 84% achieved complete re-epithelialization during follow-up [192, 193]	Clinical precedent for ECM-derived matrix-assisted tissue regeneration, but not a muscle-specific injectable hydrogel
MicroMatrix® / MicroMatrix® Flex	ECM-derived particulate matrix; porcine urinary bladder matrix (UBM); flowable particulate, not a preformed hydrogel	Commercial wound-care products; FDA 510(k) clearances K153754/K172399 and K230980 [194, 195]	Indicated for partial/full-thickness wounds, diabetic and vascular ulcers, and surgical/trauma wounds	Clinical precedent for decellularized ECM remodeling and host-cell infiltration; format differs from injectable muscle hydrogels

PuraDerm™ Gel	Synthetic peptide hydrogel; ECM-mimetic rather than tissue-derived ECM	Commercial wound-management hydrogel; FDA 510(k) clearances K143058/K193085 [196]	Used for hydration and management of partial/full-thickness wounds, including diabetic, pressure and surgical wounds	Supports the translational value of injectable/self-assembling hydrogel formats, although it does not reproduce tissue-specific ECM composition
ECMT-100 WMD	Flowable hydrogel derived from decellularized ECM; true ECM hydrogel format	FDA 510(k) cleared in 2026 (K253521) [197]; clinical investigation for anorectal fistulas is registered as NCT07035925 [198]	Cleared for wound management; an ongoing clinical study is evaluating ECMT-100 for anorectal fistulas	Most direct current regulatory and clinical precedent for a flowable ECM hydrogel; provides a relevant manufacturing and translational reference for future muscle applications
CorMatrix® ECM	ECM-derived solid scaffold; decellularized porcine small-intestinal submucosa sheet/patch	Commercial ECM surgical device; FDA 510(k) clearance for vascular repair [199]	Used clinically for cardiovascular/vascular repair and reconstruction	Shows that tissue-specific ECM products can reach surgical use, but the solid format differs from injectable hydrogels

4.2 Repair of acute muscle injury

Acute muscle injury is characterized by rapid hemorrhage, robust inflammatory responses, and the activation of muscle satellite cells. The core design priorities for hydrogels targeting acute injury include the rapid release of anti-inflammatory agents (e.g., IL-4) to suppress excessive inflammation, and the provision of aligned topographical structures to guide the oriented growth of regenerating myofibers. The stiffness of the hydrogel should also be matched to that of native muscle to promote myogenic differentiation via the YAP/TAZ signaling pathway [51, 200]. The repair of acute muscle injuries (including contusions, lacerations, and ischemia-reperfusion injuries) requires immediate and effective therapeutic intervention. ECM-mimetic hydrogels, which can be delivered to the injury site via minimally invasive injection, can rapidly form a 3D scaffold *in situ* to fill tissue defects and provide initial mechanical support for the damaged muscle.

Contusion model: For muscle contusion injuries, gelatin-based and hyaluronic acid-based hydrogels mainly exert their therapeutic effects by regulating the local immune microenvironment. The rapid release of anti-inflammatory factors promotes the polarization of macrophages toward the anti-inflammatory M2 phenotype to alleviate excessive inflammation, while the sustained release of pro-regenerative factors activates satellite cells to drive myofibril regeneration [172].

Laceration model: The repair of muscle laceration injuries mainly depends on guiding directional tissue regeneration and inhibiting fibrotic scar formation. Engineered ECM-mimetic hydrogels with oriented topological structures can promote the ordered alignment of muscle cells through the contact guidance effect [169]. In addition, TGF- β inhibitors loaded into the hydrogel can effectively inhibit the excessive activation of fibroblasts, thereby reducing scar tissue formation [157].

Ischemia-reperfusion injury model: For muscle ischemia-reperfusion injuries, hydrogels mainly function by counteracting oxidative stress and inhibiting myocyte apoptosis. Antioxidants incorporated into the hydrogel alleviate oxidative damage by scavenging excess free radicals, and synergistically promote angiogenesis to improve local blood supply, ultimately inhibiting myocyte apoptosis and accelerating tissue repair [201, 202].

4.3 Restoration of volumetric muscle loss

VML is defined as the massive loss of muscle tissue that exceeds the intrinsic regenerative capacity of native muscle, most commonly caused by severe trauma, surgical tumor

resection, or congenital malformations. VML pathology is characterized by a large tissue defect, the complete disruption of local vascular and neural networks, and persistent chronic inflammation [203]. The design of hydrogels for VML repair should address multiple spatiotemporal pathological requirements: early immune modulation to drive M2 macrophage polarization, sustained pro-angiogenic signals, and long-term neurotrophic support. The scaffolds should also have sufficient mechanical integrity to withstand repeated muscle contractile forces, while undergoing gradual degradation to allow for endogenous tissue ingrowth. VML repair remains one of the most significant challenges in muscle regeneration research, and ECM-mimetic hydrogels have demonstrated unique advantages in addressing this clinical challenge.

4.3.1 Pre-structured hydrogel scaffolds

For VML repair, researchers have developed preformed hydrogel scaffolds with complex 3D hierarchical structures. These scaffolds are fabricated using 3D printing, electrospinning, or molecular self-assembly techniques, which allow for the precise mimicry of the structural features of native muscle tissue, including the aligned arrangement of muscle fibers, vascular network architectures, and neural pathways [62]. The scaffold materials typically use decellularized muscle matrix hydrogels, which retain the biochemical composition and biological activity of native muscle ECM, often blended with synthetic polymers to enhance mechanical properties. Before implantation, these scaffolds are pre-cultured *in vitro* with seeded myogenic cells and vascular endothelial cells to form pre-vascularized, pre-myogenic tissue-like constructs. These pre-engineered scaffolds exhibit excellent *in vivo* integration capacity, can guide host cell infiltration and tissue regeneration, and ultimately form contractile neuromuscular tissue with a certain degree of neural and vascular reinnervation [204].

4.3.2 Multilevel regeneration strategy

To address the multifaceted pathological challenges of myogenesis, vascularization, neurogenesis, and immunomodulation in VML repair, research focus has shifted from monofunctional hydrogels to multifunctional systems capable of spatiotemporally coordinated regulation. However, current pre-vascularized or pre-innervated constructs still face critical limitations: preformed microvascular networks often fail to rapidly anastomose with the host vasculature after implantation, leading to core necrosis in thick tissue constructs [138]. Pre-innervated scaffolds incorporating motor neurons or Schwann cells

show enhanced NMJ formation *in vitro*, but the efficient guidance of axonal growth over distances greater than 5 mm *in vivo* remains a major challenge due to insufficient neurotrophic gradients and physical barriers [205]. Achieving true structural-functional coupling requires the simultaneous construction of spatially aligned vascular and neural networks, which remains an unresolved challenge in the field. Future hydrogel designs should incorporate the temporally staged, gradient release of angiogenic (VEGF) and neurotrophic (GDNF) factors, combined with 3D-printed multi-channel architectures that mimic the structure of native neurovascular bundles [206]. Current design strategies for VML repair can be divided into two main categories. The first is the multilayer compartmentalized design, which involves the fabrication of layered scaffolds with distinct biochemical compositions (e.g., myogenic factors and angiogenic factors) and physical structures (e.g., oriented topologies and gradient pore sizes). This design spatially guides directional myocyte regeneration, vascular ingrowth, and localized immune regulation, to achieve the synergistic repair of large structural defects [138, 205, 206].

The second strategy is the multifunctional integrated design, which incorporates multiple biological functions into a single hydrogel. For example, a hydrogel loaded with puerarin-carrying mesoporous silica nanoparticles (SiCP@InjGel) can remodel the local immune microenvironment and enhance myogenesis [54]. At the same time, researchers observed an increase in Pdpn+ macrophages and MyoG+ muscle stem cells in the defect site, which reshaped the local immune landscape and accelerated muscle regeneration at the molecular and cellular levels (Figure 10a) [66]. In another study, MXene-functionalized hydrogels with electroactivity and antioxidant capacity can simultaneously scavenge excess ROS, drive M2 macrophage polarization, and promote myogenic and neural differentiation, achieving dual structural and functional repair of VML defects (Figure 10b) [204]. In addition, novel wet-adhesive powder hydrogels (Figure 10c) [63] and bacterial-derived polysaccharide hydrogels (Figure 10d) [207] have also exhibited excellent hemostatic, anti-scarring, and pro-regenerative capabilities in VML models.

Quantitative comparisons with current clinical standards are essential to place preclinical hydrogel performance in a clinically meaningful context. Autologous muscle flaps remain an established reconstructive option for VML, but donor-site morbidity and limited tissue availability constrain their use [208]. ECM-mimetic hydrogels have achieved more than 50% recovery of tetanic muscle force in rodent VML models, indicating substantial biological activity but remaining below the functional benchmark expected from successful autologous reconstruction [209, 210]. The translational gap is particularly evident in critical-sized defects, in which acellular or hydrogel-only approaches rarely restore full force without additional cellular, vascular, or trophic support. Future studies should therefore report not only histological regeneration but also force recovery, fatigue resistance, gait or task-specific performance, persistence of vascular and neural integration, and outcomes

in large-animal models over clinically relevant follow-up periods.

4.3.3 Dynamic microenvironment regulation strategy

VML repair is a long-term, multi-stage process that requires distinct microenvironmental support at different regenerative stages. To address this challenge, researchers have developed ECM-mimetic hydrogels with environmental responsiveness, which can undergo dynamic adaptive changes throughout the entire regeneration process [65]. These smart hydrogels have been shown to have significantly better therapeutic efficacy than conventional hydrogels in VML repair, especially for large tissue defects, and can support more complete functional tissue regeneration [63, 204].

4.4 Treatment for muscular dystrophy

Muscular dystrophy is a group of chronic, progressive neuromuscular disorders characterized by continuous muscle fibrosis and wasting. For this disease, hydrogels should function as long-term depots for the sustained or repeated administration of therapeutic agents, including antifibrotic agents and gene therapies, and also provide a protective microenvironment for transplanted cells [211, 212]. The degradation rate of the hydrogel should be slow to avoid the need for frequent repeated injections, and the material should be compatible with the systemic or local delivery of various therapeutic components.

Given the complex and multifactorial pathology of muscular dystrophy, the therapeutic strategies of ECM-mimetic hydrogels for this disease have evolved from providing simple structural support to acting as multifunctional synergistic therapeutic platforms. The core value of these strategies lies in their ability to simultaneously target multiple key pathological pathways of the disease. As a cell delivery carrier, the 3D microenvironment of the hydrogel not only protects transplanted cells from immune clearance, but also provides essential survival and differentiation signals, which significantly improves the survival rate and therapeutic efficacy of the cell grafts [142, 213]. In addition, by loading multiple bioactive agents (such as antifibrotic drugs, anti-inflammatory agents, and neurotrophic factors), hydrogels can synergistically inhibit fibrosis, control chronic inflammation, and improve neuromuscular function, thereby delaying disease progression through multiple complementary mechanisms [145, 213, 214]. This multi-target integrated strategy has demonstrated superior therapeutic efficacy to monotherapies in various animal models of muscular dystrophy, providing novel therapeutic insights for this currently incurable disease. For chronic progressive conditions such as Duchenne muscular dystrophy, a single administration of therapy is insufficient to achieve long-term therapeutic effects, and repeated dosing or long-acting formulations should be considered. Hydrogels can be designed with slow degradation profiles or as injectable depots for repeated administration, and can be combined with gene editing technologies to achieve sustained therapeutic effects [213].

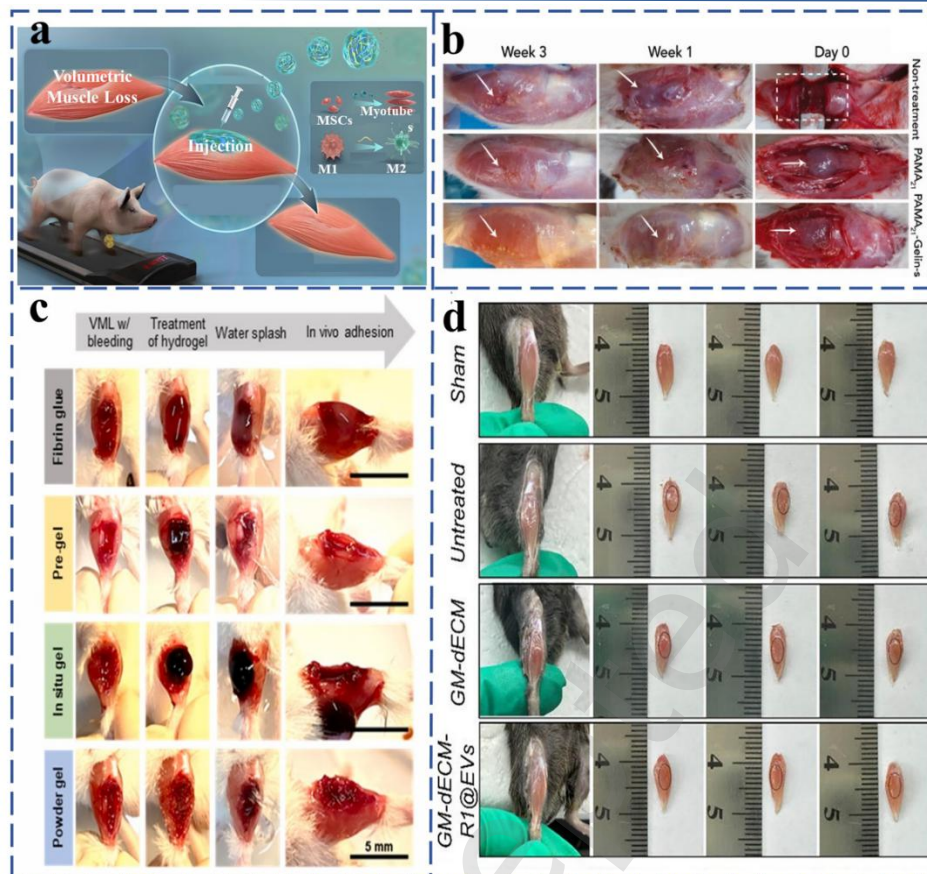


Figure 10 Therapeutic hydrogel strategies for VML repair and functional muscle restoration. a) Schematic of an ECM-mimetic hydrogel, combining puerarin and chitosan with MSNs, for muscle repair [66]. b) Comparison of VML at the tibialis anterior (TA) injury site before and after hydrogel implant treatment [204]. c) Photographs of various processed VML-damaged tibialis anterior muscle samples [63]. d) Macroscopic morphology of the tibialis anterior muscle in mice after 3 weeks of different treatments [207]. Reproduced with permission [66]. Copyright 2025, Elsevier. Reproduced with permission [204]. Copyright 2024, Elsevier. Reproduced with permission [63]. Copyright 2024, Elsevier. Reproduced with permission [207]. Copyright 2022, Elsevier.

4.5 Myocardial regeneration

4.5.1 Treatment of myocardial infarction

Myocardial infarction creates a harsh ischemic microenvironment characterized by massive cardiomyocyte death, progressive fibrosis, and electrical uncoupling between surviving cardiomyocytes. Hydrogels for myocardial infarction treatment should provide mechanical support to prevent adverse ventricular dilation, restore electrical conductivity in the infarct zone, and deliver pro-angiogenic and pro-survival factors to the damaged tissue [215]. After myocardial infarction, the necrotic myocardium is gradually replaced by fibrous scar tissue, which leads to progressive impairment of cardiac function. ECM-mimetic hydrogels, delivered to the infarct zone via direct injection or epicardial patch implantation, improve cardiac function through multiple complementary mechanisms. They provide mechanical support to prevent adverse ventricular remodeling, release bioactive factors to promote angiogenesis and cardiomyocyte survival, and recruit endogenous cardiac stem cells while supporting their differentiation into functional cardiomyocytes [31, 216, 217]. Notably, compared with ECM derived from other tissue sources, ECM-mimetic hydrogels derived from decellularized cardiac matrix, which contain heart-specific signaling

molecules, have demonstrated superior therapeutic efficacy in myocardial infarction treatment.

Hydrogels loaded with RepSox nanoparticles undergo gradual degradation *in vivo*, while the RepSox nanoparticles exhibit a sustained release profile, which effectively inhibits the excessive proliferation of cardiac fibroblasts in the infarct area, reduces myocardial fibrosis, and improves overall cardiac function (Figure 11a) [180]. In addition, a gold-loaded stem cells@platinum nanoparticle/alginate (Au@Pt/Alg) hydrogel promotes the survival of cardiomyocytes and brown adipose stem cells (BASCs) by scavenging excess ROS (Figure 11b). It facilitates the differentiation of BASCs into cardiomyocytes (CMs), enhances their paracrine function, induces angiogenesis, accelerates electrical conduction velocity in the infarcted myocardium, and effectively promotes the recovery of cardiac function [67]. Furthermore, a hybrid hydrogel co-assembled from cell-free cardiac ECM-mimetic components and immunomodulatory glycopeptides regulates macrophage differentiation through its glycopeptide units [61]. By enhancing macrophage-endothelial cell crosstalk to promote endothelial cell proliferation, it increases angiogenesis, improves cardiomyocyte survival, reduces infarct size, increases ventricular wall thickness, and enhances cardiac contractility (Figure 11c), thus facilitating endogenous cardiac repair. This strategy provides an effective therapeutic approach for endogenous cardiac repair after myocardial infarction [61]. Hydrogels coated with tissue-specific heart decellularized extracellular matrix (hdECM) can prevent the pathological adhesions that commonly occur after cardiac surgery, and mitigate severe myocardial structural disintegration (Figure 11d). At the same time, they reduce myocardial fibrosis, attenuate ventricular wall thinning to promote functional regeneration,

and stimulate neovascularization in the infarct region [218].

4.5.2 Cardiac tissue engineering

This strategy focuses on the *in vitro* construction of functional engineered cardiac tissues to replace the damaged myocardial areas. The key design principles for these engineered tissues involve the precise mimicry of the critical structural and functional features of native myocardium, including: 1) Anisotropic structure: to guide the oriented alignment and synchronized contraction of cardiomyocytes [219, 220]; 2) Electrical conductivity: the integration of conductive materials to facilitate electrical signal integration between the engineered tissue and the host myocardium [221, 222]; 3) Pre-vascularization: to ensure sufficient blood supply to thick implanted tissues, thus maintaining their long-term viability and contractile function [223, 224]. In summary, whether through *in situ* intervention via injectable hydrogels [163, 225] or tissue replacement with pre-engineered cardiac tissues [226], the core function of ECM-mimetic hydrogels in cardiac regeneration is to create a functional microenvironment that supports cardiac repair and regeneration [173, 179, 227].

4.6 Combination therapy strategy

The core advantage of ECM-mimetic hydrogels lies in their capacity as a multifunctional therapeutic platform, which enables the synergistic integration with multiple treatment modalities to achieve precise spatiotemporal control over the entire regeneration process. Hydrogels can effectively integrate and amplify the therapeutic efficacy of biophysical stimuli, such as electrical stimulation and mechanical loading [228]. Furthermore, as delivery vehicles for cell therapy, they not only significantly improve the survival rate of transplanted cells, but also guide their spatial distribution and differentiation fate through their 3D structure and physicochemical properties. They can even act as “living factories” for genetically modified cells, enabling the sustained local production of therapeutic factors for long-term efficacy. This allows for a more precise recapitulation of the natural regeneration process, enhancing therapeutic efficacy while reducing systemic side effects [229]. These synergistic therapeutic strategies collectively highlight the evolution of ECM-mimetic hydrogels from passive structural scaffolds to active regulatory systems for tissue regeneration. By integrating multiple therapeutic inputs, they provide a more robust and effective solution for the repair of complex muscle injuries.

4.7 Specialized muscle type regeneration

In addition to the common applications in skeletal and cardiac muscle regeneration, ECM-mimetic hydrogels also exhibit unique application value in the regeneration of various specialized muscle tissues.

Application in urethral sphincter function reconstruction: Impairment of urethral sphincter function has been shown to severely impact patients' quality of life. The injection of ECM-mimetic hydrogels for sphincter repair has been demonstrated to provide effective volumetric support for the damaged sphincter. More importantly, they can promote nerve reinnervation through the sustained release of neurotrophic factors, thereby restoring the precise

neuromuscular control of the sphincter [143, 230]. Researchers integrated a time-on-demand regulation (TOR) technology platform into hydrogels to develop a 4D hydrogel dressing that adapts to the urethral microenvironment (UME) (Figure 12a). This hydrogel promotes urethral wound healing by establishing an early vascularization microenvironment that activates the VEGF signaling pathway, while its subsequent antifibrotic microenvironment timely inhibits the TGF- β signaling pathway to prevent proliferative scar formation [64].

Application in laryngeal muscle regeneration: The delicate structure and complex physiological functions of laryngeal muscles make their functional regeneration particularly challenging. ECM-mimetic hydrogels have been shown to promote the specific regeneration of laryngeal muscles through precise topological design and the controlled release of neurotrophic factors. Injectable alginate (ALG)/hyaluronic acid (HA) hydrogels loaded with basic fibroblast growth factor (bFGF) have been used to induce the regeneration of aged laryngeal muscles (Figure 12b). This hydrogel induces the upregulation of myogenic regulatory factor-related genes, myofibril hypertrophy, muscle satellite cell proliferation, and angiogenesis, while reducing interstitial fibrosis, ultimately successfully restoring glottal closure function [231]. In addition, catechol-conjugated hyaluronic acid (HA-CA) hydrogels containing human adipose-derived stem cell (hASC) spheroids can effectively improve the morphological and functional characteristics of the aged larynx (Figure 12c) [232].

4.8 Intelligent design and applications

With the deep integration of materials science, biomedicine, and computational science, the research paradigm of ECM-mimetic hydrogels for muscle regeneration is undergoing a fundamental shift from traditional trial-and-error approaches to data-driven precision design and intelligent applications. Artificial intelligence (AI) and data-driven modeling are increasingly emerging as promising tools for solving multidimensional optimization problems in regenerative biomaterial engineering.

4.8.1 AI accelerates the biomimetic design and performance optimization of hydrogels

Big data-based machine learning (ML) models have emerged as powerful tools for the prediction and screening of the key components and mechanical properties of hydrogels. For example, a study combining protein databases, biomimetic experiments, and machine learning successfully predicted and developed ultra-adhesive hydrogels with underwater adhesion strengths in the megapascal range, demonstrating a complete material design workflow from “biomimetic experience-guided” to “data-driven” approaches [233]. In addition, neural network-based algorithms embedded in the parameter determination of hydrogel constitutive models can efficiently fit key material properties based on known parameters such as swelling ratio and chemical potential, which greatly improves the design efficiency of hydrogels with target properties [234].

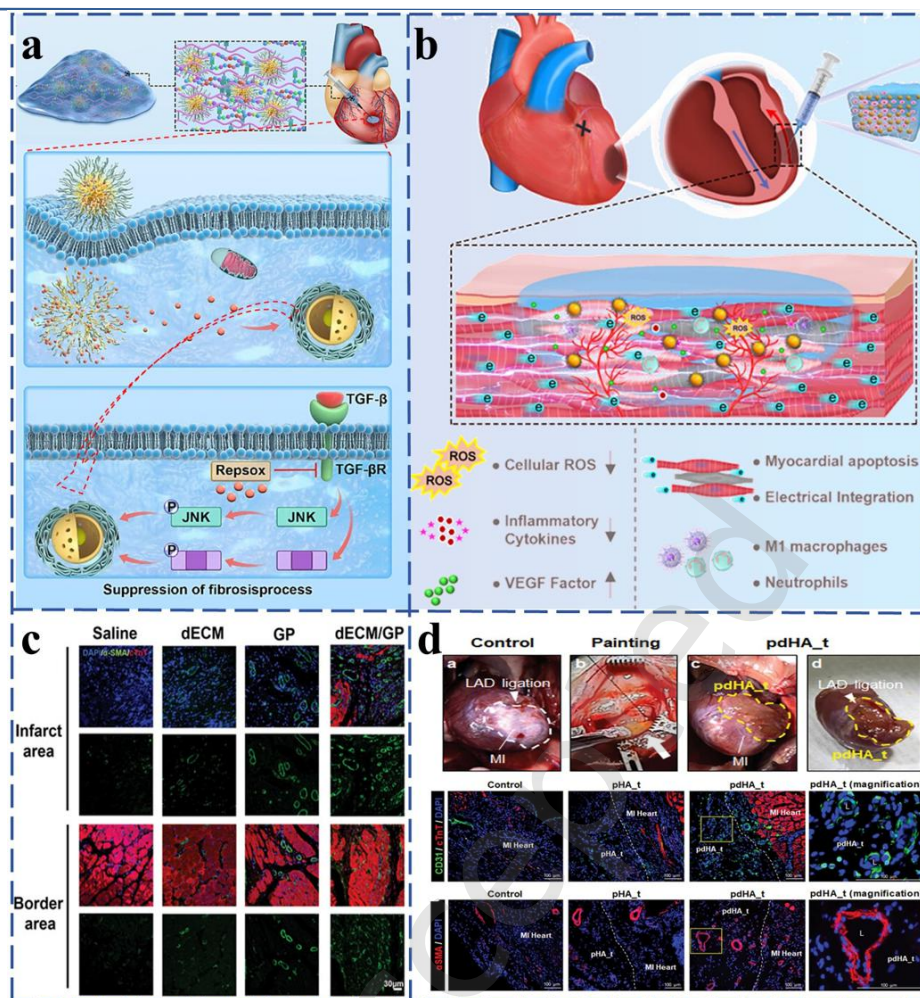


Figure 11 Therapeutic hydrogel strategies for myocardial infarction treatment and cardiac repair. a) Drug release mechanism of hydrogels for myocardial infarction treatment [180]. b) Schematic diagram of the therapeutic mechanism of basement membrane cells loaded onto hydrogels in *in vivo* cardiac repair [67]. c) Representative images of α-smooth muscle actin immunofluorescence in the infarct zone and border zone on day 28 after myocardial infarction [61]. d) Cardiac images of 28 days after MI induction and immunostaining of the samples [218]. Reproduced with permission [180]. Copyright 2023, Elsevier. Reproduced with permission [67]. Copyright 2023, American Chemical Society. Reproduced with permission [61]. Copyright 2023, John Wiley and Sons. Reproduced with permission [218]. Copyright 2024, John Wiley and Sons.

In the construction of complex regenerative microenvironments, the development of digitally programmable 3D bio-functional platforms (d3D-BP) has marked the advent of the “customized microenvironment” era for hydrogel scaffolds. Through 3D printing-guided phase separation (3D-PPS), researchers have achieved precise control over scaffold porosity, specific surface area, and mechanical properties, resulting in excellent mechanical compatibility with native muscle bundles, which provides an optimal biomimetic microenvironment for muscle satellite cells [110].

4.8.2 Multi-omics big data and Artificial Intelligence (AI) analysis of hydrogel regeneration mechanisms

An in-depth understanding of the molecular and cellular

mechanisms by which ECM-mimetic hydrogels regulate muscle regeneration is essential for their precise and rational clinical application. High-throughput technologies, including single-cell RNA sequencing (scRNA-seq), cytometry by time-of-flight (CyTOF), and proteomics, generate massive amounts of multi-omics data that capture the complex cellular and molecular responses to hydrogel implantation [66]. By combining AI-based bioinformatics analysis methods, researchers can systematically reveal the key signaling pathways and cellular population dynamics regulated by hydrogel treatment [66]. However, the predictive accuracy of current machine learning models is limited by the scarcity and heterogeneity of available data. Most hydrogel datasets contain fewer than 100 samples, and variations in synthesis conditions, cell types, and animal models severely hinder the generalization ability of the models [235]. Transfer learning and multi-omics integration (e.g., combining transcriptomics with proteomics) are emerging strategies to address this limitation, but standardized data repositories and uniform reporting guidelines are urgently needed for the field [236]. At present, the most realistic application of AI in hydrogel design is the optimization of single parameters (e.g., predicting the optimal crosslinker concentration for a target stiffness), rather than the *de novo* design of complete multifunctional hydrogels.

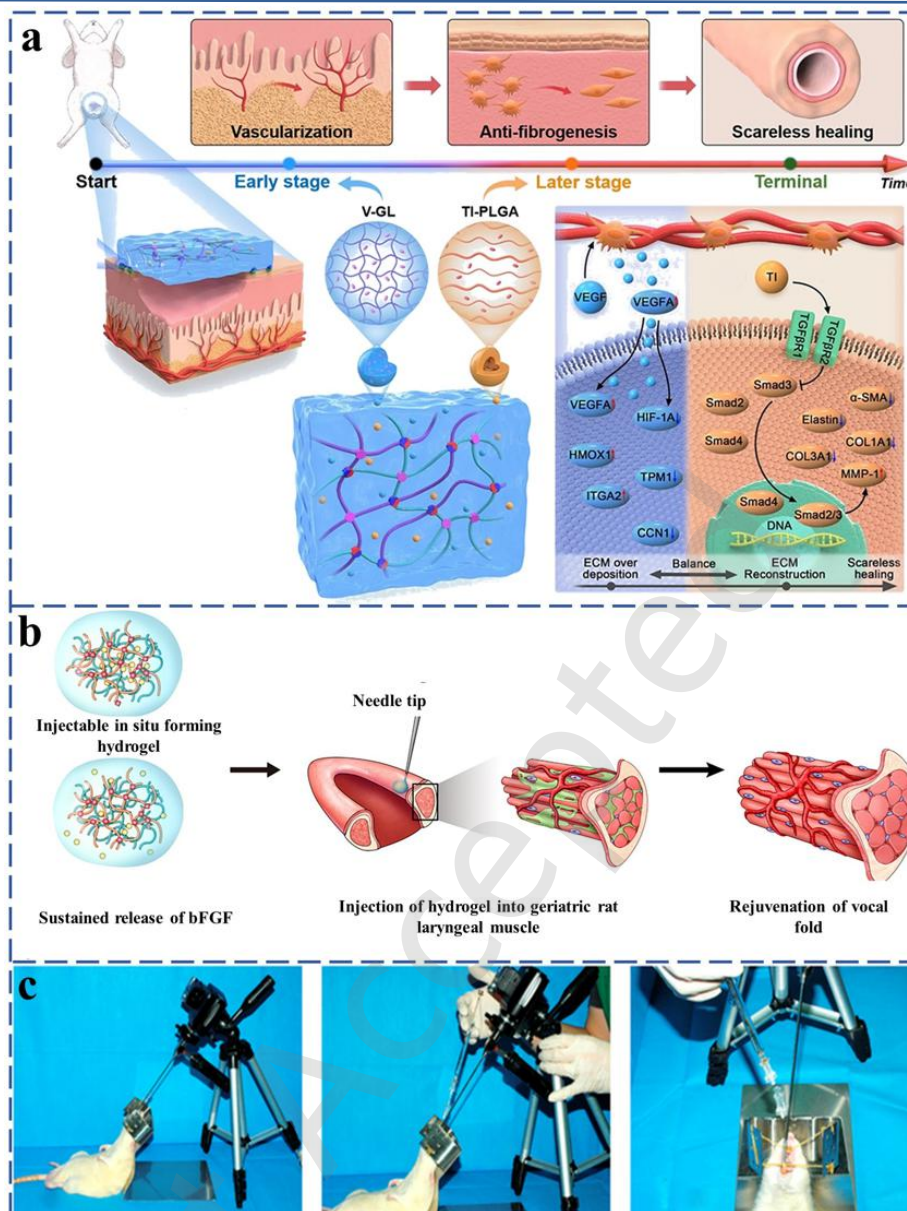


Figure 12 Adaptive and site-specific hydrogel strategies for tissue reconstruction and specialized muscle regeneration. a) Schematic illustration of UME-adaptable 4D hydrogel dressing to fully mimic time-dependent scarless urethral reconstruction [64]. b) Schematic diagram of hydrogel repairing laryngeal muscle [231]. c) Injection of hASC spheroid-loaded HA-based hydrogel into geriatric rat laryngeal muscle using a laryngoscope [232]. Reproduced with permission [64]. Copyright 2023, Springer Nature. Reproduced with permission [231]. Copyright 2019, Elsevier. Reproduced with permission [232]. Copyright 2022, The American Association for the Advancement of Science.

In addition, dual-probe micromanipulation technology enables the large-scale assessment of viscoelastic properties and contractile force in high-throughput skeletal muscle microphysiological models [237]. This biophysical screening method can directly characterize the physiological parameters of skeletal muscle tissue in solution while accounting for cellular organization and function, which improves the accuracy of evaluating the multifactorial interactions that affect skeletal muscle tissue regeneration [237]. Under resource-limited conditions, this novel approach can effectively explore the regulatory roles of various factors in muscle tissue regeneration, providing a new pathway to investigate the complex elements that influence the development and maintenance of both native

and engineered muscle tissues.

4.8.3 Smart rehabilitation systems and closed-loop therapy

The integration of injectable hydrogels with wearable/implantable bioelectronic devices has the potential to enable the development of next-generation smart closed-loop rehabilitation systems. A research team developed a HA-based injectable “tissue-mimetic hydrogel”. This electrically conductive hydrogel not only temporarily fills tissue defects and promotes muscle regeneration, but also enables the real-time monitoring of local electromyographic signals [87]. The collected physiological signals are transmitted to external AI algorithms for processing, which interpret neural intent or the functional state of the regenerating muscle, and then drive external robotic rehabilitation systems to provide patients with timely and appropriately dosed assistive movement or electrical stimulation [87]. This establishes an adaptive closed-loop rehabilitation system that spans signal sensing, AI decision-making, and functional execution, providing a novel therapeutic strategy for achieving the functional recovery of fine motor muscles.

4.8.4 Big data prediction for preclinical and clinical translation

In the translation of ECM-mimetic hydrogels from laboratory research to clinical applications, big data analytics and machine learning models are increasingly being used to predict their therapeutic efficacy and biological safety. By integrating histological and functional recovery data from various animal models and extensive preclinical literature, AI has been used to build clinical translation prediction models. These models can prioritize hydrogel formulations with the highest likelihood of success in human clinical trials, which significantly reduces research costs and timelines, and accelerates the market launch of novel regenerative medicine products [87].

In summary, ECM-mimetic hydrogels have extremely broad application prospects in the field of muscle regeneration. The value of these technological innovations lies not only in their technical sophistication, but more importantly in the new therapeutic hope and solutions they bring to patients with muscle injuries and diseases. However, despite the significant progress that has been made, ECM-mimetic hydrogels still face numerous challenges in their clinical translation and widespread application.

5 Current Challenges and Future Perspectives

5.1 Biocompatibility and safety of the materials

The immunogenicity and long-term biological safety of ECM-derived materials represent the primary barriers to clinical translation. Even after rigorous decellularization, heterologous source-derived ECM may still retain species-specific antigens, or generate new immunogenic epitopes during material processing [27, 51, 238]. More critically, the *in vivo* degradation behavior of hydrogels is difficult to accurately predict. Hydrogel degradation fragments may trigger unexpected inflammatory responses (e.g., elastin fragments can recruit monocytes and induce chronic inflammation [17]), and individual differences in degradation rates further increase the safety risk [239]. In addition, there is currently no standardized systematic evaluation system for assessing the calcification potential, fibrous encapsulation risk, and residual toxicity of chemical crosslinkers after long-term material implantation *in vivo*.

5.2 Regulation of structure and mechanical performance

Matching the mechanical properties of ECM-mimetic hydrogels with the dynamic changes of the muscle regenerative microenvironment remains a major technical challenge. The clinically relevant problem is not simply to reproduce a single elastic modulus, because muscle stiffness, viscoelasticity, stress relaxation, and anisotropy evolve during inflammation, granulation, myogenesis, and remodeling. A scaffold that is sufficiently stiff to bridge a large VML defect may simultaneously suppress cellular remodeling or increase interfacial stress, whereas a rapidly relaxing injectable gel may be favorable for cell infiltration but mechanically inadequate for a load-bearing defect [30, 240, 241]. Application-specific mechanical windows and time-dependent measurements are therefore needed, particularly under cyclic loading and after implantation, rather than relying on single end-point rheological measurements.

5.3 Precise control of bioactivity and function

When ECM-mimetic hydrogels are used as delivery carriers for bioactive factors, the main clinical bottlenecks are spatiotemporal control of release, preservation of

bioactivity, dose safety, and reproducibility between patients. These problems become more stringent when multiple signals should be delivered in sequence, as in VML or chronic muscle disease, because a burst of VEGF or IGF-1 cannot substitute for the coordinated progression from inflammation resolution to vascularization, myogenesis, and neuromuscular maturation. The therapeutic window is also narrow for many growth factors, and supraphysiological exposure can produce ectopic tissue formation, abnormal angiogenesis, or fibrosis [29, 242]. Future systems should therefore prioritize endogenous or matrix-bound signals, affinity-based retention, enzyme-responsive release, and clinically measurable dose-response relationships rather than simply increasing payload concentration.

5.4 Clinical translation, manufacturing, and regulatory bottlenecks

In the translation from laboratory research to clinical application, ECM-mimetic hydrogels face a linked set of manufacturing, standardization, regulatory, and procedural challenges. Decellularized materials require tight control over source tissue, decellularization efficiency, residual DNA, sterilization, and lot-to-lot biochemical composition, whereas synthetic or hybrid systems require reproducible control of precursor purity, crosslinking kinetics, and degradation products [17, 51]. For injectable products, syringeability, storage stability, catheter compatibility, gelation time, and sterility must be controlled alongside biological activity. Regulatory development is further complicated when a hydrogel combines ECM-derived material with cells, growth factors, nanoparticles, or gene-modifying components, because the product may fall under more than one regulatory framework. Clinical adoption will therefore depend on manufacturing processes that can define critical quality attributes and release specifications before efficacy can be meaningfully compared across studies.

In addition, for chronic progressive conditions such as muscular dystrophy, a single administration of hydrogel therapy is unlikely to achieve long-term therapeutic benefits. Repeated dosing or long-acting formulations should therefore be considered, but frequent repeated injections may exacerbate the foreign body response to the material. Hydrogels should be designed with tunable degradation profiles and the capacity to act as long-term depots for repeated administration, and can potentially be combined with gene editing technologies to achieve sustained therapeutic effects [243, 244]. Long-term functional integration of hydrogels in large animal models (e.g., porcine VML models, canine muscular dystrophy models) is rarely reported in current research. Most studies are limited to small animal models (e.g., rodents) with follow-up periods of less than 3 months [245, 246]. The vascular-nerve coupling mechanism during muscle regeneration remains poorly understood: while hydrogels can promote both angiogenesis and neurogenesis, the spatiotemporal coordination of these two processes has not been systematically optimized. Furthermore, immune heterogeneity across individuals and different disease stages further increases the difficulty of achieving predictable and consistent therapeutic outcomes.

5.5 Disease-specific clinical bottlenecks and validation priorities

VML provides the clearest test of whether ECM-mimetic hydrogels can move beyond histological repair toward functional reconstruction. The clinical problem is a large, mechanically active defect with simultaneous loss of

vascular and neural connections, so a material that only improves myofiber density is insufficient. A clinically informative VML program should therefore demonstrate restoration of tetanic force and fatigue resistance together with durable vascular perfusion, reinnervation, and functional movement, ideally in a large-animal model. The key technical bottleneck is the coupling of these processes in space and time: angiogenic and neurotrophic cues should reach the same regenerating muscle territories without causing premature or disorganized tissue growth.

Muscular dystrophy represents a different translational problem because the pathological environment persists after implantation. A hydrogel that performs well in an acute injury model may be rapidly remodeled or become ineffective in a chronically fibrotic muscle, and repeated local administration can increase procedural burden and foreign-body responses. The material therefore needs a long residence time without preventing endogenous remodeling, together with compatibility with sustained drug, protein,

nucleic-acid, or cell-based therapy. Longitudinal studies extending beyond the short follow-up periods typical of rodent experiments, are particularly important for determining whether hydrogel-mediated improvements remain after disease progression continues.

Myocardial infarction places an additional constraint on ECM-mimetic hydrogel design because the regenerated tissue should integrate electrically and mechanically with the beating myocardium. Injectable hydrogels that improve angiogenesis or reduce fibrosis may be unsuitable if their electrical properties, degradation products, or mechanical mismatch disturb conduction or promote arrhythmia. Clinical translation therefore requires simultaneous assessment of ventricular remodeling, electrical conduction, contractile function, vascularization, and long-term safety, rather than relying on infarct-size reduction alone. These disease-specific endpoints should be incorporated into preclinical study design before multifunctional hydrogels are advanced toward human trials.

Table 6 Disease-specific validation priorities for translational evaluation of ECM-mimetic hydrogels.

Clinical case	Primary translational endpoint	Major material bottleneck	Minimum preclinical evidence before clinical translation
VML	Force recovery, fatigue resistance, gait/task performance	Coordinated vascular–neural integration in a large defect	Large-animal defect model; >6-month functional follow-up; histology + perfusion + reinnervation + force testing
Muscular dystrophy	Durable improvement under progressive disease	Long-term residence, repeat dosing, fibrosis and immune heterogeneity	Chronic disease model; repeated-dose safety; long-term functional monitoring; systemic exposure assessment
Myocardial infarction	Ejection fraction, scar remodeling, electrical stability	Mechanical/electrical mismatch and arrhythmia risk	Large-animal cardiac model; electrophysiology + hemodynamics + fibrosis + vascularization; long-term safety

6 Conclusions

ECM-mimetic hydrogels have rapidly evolved from relatively simple structural materials into increasingly sophisticated regenerative platforms capable of modulating biochemical signaling, mechanical interactions, and immune responses during muscle repair. Considerable progress has been obtained in areas such as anisotropic structural engineering, electroactive modification, controlled factor delivery, and adaptive biomaterial design. These advances have expanded the potential applications of hydrogels across skeletal, cardiac, and smooth muscle regeneration.

Even so, several translational challenges remain difficult to be addressed. Current hydrogels still struggle to fully reproduce the dynamic reciprocity observed between native ECM and resident cells during long-term tissue remodeling, and the appropriate biomimetic target may change from provisional ECM during early repair to mature ECM during functional maturation. In large-volume injuries, neurovascular integration remains incomplete, while chronic diseases such as muscular dystrophy require a fundamentally different strategy based on long-term residence and repeated or sustained therapy. Manufacturing reproducibility, large-scale production, regulatory definition, and long-term biosafety also continue to limit clinical translation. Future studies should therefore focus on materials selection, fabrication, and functional evaluation with the clinical indication, rather than treating ECM mimicry as a single material property.

Future progress will likely depend on better integration of biomaterials science with mechanobiology, immunology,

bioelectronics, and computational modeling, together with clinically relevant validation. Adaptive materials should be evaluated not only for their ability to sense pathological cues, but also for whether the resulting changes improve clinically meaningful functions, such as force production, electrical stability, vascular perfusion, and coordinated movement. Artificial intelligence and multi-omics analysis may help to identify disease-specific design rules, but their usefulness will depend on standardized datasets and consistent reporting of material's composition, mechanical behavior, degradation, and functional outcomes. This application-driven framework will provide a more realistic route from ECM-mimetic hydrogel concepts to reproducible regenerative therapies.

Data availability

All data needed to support the conclusions in this Review are presented in the manuscript and/or the cited literature.

Acknowledgements

This work was supported by the Chengdu Municipal Medical Research Project (No. 2025053); Sichuan Provincial Science and Technology Innovation Cooperation Program for International, Hong Kong, Macao and Taiwan Partners (No. 2026YFHZ0088).

Declaration of competing interest

The authors declare no conflict of interest.

Author contribution statement

All authors contributed to the conception and organization of the Review, critically evaluated the literature, and approved the final manuscript.

Informed consent

Not applicable.

Ethics statement

Not applicable.

References

- [1] Frontera, W. R.; Ochala, J. Skeletal muscle: A brief review of structure and function. *Calcif. Tissue Int.* 2015, 96, 183–195.
- [2] Eugenis, I.; Wu, D.; Rando, T. A. Cells, scaffolds, and bioactive factors: Engineering strategies for improving regeneration following volumetric muscle loss. *Biomaterials* 2021, 278, 121173.
- [3] Corona, B. T.; Greising, S. M. Challenges to acellular biological scaffold mediated skeletal muscle tissue regeneration. *Biomaterials* 2016, 104, 238–246.
- [4] Rossi, A.; Furlani, F.; Bassi, G.; Cunha, C.; Lunghi, A. et al. Contactless magnetically responsive injectable hydrogel for aligned tissue regeneration. *Mater. Today Bio* 2024, 27, 101110.
- [5] Wolf, M. T.; Dearth, C. L.; Sonnenberg, S. B.; Lobo, E. G.; Badylak, S. F. Naturally derived and synthetic scaffolds for skeletal muscle reconstruction. *Adv. Drug Deliv. Rev.* 2015, 84, 208–221.
- [6] Tamo, A. K.; Djouonkep, L. D. W.; Selabi, N. B. S. 3d printing of polysaccharide-based hydrogel scaffolds for tissue engineering applications: A review. *Int. J. Biol. Macromol.* 2024, 270, 132123.
- [7] Keane, T. J.; Horejs, C.-M.; Stevens, M. M. Scarring vs. Functional healing: Matrix-based strategies to regulate tissue repair. *Adv. Drug Deliv. Rev.* 2018, 129, 407–419.
- [8] Zeimaran, E.; Pourshahrestani, S.; Fathi, A.; Razak, N. A. b. A.; Kadri, N. A. et al. Advances in bioactive glass-containing injectable hydrogel biomaterials for tissue regeneration. *Acta Biomater.* 2021, 136, 1–36.
- [9] Zhang, Y.; Zhang, C.; Li, Y.; Zhou, L.; Dan, N. et al. Evolution of biomimetic ecm scaffolds from decellularized tissue matrix for tissue engineering: A comprehensive review. *Int. J. Biol. Macromol.* 2023, 246, 125672.
- [10] Ma, Y.; Han, T.; Yang, Q.; Wang, J.; Feng, B. et al. Viscoelastic cell microenvironment: Hydrogel-based strategy for recapitulating dynamic ecm mechanics. *Adv. Funct. Mater.* 2021, 31, 2100848.
- [11] Ramos-Rodriguez, D. H.; Leach, J. K. Decellularized cell-secreted extracellular matrices as biomaterials for tissue engineering. *Small Sci.* 2025, 5, 2400335.
- [12] Xing, H.; Lee, H.; Luo, L.; Kyriakides, T. R. Extracellular matrix-derived biomaterials in engineering cell function. *Biotechnol. Adv.* 2020, 42, 107421.
- [13] Sousa, V.; Ladeira, B.; Garanger, E.; Lecommandoux, S.; Meijer, E. W. et al. Merging natural biopolymers with supramolecular chemistry: Emulating the native extracellular matrix's complexity. *ACS Nano* 2025, 19, 29833–29859.
- [14] Zhou, X.; Yu, X.; You, T.; Zhao, B.; Dong, L. et al. 3d printing-based hydrogel dressings for wound healing. *Adv. Sci.* 2024, 11, 2404580.
- [15] Liu, S.; Yu, J.-M.; Gan, Y.-C.; Qiu, X.-Z.; Gao, Z.-C. et al. Biomimetic natural biomaterials for tissue engineering and regenerative medicine: New biosynthesis methods, recent advances, and emerging applications. *Mil. Med. Res.* 2023, 10, 16.
- [16] Zhou, B.; Jiang, X.; Zhou, X.; Tan, W.; Luo, H. et al. Gelma-based bioactive hydrogel scaffolds with multiple bone defect repair functions: Therapeutic strategies and recent advances. *Biomater. Res.* 2023, 27, 86.
- [17] Capella-Monsons, H.; Crum, R. J.; Hussey, G. S.; Badylak, S. F. Advances, challenges, and future directions in the clinical translation of ecm biomaterials for regenerative medicine applications. *Adv. Drug Deliv. Rev.* 2024, 211, 115347.
- [18] Rothe, R.; Xu, Y.; Thomas, A. K.; Meister, S.; Zhang, Y. et al. A modular, injectable, non-covalently assembled hydrogel system features widescale tunable degradability for controlled release and tissue integration. *Biomaterials* 2021, 269, 120637.
- [19] Eyrich, D.; Brandl, F.; Appel, B.; Wiese, H.; Maier, G. et al. Long-term stable fibrin gels for cartilage engineering. *Biomaterials* 2007, 28, 55–65.
- [20] Zhang, X.; Wu, Y.; Gong, H.; Xiong, Y.; Chen, Y. et al. A multifunctional herb-derived glycopeptide hydrogel for chronic wound healing. *Small* 2024, 20, 2400516.
- [21] Yoon, J.; Han, H.; Jang, J. Nanomaterials-incorporated hydrogels for 3d bioprinting technology. *Nano Converg.* 2023, 10, 52.
- [22] Kim, S.; Keun Kim, H.; Eun Kim, S.; Ju Park, E.; Oh Park, J. et al. All-in-one tissue adhesive hydrogels for topical wound care. *Chem. Eng. J.* 2024, 487, 150547.
- [23] Zhou, Z.; Bu, Z.; Wang, S.; Yu, J.; Liu, W. et al. Extracellular matrix hydrogels with fibroblast growth factor 2 containing exosomes for reconstructing skin microstructures. *J. Nanobiotechnology* 2024, 22, 438.
- [24] Bertsch, P.; Sacco, P. The role of non-linear viscoelastic hydrogel mechanics in cell culture and transduction. *Mater. Today Bio.* 2025, 34, 102188.
- [25] Liu, W.; Gao, R.; Yang, C.; Feng, Z.; Ou-Yang, W. et al. ECM-mimetic immunomodulatory hydrogel for methicillin-resistant staphylococcus aureus- infected chronic skin wound healing. *Sci. Adv.* 2022, 8, eabn7006.
- [26] Jin, N.; Wang, Z.; Tang, X.; Jin, N.; Wang, X. Promoting diabetic wound healing through a hydrogel-based cascade regulation strategy of fibroblast-macrophage. *Adv. Healthc. Mater.* 2024, 13, 2400526.
- [27] Yang, J.; Xia, P.; Meng, F.; Li, X.; Xu, X. Bio-functional hydrogel microspheres for musculoskeletal regeneration. *Adv. Funct. Mater.* 2024, 34, 2400257.
- [28] Arif, M.; Zhang, J.; Xu, R.; Yu, C.; Majid, M. et al. Soft bio-electroactive hydrogels for musculoskeletal tissue repair and rehabilitation. *Adv. Healthc. Mater.* 2025, 14, 2502497.
- [29] Wu, J.; Yun, Z.; Song, W.; Yu, T.; Xue, W. et al. Highly oriented hydrogels for tissue regeneration: Design strategies, cellular mechanisms, and biomedical applications. *Theranostics* 2024, 14, 1982–2035.
- [30] Enayati, M.; Liu, W.; Madry, H.; Neisiany, R. E.; Cucchiari, M. Functionalized hydrogels as smart gene delivery systems to treat musculoskeletal disorders. *Adv. Colloid Interface Sci.* 2024, 331, 103232.
- [31] Xu, Q.; Xiao, Z.; Yang, Q.; Yu, T.; Deng, X. et al. Hydrogel-based cardiac repair and regeneration function in the treatment of myocardial infarction. *Mater. Today Bio* 2024, 25, 100978.
- [32] Liu, Z.; Zheng, Z.; Xie, J.; Wei, H.; Yu, C.-Y. Hydrogel-based cardiac patches for myocardial infarction therapy: Recent advances and challenges. *Mater. Today Bio* 2024, 29, 101331.
- [33] Zhang, Y.; Zhang, C.; Li, Y.; Zhou, L.; Dan, N. et al. Evolution of biomimetic ecm scaffolds from decellularized tissue matrix for tissue engineering: A comprehensive review. *Int. J. Biol. Macromol.* 2023, 246, 125672.
- [34] Cai, H.; Chuang, C. Y.; Vanichkitrungruang, S.; Hawkins, C. L.; Davies, M. J. Hypochlorous acid-modified extracellular matrix contributes to the behavioral switching of human coronary artery smooth muscle cells. *Free Radical Biol. Med.* 2019, 134, 516–526.
- [35] Chen, W.; Yang, A.; Jia, J.; Popov, Y. V.; Schuppan, D. et al. Lysyl oxidase (lox) family members: Rationale and their potential as therapeutic targets for liver fibrosis. *Hepatology* 2020, 72, 729–741.
- [36] Gao, F.; Su, S.; Qi, J.; Li, Z.; Wang, C. et al. Decellularized cartilage scaffolds derived from wharton's jelly facilitate cartilage regeneration and inhibit angiogenesis. *Mater. Today Bio* 2025, 33, 102023.
- [37] Mayorca-Guiliani, A. E.; Madsen, C. D.; Cox, T. R.; Horton, E. R.; Venning, F. A. et al. Isdot: In situ decellularization of tissues for high-resolution imaging and proteomic analysis of native extracellular matrix. *Nat. Med.* 2017, 23, 890–898.
- [38] Mostert, D. C. van der Putten, C. M. Sahlgren, N. A. Kurniawan, C. V. C. Bouten, Bioengineering structural anisotropy in living tissues. *Nat. Rev. Bioeng.* 2025, 3, 727–741.
- [39] Huang, R.; Cai, C.; Cheng, W.-W.; Cheng, Y.-J.; Liu, W.-L. et al. Injectable peptide liquid crystal hydrogel with hierarchical microstructure directs myoblast alignment and potentiates muscle functional recovery. *Adv. Funct. Mater.* 2026, 36, e00204.
- [40] Salamat, Q.; Moradi, R.; Nadizadeh, Z.; Kavehpour, P.; Soylak, M. et al. Chitosan based smart injectable hydrogels for biomedical applications: A comprehensive review. *Bioact. Mater.* 2026, 55, 703–753.
- [41] Xie, X.; Zhu, C.; Zhao, J.; Fan, Y.; Lei, H. et al. Combined treatment strategy of hydrogel dressing and physiotherapy for rapid wound healing. *Adv. Colloid Interface Sci.* 2025, 341, 103477.
- [42] Savitri, C.; Park, H. S.; Kim, Y.; Jang, Y.-J.; Hyun, J. et al. Immunomodulatory role of decellularized extracellular matrix in skin wound healing. *Mater. Today Bio* 2026, 36, 102672.
- [43] Bejleri, D.; Davis, M. E. Decellularized extracellular matrix materials for cardiac repair and regeneration. *Adv. Healthc. Mater.* 2019, 8, 1801217.
- [44] Liu, H.; Xing, F.; Yu, P.; Lu, R.; Ma, S. et al. Biomimetic fabrication bioprinting strategies based on decellularized extracellular matrix for musculoskeletal tissue regeneration: Current status and future perspectives. *Mater. Des.* 2024, 243, 113072.
- [45] Phang, S. J.; Basak, S.; Teh, H. X.; Packirisamy, G.; Fauzi, M. B. et al. Advancements in extracellular matrix-based biomaterials and biofabrication of 3d organotypic skin models. *ACS Biomater. Sci. Eng.* 2022, 8, 3220–3241.

- [46] Antczak, L.-A. M.; Moore, K. N.; Hendrick, T. E.; Heise, R. L. Binary fabrication of decellularized lung extracellular matrix hybridgels for *in vitro* chronic obstructive pulmonary disease modeling. *Acta Biomater.* 2024, 185, 190–202.
- [47] Wang, X.; Ansari, A.; Pierre, V.; Senyo, S. Abstract p486: Decellularized extracellular matrix microparticles promote heart regeneration and neovascularization in post-MI mice. *Circ. Res.* 2021, 129, AP486.
- [48] Wang, Y.; Wang, J.; Liu, C.; Li, J.; Lu, K. et al. Injectable decellularized extracellular matrix hydrogel loaded with exosomes encapsulating curcumin for prevention of cardiac fibrosis after myocardial infarction. *J. Mater. Sci. Technol.* 2023, 167, 50–58.
- [49] Kim, W.; Lee, H.; Lee, C. K.; Kyung, J. W.; An, S. B. et al. A bioprinting process supplemented with *in situ* electrical stimulation directly induces significant myotube formation and myogenesis. *Adv. Funct. Mater.* 2021, 31, 2105170.
- [50] Smoak, M. M.; Hogan, K. J.; Grande-Allen, K. J.; Mikos, A. G. Bioinspired electrospun decm scaffolds guide cell growth and control the formation of myotubes. *Sci. Adv.* 2021, 7, eabg4123.
- [51] Philips, C.; Terrie, L.; Thorrez, L. Decellularized skeletal muscle: A versatile biomaterial in tissue engineering and regenerative medicine. *Biomaterials.* 2022, 283, 121436.
- [52] Soliman, B. G.; Nguyen, A. K.; Gooding, J. J.; Kilian, K. A. Advancing synthetic hydrogels through nature-inspired materials chemistry. *Adv. Mater.* 2024, 36, 2404235.
- [53] Zhu, X.; Yang, Y.; Mao, S.; Liu, Q.; Li, Y. et al. Lung decm matrikine-based hydrogel reverses bleomycin-induced pulmonary fibrosis by suppressing m2 macrophage polarization. *Biofabrication* 2025, 17, 015037.
- [54] Ghosh, S.; Pati, F. Decellularized extracellular matrix and silk fibroin-based hybrid biomaterials: A comprehensive review on fabrication techniques and tissue-specific applications. *Int. J. Biol. Macromol.* 2023, 253, 127410.
- [55] Chen, L.; Xiao, L.; Ma, Y.; Xie, P.; Liu, J. et al. Bioengineered composite hydrogel scaffold for accelerated skin regeneration and wound repair. *Chem. Eng. J.* 2025, 504, 158773.
- [56] Saha, T.; Mehrotra, S.; Gupta, P.; Kumar, A. Exosomal mirna combined with anti-inflammatory hyaluronic acid-based 3d bioprinted hepatic patch promotes metabolic reprogramming in nafl-mediated fibrosis. *Biomaterials* 2025, 318, 123140.
- [57] Xue, Y.; Li, J.; Jiang, T.; Han, Q.; Jing, Y. et al. Biomimetic conductive hydrogel scaffolds with anisotropy and electrical stimulation for *in vivo* skeletal muscle reconstruction. *Adv. Healthc. Mater.* 2024, 13, 2302180.
- [58] Fan, L.; Xiao, C.; Guan, P.; Zou, Y.; Wen, H. et al. Extracellular matrix-based conductive interpenetrating network hydrogels with enhanced neurovascular regeneration properties for diabetic wounds repair. *Adv. Healthc. Mater.* 2022, 11, 2101556.
- [59] Wang, Y.; Wei, X.; Wang, L.; Qian, Z.; Liu, H. et al. Quercetin-based composite hydrogel promotes muscle tissue regeneration through macrophage polarization and oxidative stress attenuation. *Compos. B Eng.* 2022, 247, 110311.
- [60] Choi, S.; Lee, M. J.; Kim, M.; Bae, Y.; Park, J.-U. et al. Durable muscle extracellular matrix engineered with adhesive phenolic moieties for effective skeletal muscle regeneration in muscle atrophy. *Adv. Healthc. Mater.* 2024, 13, 2401826.
- [61] Kong, P.; Dong, J.; Li, W.; Li, Z.; Gao, R. et al. Extracellular matrix/glycopeptide hybrid hydrogel as an immunomodulatory niche for endogenous cardiac repair after myocardial infarction. *Adv. Sci.* 2023, 10, 2301244.
- [62] Yasue, H.; Taguchi, T.; Asoh, T.-A.; Nishiguchi, A. Cell-delivering injectable hydrogels with tunable microporous structures improve therapeutic efficacy for volumetric muscle loss. *Adv. Funct. Mater.* 2025, 35, e08278.
- [63] Lee, M.; Seo, D.; Park, J.; Lee, S. H.; Jeon, J. et al. Wet tissue adhesive polymeric powder hydrogels for skeletal muscle regeneration. *Bioact. Mater.* 2024, 40, 334–344.
- [64] Hua, Y.; Wang, K.; Huo, Y.; Zhuang, Y.; Wang, Y. et al. Four-dimensional hydrogel dressing adaptable to the urethral microenvironment for scarless urethral reconstruction. *Nat. Commun.* 2023, 14, 7632.
- [65] Park, S.; Le, T. P.; Byun, H. J.; Lee, S.; Lee, M. et al. Synergistic effects of conductive hydrogels and electrical stimulation in volumetric muscle loss. *Chem. Eng. J.* 2025, 512, 162362.
- [66] Luo, Z.; Wan, R.; Qiu, J.; Chen, C.; Chen, Y. et al. Multi-omics profiling of a self-assembling bioactive hydrogel for immunomodulation and myogenesis in volumetric muscle loss. *Chem* 2025, 11, 102645.
- [67] Liu, W.; Zhao, N.; Yin, Q.; Zhao, X.; Guo, K. et al. Injectable hydrogels encapsulating dual-functional Au@Pt core-shell nanoparticles regulate infarcted microenvironments and enhance the therapeutic efficacy of stem cells through antioxidant and electrical integration. *ACS Nano* 2023, 17, 2053–2066.
- [68] Lin, Y.; Xing, X.; Kang, X.; Liu, M.; Xiao, T. et al. Mechanically compliant hydrogel bioelectronics promote diabetic skeletal muscle regeneration through immunomodulatory and electrocoupling effects. *Adv. Funct. Mater.* 2025, 35, 2423340.
- [69] Shi, N.; Wang, J.; Tang, S.; Zhang, H.; Wei, Z. et al. Matrix nonlinear viscoelasticity regulates skeletal myogenesis through mrtf nuclear localization and nuclear mechanotransduction. *Small.* 2024, 20, 2305218.
- [70] Zelus, E. I.; Grime, J.; Saviola, A.; McCabe, M.; Hansen, K. C. et al. Development of a vaginal extracellular matrix hydrogel for combating genitourinary syndrome of menopause. *Adv. Mater.* 2025, 37, 2419977.
- [71] Fan, Q.; Zheng, Y.; Wang, X.; Xie, R.; Ding, Y. et al. Dynamically re-organized collagen fiber bundles transmit mechanical signals and induce strongly correlated cell migration and self-organization. *Angew. Chem. Int. Ed.* 2021, 60, 11858–11867.
- [72] Iglesias-Garcia, O.; Flandes-Ipparraguirre, M.; Montero-Calle, P.; Rosales, R. M.; Ullate-Agote, A. et al. Biologically-inspired melt electrowriting for the generation of highly biomimetic functional myocardium. *Adv. Funct. Mater.* 2025, 35, 2420106.
- [73] Wang, X.; Chen, S.; Chen, X.; Wu, J.; Huang, Z. et al. Biomimetic multi-channel nerve conduits with micro/nanostructures for rapid nerve repair. *Bioact. Mater.* 2024, 41, 577–596.
- [74] Kim, I.; Lee, S. S.; Ghosh, A.; Ferguson, S. J.; Bar-Nur, O. A self-renewing biomimetic skeletal muscle construct engineered using induced myogenic progenitor cells. *Adv. Funct. Mater.* 2024, 34, 2300571.
- [75] Su, W.; Yang, Q.; Li, T.; Xu, J.; Yin, P. et al. Electrospun aligned nanofiber yarns constructed biomimetic m-type interface integrated into precise co-culture system as muscle-tendon junction-on-a-chip for drug development. *Small Methods* 2024, 8, 2301754.
- [76] Zhang, M.; Yu, T.; Li, J.; Yan, H.; Lyu, L. et al. Matrix metalloproteinase-responsive hydrogel with on-demand release of phosphatidylserine promotes bone regeneration through immunomodulation. *Adv. Sci.* 2024, 11, 2306924.
- [77] Pfaff, M. R.; Wague, A.; Davies, M.; Killaars, A. R.; Ning, D. et al. Viscoelastic hya hydrogel promotes recovery of muscle quality and vascularization in a murine model of delayed rotator cuff repair. *Adv. Healthc. Mater.* 2025, 14, 2403962.
- [78] Chen, S.; Yang, L.; Leung, F. K.-C.; Kajitani, T.; Stuart, M. C. A. et al. Photoactuating artificial muscles of motor amphiphiles as an extracellular matrix mimetic scaffold for mesenchymal stem cells. *J. Am. Chem. Soc.* 2022, 144, 3543–3553.
- [79] Zhao, C.; Tian, S.; Liu, Q.; Xiu, K.; Lei, I. et al. Biodegradable nanofibrous temperature-responsive gelling microspheres for heart regeneration. *Adv. Funct. Mater.* 2020, 30, 2000776.
- [80] Zhu, S.; Zhao, B.; Li, M.; Wang, H.; Zhu, J. et al. Microenvironment responsive nanocomposite hydrogel with nir photothermal therapy, vascularization and anti-inflammation for diabetic infected wound healing. *Bioact. Mater.* 2023, 26, 306–320.
- [81] Yang, Q. Q.; Jin, J.; Sun, J.; Zhang, L.; Tang, J. B. et al. Simultaneous targeting of TGF- β 1/pd-11 via a hydrogel-nanoparticle system to remodel the ecm and immune microenvironment for limiting adhesion formation. *Acta Biomater.* 2024, 190, 447–462.
- [82] Li, Y.; Liu, S.; Zhang, J.; Wang, Y.; Lu, H. et al. Elastic porous microspheres/extracellular matrix hydrogel injectable composites releasing dual bio-factors enable tissue regeneration. *Nat. Commun.* 2024, 15, 1377.
- [83] Ding, X.; Zhuge, W.; Zhang, Y.; Ding, S.; Wang, J. et al. Microfluidic generation of bioinspired core-shell structured microfibers for cultured meat. *Chem. Eng. J.* 2023, 478, 147467.
- [84] Savekar, P. L.; Nadaf, S. J.; Killedar, S. G.; Kumbhar, V. M.; Hoskeri, J. H. et al. Citric acid cross-linked pomegranate peel extract-loaded pH-responsive β -cyclodextrin/carboxymethyl tapioca starch hydrogel film for diabetic wound healing. *Int. J. Biol. Macromol.* 2024, 274, 133366.
- [85] Kim, T. M.; Park, J.; Roy, K.; Choi, H. S.; Huh, K. M. et al. Muscle microenvironment-regulated phase transition and microstructure of injectable conductive hydrogel for injured muscle regeneration. *Chem. Eng. J.* 2025, 519, 164847.
- [86] Kong, W.; Wang, C.; Jia, C.; Kuang, Y.; Pastel, G. et al. Muscle-inspired highly anisotropic, strong, ion-conductive hydrogels. *Adv. Mater.* 2018, 30, 1801934.
- [87] Jin, S.; Choi, H.; Seong, D.; You, C.-L.; Kang, J.-S. et al. Injectable tissue prosthesis for instantaneous closed-loop rehabilitation. *Nature* 2023, 623, 58–65.
- [88] Ren, X.; Xiao, M.; Xu, Y.; Wu, Y.; Yang, J. et al. Injectable mxene conductive hydrogel improves myocardial infarction through scavenging ros and repairing myocardium electrical integrity. *Chem. Eng. J.* 2024, 481, 148791.

- [89] Wang, Y.; Wang, Q.; Luo, S.; Chen, Z.; Zheng, X. et al. 3d bioprinting of conductive hydrogel for enhanced myogenic differentiation. *Regen. Biomater.* 2021, 8, rbab035.
- [90] Hsieh, C.-C.; Dai, J.-Z.; Ni, C.-C.; Wei, S.-Y.; Tsai, M.-C. et al. Prevascularized hydrogel enhancing innervation and repair of full-thickness volumetric muscle loss in abdominal wall defects. *Adv. Healthc. Mater.* 2025, 14, 2402433.
- [91] Luo, Z.; Wan, R.; Qiu, J.; Chen, C.; Chen, Y. et al. Multi-omics profiling of a self-assembling bioactive hydrogel for immunomodulation and myogenesis in volumetric muscle loss. *Chem* 2025, 11, 102645.
- [92] Li, T.; Hou, J.; Wang, L.; Zeng, G.; Wang, Z. et al. Bioprinted anisotropic scaffolds with fast stress relaxation bioink for engineering 3d skeletal muscle and repairing volumetric muscle loss. *Acta Biomater.* 2023, 156, 21–36.
- [93] Liu, H.; Winkelbauer, M.; Janiak, J.; Weber, P.; Kalkan, A. K. et al. Filamented light (flight) bioprinting of mini-muscles with self-renewal potential. *Adv. Mater.* 2025, 37, e01147.
- [94] Roshanbinfar, K.; Evans, A. D.; Samanta, S.; Kolesnik-Gray, M.; Fiedler, M. et al. Enhancing biofabrication: Shrink-resistant collagen-hyaluronan composite hydrogel for tissue engineering and 3d bioprinting applications. *Biomaterials* 2025, 318, 123174.
- [95] Zelus, E. I.; Panduro, A.; Deshmukh, I.; Grime, J.; Alperin, M. et al. Immunomodulatory extracellular matrix hydrogel induces tissue regeneration in a model of partial glossectomy. *Bioact. Mater.* 2024, 38, 528–539.
- [96] Duran, P.; Boscolo Sesillo, F.; Cook, M.; Burnett, L.; Menefee, S. A. et al. Proregenerative extracellular matrix hydrogel mitigates pathological alterations of pelvic skeletal muscles after birth injury. *Sci. Transl. Med.* 2023, 15, eabj3138.
- [97] Yao, Z.; Yuan, Z.; Chen, Q.; Yao, L.; Zhang, X. et al. Injectable melatonin carbon dot composite hydrogel enhances anti-inflammatory and tenogenic differentiation of tendon-derived stem cells for minimally invasive treatment of achilles tendinopathy. *Chem. Eng. J.* 2025, 507, 160720.
- [98] Qin, B.-Q.; Wu, S.-Z.; Nie, R.; Zhang, Q.-Y.; Tan, J. et al. SDF-1 α /bmp-12 loaded biphasic sustained-release sis hydrogel/sa microspheres composite for tendon regeneration. *Biomaterials* 2025, 320, 123246.
- [99] Shi, N.; Li, Y.; Chang, L.; Zhao, G.; Jin, G. et al. A 3d, magnetically actuated, aligned collagen fiber hydrogel platform recapitulates physical microenvironment of myoblasts for enhancing myogenesis. *Small Methods* 2021, 5, 2100276.
- [100] Tan, L.; Wang, Y.; Huyan, C.; Li, M.; Liu, D. et al. Mechanically-adaptive janus hydrogel enhances scarless tendon healing with tissue-adhesion prevention. *Acta Biomater.* 2025, 202, 170–192.
- [101] Hu, X.; Zeng, F.; Yang, Y.; Hao, B.; Sun, L. et al. Injectable enzyme-crosslinking antioxidant hydrogel for stem cells protection and application in skeletal muscle regeneration. *Chem. Eng. J.* 2025, 503, 158135.
- [102] Xue, Y.; Yang, F.; He, Y.; Wang, F.; Xia, D. et al. Multifunctional hydrogel with photothermal ROS scavenging and antibacterial activity accelerates diabetic wound healing. *Adv. Healthc. Mater.* 2025, 14, 2402236.
- [103] Freedman, B. R.; Kuttler, A.; Beckmann, N.; Nam, S.; Kent, D. et al. Enhanced tendon healing by a tough hydrogel with an adhesive side and high drug-loading capacity. *Nat. Biomed. Eng.* 2022, 6, 1167–1179.
- [104] Kim, J.; Lee, M. C.; Jeon, J.; Rodriguez-de-laRosa, A.; Endo, Y. et al. Combinational regenerative inductive effect of bio-adhesive hybrid hydrogels conjugated with hpsc-derived myofibers and its derived evs for volumetric muscle regeneration. *Bioact. Mater.* 2025, 43, 579–602.
- [105] Qiu, Z.; Meng, Z.; Kasimu, A.; Wang, Z.; He, P. et al. Consecutive hybrid bioprinting of microfiber-reinforced living muscle constructs with highly-aligned cellular organizations. *Adv. Mater.* 2025, 37, e10222.
- [106] Sprenger, L.; Lu, H.-H.; Trippmacher, S.; Mansfeld, U.; Milkin, P. et al. Composite alginate dialdehyde-gelatin (ada-gel) hydrogel containing short ribbon-shaped fillers for skeletal muscle tissue biofabrication. *ACS Appl. Mater. Interfaces* 2024, 16, 44605–44622.
- [107] Jo, H. J.; Kang, M. S.; Heo, H. J.; Jang, H. J.; Park, R. et al. Skeletal muscle regeneration with 3d bioprinted hyaluronate/gelatin hydrogels incorporating mxene nanoparticles. *Int. J. Biol. Macromol.* 2024, 265, 130696.
- [108] Luo, Y.; Hu, Z.; Ni, R.; Xu, R.; Zhao, J. et al. Fabrication of 3D biomimetic smooth muscle using magnetic induction and bioprinting for tissue regeneration. *Biomater. Res.* 2024, 28, 0076.
- [109] Pei, M.; Hwangbo, H.; Kim, G. Hierarchical fibrous collagen/poly(ϵ -caprolactone) structure fabricated with a 3d-printing process for tissue engineering applications. *Compos. B Eng.* 2023, 259, 110730.
- [110] Zhao, S.; Wu, L.; Taiyari, S.; Li, H.; Sun, J. et al. A digitally programmable 3d microenvironment directs satellite cell function. *Biomaterials* 2026, 326, 123701.
- [111] Duong, V. T.; Nguyen, H. D.; Luong, N. H.; Chang, C.-Y.; Lin, C.-C. Photo-responsive decellularized small intestine submucosa hydrogels. *Adv. Funct. Mater.* 2024, 34, 2401952.
- [112] Duong, V. T.; Dang, T. T.; Le, V. P.; Le, T. H.; Nguyen, C. T. et al. Direct extrusion of multifascicle prevascularized human skeletal muscle for volumetric muscle loss surgery. *Biomaterials* 2025, 314, 122840.
- [113] Goedegebuure, M.; Bury, M. I.; Wang, X.; Sanfelice, P.; Cammarata, F. et al. A biodegradable microgrooved and tissue mechanocompatible citrate-based scaffold improves bladder tissue regeneration. *Bioact. Mater.* 2024, 41, 553–563.
- [114] Kim, S.; Choi, C.; Cha, C. Mechanotopography-driven design of dispersible nanofiber-laden hydrogel as a 3d cell culture platform for investigating tissue fibrosis. *Adv. Healthc. Mater.* 2021, 10, 2101109.
- [115] Ueda, N.; Okazaki, H.; Mikuma, A.; Kunieda, A.; Kawashima, S. et al. *In vivo* mechano-tissue engineering by hydrogels capable of transmitting intercellular mechanical stress. *Nat. Commun.* 2025, 16, 8847.
- [116] Bai, R.; Liu, J.; Zhang, J.; Shi, J.; Jin, Z. et al. Conductive single-wall carbon nanotubes/extracellular matrix hybrid hydrogels promote the lineage-specific development of seeding cells for tissue repair through reconstructing an integrin-dependent niche. *J. Nanobiotechnology* 2021, 19, 252.
- [117] Ge, J.; Li, Y.; Wang, M.; Gao, C.; Yang, S. et al. Engineering conductive antioxidative antibacterial nanocomposite hydrogel scaffolds with oriented channels promotes structure-functional skeletal muscle regeneration. *Chem. Eng. J.* 2021, 425, 130333.
- [118] Neves, M. I.; Bidarra, S. J.; Magalhes, M. V.; Torres, A. L.; Moroni, L. et al. Microstructured click hydrogels for cell contact guidance in 3d. *Mater. Today Bio* 2023, 19, 100604.
- [119] Zhou, B.; Yang, B.; Liu, Q.; Jin, L.; Shao, Y. et al. Effects of univariate stiffness and degradation of DNA hydrogels on the transcriptomics of neural progenitor cells. *J. Am. Chem. Soc.* 2023, 145, 8954–8964.
- [120] Shi, M.; Bai, L.; Xu, M.; Dong, R.; Yin, Z. et al. Magnetically induced anisotropic conductive in situ hydrogel for skeletal muscle regeneration by promoting cell alignment and myogenic differentiation. *Chem. Eng. J.* 2024, 484, 149019.
- [121] Luo, Y.; Chen, Y.; Gu, Z.; Ni, R.; Feng, P. et al. Engineered muscle from micro-channeled peg scaffold with magnetic Fe₃O₄ fixation towards accelerating esophageal muscle repair. *Mater. Today Bio* 2023, 23, 100853.
- [122] Chen, M.; Zhang, Y.; Zhou, P.; Liu, X.; Zhao, H. et al. Substrate stiffness modulates bone marrow-derived macrophage polarization through NF- κ B signaling pathway. *Bioact. Mater.* 2020, 5, 880–890.
- [123] Liu, S.; Chen, G.; Chen, Z.; Wang, F.; Lv, Y. Research progress on stiffness controllable scaffolds based on gelatin methacryloyl hydrogels for tissue repair and reconstruction. *Int. J. Biol. Macromol.* 2025, 321, 146485.
- [124] Wu, F.; Chen, H.; Liu, J.; Pang, Y. Generating structurally and functionally programmable hydrogels by biological membrane hybridization. *Nat. Protoc.* 2026, 21, 1597–1628.
- [125] Tan, Y. H.; Wang, K. C. W.; Chin, I. L.; Sanderson, R. W.; Li, J. et al. Stiffness mediated-mechanosensation of airway smooth muscle cells on linear stiffness gradient hydrogels. *Adv. Healthc. Mater.* 2024, 13, 2304254.
- [126] Li, L.; Griebel, M. E.; Uroz, M.; Bubli, S. Y.; Gagnon, K. A. et al. A protein-adsorbent hydrogel with tunable stiffness for tissue culture demonstrates matrix-dependent stiffness responses. *Adv. Funct. Mater.* 2024, 34, 2309567.
- [127] Cui, Y.; Li, D.; Gong, C.; Chang, C. Bioinspired shape memory hydrogel artificial muscles driven by solvents. *ACS Nano* 2021, 15, 13712–13720.
- [128] Kersey, A. L.; Cheng, D. Y.; Deo, K. A.; Dubell, C. R.; Wang, T.-C. et al. Stiffness assisted cell-matrix remodeling trigger 3d mechanotransduction regulatory programs. *Biomaterials* 2024, 306, 122473.
- [129] Monroe, T. O.; Hill, M. C.; Morikawa, Y.; Leach, J. P.; Heallen, T. et al. YAP partially reprograms chromatin accessibility to directly induce adult cardiogenesis *in vivo*. *Dev. Cell* 2019, 48, 765–779.
- [130] Gnay, K. A.; Silver, J. S.; Chang, T.-L.; Bednarski, O. J.; Bannister, K. L. et al. Myoblast mechanotransduction and myotube morphology is dependent on bag3 regulation of YAP and TAZ. *Biomaterials* 2021, 277, 121097.
- [131] Linke, P.; Munding, N.; Kimmle, E.; Kaufmann, S.; Hayashi, K. et al. Reversible host-guest crosslinks in supramolecular hydrogels for on-demand mechanical stimulation of human mesenchymal stem cells. *Adv. Healthc. Mater.* 2024, 13, 2302607.
- [132] Gandin, A.; Torresan, V.; Ulliana, L.; Panciera, T.; Contessotto, P. et al. Broadly applicable hydrogel fabrication procedures guided by YAP/TAZ-activity reveal stiffness, adhesiveness, and nuclear projected area as checkpoints for mechanosensing. *Adv. Healthc. Mater.* 2022, 11, 2102276.
- [133] Yang, Q.; Su, S.; Liu, S.; Yang, S.; Xu, J. et al. Exosomes-loaded electroconductive nerve dressing for nerve regeneration and pain relief against diabetic peripheral nerve injury. *Bioact. Mater.* 2023, 26, 194–215.

- [134] Duan, Y.; Mi, X.; Yu, Q.; Zhu, Z.; Gong, C. et al. Tailored hydrogels for 3d bioprinting: Matching tissue viscoelasticity to enhance resident cell functionality. *Adv. Funct. Mater.* 2025, 35, 2503987.
- [135] Li, L.; Wang, S.; Chen, Y.; Dong, S.; Zhang, C. et al. Hydrogels mimicking the viscoelasticity of extracellular matrix for regenerative medicine: Design, application, and molecular mechanism. *Chem. Eng. J.* 2024, 498, 155206.
- [136] Tian, H.; Hu, Y.; Wu, J.; Wang, R.; Wang, J. et al. Crystal transduction 3d printing of bio-hydrogels with high fidelity and order micro pores. *Adv. Funct. Mater.* 2025, 35, 2415799.
- [137] Wu, X.; Zhao, F.; Wang, H.; Schirhagl, R.; Włodarczyk-Biegun, M. K. Integrating melt electrowriting (mew) pcl scaffolds with fibroblast-laden hydrogel toward vascularized skin tissue engineering. *Mater. Today Bio* 2025, 31, 101593.
- [138] Narayanan, N.; Jia, Z.; Kim, K. H.; Kuang, L.; Lengemann, P. et al. Biomimetic glycosaminoglycan-based scaffolds improve skeletal muscle regeneration in a murine volumetric muscle loss model. *Bioact. Mater.* 2021, 6, 1201–1213.
- [139] Trujillo, S.; Gonzalez-Garcia, C.; Rico, P.; Reid, A.; Windmill, J. et al. Engineered 3d hydrogels with full-length fibronectin that sequester and present growth factors. *Biomaterials* 2020, 252, 120104.
- [140] Thai, V. L.; Ramos-Rodriguez, D. H.; Mesfin, M.; Leach, J. K. Hydrogel degradation promotes angiogenic and regenerative potential of cell spheroids for wound healing. *Mater. Today Bio* 2023, 22, 100769.
- [141] Lou, P.; Liu, S.; Wang, Y.; Pan, C.; Xu, X. et al. Injectable self-assembling peptide nanofiber hydrogel as a bioactive 3d platform to promote chronic wound tissue regeneration. *Acta Biomater.* 2021, 135, 100–112.
- [142] Kowala, A.; Boot, J.; Meng, J.; Mein, C. A.; Pourqui, O. et al. Engineered human myogenic cells in hydrogels generate innervated vascularized myofibers within dystrophic mouse muscle on long-term engraftment. *Cell Rep. Med.* 2025, 6, 102019.
- [143] Fang, W.; Du, X.; Yang, R.; Liu, M.; Yang, M. et al. Injectable therapeutic system incorporating neurogenesis-programmed stem cells concomitantly promoting muscle regeneration treats stress urinary incontinence. *Nat. Commun.* 2025, 16, 8404.
- [144] Hu, B.; Gao, M.; Boakye-Yiadom, K. O.; Ho, W.; Yu, W. et al. An intrinsically bioactive hydrogel with on-demand drug release behaviors for diabetic wound healing. *Bioact. Mater.* 2021, 6, 4592–4606.
- [145] An, S.; Jeon, E. J.; Kim, M.; Han, S. Y.; Song, Y. S. et al. Endomysium-permeable muscle extracellular matrix composite hydrogel for promoting functional muscle recovery in muscle atrophy. *Chem. Eng. J.* 2024, 485, 149906.
- [146] Song, Z.; Dong, Z.; Yu, X.; Li, Y.; Bai, Y. et al. Bioengineered multifunctional hydrogel integrating oxygen sustention, oxidative stress alleviation and pro-angiogenic cues for regenerative mi therapy. *Chem. Eng. J.* 2025, 520, 165859.
- [147] Borelli, A. N.; Schultze, C. L.; Young, M. W.; Kirkpatrick, B. E.; Anseth, K. S. Ligand presentation controls collective msc response to matrix stress relaxation in hybrid peg-ha hydrogels. *Bioact. Mater.* 2025, 44, 152–163.
- [148] Li, P.; Zhong, Y.; Wang, X.; Hao, J. Enzyme-regulated healable polymeric hydrogels. *ACS Cent. Sci.* 2020, 6, 1507–1522.
- [149] Shang, L.; Yu, Y.; Jiang, Y.; Liu, X.; Sui, N. et al. Ultrasound-augmented multienzyme-like nanozyme hydrogel spray for promoting diabetic wound healing. *ACS Nano* 2023, 17, 15962–15977.
- [150] Mooney, D.; Dankers, P.; Roche, E.; Wang, H. Engineering active materials for biomedical applications. *Adv. Mater.* 2024, 36, 2412651.
- [151] Yin, S.; Wu, H.; Huang, Y.; Lu, C.; Cui, J. et al. Structurally and mechanically tuned macroporous hydrogels for scalable mesenchymal stem cell-extracellular matrix spheroid production. *Proc. Natl. Acad. Sci. U. S. A.* 2024, 121, e2404210121.
- [152] Li, J.; Wang, F.; Ding, Y.; Chen, G.; Tan, Q. et al. Biomimetic ecm hydrogels loaded with adscs and polydopamine nanoparticles for chronic wound healing. *Chem. Eng. J.* 2025, 507, 160764.
- [153] Song, Y.; You, Y.; Xu, X.; Lu, J.; Huang, X. et al. Adipose-derived mesenchymal stem cell-derived exosomes biopotential extracellular matrix hydrogels accelerate diabetic wound healing and skin regeneration. *Adv. Sci.* 2023, 10, 2304023.
- [154] Silver, J. S.; Gney, K. A.; Cutler, A. A.; Vogler, T. O.; Brown, T. E. et al. Injury-mediated stiffening persistently activates muscle stem cells through YAP and taz mechanotransduction. *Sci. Adv.* 2021, 7, eabe4501.
- [155] Wang, W.; Chen, W.; Wu, C.; Zhang, C.; Feng, J. et al. Hydrogel-based molecular tension fluorescence microscopy for investigating receptor-mediated rigidity sensing. *Nat. Methods* 2023, 20, 1780–1789.
- [156] Chen, Q.; Li, S.; Li, K.; Zhao, W.; Zhao, C. A skin stress shielding platform based on body temperature-induced shrinking of hydrogel for promoting scar-less wound healing. *Adv. Sci.* 2024, 11, 2306018.
- [157] Lv, Y.; Liang, L.; Qin, M.; Jiang, R.-P.; Zong, F.-F. et al. Rgd peptide hydrogel downregulates mechanosignal YAP to inhibit postoperative scarring. *Acta Biomater.* 2025, 199, 132–141.
- [158] Wu, Y.; Chang, T.; Chen, W.; Wang, X.; Li, J. et al. Release of vegf and bmp9 from injectable alginate based composite hydrogel for treatment of myocardial infarction. *Bioact. Mater.* 2021, 6, 520–528.
- [159] Yuan, M.; Dai, X.; Yang, Y.; Liu, S.; Xu, Z. et al. An injectable bmp-2-releasing porous hydrogel regulating the paracrine effects of adscs promotes tendon-to-bone healing in rotator cuff repair. *Adv. Sci.* 2025, 12, e15923.
- [160] Yang, M.; Zhang, Y.; Fang, C.; Song, L.; Wang, Y. et al. Urine-microenvironment-initiated composite hydrogel patch reconfiguration propels scarless memory repair and reinvigoration of the urethra. *Adv. Mater.* 2022, 34, 2109522.
- [161] Zeng, Z.; Zhang, Z.; Chang, L.; Chen, H.; Ren, L. et al. Therapeutic silicate biomaterials for sarcopenia treatment by inhibiting inflammation and enhancing muscle regeneration through regulation of sarcolipin/sirt signaling pathway. *Bioact. Mater.* 2025, 51, 787–806.
- [162] Teixeira, S. P. B.; Pardo, A.; Bakht, S. M.; Gomez-Florit, M.; Reis, R. L. et al. Guiding stem cell tenogenesis by modulation of growth factor signaling and cell-scale biophysical cues in bioengineered constructs. *Adv. Funct. Mater.* 2024, 34, 2312961.
- [163] Fu, Y.; Gao, C.; Zhang, H.; Liu, J.; Li, B. et al. Fish swim bladder-derived ecm hydrogels effectively treat myocardial ischemic injury through immunomodulation and angiogenesis. *Adv. Sci.* 2025, 12, 2500036.
- [164] Zelus, E. I.; Grime, J.; Saviola, A.; McCabe, M.; Hansen, K. C. et al. Development of a vaginal extracellular matrix hydrogel for combating genitourinary syndrome of menopause. *Adv. Mater.* 2025, 37, 2419977.
- [165] Feng, Z.; Su, Q.; Zhang, C.; Huang, P.; Song, H. et al. Bioinspired nanofibrous glycopeptide hydrogel dressing for accelerating wound healing: A cytokine-free, M2-type macrophage polarization approach. *Adv. Funct. Mater.* 2020, 30, 2006454.
- [166] Witherell, C. E.; Sao, K.; Brisson, B. K.; Han, B.; Volk, S. W. et al. Regulation of extracellular matrix assembly and structure by hybrid m1/m2 macrophages. *Biomaterials* 2021, 269, 120667.
- [167] Dutta, S. D.; An, J. M.; Hexiu, J.; Randhawa, A.; Ganguly, K. et al. 3d bioprinting of engineered exosomes secreted from m2-polarized macrophages through immunomodulatory biomaterial promotes *in vivo* wound healing and angiogenesis. *Bioact. Mater.* 2025, 45, 345–362.
- [168] Wang, J.; Liu, X.; Wang, Y.; Zhang, Y.; Gao, R. et al. Pro-regenerative glycopeptide hydrogel activates type 2 immune response for wound healing via macrophage-t cell crosstalk. *Adv. Funct. Mater.* 2024, 34, 2307711.
- [169] Zhang, J.; Zheng, Y.; Lee, J.; Hua, J.; Li, S. et al. A pulsatile release platform based on photo-induced imine-crosslinking hydrogel promotes scarless wound healing. *Nat. Commun.* 2021, 12, 1670.
- [170] Yang, Q.; Miao, Y.; Luo, J.; Li, C.; Li, X. et al. Nanofibril-structured granular hydrogels harness stem cell retention and immunoregulation in diabetic microenvironment. *ACS Nano* 2025, 19, 6795–6814.
- [171] Ye, X.; Wang, K.; Peng, Z.; Wu, X.; Hu, D. et al. Bioactive bilirubin hydrogel promotes structural-functional skeletal muscle regeneration following volumetric muscle loss through regulating glycolysis-inflammation and enhancing muscle innervation. *Adv. Funct. Mater.* 2025, 35, e01272.
- [172] Li, D.; Li, S.; He, S.; He, H.; Yuan, G. et al. Restoring tendon microenvironment in tendinopathy: Macrophage modulation and tendon regeneration with injectable tendon hydrogel and tendon-derived stem cells exosomes. *Bioact. Mater.* 2025, 47, 152–169.
- [173] Fan, X.; Zhan, J.; Pan, X.; Liao, X.; Guo, W. et al. Enzymatic self-assembly nanofibers anchoring mesenchymal stem cells induce cell spheroids and amplify paracrine function for myocardial infarction therapy. *Chem. Eng. J.* 2022, 436, 135224.
- [174] Nerger, B. A.; Kashyap, K.; Deveney, B. T.; Lou, J.; Hanan, B. F. et al. Tuning porosity of macroporous hydrogels enables rapid rates of stress relaxation and promotes cell expansion and migration. *Proc. Natl. Acad. Sci. U. S. A.* 2024, 121, e2410806121.
- [175] Yuan, Y.; Zhang, Z.; Mo, F.; Yang, C.; Jiao, Y. et al. A biomaterial-based therapy for lower limb ischemia using sr/si bioactive hydrogel that inhibits skeletal muscle necrosis and enhances angiogenesis. *Bioact. Mater.* 2023, 26, 264–278.
- [176] Wei, S.-Y.; Chen, P.-Y.; Hsieh, C.-C.; Chen, Y.-S.; Chen, T.-H. et al. Engineering large and geometrically controlled vascularized nerve tissue in collagen hydrogels to restore large-sized volumetric muscle loss. *Biomaterials* 2023, 303, 122402.
- [177] Lee, M. C.; Lee, J. S.; Kim, S.; Jamaiyar, A.; Wu, W. et al. Synergistic effect of hypoxic conditioning and cell-tethering colloidal gels enhanced productivity of msc paracrine factors and accelerated vessel regeneration.

Adv. Mater. 2025, 37, 2408488.

[178] Lee, M.; Kim, Y. S.; Park, J.; Choe, G.; Lee, S. et al. A paintable and adhesive hydrogel cardiac patch with sustained release of angptl4 for infarcted heart repair. *Bioact. Mater.* 2024, 31, 395–407.

[179] Wang, Z.; Hu, C.; Zhang, W.; Liu, W.; He, S. et al. Dynamically crosslinked ecm-like hydrogels loaded with ros-responsive drug nanoparticles for treating inflammation in myocardial infarction and stroke. *Compos. B Eng.* 2024, 285, 111734.

[180] Wang, Z.; Hu, C.; Zhang, W.; Liu, W.; Dong, R. et al. An injectable ecm-like hydrogel with bioactive peptides and repox nanoparticles for myocardial infarction treatment. *Chem. Eng. J.* 2023, 474, 145878.

[181] Xie, X.-T.; Gao, C.-H.; Tan, L.-F.; Chen, L.-X.; Fan, J.-X. et al. Gene-engineered polypeptide hydrogels with on-demand oxygenation and ecm-cell interaction mimicry for diabetic wound healing. *Biomaterials* 2025, 316, 122984.

[182] Liu, J.; Kang, J.; Zou, T.; Hu, M.; Zhang, Y. et al. Functional cobalt-doped hydrogel scaffold enhances concurrent vascularization and neurogenesis. *J. Nanobiotechnology* 2025, 23, 179.

[183] Wei, Z.; Lei, M.; Wang, Y.; Xie, Y.; Xie, X. et al. Hydrogels with tunable mechanical plasticity regulate endothelial cell outgrowth in vasculogenesis and angiogenesis. *Nat. Commun.* 2023, 14, 8307.

[184] Kim, K.; Yang, J.; Li, C.; Yang, C.-Y.; Hu, P. et al. Anisotropic structure of nanofiber hydrogel accelerates diabetic wound healing via triadic synergy of immune-angiogenic-neurogenic microenvironments. *Bioact. Mater.* 2025, 47, 64–82.

[185] Carleton, M. M.; Locke, M.; Sefton, M. V. Methacrylic acid-based hydrogels enhance skeletal muscle regeneration after volumetric muscle loss in mice. *Biomaterials* 2021, 275, 120909.

[186] Li, Z.; Wu, J.; Liu, Z.; Huang, Y.; Lin, Y. et al. Mra-lnp hydrogels promote skeletal muscle regeneration in situ. *J. Control. Release* 2025, 387, 114258.

[187] Yan, L.; Liu, S.; Wang, J.; Ding, X.; Zhao, Y. et al. Constructing nerve guidance conduit using decm-doped conductive hydrogel to promote peripheral nerve regeneration. *Adv. Funct. Mater.* 2024, 34, 2402698.

[188] Alheib, O.; da Silva, L. P. A. da Silva Morais, K. A. Mesquita, R. P. Pirraco, et al. Injectable laminin-biofunctionalized gellan gum hydrogels loaded with myoblasts for skeletal muscle regeneration. *Acta Biomater.* 2022, 143, 282–294.

[189] Shi, M.; Dong, R.; Hu, J.; Guo, B. Conductive self-healing biodegradable hydrogel based on hyaluronic acid-grafted-polyaniline as cell recruitment niches and cell delivery carrier for myogenic differentiation and skeletal muscle regeneration. *Chem. Eng. J.* 2023, 457, 141110.

[190] Lin, Y.; Xing, X.; Kang, X.; Liu, M.; Xiao, T. et al. Mechanically compliant hydrogel bioelectronics promote diabetic skeletal muscle regeneration through immunomodulatory and electrocoupling effects. *Adv. Funct. Mater.* 2025, 35, 2423340.

[191] Acharya, R.; Dutta, S. D.; Mallik, H.; Patil, T. V.; Ganguly, K. et al. Physical stimuli-responsive DNA hydrogels: Design, fabrication strategies, and biomedical applications. *J. Nanobiotechnology* 2025, 23, 233.

[192] Caravaggi, C.; Grigoletto, F.; Scuderi, N. Wound bed preparation with a dermal substitute (Hyalomatrix® PA) facilitates re-epithelialization and healing: Results of a multicenter, prospective, observational study on complex chronic ulcers. *Wounds* 2011, 23, 228–235.

[193] Motolese, A.; Vignati, F.; Brambilla, R.; Cerati, M.; Passi, A. Interaction between a regenerative matrix and wound bed in nonhealing ulcers: Results with 16 cases. *BioMed. Res. Int.* 2013, 849321.

[194] U.S. Food and Drug Administration. 510(k) Premarket Notification K1 53754: MicroMatrix. U.S. FDA, Silver Spring, MD, 2026. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K153754>.

[195] U.S. Food and Drug Administration. 510(k) Premarket Notification K2 30980: MicroMatrix® Flex. U.S. FDA, Silver Spring, MD, 2026. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K230980>.

[196] U.S. Food and Drug Administration. 510(k) Premarket Notification K1 43058: PuraDerm™ Gel. U.S. FDA, Silver Spring, MD, 2026. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K143058>.

[197] U.S. Food and Drug Administration. 510(k) Premarket Notification K2 53521: ECMT-100 WMD. U.S. FDA, Silver Spring, MD, 2026. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K253521>.

[198] National Library of Medicine. Study evaluating the safety and efficacy of an ECM hydrogel for the treatment of anorectal fistulas. *ClinicalTrials.gov* v: NCT07035925, 2026. <https://clinicaltrials.gov/study/NCT07035925>.

[199] U.S. Food and Drug Administration. 510(k) Premarket Notification K1 40789: CorMatrix ECM for Vascular Repair. U.S. FDA, Silver Spring, MD, 2026. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K140789>.

[200] Martin-Saldaa, S.; Al Waeel, M.; Alsharabasy, A. M.; Daly, A.; Pandit, A. An interdisciplinary framework for the characterization of extracellular

matrix-hydrogels for biomedical applications. *Matter.* 2022, 5, 3659–3705.

[201] Cheng, N.; Luo, Q.; Yang, Y.; Shao, N.; Nie, T. et al. Injectable ph responsive conductive hydrogel for intelligent delivery of metformin and exosomes to enhance cardiac repair after myocardial ischemia-reperfusion injury. *Adv. Sci.* 2025, 12, 2410590.

[202] Luo, Q.; Li, Z.; Sun, W.; Wang, G.; Yao, H. et al. Myocardia-injected synergistically anti-apoptotic and anti-inflammatory poly(amino acid) hydrogel relieves ischemia-reperfusion injury. *Adv. Mater.* 2025, 37, 2420171.

[203] Liu, Y.; Gilchrist, A. E.; Heilshorn, S. C. Engineered protein hydrogels as biomimetic cellular scaffolds. *Adv. Mater.* 2024, 36, 2407794.

[204] Niknezhad, S. V.; Mehrali, M.; Khorasgani, F. R.; Heidari, R.; Kadumudi, F. B. et al. Enhancing volumetric muscle loss (VML) recovery in a rat model using super durable hydrogels derived from bacteria. *Bioact. Mater.* 2024, 38, 540–558.

[205] Zheng, H.; Cheng, F.; Guo, D.; He, X.; Zhou, L. et al. Nanoenzyme-reinforced multifunctional scaffold based on ti3c2tx mxene nanosheets for promoting structure-functional skeletal muscle regeneration via electroactivity and microenvironment management. *Nano Lett.* 2023, 23, 7379–7388.

[206] Lee, M. C.; Jodat, Y. A.; Endo, Y.; Rodriguez-de-laRosa, A.; Zhang, T. et al. Engineering large-scale hipsc-derived vessel-integrated muscle-like lattices for enhanced volumetric muscle regeneration. *Trends Biotechnol.* 2024, 42, 1715–1744.

[207] Shuai, Q.; Cheng, J.; Wang, X.; Li, X.; Xu, K. et al. Adipose-derived evs loaded resolvins biopotential decellularized extracellular matrix hydrogels accelerate muscle regeneration. *Chem. Eng. J.* 2025, 514, 163325.

[208] Rodríguez Ayala, A.; Christ, G.; Griffin, D. Cell-scale porosity minimizes foreign body reaction and promotes innervated myofiber formation after volumetric muscle loss. *npj Regen. Med.* 2025, 10, 12.

[209] Ding, S.; Li, S.; Shen, Z.; Chen, Y.; Wang, X. et al. Biomimetically neurovascularized engineered muscle tissue for craniofacial volumetric muscle loss. *Bio-Des. Manuf.* 2025, 8, 331–343.

[210] Jeon, E. J.; An, S.; Han, S. Y.; Jeong, E.; Song, Y. S. et al. Extracellular matrix-mediated crosslinking of adhesive hyaluronic acid patch for treating volumetric muscle injury. *Adv. Healthc. Mater.* 2025, 14, 2403747.

[211] Koliopoulos, V.; Mikos, A. G. Decellularized extracellular matrix as a drug delivery carrier. *J. Control. Release* 2025, 382, 113661.

[212] Kitana, W.; Apsite, I.; Ionov, L. 3D (bio) printing combined fiber fabrication methods for tissue engineering applications: Possibilities and limitations. *Adv. Funct. Mater.* 2025, 2500450.

[213] Bu, Z.; Jing, J.; Liu, W.; Fan, Z.; Huang, J. et al. Treatment of denervated muscle atrophy by injectable dual-responsive hydrogels loaded with extracellular vesicles. *Adv. Sci.* 2025, 12, 2412248.

[214] Li, K.; Sun, H.; Zhang, Q.; Zhao, M.; Yang, W. et al. Intermuscular septum delivery of high-mechanical injectable magnetic hydrogels to improve muscle atrophy. *Nano Lett.* 2025, 25, 12173–12183.

[215] Zhu, L.; Yuhuan, J.; Yu, H.; Zhang, B.; Huang, K. et al. Decellularized extracellular matrix for remodeling bioengineering organoid's microenvironment. *Small* 2023, 19, 2207752.

[216] Cao, Y.; Fan, R.; Zhu, K.; Gao, Y. Advances in functionalized hydrogels in the treatment of myocardial infarction and drug-delivery strategies. *ACS Appl. Mater. Interfaces* 2024, 16, 48880–48894.

[217] Wang, L.; Yu, C.; You, T.; Zhang, X.; Su, H. et al. Injection of ros-responsive hydrogel loaded with IL-1 β -targeted nanobody for ameliorating myocardial infarction. *Bioact. Mater.* 2025, 46, 273–284.

[218] Lee, J.; Lee, S.-G.; Kim, B.-s.; Park, S.; Sundaram, M. N. et al. Paintable decellularized-ecm hydrogel for preventing cardiac tissue damage. *Adv. Sci.* 2024, 11, 2307353.

[219] Jia, X.; Liu, W.; Ai, Y.; Cheung, S.; Hu, W. et al. A multifunctional anisotropic patch manufactured by microfluidic manipulation for the repair of infarcted myocardium. *Adv. Mater.* 2024, 36, 2404071.

[220] Zhang, Y.; Xu, Y.; Wu, C.; Chen, S.; Chen, Z. et al. Injectable conductive hydrogel patch with spatiotemporally tailored asymmetric adhesion for myocardial infarction repair. *Adv. Mater.* 2026, 38, e10824.

[221] Zhang, L.; Li, T.; Yu, Y.; Shi, K.; Bei, Z. et al. An injectable conductive hydrogel restores electrical transmission at myocardial infarct site to preserve cardiac function and enhance repair. *Bioact. Mater.* 2023, 20, 339–354.

[222] Zhang, L.; Bei, Z.; Li, T.; Qian, Z. An injectable conductive hydrogel with dual responsive release of rosmarinic acid improves cardiac function and promotes repair after myocardial infarction. *Bioact. Mater.* 2023, 29, 132–150.

[223] Tamo, A. K.; Doench, I.; Roshanbifar, K.; Montembault, A.; Serghei, A. et al. Electrically conductive biopolymer-based hydrogels and fibrous materials fabricated using 3d printing and electrospinning for cardiac tissue

engineering. *Bioact. Mater.* 2025, 51, 650–719.

[224] Pena, B.; Knight, W.; Cavin, M.; Ferrari, I.; Abdel-Hafiz, M. et al. Injectable carbon nanotube-functionalized hydrogel as a tool for cardiac tissue engineering. *Eur. Heart J.* 2022, 43, ehac544.3016.

[225] McLaughlin, S.; Sedlakova, V.; Zhang, Q.; McNeill, B.; Smyth, D. et al. Recombinant human collagen hydrogel rapidly reduces methylglyoxal adducts within cardiomyocytes and improves borderzone contractility after myocardial infarction in mice. *Adv. Funct. Mater.* 2022, 32, 2204076.

[226] Liu, Y.; Zhang, Y.; Mei, T.; Cao, H.; Hu, Y. et al. Hescs-derived early vascular cell spheroids for cardiac tissue vascular engineering and myocardial infarction treatment. *Adv. Sci.* 2022, 9, 2104299.

[227] Contessotto, P.; Orbanic, D.; Da Costa, M.; Jin, C.; Owens, P. et al. Elastin-like recombinamers-based hydrogel modulates post-ischemic remodeling in a non-transmural myocardial infarction in sheep. *Sci. Transl. Med.* 2021, 13, eaaz5380.

[228] Liang, J.; Zeng, H.; Qiao, L.; Jiang, H.; Ye, Q. et al. 3d printed piezoelectric wound dressing with dual piezoelectric response models for scar-prevention wound healing. *ACS Appl. Mater. Interfaces* 2022, 14, 30507–30522.

[229] Fan, W.; Yang, X.; Hu, X.; Huang, R.; Shi, H. et al. A novel conductive microtubule hydrogel for electrical stimulation of chronic wounds based on biological electrical wires. *J. Nanobiotechnology* 2024, 22, 258.

[230] Wang, Y.; Gao, G.; Liu, M.; Yang, M.; Wang, Y. et al. Engineered igf-1- expressing adipose-derived stem cell sheet fragments promote urethral sphincter tissue regeneration. *Chem. Eng. J.* 2025, 522, 167563.

[231] Choi, Y. H.; Kim, S. H.; Kim, I. G.; Lee, J. H.; Kwon, S. K. Injectable basic fibroblast growth factor-loaded alginate/hyaluronic acid hydrogel for rejuvenation of geriatric larynx. *Acta Biomater.* 2019, 89, 104–114.

[232] Lee, D. Y.; Choi, Y. H.; Choi, J. S.; Eom, M. R.; Kwon, S. K. Injection laryngoplasty of human adipose-derived stem cell spheroids with hyaluronic acid-based hydrogel improves the morphological and functional characteristics of geriatric larynx. *Biomater. Res.* 2022, 26, 13.

[233] Liao, H.; Hu, S.; Yang, H.; Wang, L.; Tanaka, S. et al. Data-driven de novo design of super-adhesive hydrogels. *Nature* 2025, 644, 89–95.

[234] Zheng, S.; Liu, Z. The machine learning embedded method of parameters determination in the constitutive models and potential applications for hydrogels. *Int. J. Appl. Mech.* 2021, 13, 2150001.

[235] Cadamuro, F.; Piazzoni, M.; Gamba, E.; Sonzogni, B.; Previdi, F. et al. Artificial intelligence tool for prediction of ecm mimics hydrogel formulations via click chemistry. *Biomater. Adv.* 2025, 175, 214323.

[236] Hong, W.; Zhang, Q.; Lin, L.; Zhang, H.; Lei, X. et al. Machine learning-driven polysaccharide-based hydrogels: Intelligent design and precision therapeutics for oral wound repair. *Adv. Funct. Mater.* 2025, e25950.

[237] Chen, X.; Sun, T.; Shimoda, S.; Wang, H.; Huang, Q. et al. A micromanipulation-actuated large-scale screening to identify optimized microphysiological model parameters in skeletal muscle regeneration. *Adv. Sci.* 2024, 11, 2403622.

[238] Zhao, Y.; Song, S.; Ren, X.; Zhang, J.; Lin, Q. et al. Supramolecular adhesive hydrogels for tissue engineering applications. *Chem. Rev.* 2022, 122, 5604–5640.

[239] Lv, B.; Lu, L.; Hu, L.; Cheng, P.; Hu, Y. et al. Recent advances in gelma hydrogel transplantation for musculoskeletal disorders and related disease treatment. *Theranostics* 2023, 13, 2015–2039.

[240] Zhang, F.-X.; Chien, M.-H.; Fan, Q.-r.; Jiang, D. Advances in bioadhesive hydrogels for musculoskeletal tissue application. *Adv. Funct. Mater.* 2024, 34, 2316540.

[241] Zhang, K.; Feng, Q.; Fang, Z.; Gu, L.; Bian, L. Structurally dynamic hydrogels for biomedical applications: Pursuing a fine balance between macroscopic stability and microscopic dynamics. *Chem. Rev.* 2021, 121, 11149–11193.

[242] Chen, G.; Yang, Z.; Pan, H.; Zhang, J.; Guo, Y. et al. A review of hydrogel fiber: Design, synthesis, applications, and futures. *Chem. Rev.* 2025, 125, 5991–6056.

[243] Zhang, C.; Shen, Y.; Huang, M.; Wang, G.; Miao, Q. et al. Dynamic hydrogel mechanics in organoid engineering: From matrix design to translational paradigms. *Bioact. Mater.* 2026, 55, 144–170.

[244] Zhou, L.; Zhang, Y.; Yi, X.; Chen, Y.; Li, Y. Advances in proteins, polysaccharides, and composite biomaterials for enhanced wound healing via microenvironment management: A review. *Int. J. Biol. Macromol.* 2024, 282, 136788.

[245] Rijns, L.; Rutten, M. G. T. A.; Vreken, A. F.; Aldana, A. A.; Baker, M. B. et al. Mimicking the extracellular world: From natural to fully synthetic matrices utilizing supramolecular biomaterials. *Nanoscale* 2024, 16, 16290–16312.

[246] Sakthiabirami, K.; Park, Y.; Jo, S. K.; Kim, M. H.; Song, J. H.

Decellularized extracellular matrix (dECM) in tendon regeneration: A comprehensive review. *Adv. Healthc. Mater.* 2025, e03676.