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综　述

外泌体 miRNA 治疗脊髓损伤的研究进展

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摘　要： 脊髓损伤(SCI)是一种严重的中枢神经系统创伤,现有治疗手段难以实现神经再生。近年来,外泌体及其携带的微 RNA(miRNA)在 SCI 治疗中展现出巨大潜力。作为细胞间通信的关键媒介,外泌体 miRNA 通过多靶点、多通路协同作用调控 SCI 后的病理生理过程。本文系统综述了其核心作用机制:(1)通过 miR-126、miR-27a-3p 等调控血管生成,并通过 miR-210、miR-2861 等促进血脊髓屏障修复,改善局部微循环;(2)通过 miR-421-3p、miR-374-5p 等精准调控自噬过程,清除毒性蛋白,并在特定时间窗口内发挥神经保护作用;(3)通过 miR-26a、miR-34a-5p 等促进轴突再生,并通过 miR-494、miR-145-5p 等调节胶质微环境,为神经再生创造有利条件。尽管外泌体 miRNA 疗法在靶向递送、标准化生产和安全性评价等方面仍面临挑战,但随着工程化修饰技术和多组学分析的不断发展,它有望成为推动 SCI 治疗从基础研究走向临床应用的突破性策略。

关键词： 脊髓损伤；　外泌体；　微 RNA；　血管生成；　轴突再生

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Research advances in exosomal miRNAs for the treatment of spinal cord injury　*LIANG Ting, LI Liang.* (*College of Traditional Chinese Medicine, Hunan University of Chinese Medicine / Hunan Engineering Technology Research Center for Medicinal and Functional Food / Key Laboratory of TCM Heart and Lung Syndrome Differentiation & Medicated Diet and Dietotherapy / Hunan Provincial Key Laboratory of TCM Diagnostics, Changsha* 410208, *China*)

Abstract: Spinal cord injury (SCI) is a severe traumatic condition of the central nervous system for which current therapeutic strategies rarely achieve neural regeneration. In recent years, exosomes and their carried microRNA(miRNA) have demonstrated considerable potential in SCI treatment. Functioning as key mediators of intercellular communication, exosomal miRNAs coordinately regulate multiple pathophysiological processes after SCI through multiple targets and pathways. This review systematically summarizes their core mechanisms of action: (1) regulating angiogenesis via miR-126 and miR-27a-3p, and promoting the repair of the blood-spinal cord barrier via miR-210 and miR-2861, thereby improving local microcirculation; (2) precisely modulating the autophagic process via miR-421-3p and miR-374-5p to clear toxic proteins, exerting neuroprotective effects within a specific time window; and (3) facilitating axonal regeneration via miR-26a and miR-34a-5p, and modulating the glial microenvironment via miR-494 and miR-145-5p, thereby creating a favorable milieu for neural regeneration. Although exosomal miRNA therapy faces challenges in targeted delivery, standardized production, and safety evaluation, the ongoing development of engineering modification strategies and multi-omics analytics promises to transform this approach into a breakthrough strategy, bridging the gap from fundamental research to clinical application in SCI treatment.

Key words: Spinal cord injury; Exosome; miRNA; Angiogenesis; Axonal regeneration

脊髓损伤(spinal cord injury,SCI)在现代常由交通事故或职业事故引起[1],总体发病率为 26. 48 例/100 万人,且呈上升趋势[2],在 2019 年,全球超过 2 000 万 SCI 患者[3],给患者家庭及社会带来沉重医疗与经济负担。当前临床治疗手段主要包括手术减压、药物治疗和康复训练[4,5],但这些方法往往难以实现神经再生和功能重建。近年来,随着细胞治疗和分子生物学研究的深入,外泌体及其携带的 miRNA 在 SCI 治疗中具有良好的应用前景。外泌体作为细胞间通信的重要媒介,通过其携带的微 RNA(microRNA,miRNA)可同时调节血管生成、自噬过程、神经元再生等多个关键病理生理环节,可有效促进神经修复及神经功能恢复[6,7]。本文系统综述外泌体 miRNA 在促进血管生成与屏障修复、诱导自噬与细胞保护、促进神经元再生与轴突生长等方面的作用机制,并讨论当前面临的挑战和未来发展方向,以期为 SCI 的临床治疗提供新思路。

1　外泌体与外泌体 miRNA

外泌体是由细胞分泌的直径为 30~150 nm 的纳米级囊泡,其生物发生过程始于细胞内吞作用形成早期内体,随后内体膜内陷形成多囊泡体,最终与质

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膜融合释放到细胞外[8]。自1983年Johnstone等[9]在网织红细胞成熟过程中首次发现外泌体以来，这类细胞外囊泡已被证实在细胞间通信中发挥重要作用。外泌体携带蛋白质、脂质、mRNA和miRNA等多种生物活性分子，其脂质双分子层结构可保护内容物免遭降解，使其能够稳定存在于血液、脑脊液等体液中，并能够穿越血脑屏障[10,11]。miRNA是一类长度为20~24个核苷酸的单链非编码RNA，通过与其靶mRNA的3'非翻译区（3' untranslated region，3′UTR）不完全互补结合，抑制翻译或促使mRNA降解，从而在转录后水平精细调控基因表达[12,13]。研究表明，单个miRNA可调节数百个靶基因的表达，形成复杂的调控网络[14]。外泌体miRNA不仅具有传统miRNA的调控功能，还因其特殊的装载形式而具有更高的稳定性和靶向递送效率[15]。

在SCI治疗研究中，间充质干细胞（mesenchymal stem cells，MSCs）来源的外泌体miRNA因来源广泛、分化能力强、免疫原性低、伦理争议小等优势，成为最具潜力的治疗工具之一[16-18]。MSCs可从骨髓、脂肪组织、脐带华通胶等多种组织中分离获取，不同来源的MSCs外泌体具有不同的miRNA表达谱[19,20]，这为其在治疗中的应用提供了多样化的选择。除了天然存在的外泌体，工程化改造的外泌体也显示出良好的应用前景[21]。通过电穿孔、超声处理、共孵育等方法可将特定miRNA装载到外泌体中，或通过基因工程技术调控供体细胞使其分泌富含特定miRNA的外泌体，从而增强其靶向性和治疗效果[22-24]。

2　外泌体miRNA治疗SCI的机制

2.1　促进血管生成与血脊髓屏障修复　SCI后局部血管网络遭受机械性破坏，微循环障碍导致缺血缺氧，继而引发一系列继发性损伤[25-27]。血脊髓屏障（blood-spinal cord barrier，BSCB）的完整性破坏使得血液中的炎症细胞和有害物质进入脊髓实质，加重神经损伤[28]。外泌体miRNA通过多途径促进血管新生与BSCB修复，改善损伤区域微环境[29]。

在血管生成方面，Bian等[30]的研究表明，MSCs在缺氧刺激下释放的细胞外囊泡可被人脐静脉内皮细胞内化，通过剂量依赖性地促进其增殖、迁移与成管，并在大鼠心肌梗死模型中增强血流恢复、减小梗死面积，从而有效促进血管生成并保护心脏组织。Huang等[31]研究发现，MSCs来源的外泌体miR-126可通过下调SPRED1与PIK3R2表达，解除对血管内皮生长因子（vascular endothelial growth factor，VEGF）信号通路的抑制，激活PI3K/AKT信号通路，显著促进大鼠SCI后血管生成，组织学分析显示miR-126治疗组损伤区域CD31阳性血管密度明显增加，局部血流量改善。Sun等[32]研究发现，$CD146^+$与$CD271^+$MSCs亚群来源的外泌体中高表达的miR-27a-3p在经鼻内给药后可有效穿越血脑屏障并靶向损伤区域，其通过抑制Notch信号通路配体Delta样蛋白4（delta-like protein 4，DLL4）的表达以解除对血管生成的抑制作用，从而增强脑微血管内皮细胞的迁移与成管能力，此作用在体外实验中进一步被证实，即过表达miR-27a-3p能使人脑微血管内皮细胞形成更完整、密集的管状结构。

在BSCB功能恢复方面，Wang等[33]利用负载超小纳米硒的神经干细胞来源外泌体，成功缓解了SCI后的炎症反应并促进了运动功能恢复。Gao等[34]研究表明，周细胞来源的外泌体miR-210可通过激活JAK1/STAT3通路，抑制血管内皮细胞脂质过氧化，进而减轻氧化应激损伤并改善内皮功能，电子显微镜观察进一步证实，经miR-210治疗后BSCB结构更加完整，紧密连接也更加致密。Kong等[35]报道调节性T细胞分泌的外泌体miR-2861能够上调紧密连接蛋白（如ZO-1、occludin和claudin-5）表达，提升屏障功能，显著降低BSCB通透性，伊文思蓝渗出实验显示，miR-2861治疗组脊髓组织中染料渗出量显著减少，表明屏障完整性得到改善。

此外，不同来源的外泌体miRNA对血管生成和屏障修复的调节作用可能存在差异。例如，Ge等[36]研究发现M1型巨噬细胞来源的外泌体miR-155通过下调细胞因子信号传导抑制因子6（suppressor of cytokine signaling 6，SOCS6）表达，激活核因子κB（nuclear factor κB，NF-κB）信号通路，促进内皮-间质转化，反而损害BSCB的恢复。因此，外泌体来源的miRNA组成影响其治疗效应，需审慎选择。

2.2　诱导自噬与细胞保护　自噬是细胞内降解受损细胞器及异常蛋白质以维持稳态的重要过程，在SCI后被激活并发挥双向调节作用。适度自噬可清除受损线粒体和错误折叠蛋白，减轻氧化应激和炎症反应；而过度自噬则可能导致细胞自我消化和死亡[37-39]。外泌体miRNA通过精确调控自噬关键分子，在SCI后发挥神经保护作用[40]。

在自噬调控机制方面，mTOR信号通路是自噬诱导过程中的核心负调控因子。Wang等[41]研究发现，M2型巨噬细胞分泌的外泌体miR-421-3p可靶向抑制mTOR表达，解除其对自噬起始的抑制作用，诱导高水平自噬流；透射电镜观察显示，治疗后神经元细胞中自噬体数量显著增加，同时caspase-3活性降低，细胞凋亡减少；动物行为学测试表明，miR-421-3p治疗组大鼠Basso-Beattie-Bresnahan评分显著改善，后肢运动功能恢复良好。

除mTOR通路外，其他自噬相关分子也受到外泌体miRNA的精细调控。Zhang等[42]报道神经干细

胞来源的外泌体miR-374-5p通过结合并抑制丝氨酸/苏氨酸激酶4（serine/threonine-protein kinase 4，STK-4），激活自噬相关蛋白LC3-Ⅱ表达，促进自噬体形成；免疫荧光染色显示，miR-374-5p治疗组脊髓组织中LC3阳性斑点（LC3 puncta）数量明显增加，表明自噬活性增强。Qin等[43]进一步揭示，表皮生长因子受体（epidermal growth factor receptor，EGFR）$^{+}$神经干细胞外泌体递送miR-34a-5p可特异性结合组蛋白去乙酰化酶6（histone deacetylase 6，HDAC6），通过增强微管稳定性，促进自噬溶酶体对泛素化蛋白聚集体（ubiquitinated protein aggregates，UPA）的清除，加速神经功能恢复。

小胶质细胞自噬也被证明参与SCI病理调节。Gu等[44]发现BMSCs外泌体携带的miR-21a-5p可下调E3泛素连接酶PELI1（E3 ubiquitin-protein ligase peli 1），促进小胶质细胞自噬并抑制焦亡，其机制在于，PELI1通过K63连接的泛素化修饰促进NLRP3炎症小体活化，而miR-21a-5p通过抑制PELI1，阻断这一过程，减轻神经炎症。

此外，自噬的时相性调控在SCI治疗中也至关重要。研究显示，SCI后早期（24~72 h）激活自噬具有保护作用，而晚期持续过度自噬可能加重损伤[45]。因此，外泌体miRNA介导的自噬调控需要考虑治疗的时间窗口，以实现最佳治疗效果。

2.3 促进神经元再生与轴突生长 轴突再生是神经功能恢复的核心环节，但成年哺乳动物中枢神经系统的再生能力极为有限。外泌体miRNA通过多靶点调节细胞骨架重组、神经营养因子表达及胶质微环境，有效促进轴突再生与突触重建[46,47]。

在细胞骨架重组方面，神经丝蛋白200（neurofilament 200，NF200）和生长相关蛋白43（growth associated protein 43，GAP-43）是轴突再生的重要标志物。研究表明，多能干细胞来源的外泌体miR-199b-5p和MSCs来源的外泌体miR-29b可显著上调NF200和GAP-43表达，治疗后损伤脊髓中NF200和GAP-43阳性纤维数量明显增加，排列更趋有序[48]。Chen等[49]研究发现，MSCs外泌体miR-26a通过抑制PTEN表达，解除对AKT/mTOR信号通路的抑制，增强神经元特异性微管蛋白表达，促进轴突延伸，体外培养的皮质神经元在miR-26a处理后，轴突长度增加约2.5倍，分支复杂度显著提高。

微管动力学在轴突生长中起着关键作用。Qin等[43]进一步揭示，神经干细胞外泌体miR-34a-5p通过靶向HDAC6提高微管乙酰化水平，增强轴突运输能力，实验表明，乙酰化的微管更加稳定，有利于马达蛋白介导的细胞器运输，为轴突再生提供物质基础，miR-34a-5p治疗后脊髓运动神经元中乙酰化微管蛋白水平显著升高，逆行示踪显示皮质脊髓束有部分再生纤维跨越损伤区域。

在胶质微环境调控方面，人脐带间充质干细胞来源外泌体（exosomes derived from human umbilical cord mesenchymal stem cells，hUCMSC-exos）miR-199a-3p与miR-145-5p通过激活NGF/TrkA信号通路，抑制损伤区炎症反应，促炎因子TNF-α和IL-1β表达下降，而神经营养因子BDNF和NGF表达上升[50]。Ye等[51]发现小胶质细胞外泌体中miR-145-5p表达下降会解除对SMAD3的抑制，促进星形胶质细胞增殖与胶质瘢痕形成；恢复其表达则可有效抑制瘢痕增生，体外划痕实验表明，过表达miR-145-5p可显著抑制星形胶质细胞的迁移能力。

Huang等[52]报道MSCs外泌体miR-494通过下调胶质纤维酸性蛋白（glial fibrillary acidic protein，GFAP）表达，抑制星形胶质细胞过度活化，治疗后损伤边缘区GFAP阳性区域面积减少约40%，胶质瘢痕的物理屏障作用减弱。此外，施万细胞在神经修复中也发挥关键作用。Huang等[53]研究表明内皮细胞外泌体miR-199-5p可通过PI3K/AKT通路促进施万细胞向修复表型转化，增强其增殖、迁移及神经营养因子分泌能力，经miR-199-5p处理的施万细胞可显著促进背根神经节神经元的轴突生长。

此外，不同类型神经元对同一外泌体miRNA的应答可能存在差异。研究表明，运动神经元和感觉神经元在miRNA表达谱和信号通路激活方面存在差异，这可能影响其再生能力[54]。因此，未来研究需要更深入了解不同类型神经元对特定外泌体miRNA的反应特性，以实现更精准的治疗。

3 挑战与展望

尽管外泌体miRNA在SCI治疗中表现出显著潜力，但其临床转化仍面临诸多挑战。首先，外泌体的标准化生产是重要瓶颈。目前外泌体的分离方法包括超速离心、尺寸排阻色谱、聚合物沉淀等，但不同方法获得的产物在纯度、产量和活性方面存在较大差异。其次，外泌体miRNA的体内递送效率有待提高。虽然外泌体具有天然的血脑屏障穿透能力，但损伤区域的实际富集量可能不足。通过表面工程修饰靶向肽或抗体可能改善其靶向性。

另一个关键问题是治疗的时间窗口和剂量优化。SCI后的病理过程具有明显的时相性，不同阶段可能需要不同的miRNA组合治疗。此外，外泌体miRNA的长期安全性也需要系统评估，包括免疫原性、致瘤风险和脱靶效应等。

未来研究方向应包括：开发标准化、可扩展的外泌体生产平台；通过多组学技术筛选最佳miRNA组合；利用生物材料构建缓释递送系统；开展大动物模

型的临床前研究。同时，结合单细胞测序和空间转录组学等新技术，深入解析外泌体miRNA在不同细胞类型特异性中的作用机制，将为精准治疗提供理论基础。

4　结　论

外泌体miRNA通过促进血管生成与BSCB修复、诱导自噬与细胞保护、促进神经元再生与轴突生长等多重机制，在SCI治疗中展现出独特优势。这些机制相互关联、协同作用，共同促进神经功能恢复。虽然目前仍面临生产标准化、靶向递送和安全性评价等挑战，但随着技术不断进步和机制研究的深入，外泌体miRNA有望成为SCI治疗的新突破点。未来的研究应注重转化医学和临床前验证，推动这一具有应用前景的治疗策略从基础研究向临床转化。

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