http://dx.doi.org/10.1097/mm9.0000000000000020

MedMat

Perspective

OPEN

Application of microenvironment biomimetic materials in spinal cord injury and future prospects

Wenzhao Wang[a,b], Mingjie Sun[a,c], Zhengdong Zhang[d], Sen Guo[e], Haijian Sun[f,*], Zhijian Wei[b,*], Bin Ning[a,g,*]

1. Introduction

Spinal cord injury (SCI) represents a major challenge in modern medicine due to its complex pathophysiology and inherently limited endogenous repair capacity. Primary physical damage rapidly triggers a cascade of complex secondary injuries, including severe inflammatory responses, disruption of the blood–spinal cord barrier, demyelination, formation of fibrotic and glial scars, and extensive expression of inhibitory molecules. Collectively, these processes establish a profoundly inhibitory microenvironment detrimental to nerve regeneration.[1]

Over the past decade (2015–2025), bionic biomaterial strategies targeting the complex spinal cord microenvironment have achieved significant breakthroughs in SCI repair (Figure 1). The core strategy of these materials has evolved beyond mere physical filling; they now actively regulate the postinjury pathological microenvironment by mimicking the physical, chemical, and biological characteristics of healthy spinal cord tissue. This approach "induces" endogenous or exogenous cells to achieve nerve regeneration and functional reconstruction, thereby creating a regenerative microenvironment conducive to nerve regeneration.[2]

2. Types and design of biomimetic materials for spinal cord microenvironment

Biomimetic materials facilitate nerve regeneration by emulating the composition and structure of the extracellular matrix (ECM), such as collagen, laminin, and fibronectin. An ideal biomimetic material should match the mechanical properties, degradation rate, and pore structure of native spinal cord tissue to promote cell migration, proliferation, and differentiation.[3]

2.1 Natural biomaterials

Collagen, a primary ECM component, bridges SCI gaps and promotes axon regeneration. Hyaluronic acid, a key constituent of the central nervous system, provides an appropriate microenvironment for neural stem cells via derivatives like hyaluronic acid-methyl methacrylate hydrogel. Chitosan exhibits antibacterial and wound-healing properties. Cross-linked chitosan hydrogels demonstrate efficacy in reducing glial scar formation and promoting neural functional recovery in SCI models.[4]

2.2 Synthetic polymers and composite materials

Poly(lactic-co-glycolic acid) offers controllable degradation rates and excellent mechanical properties. Polycaprolactone's slow degradation profile makes it suitable for long-term nerve regeneration applications. Several polymer-based biomimetic products have advanced to clinical trials. Natural-synthetic hybrid materials, combining the bioactivity of natural components with the mechanical strength of synthetics, are also employed for spinal microenvironment reconstruction. Furthermore, functionalized nanomaterials like graphene, nano-hydroxyapatite, and carbon nanotubes enhance neural signal transmission and regulate neuroimmune balance following modification.[5]

Wenzhao Wang and Mingjie Sun contributed equally to this work.

[a]Department of Orthopedics, Jinan Central Hospital, Shandong University, Jinan, Shandong, China, [b]Department of Orthopedics, Centre for Orthopedics, Qilu Hospital, Advanced Medical Research Institute, Shandong University, Jinan, China, [c]Department of Orthopedic Surgery, Center for Joint Surgery, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China, [d]Department of Orthopedics, The First Affiliated Hospital of Chengdu Medical College, Chengdu, China, [e]Department of Radiology, Juntendo University Graduate School of Medicine, Tokyo, Japan, [f]Department of Orthopaedics, The Second Hospital of Shandong University, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China, [g]Department of Orthopedics, Central Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China.

**Corresponding author: Address: Haijian Sun, Department of Orthopaedics, The Second Hospital of Shandong University, Cheeloo College of Medicine, Shandong University, No. 247, Beiyuan Street, Jinan, Shandong 250033, China. E-mail address: shj94@email.sdu.edu.cn (H. Sun); Zhijian Wei, Department of Orthopedics, Centre for Orthopedics, Qilu Hospital, Advanced Medical Research Institute, Shandong University, No. 107, Wenhua Xi Road, Jinan, Shandong 250012, China. E-mail address: weizhijian2002@126.com (Z. Wei); Bin Ning, Department of Orthopedics, Jinan Central Hospital, Shandong University, No. 105, Jiefang Road, Jinan, Shandong 250013, China. E-mail address:ningbin@sdu.edu.cn (B. Ning).*

MedMat (2025) 2:3

Received: 7 July 2025; Accepted 14 July 2025

Published online 18 July 2025

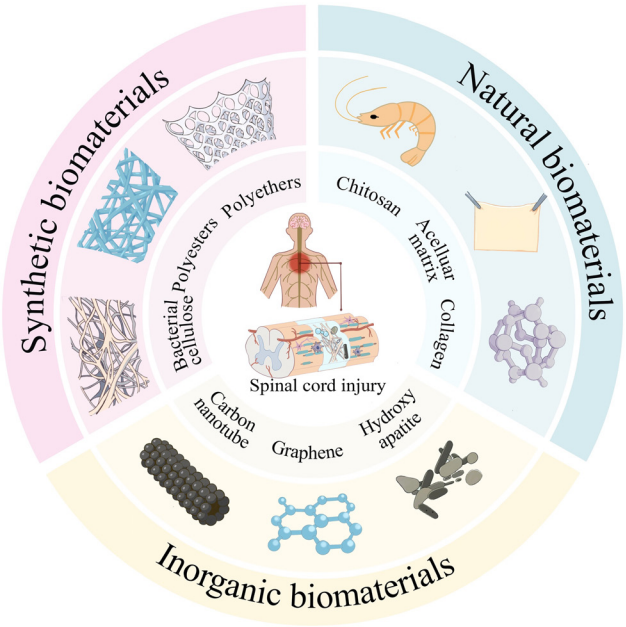

Figure 1. Over the past decade (2015–2025), bionic biomaterial strategies targeting the complex spinal cord microenvironment have achieved significant breakthroughs in SCI repair.

3. Integration of active factors and cells

Controlled-release systems for neurotrophic factors—such as brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and nerve growth factor—provide sustained growth signals to the injury site, promoting nerve regeneration. Delivering cytokines, chemokines (eg, interleukin family), and regenerative factors via material carriers modulates postinjury inflammatory responses and tissue repair processes.[6] Microenvironmental biomimetic scaffolds also provide a three-dimensional (3D) culture environment for cells. Seed cells—including neural stem cells, umbilical cord stem cells, and Schwann cells—engage in nerve regeneration through synergistic interactions with these scaffolds.[7]

4. Core application strategies and progress

Biomimetic microenvironmental materials actively regulate the damaged microenvironment by replicating physical, chemical, and biological signals from healthy spinal cord tissue, thereby supporting nerve regeneration.

4.1 Bionic physical topological structure

Techniques like electrospinning, magnetic field induction, and 3D printing fabricate scaffolds with micro/nanoscale-oriented structures (eg, aligned nanofibers, microchannel hydrogels) that simulate the directionality of nerve fiber bundles in spinal cord white matter. These scaffolds provide "tracks" for regenerating axons, guiding them across the injury site to achieve functional neural circuit reconnection. They also deliver contact guidance cues, promoting the long-distance, directional extension of host and transplanted neurons/neural precursor cells across the injury scar.[8]

4.2 Regulation of the immune microenvironment

Materials with immunomodulatory functions, such as those loaded with M2-type macrophage-inducing factors or antifibrotic drugs or those that regulate the phenotype of microglia/macrophages by utilizing their own physicochemical properties (such as surface chemistry, stiffness)[9] inhibit the activation of proinflammatory (M1 type) macrophages, promote the polarization of anti-inflammatory/repair (M2 type) macrophages, inhibit the excessive activation of pericytes, fibroblasts, and astrocytes to form dense scars, and create a more permissive environment for regeneration.[10]

4.3 Reconstruction of the nutritional microenvironment

Carriers like intelligent hydrogels, microspheres, and nanoparticles enable sustained, gradient, or on-demand release of neurotrophic factors (eg, BDNF, NT-3, glial cell-derived neurotrophic factor [GDNF]) and axon guidance molecules (eg, Netrin-1, sonic hedgehog [Shh] signaling molecule) at the injury site. This provides essential bioactive signals for neuronal survival, axonal growth, and angiogenesis while regulating inflammation, mitigating secondary damage, and guiding precise axonal targeting.[11]

4.4 Conductive and electroactive materials: restoring neural signal conduction

Conductive scaffolds or coatings constructed from conductive polymers (eg, polypyrrole, polyaniline), graphene, or carbon nanotubes bridge disrupted neural pathways to restore signal conduction. Exogenous electrical stimulation further enhances neuronal differentiation, axonal growth, and synaptogenesis.[12]

5. Future research prospects

5.1 Multifunctional integration and intelligence

Given the limited efficacy of single strategies, future biomaterials will be highly integrated platforms capable of simultaneous structural guidance, immune regulation, temporally controlled multifactor release, and electrical signal conduction within a single system. Self-assembling smart materials that trigger drug release or structural changes in response to specific pathological signals are under development. Combining biomimetic materials with physical therapies like electrical stimulation, optogenetics, and magnetic field therapy will yield synergistic effects.[13]

5.2 "4D and 5D bioprinting" and spinal cord organoid technology

High-precision 3D bioprinting is expected to enable scaffolds capable of programmed transformations in both spatial structure (3D) and time (4D). Advancements in functional dimension or free-form surface manipulation (5D) will facilitate full life-cycle design, allowing precise simulation of the spinal cord's dynamic injury-repair process. Scaffolds could initially feature dense structures to suppress inflammation, later transitioning to larger pores promoting cell infiltration and axonal growth. A 4D-designed shape-memory hydrogel scaffold transforms from a linear structure into a spiral configuration triggered by body temperature, conforming closely to the injury cavity and providing axially aligned guidance to promote axonal regeneration. Simultaneously, such scaffolds can be loaded with mesenchymal stem cells via microfluidic printing, enabling their targeted differentiation into neuron-like cells under reactive oxygen species (ROS) stimulation, thereby achieving a closed-loop "sensing-response-repair" system. Spinal cord organoids

show great promise as a potential source for cell transplantation. With reliable and scalable cell sources, and containing multiple synergistic cell types, transplanted organoid fragments can potentially provide replacement neurons, supportive glial cells, and scaffold functions to reconstruct the microenvironment simultaneously, offering greater integrative potential than single-cell-type transplants. Furthermore, spinal cord organoids provide a novel platform for drug discovery and toxicity testing in an environment more closely resembling the human body. Using patient-specific induced pluripotent stem cells (iPSC)-derived spinal cord organoids, disease-in-a-dish models can be established to simulate pathological changes under specific genetic backgrounds or injury conditions, enabling high-throughput screening of candidate drugs that promote neuroprotection, axon regeneration, myelin repair, or inhibit glial scar formation.[14]

5.3 Integration of stem cell therapy and genetic engineering

Biomedical materials will serve as advanced cell delivery vehicles and "in vitro stem cell niches." Material optimization will enable precise control over stem cell fate (survival, differentiation, integration). Coupled with gene editing (eg, clustered regularly interspaced short palindromic repeats [CRISPR]), silencing intrinsic inhibitory genes or enhancing pro-growth gene expression during cell delivery will significantly boost therapeutic potential.[15]

5.4 Collaborative reconstruction of the Neuro-Immune-Vascular network

Future research will emphasize synergistic interactions between neural regeneration, immune modulation, and vascular regeneration. Designing biomaterials that concurrently promote vascular regeneration (nutrient supply) and lymphatic vessel regeneration (clearance of metabolic waste and inflammatory factors) is crucial for establishing a truly healthy regenerative microenvironment.[16] Future material designs must increasingly address clinical requirements, including biodegradability, long-term biocompatibility, scalable manufacturing, personalized integration protocols, and surgical compatibility. Concurrently, developing more precise noninvasive imaging technologies to track material dynamics and repair efficacy in vivo is essential for clinical translation.

Funding

This work was financially supported by the National Natural Science Foundation of China (No. 82402801), Shandong Province Natural Science Foundation (Nos. ZR2023QH321 and ZR2024MH012), Shandong Provincial Education Department Project (No. 2024KJJ078), the Young Talent of Lifting engineering for Science and Technology in Shandong (No. SDAST2025QTA009), and the Open Foundation of Shandong Key Laboratory of Oral Tissue Regeneration (No. SDKQ202503).

Conflicts of interests

The authors declare that they have no conflicts of interest.

Author contributions

W.W. and M.S. conceived, organized, and wrote the manuscript. Z.Z. and S.G. organized and wrote the manuscript. H.S. and Z.W. conceptualization. B.N. conceptualization, funding acquisition, investigation, project administration, resources, and supervision. All authors discussed and approved the final manuscript.

References

[1] Wang W, Liu C, He D, et al. CircRNA CDR1as affects functional repair after spinal cord injury and regulates fibrosis through the SMAD pathway. *Pharmacol Res*. 2024;204:107189.
[2] Cao J, Zhang X, Guo J, et al. An engineering-reinforced extracellular vesicle-integrated hydrogel with an ROS-responsive release pattern mitigates spinal cord injury. *Sci Adv*. 2025;11(14):eads3398.
[3] Qiu C, Sun Y, Li J, et al. A 3D-printed dual driving forces scaffold with self-promoted cell absorption for spinal cord injury repair. *Adv Sci (Weinh)*. 2023;10(33):e2301639.
[4] Sun Z, Chen Z, Yin M, et al. Harnessing developmental dynamics of spinal cord extracellular matrix improves regenerative potential of spinal cord organoids. *Cell Stem Cell*. 2024;31(5):772–787.e11.
[5] Liu M, Zhang W, Han S, et al. Multifunctional conductive and electrogenic hydrogel repaired spinal cord injury via immunoregulation and enhancement of neuronal differentiation. *Adv Mater*. 2024;36(21):e2313672.
[6] Tan Z, Xiao L, Ma J, et al. Integrating hydrogels manipulate ECM deposition after spinal cord injury for specific neural reconnections via neuronal relays. *Sci Adv*. 2024;10(27):eado9120.
[7] Li J, Luo W, Xiao C, et al. Recent advances in endogenous neural stem/progenitor cell manipulation for spinal cord injury repair. *Theranostics*. 2023;13(12):3966–3987.
[8] Koffler J, Zhu W, Qu X, et al. Biomimetic 3D-printed scaffolds for spinal cord injury repair. *Nat Med*. 2019;25(2):263–269.
[9] Ge X, Zhou Z, Yang S, et al. Exosomal USP13 derived from microvascular endothelial cells regulates immune microenvironment and improves functional recovery after spinal cord injury by stabilizing IkappaBalpha. *Cell Biosci*. 2023;13(1):55.
[10] Bhattacharjee M, Escobar Ivirico JL, Kan H-M, et al. Injectable amnion hydrogel-mediated delivery of adipose-derived stem cells for osteoarthritis treatment. *Proc Natl Acad Sci U S A*. 2022;119(4):e2120968119.
[11] Zhang D, Wang W, Han S, et al. Nano-fiber/net artificial bionic dura mater promotes neural stem cell differentiating by time sequence external-oral administration to repair spinal cord injury. *Theranostics*. 2025;15(6):2579–2596.
[12] Gao C, Li Y, Liu X, et al. 3D bioprinted conductive spinal cord biomimetic scaffolds for promoting neuronal differentiation of neural stem cells and repairing of spinal cord injury. *Chem Eng J*. 2023;451:138788.
[13] Ma DZ, Fu C, Li F, et al. Functional biomaterials for modulating the dysfunctional pathological microenvironment of spinal cord injury. *Bioact Mater*. 2024;39:521–543.
[14] Roth JG, Brunel LG, Huang MS, et al. Spatially controlled construction of assembloids using bioprinting. *Nat Commun*. 2023;14(1):4346.
[15] Alves CRR, Ha LL, Yaworski R, et al. Optimization of base editors for the functional correction of SMN2 as a treatment for spinal muscular atrophy. *Nat Biomed Eng*. 2024;8(2):118–131.
[16] Li YH, Zhang Q, Liu Z, et al. Microenvironments-modulated biomaterials enhance spinal cord injury therapy. *Adv Funct Mater*. 2024;34(46).

How to cite this article: Wang W, Sun M, Zhang Z, Guo S, Sun H, Wei Z, Ning B. Application of microenvironment biomimetic materials in spinal cord injury and future prospects. MedMat 2025;2(3):e00020. doi: 10.1097/mm9.0000000000000020