综　述

脊髓损伤后血脊髓屏障功能障碍与修复的研究进展

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[摘要] 在脊髓损伤(SCI)后的继发性损害中，血脊髓屏障(BSCB)的破坏是启动炎症级联、加重组织水肿与神经元死亡的核心环节之一。近年来的病理学研究显示，异常血流动力学、白细胞跨膜迁移、内皮细胞衰老及自身免疫反应等多维度机制导致SCI后BSCB通透性骤增。本文综述靶向SCI后BSCB损伤的纳米医学治疗方案及分子干预策略的相关研究进展，包括采用工程化外泌体递送微小RNA或抗氧化分子修复内皮紧密连接，利用活性氧响应与病灶靶向双功能纳米载体实现药物跨屏障高效富集与智能释放，抑制核因子-κB等关键信号通路阻断炎症与氧化应激恶性循环等，旨在为SCI后BSCB的早期修复和个体化精准治疗研究提供参考。

[关键词] 脊髓损伤；血脊髓屏障；纳米医学；外泌体；分子干预

Research advances in dysfunction and repair of blood-spinal cord barrier after spinal cord injury

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[**Abstract**] Disruption of the blood-spinal cord barrier (BSCB) is one of the central events that amplifies secondary injury after spinal cord injury (SCI) by exacerbating inflammation, edema and neuronal death. Emerging pathophysiological insights indicate that abnormal hemodynamics, leukocyte transmigration, endothelial senescence and deleterious autoimmunity collectively compromise BSCB integrity. This review summarizes advances on treatment regimens of nano-medicine and molecular intervention strategy designed to restore BSCB function in recent years, such as delivering microRNAs or antioxidants to re-establish endothelial tight junctions by engineered exosomes, achieving efficient drug penetration and controlled release by reactive oxygen-responsive and lesion-targeted nanocarriers, interrupting inflammatory and oxidative cascades through pathway-specific blockade of NF-κB, *etc*. The aim is to provide a reference for research on early BSCB functional recovery and personalized therapies after SCI.

[**Key words**] spinal cord injury; blood-spinal cord barrier; nanomedicine; exosomes; molecular intervention

脊髓损伤(spinal cord injury，SCI)是严重的中枢神经系统创伤性疾病，常导致损伤平面以下的运动、感觉功能丧失，给患者、家庭和社会带来沉重负担[1-3]。SCI的病理过程可分为原发性损伤和继发性损伤两个阶段[4-5]；原发性损伤是初始机械外力直接造成的神经组织破坏，而继发性损伤则是一系列更为持久和广泛的病理生理级联反应，包括局部缺血、水肿、炎症细胞浸润、氧化应激及神经元凋亡等，进而导致损伤区域扩大和功能障碍加剧[6]。在这一系列复杂的继发性损伤事件中，血脊髓屏障(blood-spinal cord barrier，BSCB)的完整性被破坏是启动炎症级联、加重组织水肿与神经元死亡的核心环节之一[7-9]。本文综述近年来关于SCI后BSCB破坏的病理学新认知，以纳米医学、细胞外囊泡/外泌体疗法为代表的治疗方案，以及靶向关键信号通路的分子干预策略的研究进展，以期为开发更有效的SCI临床治疗方案提供新思路。

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1 SCI和BSCB的损伤与修复

1.1 BSCB的破坏加剧SCI BSCB是由血管内皮细胞、周细胞、星形胶质细胞足突及基底膜构成的精密物理与生物屏障，可调控血液与脊髓微环境之间的物质交换，对维持中枢神经系统的稳态至关重要。SCI发生后，BSCB的结构与功能遭到破坏，通透性增大，使得大量炎症细胞、细胞因子和有毒物质从外周血渗入脊髓实质，加剧神经炎症、组织水肿和细胞死亡，进而形成恶性循环[10-11]。因此，尽早修复并维持BSCB的完整性，被视为减轻SCI继发性损伤、保护存活神经组织和促进神经功能恢复的关键治疗靶点[7,10]。

当前，SCI修复的研究热点多样，如调控胶质瘢痕克服再生抑制[12]，利用组织工程支架桥接损伤腔隙[13-14]，以及应用脑机接口重建运动功能[15]等。这些策略多侧重于SCI中晚期的修复与功能代偿。然而，继发性损伤在急性期的急剧扩展是导致神经功能永久性丧失的关键，若不能在早期有效遏制这一过程，后续的再生干预措施将面临“无的放矢”的困境。相比之下，BSCB的破坏是SCI继发性损伤的早期始动事件。因此，靶向BSCB修复代表了一种“正本清源”的治疗策略：在早期时间窗内稳定微环境，可为神经组织的自发修复及后续各种再生疗法创造有利条件。此外，完整的BSCB是维持中枢神经系统稳态的基石，其修复对于控制水肿、抑制炎症至关重要，也是其他靶点难以替代的。更重要的是，即使在急性期后，成功修复的BSCB也能阻止外周有害物质的侵入，并为系统性给药或细胞疗法提供可控的递送通道。因此，深入理解BSCB的破坏机制并开发其修复策略，不仅具有独特的治疗价值，更是串联多种治疗手段、实现协同增效的潜在基础。近年来，随着对SCI病理生理机制认识的深入，以及生物材料与纳米技术的发展，涌现出多种靶向修复BSCB的新型治疗策略。

1.2 SCI后BSCB破坏的病理生理学 SCI后BSCB的破坏是一个多阶段、多机制参与的动态过程，是继发性损伤级联反应的核心事件。传统病理生理学主要关注机械力导致的紧密连接结构解体及随之而来的非特异性炎症浸润；近年相关研究不仅深化了对这些经典机制时空复杂性的理解，更揭示了诸多新的关键病理环节，推动了对BSCB破坏机制的认知从静态、单一向动态、多维的演进(图1)。

1.2.1 即时物理破坏与血流动力学紊乱 创伤瞬间的机械剪切力可导致BSCB的即时物理性破坏，经典理论关注机械力导致的血管内皮细胞间紧密连接[如紧密连接蛋白ZO-1、闭合蛋白(occludin)]快速解离与血管源性水肿[16-18]。近年研究对此进行了重要补充及拓展，发现异常的血流动力学变化是驱动并放大早期BSCB渗漏的关键物理因素；伤后静脉系统的病理性血流改变会对血管壁施加持续的异常剪切力，这不仅阻碍紧密连接的重组，更促使内皮细胞间形成新的缝隙[19-21]。这一发现将BSCB破坏的机制认知从单纯的生物化学领域显著扩展至生物物理学领域，揭示了动态力学失稳态在BSCB破坏中的主动作用[22]。

1.2.2 炎症放大与氧化应激 在物理屏障破坏后，一系列分子与细胞事件被迅速激活，进一步加重BSCB功能障碍。(1)白细胞跨膜迁移与中性粒细胞胞外诱捕网(neutrophil extracellular traps，NETs)的破坏作用。白细胞(尤其是中性粒细胞)在损伤后30 min内即开始穿越BSCB，其迁移过程会进一步撕裂内皮连接，这是经典的炎症性破坏环节[23-26]。新近研究显示，中性粒细胞在这一过程中释放的NETs扮演了更主动的破坏者角色：作为一种网状DNA-蛋白结构，NETs在伤后数小时内显著增加，能直接损伤内皮细胞并增强其通透性[27-29]。因此，针对中性粒细胞的干预不再局限于抑制细胞迁移本身，降解NETs也是一个有前景的新型治疗策略[30]。(2)氧化应激加重内皮细胞功能障碍。活性氧(ROS)大量生成是SCI后的经典病理特征，可诱导脂质过氧化、蛋白质失活和DNA损伤，直接破坏内皮细胞[31-35]。近期机制研究揭示了更为精细的分子通路，例如，在糖尿病合并SCI状态下，ROS过度激活瞬时受体电位M2型(TRPM2)离子通道，导致钙离子内流，进而通过磷酸化钙调蛋白依赖激酶II(p-CaMKII)/内皮型一氧化氮合酶(eNOS)通路形成ROS生成的恶性循环，最终加剧内皮细胞凋亡[3,36-39]。这为理解基础疾病如何加重BSCB损害提供了新视角。(3)内皮细胞衰老加剧BSCB功能障碍。传统观点主要关注SCI急性期的内皮细胞凋亡或坏死。而近年研究显示，在某些病理条件下(如合并糖尿病)，SCI后血管内皮细胞的衰老比例显著增加；这些衰老细胞通过分泌衰老相关分泌表型(SASP)，以旁分泌作用破坏周围内皮细胞的稳态，加剧BSCB功能障碍[40-45]。

1.3 自身免疫与稳态失调 若SCI的早期损害未能得到有效控制，BSCB的破坏将进入持续的慢性阶段，引发更复杂的继发性损伤。

1.3.1 适应不良的自身免疫反应 一项前瞻性纵向队列研究(55例SCI患者 *vs.* 19例单纯椎体骨折对照)结合神经病理学病例对照分析(22例脊髓损伤标本)发现，部分SCI患者在伤后约3周出现针对中枢神经系统抗原的新生自身抗体，这种现象与BSCB的晚期再开放有关，提示存在一种“创伤后中枢神经系统

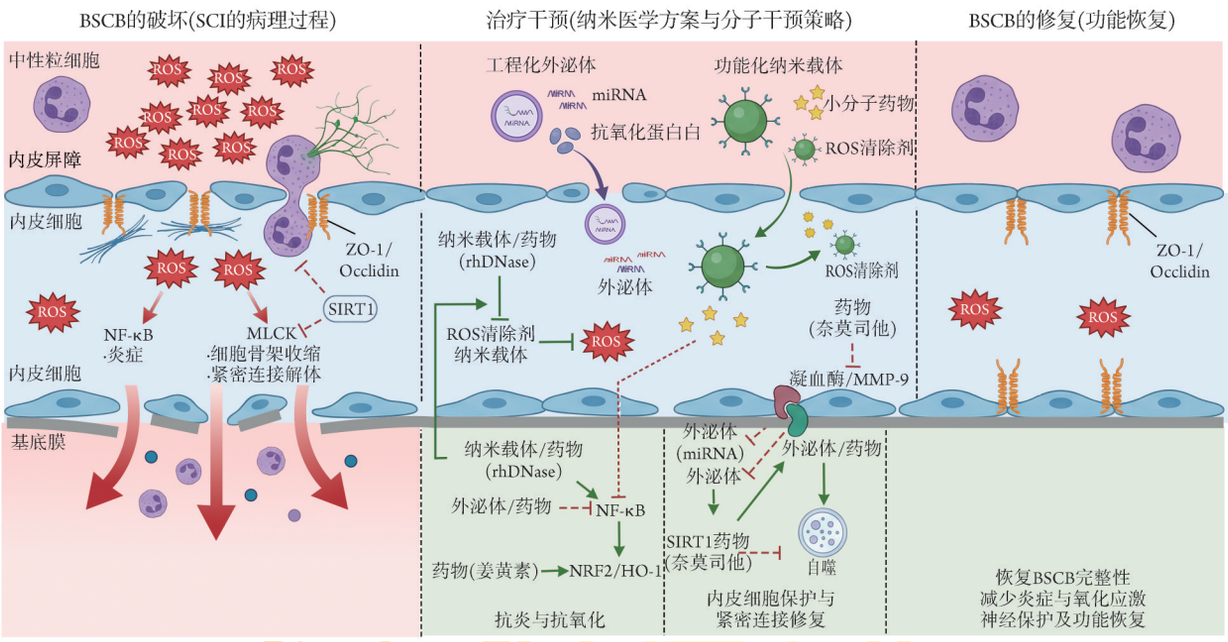

图1 脊髓损伤(SCI)后血脊髓屏障破坏与修复策略

Fig.1 Schematic illustration of blood-spinal cord barrier disruption and repair strategies following spinal cord injury (SCI)

BSCB. 血脊髓屏障；ROS. 活性氧；ZO-1. 内皮细胞间的紧密连接蛋白；Occludin. 闭合蛋白；SIRT1. 沉默信息调节因子1；NF-κB. 核因子κB；MLCK. 肌球蛋白轻链激酶；miRNA. 微小核糖核酸；rhDNase. 重组人脱氧核糖核酸酶；NRF2/HO-1. 核因子E2相关因子2/血红素加氧酶-1；MMP-9. 基质金属蛋白酶9

自身免疫综合征”[46]。该综合征与B细胞浸润、补体激活相关，并可能导致神经病理性疼痛等远期并发症。这突破了传统上认为SCI炎症主要是先天免疫的观点，将适应性免疫的作用提到了新高度[47-48]。

1.3.2 胶质淋巴系统与水通道蛋白4(AQP4)失调 中枢神经系统的废物清除依赖于功能正常的胶质淋巴系统。近期研究显示，SCI后星形胶质细胞终足上的AQP4蛋白在血管周围的定位发生动态失调，可直接损害胶质淋巴系统的功能，阻碍水肿液的清除及代谢产物的引流，进一步加重中枢神经系统包括BSCB的功能障碍[49-52]。

综上，BSCB破坏病理生理学的新进展，揭示了其在SCI后数分钟至数小时内的核心地位。靶向这些早期事件，如抑制异常血流动力学应力、阻断白细胞跨膜迁移、中和ROS以减轻内皮细胞衰老与凋亡，以及清除NETs，有望阻断SCI后继发性损伤级联反应的源头。这种早期干预不仅可保护BSCB的结构和功能，减轻水肿和炎症，更能通过维持微环境稳态，增大神经元和少突胶质细胞的存活机会，进而为后续针对轴突再生、髓鞘重塑乃至神经环路功能恢复的先进治疗策略(如组织工程、脑机接口等)保留并奠定宝贵的组织基础。从治疗时序上看，BSCB修复是承前(急性期抢救)启后(慢性期再生)的关键一环，其重要性不言而喻。

2 靶向修复BSCB的纳米医学方案

尽管针对BSCB破坏的分子机制研究已鉴定出诸多有潜力的干预靶点(如特定miRNA、多种信号通路蛋白等)，但将这些发现转化为有效的治疗方案仍面临严峻挑战。治疗性分子(如核酸、多肽、小分子药物)普遍存在体内稳定性差、非特异性分布、难以有效穿透BSCB及在损伤病灶富集度低等问题，导致疗效有限且系统性不良反应风险较高[53-54]。这些“递送瓶颈”严重制约分子干预的临床转化。而纳米医学与细胞外囊泡技术的不断进步，有望为克服这一难题提供有效的工具。将治疗性分子封装于精心设计的纳米载体中，可提升药物的溶解度和稳定性，实现靶向递送、控制释放，穿越受损的BSCB，从而最大化提升治疗效果，减少全身性不良反应[55-57]。近年来，基于细胞外囊泡/外泌体(exosomes)和功能化纳米递送系统的策略在修复BSCB、改善脊髓微环境方面展现出巨大潜力。

2.1 基于细胞外囊泡/外泌体的治疗 细胞外囊泡，特别是外泌体，作为细胞间通信的关键媒介，已成为前景广阔的“无细胞”治疗工具。它们具备低免疫原性、高稳定性的特点，可携带多种生物活性分子(如蛋白质、miRNA和脂质)，进而调控损伤微环境，对BSCB起到保护和修复作用[1,58-60]。

研究显示，多种细胞来源的外泌体可用于修复

BSCB[2,4,7-8]。在缺血缺氧条件下产生的A2型星形胶质细胞分泌的外泌体(A2-Exos)，可通过其富含的miR-5121激活内皮细胞自噬，促进BSCB的重建[2]；周细胞是BSCB的重要组成部分，其分泌的外泌体富含miR-210-5p，可通过调控JAK1/STAT3信号通路，改善内皮细胞的线粒体功能并抑制脂质过氧化，促进BSCB屏障功能的恢复[4]；调节性T细胞(Treg)来源的外泌体则通过递送miR-2861，靶向调控白细胞介素-1受体相关激酶(IRAK1)表达，修复BSCB并改善运动功能[8]；此外，富血小板血浆来源的外泌体(PRP-Exos)也可显著降低内皮细胞的通透性，恢复其紧密连接，并通过抑制核因子-κB (NF-κB)信号通路减轻神经炎症[7]。

为了提升外泌体的靶向性和治疗效能，目前已开发了多种工程化改造策略。通过将牛奶来源的小细胞外囊泡与血小板膜(PM-sEVs)融合，可显著增强其对损伤病灶的靶向能力。当负载姜黄素(Curcumin)后，这种仿生纳米平台能够有效递送药物，减轻内皮细胞衰老，将紧密连接蛋白ZO-1的表达提高4.33倍，从而保护BSCB的完整性[17]。同样，对人脐带间充质干细胞(UCMSCs)进行筛选和基因工程改造，获得的可靶向新生血管的工程化外泌体RGD-CD146CD271 UCMSC-Exos，经鼻腔给药后，可特异性地聚集在挫伤性SCI小鼠模型SCI中心的新生血管内皮细胞，通过调控miR-501-5p/肌球蛋白轻链激酶(MLCK)轴稳定BSCB[61]。Ran等[62]采用自体血浆外泌体(AP-EXO)作为生物支架，装载靶向神经元的狂犬病毒糖蛋白(RVG)肽和促进生长的胰岛素样肽(ILP)/细胞内sigma肽(ISP)肽，可实现对损伤神经元的精准靶向，诱导其轴突再生。此外，Wang等[63]将工程化的巨噬细胞源外泌体与温敏性水凝胶结合，构建“鼻腔外泌体智能缓释库”，可实现药物的持续释放，并有效绕过肝肾清除，穿透BSCB，发挥重编程胶质细胞及促进神经修复的功效。

2.2 功能化纳米递送系统与智能材料 除了利用天然的细胞外囊泡，研究者们还设计了大量功能化的人工纳米递送系统和智能材料，以实现对SCI病理微环境的精准响应和多重干预。这些系统通过表面修饰、材料选择和结构设计，赋予了药物递送过程前所未有的靶向性和智能化。

精准靶向是功能化纳米系统设计的核心目标。通过在纳米载体表面修饰特定的肽段，可实现对损伤区域的主动靶向。例如，在脂质体表面同时修饰具有损伤病灶靶向能力的半胱氨酸-丙氨酸-谷氨酰胺-赖氨酸肽(CAQK肽)和具备BSCB穿透能力的R_2KC肽，构建的双靶向脂质体可显著增强碱性成纤维细胞生长因子(bFGF)在损伤部位的富集，促进BSCB修复和血管新生[64]。RVG对神经元有高亲和力，成为另一种广受欢迎的靶向配体。负载miR-124-3p的介孔二氧化硅纳米粒，经干细胞膜伪装并修饰RVG肽，可高效穿越BSCB并在SCI损伤中心蓄积，发挥调控小胶质细胞极化和促进轴突再生的作用[56]。

智能响应性材料的开发使纳米药物可根据病理微环境的变化而“行动”。考虑到SCI区域存在大量的ROS，研究人员设计了ROS响应性纳米药物。一种由ROS敏感的两亲性共聚物自组装成的纳米颗粒，在进入高ROS的损伤区域后会发生解体，不仅释放出封装的神经递质偶联钾氯协同转运蛋白2(KCC2)激动剂以调节神经环路，其载体本身还可清除ROS，起到双重治疗作用[57]。Qian等[55]构建了“微环境自适应”的纳米医学平台(RHNP)，该平台同时利用RVG和透明质酸(HA)作为靶向配体，通过ROS敏感的二硒键连接；在SCI损伤的不同阶段，病理微环境的ROS水平变化会触发二硒键的断裂，从而选择性地暴露HA或RVG，以分别靶向炎症细胞和神经细胞，实现分阶段的精准治疗。

将纳米载体与生物材料相结合，可构建更为复杂的局部给药系统。He等[53]构建了一种由自组装纳米胶束和甲基丙烯酰化明胶微针组成的双重给药系统，可实现难溶性药物尼酮(Nit)的透硬膜递送和持续释放，重建小胶质细胞稳态，减少瘢痕形成。Wang等[54]将靶向性脂质体包封于双网络黏性水凝胶(QLipTC@HDM)中，可显著延长药物在损伤部位的滞留时间，持续释放槲皮素(Que)，从而减轻炎症、保护BSCB并促进功能恢复。此外，介孔聚多巴胺(M-PDA)纳米粒负载8-姜酚(8G)后，不仅能穿透BSCB，其载体和药物还表现出协同的抗脂质过氧化效应，可抑制铁死亡和炎症[5]。超小尺寸的硒纳米颗粒(LNT-UsSeNPs)则凭借其尺寸效应，展现出强大的BSCB穿透能力和抗氧化活性，可通过非免疫抑制途径调控多条信号通路[65]。这些创新的纳米递送策略，通过整合靶向、响应和缓释等多种功能，有望开发出高效、低创的SCI药物治疗方案。

3 靶向修复BSCB的精准分子干预策略

纳米载体与外泌体所携带的活性成分及其所调控的生物学通路，构成修复BSCB的分子基础。深入解析SCI后BSCB破坏的分子机制，有助于开发靶向这些生物学通路(如特定信号通路)和SCI病理过程的精准分子干预策略。这些策略旨在从源头上阻断或逆转导致BSCB功能障碍的级联反应，以实现对其屏障功能的保护和修复。干预的重点主要集中在抑制神经炎症、减轻氧化应激及保护血管内皮、调控通

透性等方面。

3.1 抑制神经炎症级联反应 神经炎症是SCI后继发性损伤的核心驱动力，其中小胶质细胞和巨噬细胞的持续激活及中性粒细胞的早期浸润构成关键环节[66-69]。针对这些细胞及其相关机制的干预，已成为减轻神经炎症、保护BSCB的重要策略。在调控炎症反应方面，NF-κB信号通路作为炎症应答的核心枢纽，已被广泛研究并成为关键干预靶点。研究显示，富血小板血浆来源的外泌体(PRP-Exos)[7,70-71]、负载巴多昔芬(BZA)的水凝胶膜[9,15,17]及仿生抗炎纳米平台[72-74]，均可通过抑制NF-κB通路的激活减轻炎症反应，进而保护BSCB的完整性。

中性粒细胞在SCI损伤早期大量浸润，其释放的NETs可加剧组织损伤和BSCB通透性，因而成为新兴的治疗靶点。研究显示，临床用于治疗囊性纤维化的重组人脱氧核糖核酸酶(rhDNase)可降解NETs；在小鼠SCI模型中，早期给予rhDNase，可显著降低BSCB的通透性，缩小病灶范围，并促进长期功能恢复[30]。此外，推动小胶质细胞/巨噬细胞从促炎M1表型向抗炎M2表型极化，也是缓解神经炎症的重要途径。研究显示，通过微针系统递送的Nit[53]、工程化的巨噬细胞外泌体[63,75-78]，以及负载槲皮素的脂质体水凝胶[54,79-80]等，均可调控细胞极化状态，改善损伤微环境，从而支持神经修复与BSCB的功能恢复。

3.2 减轻氧化应激与维持细胞稳态 氧化应激是SCI后BSCB功能障碍和神经元死亡的另一重要原因。因此，清除过量的ROS和维持细胞内部稳态是重要的保护策略。多种纳米系统被设计用于清除ROS，如ROS响应性纳米药物[57,81]、超小硒纳米颗粒[65,73]、二氧化硅纳米颗粒[6,82]等显示出强大的抗氧化能力，可有效降低ROS水平，保护神经元；而姜黄素可通过激活核因子E2相关因子2/血红素加氧酶-1(NRF2/HO-1)抗氧化通路，减轻内皮细胞的衰老和损伤[17,83-84]。

细胞自噬作为维持细胞稳态的关键机制，与SCI后的失调及BSCB的破坏密切相关。研究发现，上调内皮细胞的自噬流有助于保护BSCB。例如，A2型星形胶质细胞通过递送miR-5121来激活内皮细胞自噬，可促进BSCB修复[2]。转录因子Kruppel样因子2(KLF2)是调控自噬的关键分子，其在SCI后表达下降。在动物模型中，过表达KLF2可增强内皮细胞的自噬流，减少紧密连接蛋白的降解，促进BSCB的完整性维持与功能恢复[85]。此外，沉默调节蛋白1(Sirtuin 1，SIRT1)是一种关键的去乙酰化酶，在SCI后内皮细胞中表达下降。激活SIRT1可通过去乙酰化其下游靶点——氧化还原蛋白p66Shc，减轻内皮细胞的氧化应激，保护BSCB的功能[86]。铁死亡作为一种新发现的细胞死亡方式，被认为参与了SCI的继发性损伤过程[87-88]；介孔聚多巴胺(M-PDA)递送的8-姜酚也可通过抑制铁死亡来减轻BSCB损伤[5]。

3.3 保护血管内皮与调控BSCB的通透性 靶向调控血管内皮细胞功能及其紧密连接完整性的分子通路，是修复BSCB的直接策略。MLCK介导的肌球蛋白轻链(MLC)磷酸化是调节细胞收缩和紧密连接蛋白完整性的关键通路；研究发现，在内皮细胞中条件性敲除赖氨酸特异性去甲基化酶6A(KDM6A)[14]或采用工程化外泌体递送miR-501-5p[61]均可抑制此通路，进而降低BSCB的通透性，促进神经功能恢复。

凝血酶(thrombin)及其受体PAR1和下游的基质金属蛋白酶9(MMP-9)构成的信号轴，是驱动BSCB早期破坏的另一重要通路。临床药物奈莫司他(nafamostat)是一种丝氨酸蛋白酶抑制剂，在SCI伤后2~12 h给药，可抑制凝血酶活性及其在内皮细胞的富集，降低MMP-9的表达，进而保护紧密连接蛋白，抑制BSCB分解和外周免疫细胞浸润[89]。此外，骨桥蛋白(OPN)在SCI慢性期可通过蛋白激酶B(Akt)介导的转录因子叉头蛋白O1(FoxO1)磷酸化，过度激活转化生长因子-β(TGF-β)信号通路，导致病理性的血管重塑和内皮间质转化(EndMT)；Xu等[90]发现，抑制Foxo1磷酸化，可减轻这种病理性重塑，改善轴突再生。上述研究可为从分子层面精准调控BSCB的通透性提供明确的靶点和可行的干预手段。

4 总结与展望

SCI后BSCB的破坏是一个复杂且动态的病理过程，它的启动可加剧继发性损伤级联反应，是导致神经功能永久性缺损的关键因素之一。近年来关于BSCB破坏的病理生理学新认知，包括异常血流动力学、白细胞跨膜迁移、内皮细胞衰老凋亡、适应不良的自身免疫反应及关键分子信号通路的失调等[9,17,46,89]。基于此，靶向修复BSCB的治疗策略取得了显著进展，尤其是在纳米医学、外泌体疗法和分子干预领域。

纳米医学策略通过构建靶向性、响应性及多功能的递送系统，可克服传统药物的局限性，实现治疗因子在损伤区域的高效富集和智能释放[55-57,64]。细胞外囊泡/外泌体疗法作为一种新兴的“无细胞”疗法，利用其较高的生物相容性和携带复杂生物信息的能力，可调动内源性修复机制，在保护BSCB、抑制炎症和促进再生方面潜力巨大[1-2,4,8]。特别是工程化改造的外泌体，通过表面功能化或装载特定分子，有望显著提升治疗效果[17,61-62]。同时，针对关键病理通路如NF-κB、MLCK、SIRT1/p66Shc和自噬的分子

干预，为精准阻断BSCB破坏提供了明确的靶点和理论依据[7,14,85-86]。

尽管上述前沿研究在临床前模型中取得了令人鼓舞的成果，但将这些策略转化为临床应用仍面临诸多挑战。首先，大部分研究仍处于动物实验阶段，未来需要检验这些新疗法(尤其是纳米材料和工程化外泌体)的长期生物安全性、代谢途径，改进规模化生产工艺，以推动其向临床转化。其次，SCI病理过程的复杂性提示，单一靶点的干预可能不足以实现理想的功能恢复；因此，开发可同时靶向多个病理环节的联合治疗方案，例如，将外泌体与智能水凝胶相结合[7,63]，或设计能够协同发挥抗炎和抗氧化作用的多功能纳米药物[5,55]，将是未来研究的重要方向。第三，自体外泌体[62]和患者亚群特异性病理[46]的发现，预示着SCI治疗正迈向个性化和精准化时代；明确不同患者的最佳治疗窗口期[89]，并根据其特定的病理特征制定个体化治疗方案，有望显著提高疗效。

总之，以保护和修复BSCB为核心的治疗新策略，特别是纳米医学与分子生物学技术的深度融合，为攻克SCI这一医学难题带来了新的曙光。未来研究应继续深化对BSCB病理生理学的理解，并致力于开发更安全、高效、精准的治疗方案，以改善全球数百万SCI患者的预后和生活质量。

【参考文献】

[1] Ma YM, Yu XJ, Pan JX, *et al*. Exosomes: a promising microenvironment modulator for spinal cord injury treatment[J]. Int J Biol Sci, 2025, 21(8): 3791-3824.

[2] Wang XW, Zhou ZH, Zhang Y, *et al*. Exosome-shuttled miR-5121 from A2 astrocytes promotes BSCB repair after traumatic SCI by activating autophagy in vascular endothelial cells[J]. J Nanobiotechnology, 2025, 23(1): 291.

[3] Zhang SS, Zhao JX, WuM, *et al*. Over-activation of TRPM2 ion channel accelerates blood-spinal cord barrier destruction in diabetes combined with spinal cord injury rat[J]. Int J Biol Sci, 2023, 19(8): 2475-2494.

[4] Gao P, Yi J, Chen WJ, *et al*. Pericyte-derived exosomal miR-210 improves mitochondrial function and inhibits lipid peroxidation in vascular endothelial cells after traumatic spinal cord injury by activating JAK1/STAT3 signaling pathway[J]. J Nanobiotechnology, 2023, 21(1): 452.

[5] Yang JP, Wang M, Zheng S, *et al*. Mesoporous polydopamine delivering 8-gingerol for the target and synergistic treatment to the spinal cord injury[J]. J Nanobiotechnology, 2023, 21(1): 192.

[6] Jiang X, Liu XY, Yu Q, *et al*. Functional resveratrol-biodegradable manganese doped silica nanoparticles for the spinal cord injury treatment[J]. Mater Today Bio, 2021, 13: 100177.

[7] Nie XY, Liu YT, Yuan TY, *et al*. Platelet-rich plasma-derived exosomes promote blood-spinal cord barrier repair and attenuate neuroinflammation after spinal cord injury[J]. J Nanobiotechnology, 2024, 22(1): 456.

[8] Kong G, Xiong W, Li C, *et al*. Treg cells-derived exosomes promote blood-spinal cord barrier repair and motor function recovery after spinal cord injury by delivering miR-2861[J]. J Nanobiotechnology, 2023, 21(1): 364.

[9] Zhou RB, Li JZ, Chen ZY, *et al*. Pathological hemodynamic changes and leukocyte transmigration disrupt the blood-spinal cord barrier after spinal cord injury[J]. J Neuroinflammation, 2023, 20(1): 118.

[10] Xie Y, Luo ZX, Peng W, *et al*. Inhibition of UTX/KDM6A improves recovery of spinal cord injury by attenuating BSCB permeability and macrophage infiltration through the MLCK/p-MLC pathway [J]. J Neuroinflammation, 2023, 20(1): 259

[11] Xin W, Zhang B, Chen Z, *et al*. Biodegradable bilayer hydrogel membranes loaded with bazedoxifene attenuate blood-spinal cord barrier disruption *via* the NF-κB pathway after acute spinal cord injury[J]. Acta Biomater, 2023, 159: 140-155.

[12] Clifford T, Finkel Z, Rodriguez B, *et al*. Current advancements in spinal cord injury research-glial scar formation and neural regeneration[J]. Cells, 2023, 12(6): 853.

[13] Zhu S, Diao S, Liu X, *et al*. Biomaterial-based strategies: a new era in spinal cord injury treatment[J]. Neural Regen Res, 2025, 20(12): 3476-3500.

[14] Qu W, Chen B, Shu W, *et al*. Polymer-based scaffold strategies for spinal cord repair and regeneration[J]. Front Bioeng Biotechnol, 2020, 8: 590549

[15] Hu X, Xu W, Ren Y, *et al*. Spinal cord injury: molecular mechanisms and therapeutic interventions[J]. Signal Transduct Target Ther, 2023, 8(1): 245.

[16] Seblani M, Decherchi P, Brezun JM. Edema after CNS trauma: a focus on spinal cord injury[J]. Int J Mol Sci, 2023, 24(8): 7159.

[17] Deng L, Lv JQ, Sun L. Experimental treatments to attenuate blood spinal cord barrier rupture in rats with traumatic spinal cord injury: a meta-analysis and systematic review[J]. Front Pharmacol, 2022, 13: 950368.

[18] Dubayle D, Morel JL, Lemarchant S. Blood-spinal cord barrier alterations in a mouse model of centrifugation-induced hypergravity [J]. Front Physiol, 2025, 16: 1658389.

[19] Yao C, Cao X, Yu B. Revascularization after traumatic spinal cord injury[J]. Front Physiol, 2021, 12: 631500.

[20] Kim HW, Yong H, Shea GKH. Blood-spinal cord barrier disruption in degenerative cervical myelopathy[J]. Fluids Barriers CNS, 2023, 20(1): 68.

[21] Schmidt TP, Jütten K, Bertram U, *et al*. Blood spinal cord barrier disruption recovers in patients with degenerative cervical myelopathy after surgical decompression: a prospective cohort study[J]. Sci Rep, 2023, 13(1): 7389.

[22] Lee YS, Kim KT, Kwon BK. Hemodynamic management of acute spinal cord injury: a literature review[J]. Neurospine, 2021, 18(1): 7-14.

[23] Jogia T, Lübstorf T, Jacobson E, *et al*. Prognostic value of early leukocyte fluctuations for recovery from traumatic spinal cord injury [J]. Clin Transl Med, 2021, 11(1): e272.

[24] Sterner RC, Sterner RM. Immune response following traumatic spinal cord injury: pathophysiology and therapies[J]. Front Immunol, 2023, 13: 1084101.

[25] Hellenbrand DJ, Quinn CM, Piper ZJ, *et al*. Inflammation after spinal cord injury: a review of the critical timeline of signaling cues and cellular infiltration[J]. J Neuroinflammation, 2021, 18(1): 284.

[26] Feng Z, Min L, Liang L, *et al*. Neutrophil extracellular traps exacerbate secondary injury *via* promoting neuroinflammation and blood-spinal cord barrier disruption in spinal cord injury[J]. Front Immunol, 2021, 12: 698249.

[27] Li J, Chang C, Li Y, *et al*. Unveiling the temporal dynamics and molecular regulation profiles of neutrophil extracellular traps following spinal cord injury[J]. J Inflamm Res, 2025, 18: 10585-10608.

[28] Morishima Y, Kawabori M, Yamazaki K, *et al*. Intravenous administration of mesenchymal stem cell-derived exosome alleviates spinal cord injury by regulating neutrophil extracellular trap formation through exosomal miR-125a-3p[J]. Int J Mol Sci, 2024, 25(4): 2406.

[29] Shafqat A, Noor Eddin A, Adi G, *et al*. Neutrophil extracellular traps in central nervous system pathologies: a mini review[J]. Front Med (Lausanne), 2023, 10: 1083242.

[30] Reid SK, Leal-Garcia ME, Tran AV, *et al*. Recombinant human DNase treatment mitigates extracellular trap mediated damage and improves long-term recovery after spinal cord injury in male mice [J]. Brain Behav Immun, 2025, 128: 456-468.

[31] Huang Y, Bai J. Ferroptosis in the neurovascular unit after spinal cord injury[J]. Exp Neurol, 2024, 381: 114943.

[32] Shen YJ, Huang YC, Cheng YC. Advancements in antioxidant-based therapeutics for spinal cord injury: a critical review of strategies and combination approaches[J]. Antioxidants (Basel), 2024, 14(1): 17.

[33] Yu M, Wang Z, Wang D, *et al*. Oxidative stress following spinal cord injury: From molecular mechanisms to therapeutic targets[J]. J Neurosci Res, 2023, 101(10): 1538-1554.

[34] Yin Z, Wan B, Gong G, *et al*. ROS: executioner of regulating cell death in spinal cord injury[J]. Front Immunol, 2024, 15: 1330678.

[35] Scheijen EEM, Hendrix S, Wilson DM 3rd. Oxidative DNA damage in the pathophysiology of spinal cord injury: seems obvious, but where is the evidence? [J]. Antioxidants (Basel), 2022, 11(9): 1728.

[36] Ding R, Yin YL, Jiang LH. Reactive oxygen species-induced TRPM2-mediated Ca^{2+} signalling in endothelial cells[J]. Antioxidants (Basel), 2021, 10(5): 718.

[37] AlAhmad M, Shitaw EE, Sivaprasadarao A. A TRPM2-driven signalling cycle orchestrates abnormal inter-organelle crosstalk in cardiovascular and metabolic diseases[J]. Biomolecules, 2025, 15 (8): 1193.

[38] Huang P, Qu C, Rao Z, *et al*. Bidirectional regulation mechanism of TRPM2 channel: role in oxidative stress, inflammation and ischemia-reperfusion injury[J]. Front Immunol, 2024, 15: 1391355.

[39] Zielińska W, Zabrzyński J, Gagat M, *et al*. The role of TRPM2 in endothelial function and dysfunction[J]. Int J Mol Sci, 2021, 22 (14): 7635.

[40] He YZ, Zou SY, Wang JW, *et al*. Curcumin-loaded milk-derived sEVs fused with platelet membrane attenuate endothelial senescence and promote spinal cord injury recovery in diabetic mice [J]. Mater Today Bio, 2025, 33: 102036.

[41] Li C, Qin T, Zhao J, *et al*. Kdm6a-CNN1 axis orchestrates epigenetic control of trauma-induced spinal cord microvascular endothelial cell senescence to balance neuroinflammation for improved neurological repair[J]. Bone Res, 2024, 12(1): 19.

[42] Real MGC, Falcione SR, Boghozian R, *et al*. Endothelial cell senescence effect on the blood-brain barrier in stroke and cognitive impairment [J]. Neurology, 2024, 103(11): e210063.

[43] Knopp RC, Erickson MA, Rhea EM, *et al*. Cellular senescence and the blood-brain barrier: Implications for aging and age-related diseases[J]. Exp Biol Med (Maywood), 2023, 248(5): 399-411.

[44] Kim SY, Cheon J. Senescence-associated microvascular endothelial dysfunction: a focus on the blood-brain and blood-retinal barriers [J]. Ageing Res Rev, 2024, 100: 102446.

[45] Huang Z, Xu P, Hess DC, *et al*. Cellular senescence as a key contributor to secondary neurodegeneration in traumatic brain injury and stroke[J]. Transl Neurodegener, 2024, 13(1): 61.

[46] Schwab JM, Haider C, Kopp MA, *et al*. Lesional antibody synthesis and complement deposition associate with de novo antineuronal antibody synthesis after spinal cord injury[J]. Neurol Neuroimmunol Neuroinflamm, 2023, 10(3): e200099.

[47] Coenen H, Somers V, Fraussen J. Peripheral immune reactions following human traumatic spinal cord injury: the interplay of immune activation and suppression[J]. Front Immunol, 2024, 15: 1495801.

[48] Zhen-Gang L, Fan Y, Jingwei S, *et al*. Revisiting the immune landscape post spinal cord injury: more than black and white[J]. Front Aging Neurosci, 2022, 14: 963539.

[49] Salman MM, Kitchen P, Halsey A, *et al*. Emerging roles for dynamic aquaporin-4 subcellular relocalization in CNS water homeostasis [J]. Brain, 2022, 145(1): 64-75.

[50] Kato D, Kameda H, Kinota N, *et al*. Loss of aquaporin-4 impairs cerebrospinal fluid solute clearance through cerebrospinal fluid drainage pathways[J]. Sci Rep, 2024, 14(1): 27982.

[51] Generoso JS, Thorsdottir S, Collodel A, *et al*. Dysfunctional glymphatic system with disrupted aquaporin 4 expression pattern on astrocytes causes bacterial product accumulation in the CSF during pneumococcal meningitis[J]. mBio, 2022, 13(5): e0188622.

[52] Gomolka RS, Hablitz LM, Mestre H, *et al*. Loss of aquaporin-4 results in glymphatic system dysfunction *via* brain-wide interstitial fluid stagnation[J]. Elife, 2023, 12: e82232.

[53] He WB, Zhang L, Zheng DT, *et al*. Nanodrug-loaded microneedles promote scar-reduced repair after spinal cord injury by re-establishing microglial homeostasis[J]. Acta Biomater, 2025, 198: 440-451.

[54] Wang PH, Chen ZF, Li P, *et al*. Multi-targeted nanogel drug delivery system alleviates neuroinflammation and promotes spinal cord injury repair[J]. Mater Today Bio, 2025, 31: 101518.

[55] Qian DF, Xu JQ, Zhang XL, *et al*. Microenvironment self-adaptive nanomedicine promotes spinal cord repair by suppressing inflammation cascade and neural apoptosis[J]. Adv Mater, 2024, 36 (50): e2307624.

[56] Fan XC, Shi LS, Yang ZM, *et al*. Targeted repair of spinal cord injury based on miRNA-124-3p-loaded mesoporous silica camouflaged by stem cell membrane modified with rabies virus glycoprotein[J]. Adv Sci (Weinh), 2024, 11(21): e2309305.

[57] Zuo YM, Ye JJ, Cai WX, *et al*. Controlled delivery of a neurotransmitter-agonist conjugate for functional recovery after severe spinal cord injury[J]. Nat Nanotechnol, 2023, 18(10): 1230-1240.

[58] Hu X, Liu Z, Zhou X, *et al*. Small extracellular vesicles derived from mesenchymal stem cell facilitate functional recovery in spinal cord injury by activating neural stem cells *via* the ERK1/2 pathway[J]. Front Cell Neurosci, 2022, 16: 954597.

[59] Pan D, Zhu S, Zhang W, *et al*. Autophagy induced by Schwann cell-derived exosomes promotes recovery after spinal cord injury in rats [J]. Biotechnol Lett, 2022, 44(1): 129-142.
[60] Liu W, Wang X, Chen Y, *et al*. Distinct molecular properties and functions of small EV subpopulations isolated from human umbilical cord MSCs using tangential flow filtration combined with size exclusion chromatography[J]. J Extracell Vesicles, 2025, 14(1): e70029.
[61] Xie Y, Sun Y, Liu YD, *et al*. Targeted delivery of RGD-$CD146^{+}CD271^{+}$ human umbilical cord mesenchymal stem cell-derived exosomes promotes blood-spinal cord barrier repair after spinal cord injury[J]. ACS Nano, 2023, 17(18): 18008-18024.
[62] Ran N, Li WX, Zhang RJ, *et al*. Autologous exosome facilitates load and target delivery of bioactive peptides to repair spinal cord injury [J]. Bioact Mater, 2022, 25: 766-782.
[63] Wang Y, Liu J, Li P, *et al*. Nasal delivery of engineered exosomes *via* a thermo-sensitive hydrogel depot reprograms glial cells for spinal cord repair[J]. Adv Sci (Weinh), 2025, 12(34): e04486.
[64] Wu FZ, Wang PH, Wei XJ, *et al*. Barrier-penetrating liposome targeted delivery of basic fibroblast growth factor for spinal cord injury repair[J]. Mater Today Bio, 2023, 18: 100546.
[65] Liu PX, Liu XD, Wu ZH, *et al*. Size effect-based improved antioxidant activity of selenium nanoparticles regulating Anti-PI3K-mTOR and Ras-MEK pathways for treating spinal cord injury to avoid hormone shock-induced immunosuppression[J]. J Nanobiotechnol, 2025, 23(1): 17.
[66] Swarts EA, Brennan FH. Evolving insights on the role of microglia in neuroinflammation, plasticity, and regeneration of the injured spinal cord[J]. Front Immunol, 2025, 16: 1621789.
[67] Dai B, Fan Z, Chen R, *et al*. Mechanistic study of Jaceosidin in regulating secondary inflammation after spinal cord injury in mouse by inhibiting PKM2 activity [J]. Neuromol Med, 2025, 27(1): 57.
[68] St-Pierre MK, González Ibáñez F, Kroner A, *et al*. Microglia/macrophages are ultrastructurally altered by their proximity to spinal cord injury in adult female mice[J]. J Neuroinflamm, 2023, 20 (1): 273.
[69] Nascimento D, Ferreira A, Cruz CD. Immune activation following spinal cord injury: a review focused on inflammatory changes in the spinal cord[J]. Int J Mol Sci, 2025, 26(19): 9624.
[70] Li Y, Luo W, Meng C, *et al*. Exosomes as promising bioactive materials in the treatment of spinal cord injury[J]. Stem Cell Res Ther, 2024, 15(1): 335.
[71] Akbari-Gharalari N, Ghahremani-Nasab M, Naderi R, *et al*. Improvement of spinal cord injury symptoms by targeting the Bax/Bcl2 pathway and modulating TNF-α/IL-10 using platelet-rich plasma exosomes loaded with dexamethasone[J]. AIMS Neurosci, 2023, 10(4): 332-353.
[72] Tang CM, Jin YY, Wu M, *et al*. A biomimic anti-neuroinflammatory nanoplatform for active neutrophil extracellular traps targeting and spinal cord injury therapy[J]. Mater Today Bio, 2024, 28: 101218.
[73] Zhou H, Li Z, Jing S, *et al*. Repair spinal cord injury with a versatile anti-oxidant and neural regenerative nanoplatform[J]. J Nanobiotechnology, 2024, 22(1): 351.
[74] Gao X, Han Z, Huang C, *et al*. An anti-inflammatory and neuroprotective biomimetic nanoplatform for repairing spinal cord injury[J]. Bioact Mater, 2022, 18: 569-582.
[75] Gao ZS, Zhang CJ, Xia N, *et al*. Berberine-loaded M2 macrophage-derived exosomes for spinal cord injury therapy[J]. Acta Biomater, 2021, 126: 211-223.
[76] Guan X, Li C, Wang X, *et al*. Engineered M2 macrophage-derived exosomes: mechanisms and therapeutic potential in inflammation regulation and regenerative medicine[J]. Acta Biomater, 2025, 203: 38-58.
[77] Kong G, Liu J, Wang J, *et al*. Engineered extracellular vesicles modified by Angiopep-2 peptide promote targeted repair of spinal cord injury and brain inflammation[J]. ACS Nano, 2025, 19(4): 4582-4600.
[78] Peng W, Xie Y, Liu Y, *et al*. Targeted delivery of $CD163^{+}$ macrophage-derived small extracellular vesicles *via* RGD peptides promote vascular regeneration and stabilization after spinal cord injury[J]. J Control Release, 2023, 361: 750-765.
[79] Liu X, Liu X, Luo S, *et al*. Quercetin promotes angiogenesis and protects the blood-spinal cord barrier structure after spinal cord injury by targeting the PI3K/Akt signaling pathway[J]. J Transl Med, 2025, 23(1): 958.
[80] Fakhri S, Gravandi MM, Abdian S, *et al*. Quercetin derivatives in combating spinal cord injury: a mechanistic and systematic review [J]. Life(Basel), 2022, 12(12): 1960.
[81] Ma Y, Pan J, Ju C, *et al*. Antioxidant nanozymes: current status and future perspectives in spinal cord injury treatments[J]. Theranostics, 2025, 15(13): 6146-6183.
[82] Gao G, Li J, Ma Y, *et al*. Dual-responsive multi-functional silica nanoparticles with repaired mitochondrial functions for efficient alleviation of spinal cord injury[J]. Exploration (Beijing), 2025, 5 (3): 270012.
[83] Ahmed M. Targeting aging pathways with natural compounds: a review of curcumin, epigallocatechin gallate, thymoquinone, and resveratrol[J]. Immun Ageing, 2025, 22(1): 28.
[84] Cui J, Li H, Zhang T, *et al*. Research progress on the mechanism of curcumin anti-oxidative stress based on signaling pathway[J]. Front Pharmacol, 2025, 16: 1548073.
[85] He Z L, Du J Q, Zhang Y, *et al*. Kruppel-like factor 2 contributes to blood-spinal cord barrier integrity and functional recovery from spinal cord injury by augmenting autophagic flux[J]. Theranostics, 2023, 13(2): 849-866.
[86] Jiang T, Qin T, Gao P, *et al*. SIRT1 attenuates blood-spinal cord barrier disruption after spinal cord injury by deacetylating p66Shc [J]. Redox Biol, 2023, 60: 102615.
[87] Ryan F, Blex C, Ngo TD, *et al*. Ferroptosis inhibitor improves outcome after early and delayed treatment in mild spinal cord injury [J]. Acta Neuropathol, 2024, 147(1): 106.
[88] Li Q S, Jia Y J. Ferroptosis: a critical player and potential therapeutic target in traumatic brain injury and spinal cord injury[J]. Neural Regen Res, 2023, 18(3): 506-512.
[89] Zhao CX, Zhou TG, Zhao XQ, *et al*. Delayed administration of nafamostat mesylate inhibits thrombin-mediated blood-spinal cord barrier breakdown during acute spinal cord injury in rats[J]. J Neuroinflamm, 2022, 19(1): 189.
[90] Xu JQ, Shi CR, Ding YH, *et al*. Endothelial foxo1 phosphorylation inhibition *via* aptamer-liposome alleviates OPN-induced pathological vascular remodeling following spinal cord injury[J]. Adv Sci (Weinh), 2024, 11(43): e2406398.

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