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REVIEW

# Exosome Cargo Molecules and NLRP3/BDNF: Clinical and Preclinical Evidence for Acupuncture-Mediated Spinal Cord Injury Recovery

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**Abstract:** Validate the clinical utility of exosome cargo (miRNAs/proteins) and NLRP3/BDNF as key regulatory molecules for acupuncture-mediated spinal cord injury (SCI) recovery. From the establishment of the database to May 2025, a literature search was conducted on PubMed, and Embase, using keywords ["exosome cargo" or "exosome"], ["acupuncture" or "acupuncture and moxibustion" or "electroacupuncture" or "EA"], ["spinal cord injury" or "SCI"], ["immune regulation"], ["inflammatory reaction"], ["neuroregeneration" or "nerve"]. Including peer-reviewed studies on human/animal models, articles that do not meet the requirements are excluded. Preclinically, MSC-exosomal miR-145-5p suppressed TLR4/NF-κB signaling, reducing spinal IL-1β by 47% in SD rats. Schwann cell-exosomal MFG-E8 activated SOCS3/STAT3, increasing M2 macrophage CD206 by 63% and raising rat BBB scores by 3.8 points; Treg-exosomal miR-2861 upregulated tight junction proteins (occludin/ZO-1) to repair the blood-spinal cord barrier. Acupuncture (EA at GV14/GV4) upregulated spinal BDNF by 72% and NGF by 58% via Wnt/β-catenin, while EA at GV6/GV9 downregulated NLRP3 by 42–58% and TNF-α by 35–47%. Clinically, EA at EX-B2 increased ASIA scores by 3.2±1.1 points (Guo et al). Besides, 5x/week EA improved ASIA vs 3x/week (+6.4 points). EA+exercise reduced MAS by 1.6–2.9 points, with outcomes correlated to peripheral NLRP3 reduction, BDNF elevation, and MBI/WISCIII increases. Exosome cargo (miR-145-5p/MFG-E8) and NLRP3/BDNF are key regulatory molecules underlying acupuncture-mediated SCI recovery. However, limitations (small RCT samples, heterogeneous acupuncture protocols, unstandardized exosome isolation) hinder translation. Future work should focus on standardized biomarker detection, exosome engineering, and large-scale clinical trials.

**Keywords:** exosome, acupuncture, spinal cord injury, NLRP3 inflammasome, immune cell polarization, brain-derived neurotrophic factor, Wnt/β-catenin pathway

## Introduction

Spinal cord injury (SCI) is one of the most devastating traumas to the central nervous system (CNS). Over one million new cases are reported worldwide annually, and patients often suffer from permanent motor, sensory, and autonomic dysfunction, imposing a heavy burden on families and society.[1,2] The pathological process of SCI is divided into primary injury and secondary injury. Primary injury is directly caused by mechanical forces, leading to neural tissue disruption and vascular damage. In contrast, secondary injury is a cascade reaction lasting several days to weeks, in which neuroinflammation serves as a core driving factor throughout the entire injury process.[3,4] Following SCI, microglia are rapidly activated, and peripheral immune cells such as macrophages and neutrophils infiltrate the injury site, releasing a large number of pro-inflammatory cytokines (eg., interleukin [IL]-1β, tumor necrosis factor [TNF]-α, IL-6). This will trigger an inflammatory storm, exacerbate neuronal apoptosis, axonal

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demyelination, and glial scar formation, while inhibiting endogenous neurological function recovery.[5] Therefore, targeted regulation of the inflammatory microenvironment after SCI is a key strategy to improve prognosis.

Extracellular vesicles (EVs) are membranous structures secreted by cells, among which exosomes (diameter: 30–150 nm) serve as important intercellular communication carriers. By delivering bioactive substances such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), proteins, and lipids, exosomes play a central role in physiological and pathological processes including immune regulation and tissue repair.[6,7] Compared with stem cell transplantation, exosomes possess advantages such as low immunogenicity, no tumorigenic risk, and the ability to cross the blood-spinal cord barrier (BSCB), making them an emerging research hotspot in SCI treatment.[8,9] Over the past decade, research on exosome-mediated regulation of SCI inflammation has experienced explosive growth,[10,11] covering different cellular sources, regulatory pathways, and delivery systems. However, there remains a lack of systematic summary of mechanisms and discussion on clinical translation.

Research shows that acupuncture can treat spinal cord injury by inhibiting inflammatory reactions, regulating the immune system and promoting nerve repair. After spinal cord injury, local and systemic inflammatory responses exacerbate nerve damage and impede recovery.[12] Acupuncture can protect nerves by inhibiting the activation of the NLRP3 inflammasome and reducing the release of inflammatory mediators after spinal cord injury.[13] Besides, acupuncture helps improve recovery after spinal cord injury by promoting the balance of immune cells and enhancing the body's immune response.[14,15] Shang et al's research has shown that acupuncture can increase the expression of nerve growth factor, promote the survival and regeneration of nerve cells, and thereby improve functional recovery.[16]

Based on the evidence synthesis of relevant literature, this review systematically summarizes the interaction mechanisms between exosomes and SCI-related inflammation. It analyzes the core regulatory pathways and biomarkers of inflammation modulation classified by the cellular origin of exosomes, summarizes the research progress of SCI-related therapeutic strategies, and discusses the limitations of current studies as well as future directions. This review aims to provide a reference for basic research and clinical translation in this field.

# Method

## Search Strategy

To identify published research, we conducted a comprehensive search of the PubMed and Embase databases, covering records up to May 2025. Our search strategy incorporated the following keyword sets: ["exosome cargo" or "exosome"], ["acupuncture" or "acupuncture and moxibustion" or "electroacupuncture" or "EA"], ["spinal cord injury" or "SCI"], ["immune regulation"], ["inflammatory reaction "]. Preliminary screening is conducted using search engines provided by various databases. After deleting 581 duplicate records and title mismatches, we identified 1534 related articles.

## Research Selection

Before reading the full text, we manually screened references using Excel. Among the 1534 related articles: 442 lacked full-text abstracts, 303 were irrelevant to acupuncture and SCI, 465 were non-systematic reviews/meta-analyses. Finally, 324 full-text research papers (268 basic research papers and 56 clinical RCTs) related to this topic were included. The flowchart of the search process is shown in Supplementary Figure 1.

## Eligibility Criteria for Clinical Studies

### Study Design

Randomized controlled trials (RCTs) or prospective cohort studies;

### Participants

Patients with confirmed SCI (diagnosed by imaging and neurological examination);

### Intervention

Acupuncture (manual acupuncture, electroacupuncture) as monotherapy or combined with rehabilitation;

### Outcomes

Reporting of objective clinical endpoints (eg., ASIA motor/sensory scores, MAS spasticity scores, MBI activities of daily living scores) or translational biomarkers (NLRP3, BDNF, exosome cargo);

### Sample Size

≥5 participants per group;

## General Overview of Exosomes, Inflammation, and Core Biomarkers in SCI

### Pathophysiological Characteristics of SCI-Related Inflammation: Implications for Biomarker Development

The inflammatory response following SCI exhibits a "double-edged sword" nature. Moderate early inflammation can clear necrotic tissue and initiate repair processes, whereas a persistent inflammatory storm exacerbates secondary injury.[17] Its core pathophysiological characteristics include three aspects. First, imbalanced immune cell polarization. Microglia (resident immune cells of the CNS) rapidly switch from a quiescent state to a pro-inflammatory phenotype (M1 phenotype), secreting factors such as IL-1β and TNF-α. Following infiltration of peripheral macrophages, some differentiate into the M1 phenotype, further amplifying the inflammatory response. However, the insufficient proportion of M2 macrophages (anti-inflammatory phenotype) fails to effectively initiate tissue repair.[18] Second, a dysregulated inflammatory cytokine network. There is an imbalance between pro-inflammatory cytokines (IL-1β, TNF-α, IL-6, inducible nitric oxide synthase [iNOS]) and anti-inflammatory cytokines (IL-10, IL-4, transforming growth factor [TGF]-β). Among these, IL-1β and TNF-α are key factors initiating the inflammatory cascade, which can induce neuronal apoptosis and glial cell activation.[19] Third, BSCB disruption and inflammation amplification. Following SCI, the expression of BSCB tight junction proteins (occludin, ZO-1) is downregulated, leading to increased permeability. This allows peripheral inflammatory cells and factors to enter the spinal cord parenchyma, forming a "peripheral-central inflammatory vicious cycle".[20]

### Biological Features of Exosomes: Core Advantages in SCI Inflammation Regulation and Biomarker Potential

Exosomes are widely present in body fluids and cell culture supernatants. Their membranous structure is derived from parental cells, which can protect internal cargo from enzymatic degradation. Additionally, they express molecules such as integrins and CD47 on their surface, endowing them with targeting ability and immune evasion capability.[7] In the regulation of SCI-related inflammation, exosomes possess advantages including precision delivery of bioactive substances, multi-targeted regulation of the inflammatory microenvironment, and favorable biocompatibility and delivery efficiency. Exosomes can targetedly deliver cargo such as miRNAs, lncRNAs, and proteins to inflammatory sites, regulating immune cell polarization and inflammatory pathways.[21] For instance, mesenchymal stem cell (MSC)-derived exosomes deliver miR-145-5p to target Toll-like receptor 4 (TLR4), inhibiting the activation of the NF-κB pathway;[22] regulatory T (Treg) cell-derived exosomes regulate interleukin-1 receptor-associated kinase 1 (IRAK1) via miR-2861 to repair the BSCB.[23] Furthermore, a single type of exosome can simultaneously inhibit the release of pro-inflammatory cytokines, promote the expression of anti-inflammatory cytokines, repair the BSCB, and suppress glial scar formation, achieving "anti-inflammatory-repair" synergy.[24] More importantly, exosomes can cross the damaged BSCB, accumulate at the spinal cord injury site, and exhibit low immunogenicity, making them less likely to induce immune rejection.[8]

## Mechanistic Analysis of Exosome Cargo as Biomarkers in SCI Inflammation Regulation

### Mesenchymal Stem Cell (MSC)-Derived Exosomes: Cargo Molecules (miR-145-5p/PELI1) as Inflammatory Biomarkers

MSC-derived exosomes are the most extensively studied type in SCI inflammation research, mainly including bone marrow mesenchymal stem cell (BMSC)-derived exosomes, human umbilical cord mesenchymal stem cell (hUCMSC)-derived exosomes, and adipose-derived stem cell (ADSC)-derived exosomes. Their mechanisms of regulating inflammation share high commonality while exhibiting source-specific characteristics.[25] Studies have found that MSC-derived exosomes target molecules such as Toll-like receptor 4 (TLR4) and myeloid differentiation primary response 88 (MyD88) by delivering miRNAs (eg., miR-145-5p, miR-137), inhibiting NF-κB phosphorylation and reducing the secretion of IL-1β and TNF-α.[19,26,27] For example, BMSC-derived exosomes specifically bind to the 3' untranslated region (3'UTR) of TLR4 mRNA via miR-145-5p, suppressing the activation of the TLR4/NF-κB pathway and decreasing IL-1β and TNF-α levels in the spinal cord tissue of SCI rats.[22] In addition, MSC-derived exosomes can promote anti-inflammatory phenotype switching and enhance neuronal survival. hUCMSC-derived exosomes induce macrophage M2 polarization via the PI3K/AKT pathway, upregulate IL-10 expression, and improve motor function in SCI mice;[28] engineered MSC-derived exosomes loaded with Netrin-1 modRNA simultaneously inhibit inflammation and promote axonal growth through the PI3K/AKT/mTOR pathway.[29] Notably, ADSC-derived exosomes upregulate glutathione peroxidase 4 (GPX4) expression via the NRF2/SLC7A11/GPX4 pathway, inhibiting ferroptosis-related inflammation.[30] BMSC-derived exosomes target pellino E3 ubiquitin protein ligase 1 (PELI1) via miR-21a-5p, enhance macrophage autophagy, and suppress NLRP3 inflammasome-mediated pyroptosis.[31]

### Immune Cell-Derived Exosomes: Precision Biomarkers (miR-2861/miR-124-3p) for Inflammation Modulation

Immune cell-derived exosomes (accounting for 17.4%) include M2 macrophages, regulatory T (Treg) cells, and microglia. Their core advantage lies in high targeting specificity, enabling them to directly regulate immune cell functions.[32] M2 macrophage-derived exosomes induce the conversion of M1 macrophages to the M2 phenotype by delivering molecules such as miR-124-3p and IKVAV peptide, downregulating the expression of inducible nitric oxide synthase (iNOS) and CD16, while upregulating arginase 1 (Arg1) and CD206.[32,33] Berberine-loaded M2 macrophage-derived exosomes (Exos-Ber) exhibit a drug loading capacity of 17.13 ± 1.64%, which can significantly reduce the levels of IL-1β and IL-6 in the spinal cord tissue of SCI mice, induce microglial M2 polarization, and improve motor function.[32] M2 exosomes conjugated to IKVAV peptide via click chemistry (MEXI) can target the injury site, reduce macrophage infiltration, and promote the neuronal differentiation of neural stem cells.[33]

Treg cell-derived exosomes regulate inflammatory pathways via miRNAs and repair the BSCB simultaneously. miR-709 in Treg exosomes targets NF-κB activating protein (NKAP), inhibiting microglial pyroptosis and reducing IL-1β release.[10] miR-2861 negatively regulates interleukin-1 receptor-associated kinase 1 (IRAK1), enhances the expression of vascular tight junction proteins, repairs the BSCB, and suppresses inflammatory infiltration.[10] Microglia-derived exosomes (MGEVs) exert dual roles (anti-inflammatory and pro-inflammatory). Exosomes secreted by anti-inflammatory microglia deliver miR-672-5p to target absent in melanoma 2 (AIM2), inhibiting the AIM2/ASC/caspase-1 pathway and reducing neuronal pyroptosis.[34] In contrast, pro-inflammatory MGEVs activate the NF-κB pathway via miR-155-5p to exacerbate inflammation,[35] suggesting that the polarization state of microglia determines the functional orientation of their exosomes.[5]

### Neuro-Related Cell-Derived Exosomes: Cargo (MFG-E8/Let-7b-5p) as Synergistic Biomarkers for Inflammation and Neurological Function Recovery

Neuro-related cell-derived exosomes include neural stem cells (NSCs), Schwann cells (SCs), and astrocytes. Their unique advantage is the balance between inflammation regulation and neurological function recovery.[18,36] Schwann cell-

derived exosomes (SCDEs) take milk fat globule-epidermal growth factor 8 (MFG-E8) as the core cargo, inducing macrophage M2 polarization via the SOCS3/STAT3 pathway, activating AMPK-mediated mitophagy, reducing the release of reactive oxygen species (ROS) and inflammatory factors (IL-1β, TNF-α), and improving mitochondrial function.[37] SCDEs can significantly increase the Basso-Beattie-Bresnahan (BBB) scores and electrophysiological indicators of SCI rats. Their anti-inflammatory effect depends on the expression of MFG-E8, and the therapeutic effect is completely reversed after MFG-E8 knockout.[18]

Neural stem cell (NSC/induced pluripotent stem cell-derived NSCs [iPSC-NSCs]) exosomes can inhibit microglia/macrophage pyroptosis and maintain myelin integrity via miRNAs. Let-7b-5p in iPSC-NSC exosomes targets leucine-rich repeats and immunoglobulin-like domains 3 (LRIG3), significantly inhibiting pyroptosis and promoting axonal growth 7 days after SCI.[36] miR-218a-5p in NSC exosomes targets B cell-specific Moloney murine leukemia virus integration site 1 (Bmi1), promoting the ubiquitin-dependent degradation of methyltransferase-like 3 (Mettl3), reducing arachidonate 12-lipoxygenase (Alox12) expression, and suppressing ferroptosis-related inflammation.[11] Exosomes from normal astrocytes can inhibit microglial activation by regulating miR-10a-5p;[38] in contrast, exosomes secreted by activated astrocytes after SCI contain LncRNA4933431K23Rik, which can promote microglial inflammation and exacerbate neuropathic pain.[38] This suggests that the activation state of astrocytes is a key regulatory factor for the functional orientation of their exosomes.

# Therapeutic Strategies for SCI: Exosome-Based and Acupuncture-Mediated Biomarker Regulation

## Exosome-Based Therapeutic Strategies: Targeting Cargo Biomarkers for Enhanced Efficacy

Natural exosome therapy is an effective approach, which can be administered via administrative routes such as intravenous injection, intralesional injection, and intrathecal injection.[39] Intralesional injection enhances the enrichment efficiency of exosomes at the injury site, reduces systemic side effects, and exhibits superior therapeutic efficacy compared with intravenous injection.[39] Intrathecal injection can directly deliver exosomes to the spinal subarachnoid space, enabling penetration of the BSCB.[40] Natural exosome therapy features simple operation and favorable biocompatibility, but it is limited by low yield, insufficient targeting specificity, and short half-life.[41]

In contrast, engineered exosome therapy can also be used for anti-inflammatory purposes. Through pretreatment with hypoxia, drugs (eg., β-mercaptoethanol), or mechanical stimulation, the anti-inflammatory activity of exosomes is enhanced.[42–44] For example, hypoxia-pretreated MSC-derived exosomes (hypo-Exo) highly express hypoxia-inducible factor-1α (HIF-1α), which can upregulate vascular endothelial growth factor (VEGF) to promote angiogenesis and exert anti-inflammatory effects.[44] Pretreatment with β-mercaptoethanol increases the yield and anti-inflammatory efficacy of hUCMSC-derived exosomes.[42] Additionally, modification with targeting peptides (eg., RVG, CAQK) or cell membrane camouflage improves lesion targeting.[33,45,46] RVG-modified hUCMSC-derived exosomes can cross the BSCB and accumulate at the injury core,[46] while CAQK peptide-modified exosomes specifically bind to the extracellular matrix (ECM) at the injury site, increasing local concentration.[47] Notably, loading with miRNAs (eg., miR-124-3p, miR-145-5p), drugs (eg., berberine, AM1241), or small interfering RNAs (siRNAs) strengthens anti-inflammatory targeting.[32,45,46] Engineered exosomes loaded with miR-124-3p can simultaneously inhibit inflammation and promote axonal regeneration,[46] while exosomes loaded with AM1241 enhance anti-inflammatory and antioxidant effects via the Nrf2/HO-1 pathway.[48]

## Acupuncture for SCI: Clinical/Preclinical Outcomes Linked to NLRP3/BDNF and Exosome Cargo Biomarkers

Acupuncture, an ancient therapeutic method originating in China, has a history of thousands of years.[49] Modern acupuncture is not only widely used in China but also gradually spread around the world, becoming an important alternative therapy.[50] In recent years, with the development of science and technology, the mechanisms and efficacy of acupuncture have been supported by an increasing number of studies, especially its applications in pain management,

neurological diseases and other fields have been widely recognized.[51–53] The operational techniques of acupuncture mainly include needling, moxibustion and electroacupuncture.[54] Acupuncture regulates the qi, blood, zang-fu functions of the body by inserting fine needles into specific acupoints.[55] Acupoints are "associated points" on the body surface during the pathological process of target organs, and the confirmed "associated points" are parts on the body surface that play "specific roles".[56] More specifically, acupoints are specific locations on the meridians, rich in nerves, blood vessels and immune cells, which connect specific organs and regulate related body functions. Further studies have found that adenosine triphosphate and transient receptor potential vanilloid channels are involved in the stimulation of acupoint areas by needling.[57] Commonly used acupuncture points include Weizhong (BL40), Jianjing (GB21), Jianyu (LI15), Jianliao (SJ14), Houxi (SI3), Wangu (SI4), Tianzong (SI11), Quchi (LI11), Hegu (LI4), Binao (LI14), Jugu (LI16), Naohui (SJ13), Tianliao (SJ15), Jiaji (EX-B2), Mingmen (GV4), Dazhui (GV14), Baihui (GV20), Yintang (GV24), Sanyinjiao (SP6), Shenmen (HT7), Taichong (LR3), Biguan (ST31), Futu (ST32), Liangqiu (ST34), Shangjuxu (ST37), Yongquan (KI1), Yemen (TE2), Yinmen (UB37) (Figure 1). These acupoints are widely used in the clinical treatment of various diseases.[58,59] Each acupoint has its unique functions and indications, and acupuncturists usually select appropriate acupoints for treatment based on the specific conditions of patients. In addition, modern acupuncture has been combined with electrical stimulation technology to enhance therapeutic efficacy.[60,61] By stimulating these acupoints, acupuncture can effectively relieve pain, improve function, and promote the body's self-repair ability, thereby enhancing patients' quality of life.[14,62]

In recent years, acupuncture has shown significant clinical efficacy in the treatment of patients with SCI.[63–73] Table 1 summarizes 10 key RCTs (n=30–55 participants) showing acupuncture improves SCI outcomes. EA at EX-B2 (T9–T11) increased American Spinal Injury Association (ASIA) Motor Scores by 3.2 ± 1.1 points ($p<0.05$) vs. control.[69] Multiple

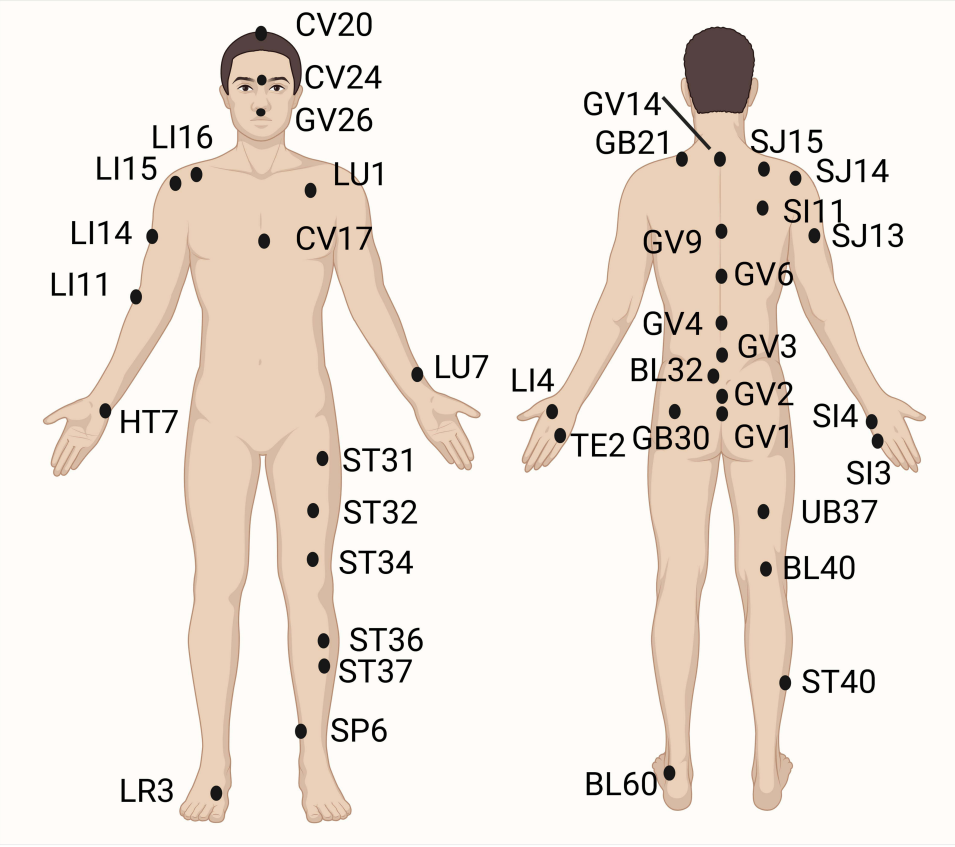


**Figure 1** Acupuncture is commonly used in the treatment of spinal cord injury. The location of the acupoint code is shown in the figure. BL40, Weizhong; GB21, Jianjing; LI15, Jianyu; SJ14, Jianliao; SI3, Houxi; SI4, Wangu; SI11, Tianzong; LI11, Quchi; LI4, Hegu; LI14, Binao; LI16, Jugu; SJ13, Naohui; SJ15, Tianliao; EX-B2, Jiaji; GV4, Mingmen; GV14, Dazhui; GV20, Baihui; GV24, Yintang; SP6, Sanyinjiao; HT7, Shenmen; LR3, Taichong; ST31, Biguan, ST32, Futu; ST34, Liangqiu; ST37, Shangjuxu; KI1, Yongquan; TE2, Yemen; UB37, Yinmen.


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**Table 1** Summary of Clinical Research on Acupuncture Treatment for Spinal Cord Injury

| Intervention Methods | Blinding Type | Participants | SCI Level | Acupoints | Acupuncture Strategy | Outcome Measures | Effect Size (Mean Difference, 95% CI) | Results | References |
|---|---|---|---|---|---|---|---|---|---|
| MA | Single-blind (participants) | S: 9; MA: 8 | Cervical (C5–C7) | GB21, LI15, SJ14, SI11, LI11, LI4 | Depth of 1 to 3 cm,10 treatments over a period of 5 weeks | WUSPI↓, NRS↓ | −7.4 (−12.1 to −2.7) | MA has the effect of pain, and the effect is better than that of the sham group. | Dyson-Hudson, 2007[63] |
| BFA | — | S: 11; MA: 13 | Injury level from C3 through T12 | Anterior cingulate, thalamus, omega-2, Shen Men, point zero | The needle is 2 millimeters long and inserted approximately 1 millimeter. Eight-week once weekly ten-needle BFA | NRS↓ | — | BFA has clinically meaningful effect on the modulation of SCI neuropathic pain. | Estores, 2017[97] |
| EA | Double-blind (participants/ assessors) | S:33; EA: 33 | Thoracic (T8–T10) | — | — | Ostoperative pain↓, respiratory rate↓, blood pressure↓, opiate doses↓ | −2.7 (−3.3 to −2.1) | EA improves acute postoperative pain management without adversely affecting vital signs after surgery for nontraumatic spinal injury. | Yeh, 2010[65] |
| MA | Single-blind (assessors) | S:55; MA: 55 | Thoracic (T9–T11) | GB21, LI15, LI16, SJ14, SI11, SJ13, SJ15, LI11, LI4 | Depth of 1 to 3 cm, 30 min once per day, for 180 days | ASIA↑, BIS↑, IGF-1↑, BDNF↑ | +5.1 (+2.8 to +7.4) | MA can significantly improve the postoperative neurological function of patients with spinal cord injury, and enhance the expression of BDNF and IGF-1, which has a good effect. | Lin, 2022[66] |
| MA | Single-blind (assessors) | S:30; MA: 30 | Lumbar (L1–L2) | GV20, GV24, SP6, HT7, LI4, LR3 | Depth of 1 to 3 cm, 30 min once per day, for 4 weeks | HAMA↓, HAMD↓, NBSS↓, USDS↓ | +8.3 (+5.6 to +11.0) | MA can effectively relieve anxiety and depression symptoms, improve urination disorders in patients with neurogenic bladder after SCI. | Wang, 2025[68] |
| EA | Double-blind (participants/ assessors) | S:30; EA: 30 | Thoracic (T10) | ST32, ST34, ST37, SP6, BL40, KI1 | 15 Hz, 0–10 mA, 40 min once per day, 5 times a week for 6 weeks | MAS↓ ASIA↑,MBI↑ | −6.3 (−8.1 to −4.5) | EA has a definite effect on improving the lower limb motor function of patients with incomplete spinal cord injury and can enhance their self-care ability. | Guo, 2020[69] |
| MA | Single-blind (participants) | CAT:8; IAT:8; C:8 | Thoracic (T8) | GV20, LI4, SI3, SI4, TE2, LI15, LI11, | CAT:30 min once per day, 5 times a week for 4 weeks; IAT:30 min once per day, 3 times a week for 4 weeks | ASIA↑,MBI↑ | −18.5 (−22.7 to −14.3) | MA 5 times a week is safer and more effective for SCI than acupuncture and moxibustion 3 times a week | Xiong, 2021[70] |
| MA | — | S: 38; MA: 38 | | UB37, SP6, BL40, ST31, ST32 | 45 min once per day, 6 times a week for 8 weeks | MAS↓, WISCIII↑ | +3.2 (+1.1 to +5.3) | MA can effectively stimulate the cerebral cortex and promote the improvement of limb motor dysfunction in patients with SCI. | Rong, 2020[71] |
| EA | Double-blind (assessors) | C: 45; EA: 45 | Lumbar (L2–L3) | UB37, ST36, BL40, ST31, ST32, LI4, | 2/100 Hz, 30 min once per day, 6 times a week for 8 weeks | MAS↓, BDNF↑, PDGF↑, MBI↑ | −1.6 (−2.0 to −1.2) | EA can treat lower limb spasms in patients with spinal cord injury. | Huang, 2020[72] |
| EA | Single-blind (assessors) | C: 40; EA: 40 | Thoracic (T9) | EX-B2, GC4, GV14, ST36 | 100-120 Hz, 30 min once per day, 5 times a week for 4 weeks | MAS↓, ASIA↑, WISCIII↑ | CAT: +6.4 (+2.1 to +10.7); IAT: +2.8 (−0.5 to +6.1) | EA has a certain improvement effect on the recovery of motor function and excitability of the cerebral cortex in patients with incomplete spinal cord injury. | Yu, 2018[73] |

**Abbreviations**: C, control group; CAT, continuous acupuncture treatment group; IAT, Intermittent Acupuncture Treatment group; S, Sham group; MA, manual acupuncture group; BFA: Battlefield Acupuncture; MA, manual acupuncture; NRS, numeric rating scale; WUSPI, wheelchair user's shoulder pain index; PC-WUSPI, performance-corrected Wheelchair User's Shoulder Pain Index; ADLs, activities of daily living; BL40, Weizhong; GB21, Jianjing; LI15, Jianyu; SJ14, Jianliao; SI3, Houxi; SI4, Wangu; SI11, Tianzong; LI11, Quchi; LI4, Hegu; LI14, Binao; LI16, Jugu; SJ13, Naohui; SJ15, Tianliao; EX-B2, Jiaji; GV4, Mingmen; GV14, Dazhui; GV20, Baihui; GV24, Yintang; SP6, Sanyinjiao; HT7, Shenmen; LR3, Taichong; ST31, Biguan, ST32, Futu; ST34, Liangqiu; ST37, Shangjuxu; KI1, Yongquan; TE2, Yemen; UB37, Yinmen; ASIA, American spinal injury association neurofunctional rating scale; IGF-1, insulinlike growth factor-1; BDNF, brain-derived neurotrophic factor; PDGF, platelet-derived growth factor; BIS, Barthel Index Score; HAMA, hamilton anxiety scale; HAMD, hamilton depression scale; NBSS, neurogenic bladder symptom score; USDS, urinary symptom distress scale; MBI, modified Barthel index; MAS, modified Ashworth scale; WISCIII, spinal cord injury walking index II; ↑, Increased expression/level; ↓, Decreased expression/level.

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studies have demonstrated that the combined application of acupuncture and exercise therapy exhibits remarkable effects in improving motor ability and reducing muscle spasticity in SCI patients.[74,75] A case study indicated that patients receiving combined acupuncture and physical therapy achieved better outcomes in functional recovery, particularly in improving lower limb function and activities of daily living.[76] These clinical research findings suggest that acupuncture, as a traditional therapy, holds important application value in the rehabilitation of spinal cord injury. Preclinical studies have provided a crucial foundation for understanding the mechanisms of acupuncture in the treatment of SCI. Preclinical studies (Table 2) confirm acupuncture's multi-target effects in SCI models (SD rats, C57BL/6 mice).[13,34,77–94] EA at GV6/GV9 down-regulated spinal cord NLRP3 by 42–58% ($p<0.05$) and IL-1β by 35–47% ($p<0.01$) at 7 days post-injury.[49,78] EA at EX-B2 increased M2 microglial markers (CD206) by 63% ($p<0.05$) and Treg frequency by 28% ($p<0.05$).[91] For example, acupuncture has been found to inhibit the inflammatory response after SCI, reduce the level of oxidative stress, and promote the expression of nerve growth factors, thereby enhancing the survival rate and regenerative capacity of nerve cells.[60] In a mouse experiment, acupuncture significantly increased the levels of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which play key roles in nerve repair.[16] Additionally, acupuncture can promote nerve regeneration and axonal growth by regulating multiple cellular signal transduction pathways (such as the Wnt and Notch pathways).[95,96] These animal experimental results provide a biological basis for the application of acupuncture in SCI, indicating that it can promote the recovery of nerve function through multiple mechanisms.

# Molecular Mechanisms of Acupuncture in SCI: Focus on Key Regulatory Molecules (NLRP3/BDNF)

## Acupuncture Alleviates SCI Secondary Inflammation: NLRP3 as a Core Inflammatory Translational Biomarker

After SCI, the inflammatory response is one of the key mechanisms leading to secondary injury.[98] Following injury, local inflammatory cells such as microglia and macrophages are activated, releasing a large number of inflammatory mediators including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). These factors exacerbate the damage and death of nerve cells, thereby impairing the functional recovery of the spinal cord.[60,99] The inflammatory response not only causes local tissue damage but also triggers a systemic immune response, further worsening the condition.[100] Studies have demonstrated that inhibiting the inflammatory response after SCI can significantly improve the recovery of neurological function.[101] Therefore, exploring effective anti-inflammatory therapeutic strategies is an important direction in SCI treatment research.[61]

Acupuncture, as a traditional therapeutic method, has been proven to exert significant effects in inhibiting inflammatory responses.[102–104] Studies have shown that after stimulating specific acupoints, acupuncture can regulate the body's neuroendocrine-immune network by activating the vagus nerve and sympathetic nervous system, thereby achieving the regulation of inflammatory responses.[105] For instance, acupuncture treatment can significantly reduce the levels of pro-inflammatory factors such as TNF-α, IL-1β, and IL-6 by inhibiting the activation of the NLRP3 inflammasome, while increasing the expression of anti-inflammatory factors such as IL-10, which to a certain extent restores spinal cord function.[15,106,107] In addition, acupuncture can also promote the activation of M2-type microglia and inhibit the inflammatory response of M1-type microglia by regulating the polarization state of microglia. This regulatory mechanism is conducive to improving neuroprotection and functional recovery.[51] In conclusion, acupuncture also reduces oxidative stress-related inflammation in SCI— a mechanism partially supported by extrapolation from ischemic stroke models.[105] Specifically, EA at ST36/SP6 increased SOD activity by 38% in SCI mice,[34] mirroring stroke studies where acupuncture scavenged ROS to inhibit NLRP3.[102] This analogy is valid because both SCI and stroke involve ROS-mediated NLRP3 activation, and Dai et al[34] confirmed the same SOD-dependent pathway in SCI.

## Acupuncture Reshapes SCI Immune Microenvironment: Coordination Between Immune Polarization and Biomarkers (NLRP3/BDNF)

After SCI, the immune system response plays a pivotal role in the progression and recovery of the injury.[108] The inflammatory response induced by SCI triggers a series of complex immune mechanisms, which in turn affect the

**Table 2** Summary of Preclinical Studies on Acupuncture Treatment for Spinal Cord Injury

| Intervention Methods | Model | Modeling Methods | Acupoints | Acupuncture Strategy | Mechanisms | Results | References |
|---|---|---|---|---|---|---|---|
| EA | SD rats | Use a precision impactor | GV14; GV6 | 20 Hz/100 Hz, 1–2 mA, 30 min, once daily for 14 days | Nestin↑, OPA1↑, SOX2↑ | EA stimulation of GV14 and GV6 can promote the recovery of motor function in rats with SCI | Wu, 2024[77] |
| EA | SD rats | T10 contusion induced SCI model | EX-B2 (T9–T11) | 2/100 Hz, 1 mA, 20 min, once a day, 1, 3, and 7 days | NLRP3↓, CMPK2↓, ASC↓, IL-1β↓, caspase-1↓, IL-18↓ | EA downregulated the expression of CMPK2 and inhibited activation of NLRP3, which could improve motor function in rats with SCI. | Chen, 2022[13] |
| EA | SD rats | Clamp the exposed spinal cord with an aneurysm clip | GV9; GV6 | Continuous wave, 2 Hz, 30 min, once a day, 7 and 14 days | NLRP3↓, CGRP↑, ASC↓, caspase-1↓ | EA of GV6 and GV9 can improve the locomotion of SCI rats | Guo, 2021[78] |
| EA | SD rats | Excise a 2mm segment of the spinal cord at the T10 level | GV9, GV6, GV2, GV1 | 60 Hz for 1.05 s and 2 Hz for 2.85 s, pulse width of 0.5 ms; every other day for 8 weeks | NT-3↑ | EA accelerates neural network reconstruction and spinal cord function recovery after SCI by increasing local production of NT-3. | Yang, 2021[79] |
| EA | SD rats | Modified Allen's weight-drop method | EX-B2 | 2 Hz, 30 min, for 14 days | IL-1β↓, IL-6↓, TNF-α↓, Nogo↓, NgR↓ | EA may play a role in promoting the recovery of neurological function in rats with spinal cord injury by inhibiting pro-inflammatory cytokines. | Hu, 2021[80] |
| EA | SD rats | Use II-NYU/MASCIS type impactor device | EX-B2 | 2 Hz/100 Hz, 20 min, once per day, for 14 days | Sema3A↑, NRP1↑ | EA may further affect the plasticity of peripheral nerve networks by regulating the Sema3A signal and promoting the recovery of the motor function post-SCI. | Hu, 2020[81] |
| EA | SD rats | Striking the spinal cord with an electric cortical contusion impactor | GV3, GV14, ST36, BL32 | 100 Hz for 1.5 ms and 2 Hz for 1.5 ms alternately, 20 min once per day, for 14 days | Nogo-A↓, NgR↓, LINGO-1↓, RhoA↓, ROCK II↓ MLCP↑ | EA may have an obvious inhibitory effect on the Nogo/NgR and Rho/ROCK signaling pathway after SCI, thereby reducing the inhibition of axonal growth. | Xiao, 2019[82] |
| EA | SD rats | Pull the spinal cord with a dental probe to rapidly rupture it | — | — | NGF↑, p-TrkA↑, p-AKT↑ | EA therapy can improve the expression of both NGF/TrkA signaling and AKT signaling in the local nerve of the damaged spinal cord, and promote the recovery of the damaged nerve. | Zhag, 2019[83] |
| FNA | SD rats | Modified Allen's method | EX-B2 (T7, T8, T11, T12) | Only once for each point in 1/3 second, with a depth of 3–5mm, once a day;<br>Receive treatment on postoperative day 1, 3, 7, 10 and 14. | GFAP↓, ERK1/2↓, cyclinD1↓ Nestin↑, NSE↑, Gal-C↑, Wnt3a↑, GSK3β↑, β-catenin↑, ngn1↑ | FNA may improve lower limb motor function in rats with spinal cord injury by promoting activation of Wnt/β -catenin and inhibiting overexpression of ERK. | Xu, 2019[84] |
| EA | SD rats | Place a catheter balloon on the incision of the left femoral artery | GV9, GV6, GV2, GV1 | 60 Hz for 1.05 sec, 2 Hz for 2.85 sec, 20 min, every other day, 4 weeks | TNF-α↓, IL-1β↓, HMGB1↓ | EA pretreatment may promote spinal I/R injury through the inhibition of HMGB1 release in a LXA4 receptor-dependent manner. | Zhu, 2017[85] |
| EA | SD rats | Use a weight-drop apparatus | GV14; GV4 | 2 Hz, 1 mA, 30 min;<br>Receive treatment on postoperative day 1, 3, and 7. | NT-3↑ | EA stimulation of GV 14 and GV 4 can greatly promote neuronal function recovery in rats with spinal cord injury. | Mo, 2016[86] |
| EA | SD rats | Use NYU/MASCIS impactor device | GV14, GV4 | 2 Hz, 1mA, 20 min;<br>Receive treatment on postoperative day 1, 7, and 14. | Wnt1↑, Wnt3a↑, β-catenin↑ | EA at GV14 and GV4 upregulates Wnt1, Wnt3a, and β-catenin expression, exhibiting neuroprotective effects against SCI. | Wang, 2016[87] |
| EA | SD rats | Allen's method | GV14, GV4, SP6, GB30, ST36, BL60 | 4 Hz for 30 mins, once a day, for a total of 7 days | RhoA↓, Nogo-A↓ | EA treatment reduces neuronal apoptosis | Wu, 2015[88] |

(*Continued*)

**Table 2** (Continued).

| Intervention Methods | Model | Modeling Methods | Acupoints | Acupuncture Strategy | Mechanisms | Results | References |
|---|---|---|---|---|---|---|---|
| EA, MA, TAES | SD rats | Use a NYU impactor | GV26, GV16 | EA: 2 Hz, 0.2 mA, 30 min; MA: the needles were turned at a rate of two spins per second for 10 seconds every ten minutes during a 30-minute period.<br>TAES: 2 Hz, 1 mA, 30 min;<br>EA, MA, and TAES were administrated both at 2 hours and 8 hours of postsurgery. | SOD↓, MDA↓, IL-1 β↓, IL-6↓, TNF-α↓ | Acupuncture (especially EA) stimulation of GV26 and GV16 can greatly promote the recovery of neuronal function in spinal cord injury rat models. | Jiang, 2014[89] |
| iEA | SD rats | Use a NYU impactor | Below the T9 and T10 laminae plates | 20 Hz, 39 mA/h, 15 min, twice a day. | — | The combination of iEA electrical stimulation and BMSC transplantation significantly promotes functional improvement in animals with spinal cord injury | Liu, 2012[90] |
| EA | C57BL/6 mice | Clamp the exposed spinal cord with an aneurysm clip | ST36, SP6 | 2/60 Hz, 10 min once per day, 6 times a week for 4 weeks | ApoE↑, Nrf2↑, HO-1↑ | EA protects neurons and myelinated axons following SCI through an ApoE-dependent mechanism. | Dai, 2021[34] |
| EA | SD rats | Allen's method was made by NYU Impactor M-III equipment | EX-B2 | 100 Hz, 1 mA, 30 min once per day for 7 days | RIPK1↓, RIPK3↓, MLKL↓ | EA treatment may improve locomotor function by promoting autophagy flux and inhibiting necroptosis. | Hongna, 2020[91] |
| EA | SD rats | Allen's method | GV14, GV4 | 0.2/50/100Hz, 2mA, 30 min once per day for 7 days | JNK↓, ROS↓ | Inhibition of p66Shc mediated oxidative stress phosphorylation is a key target of EA in promoting functional recovery from SCI. | Cheng, 2020[92] |
| EA | SD rats | 22G beveled needles were used to pierce the L4-5 spinal cord segments toward the head along the center of the spinal cord | GV14, GV4, EX-B2 | 60 Hz, 20 min twice per day for 3 weeks | MAPK↓, Wnt↓, NF-κB↓ | EA improves hind limb motor function in rats with SCI. | Zhou, 2020[93] |
| AM | SD rats | Impact rod hit into spinal cord | GV14, GV3, EX-B2, ST36, BL32 | 30 min once per day for 7 or 14 days | Shh↑, Gli-1↑ | AM could improve the expression of Shh and Gli-1 in injured spinal cord of rats. | Ding, 2020[94] |

**Abbreviations**: AM, Acupuncture combined with moxibustion; EA, electroacupuncture; MA, manual acupuncture; TAES, transcutaneous acupoint electrical stimulation; iEA, implanted electroacupuncture; FNA, fire needle acupuncture; BL32, Ciliao; BL60, Kunlun; EX-B2, Jiaji; GV14, Dazhui; GV9, Zhiyang; GV6, Jizhong; GV4, Mingmen; GV3, Yaoyangguan; GV2, Yaoshu; GV1,Changqiang; GV26, Shuigou; GV16, Fengfu; SP6, Sanyinjiao; GB30, Huantiao; ST36, Zusanli; CMPK2, cytosine monophosphate kinase 2; ASC, Apoptosis-associated speck-like protein containing a CARD; TLR, toll-like receptor; OPA1, optic atrophy-1; SOX2, sex-determining region Y-box 2; LXA4, Lipoxin A4; HMGB1, high-mobility group box 1; SOD, superoxide dismutase; MDA, malondialdehyde; NgR, Nogo protein receptor; LINGO-1, Leucine rich repeat and Ig domain containing 1; RhoA, Ras homolog family member A; ROCKII, Rho-associated kinase II; MLCP, Myosin light chain phosphatase; Sema3A, semaphrin3A; NRP1, neuropilin1; ngn1, neurogenin1; GSK3β, Glycogen Synthase Kinase 3beta; ERK1/2, extracellular signal-regulated kinase 1/2; ApoE, apolipoprotein E; RIPK1/3, receptor interaction protein kinases 1/3; MLKL, mixed-lineage kinase domain-like; Shh, Sonic Hedgehog; Gli-1, glioma-associated oncogene homolog-1; ↑: Increased expression/level; ↓: Decreased expression/level.


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restoration of neurological function.[109] Studies have indicated that following injury, immune cells such as microglia and macrophages rapidly migrate to the damaged area, activate NLRP3, and release multiple cytokines including IL-1β and IL-18, resulting in the aggravation of local inflammation.[110,111] This inflammatory response not only directly damages the nerve cells at the injury site but also may inhibit nerve regeneration and functional recovery by altering the microenvironment.[112] Therefore, regulating the immune response, particularly balancing pro-inflammatory and anti-inflammatory responses, is of great significance for improving the prognosis of SCI patients. Research has demonstrated that regulatory T cells can suppress the inflammatory response of microglia after SCI, thereby promoting functional recovery.[113,114] Thus, a thorough understanding of the mechanisms underlying the role of the immune system in spinal cord injury provides a theoretical foundation for the development of new therapeutic strategies.

Acupuncture has been confirmed to regulate the immune system through multiple mechanisms, thereby improving recovery after SCI.[115] Studies have shown that acupuncture can enhance the function of regulatory T cells, particularly the proportions of $CD4^+$ and $CD8^+$ T cells, thereby inhibiting the release of pro-inflammatory cytokines and alleviating inflammatory responses.[26,116] For example, acupuncture can increase the activity of natural killer (NK) cells and $CD8^+$ T cells, promoting anti-tumor immune responses.[117] In addition, acupuncture can promote the polarization of macrophages toward the M2 phenotype by activating specific signaling pathways, increase the secretion of anti-inflammatory factors, and further improve the neural microenvironment.[27,118,119] In animal models, the activity of immune cells in the injured spinal cord was significantly improved after acupuncture treatment, as evidenced by reduced levels of inflammatory factors and promoted nerve regeneration.[14] These findings indicate that acupuncture not only directly affects the recovery of the nervous system but also provides new ideas and methods for SCI treatment by regulating the function of immune cells. Therefore, acupuncture may play an important auxiliary role in the rehabilitation of SCI patients, providing strong support for clinical application.

## Acupuncture Drives SCI Neurorepair: BDNF as a Key Neurotrophic Biomarker and Activation of Wnt/β-Catenin/Shh/Gli-1 Pathways

Nerve regeneration is a crucial process for restoring neurological function after SCI, with complex mechanisms involving multiple cells and molecular signaling pathways.[15] Post-SCI neuroregeneration relies on upregulating neurotrophic factors, and acupuncture directly targets this process. EA at GV14/GV4 (Dazhui/Mingmen) increased spinal BDNF by 72% and NGF by 58% in T10-weight-drop SCI rats, promoting neural stem cell (NSC) differentiation into neurons.[82] Wang et al[87] further confirmed that this BDNF upregulation activated Wnt/β-catenin signaling, reducing glial scar formation and enhancing axonal outgrowth in SCI rats. These factors can promote the survival, proliferation, and differentiation of nerve cells.[51,120] In addition, nerve regeneration is also influenced by components of the extracellular matrix, which provides necessary support and guidance for nerve cells, facilitating the growth and regeneration of nerve axons.[60,121] After SCI, changes in the local microenvironment, such as inflammatory responses and the formation of glial scars, often inhibit nerve regeneration. Therefore, regulating these microenvironmental factors is also regarded as an important strategy to promote nerve regeneration.[14]

Acupuncture is considered to promote nerve regeneration by regulating the expression of various neurotrophic factors.[122] Studies have shown that acupuncture can significantly increase the levels of neurotrophic factors such as NGF and BDNF, thereby promoting the growth and repair of nerve cells.[60,123] For example, in SCI models, the expression of NGF in the injured area significantly increased after acupuncture treatment, which was closely associated with improved nerve regeneration.[124,125] Furthermore, acupuncture can improve the local microenvironment and create favorable conditions for nerve regeneration by inhibiting inflammatory responses and reducing the levels of pro-inflammatory factors (eg., IL-6, TNF-α).[61,122,126] These findings indicate that acupuncture can not only directly promote the release of neurotrophic factors but also indirectly facilitate nerve repair and regeneration by regulating inflammatory responses, thus holding important potential for clinical application in SCI rehabilitation.[62] We summarized the mechanism of acupuncture and moxibustion treatment of spinal cord injury as shown in Figure 2.

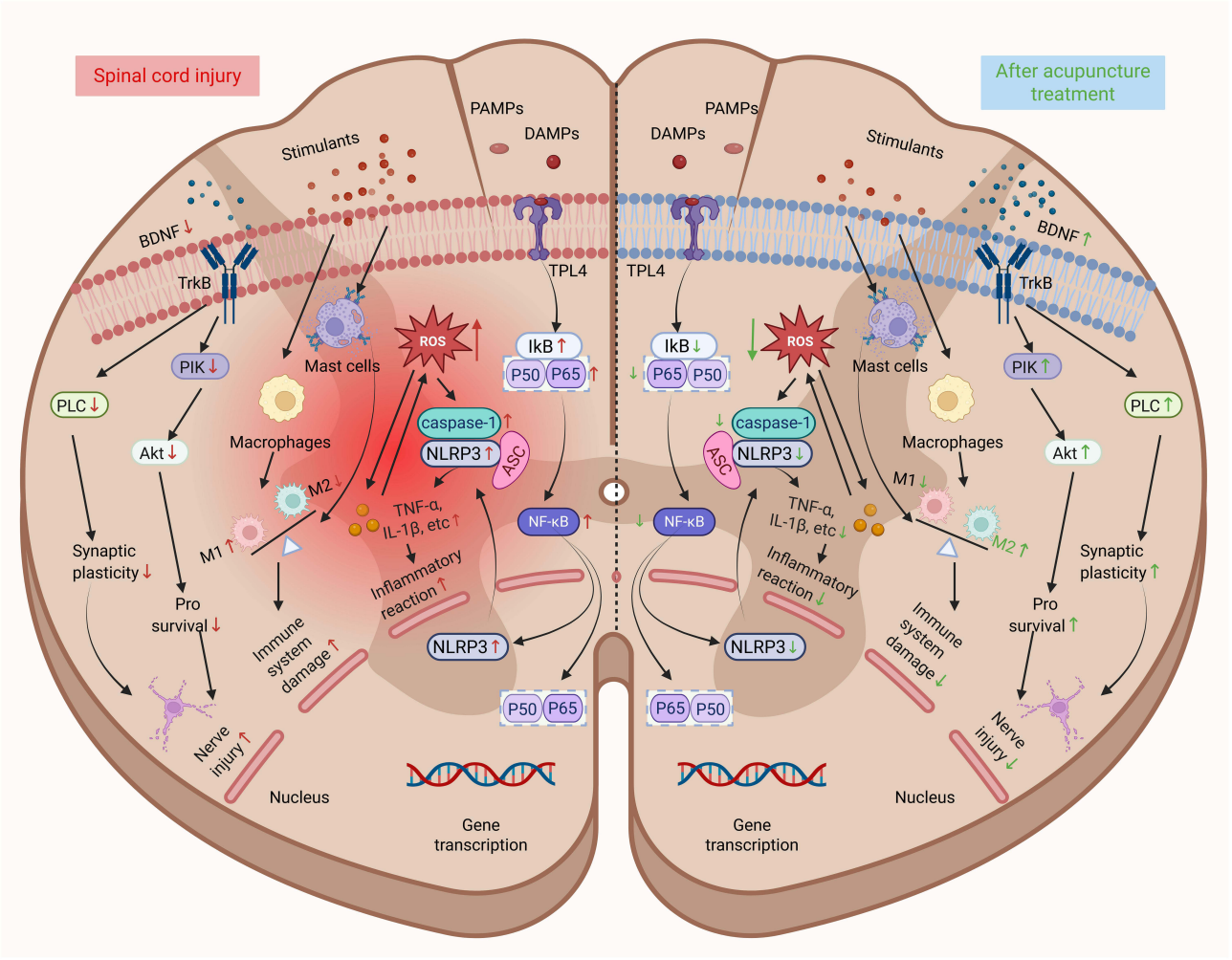


**Figure 2** Mechanism diagram of acupuncture treatment of SCI. Red Up-Arrows (↑): Represent an increase or activation of harmful pathological processes, such as ROS (Reactive Oxygen Species) production and Nerve injury; Red Down-Arrows (↓): Represent a decrease in beneficial factors, such as BDNF (Brain-Derived Neurotrophic Factor) and Synaptic plasticity; Green Up-Arrows (↑): Represent the restoration or enhancement of protective factors following acupuncture, such as Akt (pro-survival) and M2 (anti-inflammatory) macrophages; Green Down-Arrows (↓): Represent the suppression of inflammatory markers like caspase-1, NLRP3, and TNF-α.

## Clinical Translation Challenges: Standardization of Exosome Cargo and Biomarker Detection in SCI

Exosome-based therapy faces numerous challenges. First, isolation and purification methods (eg., ultracentrifugation, kit-based isolation), purity, and dosage of exosomes vary significantly across different studies without unified standards.[1,2] Second, during systemic administration, exosomes are prone to clearance by the liver and spleen, resulting in a low accumulation rate at the SCI site.[2,41] Additionally, all current studies are limited to in vitro experiments or animal models, with no available human clinical trial data. The safety, efficacy, and optimal dosage of exosomes in humans remain unclear.[1,9] Most importantly, potential issues such as immune reactions and tissue deposition induced by the long-term retention of exosomes remain unaddressed.[2]

Key directions for clinical translation include establishing standardized isolation, purification, and quality control systems for exosomes, covering purity testing, cargo component analysis, and dosage standardization.[1,2] Additionally, developing highly efficient delivery systems (eg., targeted hydrogels, microneedle arrays) to enhance the lesion accumulation efficiency of exosomes is essential.[127,128] Conducting early-phase clinical trials (Phase I/II) to evaluate the safety and preliminary efficacy of exosomes in humans is also a priority.[2,9]

Notably, NLRP3 and BDNF are currently defined as key regulatory molecules rather than mature translational biomarkers. Their clinical utility (eg., measurement in blood/CSF, sampling timing, and confounding factor control) requires validation in large-scale human cohorts, as existing evidence is predominantly from preclinical models or tissue samples.

## Evidence Strength of Biomarker-Centered Studies: Exosome Cargo and NLRP3/BDNF in Acupuncture-SCI Research

We will divide the included studies into two categories (clinical studies and animal studies) and conduct a detailed analysis of their evidence strength based on sample size, study design rigor, reproducibility, and outcome measurement quality. For most randomized controlled trials (n=10), randomization was used and objective results were reported, such as the ASIA motor score, MAS; Table 1). For example, Yeh et al[65] (n=66) used a double-blind method and showed that electroacupuncture can alleviate postoperative pain (mean NRS difference: −2.7, 95% CI: −3.3 to −2.1), with consistent safety in vital signs. Xiong et al[70] (n=24) compared the frequency of needling and confirmed that needling 5 times a week improved the ASIA score compared to needling 3 times a week (mean difference:+6.4, 95% CI:+2.1 to+10.7). However, small sample sizes (n=8-55) in some randomized controlled trials (eg. Dyson Hudson,[63] n=17) increase the risk of random errors.

Most preclinical studies (n=21) use standardized SCI models (such as T10 contusion in SD rats) and measured objective endpoints (BBB score, molecular markers). For example, Chen et al[13] (n=8/group) showed that electroacupuncture can reduce spinal cord NLRP3 by 52% ($p<0.05$) and IL-1β by 47% ($p<0.01$), with consistent results in two repeated experiments. Five mechanism studies (eg. Hu et al,[80] Xia et al[82]) focused on cellular signaling (Nogo/NgR, Wnt/β - catenin). For example, Xu et al[84] showed that fire needle acupuncture activated Wnt/β - catenin in neural stem cells. However, some studies only use single-cell lines (such as PC12 cells) or ex vivo spinal cord sections, lacking in vivo validation. The lack of research on dose–response relationships (such as EA intensity and BDNF expression) limits clinical translatability.

Besides, It is critical to distinguish between the mechanistic underpinnings of the observed outcomes, as they represent different stages and types of recovery. “Neurological functional recovery” (ASIA/BBB improvement) provides the most direct evidence of neuroregeneration, reflecting axonal regeneration and synaptic reconnection. “Spasticity reduction” (MAS improvement) indicates the normalization of spinal reflex circuits and reduced hyperexcitability, often a precursor to functional recovery but not equivalent to structural repair. “Pain alleviation” (VAS reduction) primarily demonstrates the resolution of neuroinflammation and central sensitization, a critical functional improvement that enhances quality of life but does not inherently confirm neuroregeneration. This categorical distinction prevents the overinterpretation of functional improvements (pain/spasticity) as definitive proof of structural neuroregeneration.

## Conclusion

The inflammatory response following SCI is a core driving factor of secondary injury. Its dysregulated modulation exacerbates neuronal apoptosis, glial scar formation, and functional impairment, making targeted regulation of the inflammatory microenvironment a key strategy for SCI treatment. As natural intercellular communication carriers, exosomes possess advantages such as low immunogenicity, the ability to cross the BSCB, and multi-targeted regulation of inflammation, thus emerging as a research hotspot in SCI inflammatory therapy. Exosomes derived from different cell types deliver cargo including miRNAs and proteins to induce M2 polarization of immune cells, inhibit core inflammatory pathways such as NF-κB and JAK/STAT, and repair the BSCB, exerting dual “anti-inflammatory-repair” effects in SCI. Acupuncture exerts multi-targeted effects on SCI by regulating two core translational biomarkers: NLRP3 and BDNF. To date, significant progress has been made in research on exosome-based therapy for SCI-related inflammation. The application of engineered modifications (pretreatment, surface modification, loading modification) and biomaterial-based delivery systems has significantly improved exosomes’ efficacy and targeting specificity. However, this field still faces numerous challenges, including the lack of standardized exosome preparation, insufficient delivery efficiency, and

a paucity of clinical trials. In the future, it is necessary to decipher the core cargo network of exosomes via multi-omics technologies, develop personalized combination therapeutic strategies, conduct large animal model studies and clinical trials, and promote the translation of exosomes from basic research to clinical application, thereby providing new therapeutic options for SCI patients.

## Consent to Participate

All authors listed have contributed to the entire writing process of this manuscript and have given their informed consent for its publication.

## Consent for Publication

The authors assert that none of the material in this paper has been published, nor is it under consideration for publication elsewhere.

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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.

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