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专论与综述

肠道菌群影响脊髓损伤后焦虑情绪的研究进展

王青燕，高慧，何盟泽，白心悦，席回林，杨彦玲*

延安大学医学院，陕西 延安 716000

王青燕, 高慧, 何盟泽, 白心悦, 席回林, 杨彦玲. 肠道菌群影响脊髓损伤后焦虑情绪的研究进展[J]. 微生物学通报, 2023, 50(12): 5563-5573.
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摘　要：脊髓损伤作为一种严重的创伤性应激可以引发焦虑情绪，对患者心理健康造成极大影响。研究发现，脊髓损伤后肠道菌群失调与焦虑情绪的发生存在密切联系，因此本文从 5-羟色胺系统失调、多巴胺系统失调、脑源性神经营养因子缺乏及炎症反应 4 个方面，探讨脊髓损伤后肠道菌群改变影响焦虑情绪发生的机制，为今后治疗脊髓损伤后焦虑情绪的深入研究和药物开发提供理论依据。

关键词：脊髓损伤；焦虑；肠道菌群

Gut microbiota in anxiety after spinal cord injury: a review

WANG Qingyan, GAO Hui, HE Mengze, BAI Xinyue, XI Huilin, YANG Yanling*

Medical School of Yan'an University, Yan'an 716000, Shaanxi, China

Abstract: Spinal cord injury as a traumatic stress may trigger anxiety in patients. Studies have shown that intestinal dysbacteriosis is closely related to the occurrence of anxiety after spinal cord injury. This article expounds the mechanisms by which the alteration of gut microbiota affects the occurrence of anxiety after spinal cord injury from four aspects: serotonin system dysregulation, dopamine system dysregulation, brain-derived neurotrophic factor deficiency, and inflammatory response. This review aims to provide a theoretical basis for future in-depth research and drug development for the treatment of anxiety after spinal cord injury.

Keywords: spinal cord injury; anxiety; gut microbiota

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*Corresponding author. E-mail: yangyanling8889@163.com
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脊髓损伤(spinal cord injury, SCI)是一种具有严重后果的中枢神经系统创伤性疾病，对患者身体功能、情感和社会交往等多方面造成损害[1]。大量研究表明脊髓损伤后焦虑情绪的发生已经高达 15%–32%[2]，患病率严重高出正常人焦虑。焦虑情绪的发生不仅会对脊髓损伤患者的生活质量和身心健康造成极大的影响，而且会影响疾病的后续治疗效果[3]，因此加强对脊髓损伤并发焦虑的诊断与治疗尤为重要。最近，肠道菌群被认为是情绪和心理调节的重要靶点，越来越多的证据表明，脊髓损伤后焦虑情绪的发生与肠道菌群紊乱密切相关[4-6]。因此，分析脊髓损伤后焦虑情绪障碍的发生与肠道菌群之间的内在关系，可以为临床预防、治疗此病提供新途径，具有重要的临床意义与价值。

1 脊髓损伤与焦虑

2019 年一项在全球范围内的调查显示，脊髓损伤的患病率已经高达 995 万例[7]，患病后不仅导致机体运动、感觉和自主神经功能障碍外，还能作为一种严重的创伤性应激引发焦虑、恐惧和抑郁，这些不良情绪的发生会降低患者的生活质量并增加自杀风险[8]。Le 等[2]指出，脊髓损伤后焦虑患病率在 15%–32%不等，相较而言，普通人群中焦虑的患病率仅在 9%左右[9]，提示脊髓损伤患者罹患焦虑情绪障碍的风险明显上升。

脊髓损伤导致患者罹患焦虑情绪障碍的风险值增加的同时，也会对脊髓损伤的发展产生影响。研究证明[10]，表现出焦虑样行为的小鼠其脊髓损伤后运动功能恢复不良，说明脊髓损伤后的焦虑样行为可能与运动功能恢复有关，改善焦虑可能会影响损伤后的功能恢复[11]。因此，脊髓损伤和焦虑情绪的发生之间关系紧密，但目前对其发生机制及治疗的研究较少，因此找到一种对两者都有治疗作用的方法尤其重要。

2 肠道菌群与脊髓损伤和焦虑的关系

正常情况下，肠道菌群与宿主及外部环境保持动态平衡，从而发挥保护和维持机体健康的作用，一旦发生肠道微生态紊乱就会引起各种相关疾病。研究发现，肠道菌群与多种疾病的发生发展具有紧密联系，如孤独症谱系障碍[12]、帕金森病[13]和多发性硬化[14]等，最近的研究也提示肠道菌群在脊髓损伤[15]和焦虑[4]中也表现出重要作用。

2.1 脊髓损伤与肠道菌群

研究发现，脊髓损伤后紊乱的肠道菌群具有潜在致病性[16-17]，主要表现为抗炎性物质的减少和促炎性细菌的增多[18]，这与脊髓损伤后严重的炎症反应和感染的发生有关。临床试验中[16]，对 100 名脊髓损伤患者进行肠道微生物群 16S rRNA 基因测序的结果显示，与健康对照相比，脊髓损伤患者表现出厚壁菌门(*Firmicutes*)、瘤胃球菌科(*Ruminococcaceae*)、毛螺菌科(*Lachnospiraceae*)、梭状芽孢杆菌属(*Clostridium*)相对丰度下降，其中瘤胃球菌科和梭状芽孢杆菌属是产生短链脂肪酸(short chain fatty acid, SCFA)的菌群，而短链脂肪酸具有抗炎作用，因此脊髓损伤后抗炎性物质减少；相反地，与炎症密切相关菌群，如拟杆菌(*Bacteroidetes* sp.)、肠球菌(*Enterococcus* sp.)、乳杆菌(*Lactobacillus* sp.)、链球菌(*Streptococcus* sp.)和肠杆菌(*Enterobacterceae* sp.)的相对丰度却显著升高。此外，研究表明脊髓损伤后肠道菌群失调可通过激活 TLR4/MyD88 信号通路引发促炎

因子的过表达，促进神经细胞凋亡，进一步加重脊髓损伤[19]。以上研究表明脊髓损伤后伴有肠道菌群失调且失调会影响疾病的发生发展。

2.2 焦虑与肠道菌群

焦虑患者常伴随着肠道菌群失调，提示肠道菌群可能影响焦虑的发生发展，是焦虑情绪障碍干预的主要方向。通过对广泛性焦虑障碍(generalized anxiety disorder, GAD)患者和健康对照的粪便样本进行分析[20]，显示 GAD 患者的粪便菌群 α 多样性较低；其中，瘤胃球菌科和普雷沃氏菌科(*Prevotellaceae*)表现出减少，二者与焦虑的严重程度呈负相关关系；而拟杆菌和志贺氏菌(*Shigella* sp.)的相对丰度增加，并与焦虑的严重程度呈正相关关系。此外，Jiang 等[21]对 40 名 GAD 患者和 36 名健康对照的肠道微生物组进行系统的比较分析，结果显示，在门水平上，GAD 患者肠道菌群中厚壁菌门显著减少，而梭杆菌(*Fusobacterium* sp.)和拟杆菌比例增加；在属水平上，GAD 患者中发现瘤胃球菌和梭杆菌相对丰度降低。这些结果提示焦虑后肠道菌群的改变与脊髓损伤后肠道菌群的改变具有相似性。另外，通过对无菌小鼠和无特定病原体小鼠进行焦虑行为学实验显示，无菌小鼠表现出更少的焦虑样行为，而断奶同居后，两组小鼠肠道菌群组成变得相似，焦虑行为学差异消失[22]。由此可见，肠道菌群的失调与焦虑的发生存在相关性。

以上论述表明，脊髓损伤和焦虑症患者均存在肠道菌群失调现象，且肠道菌群改变具有相似性。尽管目前针对脊髓损伤后合并焦虑患者肠道菌群变化的研究相对较少，但基于现有的证据可以发现，肠道菌群与脊髓损伤后焦虑情绪的发生之间存在密切联系。因此，深入探讨肠道菌群与脊髓损伤后焦虑之间的联系，可以为脊髓损伤后焦虑情绪发生的基础研究和临床治疗带来全新视角。

3 肠道菌群影响脊髓损伤后焦虑情绪的发生发展

脊髓损伤后焦虑情绪发生不仅损害患者身心健康，而且会影响后续功能恢复。研究发现，脊髓损伤后肠道菌群的失调与焦虑情绪的发生发展有关，体现在粪菌移植(fecal microbiota transplantation, FMT)治疗可以恢复肠道微生态并减轻焦虑样行为[23]，同时外源性给予米诺环素可以改善肠道菌群的失调，从而缓解脊髓损伤后的焦虑样行为[24]。然而，目前对于脊髓损伤后肠道菌群失调在损伤后焦虑情绪障碍中的研究较少，其具体的发病机制尚不明确。随着生物信息学分析、高通量测序等生物技术的进步，肠道菌群影响脊髓损伤后焦虑情绪的发生与 5-羟色胺系统失调、炎症反应发生、脑源性神经营养因子水平降低和多巴胺系统失调这 4 种机制密切相关(图 1)。

3.1 5-羟色胺系统失调

5-羟色胺(5-hydroxytryptamine, 5-HT)是一种来自于脑干中缝核的神经递质，在中枢神经系统中发挥着重要作用，大量研究数据证明 5-羟色胺系统在焦虑情绪中发挥着重要作用。有研究报道[25]，血清 5-HT 含量变化可及早预测脊髓损伤患者的焦虑和抑郁，5-HT 含量增加有助于改善焦虑的发生。对脊髓损伤大鼠进行研究，结果显示其结肠和脊髓中 5-HT 表达水平均降低[26]，这可能影响脊髓损伤后焦虑情绪的发生。另有研究[27]表明，脊髓损伤后结肠中 5-HT 的含量降低，但通过调节肠道菌群和代谢产物可以显著上调色氨酸氢化酶 1 (tryptophan hydroxylase, TPH1)和降低 5-羟色胺转运蛋白的表达，从而提高结肠中 5-HT 的表达水平。此外，脊髓损伤后肠道菌群失调引起的功能障碍会导致维生素 B6 的合成受损和色氨酸合成功能失

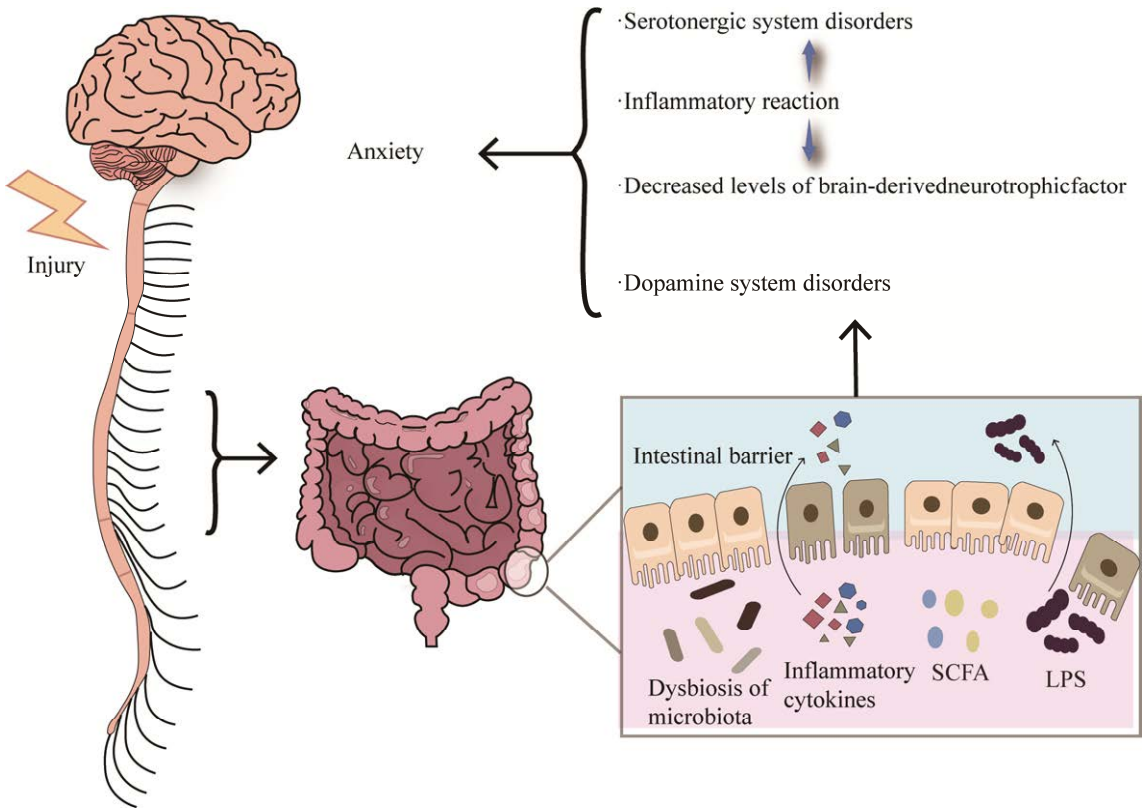

图 1　脊髓损伤后肠道菌群失调导致焦虑发生的机制

Figure 1　The mechanism by which dysbacteriosis of the intestinal flora after spinal cord injury leads to the onset of anxiety. SCFA: Short chain fatty acid; LPS: Lipopolysaccharides.

调[28]，从而间接导致 5-HT 含量下降，导致焦虑情绪的发生发展。除肠道菌群外，肠道微生物代谢产物，如乙酸盐、丁酸盐和丙酸盐可以通过直接刺激肠嗜铬细胞中的 TPH1 促进 5-HT 的合成与分泌，增加肠道和血液循环中 5-HT 的含量[29-30]。因此，脊髓损伤后肠道菌群的改变可以直接影响 5-HT 的表达或影响其合成过程，从而影响脊髓损伤后焦虑情绪的发生发展过程。

3.2　多巴胺系统失调

多巴胺(dopamine，DA)是主要的儿茶酚胺能神经递质，由中枢和外周的多巴胺能神经元合成[31]，在焦虑情绪中发挥了重要作用。Tong 等[32]研究表明，在腹侧被盖区激活多巴胺受体 D1 后发挥抗焦虑效应，抑制该受体后引起焦虑样行为。此外，中脑多巴胺的过度激活也会导致焦虑[33]。研究显示，脊髓损伤显著增加了前额叶皮层中多巴胺水平，同时使多巴胺受体 D1 和 D2 的表达降低，这可能与脊髓损伤后焦虑情绪的发生相关[34]。此外，肠道菌群对多巴胺受体具有调节作用，梭状芽胞杆菌科、瘤胃球菌科的许多属级细菌与多巴胺受体 D2 mRNA 的降低有关[35]，而脊髓损伤患者体内表现出瘤胃球菌科和梭状芽孢杆菌科的减少[19]。同时临床研究显示，焦虑患者体内也可以观察到瘤胃球菌科和梭状芽孢杆菌科的减少，并且与焦虑的严重程度呈现负相关[16]。由此可见，脊髓损伤后肠道菌群的改变会导致多巴胺系统失调，从而导致焦虑情绪障碍的发生。

3.3 脑源性神经营养因子水平降低

脑源性神经营养因子(brain derived neurotrophic factor, BDNF)作为一种关键的神经营养因子，参与调节神经细胞的生长与突触的可塑性，并具有改善焦虑情绪的作用。Lucon-Xiccato 等[36]以斑马鱼为模型进行研究，发现 BDNF 的减少会导致焦虑样行为的产生。同时，研究显示抗焦虑药物可以增加大鼠脑细胞中 BDNF mRNA 和蛋白质的表达，从而改善大鼠的焦虑症状[37]。Ilha 等[38]对脊髓损伤小鼠小脑和脊髓中的 BDNF 进行定量，发现脊髓损伤后 BDNF 的表达显著下降，经 FMT 治疗后大脑中 BDNF 出现明显上调[39]。此外，Pourkhodadad 等[40]的研究同样证实了损伤后脊髓组织中 BDNF 显示出下调。丁酸盐被认为是将肠道菌群和大脑 BDNF 联系起来的候选物质，一项动物研究表明，丁酸盐通过抑制组蛋白去乙酰化酶来促进前额叶皮层中 BDNF mRNA 的表达[41]。Zhou 等[42]研究表明，鼠李糖乳杆菌 GG 的早期定殖可以增加海马体和杏仁核中 BDNF 的水平，通过肠脑轴缓解成年期焦虑的发生。综上所述，脊髓损伤后肠道菌群变化可通过影响 BDNF 的表达来影响焦虑情绪的发生发展。

3.4 炎症反应

研究显示，炎症反应可以通过多种途径导致焦虑的发生。杏仁核是大脑中调节情感、稳态和社交功能的中心，被认为与多种情绪的发生有关[43]。过度的炎症反应会影响杏仁核中小胶质细胞活化程度，从而调节基底杏仁核神经元可塑性，导致焦虑样行为的发生[44]。此外，促炎细胞因子可以通过增强 5-HT 转运蛋白的活性促进 5-HT 再摄取[45]、激活吲哚胺 2,3-双加氧酶的活性，催化色氨酸转化为犬尿氨酸，最终降低 5-HT 含量[46]。同时，促炎因子还可阻碍如 γ-氨基丁酸(γ-aminobutyric acid, GABA)[47]、DA[48]等单胺类神经递质及抑制 BDNF 表达[49]，导致焦虑情绪的发生。

Maldonado-Bouchard 等[50]通过对脊髓损伤和脊髓损伤伴焦虑情绪患者进行促炎因子水平分析发现，表现出焦虑样行为的患者脊髓和海马中促炎细胞因子表达更高，说明脊髓损伤后炎症反应与焦虑的发生相关。通过对脊髓损伤小鼠脊髓和血浆中细胞因子进行检测发现[51]，脊髓损伤后导致局部和全身促炎因子(TNF-α、INF-γ、IL-1β 和 IL-6)显著增加，抗炎细胞因子 IL-10 显著减少。另外，脊髓损伤后肠道菌群紊乱具有潜在致病性，表现为厚壁菌相对丰度降低，伴或不伴有拟杆菌增加，导致厚壁菌与拟杆菌的比例发生变化，这种微生物群结构的变化会影响 SCFA 的产生[19-20]。然而 SCFA 的减少会导致肠道屏障完整性破坏[52]，同时由于脊髓损伤后血脑屏障通透性增加，体循环中的炎症细胞因子会通过血脑屏障到达大脑，从而增加焦虑情绪障碍的发生[53]。Schmidt 等[23]的研究显示，脊髓损伤后肠道菌群失调进一步加剧，局部和全身炎症与焦虑样行为的增加有关。对脊髓损伤大鼠给予米诺环素治疗显示药物可以通过调节肠道菌群失调缓解其焦虑样行为[24]，米诺环素的抗焦虑作用归因于其抗炎特性[54-55]。综上可知，脊髓损伤后肠道菌群的失调会引起炎症反应，导致焦虑情绪的发生(图 2)。

4 基于肠道菌群干预脊髓损伤后焦虑情绪的发生

目前针对脊髓损伤后焦虑情绪发生的治疗主要采取分开诊治的方案，在常规脊髓损伤用药的基础上结合抗焦虑药物，但近年来对抗焦虑药物的安全性、有效性存在一些质疑和争议，同时用药种类的增加使患者难以坚持，导致依

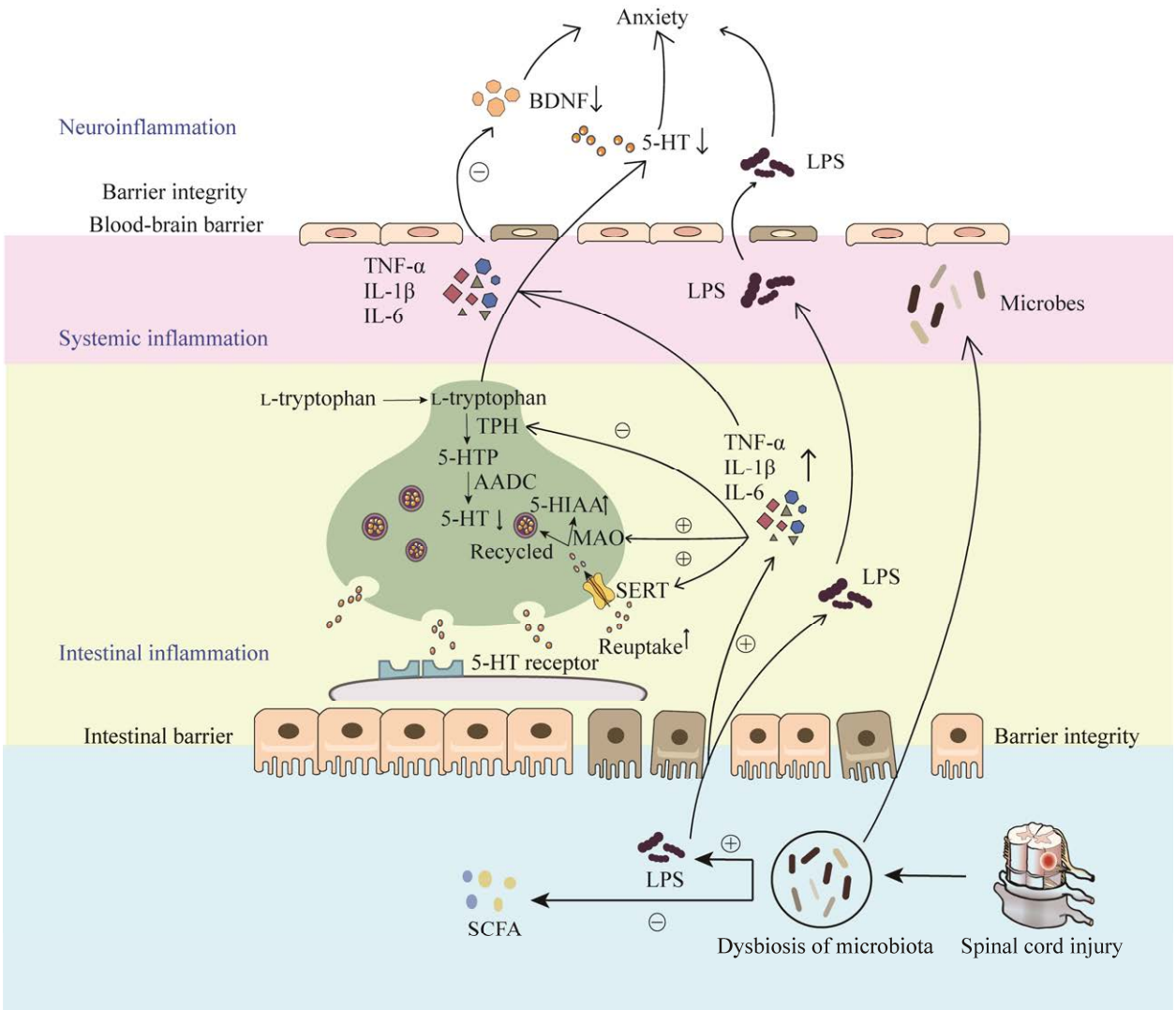

图 2 脊髓损伤后炎症反应导致焦虑情绪发生的机制 LPS：脂多糖；SCFA：短链脂肪酸；5-HT：5-羟色胺；SERT：5-HT 转运蛋白；TPH：色氨酸羟化酶；5-羟色氨酸：5-HTP；AADC：芳香族氨基酸脱羧酶；MAO：单胺氧化酶；5-HIAA：5-羟基吲哚乙酸；BDNF：脑源性神经营养因子

Figure 2 The mechanism by which the inflammatory response after spinal cord injury leads to anxiety. LPS: Lipopolysaccharides; SCFA: Short chain fatty acid; 5-HT: 5-hydroxytryptamine; SERT: Serotonin transporter; TPH: Tryptophan hydroxylase; 5-HTP: 5-hydroxytryptophan; AADC: Aromatic amino-acid decarboxylase; MAO: Monoamine oxidase; 5-HIAA: 5-hydroxyindole acetic acid; BDNF: Brain derived neurotrophic factor.

从性较低，并且增加了经济负担，亟须寻找新的治疗方案。综上所述，脊髓损伤后肠道菌群失调通过不同机制引起焦虑情绪的发生，因此可通过纠正肠道菌群失调防治脊髓损伤后焦虑情绪的发生，即肠道微生态治疗。

益生菌能够通过调节肠道微生态平衡、维持宿主良好的生理状态影响焦虑的发生发展过程，是一种有效果、安全且可靠的治疗方法。干酪乳杆菌[56]、罗伊氏乳杆菌[57]都能改善焦虑情绪的发生，后者是通过抑制活化的 NF-κB 信

号通路、促进海马体中 BDNF 表达起到治疗作用。通过对益生菌治疗后血浆中促炎细胞因子进行检测，发现焦虑的减轻伴随着促炎细胞因子水平的降低，表明益生菌可以通过调节炎症反应来缓解焦虑[58-59]。此外，粪菌移植作为一种将健康供体的粪便细菌转移到受体中重建肠道菌群使其更符合肠道原生微生态的方法[60]，已在阿尔茨海默病[61]、抑郁症[62]、帕金森病[14]和孤独症谱系障碍[63]等精神类疾病中表现出治疗作用。研究表明，以健康大鼠作为粪菌移植供体对脊髓损伤大鼠进行治疗，经焦虑行为学评估，认为 FMT 治疗显著减少焦虑样行为的发生[23]，同时 FMT 治疗对脊髓损伤大鼠发挥神经保护作用[39]。综上可知，肠道微生态治疗可对脊髓损伤及焦虑同时起到保护作用。

5 讨论与展望

随着现代医学模式的转变，疾病后患者的心理健康状态受到关注。脊髓损伤后焦虑情绪的发生严重影响患者的心理健康及后续功能的恢复。研究发现，脊髓损伤后肠道菌群失调是损伤后导致焦虑发生的关键因素，影响着此病的发生和发展。因此，本文将肠道菌群作为一个关键靶点，从脊髓损伤患者与焦虑患者肠道菌群均处于失调状态且存在相关性出发，分析了肠道菌群失调导致脊髓损伤后焦虑情绪发生的可能机制。然而，虽然有研究表明微生态治疗可改善脊髓损伤的病理表现及焦虑症状，但研究多为动物实验，缺少临床研究的证据，而且缺乏对它们相互作用的深入理解。因此，在未来的研究中，需要在大量基础和临床研究的基础上，进一步探究肠道菌群与脊髓损伤后焦虑发生的生理病理关系，从而为脊髓损伤后焦虑情绪的预防和治疗提供明确有效的新方案。

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