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专论与综述

肠道菌群在脊髓损伤后胃肠道炎症反应中的研究进展

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摘　要：脊髓损伤(spinal cord injury, SCI)目前尚无有效的治疗手段。脊髓损伤后，患者常伴有严重的胃肠功能障碍，严重影响患者的生活质量。研究发现，脊髓损伤后肠道菌群的紊乱和脊髓损伤后的胃肠道功能障碍密切相关。因此，本文围绕脊髓损伤后肠道菌群的变化，探讨肠道菌群在迷走神经、下丘脑-垂体-肾上腺和肠道菌群代谢物 3 个途径中发挥的作用，及与胃肠道炎症反应相关的研究进展。

关键词：脊髓损伤；肠道菌群；微生物-肠-脑轴；胃肠道炎症

Gut microbiota in gastrointestinal inflammatory response after spinal cord injury: a review

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Abstract: There is no way to reverse spinal cord injury. In the case of spinal cord injury, patients always suffer from gastrointestinal dysfunction which impacts the quality of life. It has been reported that gut microbiota disorder after spinal cord injury is connected to the gastrointestinal dysfunction. Thus, this paper mainly explored the role of gut microbiota in vagus nerve system, hypothalamic-pituitary-adrenal axis and gut microbiota metabolites three pathways, and the relationship with gut inflammatory through gut microbiota changes after

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spinal cord injury.
Keywords: spinal cord injury (SCI); gut microbiota; microbiota-gut-brain axis; gastrointestinal inflammatory

脊髓损伤(spinal cord injury, SCI)是一种毁灭性的神经创伤性疾病，造成损伤平面以下运动、感觉和自主神经功能障碍，严重影响患者的身体健康及正常生活，给患者家庭和社会带来严重的危害，目前尚无有效的治疗方法[1-3]。脊髓损伤后，27%−62%的患者会出现结肠转运减少、便秘和排空协同失调等胃肠道功能障碍，可能会加重神经功能障碍[4-6]。然而，目前大量的研究集中在脊髓损伤的病理生理机制上[7]，关于脊髓损伤影响胃肠道的机制尚未完全清楚[8-9]。有研究显示，脊髓损伤后产生的炎症可以刺激机体产生免疫反应，从而影响器官的生理功能[8]。近年来，肠道菌群是研究中枢神经系统疾病的一大热点，研究发现脊髓损伤后肠道菌群的紊乱和胃肠道炎症反应密切相关[10]。因此，本文综述了肠道菌群对脊髓损伤后胃肠道炎症反应的作用机制及其对脊髓损伤的调控作用，以期为今后治疗脊髓损伤的深入研究和药物开发提供理论依据。

1 肠道菌群和微生物-肠道-大脑轴

肠道菌群是一类定殖于肠道与宿主共生的微生物[11-12]，其数量与哺乳动物细胞之比约为10:1，其基因组大约是人类基因组的100倍[13-14]。肠道微生物在门水平上主要有厚壁菌门(*Firmicutes*)和拟杆菌门(*Bacteroidetes*)[15]，经过发酵产生不可消化的多糖并产生如短链脂肪酸(short chain fatty acids, SCFA)的代谢产物，其中丁酸盐是最主要的 SCFA[16]。此外，肠道微生物还影响宿主生理的许多方面，包括营养代谢、抗感染及免疫系统的发育和成熟[14,17-18]，同时还调节中枢神经系统的正常发育和疾病发病机制[19-21]。

肠-脑轴(gut-brain axis, GBA)通常是指中枢神经系统(central nervous system, CNS)和肠神经系统(enteric nervous system, ENS)之间的双向通讯，而肠道菌群在大脑和肠道之间的相互作用中发挥了重要作用，因此又提出了微生物-肠-脑(microbiota-gut-brain, MGB)轴的概念[22]，即 CNS 通过自主神经系统(autonomic nervous system, ANS)、下丘脑-垂体-肾上腺(hypothalamus-pituitary-adrenal, HPA)和免疫系统调节胃肠道的功能和完整性，包括肠道屏障通透性、胃肠道运动、肠道分泌活性物质和肠道菌群组成等，同时，胃肠道系统也可以通过应激反应激活、神经递质合成和血脑屏障完整性来影响大脑功能和行为[22-23]。

MGB 轴使大脑能够影响肠道功能效应细胞的活动，反映了中枢神经系统和胃肠道之间的持续连接[23]。脊髓损伤后，外在神经纤维的破坏导致 ENS 活性改变，使得脊髓损伤患者大脑与肠道之间的神经传导通路受损，导致胃肠功能紊乱[24]。当胃肠功能发生紊乱时肠道屏障功能受损，菌群分解产生的脂质可透过肠上皮细胞进入血液循环，氧化修饰的脂质和脂蛋白充当“危险信号”，并激活巨噬细胞 Toll 样受体 4 (Toll-like receptors 4, TLR4)和 Toll 样受体 2 (Toll-like receptors 2, TLR2)，使小胶质细胞和星形胶质细胞活化，刺激小胶质细胞向有促炎作用的 M1 型巨噬细胞极化[25-26]，从而上调肿瘤坏死因子-α (tumor necrosis factor-alpha, TNF-α)、白介素 1β (interleukin-1β, IL-1β)和一氧化氮合酶(inducible nitric oxide synthase, iNOS)等促炎因子的表达，

从而加重全身炎症反应[3,27]。例如，γ-氨基丁酸、血清素、多巴胺及短链脂肪酸等多种神经递质和神经调节剂的合成使微生物群与受体宿主之间的细胞内交流成为可能[28]。同时，体内大多数免疫细胞位于肠道相关淋巴组织(gut associated lymphoid tissue, GALT)内，脊髓损伤诱导的肠道菌群失调可激活肠相关淋巴组织中的黏膜免疫细胞，进而影响全身和脊髓内炎症[29]；还有研究表明，肠道微生物群或潜在的益生菌对大脑功能的许多影响依赖于迷走神经的激活[30-32]。此外，微生物-肠-脑轴的功能障碍已牵涉应激相关障碍，如抑郁、焦虑、肠易激综合征、炎性肠病及神经发育障碍等[28]。

脊髓损伤作为最常见的创伤性神经系统疾病之一，目前尚无有效的治疗方法。研究显示，在脊髓损伤人群中，胃肠道并发症通常占住院治疗的 11%，是影响脊髓损伤患者生活质量的严重问题[33]。同时，在脊髓损伤人群的调查中发现，肠功能的恢复优先于运动功能的恢复[34]，因此，建立微生物-肠-脑轴和脊髓损伤之间的有效联系，对病情后续的发展具有重要意义。

2 脊髓损伤后肠道菌群的变化

肠道微生物群的生长和组成取决于各种参数，包括免疫机制、饮食因素和胃肠动力等。临床资料显示[35]，脊髓损伤后会导致急慢性全身免疫紊乱、肠道运动障碍等并发症，也可引起肠道微生物群的丰度和组成发生改变及肠道细菌易位，这些变化在不同的物种之间均有体现。

例如，Kigerl 等[36]研究发现，脊髓损伤小鼠与受伤前相比拟杆菌门和厌氧菌门(*Anaerobic bacteria*)增多，而厚壁菌门和丁酸单胞菌(*Butyricimonas*)减少。Doelman 等[37]在尤卡坦小型猪脊髓损伤模型中描述了肠道微生物组成，发现脊髓损伤急性期变形菌门和蓝藻的丰度与对照相比减少，而拟杆菌门、厚壁菌门和螺旋体(*Spirochete*)种类增加。Bazzocchi 等[38]对 100 名脊髓损伤患者中的肠道微生物群进行分析发现，脊髓损伤患者肠道微生物群中与炎症性疾病有关的肠道菌群增多，如铜绿假单胞菌(*Pseudomonas aeruginosa*)数量从 0.5%增至 3.8%；肠球菌(*Enterococcus*)数量从 0.03%增至 6.30%；乳杆菌(*Lactobacillus*)数量从 0.2%增至 2.5%；链球菌(*Streptococcus*)数量从 0.6%增至 5.4%；甲烷杆菌(*Methanobacteriaceae*)数量从 0.002%增至 0.300%；肠杆菌(*Enterobacteriaceae*)数量和韦氏芽孢杆菌(*Verrucomicrobiaceae*)数量分别从 0.5%和 0.4%增至 8.3%和 7.2%；而普雷沃氏菌(*Prevotellaceae*)、梭菌科(*Clostridiaceae*)和产生短链脂肪酸的疣微菌门(*Ruminococcaceae*)数量分别从 12.6%、1.0%和 23.6%下降至 0.7%、0.6%和 23.6%，这些变化可能与脊髓损伤后病变的严重程度密切相关，从而对脊髓损伤后的长期恢复产生影响。

O'Connor 等[10]使用胸段脊髓损伤大鼠模型和微生物组测序研究了损伤 7 d 大鼠的肠道微生物区系的变化，结果发现，与对照组相比，脊髓损伤大鼠肠道内的肠乳杆菌(*Lactobacillus intestinalis*)、弥散性梭状芽胞杆菌(*Clostridium disporicum*)和乔氏双歧杆菌(*Bifidobacterium choerinum*)的数量显著增加，分别从 41.7%、1.2%和 0.961%增至 43.8%、19.3%和 12.5%；而糖链球菌(*Clostridium saccharogumia*)的数量则显著减少，从 10.7%减少至 1.2%。研究表明，双歧杆菌可以有效抑制肠道致病菌的生长，脊髓损伤后双歧杆菌数量的显著增加可能会促进后续的恢复[39-41]。此外，由于梭状芽孢杆菌在健康人的肠道菌群中不占主导地位，对于梭状芽孢杆菌的研究并不多，但是有研究发现，在克罗恩病等胃肠道功能障碍患者的微生物区系中，出现了梭状

芽孢杆菌的增加，这与 O'Connor 等[10]研究结果相对应，但是目前仍不清楚梭状芽孢杆菌在此类疾病中发挥的具体作用[42]。与上述讨论的肠道菌群相反，糖链球菌在脊髓损伤后是显著减少的，而在动物体内，糖凝胶梭菌可以将植物木脂素转化为有利于人体抗癌和心血管健康的生物活性分子——肠内酯，因此，脊髓损伤后肠道糖链球菌的减少很可能对机体产生有害影响[10]。

Yu 等[43]评估 45 名脊髓损伤患者与 24 名健康人肠道菌群改变，与健康个体相比，脊髓损伤患者的放线菌(*Actinomycetes*)、互养菌门(*Synergistetes*)、乳杆菌、梭状芽胞杆菌科和苏特氏菌科(*Sutterella*)显著富集，而拟杆菌门、蓝藻(*Cyanobacteria*)和变形杆菌(*Proteobacteria*)丰度显著降低，这可能是因为放线菌、互养菌门、乳杆菌、真细菌(*Eubacterium*)、梭状芽胞杆菌和苏特氏菌在维持肠道内环境稳定方面起着关键作用；同时，脊髓损伤患者肠道内变形杆菌的减少也应该被注意，变形杆菌是一含有内毒素且与炎症标志物相关的革兰氏阴性细菌，可能与脊髓损伤后的炎症反应相关[44]。另外，Jing 等[45]将健康未受伤的小鼠粪便移植到脊髓损伤小鼠，发现粪菌移植治疗可以改善肠道微生物失调并调节菌群代谢物，减轻神经炎症，从而减轻神经功能障碍并改善神经再生。

综上所述，由于脊髓损伤是一种不同于原发神经损伤疾病的神经损害性疾病，肠道微生物区系与脊髓损伤之间无因果关系，但是肠道微生物区系与损伤后继发性损伤及并发症之间存在一定的相关性。研究表明[46]，肠道微生物群对宿主神经功能和发育具有相当大的调节作用，肠道微生物区系可以影响和调节免疫及中枢神经系统，从而改变宿主的情绪和行为，因此，肠道微生物群对于脊髓损伤患者免疫功能障碍的调节至关重要。

3 肠道菌群通过不同方式调控脊髓损伤后胃肠道炎症的发生发展

脊髓损伤不仅能引发肠道菌群微生态失调，还能导致肠道菌群异位及胃肠道的自主神经失衡[47]，这种失衡打破了对支配胃肠道的节后神经元的稳态和控制，导致脊髓损伤后胃肠道炎症的发生，进而加重脊髓损伤后的神经炎症[36]。造成菌群失调的可能原因包括：脊髓损伤后严重的自主神经功能障碍导致的神经源性肠功能障碍[38,48]，肠屏障功能减弱造成的肠道菌群易位[49]，以及创伤导致的营养摄入和吸收发生改变等，这些改变会减弱血脑屏障的作用，从而影响脊髓损伤后神经功能的修复(图 1)。肠道菌群主要通过以下几种方式影响脊髓损伤后胃肠道炎症的发生发展(图 2)。

3.1 迷走神经

迷走神经可调节多种重要的机体功能，胃肠动力由副交感神经迷走神经支配，以调节与消化相关的推进、储存、碾磨和排空反射[50-51]。脊髓损伤后，微生物群可以通过迷走神经向大脑发出信号[52]。当迷走神经受抑制时，胃肠蠕动减弱，肠神经元对肠内血清素和营养素的敏感性降低，并导致肠道微生态发生改变[53]。此外，脊髓损伤后肠道微生物群产生的活性物质，如短链脂肪酸、γ-氨基丁酸、乙酰胆碱等可以在肠道通透性受损的条件下直接激活迷走神经，从而对 CNS 功能产生有益作用[54-55]。同时，来自肠道的迷走神经信号能以烟碱型乙酰胆碱受体 α7 亚基依赖性方式引发抗炎反应，而且胆囊收缩素(cholecystokinin, CCK)、胰高血糖素样肽 1 (glucagon-like peptide 1, GLP-1)和 5-羟色胺(5-hydroxytryptamine, 5-HT)等活性物质[51,56]也可以通过中枢调节迷走神经元的活动。相关研究

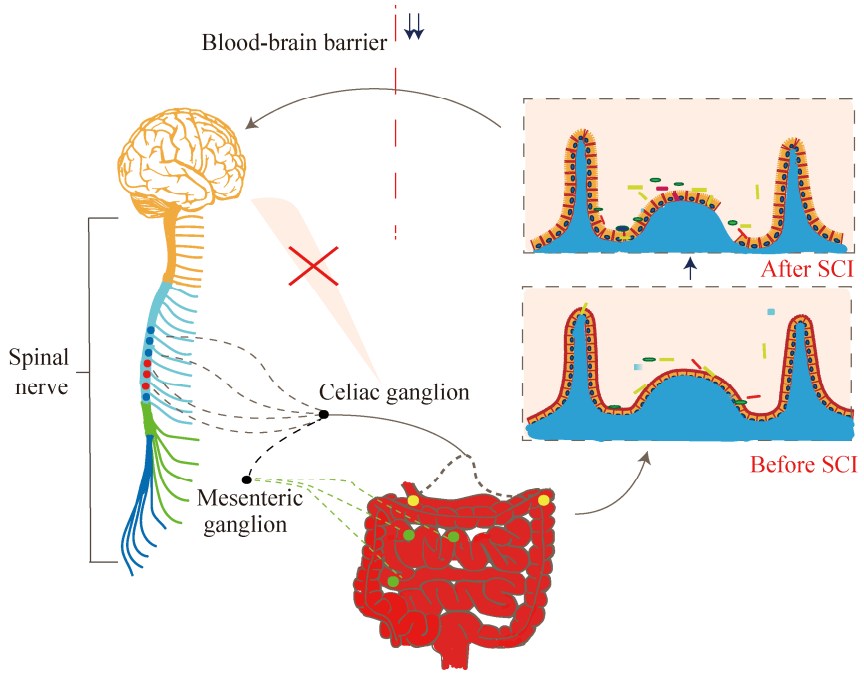

图 1 脊髓损伤后肠道菌群失调 脊髓损伤后胃肠道的自主神经失衡(腹腔神经节)，这种失衡打破了对支配胃肠道的肠系膜神经节的稳态和控制，从而导致肠道菌群异位，同时血脑屏障的功能减弱

Figure 1 Gut microbiota imbalance after SCI. After SCI, there is an autonomic nervous imbalance (celiac ganglion) in the gastrointestinal tract. This imbalance disrupts homeostasis and control of the mesenteric ganglion that innervates the gastrointestinal tract, resulting in ectopia of the intestinal flora and reduced function of the blood-brain barrier.

发现，口服鼠李糖乳杆菌会导致迷走神经节双侧神经元中 c-Fos 表达显著增加[57]，而在迷走神经切断的小鼠中却不存在这样的作用，这有力地验证了菌群紊乱导致的肠道局部感染可以激活迷走神经。

3.2 下丘脑-垂体-肾上腺

HPA 轴是一种有效的神经内分泌系统，可提供快速反应并保护急性应激[58]。该系统通过下丘脑分泌促肾上腺皮质激素释放因子(corticotropinreleasing factor, CRF)，刺激垂体分泌促肾上腺皮质激素(adrenocorticotropic hormone, ACTH)，从而导致皮质醇从肾上腺释放，进而影响肠道稳态以响应各种刺激[28,59]。脊髓损伤后肠道菌群的改变可以激活 HPA 轴，使得皮质醇或皮质酮从肾上腺皮质释放到血液中，进而导致肠道通透性改变，使菌群分解产生的脂质等其他细胞因子进入肠壁，最终导致 TLR-4 等炎症因子的激活、血脑屏障(blood-brain barrier, BBB)的破坏和脑组织的损伤[58,60]。此外，激活 HPA 轴后产生的活性物质与迷走神经相互作用，也会影响脊髓损伤后的神经修复[29]。更有相关研究表明，微生物的稳态也会影响 HPA 轴的活性[61]。与其相反的是，某些微生物释放的一些代谢物如 SCFA 却可以减弱 HPA 轴反应[62]。

3.3 肠道菌群代谢物

SCFA 是目前研究较为广泛的肠道菌群代谢物之一，其中丁酸、乙酸和丙酸是 SCFA 中的主要物质，它们是在近端结肠中由细菌发酵不可消化的碳水化合物产生[63-64]。丁酸的免疫调节特性通过抑制组蛋白去乙酰化酶(histone deacetylase,

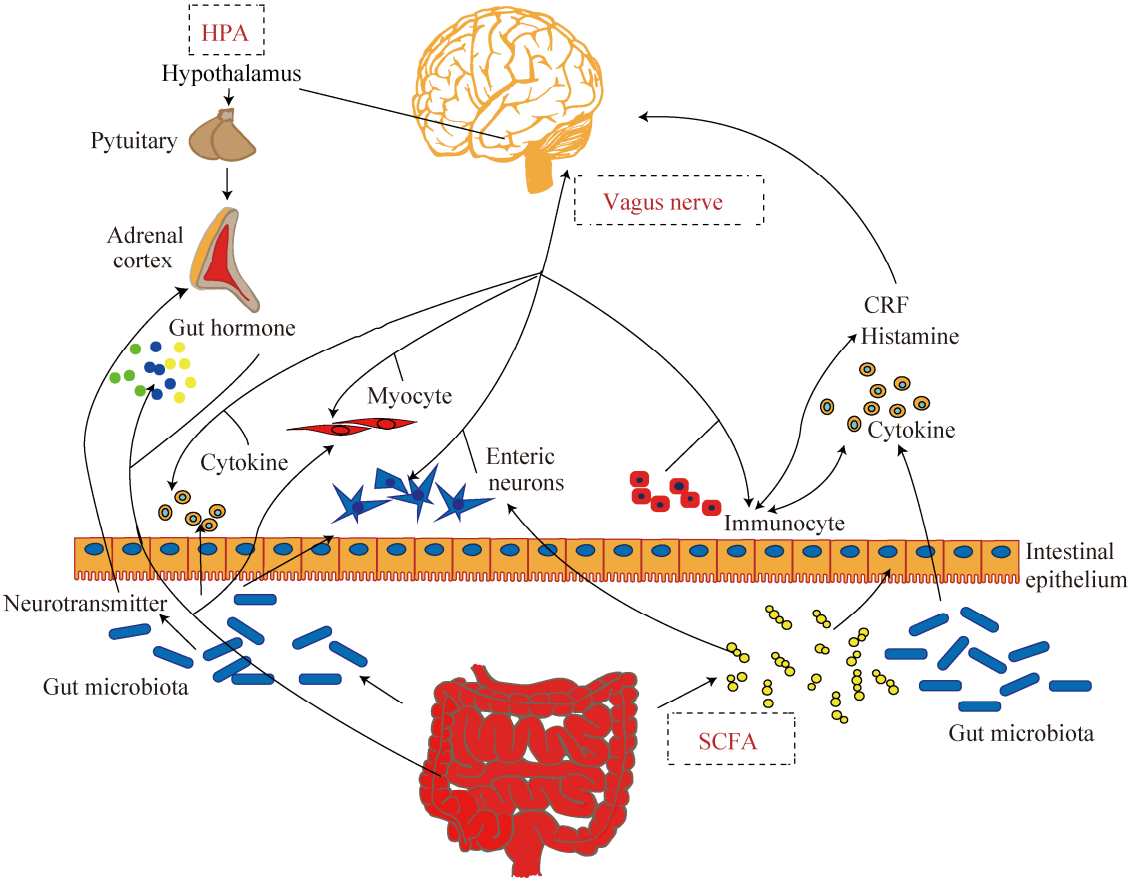

图 2　肠道菌群调控脊髓损伤后胃肠道炎症的发生发展　肠道菌群通过 3 种途径调控脊髓损伤后胃肠道炎症的发生发展

Figure 2　Regulation of gut microbiota on the occurrence and development of gastrointestinal inflammation after SCI. Gut microbiota regulates the development of gastrointestinal inflammation after spinal cord injury in three ways.

HDAC)或通过代谢物感应 G 蛋白偶联受体 41 (G protein-coupled receptors 41, GPR41)、G 蛋白偶联受体 43 (G protein-coupled receptors 43, GPR43)和 G 蛋白偶联受体 109A (G protein-coupled receptors 109A, GPR109A)的激活介导[65-66]。例如，SCFA 通过抑制 HDAC 降低神经胶质细胞中核因子(nuclear factor, NF)-κB 信号通路的活化，下调 TNF-α 表达[67]；而 SCFA 与 GPR41 或 GPR4 的结合则可以生成有抗炎作用的白介素 10 (interleukin 10, IL-10)，还能使得辅助性 T17 (helper T-17, Th17)细胞转化为调节性 T (regulatory T, Treg)细胞，进而抑制中枢神经系统的炎症反应[57]。此外，M1 型小胶质细胞能引起神经炎症，成熟的 M2 型小胶质细胞起抗炎作用[68]，而 Erny 等[69]的研究发现，无特定病原体小鼠的小胶质细胞表现出正常的发育和功能，但无菌小鼠在稳态条件下表现出发育不良的小胶质细胞，在无菌小鼠体内补充 SCFA 后，不成熟的小胶质细胞被 SCFA 补充逆转，即肠道微生物的改变会影响小胶质细胞的发育和功能。因此，SCFA 发挥有益作用一是直接作用于肠细胞，维持肠道屏障的完整性；二是通过抑制组蛋白去乙酰化酶或感应 G 蛋白

偶联受体激活间接作用,调节炎症和免疫反应从而发挥神经炎症保护作用。

4 结论与展望

脊髓损伤患者的胃肠道功能障碍使炎症反应加重,因此,研究脊髓损伤后肠道微生物群的组成、变化及相关干预措施显得迫在眉睫。目前已有研究表明[35],可以通过采用药物调整肠道菌群组成的方法而达到治疗疾病的目的。例如,Jing 等[70]基于脊髓损伤小鼠模型的数据研究表明,褪黑素可以重塑肠道微生物区系,直接或间接促进脊髓损伤后运动功能的修复。此外,赵丽萍等[71]发现,鼠李糖杆菌可能通过降低肠道致病菌丰度来抑制斑马鱼脊髓损伤引起的肠道炎症,从而进一步促进斑马鱼脊髓损伤后运动功能的恢复。

还有一些研究将微生物及其代谢物作为治疗靶点,也取得了不错的效果。研究发现[36,70],益生菌如罗伊氏乳杆菌、乳酸杆菌和双歧杆菌可以通过产生丁酸和其他短链脂肪酸神经活性代谢物及神经递质来逆转部分脊髓损伤,并有助于运动功能的修复。然而,尽管大量研究论证了肠道菌群的稳态对于脊髓损伤的重要作用,但仍缺乏对于它们相互作用的深入理解。因此,未来的研究可能会借助新技术进一步解释脊髓损伤与肠道微生物区系相互作用的病理生理机制,梳理肠道微生物区系与宿主之间的相互作用模式,并帮助开发基于微生物区系或其代谢产物的个性化靶向细菌治疗和药物,更好地帮助脊髓损伤患者恢复。

REFERENCES

[1] MARTIN JH. Neuroplasticity of spinal cord injury and repair[A]//Handbook of Clinical Neurology[M]. Amsterdam: Elsevier, 2022: 317-330.

[2] KUPFER M, FORMAL CS. Non-opioid pharmacologic treatment of chronic spinal cord injury-related pain[J]. The Journal of Spinal Cord Medicine, 2022, 45(2): 163-172.

[3] GAO F, LEI J, ZHANG ZW, YANG YL, YOU HJ. Curcumin alleviates LPS-induced inflammation and oxidative stress in mouse microglial BV_2 cells by targeting miR-137-3p/NeuroD1[J]. RSC Advances, 2019, 9(66): 38397-38406.

[4] HERRERA J, BOCKHORST K, BHATTARAI D, URAY K. Gastrointestinal vascular permeability changes following spinal cord injury[J]. Neurogastroenterology and Motility: the Official Journal of the European Gastrointestinal Motility Society, 2020, 32(7): e13834.

[5] HOLMES GM, BLANKE EN. Gastrointestinal dysfunction after spinal cord injury[J]. Experimental Neurology, 2019, 320: 113009.

[6] NASH MS, GATER DR JR. Cardiometabolic disease and dysfunction following spinal cord injury[J]. Physical Medicine and Rehabilitation Clinics of North America, 2020, 31(3): 415-436.

[7] GAO F, SHEN J, ZHAO L, HAO Q, YANG YL. Curcumin alleviates lipopolysaccharide (LPS)-activated neuroinflammation via modulation of miR-199b-5p/IκB kinase β (IKKβ)/nuclear factor kappa B (NF-κB) pathway in microglia[J]. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 2019, 25((5)): 9801-9810.

[8] SUN X, JONES ZB, CHEN XM, ZHOU LB, SO KF, REN Y. Multiple organ dysfunction and systemic inflammation after spinal cord injury: a complex relationship[J]. Journal of Neuroinflammation, 2016, 13(1): 260.

[9] AHUJA CS, NORI S, TETREAULT L, WILSON J, KWON B, HARROP J, CHOI D, FEHLINGS MG. Traumatic spinal cord injury-repair and regeneration[J]. Neurosurgery, 2017, 80(3S): S9-S22.

[10] O'CONNOR G, JEFFREY E, MADORMA D, MARCILLO A, ABREU MT, DEO SK, DIETRICH WD, DAUNERT S. Investigation of microbiota alterations and intestinal inflammation post-spinal cord injury in rat model[J]. Journal of Neurotrauma, 2018, 35(18): 2159-2166.

[11] YIN S, GUO P, HAI DF, XU L, SHU JL, ZHANG WJ, KHAN MI, KURLAND IJ, QIU YP, LIU YM. Optimization of GC/TOF MS analysis conditions for assessing host-gut microbiota metabolic interactions: Chinese rhubarb alters fecal aromatic amino acids and phenol metabolism[J]. Analytica Chimica Acta, 2017, 995: 21-33.

[12] van TREUREN W, DODD D. Microbial contribution to the human metabolome: implications for health and

disease[J]. Annual Review of Pathology, 2020, 15: 345-369.
[13] SENDER R, FUCHS S, MILO R. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans[J]. Cell, 2016, 164(3): 337-340.
[14] QIN JJ, LI RQ, RAES J, ARUMUGAM M, BURGDORF KS, MANICHANH C, NIELSEN T, PONS N, LEVENEZ F, YAMADA T, MENDE DR, LI JH, XU JM, LI SC, LI DF, CAO JJ, WANG B, LIANG HQ, ZHENG HS, XIE YL, et al. A human gut microbial gene catalogue established by metagenomic sequencing[J]. Nature, 2010, 464(7285): 59-65.
[15] COSTEA PI, HILDEBRAND F, ARUMUGAM M, BÄCKHED F, BLASER MJ, BUSHMAN FD, de VOS WM, FRASER CM, HATTORI M, HUTTENHOWER C, JEFFERY IB, KNIGHTS D, LEWIS JD, LEY RE, OCHMAN H, O'TOOLE PW, QUINCE C, RELMAN DA, SHANAHAN F, SUNAGAWA S, et al. Enterotypes in the landscape of gut microbial community composition[J]. Nature Microbiology, 2018, 3(1): 8-16.
[16] ZHOU F, WANG X, HAN BY, TANG XH, LIU R, JI Q, ZHOU ZQ, ZHANG LD. Short-chain fatty acids contribute to neuropathic pain via regulating microglia activation and polarization[J]. Molecular Pain, 2021, 17: 1744806921996520.
[17] FUNG TC, OLSON CA, HSIAO EY. Interactions between the microbiota, immune and nervous systems in health and disease[J]. Nature Neuroscience, 2017, 20(2): 145-155.
[18] SCHUPACK DA, MARS RAT, VOELKER DH, ABEYKOON JP, KASHYAP PC. The promise of the gut microbiome as part of individualized treatment strategies[J]. Nature Reviews Gastroenterology & Hepatology, 2022, 19(1): 7-25.
[19] GE YS, WANG XH, GUO YL, YAN JT, ABUDUWAILI A, AXIMUJIANG K, YAN J, WU MH. Gut microbiota influence tumor development and alter interactions with the human immune system[J]. Journal of Experimental & Clinical Cancer Research, 2021, 40(1): 42.
[20] MITREA L, NEMEŞ SA, SZABO K, TELEKY BE, VODNAR DC. Guts imbalance imbalances the brain: a review of gut microbiota association with neurological and psychiatric disorders[J]. Frontiers in Medicine, 2022, 9: 813204.
[21] DOROSZKIEWICZ J, GROBLEWSKA M, MROCZKO B. The role of gut microbiota and gut-brain interplay in selected diseases of the central nervous system[J]. International Journal of Molecular Sciences, 2021, 22(18): 10028.
[22] CARABOTTI M, SCIROCCO A, MASELLI MA, SEVERI C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems[J]. Annals of Gastroenterology, 2015, 28(2): 203-209.
[23] SHARON G, SAMPSON TR, GESCHWIND DH, MAZMANIAN SK. The central nervous system and the gut microbiome[J]. Cell, 2016, 167(4): 915-932.
[24] den BRABER-YMKER M, LAMMENS M, van PUTTEN MJAM, NAGTEGAAL ID. The enteric nervous system and the musculature of the colon are altered in patients with spina bifida and spinal cord injury[J]. Virchows Archiv: An International Journal of Pathology, 2017, 470(2): 175-184.
[25] ZHOU JH, LI ZY, WU TD, ZHAO Q, ZHAO QC, CAO Y. LncGBP$_9$/miR-34a axis drives macrophages toward a phenotype conducive for spinal cord injury repair via STAT1/STAT6 and SOCS$_3$[J]. Journal of Neuroinflammation, 2020, 17(1): 134.
[26] RONG ZJ, HUANG YL, CAI HH, CHEN M, WANG H, LIU GH, ZHANG ZW, WU JW. Gut microbiota disorders promote inflammation and aggravate spinal cord injury through the TLR4/MyD88 signaling pathway[J]. Frontiers in Nutrition, 2021, 8: 702659.
[27] GENSEL JC, ZHANG B. Macrophage activation and its role in repair and pathology after spinal cord injury[J]. Brain Research, 2015, 1619: 1-11.
[28] MAYER EA, TILLISCH K, GUPTA A. Gut/brain axis and the microbiota[J]. The Journal of Clinical Investigation, 2015, 125(3): 926-938.
[29] BANKS W. Blood-brain barrier transport of cytokines: a mechanism for neuropathology[J]. Current Pharmaceutical Design, 2005, 11(8): 973-984.
[30] GERSHON MD, MARGOLIS KG. The gut, its microbiome, and the brain: connections and communications[J]. The Journal of Clinical Investigation, 2021, 131(18): e143768.
[31] CHOI TY, CHOI YP, KOO JW. Mental disorders linked to crosstalk between the gut microbiome and the brain[J]. Experimental Neurobiology, 2020, 29(6): 403-416.
[32] HOFFMAN JD, PARIKH I, GREEN SJ, CHLIPALA G, MOHNEY RP, KEATON M, BAUER B, HARTZ AMS, LIN AL. Age drives distortion of brain metabolic, vascular and cognitive functions, and the gut microbiome[J]. Frontiers in Aging Neuroscience, 2017, 9: 298.
[33] AHUJA CS, WILSON JR, NORI S, KOTTER MRN, DRUSCHEL C, CURT A, FEHLINGS MG. Traumatic spinal cord injury[J]. Nature Reviews Disease Primers, 2017, 3: 17018.
[34] LO C, TRAN Y, ANDERSON K, CRAIG A, MIDDLETON J. Functional priorities in persons with spinal cord injury: using discrete choice experiments to determine preferences[J]. Journal of Neurotrauma, 2016,

33(21): 1958-1968.

[35] JING YL, BAI F, YU Y. Spinal cord injury and gut microbiota: a review[J]. Life Sciences, 2021, 266: 118865.

[36] KIGERL KA, MOSTACADA K, POPOVICH PG. Gut microbiota are disease-modifying factors after traumatic spinal cord injury[J]. Neurotherapeutics: the Journal of the American Society for Experimental Neurotherapeutics, 2018, 15(1): 60-67.

[37] DOELMAN A, TIGCHELAAR S, McCONEGHY B, SINHA S, KEUNG MS, MANOUCHEHRI N, WEBSTER M, FISK S, MORRISON C, STREIJGER F, NISLOW C, KWON BK. Characterization of the gut microbiome in a porcine model of thoracic spinal cord injury[J]. BMC Genomics, 2021, 22(1): 775.

[38] BAZZOCCHI G, TURRONI S, BULZAMINI MC, D'AMICO F, BAVA A, CASTIGLIONI M, CAGNETTA V, LOSAVIO E, CAZZANIGA M, TERENGHI L, de PALMA L, FRASCA G, AIACHINI B, CREMASCOLI S, MASSONE A, OGGERINO C, ONESTA MP, RAPISARDA L, PAGLIACCI MC, BISCOTTO S, et al. Changes in gut microbiota in the acute phase after spinal cord injury correlate with severity of the lesion[J]. Scientific Reports, 2021, 11: 12743.

[39] KIGERL KA, HALL JCE, WANG LL, MO XK, YU ZT, POPOVICH PG. Gut dysbiosis impairs recovery after spinal cord injury[J]. The Journal of Experimental Medicine, 2016, 213(12): 2603-2620.

[40] O'CALLAGHAN A, BOTTACINI F, O'CONNELL MOTHERWAY M, van SINDEREN D. Pangenome analysis of *Bifidobacterium longum* and site-directed mutagenesis through by-pass of restriction-modification systems[J]. BMC Genomics, 2015, 16: 832.

[41] SPLICHALOVA A, TREBICHAVSKY I, RADA V, VLKOVA E, SONNENBORN U, SPLICHAL I. Interference of *Bifidobacterium choerinum* or *Escherichia coli* Nissle 1917 with *Salmonella* Typhimurium in gnotobiotic piglets correlates with cytokine patterns in blood and intestine[J]. Clinical and Experimental Immunology, 2011, 163(2): 242-249.

[42] MANGIN I, BONNET R, SEKSIK P, RIGOTTIER-GOIS L, SUTREN M, BOUHNIK Y, NEUT C, COLLINS MD, COLOMBEL JF, MARTEAU P, DORÉ J. Molecular inventory of faecal microflora in patients with Crohn's disease[J]. FEMS Microbiology Ecology, 2004, 50(1): 25-36.

[43] YU BB, QIU HD, CHENG SP, YE F, LI JH, CHEN SJ, ZHOU L, YANG YM, ZHONG CY, LI JN. Profile of gut microbiota in patients with traumatic thoracic spinal cord injury and its clinical implications: a case-control study in a rehabilitation setting[J]. Bioengineered, 2021, 12(1): 4489-4499.

[44] BINDA C, LOPETUSO LR, RIZZATTI G, GIBIINO G, CENNAMO V, GASBARRINI A. *Actinobacteria*: a relevant minority for the maintenance of gut homeostasis[J]. Digestive and Liver Disease, 2018, 50(5): 421-428.

[45] JING YL, YU Y, BAI F, WANG LM, YANG DG, ZHANG C, QIN C, YANG ML, ZHANG D, ZHU YB, LI JJ, CHEN ZG. Effect of fecal microbiota transplantation on neurological restoration in a spinal cord injury mouse model: involvement of brain-gut axis[J]. Microbiome, 2021, 9(1): 59.

[46] GUNGOR B, ADIGUZEL E, GURSEL I, YILMAZ B, GURSEL M. Intestinal microbiota in patients with spinal cord injury[J]. PLoS One, 2016, 11(1): e0145878.

[47] 白春宏, 王莎莉, 安洪, 蒋电明, 聂海, 李雷雷. 急性脊髓损伤后家兔肠道菌群移位和内毒血症的肠道病理生理机制[J]. 第三军医大学学报, 2010, 32(6): 580-583.
BAI CH, WANG SL, AN H, JIANG DM, NIE H, LI LL. Intestinal pathophysiological mechanism of bacterial translocation and endotoxemia in rabbits with acute spinal cord injury[J]. Acta Academiae Medicinae Militaris Tertiae, 2010, 32(6): 580-583 (in Chinese).

[48] YOO BB, MAZMANIAN SK. The enteric network: interactions between the immune and nervous systems of the gut[J]. Immunity, 2017, 46(6): 910-926.

[49] BILOTTA AJ, CONG YZ. Gut microbiota metabolite regulation of host defenses at mucosal surfaces: implication in precision medicine[J]. Precision Clinical Medicine, 2019, 2(2): 110-119.

[50] CAMILLERI, FORD. Review article: colonic sensorimotor physiology in health, and its alteration in constipation and diarrhoeal disorders[J]. Alimentary Pharmacology & Therapeutics, 1998, 12(4): 287-302.

[51] BESECKER EM, BLANKE EN, DEITER GM, HOLMES GM. Gastric vagal afferent neuropathy following experimental spinal cord injury[J]. Experimental Neurology, 2020, 323: 113092.

[52] BONAZ B, BAZIN T, PELLISSIER S. The vagus nerve at the interface of the microbiota-gut-brain axis[J]. Frontiers in Neuroscience, 2018, 12: 49.

[53] WILLIAMS EK, CHANG RB, STROCHLIC DE, UMANS BD, LOWELL BB, LIBERLES SD. Sensory neurons that detect stretch and nutrients in the digestive system[J]. Cell, 2016, 166(1): 209-221.

[54] BROWNING KN, VERHEIJDEN S, BOECKXSTAENS GE. The vagus nerve in appetite regulation, mood, and intestinal inflammation[J]. Gastroenterology, 2017,

152(4): 730-744.
[55] YANO JM, YU K, DONALDSON GP, SHASTRI GG, ANN P, MA L, NAGLER CR, ISMAGILOV RF, MAZMANIAN SK, HSIAO EY. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis[J]. Cell, 2015, 161(2): 264-276.
[56] LEGAN TB, LAVOIE B, MAWE GM. Direct and indirect mechanisms by which the gut microbiota influence host serotonin systems[J]. Neurogastroenterology & Motility, 2022: e14346.
[57] KIBBIE JJ, DILLON SM, THOMPSON TA, PURBA CM, MCCARTER MD, Wilson CC. Butyrate directly decreases human gut *Lamina propria* CD4 T cell function through histone deacetylase (HDAC) inhibition and GPR43 signaling[J]. Immunobiology, 2021, 226(5): 152126.
[58] CUCE E, DEMIR H, CUCE I, BAYRAM F. Hypothalamic—pituitary-–adrenal axis function in traumatic spinal cord injury-related neuropathic pain: a case-–control study[J]. Journal of Endocrinological Investigation, 2019, 42(8): 923-930.
[59] YUAN B, LU XJ, WU Q. Gut microbiota and acute central nervous system injury: a new target for therapeutic intervention[J]. Frontiers in Immunology, 2021, 12: 800796.
[60] MISIAK B, ŁONIEWSKI I, MARLICZ W, FRYDECKA D, SZULC A, RUDZKI L, SAMOCHOWIEC J. The HPA axis dysregulation in severe mental illness: can we shift the blame to gut microbiota? [J]. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 2020, 102: 109951.
[61] WU Q, XU ZY, SONG SY, ZHANG H, ZHANG WY, LIU LP, CHEN YP, SUN JH. Gut microbiota modulates stress-induced hypertension through the HPA axis[J]. Brain Research Bulletin, 2020, 162: 49-58.
[62] SHEN Y, XU JT, LI ZY, HUANG YC, YUAN Y, WANG JX, ZHANG M, HU SN, LIANG Y. Analysis of gut microbiota diversity and auxiliary diagnosis as a biomarker in patients with schizophrenia: a cross-sectional study[J]. Schizophrenia Research, 2018, 197: 470-477.
[63] TAKAHASHI D, HOSHINA N, KABUMOTO Y, MAEDA Y, SUZUKI A, TANABE H, ISOBE J, YAMADA T, MUROI K, YANAGISAWA Y, NAKAMURA A, FUJIMURA Y, SAEKI A, UEDA M, MATSUMOTO R, ASAOKA H, CLARKE JM, HARADA Y, UMEMOTO E, KOMATSU N, et al. Microbiota-derived butyrate limits the autoimmune response by promoting the differentiation of follicular regulatory T cells[J]. EBioMedicine, 2020, 58: 102913.
[64] WU SE, HASHIMOTO-HILL S, WOO V, ESHLEMAN EM, WHITT J, ENGLEMAN L, KARNS R, DENSON LA, HASLAM DB, ALENGHAT T. Microbiota-derived metabolite promotes HDAC3 activity in the gut[J]. Nature, 2020, 586(7827): 108-112.
[65] FILIPPONE A, LANZA M, CAMPOLO M, CASILI G, PATERNITI I, CUZZOCREA S, ESPOSITO E. Protective effect of sodium propionate in Aβ $_{1-42}$-induced neurotoxicity and spinal cord trauma[J]. Neuropharmacology, 2020, 166: 107977.
[66] BOSE P, DAI Y, GRANT S. Histone deacetylase inhibitor (HDACI) mechanisms of action: emerging insights[J]. Pharmacology & Therapeutics, 2014, 143(3): 323-336.
[67] LONG-SMITH C, O'RIORDAN KJ, CLARKE G, STANTON C, DINAN TG, CRYAN JF. Microbiota-gut-brain axis: new therapeutic opportunities[J]. Annual Review of Pharmacology and Toxicology, 2020, 60((4)): 477-502.
[68] 何科学, 刘燕, 高小川, 陈玉洁, 陈志阳, 刘玲, 邝芳, 杨彦玲. 聚乙二醇对大鼠原代小胶质细胞生物活性的影响[J]. 神经解剖学杂志, 2022, 38(2): 154-162.
HE KX, LIU Y, GAO XC, CHEN YJ, CHEN ZY, LIU L, KUANG F, YANG YL. The effects of polyethylene glycol on bioactivity of rat primary microglia[J]. Chinese Journal of Neuroanatomy, 2022, 38(2): 154-162 (in Chinese).
[69] ERNY D, LENA HRABĚ de ANGELIS A, JAITIN D, WIEGHOFER P, STASZEWSKI O, DAVID E, KEREN-SHAUL H, MAHLAKOIV T, JAKOBSHAGEN K, BUCH T, SCHWIERZECK V, UTERMÖHLEN O, CHUN E, GARRETT WS, McCOY KD, DIEFENBACH A, STAEHELI P, STECHER B, AMIT I, et al. Host microbiota constantly control maturation and function of microglia in the CNS[J]. Nature Neuroscience, 2015, 18(7): 965-977.
[70] JING YL, YANG DG, BAI F, ZHANG C, QIN C, LI D, WANG LM, YANG ML, CHEN ZG, LI JJ. Melatonin treatment alleviates spinal cord injury-induced gut dysbiosis in mice[J]. Journal of Neurotrauma, 2019, 36(18): 2646-2664.
[71] 赵丽萍, 黄术兵, 张博枰, 周芝兰, 贾雪冰, 孙孟菲, 乔晨萌, 陈雪, 申延琴, 崔春. 鼠李糖乳杆菌对斑马鱼脊髓损伤后肠道炎症的抑制作用及其机制[J]. 吉林大学学报(医学版), 2020, 46(4): 680-686.
ZHAO LP, HUANG SB, ZHANG BP, ZHOU ZL, JIA XB, SUN MF, QIAO CM, CHEN X, SHEN YQ, CUI C. Inhibitory effect of *Lactobacillus rhamnosus* on intestinal inflammation after spinal cord injury in zebrafishes and its mechanism[J]. Journal of Jilin University (Medicine Edition), 2020, 46(4): 680-686 (in Chinese).