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REVIEW

Current Advancements in the Arsenal for Spinal Cord Injury Repair: Novel Drug Formulations

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Abstract: Spinal cord injury (SCI) is a devastating condition associated with high rates of disability and mortality, as well as a significant financial burden. The current clinical interventions have limited therapeutic effectiveness, primarily due to relentless secondary injury cascades and the inherent challenge of neuronal circuit regeneration. Advances in biomaterials and fabrication technologies have led to the emergence of various novel formulations designed to specifically address these challenges and serve as a high-tech arsenal for researchers. This review delineates the pathophysiological mechanisms underlying SCI and the development of its self-propagating injury cascade. It also provides a comprehensive summary of recent advancements in the development and application of novel drug formulations, highlighting their distinct advantages in interrupting the injury cascade. This review aims to foster the development of more effective therapeutic strategies and ultimately improve therapeutic outcomes for patients with SCI.

Keywords: spinal cord injury, drug delivery systems, tissue regeneration, scaffolds, secondary injury

Background

Spinal cord injury (SCI) refers to an insult to the spinal cord that results in a change in motor, sensory, or autonomic function. In 2021, approximately 574,500 new SCI cases were reported globally, with more than 15.4 million individuals living with SCI, leading to a loss of 4.6 million life-years.[1] The current clinical management of SCI encompasses pre-hospital first aid, the administration of high doses of methylprednisolone, localized hypothermia treatment, combined extramedullary and intramedullary decompression surgeries, rehabilitation training, and others.[2] However, therapeutic outcomes remain suboptimal due to the complex pathophysiology of SCI and the limited regenerative capacity of neural tissues. Patients often face high disability rates, high mortality rates, and high treatment costs.[3] The initial mechanical insult induces immediate tissue damage and ischemia, which subsequently initiates a cascade of secondary pathological processes, including widespread neurotoxicity, ionic imbalance, persistent neuroinflammation, free radical damage, and the demyelination of adjacent neural tissues. Moreover, the intrinsic inability of neurons to regenerate, combined with glial scar formation and the presence of myelin-associated inhibitors, significantly impedes functional recovery.

The progressive elucidation of SCI pathophysiology and progress in biomedical research have led to the development of numerous innovative therapeutic strategies in recent years, including cell therapy, gene therapy, immunotherapy, and targeted molecular interventions. These strategies are designed to enhance axonal regeneration, facilitate remyelination, support neural circuit reorganization, modulate the hostile microenvironment, and exert neuroprotective effects at both the molecular and cellular levels, offering potential for treating SCI.[4] However, the delivery and efficacy of these novel bioactive agents are substantially constrained by multiple barriers inherent to the injured spinal cord. Obstacles such as the inhibitory microenvironment, the blood-spinal cord barrier (BSCB), and the inherent vulnerability of spinal cord

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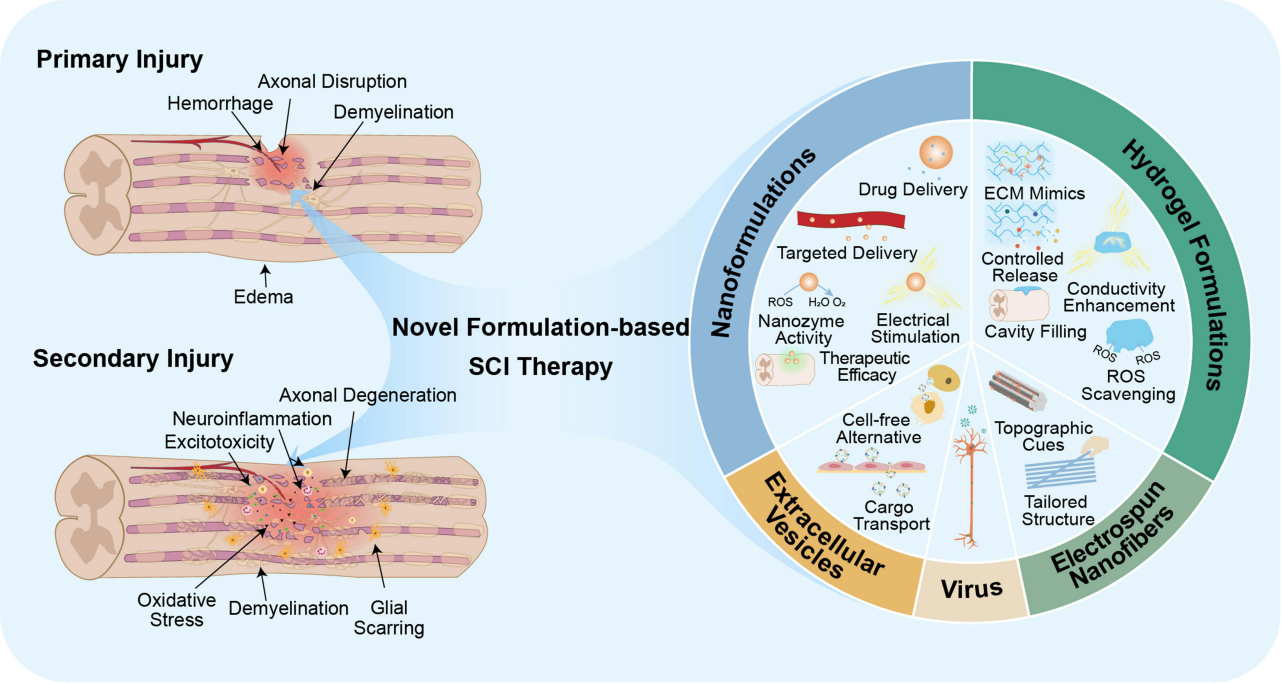

Figure 1 Summative scheme of novel formulation-based therapies to SCI.

tissue impede optimal biodistribution and the functional integration of therapeutics. Consequently, there is a pressing need to develop effective strategies to address these challenges and optimize therapeutic outcomes.

Pharmaceutics has opened new avenues for developing bioactive substances as viable medicines by enhancing their bioavailability, improving stability, enabling customizable morphology, masking undesirable odors, controlling release profiles, and increasing biosafety.[5–7] A wide range of novel drug formulations have been developed with advances in biomaterials and fabrication technologies. These formulations exhibit diverse structural forms, multifunctional capabilities, and tunable biological activities. These innovative systems allow for precise spatiotemporal control over the distribution of therapeutic agents, exhibit intelligent responses to specific physiological signals, and incorporate biomimetic architectures.[8–10] In the context of SCI treatment, these capabilities provide tailored therapeutic benefits, such as improving drug accumulation, bonding wounds, regulating regeneration, and enhancing function integration. By addressing critical delivery and microenvironment challenges, novel drug formulations hold significant potential to overcome existing barriers and accelerate the translation of new treatment strategies into clinical practice, ultimately improving therapeutic outcomes for SCI patients.

In this review, we first outline the pathological progression of SCI. We generalize the recent advances, application status, and unique advantages of novel drug formulations in SCI treatment, including nanoformulations, hydrogel formulations, electrospun nanofibers, extracellular vesicles, and viral vector. (Figure 1) A comprehensive understanding of the mechanisms underlying these novel formulations is essential to fostering the development of innovative and effective therapeutic strategies, thereby facilitating their translation into clinical SCI management.

Search and Screening Strategy

Literature search about pathophysiological processes after SCI was performed across PubMed and Google Scholar using the following keywords search strategy: (spinal cord injury OR SCI) AND (mechanism OR pathophysiology). The search encompasses original research articles and high-impact reviews. Studies were selected based on their relevance to the molecular and cellular mechanism following trauma, including excitotoxicity, ionic imbalance, oxidative stress, demyelination, axonal degeneration, glial scar formation, and aberrant repair. Articles underwent a manual screening process involving title, abstract, and full-text evaluations, with a priority placed on methodological soundness and the ability to

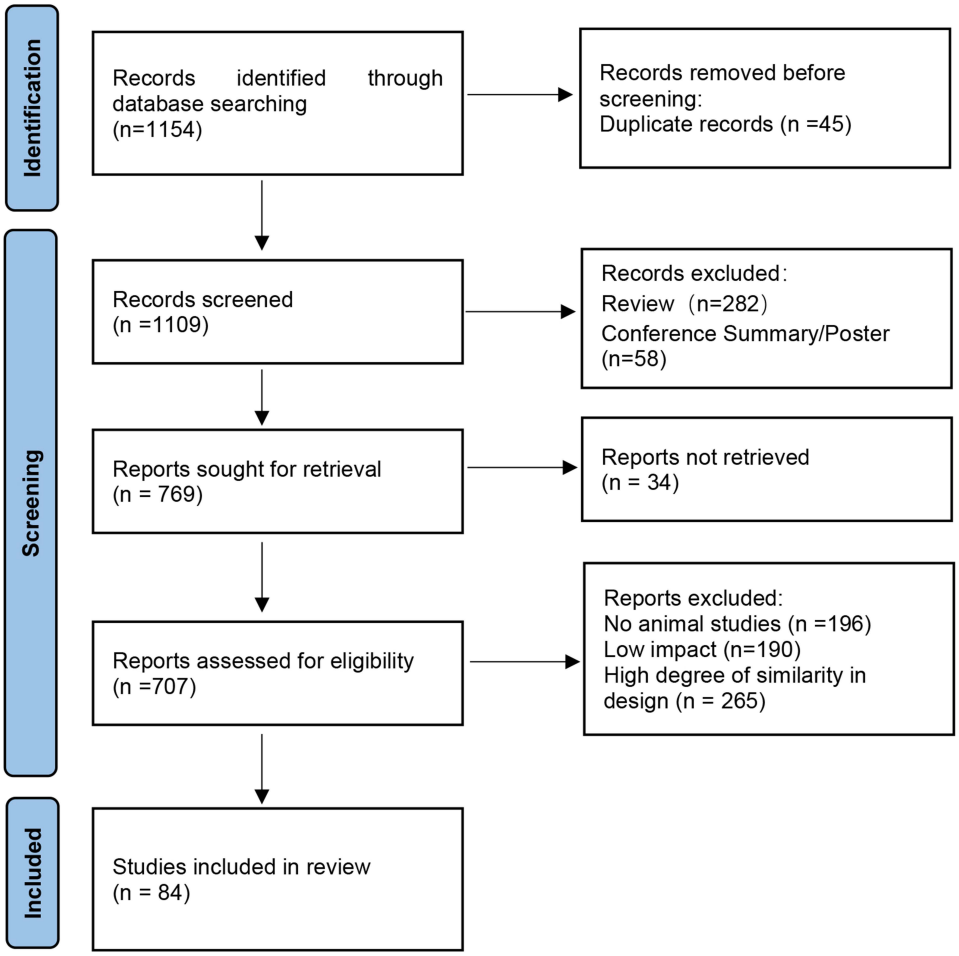

Figure 2 Flowchart illustrating the identification, screening, and inclusion of studies for the review.

elucidate the evolution of the injury microenvironment. Exclusion criteria applied to non-peer-reviewed reports, duplicates, and studies focused solely on surgical techniques without pathological analysis.

To examine recent advancements in novel drug formulations, we conducted a search on PubMed for English-language articles in 2022–2025. The search strategy employed the following keywords: biomaterials AND (hydrogel OR scaffold OR nanomaterials) AND (spinal cord injury OR SCI OR nerve regeneration). A total of 1154 records were initially identified through database searching. After removing 45 duplicate records, 1109 records remained for the initial screening phase. During the screening of titles and abstracts, 340 records were excluded, consisting of 282 review articles and 58 conference summaries or posters. Out of the 769 reports sought for retrieval, 34 reports could not be retrieved, leaving 707 articles for full-text eligibility assessment. Following evaluation based on predefined inclusion and exclusion criteria, 623 reports were excluded for the following reasons: non-animal studies; low impact; high degree of similarity in study design. Consequently, a final set of 84 studies were included in this narrative review. The detailed summary of this selection protocol is illustrated in Figure 2.

Pathophysiological Processes After SCI

Primary Injury

Primary injury refers to the initial traumatic events on the spinal cord that disrupt the neural tissue and vascular structures. The initial traumatic events include external physical impact (such as a motor vehicle injury, fall, sports-related injury or violence) or disease process (such as a tumor, infection or degenerative disc disease).[4] These mechanical

insults lead to the rupture of blood vessels, axons, and neurons, subsequently inducing spinal cord edema. Due to the confined anatomical space bounded by the vertebral laminae, the swollen tissue exerts pressure on adjacent blood vessels and tissues, causing ischemia once this pressure surpasses the venous blood pressure.[11] Additionally, the impairment of sympathetic nervous system function may induce systemic hypotension, further exacerbating ischemic conditions.[12] Consequently, prompt decompression is critical to improving patient prognosis following SCI.

Secondary Injury

Secondary injury denotes the delayed injury occurring in the tissue adjacent to the primary lesion, which remains viable during the initial injury. This phenomenon involves a cascade of biochemical and molecular processes triggered by the primary injury, leading to further tissue loss and functional impairment.[13] In 1911, Allen reported observations of neurological function recovery following post-traumatic hematoma removal in dogs and suggested that certain deleterious substances exist in hemorrhagic necrotic tissue that cause secondary spinal cord damage.[14] Contemporary neuroscience has been exploring these intricate and interconnected biochemical events, including excitotoxicity, ionic imbalance, neuroinflammation, free radical damage, demyelination, axonal degeneration, glial scar formation, and aberrant repair.

Excitotoxicity and Ionic Imbalance

Excitotoxicity and ionic imbalance are closely interconnected processes that culminate in extensive cellular damage. Under physiological conditions in the spinal cord, axon terminals release minimal quantities of glutamate. Glutamate binds to receptors on postsynaptic neurons, facilitating the opening of sodium (Na^+) channels, allowing Na^+ influx and the generation of action potentials.[15] Following SCI, glutamate concentrations increase sharply due to a massive release from damaged neurons and the impaired clearance of astrocytes. This glutamate accumulation results in the excessive activation of glutamate receptors, leading to substantial influxes of calcium (Ca^{2+}) and Na^+ ions.[13] Concurrently, ischemia-induced ATP depletion exacerbates Na^+ influx by impairing Na^+/K^+-ATPase pump function. The resultant excessive entry of Na^+ increases intracellular osmotic pressure, promoting water influx and cellular swelling.[16] Moreover, elevated intracellular Ca^{2+} concentrations trigger the opening of the mitochondrial permeability transition pore (mPTP) on the inner mitochondrial membrane, disrupting the proton gradient between the mitochondrial matrix and the intermembrane space. This disruption impairs the mitochondrial electron transport chain and ATP synthesis. Additionally, Ca^{2+} serves as a cofactor for various enzymes, including phospholipase, xanthine oxidase, and calcium-dependent proteases. The overactivation of these enzymes drives inflammation by liberating free fatty acids, generating free radicals, and degrading the cellular ultrastructure.[17] In summary, the primary injury initiates glutamate release and ischemia, which together induce secondary cell death in the surrounding tissue through excitotoxicity and ion imbalance. This cell death further propagates glutamate release, thereby perpetuating and expanding the injury. Consequently, therapeutic interventions aimed at disrupting this glutamate-mediated cycle, such as blocking glutamate receptors, enhancing glutamate clearance, blocking sodium or calcium channels, preventing mPTP opening, and suppressing Ca^{2+}-dependent enzymatic activity, represent promising strategies for treating SCI.

Neuroinflammation

The neuroinflammatory response in SCI is both robust and sustained. Resting microglia are rapidly activated post-injury, leading to the release of cytokines and chemokines that facilitate the recruitment of neutrophils. These activated neutrophils then attract monocytes and lymphocytes to the lesion site, resulting in persistently elevated levels of inflammatory mediators, including interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNFα), and IL-6. These mediators enhance the activity of inflammatory cells and exert direct cytotoxic effects to exacerbate tissue damage.[18] Additionally, due to the immune-privileged status of the spinal cord, proteins such as myelin proteins and neuronal antigens are perceived as foreign by the immune system after BSCB destruction, causing the overactivation of the immune system to continuously destroy normal tissues around the injury.[19] Thus, strategies aimed at modulating microglia and macrophage polarization, antagonizing inflammatory factors, inhibiting inflammatory signaling pathways, and inducing immune system tolerance to central nervous system (CNS) antigens may facilitate the conversion of the pro-inflammatory microenvironment into an anti-inflammatory milieu, potentially promoting repair and recovery after SCI.

Free Radical Damage

Ischemia-reperfusion, Ca^{2+} overload, and neuroinflammation collectively contribute to the generation of substantial quantities of free radicals at the injury site. The mitochondrial electron transport chain is interrupted due to oxygen deprivation during ischemic episodes, resulting in the accumulation of electrons within transport complexes. Reperfusion after spontaneous body compensation or medical intervention causes a sudden and significant increase in mitochondrial oxygen concentrations. This sudden oxygen influx facilitates the rapid and incomplete reduction of oxygen by the accumulated electrons, producing electron-deficient and highly reactive oxygen species (ROS).[20] Additionally, Ca^{2+} overload excessively activates xanthine oxidase and nitric oxide synthase to produce nitric oxide ($NO\cdot$) and superoxide anion ($O_2^{-}\cdot$).[17] The activation of enzymes such as NADPH oxidase in infiltrating neutrophils and macrophages at the injury locus contributes to the increased generation of free radicals.[21] The high free radical activity induces the peroxidation of unsaturated fatty acid double-bonds within lipid membranes, compromising membrane integrity and generating more free radicals. This self-propagating free radical chain reaction results in cellular lysis, organelle dysfunction, and increased calcium influx, ultimately expanding the injury area.[22] Consequently, the scavenging of free radicals is a critical therapeutic strategy in the management of SCI.

Demyelination

Oligodendrocytes are specialized glial cells responsible for the formation of myelin sheaths. Each oligodendrocyte extends multiple processes that wrap concentrically around 30 to 50 axons, creating an insulating myelin layer that enables simultaneous signal transmission along multiple axons without mutual interference.[23] The integrity of the myelin structure in spinal cord is essential for higher-order neurological functions such as sensory processing and motor control. In SCI, glutamate excitotoxicity, Ca^{2+} overload, oxidative stress, and inflammatory cytokines cause significant damage to oligodendrocytes. Notably, because a single oligodendrocyte myelinates numerous axons, demyelination occurs extensively and often surpasses the boundaries of the primary injury. This demyelination results in a reduction or the complete cessation of conduction velocity along affected axons. Furthermore, signal transmission between demyelinated axons causes mutual interference, generating uncoordinated neural noise that manifests as tremors, motor incoordination, and sensory dysfunction.[13] Therefore, reducing myelin loss by regulating the local microenvironment and promoting correct myelin regeneration are critically associated with functional recovery following SCI.

Axonal Degeneration

Following primary injury, the progressive and active process of axonal degeneration distal to the site of injury is known as Wallerian-like degeneration.[13] This phenomenon results from the cessation of energy transport and the supply of essential axonal survival factors due to axon interruption. Additionally, pro-degenerative proteins are activated to promote axonal fragmentation.[24] Although the proximal segment of the axon remains connected to the neuronal cell body, it retracts to form dystrophic end-balls and loses its regenerative capacity, primarily due to the presence of myelin-associated inhibitors, glial scar formation, and insufficient growth factors.[25] Mitigating these inhibitory constraints, providing neurotrophic support, inhibiting growth-suppressive signaling pathways, and stimulating regenerative signaling pathways could enhance axonal outgrowth in surviving neurons.

Glial Scar Formation

At the periphery of the glial scar, spared astrocytes undergo hypertrophy and proliferation, differentiating into reactive astrocytes characterized by a marked upregulation of glial fibrillary acidic protein (GFAP) expression. These reactive astrocytes extend numerous large cellular processes that interweave to form an astrocytic scar that presents as a narrow border comprising only a few cell layers. This scar functions to segregate the destructive inflammatory and oxidative stress milieu from the adjacent healthy tissue, thereby limiting the propagation of injury.[26] The core of the lesion is a fibrotic scar, primarily comprising fibroblasts, inflammatory immune cells, and abundant extracellular matrix (ECM).[27] While glial scars contribute to stabilizing vulnerable spinal cord tissue post-injury, their dense reticular architecture and the presence of substantial quantities of axon growth-inhibitory molecules impede axonal regeneration. Thus, the enzymatic degradation of these inhibitory molecules or blockade of the associated signaling pathways may facilitate axonal regeneration. Furthermore, glial scars are not necessarily static structures. In certain patients, they may evolve into

cystic cavities or myelomalacia, potentially leading to the progressive enlargement of the lesion and the emergence of new neurological deficits. However, the underlying mechanisms driving this pathological progression remain to be elucidated.[28]

Aberrant Repair

Following incomplete SCI, the surviving and responsive neural tissue may spontaneously form new synaptic connections through axonal sprouting, thereby reorganizing neuronal relay. This process can lead to either the adaptive restoration of certain functions or maladaptive outcomes, such as muscle spasticity, autonomic dysreflexia, and neuropathic pain.[26] Furthermore, remyelination occurs gradually after SCI. This process mainly depends on the recruitment and proliferation of oligodendrocyte precursor cells to differentiate into oligodendrocytes and extend processes to ensheath axons. However, this regenerative process is aberrant and characterized by short ranvier nodes, thinner myelin sheaths, and an atypical correlation between axon diameters and myelin thickness that cannot support fine and rapid motor coordination.[23] Therefore, interventions aimed at promoting both adaptive neural circuit reorganization and normal myelin regeneration hold significant potential for enhancing functional outcomes and quality of life in individuals affected by SCI.

Novel Drug Formulations

A comprehensive understanding of the pathophysiological alterations of SCI is essential for the development of effective therapeutic interventions. However, the intricate pathological processes and persistent injury process after SCI pose significant challenges to clinical management. The oxidative and inflammatory environment may contribute to the inactivation of pharmacological agents. The BSCB and cerebrospinal fluid flushing hinder the distribution of drugs to the lesion site. The delicate nature of the spinal cord also renders it vulnerable to secondary damage during therapeutic procedures. In response to these barriers, researchers have developed a variety of novel drug formulations, such as nanoformulations, hydrogel formulations, electrospun nanofibers, extracellular vesicles, and viruses to enhance treatment efficacy.

Nanoformulations

Nanoformulations represent an advanced preparation form characterized by structures with at least one dimension within the 1–100 nanometers (nm) range.[29] The main types of commonly used nanoformulations include nanomicelles, lipid-based nanoparticles, liposomes, dendrimers, carbon-based nanomaterials, and metal-based nanomaterials. Owing to their nanoscale dimensions and large specific surface area, these formulations are capable of loading and releasing therapeutic agents, enhancing drug dispersion, and modulating the pharmacokinetic and pharmacodynamic behaviors of drugs in vivo.[30] In SCI treatment, nanoformulations can serve as delivery vehicles that protect therapeutic agents, enable controlled release, and promote targeted accumulation. They can also play active roles as nanoenzymes, nanogenerators, or therapeutic agents. When designing delivery vehicles for therapeutic agents, nanoformulations could be served as a detachable barrier to protect the payload from degradation during systemic circulation and within the complex biochemical environment of the SCI site. Upon reaching the lesion, this barrier disassembles via non-destructive release triggered by SCI-specific pathological signals or through lysosomal escape following cellular uptake. Material options for this barrier include polymers, liposomes, lipidoids, and inorganic/hybrid materials. To achieve controlled release at the SCI site, environment-sensitive linkages such as ester bonds, disulfide bonds, hydrazine, acetal bonds, and matrix metalloproteinase-responsive bonds are utilized to facilitate the disassembly of the barrier. Furthermore, the surface of these nanowalls can be engineered with specific peptide ligands or biomimetic membranes to achieve targeted delivery to the SCI site. To mimic the metal-organic ligand active centers of biological enzymes, materials such as metal oxides, metal-organic frameworks and single-atom nanozymes could be selected. Additionally, to enable the generation of bioelectricity, materials exhibiting piezoelectric or magnetoelectric effects can be incorporated.

Deliver Active Substances

Conventional drug formulations face significant challenges in effectively delivering drugs to the SCI site. The injury site generates substantial inflammatory factors, free radicals, and other toxic substances, which could decompose or inactivate drugs administered orally or by injection before they reach the intended cellular targets. Additionally, after oral administration or injection, some drugs disseminate throughout the body, affecting healthy tissues and causing undesirable side effects. Some therapeutic agents used in SCI treatment also possess inherent limitations related to their solubility, hindering their development into viable pharmaceuticals. With advancements in biomaterials and nanotechnology, nanoformulations have emerged as promising strategies to address these challenges. For example, nanoformulations can serve as a wall to preserve the structural integrity of therapeutic agents, shielding therapeutic agents from the external hostile SCI microenvironment. Gao et al constructed a micelle with a core-shell structure to effectively deliver small interfering RNA into the SCI site. The negatively charged siRNA was electrostatically bound to the positively charged core and subsequently encapsulated within a PEGylated shell, thereby isolating the vulnerable siRNA from the pervasive nucleases present in the SCI microenvironment. Nucleic acid gel electrophoresis analysis demonstrated that the siRNA encapsulated within the nanoformulation retained its structural integrity even after 4 hours of exposure to RNase A, an enzyme known for its robust phosphodiester bond cleavage activity. Therefore, the siRNA was able to enter cells effectively, maintaining its bioactivity to mitigate axonal growth inhibition and inflammation.[31] Due to the protective effect conferred by nanoformulations, more biomedicines could play roles in treating SCI. Furthermore, the development of intelligent nanoformulations capable of controlled payload release in response to specific pathological stimuli is important to ensure that therapeutic agents exert their effects exclusively at injury sites rather than in healthy tissues. Liu et al synthesized an amphiphilic polymer called PAH to self-assemble into nanoparticles to deliver curcumin in the treatment of SCI. Curcumin demonstrates therapeutic efficacy by protecting neurons from apoptosis, modulating the polarized phenotype of microglia, and promoting the proliferation of neural stem cells (NSCs) at the injured spinal site.[32] However, its clinical application is limited by potential adverse effects, including hepatotoxicity, nephrolithiasis, and cardiac conduction abnormalities.[33] The PAH polymer with hydrazide groups on the side-chain can form pH-sensitive hydrazine bonds with 4-formylphenylboronic acid (4FPBA), while curcumin, with a hydroxyl group, can form an ROS-sensitive boronate ester with 4FPBA, thereby conjugating curcumin to the PAH polymer backbone. Consequently, curcumin release from the PAH nanoparticles occurs selectively under acidic or the ROS-rich environment of the SCI site, significantly reducing toxicity to normal tissues.[32] In addition, nanoformulations can address the inherent poor solubility of certain bioactive compounds. For example, ginsenoside Rb2 (G-Rb2) exhibits significant anti-inflammatory and antioxidant effects in treating SCI. However, its lipophilic steroidal structure results in poor aqueous solubility, impeding uniform dissolution, cellular uptake, systemic administration, and the maintenance of therapeutic concentrations due to rapid clearance.[34,35] Li et al employed liposomes to encapsulate the compound to achieve uniform G-Rb2 dissolution. G-Rb2 was incorporated into the hydrophobic region of the phospholipid bilayers, and a loading efficiency of 27.87% ± 0.96% was achieved. The hydrophilic surface of the liposomes, combined with the dynamic stability of their nanoscale size, facilitated the even dispersion of G-Rb2 in aqueous solutions. Because of the enhanced solubilization capacity of liposomes in water, liposome-encapsulated G-Rb2 demonstrated superior efficacy in alleviating mitochondrial damage, modulating oxidative stress, and inhibiting neuronal ferroptosis compared with free G-Rb2.[36] Kwon et al, Gao et al, and Yuan et al also employed nanomaterials to efficiently load and protect active substances to ameliorate SCI progression.[37–39]

Target the Injury Site

The delivery efficiency of nanocarrier systems used in the treatment of SCI is often insufficient due to the physical obstruction of the BSCB and glial scars. Thus, researchers have been committed to developing strategies to enhance the accumulation of drug-loaded nanoparticles at the SCI site using techniques such as ligand modification, bacteria or cellular component encapsulation, and BSCB vasodilation[40,41] Li et al engineered a targeted nanoformulation by conjugating zein-based spherical nanoparticles with the Cys-Ala-Gln-Lys (CAQK) peptide using the heterobifunctional cross-linker NHS-PEG5000-Mal to prolong the half-life and the retention time of therapeutics at the injury site. The CAQK peptide is a scar-homing peptide screened using in vivo phage display to specifically bind with chondroitin sulfate

proteoglycans (CSPGs), which predominantly constitute the glial scar and are markedly upregulated at SCI sites. Upon intravenous administration, the CAQK-modified nanoformulation demonstrated an extended half-life of 2 hours and an area under the plasma concentration-time curve (AUC) of 2217.63 ± 28.70 μg•mL^{-1}•h^{-1}, compared with 0.25 hours and 413.32 ± 19.42 μg•mL^{-1}•h^{-1} for the drug in aqueous solution.[42] Wu et al observed that CAQK-functionalized nanoparticles persisted at the injury site for over 24 hours.[43] These findings underscore the capacity of targeted nanoparticles in ameliorating the pharmacokinetic profile of therapeutics to adapt to the treatment need, which is precisely the appeal of pharmaceuticals. Moreover, targeted nanoformulations can concentrate therapeutic agents at the SCI site through diverse modifications. Li et al developed biomimetic bacterial outer membrane nanoparticles (BM-NPs) by integrating detoxified outer membrane vesicles derived from msbB-deficient Escherichia coli into liposomes. (Figure 3) Neutrophils and monocyte-derived macrophages can recognize and internalize BM-NPs, carrying the nanoparticles to the SCI site by the innate chemotactic properties of immune cells, and sustaining the release of the drug-loaded BM-NPs to exert their therapeutic effects. In vivo imaging system (IVIS) and ex vivo images demonstrated the extensive distribution and accumulation of DiD-labeled BM-NPs in the spinal cord of SCI rats after a tail vein injection.[44] This evidence highlights the potential of injury-targeted nanoformulations to address large, deep, and multifocal wounds in the spinal cord and outside the spinal cord, which often accompany SCI. In addition, Ciciriello et al and Zhou et al designed targeted nanoformulations to realize precise and effective SCI treatment.[45,46]

Function as Enzymes

ROS burden is one of the primary contributors to secondary cascade injuries in SCI. Thus, the application of antioxidant enzymes represents a promising therapeutic strategy. However, biological enzymes are prone to activity loss under conditions of elevated temperature, extreme pH, and proteolytic degradation. Recently, researchers have identified a novel class of nanoformulations termed nanozymes, which are defined as nanomaterials exhibiting enzyme-mimetic catalytic activities. These nanozymes emulate the catalytic centers of natural enzymes through metal active sites or coordination structures.[47] Jiang et al developed a nanoenzyme using a template-mediated carbonization method to relieve ROS burden in treating SCI. This method entailed polymerizing dopamine monomers on silica nanoparticle surfaces, carbonizing the polydopamine to generate a nitrogen-doped carbon graphitized carbon layer, coordinating with metal ions, reducing these ions to a single atom to exert enzymatic catalysis, and removing silica nanoparticles through acid etching. The resulting nanoenzyme demonstrated sustained ROS-scavenging activity over five successive substrate additions, indicative of its robust catalytic performance attributable to the preservation of its chemical structure.[48] This property was similar to that of natural enzymes, which are not consumed during catalysis and maintain their structural integrity before and after reactions. While both biological enzymes and nanozymes remain structurally unaltered after reaction, nanozymes possess a distinct advantage in vivo due to their superior stability. Wang et al engineered a rare-earth metal-doped nanoenzyme using a thermal solvent method for ROS scavenging in SCI treatment. This nanozyme not only catalyzed the conversion of hydrogen peroxide (H_2O_2) and superoxide anion (O_2•−) to water but also exhibited luminescence upon near-infrared excitation. Following administration, it persisted at the injury site for over 48 hours in SCI mouse models, while biological enzymes, such as superoxide dismutase (SOD) and catalase (CAT), have markedly short half-lives (8–11 min) due to rapid renal clearance via glomerular filtration.[49] Additionally, catalytic nanoparticles can interact with a broad spectrum of substrates, distinguishing them from traditional enzymes that exhibit high substrate specificity. Shen et al employed a Food and Drug Administration-approved nanoenzyme called prussian blue in the treatment of SCI. This blue nanoparticle was synthesized through a coordination reaction of Fe^{2+}/Fe^{3+} ions with cyanide (CN^-). Prussian blue exhibits enzymatic activities analogous to multiple natural enzymes; it reduces •O_2 to H_2O_2 like SOD, catalyzes H_2O_2 to hydroxyl radicals (•OH) akin to CAT, and converts H_2O_2 or •OH to water, comparable to glutathione peroxidase (GPX).[50] This multifunctional enzymatic behavior endows the nanoenzyme with significant ROS-scavenging ability, surpassing that of biological enzymes in the context of SCI therapy. Zheng et al, Mai et al, and Zhao et al also cultivated various nanoenzymes to relieve ROS burden in treating SCI.[51–53]

Generate Bioelectric Signals

The nervous system generates rapid, digital-like electrical signals within neurons to facilitate communication across distances that far exceed the dimensions of the neuronal soma.[54] In SCI, the destruction of axons and neurons terminates

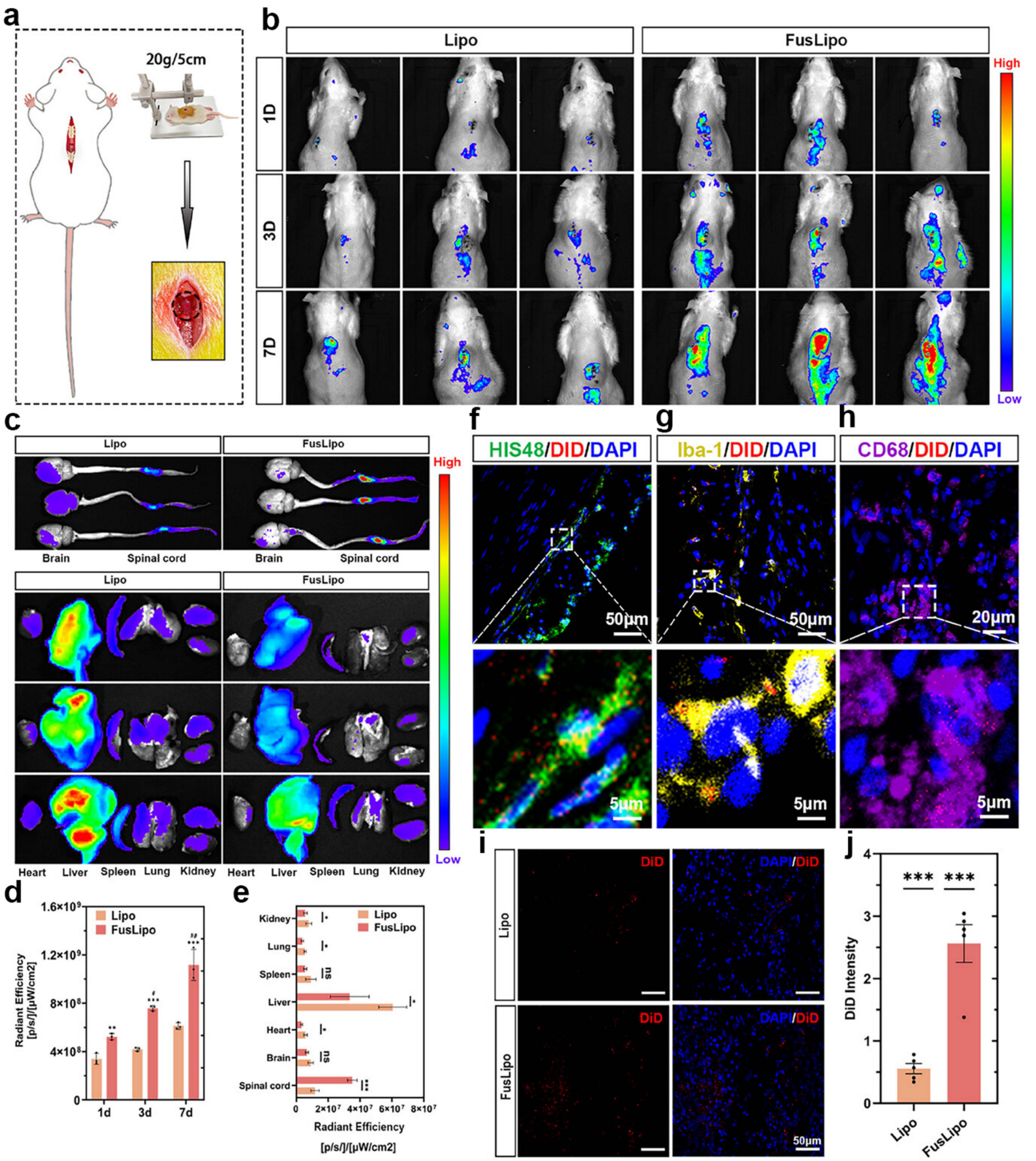

Figure 3 Targeting analysis of the biomimetic bacterial outer membrane fused liposome (FusLipo) and standard liposomes (Lipo). (**a**) Schematic of the SCI rat model. (**b** and **d**) In vivo fluorescence imaging and quantification of the fluorescence intensity in SCI rats treated with DiD (a lipophilic fluorescent dye)-labeled Lipo or FusLipo on days 1, 3, and 7 post-injury (n = 3). * indicates comparisons between the Lipo and FusLipo at the same time point, # indicates comparisons within the FusLipo between 3 and 1 day, ## indicates comparisons within the FusLipo between 7 and 3 days. (**c** and **e**) Ex vivo fluorescence imaging and quantification of the fluorescence intensity in the major organs, collected on day 7 post-SCI (n = 3). (**f–h**) Immunofluorescence images of the injury site showing colocalization of the DiD-labeled FusLipo with immune cell markers, including His48 (neutrophils, F), Iba-1 (microglia, G), and CD68 (a major macrophage marker, H) at days 1, 3, and 7 post-SCI. (**i** and **j**) Fluorescence imaging of spinal cord sections and quantification of the DiD fluorescence intensity on day 7 post-SCI, (n = 5). *, $p < 0.05$; **, $p < 0.01$; *** $p < 0.001$; # $p < 0.05$; ## $p < 0.01$; Reproduced from Li P, Liu J, Wang Y et al. Spatiotemporal Targeted Delivery of Biomimetic Bacterial Outer Membrane Nanoparticles for Enhanced Spinal Cord Injury Repair. Adv Mater. Published online May 20, 2025:2502795. Copyright 2025 John Wiley & Sons.

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the passage of electrical signals. Electrical stimulation (ES) synchronized with neural activity has been demonstrated to enhance neuronal growth, axonal elongation, and synaptogenesis to complete the reconstruction of neural networks, which is particularly important for nerve regeneration after injury.[55] ES has been applied to treat spinal cord injuries for over half a century.[56] However, conventional ES devices require implanted electrodes and external power sources and necessitate a secondary surgical procedure for electrode removal, resulting in patient discomfort and inconvenience. Also, the efficacy of conventional ES in modulating cell behavior is constrained by the size mismatch between relatively large electrodes and micron-scale cells. Nanogenerators present a promising solution to these limitations due to their nanoscale dimensions and piezoelectric properties, which can convert ambient mechanical energy into electrical signals without relying on external power supplies or complex circuitry. The underlying mechanism involves the non-coincidence of positive and negative charge centers within the nanogenerator's unit cell; mechanical stress induces a relative displacement of these charge centers, generating surface charges that cannot be internally neutralized due to the insulating nature of the material, thereby creating a potential difference and facilitating the transduction of mechanical energy into electrical energy. Conversely, when subjected to an external electric field, piezoelectric nanogenerators undergo deformation, converting electrical energy back into mechanical energy.[57] These characteristics confer several advantages for SCI treatment. For example, nanoscale wireless electrical stimulators can be dispersed in aqueous solutions that can be injected into the injury site using minimally invasive surgery. Wang et al innovatively proposed to use cellulose nanofibers (CNFs) as electrical stimulators in treating CNS injuries. Piezoelectric force microscopy results revealed that CNFs exerted a pronounced piezoelectric effect attributable to their asymmetrical crystalline structure. The SEM image demonstrated that CNFs were a single fiber with excellent dispersibility, maintaining uniform suspension in aqueous solutions even at concentrations as high as 160 μg/mL. When CNFs were locally injected with NSCs into injury sites in SCI mice and ultrasound was applied, the mechanical force of the ultrasonic waves was shown to spread through tissue and induce the ES of CNFs on NSCs to differentiate into functional neurons and form neural networks capable of transmitting nerve impulses.[58] This wireless and non-invasive electrical nanogenerator could effectively circumvent the surgical risks and complications associated with implanted electrodes. Furthermore, due to the sensitivity of nanogenerators to external forces, the magnitude of ES can be fine-tuned by facilely adjusting the applied force. Liu et al employed magnetoelectric Fe_3O_4@$BaTiO_3$ core-shell nanoparticles as nanogenerators to establish a remote and noninvasive ES platform for the synergistic treatment of SCI. The output current of the nanogenerator was found to increase in proportion to the magnetic field intensity; this enhancement is attributed to the increased separation of positive and negative charge centers within the nanoparticles under higher magnetic field strengths.[59] The adjustable timeline, duration, and strength of nanogenerators enable personalized therapeutic regimens tailored to SCI severity. Notably, nanoscale piezoelectric materials exhibit closer interfacing with cells than bulk piezoelectric materials, thereby more effectively modulating cellular behavior. Li et al proposed the functionalization of gold nanowires with laminin to facilitate robust adhesion to NSCs. (Figure 4) Gold nanowires possess excellent electrical conductivity and can generate electric pulses under magnetic field stimulation. SEM and fluorescence imaging confirmed intimate attachment between NSC membranes and gold nanowires. This close contact permits direct ES of the cells under magnetic fields and the efficient activation of the calcium channel and MAPK/ERK signaling pathway to promote neuronal differentiation.[60]

Exert Therapeutic Effects

In conventional pharmaceutics, medicinal excipients are defined as all constituents of pharmaceutical formulations, excluding active pharmaceutical ingredients (APIs) and packaging materials; these excipients primarily facilitate the formulation and manufacturing processes of dosage forms intended for patient administration.[61] However, within the domain of nanomedicine, emerging evidence indicates that nanomaterials can function not only as medicinal excipients to deliver drugs but also possess intrinsic therapeutic properties. This dual functionality is particularly valuable in SCI treatment due to their spatiotemporal synergy with active substances, the comprehensive utilization of formulation components, and the capacity to reduce medicinal dosages. Such attributes enable these nanomaterials to effectively address the complex, acute, and severe pathological processes characteristic of SCI. For example, Chen et al employed zein nanoparticles as a drug delivery system in SCI therapy. Zein, a corn-derived protein composed of both hydrophobic and hydrophilic amino acids, can self-assemble into nanoparticles owing to its amphipathic nature. Notably, when naked zein nanoparticles were used as the control group,

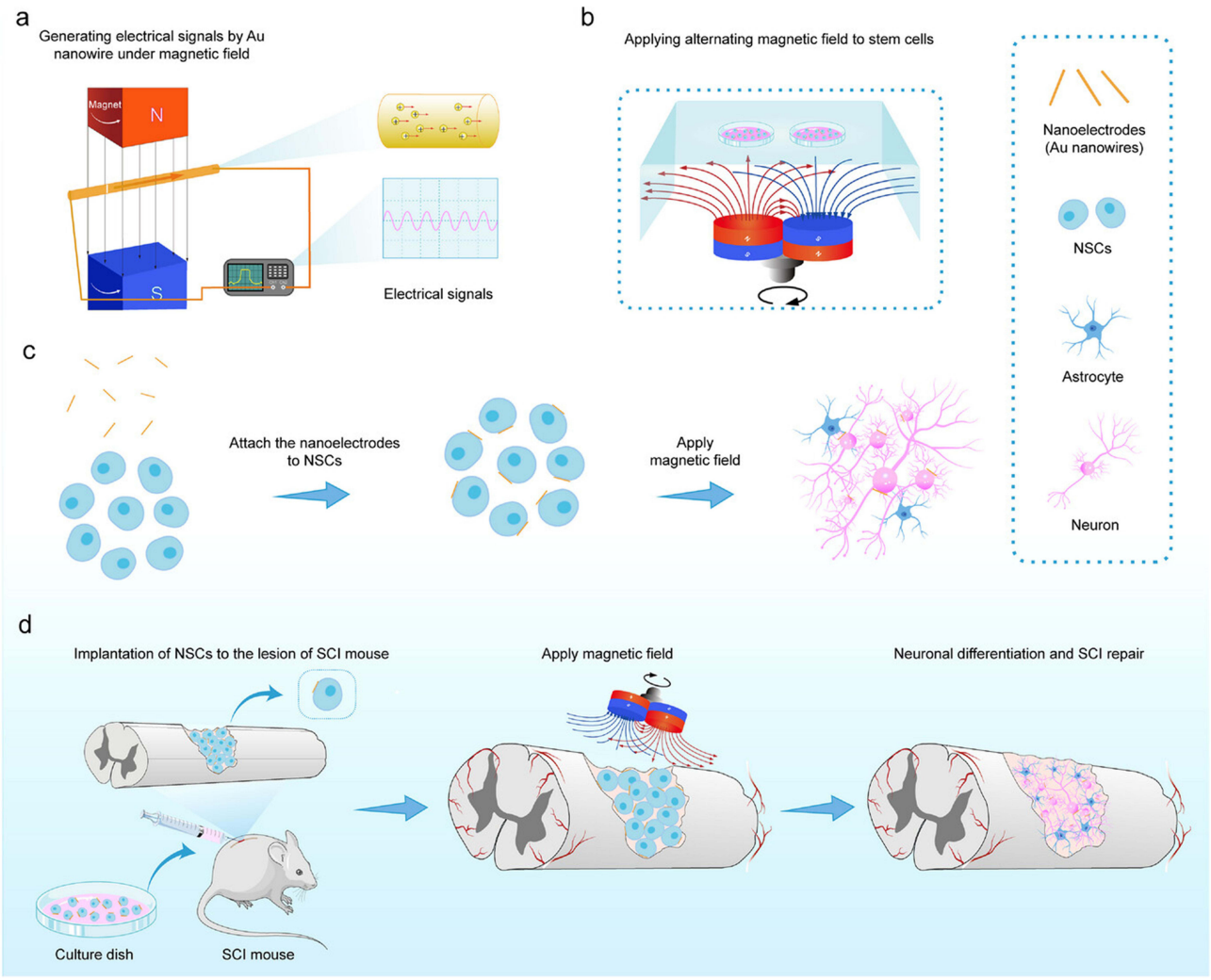

Figure 4 Schematic illustrating the use of Au nanowires as cell follow-up magnetoelectric stimulators for inducing the NSCs differentiation and SCI repair. (**a**) Generation of periodic electrical signals by Au nanowires under the alternating magnetic field due to electromagnetic induction. (**b**) Schematic showing the application of the alternating magnetic field to the stem cells. (**c**) The NSCs attached the Au nanowires and differentiated into neurons under an alternating magnetic field. (**d**) Injection of the NSCs with Au nanowires into the injured spinal cord for promoting the restoration of SCI mice under a periodic alternating magnetic field. Reproduced from Li Y, Du J, Zhou W et al. Au Nanowires as Membrane-Attached Magnetoelectric Nanoelectrodes to Promote Neuronal Differentiation and Spinal Cord Injury Repair. Adv Funct Mater. Published online May 15, 2025:2421547. Copyright 2025 John Wiley & Sons.

M2 phenotype macrophages levels were increased in the zein nanoparticle group to alleviate inflammation in SCI mouse models.[62] Beyond anti-inflammatory effects, Chen et al demonstrated that the co-administration of black phosphorus nanosheets (BPNSs) with NSCs caused motor function recovery in SCI mice superior to NSCs alone. Mechanistic investigations revealed that BPNSs were rapidly internalized by NSCs within 6 h and promoted neuronal differentiation by upregulating the p53 signaling pathway.[63] Moreover, Chen et al engineered the active compound betulinic acid (BA) into a nanoparticle form. BA, a natural extract from betula platyphylla suk, exhibits notable antioxidant and anti-inflammatory effects in SCI models. A hydrophobic cholesterol-like polymer (PBA) was synthesized by polymerizing its carboxyl and hydroxyl groups, which could self-assemble into liposomes in combination with DSPE-PEG 2000. The uniform size of 560.7 nm and high loading capacity facilitated motor function recovery. The resulting PBA nanoparticles could also mitigate neuroinflammation and alleviate neuronal apoptosis by activating the Nrf-2 signaling pathway.[64] Investigations by Zhao et al, Shi et al, and Han et al also corroborated the therapeutic potential of various nanomaterials in treating SCI.[65–67]

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Hydrogel Formulations

Hydrogels are three-dimensional (3D) networks comprising cross-linked hydrophilic polymer chains and abundant water.[68] In drug formulation, hydrogels primarily comprise natural polymers, synthetic polymers, or combinations thereof.[69] As a topical and sustained-release therapeutic modality, hydrogel formulations can reduce the frequency of drug administration, protect API from degradation, and extend their maintenance. In SCI treatment, hydrogel formulations present unique benefits, such as mimicking the ECM, enabling localized sustained drug release, conforming to irregular cavity shapes, facilitating bioelectric signal transmission, and scavenging free radicals. To mimic the ECM, natural polymers are employed as the structural backbone for scaffolds. By precisely modulating precursor concentrations and crosslinking densities, their properties can be finely tuned to match the native ECM. To design hydrogel for localized sustained drug release, the crosslinking network must be tailored based on the molecular weight of drug, with strategies implemented to enhance the affinity between the scaffold and the therapeutic payload. To achieve seamless filling of irregular cavities, hydrogels must exhibit superior injectability and self-healing capabilities. These properties rely on the reversible nature of dynamic bonds and in-situ crosslinking technologies, allowing the precursor solution to penetrate deep into tissue gaps and entangle with the host tissue, thereby generating robust interfacial adhesion. Furthermore, conductivity can be enhanced by incorporating conductive polymers or other conductive media into the hydrogel matrix. To engineer hydrogels with radical-scavenging abilities, chemical bonds or functional groups with high reactivity toward free radicals can be integrated into the network.

Extracellular Matrix Simulation

Cell therapy represents a promising and advanced approach for treating SCI. However, the survival rate of transplanted cells within conventional formulations remains suboptimal due to the hostile post-injury microenvironment.[70] Even worse is that implanted cells can release cytotoxic by-products upon their death, which counteract therapeutic objectives.[71] Consequently, enhancing the viability of transplanted cells is critical for advancing the clinical translation of cell therapies. In recent years, considerable research has focused on the development of hydrogels that recapitulate the ECM, thereby providing a supportive milieu for cell proliferation, regulating cell migration, guiding axonal orientation, and facilitating synapse formation. These biomimetic hydrogels can replicate various ECM characteristics, including mechanical, structural, and biochemical properties. For example, to replicate the mechanical stiffness of native ECM, Li et al utilized alginate and hyaluronic acid to fabricate hydrogels using 3D printing technology. The resulting hydrogel exhibited a mechanical strength of approximately 1 kPa, close to that of the adult rat spinal cord (~1.2 kPa). NSCs cultured in this hydrogel demonstrated stable proliferation over 7 days and extended pseudopodia to establish intercellular connections, indicating that the hydrogel provided a mechanically conducive environment for NSC growth.[72] The sensitivity of neural cells to the mechanical properties of hydrogels underscores the importance of mechanical compatibility. These results reflect that mismatched stiffness can inflict damage on delicate neural structures, leading to neurite overstretching, rupture, and neuronal soma degeneration. Zhang et al synthesized poly (β-amino ester) hydrogels via free radical polymerization. Hydrogel exhibiting varying mechanical strengths was produced by modulating the concentration of the raw materials. When primary mouse dorsal root ganglion (DRG) cells were inoculated into hydrogels of differing stiffness, those cultured in hydrogels with a mechanical strength of 27.1 kPa exhibited markedly reduced cell numbers and viability, highlighting the detrimental effects of a mechanical mismatch.[73] These findings emphasize that hydrogel formulations should mimic the soft mechanical properties of native ECM to prevent secondary injury to spinal tissue. Beyond macroscopic mechanical properties, ECM also exhibits specialized microstructural features, whose macromolecular components form a complex network that facilitates the transport of oxygen and nutrients. Hydrogels inherently possess a 3D porous network analogous to the ECM topology. Cao et al employed gelatin methacryloyl (GelMA) scaffolds to generate 3D cultures of mesenchymal stem cell (MSC) spheroids to treat SCI. SEM images revealed a porous network structure resembling native ECM. MSC spheroids were incorporated into the scaffold by mixing with a porous GelMA solution, crosslinked under an ultraviolet light, and cultured in MSC medium. The live/dead staining results confirmed high MSC cell viability, indicating that the porous GelMA scaffold permitted the adequate diffusion of oxygen and nutrients, thereby providing an ECM-mimetic environment conducive to MSC growth.[74] ECM regulates cellular survival, proliferation, migration, and differentiation by transmitting signals from the

specific function site on ECM to cells through cell surface receptors. Doulames et al engineered recombinant proteins containing the RGDS peptide sequence to form hydrogels through peptide self-assembly to replicate this signaling function. RGDS peptides are derived from ECM fibronectin, which can provide cell adhesion signals to prevent neuronal anoikis. Compared with hydrogels lacking adhesion peptides, hydrogels incorporating RGDS peptide significantly enhanced the survival and axonal outgrowth of deep cortical neurons derived from human induced pluripotent stem cells.[75] These findings indicate that hydrogels with functional ECM motifs can provide essential biochemical cues to mitigate cell death. In addition to using natural or synthetic materials to mimic ECM, dECM hydrogels have been used to directly duplicate the microenvironment of native tissues. Deng et al decellularized spinal cord tissue from young pigs to fabricate a 3D-printed hydrogel. The decellularization process removes cellular and immunogenic components while preserving structural proteins and glycosaminoglycan. NSCs cultured within this dECM hydrogel exhibited a high viability of 93.7% after 7 days, comparable to conventional 2D culture conditions. After 21 days, the cells preferentially differentiated into neurons rather than glial cells, which was attributable to the non-inflammatory and oxidative stress-free environment provided by the dECM hydrogel. The implantation of NSC-loaded dECM hydrogels into SCI sites effectively promoted neuronal relay reconstruction and motor function recovery.[76] In addition, Zhao et al developed alginate-methylcellulose hydrogels, Li et al used dECM hydrogel, and Sun et al developed self-assembling peptide mixed cellulose to simulate the ECM environment, thereby advancing the efficacy of cell therapy for SCI.[77–79]

Local Sustained-Release Drug

Administering therapeutic agents to the spinal cord remains a significant challenge in the clinical management of SCI. Systemic administration has difficulty crossing the BSCB because of the continuous intercellular tight junctions, lack of fenestrations, and extremely low rates of endothelial cell transcytosis.[80] Local administration faces the continuous flow of cerebrospinal fluid (flow rate of approximately 0.3–0.4 mL/min), which rapidly dilutes and removes the injected agents.[81] Repeated administrations pose issues of patient discomfort and inconvenience. Thus, novel drug delivery strategies for SCI therapy are urgently needed. Hydrogels represent an ideal drug formulation pattern in SCI, as they can function as drug depots that adhere to the injury site, thereby locally enriching therapeutic agents, preventing their clearance by cerebrospinal fluid, and circumventing the BSCB barrier. Hashimotoa et al employed a collagen scaffold to deliver and release recombinant human hepatocyte growth factor (rhHGF) to improve drug accumulation at the SCI site. Enzyme-linked immunosorbent assay (ELISA) measurements revealed that the concentration of rhHGF around the lesion site reached 0.242 ± 0.007 ng/mL at 7 days when a hydrogel formulation was used, whereas rhHGF was undetectable following administration in an aqueous solution. This result underscores the local residency capability of hydrogel formulations.[82] In addition, the pathophysiological progression of SCI is chronic in nature, necessitating sustained intervention over an extended period to achieve meaningful therapeutic efficacy. Zhang et al developed an interpenetrating polymer network composed of bisphosphonate-modified alginate and silk fibroin to achieve controlled drug release. Through the successful coordination between bisphosphonate groups and Zn^{2+} ions, the system achieved a high Zn^{2+}-loading capacity of 8 mM and maintained drug release within a targeted concentration range for 30 days. A single administration was adequate to facilitate the recovery of motor function by promoting neuronal axon growth, regulating the proliferation and differentiation of NSCs, and modulating the inflammatory microenvironment.[83] Similar hydrogel-based drug delivery approaches were also explored by Geng et al, Zhou et al, and Chen et al to facilitate long-term therapeutic regimens.[84–86]

Fit into Irregular Cavities

In the case of traumatic SCI, the primary injury causes tissue loss, leading to the formation of an irregular cavity at the injury site. This irregular cavity compromises tissue integrity and may cause a secondary tear to the fragile spinal cord when posture changes. Moreover, such cavities can evolve into cystic spaces or glial scars, which are obstacles to CNS tissue repair, as they provide an unfavorable substrate for cellular migration and regeneration.[87] Thus, it is imperative to closely fill these irregular and multi-shaped cavities. In clinical wound management outside the spinal cord, physicians tend to use a variety of methods to align irregular wounds, such as suturing, bandaging, and dressing.[88] However, the spinal cord is too soft and fragile to use the above methods to align the stumps. Recent researches have demonstrated that

hydrogels can serve as a tissue glue in SCI to closely contact with the spinal stumps, fill irregular cavities, and align the wounds without secondary damage to normal spinal cord tissue. This is attributed to the high adhesive properties and soft mechanical characteristics of hydrogel. Proper wound alignment facilitated by hydrogels has been shown to reduce glial scar formation. Liu et al used hyaluronic acid to fabricate hydrogel to fill gaps in an SCI spine. Luxol Fast Blue (LFB) staining and ex vivo images revealed that this adhesive hydrogel could effectively align the injured spinal cord stumps to maintain structural integrity. Notably, the hydrogel-treated group exhibited decreased CSPGs at the lesion site compared with untreated SCI controls, indicating that hydrogel-mediated stump alignment could inhibit glial scar formation.[89] In addition, the polymer chains within hydrogels can topologically entangle with spinal cord tissue, effectively stitching the hydrogel to the wet tissue at a molecular level following crosslinking. This adhesive interaction preserves the anatomical structure integrity of the injured spinal cord and prevents secondary trauma induced by postural change. Liu et al engineered an in situ-formed glycidyl methacrylated silk fibroin/laminin acrylate (SF-GMA/LM-AC) hydrogel to fill gaps in SCI. (Figure 5) This hydrogel exhibited strong adhesion strength (4.2 ± 0.7 kPa), and it could adhere firmly to native spinal cord tissue, even the spinal cord was under stretching conditions. The ex vivo spinal cord images demonstrated that the rostral and caudal stumps maintained intact and natural anatomical configurations when bridged by the adhesive hydrogel, whereas both stumps in the control group without hydrogel exhibited a deformed and twisted appearance caused by postural changes.[90] Additionally, hydrogel that adheres tightly to the spinal cord can enhance the

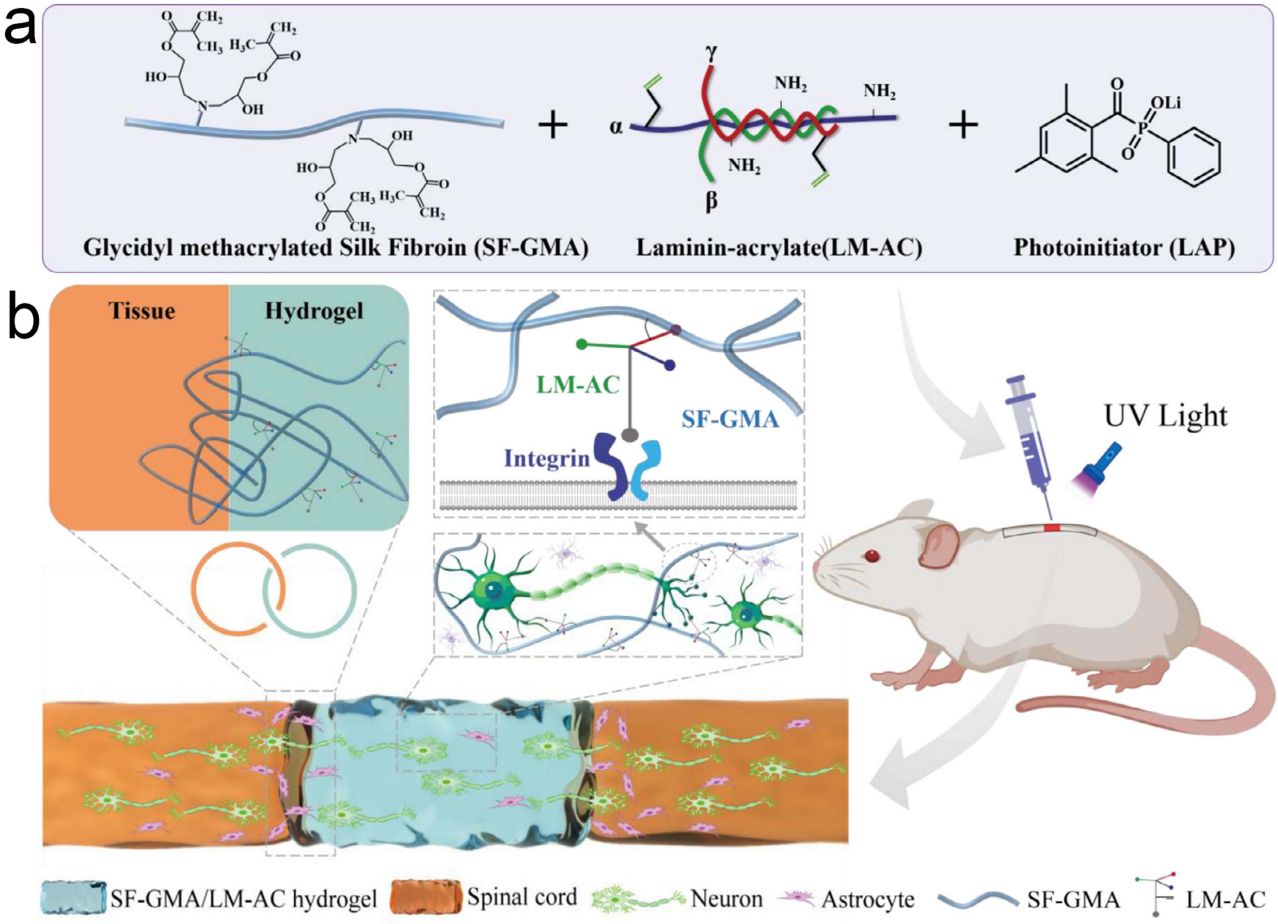

Figure 5 Schematic of the in situ forming adhesive and bioactive glycidyl methacrylated silk fibroin/ laminin-acrylate (SF-GMA/LM-AC) hydrogel to improve neural regeneration in SCI rats. (**a**) The preparation of hydrogel precursor solution by mixing the photoinitiator LAP with SF-GMA and LM-AC. (**b**) The administration of hydrogel. Upon ultraviolet irradiation, LAP trigger the covalent cross-linking of vinyl groups in both SF-GMA and LM-AC. At the interface, the precursor solution infiltrates the spinal cord tissue, creating a tight integration with the host tissue through topological entanglement during the in situ gelation process. Within the hydrogel matrix, integrin on the cell surfaces recognize LM, significantly promoting cell adhesion and survival. Reproduced from Liu Y, Zhang Z, Zhang Y et al. Construction of adhesive and bioactive silk fibroin hydrogel for treatment of spinal cord injury. Acta Biomater. 2023;158:178–189. Copyright 2023 Elsevier.

efficacy of therapeutic cargo by maintaining its position at the optimal site. Gao et al used a gelatin and hyaluronic acid-based hydrogel scaffold to support adult spinal cord tissue (aSCT) transplantation. Hematoxylin and eosin staining confirmed that aSCT could be correctly fixed between the stumps in a SCI rat due to the encapsulation of adhesive hydrogel. After 8 weeks, the Basso, Beattie, and Bresnahan locomotor rating scale score of hydrogel scaffold with aSCT increased to 8.7 ± 1.2 in a rat SCI model (n=3), which was higher than the control group (3.0 ± 1.0, $p<0.05$). This result indicated that the adhesive hydrogel facilitated functional integration and accelerated motor recovery in rats with complete SCI.[91] Similarly, Zhu et al and Yang et al also used hydrogels to anchor spinal cord stumps together.[92,93]

Transmit Bioelectric Signals

The native spinal cord exhibits slight electrical conductivity attributable to its abundant neuronal population and the dynamic ionic flux across cellular membranes, with a resistivity of approximately 150 Ω·cm (in contrast, normal saline exhibits a resistivity of 72.1 Ω·cm).[94] Following SCI, conductivity was sharply decreased due to the glial scar, cavity formation, and ionic imbalance. These alterations impede neural regeneration, disrupt bioelectrical signaling, and diminish the efficacy of ES therapies. Given that electrical signal transmission and stimulation are fundamental to neuronal function, because cellular communication and behavior in the CNS depend on bioelectrical cues, restoring the conductivity of the injured spinal cord is imperative.[95] In this context, considerable research efforts have focused on developing conductive hydrogels to facilitate electrical signal transmission in SCI, owing to their favorable biocompatibility, accessibility, and versatile capacity for functional loading. Luo et al doped poly-pyrrole into chondroitin sulfate hydrogel under oxidative conditions to promote SCI repair by regulating the neuronal differentiation, migration, and axon outgrowth of NSCs. This composite hydrogel demonstrated a conductivity of 6.38 ± 0.33 mS/cm and a low charge-transfer resistance. NSCs cultured within this conductive microenvironment preferentially differentiated into neurons and oligodendrocytes, with reduced astrocytic differentiation compared with nonconductive hydrogel. The in vivo implantation of NSC-laden conductive hydrogels resulted in significantly increased cell spreading and neuronal density, indicating that endogenous stimuli could be effectively transmitted through the conductive matrix to modulate stem cell differentiation pathways.[96] Moreover, in wireless ES therapies for SCI, synthetic and inorganic piezoelectric materials exhibit poor compatibility with neural tissue. Hydrogel with conductivity could function analogously to electronic cables by providing a separation between the piezoelectric materials and spinal cord tissue, thus enhancing biocompatibility. Li et al incorporated silk fibroin hydrogel with polydopamine-coated barium titanate ($BaTiO_3$) nanoparticles ($BaTiO_3$@PDA) to construct an ES hydrogel. NSC viability remained at nearly 100%, even after incubation with 50,000 μg/mL hydrogel-capsulated $BaTiO_3$@PDA. In contrast, a previous study reported that direct exposure to $BaTiO_3$ nanoparticles at a much lower concentration of 50 μg/mL induced significant cytotoxic effects in A549 cells.[97,98] This suggests that the separation function of conductive hydrogel mitigates the cytotoxic effects of piezoelectric materials, thereby enhancing their bioavailability and expanding their potential applications in SCI repair. However, the limited stimulation area achieved by nanogenerators necessitates further optimization to reduce the dosage required for effective nerve injury repair. Zhong et al fabricated a conductive hydrogel by blending poly(3,4-ethylenedioxythio-phene): poly (styrenesulfonate) (PEDOT: PSS) with GelMA to address this, subsequently loading $BaTiO_3$@PDA for application in ES therapy for SCI. (Figure 6) When incorporated into a closed electrical circuit and connected to a light-emitting diode (LED), this ES hydrogel generated a continuous electric current adequate to illuminate the LED. $BaTiO_3$@PDA loaded in conductive hydrogel significantly improved the motor function recovery of SCI rats compared with control group, indicating the stronger ES effect of $BaTiO_3$@PDA hydrogel.[99] Other studies by Deng et al, Chen et al, and Zhu et al also developed various conductive hydrogels to promote neuronal regeneration.[100–102]

Scavenge Free Radicals

The presence of free radicals at the site of SCI not only inflicts damage upon healthy tissue but also compromises the efficacy of various therapeutic agents, such as cells, readily oxidizable compounds, and nucleic acids. Consequently, scavenging free radicals is a critical step in treating SCI. Hydrogels functionalized with boronic acid groups can react with ROS owing to their susceptibility to oxidation, thereby competing with healthy tissues and therapeutics for oxidative interactions. Ying et al employed laponite and N_1-(4-boronobenzyl)-N_3-(4-boronophenyl)-N_1, N_1, N_3, N_3-

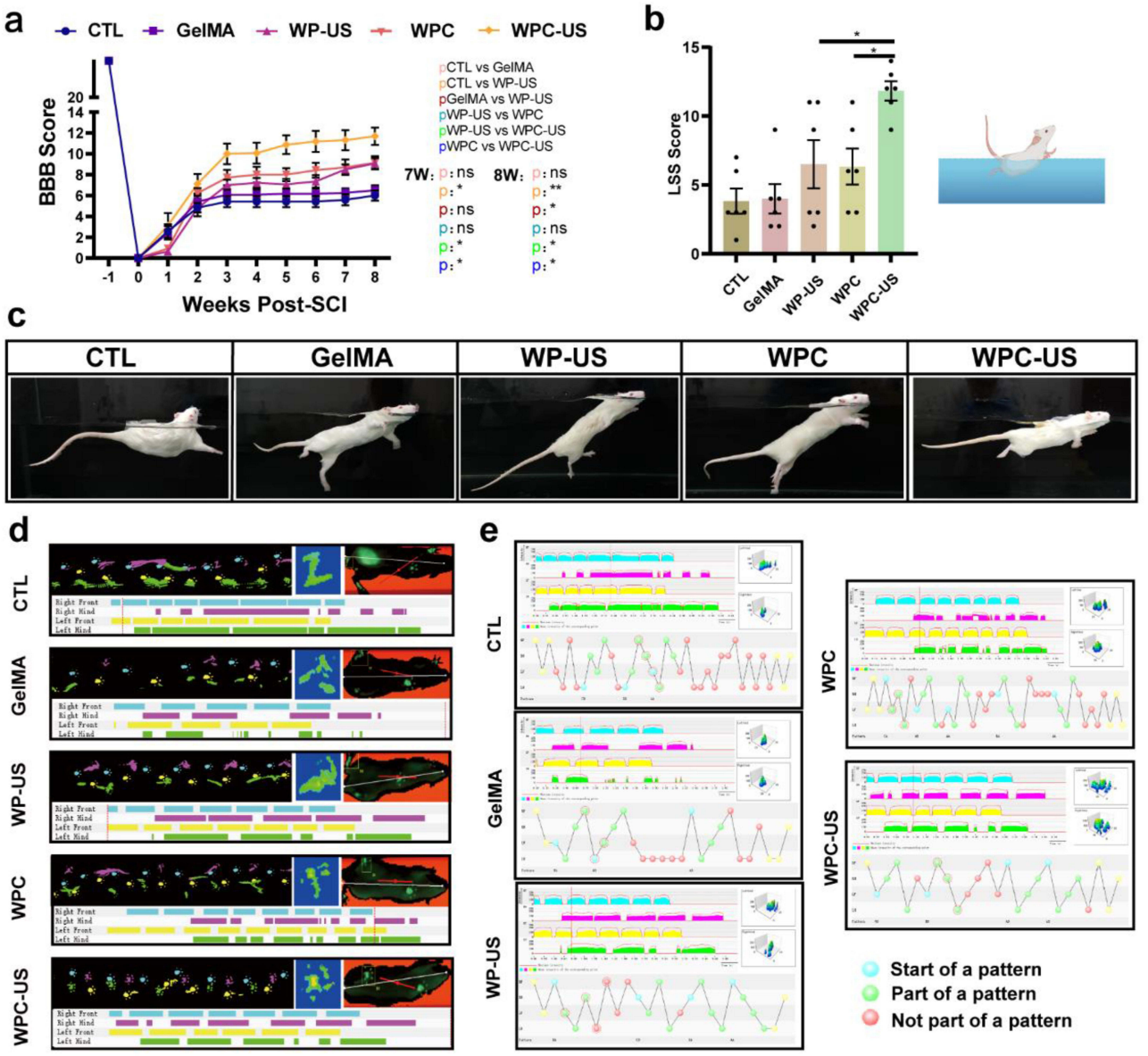

Figure 6 Wireless-powered piezoelectric composite hydrogel with wireless electrical stimulation promotes locomotor function recovery after SCI. (**a**) Basso Beattie Bresnahan scores from preinjury to 8 weeks postinjury (n = 6). The group that received PBS injection served as the CTL group; the group injected with the GelMA hydrogel was termed GelMA; the group injected with the Wireless-powered piezoelectric hydrogel and received US stimulation was termed WP-US; the group injected with Wireless-powered piezoelectric hydrogel-incorporated NSCs and hUCMSCs was termed WPC; and the group injected with wireless-powered piezoelectric WP hydrogel-incorporated NSCs and hUCMSCs and received US stimulation until the end of the experiment was termed WPC-US. (**b** and **c**) Louisville Swim Scale scores and photographs of swimming test at 56 days postinjury (n = 6). (**d** and **e**) Representative images of footprint tracks and gait patterns. Reproduced from Zhong H, Zhou M, Guo J et al. Ultrasound-driven wireless piezoelectric hydrogel synergizes with cotransplantation of NSCs–hUCMSCs for structural and functional recovery in spinal cord injury. Mater Today Bio. 2025;32:101805. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
Abbreviation: LF, Left forelimb (yellow); RF, right forelimb (blue); LH, left hindlimb (green); RH, Reproduced from Zhong H.

tetramethylpropane-1, 3-diaminium (TPA) to fabricate a ROS-scavenging hydrogel via electrostatic crosslinking and protect sensitive and fragile therapeutics from oxidative reactions. Dental pulp stem cells (DPSCs) were encapsulated within this hydrogel for treating SCI. Immunofluorescence staining revealed that the good effective scavenging ability of the phenylboronic acid group in TPA decreased ROS while the population of DPSCs increased at the injury site compared with controls. This protective effect enabled DPSCs to efficiently differentiate into motor neurons, integrate into neural circuits, and promote synaptic regeneration.[103] These findings indicate that the ROS-scavenging hydrogel significantly enhanced stem cell survival within the oxidative microenvironment characteristic of SCI. Inspired by the ROS-induced

degradation ability of hydrogels, smart drug delivery systems have been developed to modulate drug release rates in accordance with the progression of SCI. Li et al synthesized a ROS-scavenging hydrogel by crosslinking polyvinyl alcohol (PVA) with 4,4'-(diphenylsilanediyl) bis (N, N-diphenylaniline) (TSPBA) through borate ester bonds. The strong oxidative activity of ROS targets these borate ester linkages, disrupting the hydrogel network, facilitating the release of therapeutic agents, and concurrently reducing ROS levels during the acute injury phase. Following intensive ROS clearance and rapid injury mitigation, spinal cord repair enters a chronic phase that necessitates sustained and mild treatment. Accordingly, drug release decelerates due to the sluggish degradation of this hydrogel under the ROS-reduced environment and limited drug diffusion.[104] Thus, ROS-responsive hydrogels could not only exhibit antioxidative properties but also enable adaptive cargo release aligned with the evolving therapeutic requirements of SCI. Hydrogels designed by Chen et al and Wei et al, similarly demonstrated efficacy in reducing ROS levels during SCI treatment.[105,106]

Electrospun Nanofibers

Nanofibers are elongated, wire-like materials with nanoscale diameters and a specific length-to-diameter ratio.[107] The emergence of electrospinning technology has expanded the range of raw materials available for nanofiber fabrication, simplified the production process, and extended the application of nanofibers to fields such as biomedicine, filtration materials, and energy storage. Electrospinning is a technique that employs an electric field to direct the deposition of polymer fibers onto designated substrates. This method was notably advanced by the research groups of Darrell Reneker and Gregory Rutledge in the early 1990s.[108] In brief, a polymer solution is gradually extruded from a needle pushed by a syringe pump and forms a pendant droplet due to surface tension. The droplet becomes charged by the application of a high-voltage direct current electric field between the needle and the collector. The droplet deforms into a conical-shaped structure known as a Taylor cone due to the electrostatic repulsion between surface charges bearing identical polarity within the droplet. When the electric field strength surpasses the surface tension, the droplet elongates into a jet that travels rapidly toward the collector with solvent evaporation, ultimately yielding ultrafine fibers deposited on the collector surface.[109] Electrospun nanofibers can be arranged in highly ordered and customized configurations by employing various collector designs compared with nanofibers self-assembled via noncovalent interactions.[110] In SCI management, electrospun nanofibers offer considerable advantages include high surface area for drug delivery and the ability to function as biomimetic scaffolds with tailored architecture and a highly aligned orientation. When designing electrospun nanofibers, synthetic polymers such as polylactic acid (PLA), poly(L-lactic acid) (PLLA), poly(lactic-co-glycolic acid) (PLGA), and polycaprolactone (PCL) are widely utilized in the context of selecting electrospun materials for SCI repair. To enhance cell adhesion and spreading, the wettability of these polymers can be improved by incorporating hydrophilic components, such as PEG and natural biopolymers. Natural polymers can also serve as the precursors for electrospinning. Post-treatment methods such as photo-crosslinking, ionic crosslinking, or chemical crosslinking could be employed to construct stable, structurally sound nanofibers. Furthermore, the electrophysiological microenvironment of neural tissue can be mimicked by integrating conductive or electrogenic substances into the spinning dope.

Customize Scaffold Structure

The therapeutic demands for SCI, with prolonged and intricate disease progression, are multifaceted. Conventional drug release, which typically involves the direct release of a single drug from its carrier, is insufficient to address the complex and dynamic treatment requirements. Moreover, biomimetic therapeutic strategies have emerged as a promising avenue for SCI management due to their superior potential for tissue regeneration and functional integration.[111] Nonetheless, replicating the intricate and delicate microarchitecture of native tissues through purely physical or chemical approaches remains challenging. Electrospun nanofibers offer a promising solution to these challenges, owing to their precisely controlled fabrication processes and customizable structural properties. Zhang et al developed a core-shell nanofiber by utilizing coaxial electrospinning technology to explore the novel drug release pattern. This system employed a coaxial nozzle connected to two independent syringes; one contained a PLGA solution loaded with nafamostat mesylate, and the other contained a PLLA solution with neurotrophins-3. TEM images verified the presence of a core-shell bilayer structure, which was capable of sequential and spatiotemporal drug release. This dual-release platform could initially deliver nafamostat to mitigate inflammation during the acute phase of SCI, thereby establishing an optimal microenvironment for NSC survival. Subsequently, the controlled release of neurotrophin-3 was absorbed by endogenous NSCs, facilitating their differentiation.[112] Beyond microscopic customization,

electrospun nanofibers can be woven into various macroscopic forms to emulate native tissue architecture. Zeng et al engineered a PLGA film by electrospinning to function as an external hood over a hydrogel scaffold. This thin PLGA layer restricted the swelling of the hydrogel in a manner analogous to the dura mater, thereby preventing excessive compression of the spinal cord. The hydrogel was stabilized on a collector by the longitudinal insertion of a custom-fabricated fine wire, around which PLGA fibers were electrospun to encapsulate a gelatin sponge. SEM images showed that PLGA fibers were closely attached to the surface of the hydrogel and encapsulated it. This composite structure facilitated motor function recovery in Macaca fascicularis with hemisected SCI.[113]

Imitate Nerve Fibers

Spinal cords contain several ascending and descending nerve tracts organized longitudinally at the mesoscopic scale, with each tract comprising thousands of axons aligned in parallel at the nanoscale.[114] In SCI, this highly ordered architecture is disrupted due to mechanical insults such as compression, distraction, transection, and subsequent secondary injury. Promoting axon regeneration represents one of the most fundamental strategies for SCI repair. However, regenerated axons often display disordered growth trajectories, posing significant difficulties in traversing the lesion site and establishing functional connections with distal targets. This disorganization often results in suboptimal functional recovery, aberrant neural electrical activity, and neuropathic pain. Electrospun nanofibers can aggregate into fascicles with parallel nanoscale grooves on their surfaces and have been proposed to emulate the structural characteristics of native nerve tracts and provide hierarchical guidance cues to regenerating axons. Chu et al designed a homemade wet-spinning apparatus to fabricate nanofiber bundles. (Figure 7) In their method, a precursor solution composed of alginate and gelatin was extruded through a needle into a coagulation bath containing 3% $CaCl_2$ and 5 mg/mL photoinitiator at 37°C. The resulting continuous filaments were exposed to ultraviolet irradiation for 10 min and were collected using a take-up roller analogous to that employed in weaving looms. SEM images clearly showed nanoscale grooves on the surface of the nanofiber bundles. When seeded with NSCs, these fibers could promote differentiation into neurons with longer axonal neurites and lower intersection angles between axon extending axis and fiber axis in murine models of SCI than those of bulk hydrogels, thereby significantly enhancing motor functional recovery and integration.[115] These phenomena demonstrate that electrospun nanofibers could serve as scaffolds analogous to agricultural trellises, providing nanoscale guidance that precisely regulates axonal alignment and facilitates the reestablishment of complete neural connections. Chen et al incorporated piezoelectric potassium sodium niobate ($K_{0.5}Na_{0.5}NbO_3$) nanowires into poly (lactic acid) nanofibers to better mimic the electrical properties of axons. Under an acoustic pressure of 150 kPa, this nanofiber generator produced an open-circuit voltage of 12.09 V and a short-circuit current of 20.8 μA, effectively promoting NSC differentiation and endogenous angiogenesis.[116] Studies by Yao et al, Zhu et al, and Chen et al also demonstrated the effectiveness of electrospun nanofibers in mimicking nerve fibers to promote SCI repair.[117–119]

Extracellular Vesicles

Extracellular vesicles (EVs), including exosomes, microvesicles, and apoptotic bodies, are nanoscale lipid bilayer membrane capsules secreted by cells. These vesicles are found in tissue culture supernatants, as well as various biological fluids, such as blood, saliva, breast milk, cerebrospinal fluids, and malignant ascites.[120] EVs serve as critical mediators of intercellular communication by transporting a diverse array of biomolecules to recipient cells, such as membrane proteins, membrane lipid RNAs, DNA, cytosolic proteins, and other signaling molecules.[121] Due to the high biocompatibility, enhanced stability, and limited immunogenicity of EVs, they are employed in SCI treatment as vehicles for the delivery of therapeutic agents and as substitutes for the paracrine function of cell therapy. When designing EVs as delivery vehicles, drug loading can be achieved through two primary strategies: pre-loading and post-loading. Pre-loading involves engineering parent cells so that active substances are encapsulated within the cavity or modified onto the surface of EVs during their biogenesis. In contrast, post-loading refers to the direct loading of therapeutic agents into EVs using physicochemical methods after they have been isolated. To enhance the accumulation of drug-loaded exosomes at the lesion site, EVs derived from cells with innate chemotactic properties can be selected. Furthermore, to promote anti-inflammation and tissue repair, EVs can be sourced from anti-inflammatory cells or those with high regenerative potential.

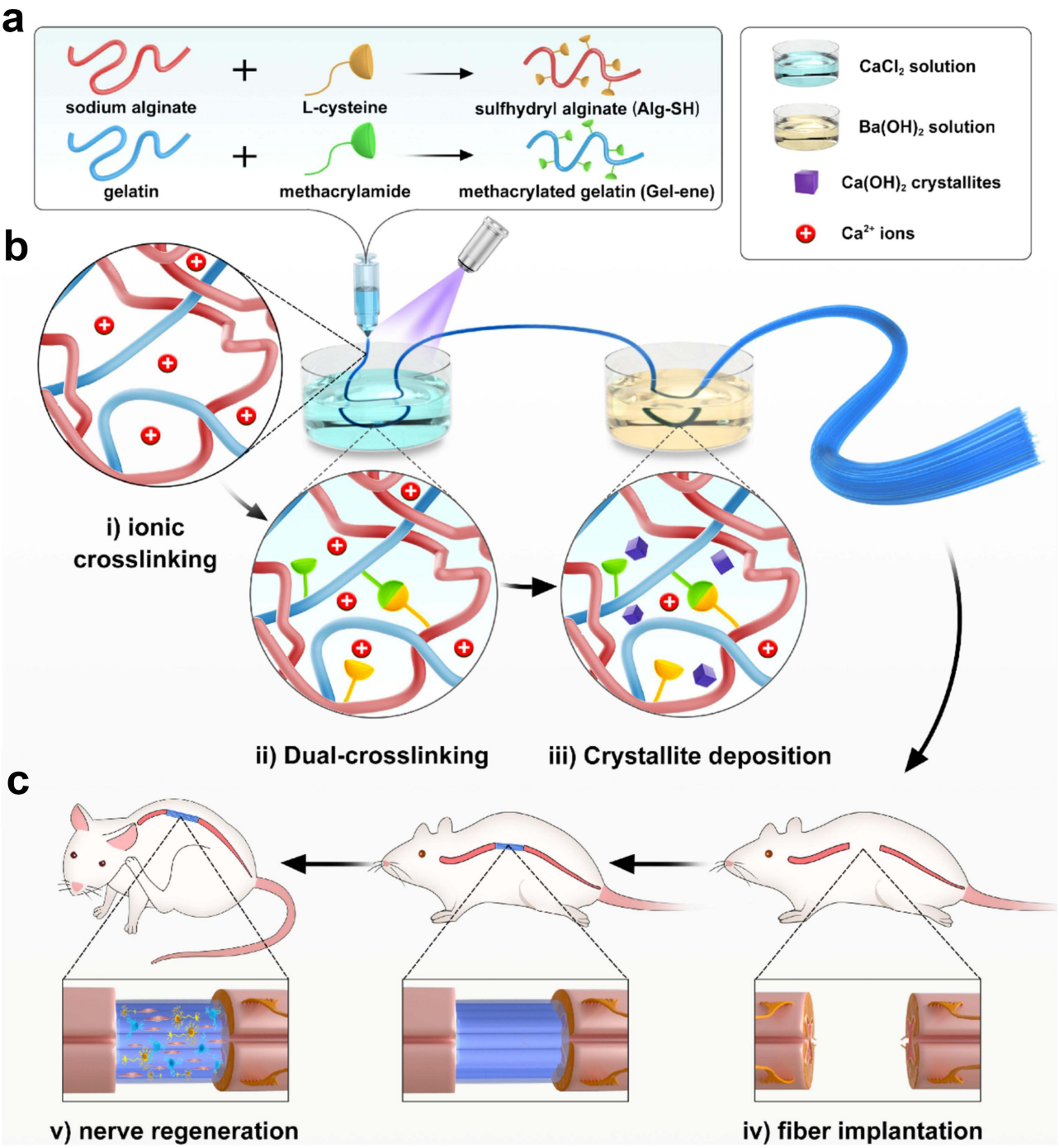

Figure 7 Schematic illustrations of the preparation and application of fibrous bioscaffold. (**a**) The synthesis of sulfhydryl alginate (Alg-SH) and methacrylated gelatin (Gel-ene). (**b**) The wet-spinning process for fibrous bioscaffold fabrication: (i) extrusion of the hydrogel precursor solution composed of Alg-SH and Gel-ene followed by ionic crosslinking in a coagulation bath containing calcium chloride and photoinitiator; (ii) exposure of the filaments to ultraviolet light, forming of an ionic and covalent dual-crosslinking network; and (iii) immersion of the filament in a barium hydroxide solution, resulting in crystallite deposition. (**c**) Schematic showing the implantation into the lesion area of SCI rats (iv), with outcomes of SCI repair (v). Reproduced from Chu Y, Yang K, Huang L et al. Bioinspired fibrous scaffolds with hierarchical orientations for enhanced spinal cord injury repair. Chem Eng J. 2024;502:157969. Copyright 2024 Elsevier.

Transport Therapeutic Agents

In SCI treatment, a prevalent therapeutic strategy is to modify or PEGylate the drug delivery system to facilitate the penetration of the BSCB and prolong circulation time, thereby enhancing drug concentration at the injury site. However, the efficiency of such artificial conjugations remains limited. Moreover, the repeated administration of PEGylated

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nanoparticles may provoke the production of anti-PEG antibodies, leading to the accelerated clearance of subsequently administered nanoparticles.[122] The PEGylation layer may sterically impede the binding of the modified targeting ligand on nanoparticles to the receptors. Consequently, a natural delivery system is needed that can traverse the BSCB and maintain prolonged circulation without modification. EVs inherently carry signaling biomolecules of the parent cell and may inherit the parent cell's ability to migrate to the spinal cord lesion. As illustrated by Guo et al, exosomes secreted by MSCs could bypass the BSCB following intranasal administration. Micro-computed tomography displayed the significant accumulation of these exosomes at the spinal cord lesion site, with minimal distribution to the brain or major organs. Importantly, blocking chemokine receptors on the exosomes markedly reduced their accumulation, confirming that their BSCB-penetrating capacity is dependent on chemokine receptors inherited from the parent cells. Thus, the intranasal delivery of siRNA-loaded exosomes effectively targeted neurons and promoted functional recovery in rat models of complete SCI.[123] Furthermore, certain exosomes have a long circulation time. Gao et al employed exosomes derived from M2 macrophages to encapsulate berberine for SCI therapy. Pharmacokinetics analysis revealed that the half-life of exosome-encapsulated berberine was 15.06 ± 1.35 hours, significantly longer than the 4.67 ± 0.28 hours observed for free berberine. IVIS data further demonstrated that exosome-loaded berberine remained on the injured spinal cord over 24 hours due to its long circulation period. This prolonged exosome circulation time may be attributed to the presence of the surface protein CD47 derived from M2 macrophages, which could inhibit their phagocytosis by the mononuclear phagocyte system. Moreover, the negatively charged surface of exosomes reduces nonspecific interactions with plasma proteins, representing another critical factor contributing to prolonging their half-life.[124] Studies by Rong et al, Liu et al, and Ran et al also used EVs as drug vehicles to deliver siRNA, microRNA, and bioactive peptides to reach high therapeutic concentrations at the SCI site.[125–127]

Substitute Cell Therapy

Cell therapy partially relies on its paracrine functions in regeneration medicine.[128] However, using cells as sources of therapeutic factors presents several limitations, including the potential for severe adverse reactions such as immune rejection, pulmonary vascular obstruction, and malignant transformation. Additionally, cell therapy requires stringent production conditions and incurs high costs. As cells age and die, the secretion of therapeutic factors decreases, while cellular debris may generate toxic substances. Consequently, alternative media that can replicate the paracrine therapeutic effects of cell therapy are needed. As one of the most important paracrine substances, EVs have the capacity to transfer proteins, mRNAs, and microRNAs from parent cells to target cells, facilitating intercellular communication, genetic material delivery, the regulation of signaling pathways, and nutrient administration. Therefore, EVs can partially recapitulate the therapeutic functions of their parent cells in SCI repair, such as promoting neuroprotection, immunomodulation, axonal regeneration, neuronal relay formation, and myelin restoration.[129] Zhang et al employed M2 microglia-derived EVs to mitigate local inflammation at the SCI site. These M2 microglia-derived EVs were reported to enhance M2 polarization, reduce the infiltration of inflammatory cells, and consequently attenuate neuronal apoptosis in SCI rat models. These effects are attributed to the presence of anti-inflammatory factors, immunomodulatory microRNAs/long non-coding RNAs, and signaling pathway regulators within the EVs.[130] Similarly, Xiong et al investigated the therapeutic potential of exosomes derived from regulatory T (Treg) cells. Bioinformatic analysis revealed a significant enrichment of miRNA-709 in Treg cell-derived exosomes. Upon uptake by microglia, miRNA-709 was released and negatively regulated nuclear factor (NF)-κB activating protein, thereby reducing microglial pyroptosis, diminishing inflammatory responses, and enhancing motor function recovery after SCI.[131] Qin et al isolated epidermal growth factor receptor-positive NSCs ($EGFR^+$ NSCs) to obtain exosomes with superior regenerative properties to enhance neuroprotection. MicroRNA sequencing identified a high abundance of miR-34a-5p in $EGFR^+$ NSC-derived exosomes. This microRNA was transferred to neurons, where it downregulated histone deacetylase 6 expression, thus rescuing autophagy and stabilizing neuron microtubules at the injury site.[132] In addition, EVs capable of repairing the BSCB offer therapeutic benefits for SCI. Xie et al discovered that exosomes derived from $CD146^+CD271^+$ human umbilical cord mesenchymal stem cells (UCMSCs) effectively restored BSCB integrity in SCI rat models after intranasal administration. miR-501-5p was abundantly expressed in these exosomes, which targeted the microvasculature to downregulate myosin light chain kinase expression, thus stabilizing the BSCB, preserving vascular integrity, and promoting functional recovery after SCI.[133] Wang et al, Ren et al, and Wang et al also explored the use of

macrophage-derived, Schwann cell-derived, and dendritic cell-derived EVs to modulate the immune response and promote regeneration for SCI therapy.[134–136]

Virus

Gene therapy offers a promising approach for treating SCI by manipulating gene expression through precisely regulating the complex and dynamic microenvironment of the injury site. However, the effective delivery of therapeutic nucleic acids into target cells is hindered by several biological barriers, including the cell membrane, ubiquitous nucleases, and lysosomal degradation. Consequently, the use of delivery vectors is essential to safely and efficiently transporting therapeutic genes into target cells. In SCI treatment, viral vectors have garnered significant attention due to their high transduction efficiency in neuronal cells and their unique capacity to transport gene therapeutics along axons, enabling the robust and widespread production of therapeutic agents.[137] Therefore, the design core for virus application in SCI treatment is to choose the virus with high affinity with CNS. For example, adeno-associated virus serotype 1 (AAV1) was internalized by cells after recognizing the sialoglycoprotein receptor, which is abundantly expressed on the axonal and soma membranes of motor neurons.[138] Leveraging this mechanism, Stepankova et al employed an AAV1 vector to achieve the high-level expression of target genes in SCI models. After the direct injection of green fluorescent protein (GFP)-encoding AAV1 into DRG in vivo, a transduction efficiency of approximately 36.59% was observed. The transfection efficiency of liposomes in isolated DRG was reported to be less than 1%. The administration of alpha 9 integrin-expressed AAV1 into the DRG of SCI mice resulted in significant axonal regeneration extending rostrally to the medulla, which contributed to improvements in motor and sensory functions.[139] These findings underscore the strong neuronal tropism of viral vectors due to their inherent neuroinfectivity. Additionally, certain viral vectors can exploit axonal transport mechanisms to deliver gene therapeutics along and across axons.[140] Axonal transport is a vital physiological process facilitating the bidirectional movement of materials between neuronal cell bodies and axon terminals. Leibinger et al injected AAV1-Cre into the unilateral sensorimotor cortex of Rosa26-tdTomato reporter mice. In this model, tdTomato is expressed only upon exposure to Cre recombinase. Notably, red-labeled neurons were observed in the raphe nuclei of the brainstem, a region distant from the cortex. This indicates that AAV1-Cre particles were transported anterogradely along cortical axons and crossed synapses to infect downstream raphe neurons, thereby triggering Cre-dependent tdTomato expression. This axonal transport ability of virus enables the extensive distribution of gene therapy throughout interconnected spinal regions due to the numerous axonal projections and intricate neuronal network in the spinal cord. Consequently, a single unilateral injection of hyper IL-6-encoding virus into the sensorimotor cortex could promote corticospinal tract axon regeneration and facilitate locomotor recovery in both hind limbs.[141] Additional studies by Wu et al, Squair et al, and Chen et al explored various virus-based gene therapy strategies in SCI treatment.[142–144]

Summary

The treatment of SCI represents a multidimensional intervention paradigm, transitioning from physical stabilization to complex biochemical modulation. For primary injuries, the therapeutic focus lies in spinal cord decompression and ischemia mitigation. As the pathology evolves into the secondary injury phase, the therapeutic emphasis shifts toward the intricate biochemical microenvironment. Strategies aim to disrupt the vicious cycle of excitotoxicity and ionic imbalance by blocking glutamate receptors, inhibiting Na^{+}/Ca^{2+} channels, and preventing the opening of mPTP. Concurrently, targeting neuroinflammation requires modulating the polarization of microglia and macrophages to convert the hostile environment into a pro-regenerative anti-inflammatory niche. To counteract lipid peroxidation induced by ROS, the deployment of high-efficiency radical scavengers is critical to terminate sequential damage. At the level of neural circuit reconstruction, therapeutic interventions focus on oligodendrocyte preservation, the inhibition of axonal degeneration, and the degradation of glial scars. Also, supplementing neurotrophic support and antagonizing inhibitory molecules within the scar microenvironment provides the necessary impetus for neural regrowth while simultaneously dismantling physical and biochemical barriers to regeneration.

The emergence of novel pharmacological formulations has propelled breakthrough progress in SCI therapy, yet distinct challenges persist in their clinical translation. Nanoformulations effectively shield bioactive payloads and optimize pharmacokinetic profiles. However, the blood-brain barrier and the complex neural architecture often lead to suboptimal intracellular delivery in CNS cells. Hydrogel formulations, characterized by their superior biomimetic properties resembling the ECM, serve as ideal scaffolds for cell therapy. And their high biocompatibility and tissue

adhesiveness facilitate the preservation of spinal cord anatomical integrity. However, caution must be exercised regarding the risk of secondary mechanical compression on fragile spinal tissues caused by the hygroscopic swelling of the hydrogel after implantation. Electrospun nanofibers provide physical guidance for axonal regrowth and pathway reconstruction through highly ordered topographical cues. Nevertheless, their dense fibrous arrangement often hinders cellular infiltration, and residual organic solvents from the fabrication process pose potential cytotoxic risks. Furthermore, EVs and viral vectors exhibit superior CNS affinity. However, EVs are hampered by complex large-scale manufacturing and inconsistent quality control standards, while the limited packaging capacity of viral vectors struggles to address the multi-target intervention requirements necessitated by the complex pathology of SCI. (Table 1).

There is an urgent clinical demand for advanced formulations. The BSCB and the flushing effect of CSF prevent the localized enrichment of most biopharmaceuticals, while conventional delivery methods fail to bridge physical defects or effectively intervene in secondary injury cascades. Therefore, there is a critical need for integrated systems that combine targeted delivery, structural support, multi-target synergy, and sustained release. Recent clinical milestones of novel drug formulations in SCI repair include professor Jianwu Dai's trials (NCT02688049, NCT02352077, NCT02510365, NCT03966794, NCT02688062) of evaluating collagen scaffolds combined with cell or electrical stimulation, the exploring dECM-laden stem cells in Phase II trials of Russian Federal Research Clinical Center (NCT02326662). Moreover, in 2025, Xuanwu Hospital initiated a Phase I trial (NCT07295067) using intrathecal MSC-derived EVs for syringomyelia, and Yonsei University launched a Phase II study (NCT06922890) employing AAV vectors for NeuroD1-mediated spinal cord regenerative therapy. However, the path from bench to bedside remains arduous due to the lack of standardized biosafety metrics, challenges in quality control for complex formulations, lacking long-term safety data, and insufficient preclinical research on non-rodent animals. (Table 2).

Table 1 Comprehensive Evaluation of Novel Drug Fomulations in SCI Treatment

Formulation Type	Nanoformulations	Hydrogel Formulations	Electrospun Nanofibers	Extracellular Vesicles	Virus
Key Advantages	• Improving drug-like properties[34] • Constraining the drug release at injury site[32] • Enabling targeted modification[42] • High stability and broad-spectrum catalytic power[50] • Enabling wireless, cellular-level electrical stimulation[60]	• Improving cell therapy survival rates[75] • Enriching drug locally[83] • Maintaining spinal cord anatomical integrity[90] • Enhancing electrical stimulation safety and conductivity[98,99] • Consuming free radicals[104]	• Guiding axonal regrowth via highly ordered structures[115] • Enabling complex drug release modes with customizable structures[112]	• Inherently penetrating the blood-spinal cord barrier[123] • Long systemic circulation[124] • Carrying parental cell therapeutic mediators[131]	• Superior transfection efficiency in nerve cells[139] • Achieves wide neural distribution via transaxonal transport[141] • Enables long-lasting protein expression[144]
Major Limitations	• Suboptimal intracellular delivery in CNS cells[145] • Concerns on biocompatibility and immune compatibility[146]	• Potential for "swelling pressure" on the spinal cord[147] • Poorly controlled degradation kinetics[148]	• Poor cell infiltration between fiber layers[149] • Risk of organic solvent residues[150]	• Limited drug loading capacity[151] • Notable heterogeneity[152]	• Risks of immunogenicity and insertional mutagenesis[153] • Limited genetic payload capacity[153]
Applicable Scenarios	• Delivery of poorly soluble or nucleic acid drugs[31,36] • ROS scavenging[49] • Electrical stimulation[58,59]	• Seamless stitching[90] • Transplant substrate[72] • Tissue engineering[76]	• Biomimetic scaffolds for axon guidance[116] • Multifunctional drug delivery devices[112]	• Cell-free therapy[132] • Transporting therapeutic agents[124]	• Gene therapy[139] • Tracing neural circuits[143]

Table 2 Comparison of Clinical Translational Attributes and Challenges of Novel Drug Formulations in SCI Treatment

Formulation Type	Common Delivery Routes	BSCB Relevance	Long-term Safety	Potential Immunogenicity	Chemistry, Manufacturing, and Controls Challenges	Evidence Level
Nanoformulations	Local injection[154] Intravenous injection[154]	Low relevance; Direct BSCB bypass[155] High relevance; Transient permeability window; Ligand/biomimetic-enhanced BSCB crossing[145]	• Long-term retention concerns[146] • Possible off-target deposition[146] • Unknown dose-dependent adverse effects[146]	• Potential inflammation degradation[146] • Carrier-induced specific antibody formation[156]	• Batch-to-Batch variability and reproducibility[157] • Challenges in detecting structural modifications[157]	• Rodents[145] • Non-rodent[158,159]
Hydrogel formulations	Local injection or implantation[160]	Low relevance; Direct BSCB bypass[155]	• High bioavailability[95] • Lacking long-term safety data[95]	• Low immunogenicity[161] • Potential for chronic foreign-body responses[161]	• Challenges in GMP-compliant scale-up[161] • Challenges in maintaining bioactivity post-sterilization[161]	• Rodents[162] • Non-rodent[163] • Non-human primates[113] • Humans (NCT02688049, NCT02352077, NCT02510365, NCT03966794, NCT02688062, NCT02326662)
Electrospun nanofibers	Local implantation[149]	Low relevance; Direct BSCB bypass[155]	• Partial FDA-approved precursors[164] • Lacking long-term safety data[164]	• Potential inflammation degradation[165] • Surface-mediated foreign body response risk[165]	• Suboptimal yield and batch variability[166]	• Rodents[150]
Extracellular vesicles	Intravenous injection[152] Intrathecal injection[152] Local administration[171] Intranasal administration[123]	High relevance; High intrinsic permeability[133] Low relevance; Bypassing BSCB via direct CSF delivery[170] Low relevance; Direct BSCB bypass[155] Low relevance; Bypassing BSCB via neural pathways; Improve BSCB integrity[133]	• Lacking long-term safety data[167]	• Low immunogenicity[168] • Potential immunogenicity from donor MHCs[168]	• Standardization of separation and purification techniques[168] • Storage stability and integrity[168]	• Rodents[169] • Humans (NCT07295067)
Virus	Local injection[172]	Low relevance; Direct BSCB bypass[155]	• Insertional mutagenesis[173] • Replication-competent virus generation[174]	• Risks of acute innate immune activation[153] • Inducing neutralizing antibody	• Assessment and control of empty capsids[175]	• Rodents[176] • Non-rodent[177] • Humans (NCT06922890)

Perspective

Although noteworthy advancements have been achieved in the development of novel drug formulation and in the validation of their therapeutic potential for SCI, several critical bottlenecks remain to be addressed. Primarily, the molecular mechanisms underlying pathological progression and regeneration inhibition following SCI have not been fully elucidated. Further in-depth exploration of these pathological mechanisms is required to reveal more potential therapeutic targets, such as the key mechanisms of axonal regeneration failure, core factors of the inflammatory storm, and critical drivers of secondary injury. The application of cutting-edge high-throughput platforms, such as multi-omics and single-cell transcriptomic, will facilitate the discovery of further candidate targets. Moreover, incorporating clinical specimens such as tissues and biofluids collected during surgical debridement into research frameworks could help bridge the gap and address the limitations inherent in animal-based mechanistic studies. Secondly, the pathophysiological process of SCI is complex and dynamically evolving. As such, mono-functional drug delivery platforms fall short of achieving desired clinical outcomes. This necessitates the engineering of novel multifunctional integrated delivery systems that synergize diverse pharmacological mechanisms to maximize therapeutic efficacy. Moreover, the development of smart delivery systems capable of real-time surveillance and stage-specific drug release holds significant promise. For instance, the convergence of wearable electronics with these systems could facilitate dynamic monitoring of the local microenvironment and enable on-demand drug delivery. Furthermore, integrating innovative drug delivery modules with brain-computer interface chips for real-time detection and analytics of pathological shifts to govern drug release represents a paradigm shift toward adaptive therapeutic interventions. Furthermore, the screen of novel formulation with optimal delivery efficiency, targeting capability, and smart releasing properties often relies on luck or labor. It is imperative to establish efficient high-throughput synthesis and screening platforms to accelerate the discovery and evaluation of formulations with ideal performance. In this context, artificial intelligence offers a transformative approach for the virtual generation and computational screening of structural scaffolds and material compositions, significantly augmenting research and development efficiency and the probability of clinical translation. With the deepening understanding of SCI pathology, the identification of novel therapeutic targets, and the iterative upgrading of smart delivery platforms, the development of highly specific and efficacious therapeutic regimens is on the horizon, promising a new era of hope for enhancing the quality of life in SCI patients.

Abbreviations

4FPBA, 4-formylphenylboronic acid; APIs, Active pharmaceutical ingredients; AUC, Area under the plasma concentration-time curve; BM-NPs, Biomimetic bacterial outer membrane nanoparticles; BSCB, Blood-spinal cord barrier; Ca^{2+}, Calcium ions; CAT, Catalase; CNS, Central nervous system; CNFs, Cellulose nanofibers; CSPGs, Chondroitin sulfate proteoglycans; ECM, Extracellular matrix; ES, Electrical stimulation; EVs, Extracellular vesicles; GFAP, Glial fibrillary acidic protein; GFP, Green fluorescent protein; GPX, Glutathione peroxidase; G-Rb2, Ginsenoside Rb2; IL-1β, Interleukin-1β; IL-6, Interleukin-6; IVIS, In vivo imaging system; MAPK/ERK, Mitogen-activated protein kinase/extracellular signal-regulated kinase; mPTP, Mitochondrial permeability transition pore; Na^{+}, Sodium ions; NSCs, Neural stem cells; PEG, Polyethylene glycol; PLGA, Poly(lactic-co-glycolic acid); PLLA, Poly(L-lactic acid); PVA, Polyvinyl alcohol; RONS, Reactive oxygen and nitrogen species; ROS, Reactive oxygen species; SCI, Spinal cord injury; SEM, Scanning electron microscope; siRNA, Small interfering RNA; SOD, Superoxide dismutase; TNFα, Tumor necrosis factor-alpha; TSPBA, 4,4'-(diphenylsilanediyl) bis (N, N-diphenylaniline).

Data Sharing Statement

Data will be made available on request from the corresponding author, Qingchuan Wei.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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