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Research Article 研究报告

姜黄素通过肠道菌群调节 Treg/Th17 平衡改善脊髓损伤

田春平[1]，吴佳俊[1]，肖林峰[1]，王青燕[1]，杜嘉妮[1]，胡倩倩[1]，强京灵[2]，常小卫[1*]，杨彦玲[1*]

1 延安大学延安医学院，陕西 延安
2 延安大学附属医院神经外科，陕西 延安

田春平, 吴佳俊, 肖林峰, 王青燕, 杜嘉妮, 胡倩倩, 强京灵, 常小卫, 杨彦玲. 姜黄素通过肠道菌群调节 Treg/Th17 平衡改善脊髓损伤[J]. 微生物学报, 2026, 66(5): 2416-2429.
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摘　要：【目的】脊髓损伤后引发的免疫炎症反应是阻碍神经功能恢复的关键因素。近期研究表明，肠道菌群紊乱可通过“肠-脊髓轴”参与中枢神经系统的免疫调控。本研究旨在探讨姜黄素能否通过重塑肠道菌群，调节脊髓局部 Treg/Th17 平衡，从而发挥对脊髓损伤的保护作用。【方法】将 200−220 g 左右的雌性 Sprague-Dawley (SD)大鼠随机分为假手术组、脊髓损伤组、姜黄素组、粪菌移植组、粪菌移植姜黄素组、粪菌移植姜黄素+GPRs 抑制剂组。通过 Basso-Beattie-Bresnahan (BBB)运动功能评分和步态分析评估神经功能恢复情况；采用苏木精-伊红染色、尼氏染色和劳克坚牢蓝染色观察损伤区域的组织病理学变化；运用实时荧光定量逆转录 PCR 检测、酶联免疫吸附测定和蛋白印迹分析，检测各组脊髓中 Treg 细胞关键转录因子 FOXP3、抗炎因子 IL-10 和 TGF-β1，以及 Th17 细胞关键转录因子 RORγt、促炎因子 IL-17 和 IL-6 的表达情况。【结果】与脊髓损伤组和粪菌移植组相比，姜黄素组和粪菌移植姜黄素组大鼠的神经功能改善最为显著，具体表现为 BBB 运动功能评分和步态协调性显著提升，同时脊髓组织损伤范围明显缩小。在分子水平上，这 2 组脊髓组织中 FOXP3、IL-10 和 TGF-β1 的基因和蛋白表达显著上调，而 RORγt、IL-17A 和 IL-6 的表达则被显著抑制，这提示姜黄素干预肠道菌群后免疫平衡向 Treg 主导的抗炎状态倾斜。值得注意的是，联合使用 GPRs 抑制剂后，姜黄素修饰菌群带来的上述有益

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*Corresponding authors. E-mail: CHANG Xiaowei, changxw@yau.edu.cn; YANG Yanling, yangyanling8889@163.com
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效应被逆转。【结论】本研究表明，姜黄素干预后的肠道菌群能够有效促进脊髓损伤后的运动功能恢复，其作用机制可能与激活 GPRs 信号通路，上调 Treg 细胞活性、抑制 Th17 细胞分化，最终纠正 Treg/Th17 免疫失衡密切相关。这为将姜黄素及其修饰后的肠道菌群作为脊髓损伤的辅助治疗策略提供了新的实验依据和应用价值。

关键词：姜黄素；肠道菌群；短链脂肪酸；脊髓损伤

Curcumin ameliorates spinal cord injury by regulating the Treg/Th17 balance *via* gut microbiota

TIAN Chunping[1], WU Jiajun[1], XIAO Linfeng[1], WANG Qingyan[1], DU Jiani[1], HU Qianqian[1], QIANG Jingling[2], CHANG Xiaowei[1*], YANG Yanling[1*]

1 Yan'an Medical College, Yan'an University, Yan'an, Shaanxi, China

2 Neurosurgery Department, Yan'an University Affiliated Hospital, Yan'an, Shaanxi, China

Abstract: [Objective] The immunoinflammatory response induced by spinal cord injury is a key factor hindering the recovery of neurological functions. Recent studies have shown that gut microbiota dysbiosis can participate in the immune regulation of the central nervous system through the gut-spinal cord axis. This study aims to explore whether curcumin can exert its protective effect on spinal cord injury by reshaping the gut microbiota and thereby regulating the local Treg/Th17 balance in the spinal cord. **[Methods]** Female Sprague-Dawley rats weighing 200–220 g were randomly assigned into the sham operation group, spinal cord injury group, curcumin group, fecal microbiota transplantation group, fecal microbiota transplantation+ curcumin group, and fecal microbiota transplantation+curcumin+GPR inhibitor group. Neurological function recovery was evaluated based on the Basso-Beattie-Bresnahan motor function score and gait analysis. Histopathological changes in the injured area were observed *via* hematoxylin-eosin staining, Nissl staining, and Luxol Fast Blue staining. RT-qPCR, ELISA, and Western blotting were employed to quantify the expression levels of key transcription factor forkhead box protein 3 (FOXP3) for Treg cells, anti-inflammatory cytokines interleukin (IL)-10 and transforming growth factor (TGF)-β1, as well as key transcription factor retinoic acid receptor-related orphan receptor gamma t (RORγt) for Th17 cells and pro-inflammatory cytokines IL-17 and IL-6 in the spinal cord of each group. **[Results]** Compared with the spinal cord injury group and fecal microbiota transplantation group, the curcumin group and fecal microbiota transplantation+ curcumin group showed the most significant improvement in neurological function, specifically manifested by significant increases in BBB motor function scores and gait coordination, along with a marked reduction in the scope of spinal cord injury. At the molecular level, the two groups showed significantly upregulated gene and protein levels of FOXP3, IL-10, and TGF-β1 and significantly inhibited expression of RORγt, IL-17A, and IL-6 in the spinal cord tissue. This suggests that after curcumin intervention in the gut microbiota, the immune balance shifted toward

a Treg-dominated anti-inflammatory state. Notably, the aforementioned beneficial effects of curcumin-modified gut microbiota were reversed after combined use of the GPR inhibitor. **[Conclusion]** This study indicates that curcumin can act on the gut microbiota to promote the recovery of motor function after spinal cord injury. Curcumin may exert the effect by activating the GPR signaling pathway, thereby upregulating Treg viability, inhibiting Th17 differentiation, and ultimately correcting the Treg/Th17 imbalance. This provides new experimental evidence and application value for using curcumin and its modified gut microbiota as an adjuvant therapeutic strategy for spinal cord injury.

Keywords: curcumin; gut microbiota; short-chain fatty acids; spinal cord injury

脊髓损伤(spinal cord injury, SCI)是一种严重的创伤性中枢神经系统疾病，通常由外力对脊髓或脊髓周围结构造成损害而引发，其临床表现为感觉、运动和自主神经功能障碍，严重影响患者的生活质量和日常功能[1-2]。脊髓损伤可分为原发性脊髓损伤和继发性脊髓损伤，继发性脊髓损伤包括脂质过氧化、神经胶质细胞激活、神经炎症和氧化应激等，其中神经炎症被认为是导致脊髓继发性损伤加重的关键因素[3-5]。因此，抑制脊髓损伤后神经细胞炎症的发生是治疗成功的关键。

辅助性 T 细胞 17 (T helper cell 17, Th17 cell)是 $CD4^+$ T 细胞的一个亚群，白细胞介素-6 (interleukin-6, IL-6)通过信号转导与转录激活因子 3 (signal transducer and activator of transcription, STAT3)诱导视黄醇相关孤儿受体 γt (retinoid-related orphan receptor gamma t, RORγt)转录，促进 Th17 细胞的增殖和分化，产生更多的白细胞介素-17A (interleukin-17A, IL-17A)等促炎细胞因子，进而介导炎症反应和自身免疫性疾病的发生发展[6-7]。调节性 T 细胞(regulatory T cells, Treg cell)是 $CD4^+$ T 细胞的另一个亚群，转化生长因子-β (transforming growth factor-β, TGF-β)诱导叉头样转录因子 3 (forkhead box P3, FOXP3)转录，促进 Treg 细胞的增殖和分化，使其分泌白细胞介素-10 (interleukin-10, IL-10)等抗炎细胞因子，发挥免疫抑制作用[8-9]。在正常生理状态下 Treg/Th17 细胞处于动态平衡，共同维持机体的免疫稳态[10]。然而，在脊髓损伤等病理状态下这种平衡被打破，Th17 细胞功能亢进，Treg 细胞功能相对不足，导致过度炎症反应，加重脊髓损伤[11-12]。因此，调节 Treg/Th17 平衡成为治疗脊髓损伤的潜在靶点。

肠道菌群作为人体重要的“微生物器官”，近年来被发现与机体免疫系统及神经系统存在密切联系[13-14]。肠道菌群失衡不仅会影响肠道局部免疫，还可通过“肠-脑轴”影响中枢神经系统的免疫和炎症状态[15-16]。研究发现，肠道菌群可通过代谢产物及其衍生物与宿主相互作用，其中菌群代谢产生的芳香烃受体激动剂、短链脂肪酸(short chain fatty acids, SCFAs)及菌群衍生物脂多糖等对中枢神经系统炎症具有重要的调节作用[17-19]。SCFAs 是肠道菌群重要的代谢产物之一，正常人肠道每天产生的 SCFAs 为 50−100 mmol，由肠道产生的 SCFAs 不仅是宿主肠上皮细胞的首选能量代谢原料和细胞增殖分化的主要调控因子，还具有抗氧化、抗炎、抗肿瘤以及调控基因表达、调控宿主肠道免疫、改善肠道功能等多种重要作用[19-21]。已有文献报道，肠道菌群代谢产物 SCFAs 可与细胞表面的 G 蛋白偶联受体结合，通过调节 Treg/Th17 平衡调控宿主的免疫应答[22-24]。

姜黄素是一种从姜科植物根茎中分离出的黄橙色天然多酚类物质，具有抗炎、抗氧化、抗肿瘤和抑制细胞凋亡的作用[25-26]。研究发现，姜黄素在脊髓损伤[27]、阿尔茨海默病[28]、帕金

森病[29]等中枢神经系统疾病中具有显著的神经保护功能。此外，课题组前期研究表明，姜黄素在促进脊髓损伤修复的过程中能显著重塑肠道微生物群的结构和丰度，并提升其代谢产物SCFAs的水平[30-31]。基于以上研究基础，提出科学假说(图1)，姜黄素可能通过调控肠道菌群提高SCFAs的水平，进而影响Treg/Th17平衡，最终发挥其对脊髓损伤的修复作用。为此，本研究通过粪菌移植实验，结合实时荧光定量逆转录PCR检测(real-time RT-qPCR, RT-qPCR)、酶联免疫吸附(enzyme-linked immunosorbent assay, ELISA)和蛋白印迹分析(Western blotting)等技术，检测脊髓局部Treg和Th17细胞相关转录因子及炎症因子的表达，探讨姜黄素干预后的肠道菌群改善脊髓损伤的具体机制，为临床应用姜黄素治疗脊髓损伤提供理论基础和实验依据。

1 材料与方法

1.1 动物及实验分组

Specific pathogen free (SPF)级健康雌性SD大鼠，6周龄，体重200−220 g，购自西安交通大学，动物许可证：SCXK(陕)2018-001。大鼠置于动物房，室温25 ℃左右，适应性饲养2周，自由进食进水，每天给予大鼠12 h光照/12 h黑暗环境。先用随机数字表将动物分为2组：对照组和姜黄素(curcumin, CUR)组，每组8只。按照之前的经验，实验组每只大鼠每天灌胃100 mg/kg的姜黄素(Sigma-Aldrich公司)，对照组不做处理。于灌胃后的第14天收集新鲜粪便进行后续实验。然后，再用随机数字表将动物分为5组，

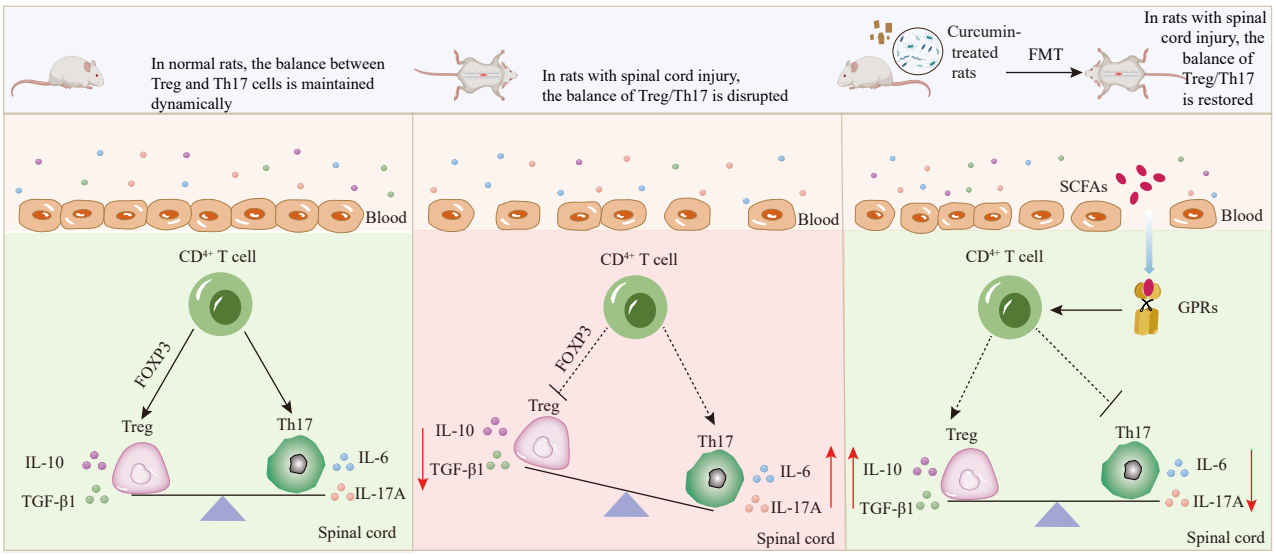

图1 Treg/Th17在3种大鼠模型体内的表达

Figure 1 Expression patterns of Treg and Th17 cells in three rat models. In normal rats, $CD4^+$ T cells can differentiate into Treg cells by inducing FOXP3 transcription, leading to the secretion of anti-inflammatory cytokines such as IL-10 and TGF-β1. Alternatively, $CD4^+$ T cells can differentiate into Th17 cells by inducing RORγt transcription, promoting the secretion of pro-inflammatory cytokines including IL-6 and IL-17A, thereby maintaining a dynamic balance between Treg and Th17 cells. After SCI, Th17 cell function becomes overactivated, Treg cell function is impaired, and the Treg/Th17 balance is disrupted, resulting in increased pro-inflammatory cytokines. FMT following curcumin intervention restores this balance in SCI rats, reducing inflammation and promoting immune homeostasis.

分别为假手术(sham operation, Sham)组、脊髓损伤(SCI)组、姜黄素组、粪菌移植(fecal microbiota transplantation, FMT)组、粪菌移植姜黄素(FMT+CUR)组，粪菌移植姜黄素加抑制剂(FMT+CUR+GLPG0974)组，每组各 5 只，假手术组仅打开椎板以暴露硬脊膜，不进行脊髓损伤操作(图 2)。FMT 组和 FMT+CUR 组，参考 Tian 等[32]的方法，进行为期 2 周的抗生素处理以清除原有肠道菌群后，行脊髓损伤术，术后每 2 d 灌胃 1 mL 供体粪便上清液。FMT+CUR+GLPG0974 组，参考 Akiba 等[33]的方法加入抑制剂并确定给药量。若试验过程中出现动物死亡情况，无法完成实验时应及时补充并重新制作模型。本研究所有动物实验获得延安大学动物伦理委员会批准，编号为 S-S20240038。

1.2 脊髓损伤模型建立

正式造模前，将所用手术器械和医用耗材进行无菌处理，同时准备医用酒精、碘伏、生理盐水、2% 戊巴比妥钠(上海山浦化工有限公司)、氨苄青霉素钠(武汉赛维尔生物科技有限公司)等。术前 12 h 大鼠禁食、禁水，正式造模在无菌环境下进行。将大鼠用戊巴比妥钠(15−40 mg/kg)进行腹腔麻醉，确定大鼠麻醉后，将其以俯卧位固定于操作台上，手指触摸寻找 T10 棘突，判断 T10 棘突位置，以此为中心，半径 3−5 cm 备皮。消毒后于此处切开皮肤约 1.5 cm，使用镊子、止血钳和眼科剪将浅筋膜及棘突边缘两侧竖脊肌和韧带分离。根据棘突方向确定 T10 位置：T9 棘突朝向尾侧，T10 棘突呈中立位，T11 棘突朝向头侧。使用止血钳提起 T10 棘突，

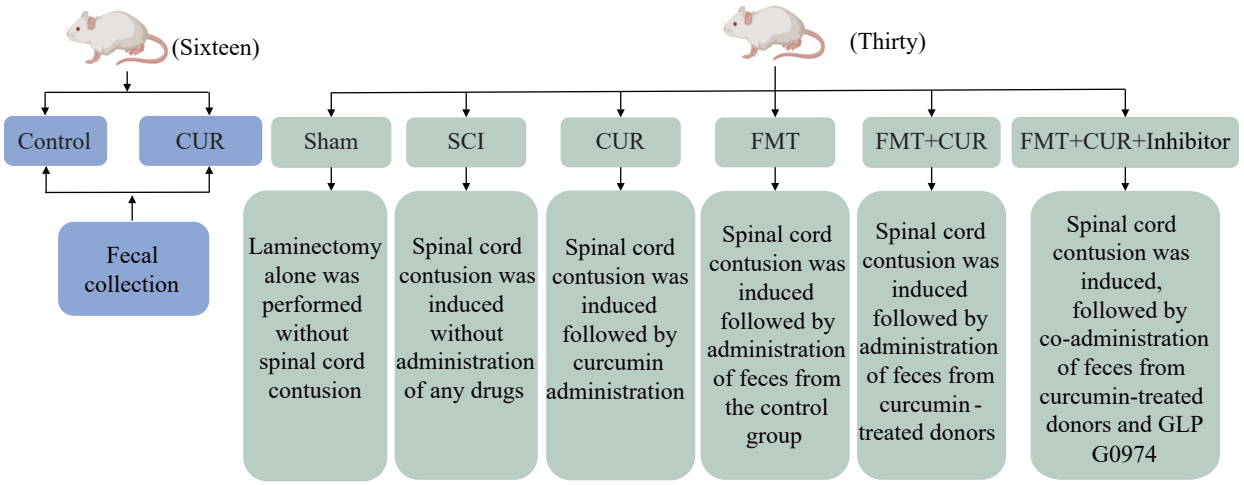

图2 动物实验分组

Figure 2 Grouping of animals in the experiment. This experiment consists of two parts. In the first part, 16 rats are divided into a control group and a curcumin group, with 8 rats in each group. The control group has free access to drinking water, while the experimental group is given intragastric administration of curcumin at a dose of 100 mg/kg per day, and feces of the two groups are collected after 14 days. In the second part, 30 rats are divided into 6 groups, with 5 rats in each group: The Sham group only has the lamina removed without spinal cord contusion; The SCI group receives no drug intervention; The CUR group is directly given intragastric administration of curcumin; The FMT group is given intragastric administration of gut microbiota from normal feces; The FMT+CUR group is given intragastric administration of gut microbiota from curcumin-intervened feces; The FMT+CUR+GLPG0974 group is given intragastric administration of gut microbiota from curcumin-intervened feces and GLPG0974.

并使用眼科剪逐步且轻缓地剪开 T10 和 T11 椎板之间的韧带。最后，利用精细咬骨钳逐步咬除 T10 椎板，从而暴露硬脊膜。将大鼠稳固于打击器台面，使用 IH-0400 脊髓打击器对 T10 进行力度为 200 千达因的打击。打击成功后，脊髓被打击部位出现充血现象，同时大鼠出现短暂的呼吸骤停，尾部出现摆尾反射，双下肢及躯体回缩样扑动，麻醉清醒后双下肢呈弛缓性瘫痪。将大鼠肌肉和皮肤逐层缝合，伤口消毒 3 次。对大鼠双后肢注射 5 mL 生理盐水，任意一侧后肢肌内注射青霉素钠 4×10^5 U/支，将大鼠置于电热毯上，待其苏醒后回笼饲养，每天 3 次人工排尿，直至大鼠实现自主排尿。保持 12 h 光照/12 h 黑暗，动物房温度控制在 25 ℃左右。

1.3 抗生素溶液

分别准确称量硫酸新霉素 1 g、盐酸万古霉素 0.5 g、氨苄青霉素钠 1 g 和甲硝唑 1 g，充分溶解于 900 mL 去离子水中，定容至 1 L，4 ℃保存备用[34]。

1.4 粪菌移植

收集的新鲜粪便，浸泡在无菌 PBS (1 粪便颗粒/mL)中约 15 min，匀浆，4 ℃、1 000 r/min 离心 5 min 以沉淀颗粒物，收集悬浮液，4 ℃、8 000 r/min 离心 5 min 以获得总细菌，将最终细菌悬浮液与终浓度为 20% 无菌甘油混合，然后储存在−80 ℃直至移植。调整悬浮液浓度，使其 OD_{600} 值为 0.5，在无菌 PBS 中对应约 10^8 CFU/mL[35]。

1.5 运动功能测试

根据 BBB 运动评定量表[36]评分评估后肢运动功能的恢复。该量表基于让大鼠在 100 cm 的场地中自由行走 5 min，同时密切观察后肢的运动和协调性。Sham 组、SCI 组、FMT 组和 FMT+CUR 组分别于术后 1、3、5、7、14、21 和 28 d 进行评估。该评分由 2 位熟练掌握细则但不参与本研究的其他人员进行，评估重复 3 次并立即记录。分数范围从 0 到 21，其中 0 表示无运动功能，21 表示正常。术后 28 d 进行足迹分析以评估步态和运动协调性[37]。在老鼠的前肢和后肢上涂上不同颜色的染料，然后将老鼠放在白纸上让其进行直线行走，重复实验 3 次并记录。

1.6 组织制备

术后 28 d，每组大鼠麻醉后灌注生理盐水。然后取损伤点上方和下方 2 cm 的脊髓，并在 4% 多聚甲醛(武汉赛维尔生物科技有限公司)中固定 48 h。梯度脱水后，将样品包埋在石蜡中，并切成 10 μm 厚的切片。

1.7 苏木精-伊红染色、尼氏染色和劳克坚牢蓝染色

按照苏木精-伊红染色(hematoxylin-eosin staining, HE)、尼氏染色(Nissl)和劳克坚牢蓝染色(Luxol Fast Blue, LFB)试剂盒(Solarbio 公司)的说明书，对切片进行染色，然后用梯度乙醇逐级脱水，最后将载玻片用二甲苯透明化，并用中性树胶(上海标本模型厂)封片。

1.8 实时荧光定量逆转录 PCR 检测

使用 M5 Total RNA Extraction Reagent (TRIgent) (北京聚合美生物科技有限公司)按照说明书从大鼠脊髓中分离提取总 RNA，用 RNA 逆转录酶反转录为 cDNA，RT-qPCR 检测 β-actin、IL-17A、IL-6、RORγt、TGF-β1 和 FOXP3 的 C_t 值。PCR 反应体系(20 μL)：Hieff® qPCR SYBR Green Master Mix (High Rox Plus) 10 μL，上、下游引物(10 μmol/L)各 0.4 μL，DNA 模板 2 μL，ddH_2O 7.2 μL。PCR 反应条件：95 °C 预变性 5 min；95 °C 变性 10 s，60 °C 退火 20 s，72 °C 延伸 20 s，40 个循环。反应使用 $2^{-\Delta\Delta C_t}$ 方法计算基因的相对表达量[38]。PCR 引物设计：从 GenBank 数据库检索大鼠源 β-actin、IL-17A、IL-6、RORγt、TGF-β1 和 FOXP3 mRNA 序列号及相应序列，设计 PCR 引物如表 1 所示。

1.9 酶联免疫吸附测定

称取脊髓组织，放入 900 mL 生理盐水中，超声研磨并以 3 000 r/min 离心 10 min 以获得脊

表1　本研究所用引物

Table 1　Primers used in this study

Primer names	Primer sequences (5′→3′)	Accession No.	Product length/bp
β-actin	F: CACTATCGGCAATGAGCGGTTC R: CAGCACTGTGTTGGCATAGAGG	NM_031144.3	154
FOXP3	F: AGAGAGGCAGAGGACACTCAATG R: GGTTGTGGCGGATGGCATTC	NM_001108250.2	104
IL-10	F: CCCTGGGAGAGAAGCTGAAGAC R: TCACCTGCTCCACTGCCTTG	NM_012854.2	96
TGF-β1	F: GACCGCAACAACGCAATCTATGAC R: CTGGCACTGCTTCCCGAATGTC	NM_021578.2	94
RORγt	F: ACCACCCTCTTCTCACGGG R: CTTCCATTGCTCCTGCTTTC	XM_017591313.3	190
IL-17A	F: CCTGATGCTGTTGCTGCTACTG R: GCGTTTGGACACACTGAACTTTG	NM_001106897.1	84
IL-6	F: GTTTCTCTCCGCAAGAGACTTC R: TCTCCTCTCCGGACTTGTGAA	NM_012589.2	96

髓组织匀浆。细胞因子包括 IL-10、IL-6 (武汉三鹰生物技术有限公司)、IL-17A (深圳欣博盛生物科技有限公司)，根据说明书通过 ELISA 试剂盒进行测量。最后，使用酶标仪检测吸光度值。根据标准曲线获得各细胞因子的浓度。

1.10　蛋白印迹分析

使用 RIPA 裂解缓冲液(上海碧云天生物技术股份有限公司)从脊髓组织中提取总蛋白样品，通过 BCA 蛋白检测试剂盒(武汉博士德生物工程有限公司)定量提取物中的蛋白质浓度，确定上样量后将每组样品上到凝胶中电泳，电泳结束后进行 PVDF (Merck Millipore 公司)转膜，5%脱脂奶粉(内蒙古伊利实业集团股份有限公司)封闭 2 h 后孵育一抗 FOXP3 抗体、IL-17A 抗体、TGF-β1 抗体(江苏亲科生物研究中心有限公司)；RORγt 抗体购自武汉博士德生物工程有限公司，4 ℃过夜孵育二抗(抗鼠、抗兔)，洗膜后，用化学发光试剂(北京索莱宝科技有限公司)观察蛋白质条带，最后通过 ImageJ 软件分析条带强度，并归一化为 β-肌动蛋白(武汉三鹰生物技术有限公司)的强度。

1.11　数据分析和统计

使用 GraphPad Prism 8.0 软件进行数据的统计分析及绘图。所有的实验结果均重复 3 次及以上后获得，数据结果以平均数±标准差展示，2 组数据之间的比较使用独立样本 *t* 检验，多组数据之间的比较使用单因素方差分析后，使用 Tukey’s 检验进行两两比较。$P<0.05$ 为差异有统计学意义。

2　结果与分析

2.1　姜黄素干预后的肠道菌群对脊髓损伤大鼠运动功能和组织形态的影响

为探究姜黄素干预后的肠道菌群对脊髓损伤大鼠运动功能和组织形态的影响，本研究开展了粪菌移植实验。将灌有姜黄素处理和正常饲养大鼠粪便的悬浮液灌饲至脊髓损伤大鼠体内，依据 BBB 评分量表评估大鼠 SCI 后双后肢运动功能恢复情况。BBB 评分结果显示，脊髓损伤后各组大鼠的评分均降为 0 分；随着时间的推移，SCI 组、CUR 组、FMT 组和 FMT+CUR 组的评分逐渐增加，且 CUR 组和 FMT+CUR 组的评分明显高于其他 2 组，但各组评分

依低于 Sham 组(图 3A)。步态分析结果显示，脊髓损伤后大鼠前、后爪运动协调性显著下降；与 SCI 组相比，CUR 组、FMT 组和 FMT+CUR 组大鼠后爪的步幅更长、后肢拖拽更短，表明

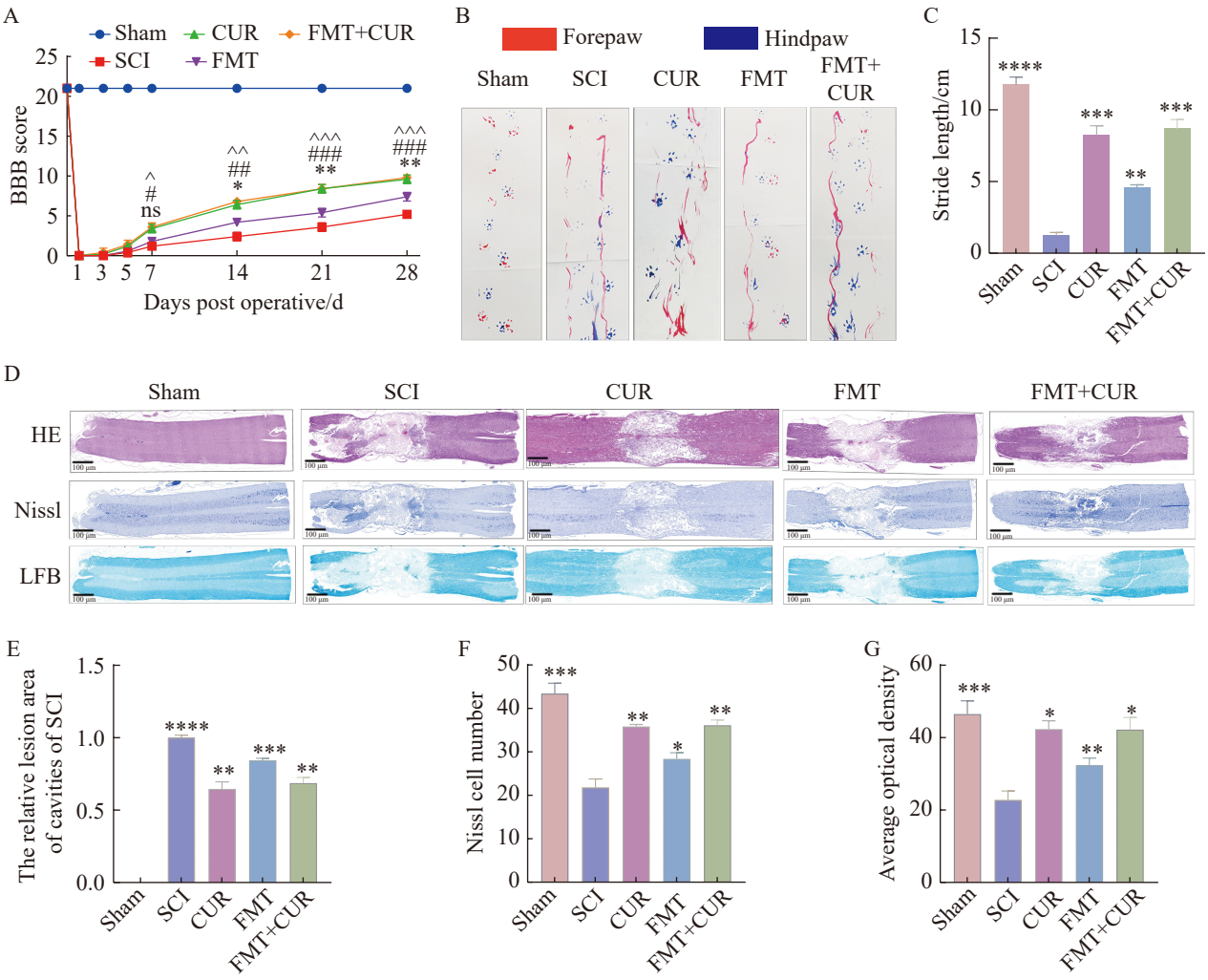

图3　姜黄素粪菌移植在脊髓损伤模型中的疗效

Figure 3　Therapeutic effects of curcumin-modulated FMT in a SCI rat model. A: BBB scores of rats in each group at different time points [$^{*}P$<0.05, $^{**}P$<0.01, SCI group *vs*. FMT group; ns: No significant difference; $^{\#}P$<0.05, $^{\#\#}P$<0.01, $^{\#\#\#}P$<0.001, SCI group *vs*. CUR group; $^{\wedge}P$<0.05, $^{\wedge\wedge}P$<0.01, $^{\wedge\wedge\wedge}P$<0.01, SCI group *vs*. FMT+CUR group (mean±SD, n=5)]; B: Representative footprint analysis of rats at 28 days after SCI [Blue: Forepaw prints; Red: Hindpaw prints (mean±SD, n=5)]; C: Qualitative analysis of hindpaw footprint length [(mean±SD, n=5); $^{*}P$<0.05, $^{**}P$<0.01, $^{***}P$<0.001, SCI group *vs*. other groups]; D: Hematoxylin-eosin (HE) staining, Nissl staining, and Luxol fast blue (LFB) staining of spinal cord sections at 28 days after SCI; E: Statistical analysis of HE staining [(mean±SD, n=5); $^{**}P$<0.01, $^{***}P$<0.001, $^{****}P$<0.000 1, Sham group *vs*. other groups]; F: Statistical analysis of Nissl staining [(mean±SD, n=5); $^{*}P$<0.05, $^{**}P$<0.01, $^{***}P$<0.001, SCI group *vs*. other groups]; G: Statistical analysis of LFB staining [(mean±SD, n=5); $^{*}P$<0.05, $^{**}P$<0.01, $^{***}P$<0.001, SCI group *vs*. other groups].

其步态恢复更快、运动协调性更好(图 3B−3C)。HE 染色结果显示，脊髓损伤后 4 周，CUR 组和 FMT+CUR 组的损伤区域和空洞明显少于 SCI 组和 FMT 组；Nissl 染色结果显示，CUR 组和 FMT+CUR 组神经元数量多于 SCI 组和 FMT 组；LFB 染色结果显示，CUR 组和 FMT+CUR 组髓鞘密度大于 SCI 组和 FMT 组(图 3D−3G)。以上数据表明，姜黄素干预后的肠道菌群能显著促进脊髓损伤大鼠的运动功能和组织形态学恢复。

2.2 姜黄素干预后的肠道菌群对 Treg 和 Th17 细胞的影响

为探究姜黄素干预后的肠道菌群对 Treg 和 Th17 细胞的影响，分别检测脊髓组织中 Treg 和 Th17 细胞相关转录因子 FOXP3、RORγt 及炎症因子 IL-10、TGF-β1、IL-17A 和 IL-6[39]在 RNA 和蛋白水平的表达。结果发现，在 RNA 水平上，与 SCI 组和 FMT 组相比，FMT+CUR 组的 FOXP3、IL-10 和 TGF-β1 的表达明显升高，而 RORγt、IL-17A 和 IL-6 的表达明显降低(图 4A−4F)。在蛋白水平上，采用 ELISA 和 Western blotting 2 种方法进行检测。ELISA 检测结果显示，与 SCI 组和 FMT 组相比，FMT+CUR 组 IL-10 的表达明显升高，而 IL-17A 和 IL-6 的表达明显降低(图 4G−4I)，Western blotting 检测结果显示，与 SCI 组和 FMT 组相比，FMT+CUR 组 RORγt 的表达明显降低，而 FOXP3 和 TGF-β1 的表达升高(图 4J−4M、图 5)，这些数据表明，经姜黄素干预后的肠道菌群可促进脊髓损伤大鼠体内 Treg 细胞的分化，同时抑制 Th17 细胞的活化。

2.3 姜黄素干预后的肠道菌群通过调节 Treg/Th17 平衡促进脊髓损伤恢复

据报道，短链脂肪酸可通过 G 蛋白偶联受体调节免疫细胞的分化[40]。实验结果表明，姜黄素可使短链脂肪酸中乙酸的浓度增加[30]，而乙酸又可与 GPR43 受体结合发挥免疫作用[41]。为进一步验证姜黄素是否通过肠道菌群调节短链脂肪酸中乙酸的浓度水平，进而影响 Treg/Th17 平衡，促进脊髓损伤修复，在粪菌移植的同时加入 GPR43 受体的抑制剂 GLPG0974[33,42]。通过 Western blotting 和 ELISA 检测发现，加入抑制剂后 Treg 和 Th17 相关炎症因子及转录因子的表达发生逆转，RORγt、IL-17A 和 IL-6 的蛋白表达升高，而 FOXP3、TGF-β1 和 IL-10 的表达降低(图 5、图 6A−6C)。基于以上数据，提出姜黄素通过短链脂肪酸调节 Treg/Th17 平衡促进脊髓损伤的恢复。

3 讨论与结论

本研究通过体内实验系统探究了姜黄素、肠道菌群与 Treg/Th17 平衡之间的复杂调控关系在脊髓损伤修复中的关键作用。这一发现为神经-免疫-肠道菌群轴在脊髓损伤修复中的作用机制提供了新的实验依据。传统的神经损伤修复研究主要聚焦于神经细胞自身的再生能力、神经生长因子的作用以及炎症反应对神经组织的直接影响等方面，而本研究将研究视角拓展到了肠道菌群这一新兴领域。研究发现，姜黄素能够重塑肠道菌群结构，增加有益菌的丰度，减少有害菌的数量，进而改善肠道微生态环境。这种改变不仅局限于肠道局部，还通过一系列复杂的信号传导机制，远程调控机体的免疫反应，特别是对 Treg/Th17 平衡进行精准调节。这一过程涉及肠道菌群代谢产物的介导作用，如短链脂肪酸等物质在免疫细胞分化和功能调节中发挥关键作用，为神经损伤修复过程中免疫调节机制的研究提供了全新视角。未来研究可从多个层面深入探究姜黄素的作用机制。在分子机制层面，应进一步研究姜黄素与肠道菌群之间的直接相互作用，明确姜黄素影响肠道菌群代谢和基因表达的具体分子靶点。通过高通量测序技术和代谢组学分析，全面揭示姜黄素干预后肠道菌群的基因表达谱和代谢产物谱的变化，筛选出关键的分子标志物和代谢通路。

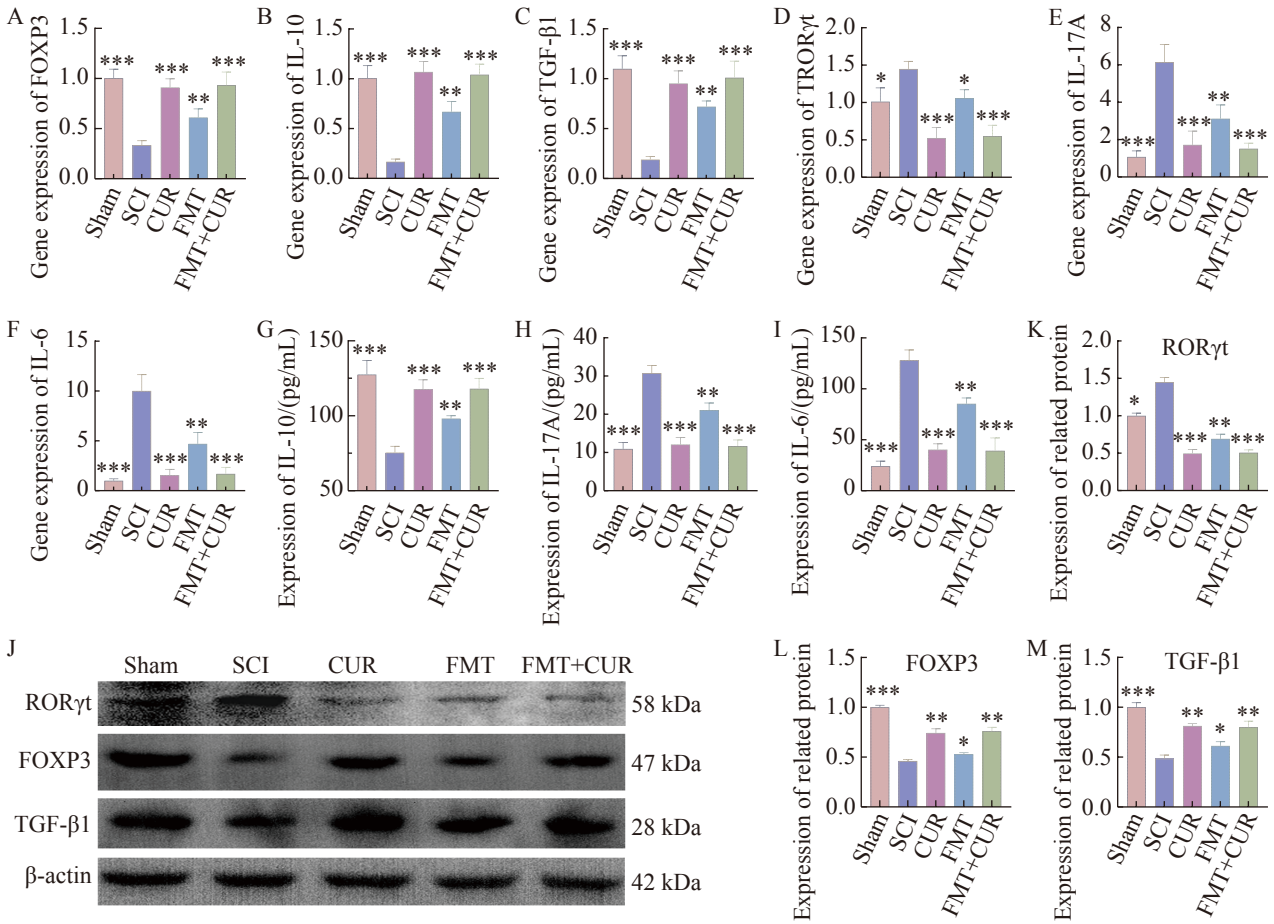

图4　姜黄素粪菌移植对Treg和Th17细胞的影响

Figure 4　Effects of curcumin-modulated FMT on Treg and Th17 cell-associated markers in spinal cord tissues. A: Statistical chart of the RNA-level expression of FOXP3, a transcription factor related to Treg cells, in rat spinal cord tissues detected by RT-qPCR; B: Statistical chart of the RNA-level expression of IL-10, an inflammatory factor related to Treg cells, in rat spinal cord tissues detected by RT-qPCR; C: Statistical chart of the RNA-level expression of TGF-β1, an inflammatory factor related to Treg cells, in rat spinal cord tissues detected by RT-qPCR; D: Statistical chart of the RNA-level expression of RORγt, a transcription factor related to Th17 cells, in rat spinal cord tissues detected by RT-qPCR; E: Statistical chart of the RNA-level expression of IL-17A, an inflammatory factor related to Th17 cells, in rat spinal cord tissues detected by RT-qPCR; F: Statistical chart of the RNA-level expression of IL-6, an inflammatory factor related to Th17 cells, in rat spinal cord tissues detected by RT-qPCR; G: Statistical chart of the protein-level expression of IL-10 in rat spinal cord tissue homogenates detected by ELISA; H: Statistical chart of the protein-level expression of IL-17A in rat spinal cord tissue homogenates detected by ELISA; I: Statistical chart of the protein-level expression of IL-6 in rat spinal cord tissue homogenates detected by ELISA; J: Analysis of the changes in protein expression levels of TGF-β1, FOXP3 and RORγt in rat spinal cord tissues detected by Western blotting; K: Statistical analysis chart of the protein-level expression of RORγt in rat spinal cord tissues; L: Statistical analysis chart of the protein-level expression of FOXP3 in rat spinal cord tissues; M: Statistical analysis chart of the protein-level expression of TGF-β1 in rat spinal cord tissues. All data are presented as mean±SD (n=3). $^{*}P$<0.05, $^{**}P$<0.01, $^{***}P$<0.001 in other groups *vs*. SCI group.

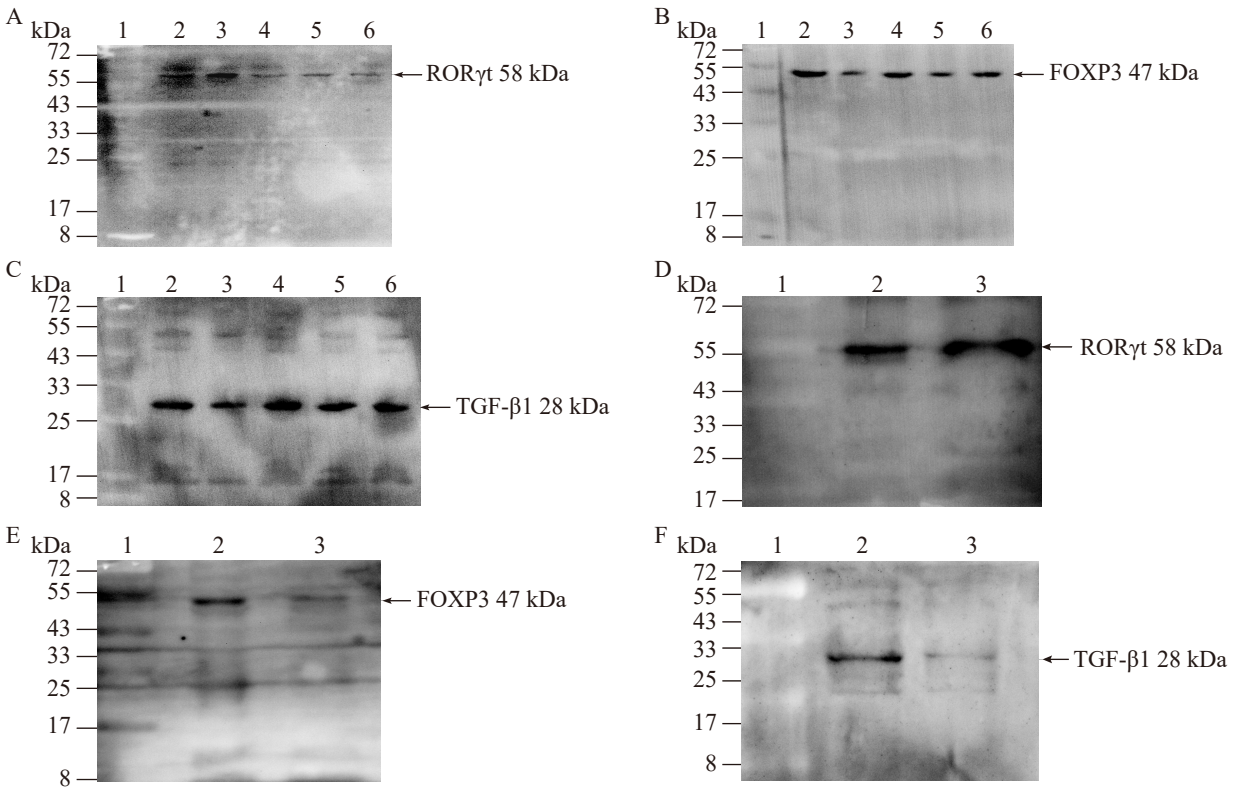

图5 Western blotting原图

Figure 5 Original Western blotting images. A: Original RORγt image corresponding to Figure 4J; B: Original FOXP3 image corresponding to Figure 4J; C: Original TGF-β1 image corresponding to Figure 4J; D: Original RORγt image corresponding to Figure 6B; E: Original FOXP3 image corresponding to Figure 6B; F: Original TGF-β1 image corresponding to Figure 6B.

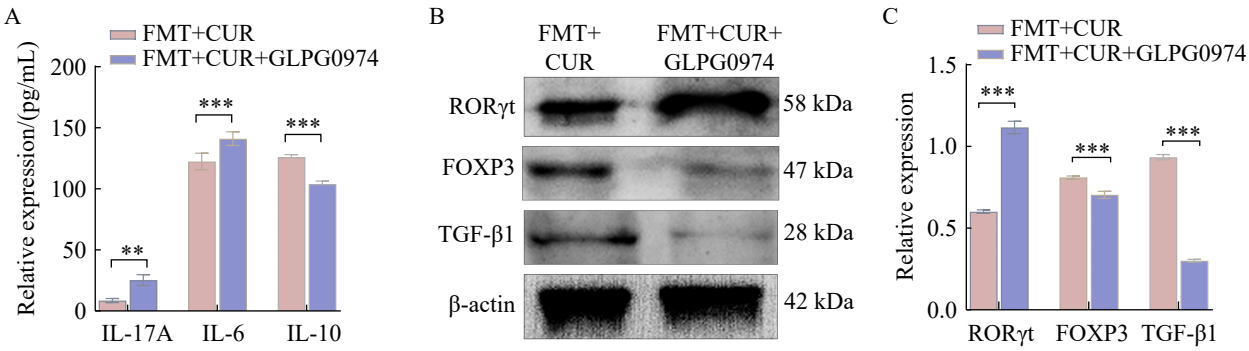

图6 姜黄素通过肠道菌群调节Treg/Th17细胞分化

Figure 6 Curcumin regulates Treg/Th17 cell differentiation *via* modulation of the gut microbiota. A: Statistical graphs of the protein expression levels of IL-10, IL-17A, and IL-6 in rat spinal cord tissue homogenates detected by ELISA; B: Analysis of the changes in protein expression levels of TGF-β1, FOXP3, and RORγt in rat spinal cord tissues; C: Statistical analysis chart of the protein-levels expression of RORγt, FOXP3, and TGF-β1 in rat spinal cord tissues. All data are presented as mean±SD (n=3). $^{*}P$<0.05, $^{**}P$<0.01, $^{***}P$<0.001 in other groups *vs*. SCI group.

深入研究姜黄素调节 Treg/Th17 平衡过程中涉及的细胞内信号传导通路，如 Wnt/β-catenin 信号通路、Notch 信号通路等的作用，明确这些信号通路之间的相互调控关系，为进一步阐明姜黄素的作用机制提供理论依据[43-44]。在细胞间通讯层面，研究肠道上皮细胞、免疫细胞与肠道菌群之间的信号交流在姜黄素调节 Treg/Th17 平衡中的作用。探索肠道上皮细胞如何感知肠道菌群的变化并将信号传递给免疫细胞，以及免疫细胞如何通过分泌细胞因子和趋化因子调节肠道菌群的组成和功能。在基因调控层面，利用基因编辑技术，如 CRISPR/Cas9 系统，研究关键基因在姜黄素调节脊髓损伤修复中的功能[45]。通过敲除或过表达相关基因，观察姜黄素对脊髓损伤修复、肠道菌群调节和 Treg/Th17 平衡的影响，深入揭示基因调控在这一过程中的作用机制。

作者贡献声明

田春平：数据收集与监管，撰写文章；吴佳俊：验证，软件程序，数据分析；肖林峰：执行调研，验证；王青燕：执行调研，方法论；杜嘉妮：执行调研，监督管理；胡倩倩：监督管理；强京灵：方法论；常小卫：提供资源，项目管理，获取基金；杨彦玲：提出概念，提供资源，项目管理，获取基金。

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