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REVIEW

Extracellular Vesicles in Peripheral Nerve Regeneration: From Biology to Therapeutic Engineering

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Abstract: Peripheral nerve injuries (PNIs) pose a significant clinical challenge, often resulting in irreversible functional deficits due to limited spontaneous regeneration. While current therapeutic approaches offer partial solutions, their efficacy remains suboptimal. In recent years, extracellular vesicles (EVs) have emerged as bioactive carriers capable of orchestrating complex regenerative processes without the risks associated with live-cell transplantation. Derived from sources, EVs deliver a repertoire of functional cargos that modulate immune responses, promote axonal regrowth, enhance remyelination, and stimulate angiogenesis. Furthermore, bioengineering strategies enable EVs to be loaded with therapeutic molecules, surface-modified for targeted delivery, and incorporated into stimuli-responsive scaffolds for controlled release. When integrated with biomaterials, EVs demonstrate synergistic effects that enhance spatial guidance, immune modulation, and neurovascular remodeling in preclinical models. However, significant challenges remain, including large-scale EV production, standardization of isolation methods, and meeting regulatory requirements for clinical translation. In this review, we provide a comprehensive overview of the biological roles of native and engineered EVs in peripheral nerve regeneration, highlights advances in EV-functionalized scaffolds, and discusses translational challenges and future directions for clinical implementation.

Keywords: extracellular vesicles, nerve injuries, regeneration, nanomedicine, biomaterials

Introduction

Peripheral nerve injuries (PNIs) present a significant clinical and socioeconomic burden, often leading to irreversible sensory and motor deficits, chronic neuropathic pain, and long-term disability. Globally, millions of patients are affected annually due to trauma, surgical resection of tumors, or iatrogenic damage.[1,2] While the peripheral nervous system (PNS) possesses an inherent ability to regenerate, this regenerative capacity is typically limited to short-distance injuries and is highly dependent on the timely and coordinated response of supporting cellular and molecular mechanisms. In cases involving large nerve gaps, segmental loss, or delayed repair, spontaneous regeneration is rarely sufficient to restore meaningful function, necessitating surgical intervention.[3,4]

Current clinical approaches to PNI repair primarily rely on direct end-to-end neurorrhaphy for short gaps, or autologous nerve grafting for more extensive damage. However, these methods face several persistent challenges. Autografts, considered the gold standard, are constrained by limited donor availability, donor site morbidity, and inconsistent outcomes.[5] Allografts and synthetic conduits have been explored as alternatives, but issues such as immune rejection, limited bioactivity, poor integration with host tissue, and suboptimal support for long-distance axonal regeneration continue to impede their effectiveness.[6] As such, the development of novel, biologically active, and clinically translatable strategies remains an urgent priority in peripheral nerve repair.

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In recent years, the field of regenerative medicine has seen increasing interest in cell-based therapies due to their ability to recapitulate key features of the regenerative microenvironment.[7] These cells can release neurotrophic factors, modulate inflammation, and support axon remyelination.[8] However, several translational barriers persist, including challenges in cell survival and integration, immunogenicity, tumorigenic potential, and ethical or regulatory concerns.[9] As a result, attention has shifted toward acellular, cell-free modalities that can preserve the regenerative benefits of cellular therapies while minimizing associated risks.

Extracellular vesicles (EVs), including exosomes and microvesicles, have emerged as a promising alternative.[10] These nanoscale, lipid bilayer-bound vesicles are secreted by nearly all cell types and play critical roles in intercellular communication by delivering a complex cargo of signaling molecules—such as proteins, lipids, microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and metabolites—to recipient cells.[11] Functionally, EVs derived from regenerative cell types have demonstrated the ability to modulate immune responses, attenuate inflammation, promote neurite outgrowth, enhance angiogenesis, and facilitate remyelination in various preclinical models of PNI.[12] Notably, these vesicles retain the regenerative functionality of their parent cells while offering advantages in terms of stability, storage, scalability, and safety.[13]

Advances in EV isolation, characterization, and engineering have further accelerated their therapeutic potential. Bioengineering strategies now enable the modification of EVs to enhance their targeting specificity, cargo loading capacity, and bioactivity.[13] Techniques such as surface functionalization, genetic manipulation of donor cells, or electroporation-based loading allow for the designing of EVs to specific regenerative cues.[14] Moreover, when incorporated into biomaterial-based delivery systems, EVs can be spatially and temporally controlled to better mimic the physiological healing process.[14,15] These hybrid platforms facilitate sustained release, directional axon growth, and protection of EVs from enzymatic degradation, thereby amplifying their therapeutic efficacy.

In this review, we aim to provide a comprehensive and up-to-date overview of EV-based strategies for peripheral nerve regeneration. We begin by summarizing the biological functions of EVs and their mechanisms of action in neural repair. We then explore the latest developments in engineered EVs, highlighting their design, functional optimization, and therapeutic potential. Finally, we discuss the integration of EVs with biomaterial scaffolds and the key challenges that should be overcome to translate these technologies from bench to bedside. Through this synthesis, we hope to illuminate the promising path ahead for EVs as next-generation therapeutics in peripheral nerve repair.

Biological Basis of Peripheral Nerve Regeneration

Peripheral nerve regeneration is a complex, highly coordinated process involving multiple cellular and molecular events aimed at restoring nerve function after injury. The repair begins with Wallerian degeneration, where the distal portion of the injured axon breaks down, and debris is cleared to prepare the environment for new growth.[16] This is followed by axonal regeneration, during which surviving neurons extend new axonal sprouts toward the target tissue. Finally, successful remyelination by Schwann cells restores the protective myelin sheath, enabling efficient signal conduction. Key players in this regenerative cascade include Schwann cells (SCs), macrophages, and vascular elements.[17]

Schwann Cells

SCs play a significant and multifaceted role in orchestrating peripheral nerve regeneration, actively modulating the complex interplay of cellular and molecular signals that define the post-injury microenvironment.[18] Following peripheral nerve injury, SCs undergo a dramatic phenotypic reprogramming into a repair-supportive state, characterized by enhanced plasticity and the upregulation of genes associated with axon guidance, myelin clearance, and immune modulation.[19] This reprogramming enables SCs to execute a range of regenerative functions: they phagocytose myelin and axonal debris, form Büngner bands to guide axonal sprouts, and secrete neurotrophic factors that foster neuronal survival and outgrowth.[20]

Importantly, emerging evidence challenges the notion of SCs as merely supportive bystanders, instead revealing their role as active regulators of both repair and pathology.[21,22] For instance, SCs secrete secreted frizzled-related protein 1 (sFRP1), which has been shown to exacerbate neuroinflammation by engaging macrophage-expressed heat shock protein 90 (HSP90). This interaction skews macrophages toward a pro-inflammatory phenotype, thereby amplifying secondary injury and hindering repair. Genetic ablation of either SC-derived sFRP1 or macrophage HSP90 significantly attenuates

this deleterious inflammatory loop, highlighting a critical axis of intercellular crosstalk that modulates the trajectory of nerve degeneration and regeneration.[22]

Beyond immune signaling, SCs exhibit remarkable metabolic adaptability to meet the high energy demands of nerve repair.[23] Leptin-mediated adipocyte-to-glial communication has recently been identified as a key regulator of SC metabolic reprogramming, modulating mitochondrial activity and autophagic flux to enhance myelin clearance and support axonal regeneration.[17] This metabolic shift underscores the intrinsic plasticity of SCs and their capacity to integrate systemic metabolic cues into localized repair responses.

Moreover, SCs contribute directly to axonal regeneration through the secretion of trophic molecules. One notable example is GDNF family receptor alpha-1 (GFRα1), which is released by repair SCs and promotes axonal regrowth via an unconventional signaling mechanism. Instead of relying on the canonical GDNF-RET pathway, GFRα1 engages alternative receptors such as neural cell adhesion molecule (NCAM) and integrin α7β1 on dorsal root ganglion neurons, thereby triggering regenerative signaling cascades independently of RET activation.[24] This finding expands the repertoire of SC-derived regenerative factors and offers new molecular targets for therapeutic intervention.

Collectively, these discoveries redefine SCs as central coordinators of peripheral nerve repair, integrating immune, metabolic, and trophic signaling networks to facilitate regeneration. Their ability to dynamically sense and respond to the changing microenvironment, while simultaneously directing the behavior of surrounding immune and neuronal cells, positions SCs as both sentinels and architects of functional nerve recovery.

Macrophage

Following peripheral nerve injury, macrophages are among the earliest immune cells recruited to the lesion site, where they serve as indispensable regulators of the regenerative microenvironment.[25] Their accumulation at the injury site initiates a cascade of immunological and structural events that are tightly orchestrated to support axonal regrowth and tissue restoration. Once localized, macrophages undergo dynamic phenotypic polarization in response to local cues, transitioning along a spectrum from pro-inflammatory (M1-like) to anti-inflammatory and pro-regenerative (M2-like) states.[26]

M2-polarized macrophages, in particular, have emerged as key drivers of regenerative signaling. One notable mechanism involves the secretion of cathepsin S, which facilitates a fibroblast-to-Schwann cell relay, ultimately promoting SCs activation and axonal regeneration.[26] This intercellular communication emphasizes the macrophage's role as a signaling hub, bridging diverse cellular compartments to synchronize repair processes.

In addition to their immunomodulatory roles, macrophages also undergo metabolic reprogramming that is critical for sustaining regenerative function. The expression of monocarboxylate transporter 1 (MCT1) by macrophages has been shown to support the transport of lactate and other metabolites, fueling reparative processes and enabling cross-talk with metabolically active glial cells.[25] Such metabolic flexibility reinforces the idea that nerve regeneration is not merely a structural event, but one that is intricately linked to bioenergetic remodeling at the cellular level.

Macrophages also contribute to the spatial organization of regenerating axons. Through the expression of Plexin-B2, a semaphorin receptor typically involved in developmental axon guidance, macrophages help establish aligned "regeneration tracks" that guide axonal growth cones toward their distal targets.[27] This guidance function reveals a critical structural role of immune cells in shaping the physical topology of the regenerative landscape.

Of note, macrophage activity can be pharmacologically modulated to enhance repair outcomes. For example, ropivacaine has been shown to potentiate macrophage-mediated regeneration via $Nav_{1.8}$-dependent signaling, suggesting that fine-tuning macrophage electrophysiology can have therapeutic benefit.[28] Conversely, dysregulation of macrophage function can derail repair. Excessive M1 polarization and inflammasome activation, particularly via the NLRP3 pathway, have been implicated in chronic inflammation and impaired regeneration. Agents such as berberine have demonstrated efficacy in restoring immunological balance by inhibiting NLRP3 activation and suppressing M1 polarization, thereby fostering a more conducive microenvironment for regeneration.[29] Taken together, these findings establish macrophages as highly adaptable and active participants in peripheral nerve repair. Far from being passive responders, macrophages integrate immunological, metabolic, and structural signaling to orchestrate a pro-regenerative milieu. Their capacity to interact with SCs, fibroblasts, and neuronal elements places them at a central nexus of cellular communication.

Angiogenesis

Recent advances have demonstrated that angiogenesis not as a secondary or supportive process, but as an active and indispensable orchestrator of neural repair.[30] Traditionally, efforts in PNIs therapy have focused on axonal regeneration and remyelination. However, a growing body of evidence reveals that the re-establishment of a functional vascular network is not only temporally synchronized with nerve regeneration, but is mechanistically interlinked with axonal growth, immune modulation, and SCs activity.[13]

Immediately following nerve injury, a vascular response is rapidly initiated to reshape the lesion microenvironment. Among the early players, Netrin-1–expressing endothelial cells ($NTN1^+$ECs) and their derived exosomes have emerged as key regulators of the initial regenerative phase. These vascular niches initiate a molecular cascade involving PI3K-AKT and mTOR signaling pathways, promoting axonal elongation, cellular adhesion, and metabolic activation.[13] By releasing bioactive vesicles and soluble cues, $NTN1^+$ ECs modulate the behavior of neighboring cells, including SCs and macrophages, thus establishing a permissive microenvironment for nerve regrowth. Such findings underscore the notion that vascular cells not only serve as structural scaffolds but also function as dynamic signal transducers that shape the regenerative trajectory from the earliest stages.

In the later stages of repair, vascular remodeling becomes essential for stabilizing the regenerative niche and supporting long-term functional recovery. High-resolution three-dimensional imaging has shown that mature, hierarchically organized vascular networks are associated with reduced inflammatory burden, improved myelin sheath formation, and more effective axonal signal transmission.[31] Disruption of this remodeling process, either genetically or pharmacologically, leads to impaired axonal alignment and diminished sensory and motor recovery, underscoring the indispensable role of vascular maturation in complete nerve repair.

Bioengineering strategies have increasingly exploited this vascular–neural crosstalk to enhance regeneration. For example, the incorporation of VEGF-A–overexpressing Schwann cells into biomimetic nerve conduits has been shown to synergistically enhance angiogenesis and neurogenesis, with functional outcomes rivaling those achieved by autologous nerve grafts.[32] Such dual-function scaffolds mimic the native neurovascular niche and offer spatial and temporal control over angiogenic and neurotrophic signaling. Additionally, overexpression of angiogenic mediators such as epidermal growth factor–like domain 7 (EGFL7) not only promotes endothelial proliferation but also elevates the local expression of neurotrophic factors including NGF and BDNF, reinforcing the bidirectional nature of vascular–neural interactions.[33] In summary, these findings reposition the vasculature as a central regulator of peripheral nerve regeneration. Vascular systems do more than deliver oxygen and nutrients; they act as dynamic biological platforms that direct cellular responses, shape immune profiles, and synchronize tissue remodeling.

EVs in Peripheral Nerve Regeneration

EVs have emerged as critical regulators in tissue regeneration, including the repair of peripheral nerves (Figure 1).[10] These vesicles are nano-sized membrane-bound particles secreted by nearly all cell types and serve as potent carriers of bioactive molecules that mediate intercellular communication.[34] Their natural composition and targeted effects make them ideal candidates for promoting functional recovery in the context of PNI.

Origin and Characteristics of EVs

EVs have emerged as potent biological mediators in regenerative medicine, owing to their inherent capacity for intercellular communication and cargo delivery. These nanoscale to microscale vesicles are secreted by a wide variety of cell types, including mesenchymal stem cells (MSCs), SCs, endothelial cells, fibroblasts, and components of peripheral blood plasma (Table 1), and their functional diversity is closely associated with their cellular origin and biogenetic pathway.[35]

Among the heterogeneous EV population, exosomes are the most extensively studied subclass. They are generated via the endosomal pathway, wherein intraluminal vesicles are formed within multivesicular bodies (MVBs) and subsequently secreted through MVB fusion with the plasma membrane.[36] In contrast, microvesicles arise through direct budding from the plasma membrane, while apoptotic bodies are formed during programmed cell death.[37] Although exosomes dominate

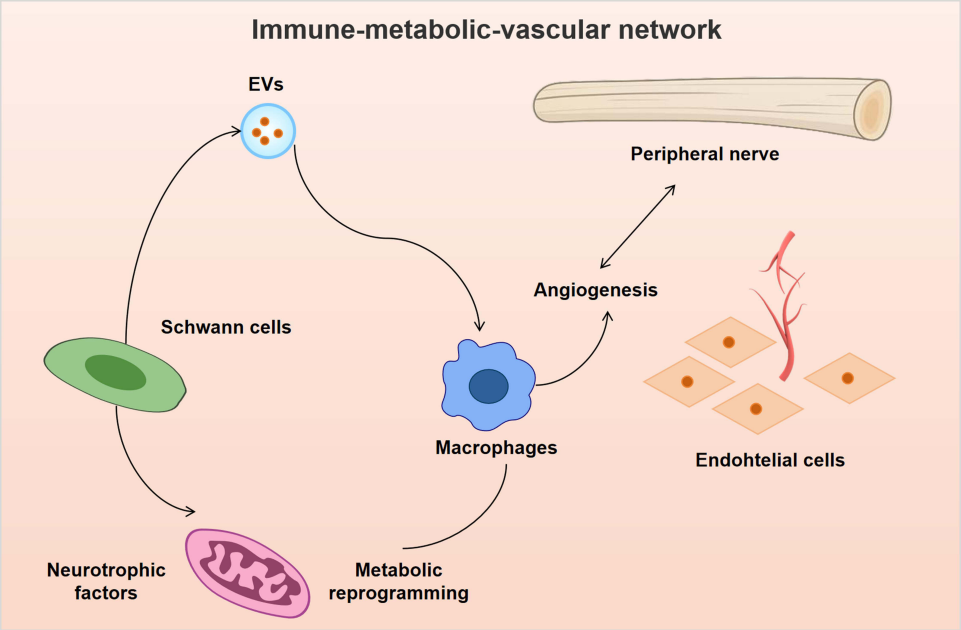

Figure 1 Schematic illustration of EVs-mediated immune-metabolic-vascular network.

current therapeutic investigations, accumulating evidence suggests that all EV subtypes contribute to extracellular signaling, each with distinct functional properties and biophysical signatures.[38]

A defining feature of EVs is their molecular cargo: a rich and tunable repertoire of regulatory miRNAs, proteins, lipids, and, in certain cases, long non-coding RNAs (lncRNAs).[39] This cargo not only reflects the physiological or pathological state of the parent cell but also modulates recipient cell behavior through the horizontal transfer of bioactive molecules. Importantly, recent advances in EV profiling and engineering have enabled selective enrichment of specific cargo elements, thereby modifying vesicles for targeted regenerative functions.[40] For instance, exosomal miRNAs derived from MSCs have been shown to regulate immune responses and promote axonal growth, while SC-derived EVs can carry neurotrophic proteins that enhance remyelination and axon guidance.[41,42]

The biological plasticity and inherent biocompatibility of EVs, combined with their ability to traverse biological barriers and avoid immunogenicity, make them an attractive platform for peripheral nerve regeneration. Moreover, their nanoscale size enables deep tissue penetration and uptake by specific cell types, offering opportunities for precision delivery in both free form and biomaterial-integrated formats.

Multifunctional Regulators in Peripheral Nerve Regeneration

EVs have emerged as versatile biological effectors in the dynamic microenvironment of PNIs. By delivering a diverse repertoire of proteins, lipids, and nucleic acids, EVs orchestrate intercellular communication among SCs, macrophages,

Table 1 Summary of Key Characteristics and Cargo of Therapeutical EVs

EVs Source	Main Cargo	Functional
MSCs	miR-21, miR-146a, GDNF, VEGF, IL-10	Immunomodulation, Schwann cell support, axon growth
Schwann cell	miR-223, miR-199a, MBP, NGF	Myelination, axon elongation, remyelination
Endothelial cell	miR-126, miR-199a-5p, Netrin-1, angiopoietin-1	Angiogenesis, repair-related Schwann cell activation
Platelet-rich	TGF-β, HGF, IGF-1, miR-20b-3p	MSC activation, reduced apoptosis, enhanced neurotrophic signaling
Fibroblast	Rps5, miR-181, lncRNA Ftx/Miat	ECM remodeling, scar inhibition, axonal regeneration

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vascular endothelial cells, and neurons.[43] This paracrine signaling network facilitates a coordinated cascade of cellular responses that underlie structural restoration and functional recovery. Recent findings emphasize that EVs not only mimic the regenerative benefits of their parental cells but also provide a cell-free platform with enhanced safety, stability, and tunability, making them promising candidates for translational nerve repair strategies.[44]

A hallmark of successful peripheral nerve regeneration is the phenotypic plasticity of SCs, which dedifferentiate into a repair-promoting phenotype following injury. This transition is tightly regulated by exogenous cues, and EVs serve as potent inducers of SC activation. For instance, Li et al revealed the regenerative potential of plasma-derived exosomes from healthy rats (hplasma-exos) in the treatment of type 1 diabetic peripheral neuropathy (DPN), primarily through the enrichment of miR-20b-3p.[45] Systemic administration of hplasma-exos significantly improved mechanical and thermal sensitivity as well as motor function in DPN rats, while promoting sciatic nerve remyelination, increased nerve fiber density, and reconstruction of neuromuscular junctions. Mechanistically, miR-20b-3p targets and inhibits Stat3 expression, thereby alleviating high glucose-induced autophagy impairment in SCs and mitigating DPN progression. These findings suggest that exosomal miRNAs represent a promising regenerative strategy to modulate the neural microenvironment and promote peripheral nerve regeneration (Figure 2). Similarly, MSC-derived exosomes—particularly from dental pulp stem cells (DPSCs) and adipose-derived MSCs (ADMSCs)—have been shown to stimulate SC repair phenotypes through the horizontal transfer of pro-growth miRNAs. These effects collectively accelerate SC migration to the injury site, support extracellular matrix (ECM) remodeling, and foster axonal guidance.[46,47]

The regenerative outcome of PNIs is significantly influenced by the inflammatory landscape. EVs play a critical role in shifting macrophage polarization toward an anti-inflammatory, pro-regenerative M2 phenotype. SC-derived exosomes enriched with OTULIN, a deubiquitinase, enhance ERBB2 signaling in macrophages, thereby promoting IL-10 secretion and dampening inflammatory cascades that impair axon regeneration.[48] Furthermore, exosomes from lipopolysaccharide (LPS)-preconditioned MSCs suppress NF-κB and NLRP3 inflammasome activation through miRNA-mediated mechanisms, thus establishing a permissive immunological niche for neural repair.[49] These findings emphasize the potential of EVs as immune modulators that fine-tune inflammation without systemic immunosuppression.

Efficient vascularization is indispensable for nutrient delivery, oxygen supply, and metabolic support during nerve regeneration. EVs from ECs and ADMSCs have been shown to promote angiogenesis by transferring key angiogenic mediators such as VEGF, FGF, and miR-21. These vesicular cues stimulate endothelial cell proliferation and tubulogenesis, facilitating neovascular network formation.[50,51] Additionally, exosomes from hypoxia-conditioned SCs activate endothelial glycolysis, further enhancing angiogenic responses.[52] In parallel, EVs enrich the neurotrophic microenvironment: SCLC-derived exosomes significantly upregulate GDNF, CNTF, and NT-3, while MSC-derived EVs activate the PI3K/AKT axis in neurons, enhancing cell survival, metabolic resilience, and neurite extension.[53] These dual functions position EVs as key modulators linking vascular remodeling to neurogenesis.

EVs exert direct effects on axonal elongation and remyelination through targeted intercellular exchange with neurons and SCs. Schwann cell-derived exosomes have been shown to deliver ribosomes, RNA-binding proteins, and regulatory miRNAs such as miR-673-5p to injured axons. This cargo activates the mTORC1 signaling pathway and drives cytoskeletal remodeling, facilitating growth cone advancement and directional axonal extension.[54,55] Furthermore, remyelination is tightly regulated by EV cargo: miR-615-5p suppresses MYRF to prevent premature myelin compaction, while miR-23b-3p promotes SC differentiation into mature, myelinating phenotypes.[56,57] Human endometrial stem cell-derived EVs additionally enhance PI3K/AKT-mediated pathways, accelerating SC maturation and myelin sheath formation.[58]

Engineering EVs for Enhanced Therapeutic Efficacy

Techniques for Loading Bioactive Molecules

The intrinsic regenerative potential of exosomes can be further amplified through bioengineering strategies that enable precise cargo customization and controlled delivery. A variety of methodologies have been developed to load exosomes with therapeutic payloads, including small RNAs, proteins, and hydrophobic small molecules, thereby expanding their functional repertoire in nerve repair applications.[59,60]

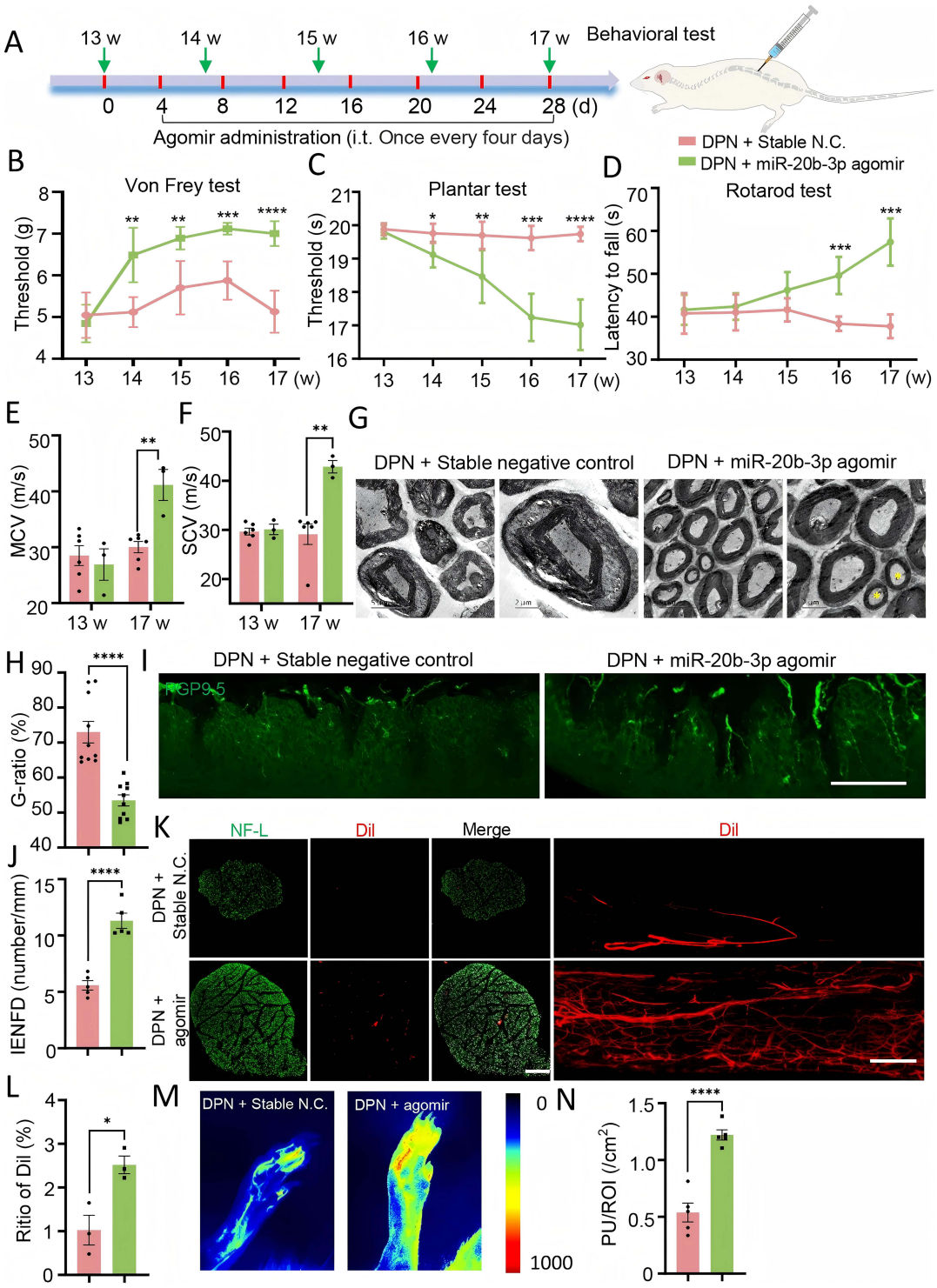

Figure 2 Therapeutic efficacy of miR-20b-3p agomir in alleviating high glucose induced peripheral nerve injury. (**A**) Schematic illustration of the in vivo administration protocol for miR-20b-3p agomir. (**B**–**D**) Behavioral assessments of mechanical allodynia (Von Frey), thermal sensitivity (plantar test), and motor coordination (rotarod) in DPN rats treated with miR-20b-3p agomir or negative control (N.C)., n = 5. (**E** and **F**) Measurement of motor conduction velocity (MCV) and sensory conduction velocity (SCV) post-treatment, n = 3, 6. (**G**) Transmission electron microscopy (TEM) images of sciatic nerve cross-sections reveal ultrastructural changes and newly formed myelin (marked by *), scale bars: 5 μm and 2 μm. (**H**) Quantification of G-ratio under different conditions, n = 10. (**I**) Immunofluorescence images showing PGP9.5-positive intraepidermal nerve fibers in plantar skin, scale bar: 100 μm. (**J**) Quantitative analysis of intraepidermal nerve fiber density (IENFD), n = 5. (**K**) Representative images of DiI perfusion in transverse and longitudinal sections of hindlimb tissue; scale bars: 200 μm (transverse), 1000 μm (longitudinal). (**L**) Analysis of DiI-positive vascular area in transverse sections, n = 3. (**M**) Laser Doppler images illustrating plantar blood flow in different treatment groups. (**N**) Quantification of regional plantar perfusion per unit area, n = 5. Data in B–D are presented as mean ± SD; all other data as mean ± SEM. Statistical significance: *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. Reproduced under the terms of a Creative Commons Attribution 4.0 International License.[45] Copyright 2023, the authors.

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Electroporation remains one of the most widely employed techniques for loading small RNAs into purified exosomes.[61] This approach transiently disrupts the vesicle membrane to allow efficient encapsulation of nucleic acids, promoting axonal elongation through modulation of downstream gene networks.[62] Alternatively, donor cells can be genetically engineered via plasmid or viral transfection to overexpress therapeutic molecules which are subsequently packaged into secreted exosomes through endogenous biogenesis pathways.[63,64] These genetically encoded cargoes offer sustained and physiologically relevant delivery of growth factors at the injury site.

In addition to active loading strategies, passive methods have been employed for compound incorporation.[65] Hydrophobic molecules can be integrated into the lipid bilayer of exosomes via simple incubation, enabling membrane-bound presentation or gradual release.[66] Moreover, co-incubation of exosomes with soluble bioactive factors facilitates non-covalent encapsulation through diffusion-driven loading, offering a less invasive alternative that preserves exosome integrity.[67]

These engineering approaches have demonstrated promising outcomes in preclinical models. For instance, NT-3 mRNA-enriched exosomes significantly enhanced axonal regeneration and functional recovery in sciatic nerve defect models by enabling prolonged neurotrophic support and guiding axonal sprouting (Figure 3).[68] Such strategies emphasize the capacity of exosome engineering to overcome the limitations of conventional delivery systems, including rapid degradation, off-target effects, and immunogenicity.

Surface Modifications for Targeted Delivery

Surface functionalization represents a feasible strategy to enhance the targeting specificity and therapeutic efficacy of exosome-based interventions in peripheral nerve regeneration.[69] By modifying the exosomal membrane with targeting ligands, we can direct vesicle biodistribution toward specific cell types within the injured nerve microenvironment, such as SCs, neurons, or endothelial cells.[70]

A variety of molecular motifs have been employed for this purpose. For instance, rabies virus glycoprotein (RVG) peptides, which exhibit high affinity for neuronal acetylcholine receptors, have been chemically conjugated to exosome surfaces or genetically encoded via donor cell engineering.[71] Similarly, cyclic RGD (cRGD) peptides selectively bind integrin αvβ3 expressed on activated endothelial cells, thereby enabling preferential localization to angiogenic vasculature.[72]

These surface modifications have demonstrated functional advantages in peripheral nerve regeneration. For instance, effective therapeutic delivery to peripheral nerve tissue remains a major challenge due to the structural intricacies of the peripheral nervous system and the restrictive nature of the blood–nerve barrier (BNB). Engineered exosomes offer a promising solution by combining the intrinsic biocompatibility and nanoscale transport properties of natural vesicles with enhanced targeting capabilities. In particular, erythrocyte-derived exosomes represent a clinically translatable platform owing to their immune-evasive membrane composition and scalable production.[73] In a prior study, surface functionalization with the tetanus toxin C-fragment (TTC), a presynaptic targeting ligand, was achieved via catalyst-free bio-orthogonal click chemistry, enabling precise localization of exosomes to peripheral nerve terminals.[73] The modified exosomes (TTC-Exos) demonstrated significantly improved cellular uptake and axonal localization in Neuro-2a cells, as well as efficient retrograde transport to neuromuscular junctions and sciatic nerves following intramuscular injection in vivo (Figure 4). This engineered exosome system exemplifies a rational design strategy for targeted nanotherapeutics, offering improved delivery efficiency and therapeutic specificity for peripheral nerve repair.

EVs-Scaffold Hybrid Strategies

The integration of EVs with biomaterial scaffolds represents a promising approach to overcoming the limitations of standalone EV therapy or passive scaffolds in peripheral nerve regeneration. This hybrid strategy leverages the bioactive cargo of EVs while utilizing scaffolds to provide critical structural support, localized delivery, and a conducive microenvironment for nerve repair.

Types of Biomaterials

Chitosan, a naturally derived cationic polysaccharide, has garnered considerable attention due to its excellent biocompatibility, tunable biodegradability, and structural resemblance to glycosaminoglycans in the native ECM.[74] Its positively charged surface enables electrostatic interaction with the negatively charged membranes of EVs, facilitating high loading

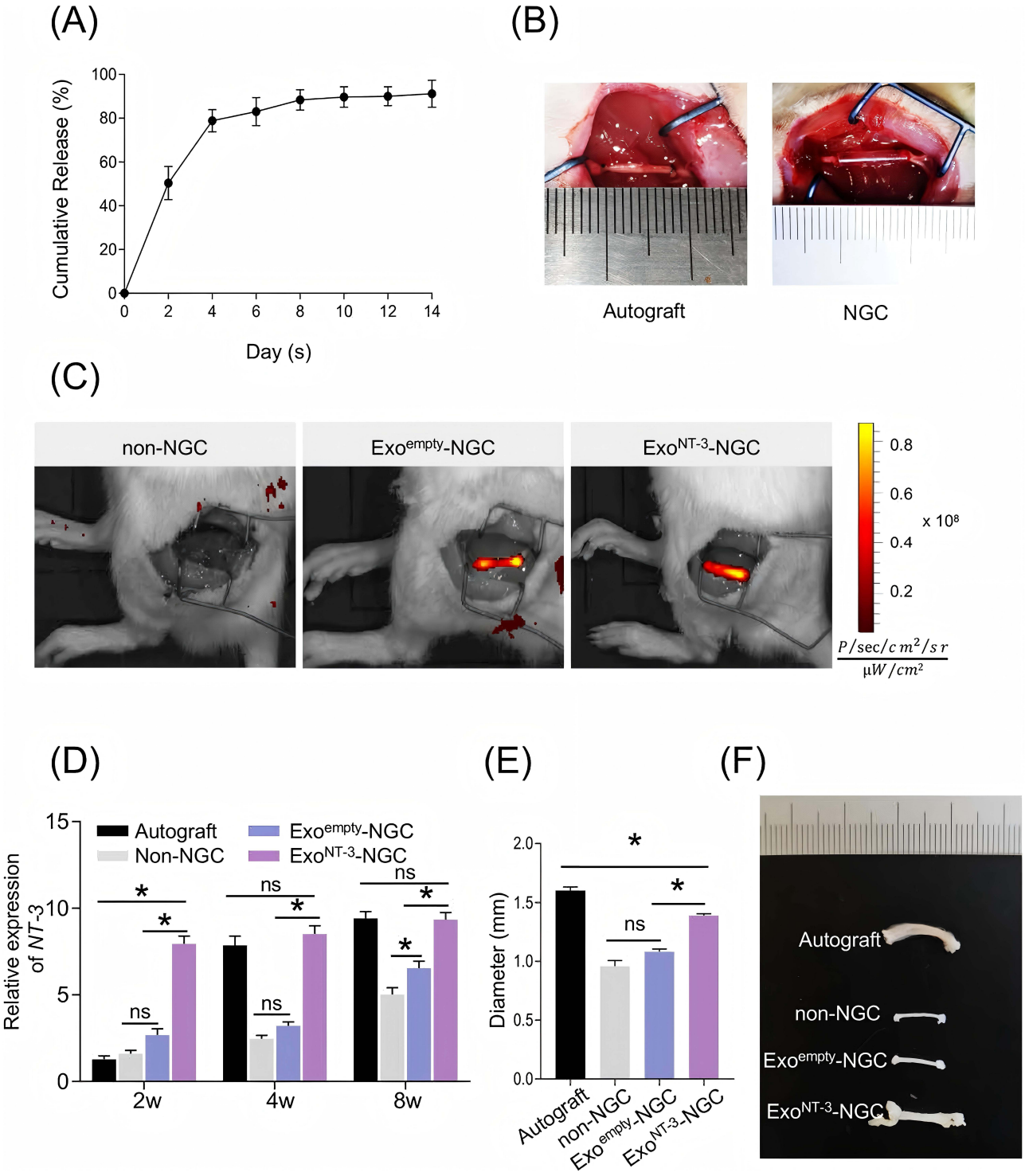

Figure 3 Fabrication and In Vivo Evaluation of Nerve Guidance Conduits. (**A**) Exosome release profile from alginate hydrogels. Cumulative exosomal protein content was quantified using the Bradford assay. (**B**) Schematic of the rat sciatic nerve defect model and NGC implantation. Silicone conduits (10 mm) were filled with alginate hydrogel (1 mg/mL) containing either Exo^{empty}, Exo, NT-^{3} or no exosomes (1:1 vol/vol), and implanted at the injury site. Autologous nerve grafts served as controls. (**C**) Representative in vivo imaging (IVIS, Caliper Lumina II) of DiR-labeled exosomes post-implantation. Imaging was performed to visualize exosome biodistribution. (**D**) Quantitative RT-PCR analysis of NT-3 mRNA expression in the distal nerve stumps at 2, 4, and 8 weeks post-surgery. (**E**) Quantification of the diameter of regenerated nerve tissues at 8 weeks. (**F**) Gross morphological observation of nerve regeneration across different treatment groups. Data are presented as mean ± SEM (n = 6 per group). Statistical analysis was performed using one-way ANOVA followed by Bonferroni's post hoc test. $P < 0.05$. Reproduced under the terms of a Creative Commons Attribution 4.0 International License.[68] Copyright 2021, the authors.

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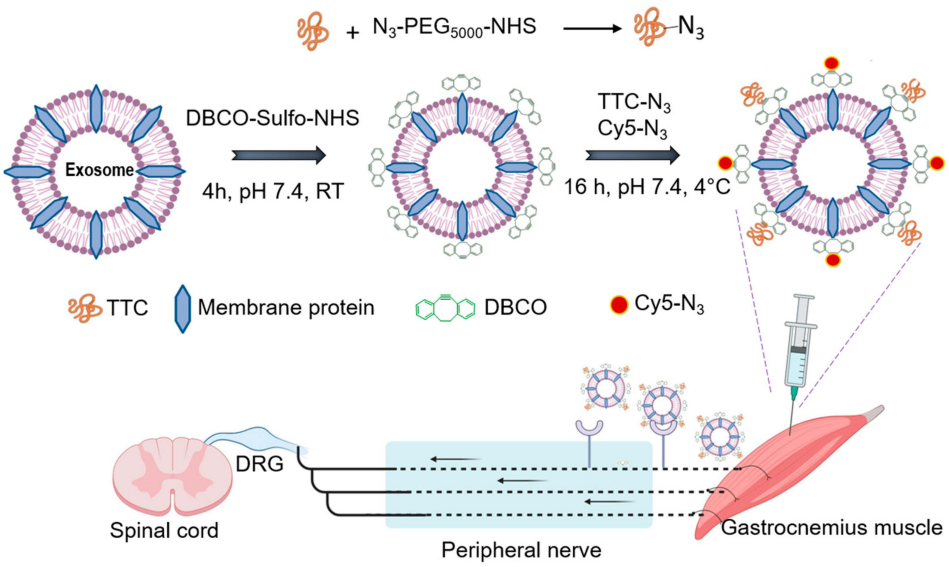

Figure 4 Schematic illustration depicting the sequential process of fabricating TTC-functionalized exosomes conjugated with Cy5 fluorophores via a catalyst-free click chemistry approach. The diagram further outlines the post-injection distribution of TTC-Exos, highlighting their targeted transport to peripheral nerve tissues following administration into the gastrocnemius muscle. Reproduced under the terms of a Creative Commons Attribution 4.0 International License.[73] Copyright 2024, the authors.

efficiency and sustained release.[75] Furthermore, chitosan's inherent antimicrobial activity and mechanical adaptability make it a versatile scaffold for clinical translation.[76] In a recent study, EVs derived from skin precursor-derived SCs (SKP-SC-EVs) were integrated into a chitosan/poly(lactic-co-glycolic acid) (PLGA) composite scaffold to fabricate a bioactive tissue-engineered nerve graft (TENG) for bridging 40-mm sciatic nerve defects in a canine model.[75] The SKP-SC-EV-functionalized TENG markedly enhanced axonal regeneration and remyelination, improved hindlimb motor and electrophysiological recovery, and mitigated denervation-induced muscular atrophy. Mechanistic investigations revealed that SKP-SC-EVs are enriched in axon growth–associated miRNAs, particularly miR-30b-5p, which targets the Sin3a/HDAC complex and activates ERK, STAT3, and CREB signaling pathways to potentiate neural repair. These findings highlight SKP-SC-EV-loaded chitosan scaffolds as a promising platform for clinical translation in peripheral nerve repair (Figure 5).

Collagen remains a foundational biomaterial in regenerative medicine, offering structural support and bioactive cues that emulate the native ECM.[77] Its combination with hyaluronic acid (HA)—a highly hydrated glycosaminoglycan that facilitates cell migration, proliferation, and intercellular signaling—results in composite matrices with enhanced regenerative capacity.[78] Collagen/HA hybrid sponges, when integrated into electrospun outer conduits, create a three-dimensional scaffold conducive to cellular infiltration and axonal pathfinding. When loaded with EVs, such composite constructs promote Schwann cell migration, neovascularization, and axonal elongation.

Electroconductive hydrogels (ECHs) bridge the gap between biological and electrical functionality, providing an ideal platform for neuromodulatory therapies.[79] Polymers such as hyaluronic acid methacrylate (HAMA), polyaniline, and polypyrrole have been engineered to mimic both the viscoelastic properties and conductivity of native neural tissue.[80] ECHs facilitate endogenous bioelectrical signaling, which is crucial for synaptic activity and axonal regeneration. When combined with EVs conductive hydrogels support multi-modal regeneration by delivering anti-inflammatory signals, promoting neurotrophic factor expression, and enhancing Schwann cell activation. In a prior study, a multifunctional, self-adherent, and self-healing ECH integrated with bone marrow mesenchymal stem cell-derived exosomes (ECH-Exos) was developed as a nerve dressing for the treatment of diabetic PNI.[79] This laminar construct conforms spontaneously to damaged nerves, forming a tube-like structure without requiring surgical implantation. In vitro, ECH-Exos promoted Schwann cell adhesion and migration, while exosomes modulated macrophage polarization toward the M2 phenotype via inhibition of the NF-κB pathway, thereby alleviating inflammatory pain. Furthermore, the ECH-Exos dressing facilitated axonal remyelination and regeneration through MEK/ERK signaling, attenuated muscle atrophy, and enhanced functional

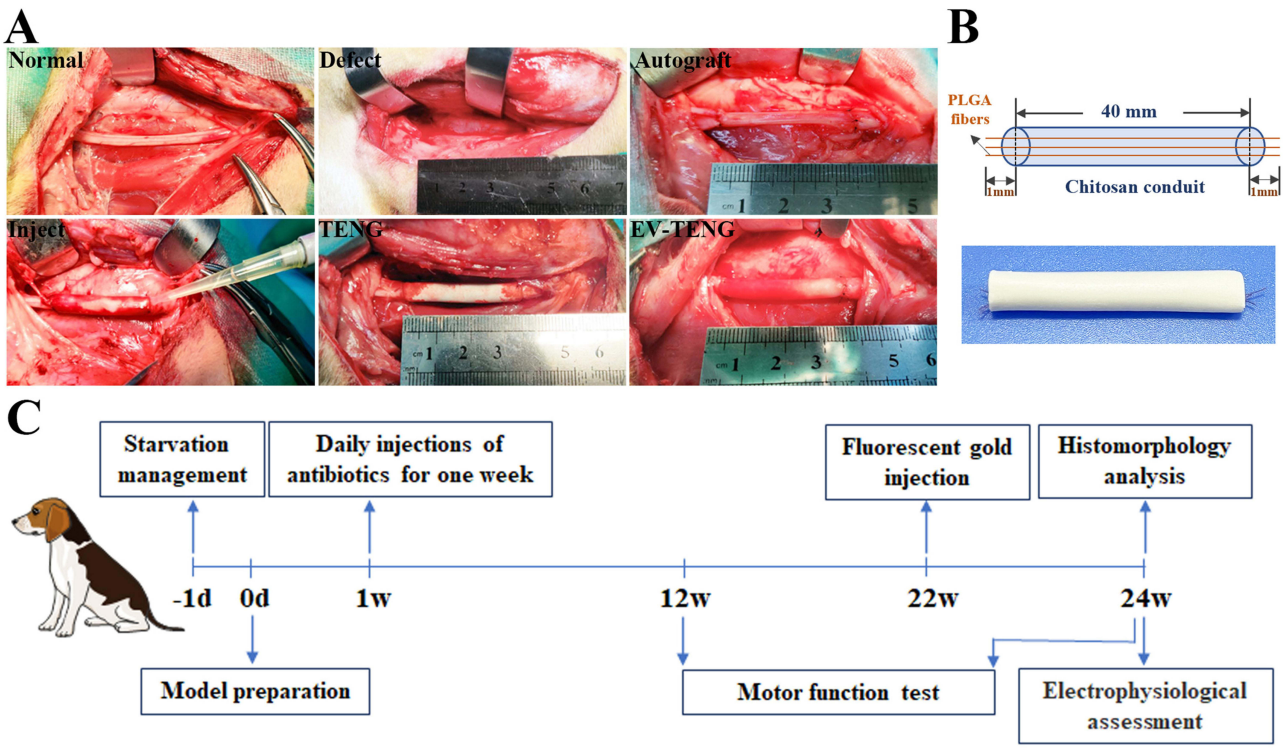

Figure 5 Establishment of a canine sciatic nerve defect model and experimental design. (**A**) Representative macroscopic images acquired immediately following the implantation of nerve grafts bridging a 40 mm sciatic nerve gap in three experimental groups. (**B**) Schematic illustration of the chitosan/PLGA-based nerve guidance conduit (NGC) structure. (**C**) Experimental timeline outlining the surgical procedures, treatment interventions, and subsequent assessments conducted at defined pre- and post-operative time points. Reproduced under the terms of a Creative Commons Attribution 4.0 International License.[75] Copyright 2024, the authors.

recovery in diabetic PNI models. These findings emphasize the therapeutic potential of ECH-Exos as a minimally invasive, bioelectronic interface for nerve repair and pain modulation in diabetic neuropathy (Figure 6).

Each biomaterial system offers distinct physicochemical properties that can be designed to address specific challenges in peripheral nerve regeneration. Chitosan ensures electrostatic loading and anti-infective protection; collagen/HA composites provide a structurally biomimetic and cell-permissive environment; and conductive hydrogels introduce an electroactive dimension to guide functional recovery. When integrated with exosome technology, these scaffolds act not merely as passive carriers but as active participants in the orchestration of neural repair.

Synergistic Effects of EVs-Biomaterial Systems on Nerve Regeneration

Biomaterials act as spatiotemporal regulators of EV release, adapting to the dynamic needs of each healing stage. For example, injectable soft hydrogels allow rapid EV diffusion to resolve acute inflammation, while stiffer matrices support prolonged retention and sustained signaling required for long-term tissue remodeling.[35,81] Moreover, biomaterial encapsulation protects EVs from enzymatic degradation and enhances their bioavailability.[82] Targeted delivery can be further achieved through scaffold surface modification or topographical design. Beyond controlled delivery, these hybrid systems recapitulate the structural and biochemical complexity of native tissue microenvironments. In nerve regeneration, aligned nanofibers within nerve guidance conduits (NGCs) provide directional cues for axon pathfinding, while conductive hydrogels embedded with EVs synchronize electrical and biochemical signals to enhance Schwann cell activation and remyelination.[68,82] Concurrently, EV-laden hydrogels modulate the immune microenvironment by suppressing pro-inflammatory cytokine production and promoting M2 macrophage polarization, creating a permissive environment for regeneration.[81]

The coalescence of EVs with biomaterial scaffolds enables a multifaceted regenerative strategy that integrates immunomodulation, trophic support, directional guidance, and dynamic release control. These systems are not merely passive carriers but active participants in orchestrating the regenerative cascade.

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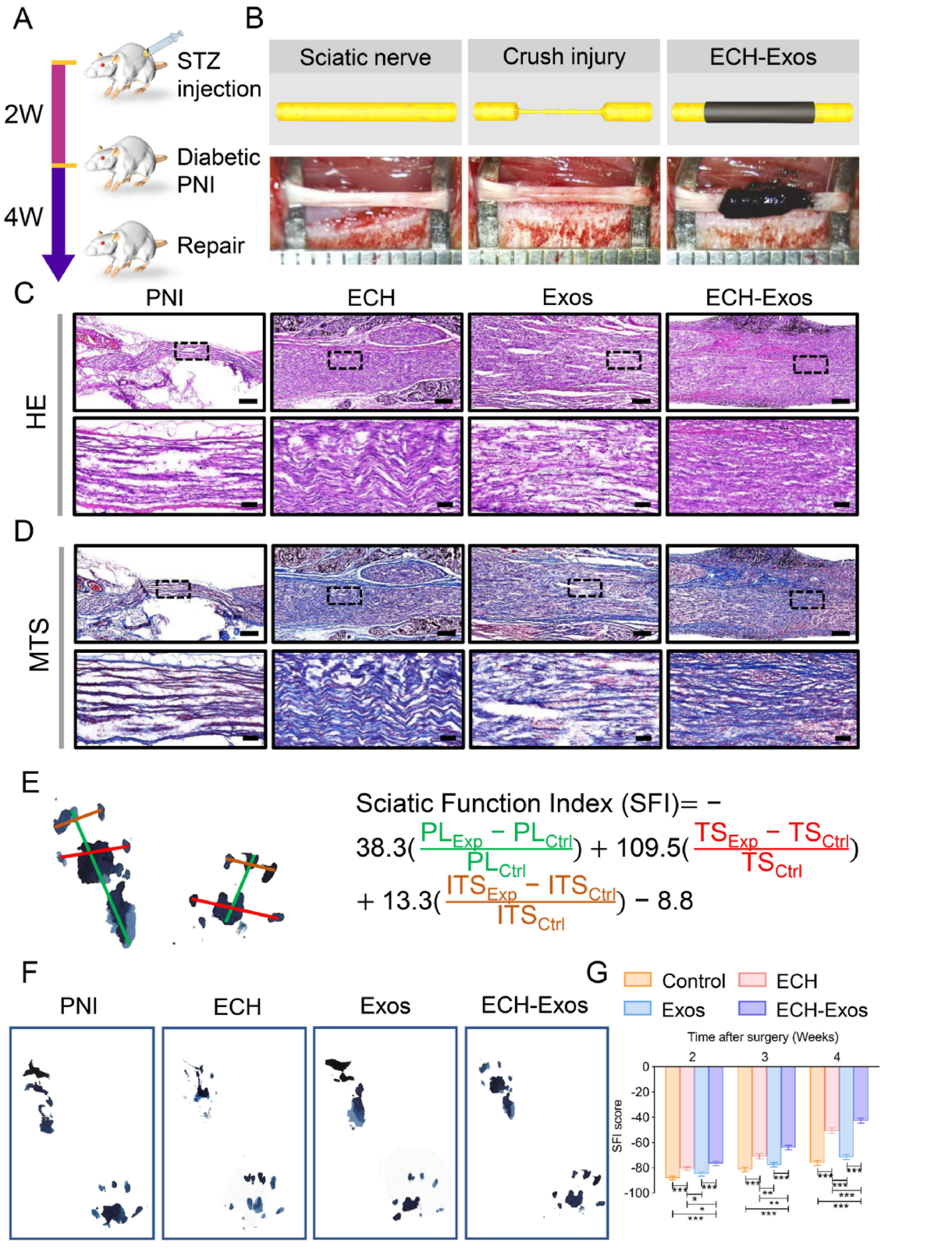

Figure 6 Evaluation of nerve regeneration and functional recovery following ECH-Exos treatment in diabetic PNI models. (**A**) Schematic overview depicting the therapeutic process of diabetic peripheral nerve injury. (**B**) Illustrative diagram and intraoperative images demonstrating the application of the ECH-Exos dressing enveloping the crushed sciatic nerve in diabetic rats. (**C** and **D**) Hematoxylin and eosin (HE) staining and Masson's trichrome staining (MTS) reveal morphological restoration of the sciatic nerve at 4 weeks post-treatment. Scale bars: 500 μm (low magnification), 100 μm (high magnification). (**E**) Formula used to calculate the sciatic functional index (SFI) based on footprint analysis parameters. (**F**) Representative footprint images obtained from experimental animals. (**G**) Quantitative SFI results at 2, 3, and 4 weeks post-surgery across different treatment groups (n = 4). Data are presented as mean ± SD. Statistical analysis was performed using one-way ANOVA followed by Bonferroni's post hoc test (*P < 0.05, **P < 0.01, ***P < 0.001). Reproduced under the terms of a Creative Commons Attribution 4.0 International License.[79] Copyright 2023, the authors.

Extracellular Vesicles and Functional Materials: Advantages, Limitations, and Design

Peripheral nerve regeneration relies heavily on the precise regulation of cellular and molecular cues. EVs derived from different cell sources offer distinct bioactive profiles, influencing their regenerative efficacy. SC-EVs are enriched in neurotrophic factors such as NGF, BDNF, and GDNF, which directly promote axonal outgrowth and remyelination. They also modulate local immune responses, creating a permissive microenvironment for nerve repair.[19,23] Mesenchymal stem cell-derived EVs (MSC-EVs) are characterized by anti-inflammatory and immunomodulatory cargos, including miRNAs that suppress pro-inflammatory cytokines and enhance angiogenesis.[83] Neural stem cell-derived EVs (NSC-EVs) carry neurogenic factors that support neuronal differentiation and synaptic plasticity.[84] Immune cell-derived EVs, such as those from macrophages, can either support regeneration by promoting a pro-repair M2 phenotype or, if mismanaged, exacerbate inflammation. While these EV types retain the regenerative advantages of their parent cells without the risks of tumorigenicity or immune rejection, their limitations include low yield, heterogeneity, and potential off-target effects.[85] Engineering strategies, including cargo enrichment, surface modification, and hybrid vesicle formation, have been developed to overcome these issues, enhancing targeting specificity and functional potency.

The choice of functional biomaterials for EV delivery is equally critical in determining regenerative outcomes. Natural polymers, such as collagen, hyaluronic acid, and chitosan, offer excellent biocompatibility and intrinsic cell-adhesive properties, facilitating EV retention and gradual release. However, their mechanical strength is often insufficient for long-gap nerve repair.[86] Synthetic materials, including PLGA, PCL, and PEG-based hydrogels, provide tunable mechanical properties, degradation rates, and scalability but may lack bioactive cues, necessitating surface functionalization or incorporation of additional molecules to support regeneration.[87] Conductive materials, such as polypyrrole or graphene composites, can provide electrical stimulation conducive to axonal guidance and Schwann cell activity, but their long-term biocompatibility and potential cytotoxicity require careful optimization.[88] Hybrid scaffolds combining natural and synthetic components can leverage the advantages of both, achieving optimal EV delivery, spatial guidance, and mechanical support. These design strategies are particularly important when integrating EVs into three-dimensional conduits or hydrogel matrices for long-gap peripheral nerve defects.

Clinical Translation and Future Perspective

EV-based therapies have demonstrated significant regenerative potential in animal models of PNIs; however, their clinical translation remains hindered by multifactorial challenges. The major bottlenecks include the lack of standardized manufacturing workflows, low cargo-loading efficiency, inadequate in vivo stability, and limited targeting capability.

Current isolation methods, such as ultracentrifugation or precipitation, often yield heterogeneous EV populations with considerable variation in purity and biological activity. Additionally, variables such as donor cell type, culture conditions, and passage number introduce batch-to-batch inconsistencies, compromising clinical reproducibility. Although EVs are generally considered low immunogenic, potential risks—including unintended immune activation, off-target biodistribution, and cargo-mediated toxicity—require systematic safety assessments under Laboratory Practice (GLP) conditions. Furthermore, the absence of unified quality control metrics and release criteria exacerbates these challenges.[11,89,90]

To address these limitations, researchers are exploring several innovative strategies. Microfluidic-assisted engineering combined with electroporation enables precise control over therapeutic cargo incorporation, significantly improving loading efficiency and uniformity.[91,92] CRISPR/Cas-based genetic modification of donor cells can be employed to enrich EVs with neurotrophic factors, immunomodulatory molecules, or angiogenic mediators, thereby enhancing their therapeutic specificity.[93,94] Additionally, ligand-based surface functionalization, when integrated with stimuli-responsive hydrogels, allows for targeted delivery and spatiotemporally controlled release, improving local retention and biological stability.[95] The integration of these technologies not only enhances EV delivery efficiency but also lays the foundation for intelligent and personalized nerve repair strategies.

Despite promising outcomes in small-animal studies, the lack of large-animal models and early-phase clinical trials remains a significant translational barrier, which we refer to as the "translational gap." Current EV–biomaterial systems have not been adequately evaluated for mechanical integrity, biodegradation kinetics, and functional recovery in physiologically

relevant models that mimic human nerve architecture and biomechanical loading. Bridging this gap requires the development of scalable, GMP-compliant bioreactor-based production systems to ensure high-yield EV manufacturing without compromising functional integrity. Additionally, the establishment of standardized quality control frameworks, including potency assays, immunogenicity testing, and stability evaluations, is essential for product consistency. Furthermore, multi-center, large-animal preclinical frameworks integrating electrophysiological, biomechanical, and behavioral assessments will be critical for generating clinically predictive data prior to human trials.

The future clinical translation of EV-based therapies will rely heavily on interdisciplinary integration. Artificial intelligence (AI)-driven data analytics can accelerate the rational design of EV therapeutics by decoding multi-omics datasets, predicting optimal cargo profiles, and modeling biodistribution within complex tissue environments.[96] Coupled with pharmacokinetic modeling, AI can also reduce empirical trial-and-error, thereby shortening development timelines. Meanwhile, smart, stimuli-responsive biomaterials—including conductive hydrogels and implantable release platforms—offer the potential for closed-loop systems that dynamically adjust EV release based on real-time monitoring of nerve repair biomarkers, enabling personalized and adaptive therapy.[97] As regulatory standardization, scalable manufacturing, and intelligent delivery technologies converge, EV-based therapeutics are poised to transition from experimental tools to reproducible, precision-engineered solutions for peripheral nerve regeneration.

Conclusion

EV-based therapies are promising in peripheral nerve regeneration by recapitulating the therapeutic benefits of their parent cells while circumventing the risks associated with direct cell transplantation. Recent advances in EV bioengineering have expanded the therapeutic landscape, enabling precise, sustained, and context-responsive delivery at sites of nerve injury. Despite persistent challenges related to large-scale manufacturing, regulatory standardization, and clinical translation, the emerging preclinical evidence accumulated to date emphasizes the transformative potential of EV-based interventions.

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Disclosure

The authors report no conflicts of interest in this work.

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