

干细胞与神经营养因子联合用于脊髓损伤修复的研究进展

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摘要

目的: 系统梳理干细胞与神经营养因子(neurotrophic factors, NTFs)联合应用于脊髓损伤(spinal cord injury, SCI)修复的研究现状, 明确协同机制、技术突破与临床转化瓶颈, 为后续研究提供方向。方法: 检索近年国内外核心文献, 从SCI病理特征、单一成分作用局限、联合治疗机制、载体技术创新及临床转化挑战等维度展开分析。主要发现神经干细胞(neural stem cells, NSCs)、诱导神经干细胞(induced neural stem cells, iNSCs)及其外泌体, 与脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)、神经营养素-3 (neurotrophin-3, NT-3)、胶质细胞源性神经营养因子(glial cell line-derived neurotrophic factor, GDNF)等联合时, 可通过免疫微环境调控、损伤区域基质重塑、轴突定向生长及髓鞘再生四重机制发挥作用。挑战: 现存问题包括: 细胞来源与制备工艺异质性导致疗效差异较高; 干细胞潜在肿瘤原性缺乏5年以上长期随访数据; NTFs递送的时空精度不足; 临床前试验设计无统一标准(如损伤节段、评价指标不统一), 制约结果可比性。结论: 倡导构建“干细胞 - NTFs - 生物材料 - 康复干预”一体化治疗体系, 重点优化亚急性/慢性期(损伤后2~8周)的细胞 - 因子剂量配比及时序方案, 需通过多中心、大样本量的随机对照临床试验验证安全性与有效性, 推动SCI修复从基础研究向临床应用转化。

关键词

脊髓损伤, 干细胞, 神经营养因子, 外泌体, 生物材料, 电刺激, 临床转化

Advances in Combined Stem Cell and Neurotrophic Factor Therapies for Spinal Cord Injury Repair

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Abstract

Spinal cord injury (SCI) leads to irreversible neurological deficits and remains a major challenge in regenerative medicine. Recent research has highlighted the potential synergy between stem cells and neurotrophic factors (NTFs) in promoting neuronal survival, axonal regeneration, and functional recovery. This review outlines current advances in combinatorial strategies involving neural stem cells, mesenchymal stem cells, Schwann cells, and exosome-based approaches with NTFs such as brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and glial cell line-derived neurotrophic factor (GDNF). The underlying mechanisms include immune modulation, extracellular matrix remodeling, axon guidance, and remyelination, which collectively contribute to microenvironmental restoration after SCI. Furthermore, we discuss emerging biomaterial-assisted delivery systems that enable controlled and sustained release, as well as their role in enhancing cell survival and integration. Despite promising preclinical findings, major challenges persist, including manufacturing heterogeneity, long-term safety, and standardized clinical trial design. Future research should focus on integrating cellular, molecular, and rehabilitative interventions to establish programmable, stage-specific therapeutic frameworks that bridge basic science and clinical translation.

Keywords

Spinal Cord Injury, Stem Cells, Neurotrophic Factors, Exosomes, Biomaterials, Rehabilitation, Clinical Translation

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1. 引言

脊髓损伤(SCI)致残率高,是中枢神经系统严重创伤,全球发病率约 23~45 例/百万人口,患者常伴随终身运动障碍、感觉缺失及自主神经功能紊乱,致残率高达 90%,给家庭与社会带来沉重医疗负担[1][2]。现行临床手段(减压、药物与康复)仅能部分缓解症状,对轴突再生与长期功能恢复贡献有限[1][2]。再生医学的发展为 SCI 修复提供了新路径,但单一疗法的瓶颈日益凸显。干细胞——尤其神经干细胞(NSCs)及诱导多能干细胞(iPSCs)衍生神经前体——具备替代与旁分泌双重作用,可调控微环境、抑制瘢痕并诱导再髓鞘化,但受限于移植存活率、分化精确性与宿主网络整合不足等瓶颈[3]。神经营养因子(NTFs),如 BDNF、NT-3 和 GDNF 能维持细胞存活、促进轴突延伸并缓和炎症,然体内半衰期短、递送不稳定使单药疗效受限[4][5]。基于“多靶点协同修复”理念,干细胞与 NTFs 的联合策略成为研究热点:干细胞可作为 NTFs 的“活体载体”,通过基因工程实现局部持续分泌;NTFs 可预先改善损伤微环境,提高干细胞存活与分化效率,二者形成“相互赋能”闭环[6]。此外,水凝胶、纳米颗粒、3D 打印支架等生物材料的介入,可进一步实现“细胞-因子”的精准定位与定向引导,放大协同效应[6]。然而,免疫排斥、细胞致瘤风险、递送可控性不足及临床试验设计碎片化等问题,仍阻碍该策略的临床转化[7]-[15]。本文系统综述干细胞与 NTFs

联合修复 SCI 的核心机制、技术进展及转化瓶颈，为后续研究提供清晰路径。

2. 病理生理与干预靶点

SCI 的病理进程呈现“原发性损伤 - 继发性级联反应”的时序特征，不同阶段的病理机制差异为联合治疗提供了精准靶点，需结合“细胞 - 因子 - 材料”协同框架制定分层干预方案。

2.1. 病理进程的时序特征与核心机制

急性期(损伤后数小时至数天): 机械外力直接导致脊髓组织撕裂、血管破裂，引发缺血缺氧；随后中性粒细胞、巨噬细胞及活化小胶质细胞迅速聚集，释放肿瘤坏死因子- α (TNF- α)、白细胞介素- 1β (IL- 1β) 等促炎介质，以及活性氧(ROS)、活性氮(RNS)，诱发线粒体功能障碍与神经元凋亡；同时，损伤区域谷氨酸大量释放，过度激活 N-甲基-D-天冬氨酸(NMDA)受体，导致 Ca^{2+} 内流超载，进一步加剧神经细胞坏死[1] [2]。此阶段干预核心为“神经保护”，需重点抑制过度炎症、拮抗兴奋性毒性、减轻氧化应激。

亚急性/慢性期(损伤后数周至数月): 星形胶质细胞、少突胶质前体细胞(oligodendrocyte precursor cells, OPCs)及成纤维细胞大量增殖，形成以硫酸软骨素蛋白多糖(chondroitin sulfate proteoglycans, CSPGs)为核心的胶质瘢痕[16]。早期瘢痕可隔离损伤区域、减少炎症扩散，但长期存在的 CSPGs 会通过抑制轴突生长锥活性，显著阻滞轴突延伸与髓鞘再生；同时，OPCs 在瘢痕微环境中分化成熟率不足 30%，导致脱髓鞘区域无法有效修复，神经传导功能持续受损[16]。单细胞转录组学研究显示，此阶段巨噬细胞可在 M1 (促炎)与 M2 (抗炎修复)表型间动态转化，星形胶质细胞也存在“促瘢痕”与“促再生”亚型差异，为免疫重编程与瘢痕调控提供了精细靶点[17]。

2.2. “细胞 - 因子 - 材料”协同靶向框架

基于上述病理特征，联合治疗需构建多维度靶向体系，实现“时序适配 - 机制协同”：干细胞靶向作用：NSCs、iNSCs 及其外泌体可通过旁分泌 IL-10、转化生长因子- β (TGF- β)等抗炎因子，调控免疫稳态，降低急性期毒性损伤；干细胞分化的少突胶质细胞可补充髓鞘形成细胞，促进脱髓鞘区域修复；外泌体携带的 miRNA (如 miR-21)可通过抑制 p53 通路，减少神经元凋亡[18]。

NTFs 靶向作用：BDNF 通过 TrkB 受体激活 PI3K-AKT 通路，促进轴突延伸与突触形成；NT-3 通过 TrkC 受体调控感觉神经元定向生长；GDNF 通过 RET 受体维持运动神经元存活[18] [19]；但 NTFs 需依赖干细胞载体或生物材料实现局部持续递送，避免快速降解。

生物材料靶向作用：急性期可采用聚多巴胺纳米颗粒，通过广谱吸附炎症因子(如 TNF- α 、IL- 1β)改善微环境；亚急性/慢性期可利用平行纳米纤维支架(如 PCL 支架)引导轴突定向生长，结合可降解水凝胶(如海藻酸盐水凝胶)实现 NTFs 缓慢释放(持续 2~4 周)，为干细胞存活与分化提供支撑[19] [20]。

此外，分子通路调控可作为补充靶点：如 Noggin 蛋白通过拮抗骨形态发生蛋白(BMP)信号，可同时实现神经保护与抑制胶质瘢痕形成[21]；抑制 p21 蛋白可增强干细胞增殖能力，调控 miR-21 可提升神经元抗凋亡效率，进一步放大联合治疗效果[18] [22]。

3. 干细胞在脊髓损伤修复中的作用

SCI 修复需贯穿急性期至慢性期，干细胞在不同阶段通过多机制发挥作用，同时为与 NTFs 的联合提供“功能载体”基础，其核心价值在于“免疫调节 - 细胞替代 - 旁分泌支持”的三重效应。

3.1. 神经干细胞(NSCs): 神经回路重建的核心细胞

NSCs 具有自我更新能力与三向分化潜能(神经元、星形胶质细胞、少突胶质细胞)，可实现“修复髓

鞘-重塑神经回路”的双重效应[23]。干细胞在这一过程中通过旁分泌信号、免疫微环境重编程、血脊髓屏障修复等多种机制发挥作用,也可作为神经营养因子(NTFs)的“生物工厂”或载体,为联合治疗提供支持[24][25]。NSCs的自我更新和多向分化潜力,能够定向生成少突胶质细胞与神经元,推动“重建髓鞘-重塑回路”双重效应。动物实验和早期临床研究表明,NSCs能改善神经传导和功能结局[23]。然而,长期整合、异位分化及制造一致性问题仍需解决,标准化工艺和客观终点评估对其临床应用至关重要[18][23]。

3.2. 间充质干细胞(MSCs): 免疫调节与旁分泌支持的关键力量

MSCs(如骨髓 MSCs、华通氏胶 MSCs)虽不具备定向分化为神经细胞的能力,但其强大的免疫调节与旁分泌功能使其成为 SCI 急性期干预的理想选择[10]。MSCs 可通过分泌前列腺素 E2 (PGE2)、吲哚胺 2,3-双加氧酶(IDO),抑制 T 细胞活化与巨噬细胞 M1 极化,使损伤区域促炎因子(TNF- α , IL-1 β)浓度降低[18][21];同时,其分泌的 BDNF、血管内皮生长因子(VEGF)可改善局部血供,减少神经元凋亡[26]。然而,运动功能和生活质量的改善并不一致,表明治疗效果受到个体差异的影响,临床试验设计应考虑受试者的分层和个性化治疗[26]。

3.3. 施万细胞: 轴突再生与髓鞘修复的“专业化细胞”

施万细胞是周围神经系统的髓鞘形成细胞,天然具备促轴突再生能力(如分泌 NT-3、睫状神经营养因子 CNTF),且可形成髓鞘样结构包裹轴突,改善神经传导[3][27],被视为“修复导向”治疗的理想细胞类型。为克服施万细胞在中枢神经系统中的存活、迁移与整合限制,研究者将其与水凝胶、纳米纤维或仿生 ECM 支架结合,优化空间引导与生物力学匹配,提升移植物与宿主之间的功能耦合度,并为 NTFs 或基因载荷提供稳定平台[18][19][27]。无细胞治疗路径中, MSCs 来源的外泌体通过免疫调节、促血管生成和轴突再生等作用,降低血脊髓屏障的通透性,显示出治疗潜力。

3.4. 干细胞外泌体: 无细胞治疗的新型载体

干细胞外泌体(如 MSCs 外泌体)具有低免疫原性、易穿透血脊髓屏障、可规模化生产等优势,成为无细胞治疗的理想选择[25]。外泌体可通过转运 miR-21、miR-124,下调损伤区域 PTEN 基因表达,激活 AKT 信号通路,促进血管生成与神经元存活;同时,外泌体携带的抗炎蛋白(如 TGF- β)可抑制小胶质细胞过度活化,减轻继发性损伤[25]。规模化生产和低免疫原性使其成为 SCI 治疗中的理想选择,但剂量学、体内分布、持久性和质控标准化仍然是转化应用的瓶颈[25]-[29]。例如,脐带 MSCs 来源的 miR-216 富集外泌体通过下调 PTEN、激活 AKT 通路,促进血管生成,减轻神经元凋亡,并改善动物模型中的运动功能[26]。整体转化策略应采用“细胞类型 $\times$ 疾病阶段 $\times$ 递送路径 $\times$ 辅助平台(如生物材料、基因或药物调控、康复)”的组合框架。在急性期,重点通过局部、持续递送 MSCs/NSCs 与 NTFs 稳定免疫与微环境。在亚急性至慢性期,通过材料学和化学梯度促进轴突导向和再髓鞘化,施万细胞与 NSCs 互为补充,外泌体作为跨阶段的放大器与连接器提供支持[6][24]-[28]。同时,治疗过程中潜在的肿瘤形成、异位组织化及非目标效应等风险,需通过规范化临床试验、GMP 生产与严格质控加以管理,伦理审查与随访体系应与适应症拓展同步进行[29]。在制造学方面,如何利用自动化手段对多能系及其衍生谱系进行早期身份与质量判定,是减少批次差异、提升可重复性的关键。深度学习驱动的形态-分子耦合识别技术,已成为提升工艺管控的有效工具,未来可能成为推动 SCI 修复治疗转化的关键技术[30]。

4. 神经营养因子在脊髓损伤修复中的作用

SCI 治疗初期通过免疫稳态和神经营养因子(NTFs)支持减轻继发性损伤;随着病情发展,重点转向轴

突生长、再髓鞘化和神经网络重塑,并与生物材料、递送系统及康复策略协同作用[24]。脑源性神经营养因子(BDNF)、神经营养因子-3 (NT-3)与胶质细胞源性神经营养因子(GDNF)通过其受体通路在神经保护、轴突再生和突触可塑性中发挥作用: BDNF 通过 TrkB 受体促进轴突延伸和突触传递, NT-3 通过 TrkC 受体调节感觉神经元导向与突触重塑, GDNF 则通过 RET 受体支持运动神经元的生存与可塑性[22] [31]。BDNF 与 GDNF 在成熟脊髓感觉系统中的互作为组合用药和时序递送提供了理论依据[31]。细胞治疗通过上调神经营养因子放大这些信号,改善局部修复微环境[4]。然而,外源性因子的半衰期短、易降解及低生物利用度使其疗效有限,因此,亟需开发“时空可编程”的局部递送和微环境调控策略[32] [33]。功能性生物材料,如水凝胶、纳米颗粒和三维支架,通过囊载、交联和多层结构实现缓释与靶向递送,并通过表面化学诱导免疫细胞表型转化,调节免疫反应并重塑损伤后的微环境[32]-[34]。在急性期,聚多巴胺纳米颗粒通过广谱吸附炎症因子,能够下调促炎介质,减少继发性损伤,为后续神经营养因子的递送创造条件[33]。细胞与外泌体载体能够进一步提升局部递送效率。多能干细胞和间充质干细胞通过旁分泌释放 BDNF、NT-3 等多因子簇,具备免疫调节与神经回路重建的潜力[33]-[36]。施万细胞来源的外泌体具有较低免疫原性和良好的生物相容性,作为稳定的无细胞载体定向递送关键信号,并与材料平台结合,优化其在损伤区的定位和停留[35]。治疗策略应根据 SCI 的不同阶段进行调整,形成“阶段-目标-递送”的匹配策略。急性期治疗目标是抑炎、减少细胞凋亡和组织丢失,适宜采用短程高局部暴露方案;在亚急性和慢性期,应侧重长期低剂量、多靶点的神经可塑性维持和回路重建,适宜使用可编程释放和多通路协同策略[5] [32]。药物与康复的联合治疗可产生叠加或协同效应。例如,锂剂在小鼠模型中促进神经元存活、灰质与白质重塑及长距离轴突再生,提示其与神经营养因子及材料策略具有互补作用[37]。系统综述显示,药物与康复训练联合效果优于单一干预,临床试验设计中应优先考虑分层与联合治疗[38]。综上,BDNF、NT-3 和 GDNF 通过 TrkB、TrkC 和 RET 通路在 SCI 修复中发挥关键作用。围绕“时空可编程递送-免疫微环境重塑-神经回路重建”的技术路径,功能性材料与细胞/外泌体平台为神经营养因子治疗提供了可控且可转化的支持[4]-[8] [32]-[38]。未来研究应聚焦最佳治疗窗口、剂量控制、载体-因子-康复的组合优化,并推动跨物种和跨尺度的评估体系,为临床转化提供更有力的支持[3]-[8] [36]-[38]。

5. 干细胞与神经营养因子的联合作用

干细胞与 NTFs 的联合策略核心是“结构替代与功能调控的同步推进”——干细胞提供“结构基础”(细胞替代、回路重建), NTFs 提供“功能驱动”(神经保护、可塑性调控),二者结合生物材料与康复干预,形成多维度协同体系,其机制可分为三个核心层面。成熟脊髓体感系统的 BDNF-TrkB 与 GDNF-RET 互作,为因子配伍与时序化递送奠基[19]; BDNF 亦关联自主功能网络,提示跨功能域收益[39]。在“细胞×因子”层面, NSCs 与多能/间充质系细胞通过旁分泌输出 NTFs,改善存活、诱导轴突并促进再髓鞘化;移植后 NTFs 上调与再生标志物相关[36]-[42]。在“因子×材料”层面,水凝胶/导电复合/三维支架实现可编程释放并提供拓扑/力学/电学线索,增强方向性与持续性,同时经由免疫极化缓解继发性炎症[40]-[45];聚多巴胺纳米颗粒在急性期“清场”,为后续因子与细胞介入创造窗口[46];施万细胞与材料耦合可优化移植物-宿主界面并提高功能耦合度[46]。在“细胞×材料”层面,仿 ECM 三维支架提升细胞存活与定向分化并促髓鞘相关通路;“外源移植+内源激活”可形成双轨策略,以弥合空腔并维持长期可塑[21];iPSC-NS/PC 结合突触组织者(如 CPTX)显著增强突触整合,展示“细胞×因子×遗传调控×材料”的纵深组合潜力[47]。此外, MSC-Exos 与施万细胞来源外泌体兼具低免疫原性与天然膜配体,是稳定的无细胞递送体与细胞效应的远程延伸[48];工程化外泌体(miR-216 富集)通过 PTEN/AKT 轴改善血管生成/凋亡/炎症并提升运动结局[49]。康复/电刺激提供使用依赖的可塑窗口,系统评价支持其对功能恢复的增益,可作为标准化“放大器”纳入组合方案[47]-[49];锂在动物中促进灰/白质重塑与长距

离轴突,为药物与“细胞-因子-材料”互补提供依据[49]。以酶响应为例:MMP-2/9 高峰期触发的明胶-PPy 智能水凝胶,通过 TIMP 锚定按需释放 bFGF,降低 MMP、促轴突与血管再生;在大鼠挫伤模型显著提升 BBB 与 MEP,验证“按需给药”优于恒释[50]。随后提出的序贯 ROS/MMP 双响应体系进一步贴合病程时序,增强组织连续修复与运动评分[51]。同时,负载 NT-3 或 GDNF 的水凝胶实现持续释放并带来行为学获益,且与外泌体/去细胞基质协同强化功能恢复[4][5][52][53]。总体上,多维证据支持“细胞-因子-材料-康复/电刺激”的协同框架,但需多中心、盲法与长期随访以验证临床可转化性与稳定度[24][25][47]-[53]。

6. 联合治疗的风险及展望

干细胞与 NTFs 联合治疗在 SCI 修复中已展现明确潜力,但从基础研究到临床应用仍需突破多重瓶颈,需通过“风险管控-技术优化-体系建设”三方面推进转化。主要瓶颈:① 免疫排斥与潜在肿瘤原性——临床耐受性总体尚可,但远期致瘤/异位分化的对照性证据不足,长期获益-风险尚待更大样本与更长随访界定[54][55]。② 来源与制造异质性——NSCs、MSCs 等在谱系偏向、分泌谱与免疫原性上差异显著;跨中心 GMP 与放行标准不一削弱证据可比性,定向分化与核型/基因组稳定性虽有进展,仍需标准化流程与工艺变更的桥接验证固化[42]。③ 递送时空可控性——炎症与力学顺应性改变易破坏水凝胶/支架释放梯度;降解-孔径-模量失配可致空腔化并抑制再髓鞘化[42][56]。④ 外泌体工程化瓶颈——放大、效价与体内分布-清除学未统一,且缺少与细胞移植的头对头比较,导致路径与剂量学难以精细化[57]。⑤ 长期整合与网络稳定性——慢性瘢痕微环境下,移植物的持续存活、定向分化及与宿主形成稳定双向连接尚不确定;“神经中继”具潜力但持久性与可复制性仍待高质量研究验证[42][43][56][57]。⑥ 试验与终点异质——单臂小样本常见,分期/康复方案不一致;终点多限于 AIS 与感觉-运动量表,难以敏感反映生活质量与自主功能,限制跨研究整合[58]。面向临床转化,建议沿“四环联动”推进:一,源-制-放行一体化。以 GMP 与全链路可追溯为底座,构建 MoA 锚定的放行矩阵(身份、核型/基因组稳定性、效力、安全),明确定量阈值、拒收标准与变更桥接,降低批间差、提升跨中心可比性[57]-[59]。二,时空可编程递送。采用可降解/分层与免疫可调控材料,急性期优先“清场/抑炎”,随后分阶段递送 NTFs 与导向信号以支持轴突再生与再髓鞘化;通过材料化学-孔径演变-释放动力学的耦合优化,提高在高炎微环境中的稳定性与有效暴露[57]-[59]。三,组合干预整合。搭建“细胞-因子-材料-康复/电刺激”的可配置管线,按急/亚急/慢性期优化剂量-时机-位点;采用析因或平台式试验解析主效应与交互效应,并将电刺激与康复作为经验证的“放大器”纳入标准路径[59]。四,安全阈值与可关断。在多能系及其衍生谱系嵌入药物诱导型安全开关/自毁模块,探索基因修饰细胞与细胞外囊泡联用;同步规划多年期风险监测与必要时的清除预案,以兼顾疗效延展与长期安全[58][59]。证据与评价体系需同步升级:优先开展多中心、随机、盲法、长随访研究,统一分期、节段与康复策略,并以真实世界证据补强外部效度;重构复合终点,将临床量表与影像、生物标志物、电生理、可穿戴/数字行为读出分层整合,提高对“结构-功能-参与”的灵敏度与可比性;并推进材料-细胞-基因-康复的共同评审与数据标准,以强化复现与审查。干细胞与神经营养因子联合治疗标志着脊髓损伤修复领域进入了多模态协同干预的新时代。其在机制上的协同性与技术上的创新性,为攻克这一医学难题带来了前所未有的希望。未来的成功转化,必将依赖于生物学、材料工程、临床医学与监管科学的深度融合,以工程化的思维系统解决从实验室到病床的一系列复杂问题,最终将这一前沿科学转化为能切实改善患者生活质量的革命性疗法。

7. 挑战与争议

多项“干细胞+神经营养因子/康复/载体”联合方案在动物到临床转化中疗效不稳,部分研究甚至

与单一康复相当,提示协同并非必然成立,受分期、微环境与给药学影响显著[60]。临床鞘内干细胞试验总体安全,但常见头痛、肌骨痛,影像可见反应性蛛网膜改变;个案还报道马尾神经根炎性肥厚,提示递送途径、细胞质量与免疫激活需严格控制[61][62]。机制层面,BDNF等神经营养因子在脊髓背角可促进兴奋/抑制失衡与KCC2下调,可能诱发或放大神经病理痛,导致“获益-风险”反转[63][64]。此外,所谓“一体化体系”(细胞+因子+支架/泵)在放大生产中易出现释放动力学/信号串扰与质控一致性难题;在监管上通常按“组合产品”路径审评,需同时满足生物制品CMC与器械要求,沟通与申报更为复杂,这亦是临床落地的现实障碍[65][66]。

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