Proceedings of ICBioMed 2026 Symposium: Biomedical Engineering and Smart Medicine
DOI: 10.54254/2753-8818/2026.HZ38779

Research Progress on Functional Hydrogels for Regulating Stem Cell Fate and Tissue Regeneration

Jiangweiyi Wang

College of Animal Science and Technology, China Agricultural University, Beijing, China
2727037295@qq.com

Abstract. Functional hydrogels provide hydrated, tunable, and biomimetic matrices for regulating stem cell behavior during tissue regeneration. Their physicochemical properties can be designed to approximate native extracellular matrices, including stiffness, viscoelasticity, degradability, porosity, adhesive ligand presentation, growth factor retention, ionic conductivity, and responsiveness to biochemical or physical stimuli. Recent studies have shifted hydrogel design from passive cell delivery toward dynamic regulation of stem cell fate, endogenous cell recruitment, paracrine signaling, immune modulation, and tissue-specific remodeling. Hydrogel-mediated control of stem cells is mainly achieved through integrin-dependent adhesion, cytoskeletal tension, YAP/TAZ and focal adhesion signaling, lineage-specific morphogen delivery, extracellular vesicle retention, macrophage polarization, angiogenesis, and matrix remodeling. These mechanisms are increasingly applied in bone, cartilage, intervertebral disc, neural, cardiovascular, cutaneous, corneal, and reproductive tissue repair. This review summarizes recent progress in the construction of functional hydrogels, microenvironmental biomimicry, molecular regulation of stem cell fate, and tissue regeneration applications. The discussion emphasizes evidence from 2021 to 2026 and focuses on design principles that connect material properties with stem cell responses and regenerative outcomes.

Keywords: Functional hydrogel, Stem cell fate, Tissue regeneration, Biomimetic microenvironment, Mechanotransduction

1. Introduction

Stem cell-based regeneration depends on more than the intrinsic differentiation capacity of transplanted or endogenous cells. In injured tissues, stem cells encounter altered extracellular matrix composition, abnormal stiffness, inflammatory cytokines, oxidative stress, hypoxia, insufficient vascularization, and disrupted paracrine communication. These signals can weaken cell survival, impair lineage commitment, and drive fibrotic repair rather than functional tissue reconstruction. Functional hydrogels have become a central material platform because they can localize cells and instruct host responses while reproducing selected features of the stem cell niche [1].

Hydrogels are polymer networks containing high water content and can be prepared from natural polymers, synthetic polymers, supramolecular assemblies, decellularized extracellular matrix, peptides, proteins, or hybrid systems. Their value in regenerative medicine lies in the capacity to

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2026.HZ38779

tune mechanical properties, degradation behavior, ligand density, pore architecture, drug release, electrical conductivity, and responsiveness to enzymes, pH, redox signals, light, magnetic fields, or ultrasound. Hydrogels are allowed to regulate stem cell adhesion, migration, proliferation, differentiation, and paracrine activity in a spatially and temporally controlled manner by these properties [2].

The field has moved from simple encapsulation matrices toward instructive microenvironments,which indicateds that under cell-generated forces,dynamic hydrogels can be stiffened, softened, self-heaedl, or remodeled. Decellularized matrix hydrogels provide tissue-specific biochemical motifs. Exosome-loaded hydrogels prolong paracrine signaling. Conductive or piezoelectric hydrogels deliver bioelectrical cues to neural, cardiac, and cartilage tissues. Immunomodulatory hydrogels regulate macrophages, fibroblasts, and inflammatory communication during repair [3]. These material functions are relevant because stem cell fate is sensitive to the coordinated presentation of mechanical, biochemical, and immune signals rather than to any single material parameter.

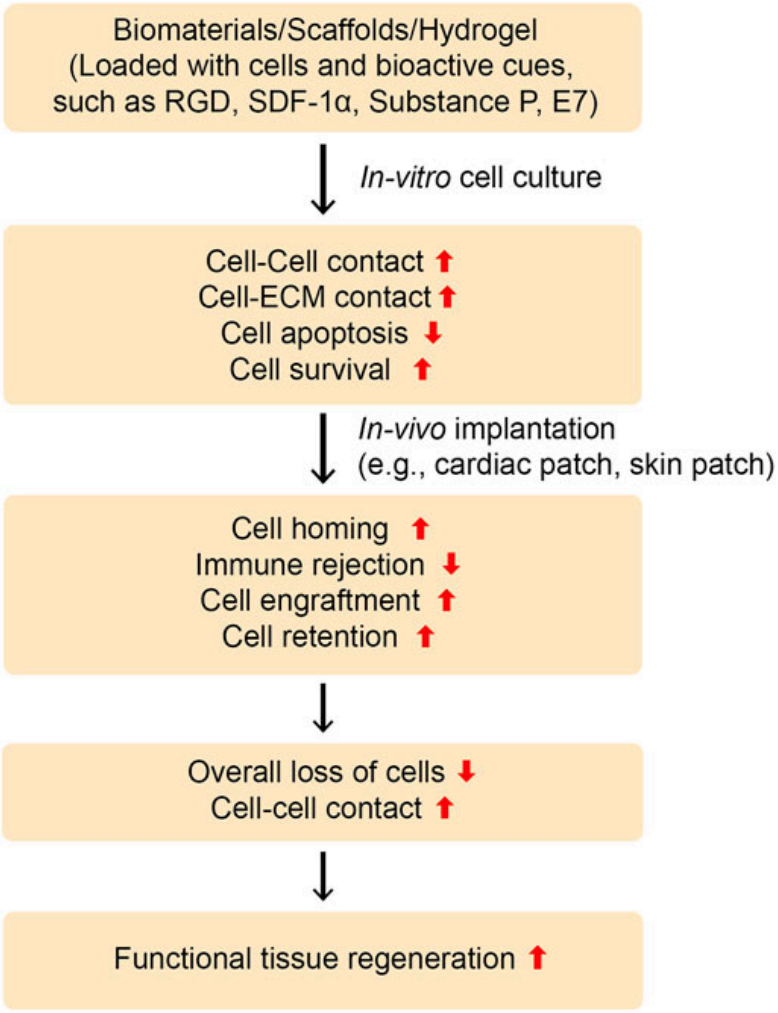


Figure 1. Mechanobiological regulation of stem cell therapy by biomaterial-mediated control of survival, retention, immune, response, and tissue regeneration [4]

The material-to-cell logic outlined above is summarized schematically in Figure 1, which links hydrogel-mediated mechanobiological support with cell survival, retention, and functional tissue

DOI: 10.54254/2753-8818/2026.HZ38779

regeneration [4].

A review of functional hydrogels therefore needs to connect material design with stem cell biology and tissue-level repair. The relevant evidence cannot be interpreted only by hydrogel composition or by short-term differentiation markers. Effective systems usually combine cytocompatible gelation, controllable degradation, transport of oxygen and nutrients, mechanical compatibility with the target tissue, and defined biological activity. In this context, stem cell fate includes survival, quiescence, activation, proliferation, lineage specification, maturation, and paracrine reprogramming of host cells. Tissue regeneration further requires vascularization, innervation, immune resolution, matrix organization, and restoration of structural function.

This review summarizes recent progress on functional hydrogels for regulating stem cell fate and tissue regeneration. The discussion follows the required structure of niche biomimicry, physical microenvironment regulation, biochemical and dynamic signal construction, mechanisms of adhesion and mechanotransduction, intracellular signaling, paracrine remodeling, and tissue-specific applications. The included references are restricted to publications from 2021 to 2026, with emphasis on experimentally supported links between hydrogel design, stem cell response, and tissue repair.

2. Construction basis and microenvironmental biomimicry of functional hydrogels

Functional hydrogel construction begins with an analysis of the target regenerative niche. Native tissues differ in matrix stiffness, fiber alignment, biochemical ligand distribution, oxygen tension, ionic environment, immune cell composition, and remodeling kinetics. A hydrogel intended for cartilage repair requires different mechanical and diffusion properties from one designed for neural implantation or cutaneous wound healing. Design therefore requires matching material cues with the developmental and injury-specific requirements of the resident or delivered stem cells.

2.1. Stem cell niches and biomimetic foundations

A stem cell niche integrates extracellular matrix molecules, soluble factors, neighboring cells, mechanical loading, oxygen availability, and immune signals. Hydrogels can mimic parts of this niche by providing three-dimensional confinement, matrix ligands, degradable networks, and local retention of morphogens or extracellular vesicles. Hydrogel systems for stem cell expansion illustrate this principle. Hematopoietic stem cells, mesenchymal stromal cells, and pluripotent stem cells each require different combinations of stiffness, ligand presentation, and diffusional access to maintain self-renewal or enter differentiation [5].

Tissue-derived extracellular matrix hydrogels provide biochemical information that synthetic networks do not fully reproduce. Decellularized disc hydrogels promoted tissue-specific differentiation of human bone marrow mesenchymal stem cells, indicating that matrix composition can bias lineage behavior toward a target tissue phenotype [6]. Nucleus pulposus matrix hydrogel microspheres have also been used to combine exogenous stem cell therapy with endogenous repair signals for disc regeneration [7]. These approaches show that biomimicry requires more than matching stiffness. Matrix-bound biochemical motifs, proteoglycan content, degradation products, and tissue-specific architecture can alter stem cell interpretation of the material environment.

Synthetic and hybrid hydrogels offer a complementary route because their composition can be controlled with higher reproducibility. Polyethylene glycol, hyaluronic acid, gelatin methacryloyl, alginate, fibrin, collagen, peptide amphiphiles, and supramolecular polymers can be modified with adhesive sequences, protease-cleavable motifs, mineral components, or affinity-binding domains.

DOI: 10.54254/2753-8818/2026.HZ38779

This modularity permits systematic analysis of single variables, including ligand density or relaxation time, while hybridization with extracellular matrix components increases biological relevance. The central design issue is not whether a hydrogel is natural or synthetic, but whether its molecular architecture can present the correct combination of niche cues at the correct regenerative stage.

2.2. Biomimetic regulation of the physical microenvironment

The physical microenvironment includes elastic modulus, viscoelastic relaxation, stress stiffening, porosity, topography, anisotropy, and confinement. Stem cells convert these properties into intracellular signals through integrin adhesion, focal adhesion maturation, cytoskeletal contractility, nuclear deformation, and mechanosensitive transcription. Muscle stem cell studies using engineered hydrogels have shown that soft matrices resembling healthy muscle support activation and expansion, whereas stiff fibrotic-like matrices impair proliferative and myogenic progression [8]. Hydrogels that stiffen or soften on demand further demonstrated that muscle stem cells can retain mechanical memory after exposure to high stiffness [9].

Three-dimensional hydrogel mechanics also differs from two-dimensional substrate stiffness. Dynamic supramolecular hydrogels with locally stiffened network domains can promote spreading, focal adhesion kinase activation, YAP signaling, osteogenic differentiation, and bone regeneration while retaining cell-adaptable network properties [3]. Viscoelastic hydrogels regulate adipose-derived mesenchymal stem cells in nucleus pulposus regeneration, and matrix viscoelasticity can influence macrophage metabolic switching during osteogenesis [9]. Physical biomimicry therefore requires control over time-dependent mechanics and local force transmission rather than bulk modulus alone.

2.3. Construction of biochemical signals and dynamic microenvironments

Biochemical regulation is achieved through adhesive peptides, matrix proteins, growth factors, cytokines, minerals, metabolites, nucleic acids, extracellular vesicles, and tissue-specific decellularized components. Hydrogels can retain these signals at injury sites and regulate their release through diffusion, degradation, affinity binding, or stimulus-responsive network changes. Pulp regeneration studies have used hydrogel-mediated sustained delivery of tissue-specific developmental signals, while mineralized hydrogel microenvironments have been used to guide osteogenesis [10]. Metabolite-coordinated biohydrogels can also augment cranial bone regeneration through immune cell recruitment and histone acetylation-mediated osteogenesis [11].

Dynamic microenvironments allow hydrogels to adapt to cell behavior or external stimulation. Self-healing injectable hydrogels flow under shear and recover their network structure after administration, improving minimally invasive delivery and defect filling [12]. Stimuli-responsive cell-adhesive micromaterials embedded in living composite tissues can steer stem cell fate through externally controlled adhesive presentation [13]. Magneto-electric and exosome-loaded hydrogels have been used for remote non-invasive electrical stimulation after spinal cord injury, linking physical stimulation with neuronal differentiation and immunoregulation [14]. These systems move hydrogel design toward active regulation of regeneration rather than static support.

DOI: 10.54254/2753-8818/2026.HZ38779

3. Mechanisms by which functional hydrogels regulate stem cell fate and tissue regeneration

Hydrogels regulate stem cell fate through combined effects on adhesion, mechanotransduction, intracellular signaling, paracrine activity, immune state, and vascular remodeling. The same material property may produce different outcomes depending on cell type and tissue context. Mesenchymal stem cells, neural stem cells, epidermal stem cells, muscle stem cells, and pluripotent stem cell derivatives respond to distinct mechanical and biochemical ranges. Mechanistic interpretation should therefore connect a defined hydrogel feature with a measurable stem cell response.

3.1. Cell adhesion and mechanotransduction

Cell adhesion provides the first interface between stem cells and hydrogels. Integrin engagement with RGD peptides, collagen, laminin, fibronectin, or tissue-derived extracellular matrix motifs initiates focal adhesion assembly and cytoskeletal tension. These events regulate FAK, Src, RhoA, Rac, myosin contractility, YAP/TAZ localization, and nuclear mechanics. In three-dimensional matrices,whether cells can spread, generate traction, and remodel their surroundings is determined by ligand tethering, stress relaxation, degradability, and pore structure. With poorly accessible ligands, hydrogels can maintain cell viability while failing to provide sufficient mechanical feedback for lineage specification.

Mechanotransduction studies have clarified why dynamic mechanics matter. Muscle stem cells exposed to stiff hydrogels develop a persistent mechanical memory associated with RhoA activity and altered YAP-related signaling, and later softening does not fully rescue myogenic progression [8]. Mechanically heterogeneous hydrogels with cell-programmed network restructuring can promote tissue regeneration through mechano-epigenetic modulation [15]. These observations indicate that stem cells record mechanical history, not only current stiffness. Hydrogel design should therefore consider when mechanical cues are presented during activation, expansion, lineage commitment, and maturation.

Also,adhesion and mechanics regulate nuclear organization. The very force can be transmitted by cytoskeletal tension to the nucleus through linker of nucleoskeleton and cytoskeleton complexes, thereby changing chromatin accessibility, transcription factor residence time, and lineage-associated gene expression. In soft and stress-relaxing matrices, cells may adopt rounded morphologies with reduced actomyosin tension, which can support chondrogenic or adipogenic tendencies depending on biochemical context. In stiffer or locally reinforced networks, increased spreading and focal adhesion maturation can promote osteogenic or myogenic programs. These relationships are not linear because excessive stiffness may induce senescence, fibrotic activation, or impaired differentiation. Therefore,functional hydrogels are increasingly designed to provide permissive early survival conditions followed by stronger instructive cues during maturation.

3.2. Biochemical signals and intracellular signaling regulation

Canonical developmental pathways and stress-responsive signaling can be regulated by biochemical cues which are delivered by hydrogels. Wnt, Notch, BMP, TGF-beta, FGF, VEGF, AMPK, ERK, AKT, and NRF-related pathways have been implicated in lineage specification, survival, angiogenesis, and matrix deposition. Chirality-regulated hydrogels have been reported to influence stem cell fate and corneal epithelial regeneration through Notch pathway modulation [16]. Brain extracellular matrix hydrogels incorporating melatonin enhanced neural stem cell mitochondrial

DOI: 10.54254/2753-8818/2026.HZ38779

metabolism and neuroregeneration through an AMPK-PGC-1alpha-NRF1/TFAM axis after spinal cord injury [17].

Biochemical regulation is often coupled with matrix remodeling. Degradable hydrogels allow cells to create pericellular space, deposit new extracellular matrix, and change local ligand availability. Growth factor and morphogen release can be timed to match phases of repair, including early immunomodulation, stem cell recruitment, lineage commitment, and tissue maturation. In osteochondral repair, functionally graded hydrogels with opposing biochemical cues are designed to reproduce the transition between cartilage and subchondral bone [18]. This principle is relevant for interfaces because abrupt material uniformity rarely matches native tissue gradients.

3.3. Paracrine effects and regenerative microenvironment remodeling

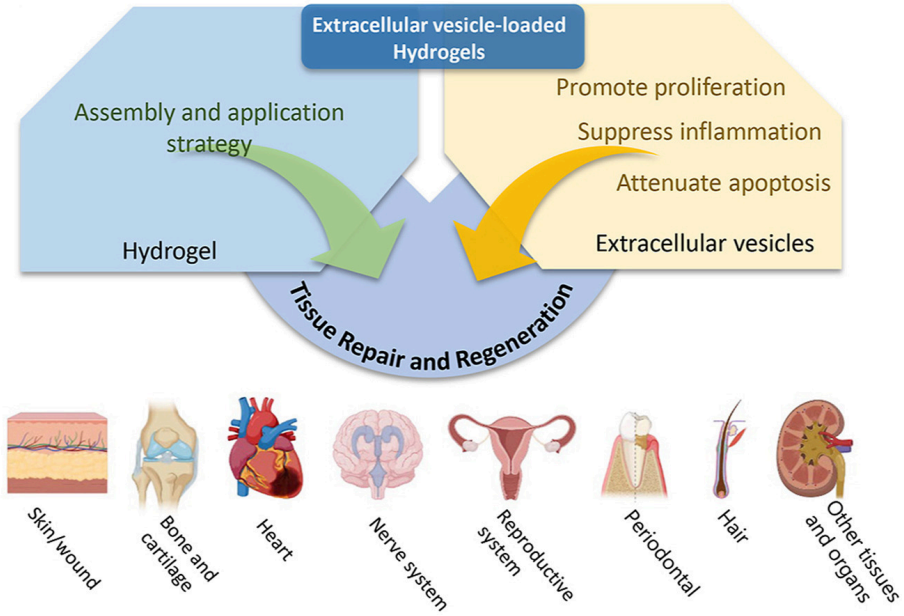


Figure 2. Extracellular vesicle-loaded hydrogels provide matrix support and sustained paracrine delivery for tissue repair and regeneration [19]

Stem cells contribute to regeneration through paracrine signaling as well as direct differentiation. Extracellular vesicles, cytokines, growth factors, microRNAs, and metabolites released by stem cells regulate immune cells, endothelial cells, fibroblasts, and resident progenitors. Hydrogels can localize these signals and protect extracellular vesicles from rapid clearance. Extracellular vesicle-loaded hydrogels have been reviewed as tissue repair platforms because they combine sustained paracrine delivery with defect-adapted matrix support [19].

This paracrine delivery concept is illustrated in Figure 2, where extracellular vesicles are retained in hydrogel networks to combine sustained signal release with regenerative matrix support [19].

Paracrine remodeling is closely linked to inflammation. Hydrogel crosslinking chemistry modulates macrophages, fibroblasts, and their communication during wound healing [20]. Exosome-functionalized hydrogels can improve cartilage repair by regulating bone marrow mesenchymal stem cell migration and differentiation [21]. GelMA/HAMA hydrogels functionalized with extracellular vesicles have promoted facial nerve recovery through inflammatory microenvironment regulation [22]. These findings indicate that functional hydrogels can regulate stem cell fate indirectly by reshaping the immune and stromal environment in which endogenous repair occurs.

DOI: 10.54254/2753-8818/2026.HZ38779

This indirect regulation is particularly relevant in chronic or poorly vascularized defects, where transplanted cells often experience nutrient limitation and inflammatory stress before stable engraftment. A hydrogel that reduces oxidative injury, recruits pro-regenerative immune cells, or promotes endothelial invasion may improve stem cell function even without direct differentiation induction. Conversely, a material that releases potent morphogens but provokes persistent foreign-body inflammation may fail to support durable repair. Current studies increasingly evaluate macrophage polarization, fibroblast activation, endothelial sprouting, and extracellular matrix deposition together with stem cell markers. Such integrated assessment is required because regenerative outcome emerges from communication among implanted cells, endogenous progenitors, immune cells, stromal cells, and the hydrogel network.

4. Applications of functional hydrogel-mediated stem cell fate regulation in tissue regeneration

Tissue-specific applications of functional hydrogels reflect the diversity of regenerative microenvironments. Bone and cartilage require control of mineralization, load-bearing mechanics, chondrogenesis, osteogenesis, and angiogenesis, and recent studies have applied whitlockite-containing, self-curing, nanoplatelet vesicle-loaded, and gradient hydrogel systems to these requirements [23]. Neural and cardiovascular tissues require electrical, metabolic, and inflammatory regulation. Skin, cornea, and other epithelial tissues require barrier restoration, epithelial stem cell maintenance, vascularization, and immune balance. Hydrogels are adaptable to each context because network chemistry and biological payloads can be adjusted without abandoning the hydrated matrix format.

4.1. Bone and cartilage regeneration

Bone regeneration requires osteogenic differentiation, vascular invasion, immune regulation, and matrix mineralization. Hydrogels support these processes by delivering mesenchymal stem cells, recruiting endogenous progenitors, presenting mineral ions, or providing matrix cues that regulate osteogenic transcription. Whitlockite-enabled hydrogels have been developed for craniofacial bone regeneration [24]. Injectable and self-curing single-component hydrogels have supported stem cell encapsulation and in vivo bone regeneration [25]. Sequential simulation of regeneration-specific microenvironments using scaffolds loaded with nanoplatelet vesicles has also enhanced bone regeneration, indicating that temporally organized signals may better reproduce natural repair [26].

Cartilage and osteochondral regeneration require chondrogenic differentiation, maintenance of hyaline cartilage matrix, integration with subchondral bone, and control of inflammation. Gradient hydrogels have been used to optimize niche cues for cell-based cartilage regeneration, showing that mesenchymal stem cells and chondrocytes can prefer different stiffness ranges for matrix deposition [27]. Cartilage lacuna-inspired microcarriers, cartilage-inspired artificial stem cell niches, alkaline phosphatase gradient-driven stiffness-adaptive hydrogels, and dopamine-functionalized pre-chondrogenic hydrogels have extended this approach toward more tissue-specific cartilage repair [28].

4.2. Neural and cardiovascular regeneration

Neural regeneration requires permissive matrices for cell survival, axonal growth, synaptic maturation, immune regulation, and electrical activity. Custom-engineered hydrogels have been used to deliver human induced pluripotent stem cell-derived neurons into injured cervical spinal cord

DOI: 10.54254/2753-8818/2026.HZ38779

tissue [29]. Magneto-electric exosome-loaded hydrogels and melatonin-incorporated brain extracellular matrix hydrogels provide examples in which hydrogel function extends to electrical stimulation, mitochondrial metabolic regulation, and immune modulation [20]. Conductive injectable silk and PEDOT PSS hydrogels have also been used to promote neural network formation, supporting the relevance of electroactive hydrogel design for neural repair [30].

Cardiovascular regeneration requires retention of therapeutic cells, attenuation of inflammatory damage, electrical coupling, vascularization, and mechanical integration with beating tissue. Injectable hydrogels can increase cell residence at myocardial injury sites and provide local mechanical support. Cardiac tissue engineering studies have explored shear-thinning nanocomposite hydrogels, collagen-hyaluronic acid conductive hydrogels containing bacterial cellulose and gold nanoparticles, and broader biomaterials-based cell therapy strategies [29]. Although complete myocardial regeneration remains difficult, hydrogel systems can improve the local environment for delivered cells and paracrine factors.

The neural and cardiovascular fields illustrate why functional hydrogels must be evaluated against tissue-specific physiology. In the spinal cord, hydrogel stiffness, degradation rate, and anisotropic guidance influence axonal extension and glial scar interaction, whereas inappropriate swelling or prolonged persistence can compress fragile tissue. In myocardium, injected materials must withstand repetitive deformation and avoid electrical isolation of regenerating regions. Conductivity alone is insufficient if the network lacks fatigue resistance, vascular compatibility, or controlled degradation. For both tissue types, hydrogel-mediated stem cell therapy is moving toward combined regulation of electrical activity, mitochondrial metabolism, inflammation, and paracrine signaling rather than isolated cell replacement.

4.3. Skin, cornea, and other tissue regeneration

Skin repair requires rapid closure, restoration of epidermal architecture, vascularization, and balanced inflammation. Composite hydrogels designed to reconstruct epidermal rete ridges have been used to enhance signaling pathways that maintain the epidermal stem cell niche [30]. Hydrogel crosslinking can also regulate macrophage-fibroblast communication during wound healing, linking material chemistry with scar formation and regenerative quality [20]. These studies demonstrate that cutaneous hydrogels should be evaluated by epithelial organization and stromal immune behavior rather than closure rate alone.

Corneal and other specialized epithelial tissues require transparent, tissue-compatible, and lineage-instructive matrices. Chirality-regulated hydrogels have promoted corneal epithelial regeneration through Notch-associated stem cell fate regulation [16]. Biomolecule-based hydrogels have been reviewed as delivery systems for limbal stem cell transplantation, reflecting the need for epithelial progenitor support without compromising optical clarity [31]. Endometrial regeneration, dental pulp regeneration, and disc repair further show that tissue-specific hydrogels can combine stem cell delivery, endogenous recruitment, angiogenesis, immune regulation, and extracellular matrix remodeling [32].

The tissue-specific delivery requirement in epithelial repair is further illustrated in Figure 3, which summarizes hydrogel-assisted biomolecule delivery for limbal stem cell transplantation and corneal regeneration [31].

DOI: 10.54254/2753-8818/2026.HZ38779

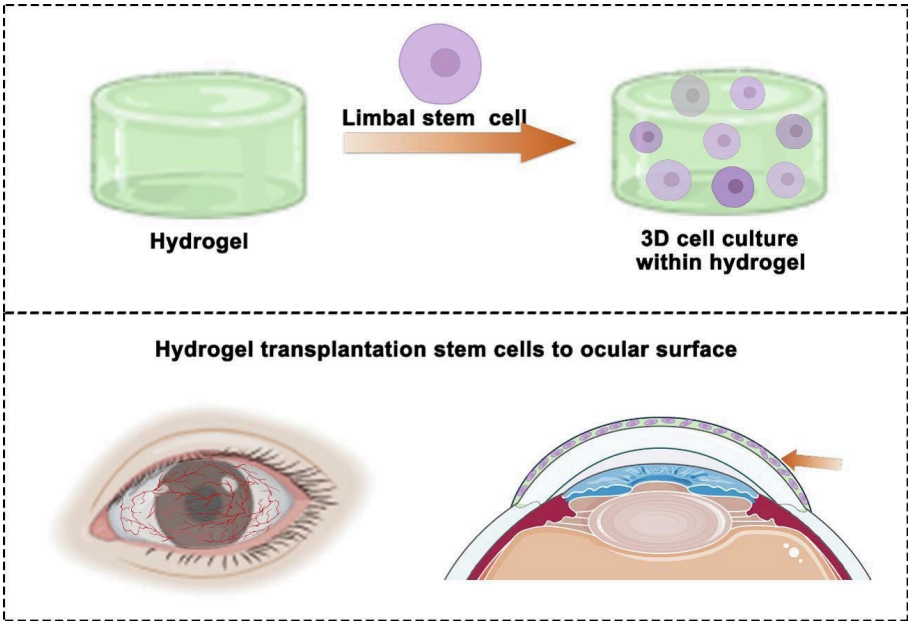


Figure 3. Biomolecule-based hydrogel delivery supports limbal stem cell transplantation and corneal surface regeneration [31]

5. Challenges and outlook

Functional hydrogels have established a strong mechanistic basis for regulating stem cell fate and tissue regeneration, but several barriers remain before broad clinical translation. Material complexity can improve biological instruction while increasing manufacturing difficulty, batch variability, regulatory burden, and uncertainty about degradation products. Stem cell responses are also highly context-dependent. A stiffness range that supports myogenesis may not support chondrogenesis, and a hydrogel that enhances immune activation during infection control may aggravate inflammatory injury in another tissue. Design rules must therefore be tissue-specific and cell-type-specific.

Future hydrogel development should focus on measurable links between material properties and biological outcomes. Mechanical parameters need to include viscoelasticity, stress relaxation, local stiffness heterogeneity, degradation, and cell-mediated remodeling rather than static elastic modulus alone. Biochemical evaluation should quantify ligand density, release kinetics, extracellular vesicle stability, morphogen gradients, and immune mediator profiles. Single-cell sequencing, spatial transcriptomics, proteomics, live-cell mechanobiology, and in vivo imaging can help distinguish direct stem cell fate regulation from indirect effects mediated by macrophages, endothelial cells, or fibroblasts.

Clinical translation will require simpler but mechanistically defined systems. Injectable and self-healing hydrogels are attractive for irregular defects and minimally invasive treatment, whereas printed or prefabricated hydrogels may be more suitable for tissues requiring anisotropy or layered architecture. Cell-free hydrogels that recruit endogenous stem cells or deliver extracellular vesicles may avoid some manufacturing challenges of cell transplantation, but their potency assays need stronger standardization. A mature hydrogel therapy should define the target stem cell population, material cue, molecular pathway, tissue repair endpoint, degradation profile, and safety window in the same development plan.

Functional hydrogels now provide a practical means to connect biomaterials engineering with stem cell biology. Their future value will depend on reducing unnecessary material complexity while

DOI: 10.54254/2753-8818/2026.HZ38779

preserving instructive control over adhesion, mechanics, biochemical signaling, paracrine activity, and immune remodeling. When these parameters are aligned with the biology of a specific tissue, hydrogels can move from passive carriers toward regenerative microenvironments capable of directing endogenous and transplanted stem cells toward functional repair.

References

[1] Vo TN, Shah SR, Lu S, et al. Injectable dual-gelling cell-laden composite hydrogels for bone tissue engineering. *Biomaterials* 2016.

[2] Liu G, Zhou Y, Zhang X, Guo S. Advances in hydrogels for stem cell therapy: regulation mechanisms and tissue engineering applications. *Journal of Materials Chemistry B* 2022.

[3] Yuan W, Wang H, Fang C, et al. Microscopic local stiffening in a supramolecular hydrogel network expedites stem cell mechanosensing in 3D and bone regeneration. *Materials Horizons* 2021.

[4] Shafiq M, Ali O, Han S-B, Kim D-H. Mechanobiological Strategies to Enhance Stem Cell Functionality for Regenerative Medicine and Tissue Engineering. *Frontiers in Cell and Developmental Biology* 2021.

[5] Yin S, Cao Y. Hydrogels for Large-Scale Expansion of Stem Cells. *Acta Biomaterialia* 2021.

[6] Peng Y, Qing X, Lin H, et al. Decellularized Disc Hydrogels for hBMSCs tissue-specific differentiation and tissue regeneration. *Bioactive Materials* 2021.

[7] Peng Y, Chen X, Zhang Q, et al. Enzymatically Bioactive Nucleus Pulposus Matrix Hydrogel Microspheres for Exogenous Stem Cells Therapy and Endogenous Repair Strategy to Achieve Disc Regeneration. *Advanced Science* 2023.

[8] Madl CM, Wang YX, Holbrook CA, et al. Hydrogel biomaterials that stiffen and soften on demand reveal that skeletal muscle stem cells harbor a mechanical memory. *Proceedings of the National Academy of Sciences of the United States of America* 2024.

[9] Tao D, Wang H, Chang S, et al. Matrix Viscoelasticity Orchestrates Osteogenesis via Mechanotransduction Mediated Metabolic Switch in Macrophages. *Advanced Healthcare Materials* 2025.

[10] Xie Z, Zhan P, Zhang X, et al. Providing biomimetic microenvironment for pulp regeneration via hydrogel-mediated sustained delivery of tissue-specific developmental signals. *Materials Today Bio* 2024.

[11] Liu T, You Z, Shen F, et al. Tricarboxylic Acid Cycle Metabolite-Coordinated Biohydrogels Augment Cranial Bone Regeneration Through Neutrophil-Stimulated Mesenchymal Stem Cell Recruitment and Histone Acetylation-Mediated Osteogenesis. *ACS Applied Materials & Interfaces* 2024.

[12] Bertsch P, Diba M, Mooney DJ, Leeuwenburgh SCG. Self-Healing Injectable Hydrogels for Tissue Regeneration. *Chemical Reviews* 2022.

[13] Kamperman T, Willemen NGA, Kelder C, et al. Steering Stem Cell Fate within 3D Living Composite Tissues Using Stimuli-Responsive Cell-Adhesive Micromaterials. *Advanced Science* 2023.

[14] Liu W, Liu Q, Li Z, et al. Multifunctional magneto-electric and exosome-loaded hydrogel enhances neuronal differentiation and immunoregulation through remote non-invasive electrical stimulation for neurological recovery after spinal cord injury. *Bioactive Materials* 2025.

[15] Ling Q, Li H, Zhao J, et al. Mechanically heterogeneous hydrogel with cell-programmed network restructuring promotes tissue regeneration by mechano-epigenetic modulation. *Nature Communications* 2026.

[16] Li S, Zhao Y, Chen J, et al. Chirality Regulates Stem Cell Fate and Promotes Corneal Epithelial Regeneration via Manipulating Notch Pathway. *Advanced Science* 2025.

[17] Wei R, Mei Q, Zhou T, et al. Melatonin-incorporated brain extracellular matrix hydrogel enhances NSCs mitochondrial metabolism to promote neuroregeneration via the AMPK-PGC-1α-NRF1/TFAM axis after spinal cord injury. *Bioactive Materials* 2026.

[18] Mahajan A, Zaidi ZS, Shukla A, Saxena R, Katti DS. Functionally graded hydrogels with opposing biochemical cues for osteochondral tissue engineering. *Biofabrication* 2024.

[19] Ju Y, Hu Y, Yang P, Xie X, Fang B. Extracellular vesicle-loaded hydrogels for tissue repair and regeneration. *Materials Today Bio* 2022.

[20] Butenko S, Nagalla RR, Guerrero-Juarez CF, et al. Hydrogel crosslinking modulates macrophages, fibroblasts, and their communication, during wound healing. *Nature Communications* 2024.

[21] Pei L, Wang Y, Ye M, et al. Exosome-Functionalized Hydrogels Improve Cartilage Repair by Modulating BMSCs Migration and Differentiation. *ACS Applied Materials & Interfaces* 2025.

[22] Chen C, Zhang Y, Zhang L, et al. Exosome-functionalized photocrosslinked GelMA/HAMA hydrogel promotes facial nerve recovery via inflammatory microenvironment regulation. *Bioactive Materials* 2026.

DOI: 10.54254/2753-8818/2026.HZ38779

[23] Pouraghaei Sevari S, Kim JK, Chen C, et al. Whitlockite-Enabled Hydrogel for Craniofacial Bone Regeneration. *ACS Applied Materials & Interfaces* 2021.
[24] Ding SL, Zhao XY, Xiong W, et al. Cartilage Lacuna-Inspired Microcarriers Drive Hyaline Neocartilage Regeneration. *Advanced Materials* 2023.
[25] Zhou Z, Hou Y, Yao Z, et al. Artificial human stem cell niche created in cartilage-inspired hydrogel for enhanced articular cartilage regeneration. *Biomaterials* 2026.
[26] Gao Y, Zhuang Y, Liu E, Chang F, Ding J, Chen X. Endogenous alkaline phosphatase gradient-driven stiffness-adaptive hydrogel regulates stem cell fate for osteochondral repair. *Biomaterials* 2026.
[27] Zhu Q, Zhu L, Lang J, et al. Dopamine-functionalized bioinspired pre-chondrogenic hydrogel for cell-free cartilage regeneration. *Journal of Controlled Release* 2025.
[28] Doulames VM, Marquardt LM, Hefferon ME, et al. Custom-engineered hydrogels for delivery of human iPSC-derived neurons into the injured cervical spinal cord. *Biomaterials* 2023.
[29] Fang J, Li JJ, Zhong X, et al. Engineering stem cell therapeutics for cardiac repair. *Journal of Molecular and Cellular Cardiology* 2022.
[30] Shen Z, Liu Z, Sun L, et al. Constructing epidermal rete ridges using a composite hydrogel to enhance multiple signaling pathways for the maintenance of epidermal stem cell niche. *Acta Biomaterialia* 2023.
[31] Wang F, Xu Y, Zhou Q, Xie L. Biomolecule-based hydrogels as delivery systems for limbal stem cell transplantation: A review. *International Journal of Biological Macromolecules* 2024.
[32] Zhang D, Du Q, Li C, et al. Functionalized human umbilical cord mesenchymal stem cells and injectable HA/Gel hydrogel synergy in endometrial repair and fertility recovery. *Acta Biomaterialia* 2023.