论著·基础医学

隔日限食通过调控肠道菌群促进小胶质细胞M2型活化减轻脊髓损伤后继发性神经炎症

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[摘要] **目的** 脊髓损伤(spinal cord injury,SCI)后肠道菌群紊乱可通过肠-脑轴影响小胶质细胞活化并加剧继发性神经炎症,隔日限食(every-other-day fasting,EODF)虽能重塑肠道菌群、促进小胶质细胞M2型活化并改善SCI后神经炎症,但其是否依赖肠道菌群发挥作用尚不明确。本研究基于伪无菌(gut microbiota depletion,GMD)模型与粪菌移植(fecal microbiota transplantation,FMT)模型,探讨EODF能否通过调控肠道菌群促进SCI后小胶质细胞M2型活化,进而减轻继发性炎症。**方法** 采用随机数字表法对89只5~6周龄,体质量160~180 g的健康雄性SPF级SD大鼠进行分组。GMD组(饮用联合抗生素水,n=6)与正常饮食(ad libitum,AL)组(饮用灭菌水,n=6)干预14 d后采集大鼠粪便,通过16S rDNA高通量测序进行GMD模型验证;通过正常饮食(AL组,n=12)与隔日限食(EODF组,n=20)干预4周后分别制备正常饮食粪菌移植液(AL-FMT)和隔日限食粪菌移植液(EODF-FMT);45只大鼠采用C5右侧半钳夹的方法在GMD模型的基础上建立SCI模型,分为假手术(Sham)组、正常饮食(AL-SCI)组、隔日限食(EODF-SCI)组、移植正常菌群(AL-FMT-SCI)组及移植隔日限食菌群(EODF-FMT-SCI)组,每组9只,干预28 d。通过16S rDNA高通量测序分析肠道菌群;每周记录各组大鼠的摄食量与体质量;采用梳理试验评估上肢运动功能;ELISA法检测血清脑源性神经营养因子(brain-derived neurotrophic factor,BDNF)、IL-4、脂多糖(lipopolysaccharide,LPS)水平;Western blotting检测M1型小胶质细胞标记物iNOS和M2型小胶质细胞Arg-1的相对表达及脊髓组织炎症相关蛋白IL-1β、TNF-α的相对表达。**结果** 与AL组相比,GMD组的α与β多样性均显著降低(P<0.05),在科水平上,GMD组*Bacteroidaceae*等菌群相对丰度均显著降低(P<0.05),GMD大鼠模型构建成功;在SCI模型中,与EODF-SCI组和AL-SCI组相比,EODF-FMT-SCI组的产短链脂肪酸(short-chain fatty acids,SCFAs)相关菌群相对丰度增加,且与AL-FMT-SCI组相比,EODF-FMT-SCI组显著增加了*Bacteroidaceae*、*Lactobacillus gasseri*等有益菌的相对丰度;EODF-FMT-SCI组术后14 d体质量与术后7 d形成显著差异(P<0.05);术后14 d,EODF-FMT-SCI组的梳理实验评分已较术后第3天显著提高(P<0.05),术后7、14、28 d,EODF-FMT-SCI组梳理实验评分显著高于AL-SCI组(P<0.05);与EODF-SCI组和AL-SCI组相比,EODF-FMT-SCI组血清IL-4、BDNF含量显著增加,LPS含量降低,脊髓组织中IL-1β蛋白与TNF-α蛋白相对表达下降(P<0.05),EODF-FMT-SCI组脊髓组织iNOS蛋白相对表达明显下调,Arg-1蛋白相对表达明显上调(P<0.05),且EODF-FMT-SCI组脊髓组织Arg-1蛋白相对表达水平显著高于AL-FMT-SCI组(P<0.05)。**结论** EODF可能通过重塑肠道菌群,促进SCI后小胶质细胞M2型活化,从而减轻继发性炎症,促进运动功能恢复。

[关键词] 隔日限食;肠道菌群;粪菌移植;脊髓损伤;小胶质细胞M2型活化

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Every-other-day fasting alleviates secondary neuroinflammation after spinal cord injury by modulating gut microbiota to promote microglial M2 polarization

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[**Abstract**] **Objective** Gut microbiota dysbiosis after spinal cord injury (SCI) can affect microglial activation and exacerbate secondary neuroinflammation *via* the gut-brain axis. Although every-other-day fasting (EODF) reshapes gut microbiota, promotes microglial polarization toward the M2 phenotype, and ameliorates neuroinflammation after SCI, whether it exerts these effects depending on gut microbiota remains unclear. Using a pseudo-germ-free (gut microbiota depletion, GMD) model and fecal microbiota transplantation (FMT), this study aims to investigate whether EODF promotes microglial M2 polarization after SCI by modulating gut microbiota, thereby alleviating secondary inflammation. **Methods** A total of 89 healthy male SPF grade SD rats (age 5 to 6 weeks, weighing 160 to 180 g) were randomly divided into groups. The GMD group (drinking antibiotic cocktail, n=6) and the ad libitum (AL) group (drinking sterilized water, n=6) were treated for 14 d before rat feces were collected for 16S rDNA high-throughput sequencing to validate the GMD model. Normal diet fecal microbiota transplantation (AL-FMT) and EODF-FMT were prepared after 4 weeks of intervention with normal diet (AL, n=12) and EODF (n=20), respectively. 45 rats were subjected to C5 right-sided hemiclamp SCI modeling on the basis of the GMD model, and then divided into a Sham group, an AL-SCI group, an EODF-SCI group, an AL-FMT-SCI group, and an EODF-FMT-SCI group, with 9 rats in each group. All of the above interventions lasted for 28 d. Gut microbiota was analyzed by 16S rDNA high-throughput sequencing. Food intake and body weight of rats in each group were recorded weekly. Upper limb motor function was evaluated using grooming test. Serum levels of brain-derived neurotrophic factor (BDNF), IL-4, and lipopolysaccharide (LPS) were measured by ELISA. The protein levels of the M1 microglial marker iNOS and the M2 microglial marker Arg-1, as well as the levels of the spinal cord tissue inflammation-related proteins IL-1β and TNF-α, were detected by Western blotting. **Results** Compared with the AL group, both α-diversity and β-diversity were significantly decreased in the GMD group (P<0.05). At the family level, the relative abundances of *Bacteroidaceae* and other microbiota were markedly reduced in the GMD group (P<0.05), indicating successful establishment of the GMD model. In the SCI model, compared with the EODF-SCI and AL-SCI groups, the relative abundances of short-chain fatty acids (SCFAs)-producing microbiota were increased in the EODF-FMT-SCI group, whereas compared with the AL-FMT-SCI group, the EODF-FMT-SCI group exhibited significantly increased relative abundances of beneficial bacteria such as *Bacteroidaceae* and *Lactobacillus gasseri*. A significant difference in body weight was observed in the EODF-FMT-SCI group between 14 and 7 d postoperatively (P<0.05). In the grooming test, the scores at 7 d postoperatively were significantly higher in the EODF-FMT-SCI group than those at 3 d after surgery (P<0.05), and the scores at 7, 14 and 28 d after surgery in the EODF-FMT-SCI group were obviously higher than those in the AL-SCI group at corresponding time points (P<0.05). Compared with the EODF-SCI and AL-SCI groups, the EODF-FMT-SCI group showed significantly increased serum levels of IL-4 and BDNF, decreased LPS content, and reduced protein levels of IL-1β and TNF-α in the spinal cord tissues (P<0.05), downregulated expression of iNOS and upregulated expression of Arg-1 in the spinal cord tissues (P<0.05). Furthermore, the expression level of Arg-1 protein in the spinal cord tissue was significantly higher of the EODF-FMT-SCI group than that of the AL-FMT-SCI group (P<0.05). **Conclusion** EODF may alleviate secondary inflammation and promote motor

functional recovery by reshaping gut microbiota and promoting microglial M2 polarization after SCI.

[**Key words**] every-other-day fasting; gut microbiota; fecal microbiota transplantation; spinal cord injury; microglial M2 activation

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脊髓损伤(spinal cord injury,SCI)是一种致残率高、预后差的中枢神经系统创伤性疾病,常导致严重的运动、感觉及自主神经功能障碍,给患者家庭和社会带来沉重的经济负担[1-2]。目前SCI临床治疗重点在于减轻继发性损伤,其中继发性神经炎症是导致损伤扩大和神经再生障碍的关键环节[3]。小胶质细胞作为脊髓固有免疫细胞,在SCI后被激活并活化为促炎M1型或抑炎M2型,参与了SCI继发性神经炎症的整个过程[4-5]。推动小胶质细胞M2表型活化,是减轻神经炎症、促进功能恢复的潜在策略[6-7]。

SCI后常常伴随肠道菌群紊乱[8-9],这种紊乱的肠道菌群通过"肠-脑轴"与中枢神经系统进行双向通信,可以影响小胶质细胞的活化状态,从而加剧神经炎症[9-11]。隔日限食(every-other-day fasting,EODF)作为一种间歇性禁食模式,已被证明可改善代谢、增强抗炎能力,并能重塑SCI后紊乱的肠道菌群[12-14]。前期研究发现,EODF可促进SCI大鼠运动功能恢复,增加脊髓M2型小胶质细胞比例,降低血清炎症因子水平[15-16]。然而,EODF是否通过调节肠道菌群来调控小胶质细胞活化,减轻继发性炎症,尚不清楚。

因此,本研究构建伪无菌(gut microbiota depletion,GMD)大鼠SCI模型,并通过粪菌移植(fecal microbiota transplantation,FMT)干预,探讨EODF能否经由肠道菌群调控小胶质细胞M2活化,从而改善SCI后继发性炎症。研究结果有望为基于饮食干预或菌群制剂的减轻SCI后的继发性炎症治疗提供新的实验依据。

1 材料与方法

1.1 实验动物与伦理

健康雄性SPF级SD大鼠89只,5~6周龄,体质量160~180 g,购自成都达硕实验动物有限公司(许可证号:SCXK川2025-0030)。大鼠分笼饲养于独立通风笼具系统,环境条件为温度21.0 ℃、湿度55.9%、压差12 Pa。所有动物自由摄食、饮水,适应性饲养7 d后通过随机数字表法进行分组。实验方案经西部战区总医院动物伦理委员会批准(2021EC4-83),实验过程遵循"3R"原则,使用戊巴比妥钠腹腔注射麻醉,尽可能减轻动物痛苦。预期的不良事件有体质量下降、腹泻、活动减少等,每日3次观察大鼠一般情况,如出现严重腹泻、明显呼吸困难等状态立即予以腹腔注射戊巴比妥钠(150 mg/kg)安乐死。

1.2 主要试剂

万古霉素(Y25829)、甲硝唑(S17079)、氨苄青霉素钠(S17018)、新霉素硫酸盐(S17028)购自四川博杰瑞生物公司;NEBNext Ultra Ⅱ DNA Library Prep Kit for Illumina(NEB#E7645L)购自美国New England Biolabs公司;Hiseq Rapid SBS Kit v2测序试剂盒(FC-402-4023 500 Cycle)购自美国Illumina公司;大鼠IL-4、BDNF、LPS ELISA试剂盒均购自上海江莱公司。BCA蛋白浓度测定试剂盒购自江苏凯基公司;全蛋白提取试剂盒、彩虹180广谱蛋白Marker购自北京索莱宝公司;β-actin(13E5)Rabbit mAb购自美国CST公司;iNOS兔多克隆抗体(bs-0162R)购自北京博奥森公司;Arg-1兔多克隆抗体(ab91279)、IL-1β兔多克隆抗体(ab283818)购自英国Abcam公司;TNF-α兔多克隆抗体(17590-1-AP)购自武汉三鹰公司。

1.3 实验方法

1.3.1 抑制肠道菌群建立GMD模型 为了构建GMD模型,将12只大鼠分为正常饮食(ad libitum,AL)组和GMD组(n=6)。2组均自由饮食,AL组饮用高温灭菌水,GMD组饮用联合抗生素水(antibiotic cocktail,ABX)(万古霉素0.5 g/L、新霉素1 g/L、氨苄西林1 g/L、甲硝唑1 g/L),连续喂养14 d。

1.3.2 制备FMT 单独饲养32只大鼠,分为AL组(n=12)与EODF组(n=20)。AL组不受限制进食,EODF组以24 h禁食与24 h自由进食交替进行,持续4周。干预结束后,分别收集2组新鲜粪便,每颗粪粒溶解于2 mL无菌PBS溶液中,在4 ℃下以6 000×g离心20 min,收集上清粪菌液与30%甘油等体积混合,制备成AL-FMT与EODF-FMT,分别冻存于-80 ℃冰箱中备用。

1.3.3 SCI模型的建立与干预 45只大鼠预先给予上述ABX饮水14 d以构建GMD状态,在此基础上采用C5右侧半钳夹方法建立SCI模型:以1.5%的戊

巴比妥钠(3.3 mL/kg)腹腔麻醉，行椎板切除暴露C5脊髓，使用70 g夹闭力的动脉瘤夹(FT228T型)钳夹C5右侧脊髓组织30 s，可见局部血肿形成，随后逐层缝合。术后1 d将出现患侧前肢呈杵状、身体向患侧倾斜、提尾悬空侧前肢无法向前下方伸直视为造模成功。脊髓损伤组共36只，Sham组共9只。Sham组仅切除椎板，不损伤脊髓。术后每只大鼠给予腹腔注射生理盐水(1 mL)，1次/d，共持续3 d，防止大鼠术后脱水和电解质紊乱。

脊髓损伤组进一步分为4组，每组9只：正常饮食(AL-SCI)组，自由无菌饮食饲养加生理盐水灌胃；隔日限食(EODF-SCI)组，术后即刻开始EODF干预加生理盐水灌胃；移植正常菌群(AL-FMT-SCI)组，自由无菌饲养加AL-FMT灌胃；移植隔日限食菌群(EODF-FMT-SCI)组，予自由无菌饲养加EODF-FMT灌胃。Sham组自由无菌饲养并予以生理盐水灌胃。实验流程见图1。

1.4　观察指标

1.4.1　摄食量及体质量监测　　分别记录各组大鼠于SCI造模术前1 d及术后7、14、21、28 d体质量及摄食量情况。对于EODF-SCI组，本研究将第1天上午10点至第2天上午10点定义为进食日，将第2天上午10点至第3天上午10点定义为断食日。各组均为每2日进行1次投食，EODF-SCI组在断食日拿走食物。大鼠每日平均摄食量=(该笼投食量−剩余量)÷2÷该笼大鼠只数。

1.4.2　行为学评价　　采用梳理实验评估SCI大鼠前肢运动功能。于造模前7 d进行适应性训练。正式测试时，将大鼠置于透明圆筒(半径10 cm，高30 cm)内，向其头背部滴加生理盐水诱导理毛行为，并用固定数码相机记录15 min。分别于术前1 d，术后3、7、14、28 d进行测试。由3名不知晓分组的研究人员根据视频对大鼠患侧前肢活动范围进行独立评分。评分标准为：患侧前肢无梳理活动，0分；患侧前肢活动范围在鼻平面以下，1.0分；患侧前肢活动范围能够达鼻平面到双眼水平面以下，2.0分；患侧前肢活动范围能够达双眼水平面，3.0分；患侧前肢活动范围在眼水平面以上至双耳水平面以下，3.5分；患侧前肢活动范围能够达两耳水平面，4.0分；患侧前肢活动范围能够达双耳后，5.0分。

1.4.3　16S rDNA高通量测序对肠道菌群分析　　分别收集伪无菌造模术后14 d及脊髓损伤术后28 d各组的粪便样本，采用Zymo Research BIOMICS DNA Microprep Kit对正常对照组与伪无菌模型组的粪便样本gDNA纯化并检测其完整性，使用Tecan F200进行浓度检测。使用引物515F(5'-GTGYCAGCMGCCGCGGTAA-3')和806R(5'-GGACTACHVGGGTWTCTAAT-3')对细菌16S rDNA基因的V4区进行PCR扩增。使用illumina Miseq测序仪通过PE250测序方式进行测序。运用QIIME2对测序数据进行分析及质量控制，本部分测序实验由成都罗宁生物科技有限公司协助完成。①群落组成分析：将高度相似的序列聚类为操作分类单元(operational taxonomic unit，OTU)，绘制Venn图及物种相对丰度柱状图(科、种水平)，并通过稀释曲线评估测序深度。②α多样性分析：采用Chao1指数和Shannon指数进行评估，反映微生物丰富度与均匀度。③β多样性分析：基于Bray-Curtis距离和Jaccard距离进行主坐标分析(principal coordinates analysis，PCoA)，比较组间微生物群落结构差异。

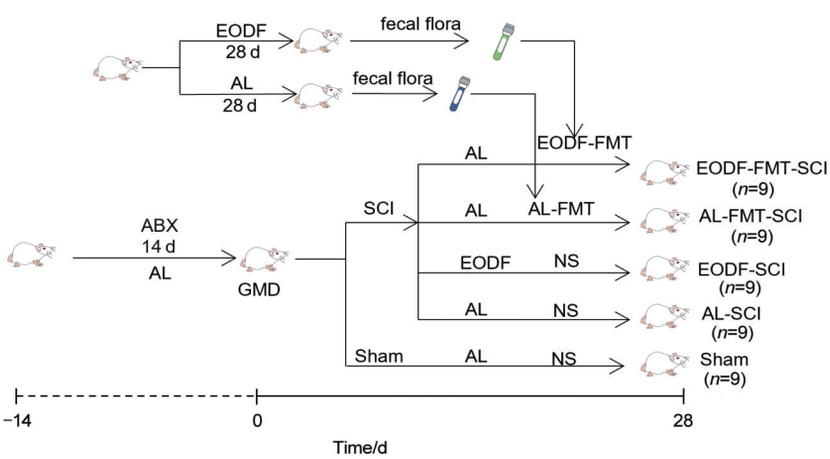


图1　基于粪菌移植探究隔日限食调控小胶质细胞表型改善脊髓损伤的实验流程

Figure 1　Flowchart of experimental procedures in exploring the ameliorative mechanism of every-other-day fasting (EODF) on spinal cord injury (SCI) by regulating microglial phenotype based on fecal microbiota transplantation (FMT)

1.4.4 ELISA检测血清中炎症与神经营养因子水平 于脊髓损伤术后28 d使用心脏采血法采集新鲜血液,使用血清严格按照大鼠脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)、脂多糖(lipopolysaccharide,LPS)、IL-4水平ELISA试剂盒说明书进行操作,于450 nm波长处测定*OD*值。根据标准品浓度与[$OD_{(450)}$]值绘制标准曲线,计算各样本中因子浓度。

1.4.5 Western blotting检测脊髓中炎性蛋白与小胶质细胞表型蛋白表达 于脊髓损伤术后28 d取新鲜脊髓组织,使用蛋白提取试剂盒提取总蛋白,BCA法测定浓度。每孔上样10 μg总蛋白,经SDS-PAGE电泳分离后转至PVDF膜。用5%脱脂牛奶室温封闭1 h,随后加入相应一抗:iNOS(1∶1 000)、Arg-1(1∶1 000)、TNF-α(1∶1 000)、IL-1β(1∶1 000)及β-actin(1∶5 000),4 ℃孵育过夜。TBST洗膜后,加入对应二抗在室温中孵育1 h,ECL显影。采用Image J软件分析条带灰度值,以目的蛋白与β-actin的灰度比值表示相对表达量。

1.5 统计学分析

肠道菌群测序数据的分类学注释在QIIME2中完成,其余菌群数据的转换与分析使用R软件(4.0.5)。其他实验数据采用SPSS 26.0及GraphPad Prism 9.0进行统计分析与作图。计量资料以$\bar{x}\pm s$表示。体质量、摄食量及梳理实验涉及分组与时间采用重复测量的方差分析,若二者存在交互作用,进行多因素的简单效应分析[17]。其余实验结果多组之间比较采用单因素方差分析(ANOVA),组间两两比较采用LSD-*t*检验。以*P*<0.05为差异具有统计学意义。

2 结果

2.1 联合抗生素饮水可以建立GMD模型

AL组与GMD的肠道菌群结果如图2所示。Venn图分析显示,2组共有OTU总数为290个,其中AL组独有126个OUT,GMD组独有9个OTU,2组共有155个OTU(图2A)。与AL组相比,GMD组的OTU总数减少了117个,提示其菌群丰度显著降低(图2B)。稀释曲线显示,2组测序深度充足,且GMD组OTU数量明显低于AL组,进一步证实其菌群丰富度大幅降低。α多样性分析显示,GMD组Chao1指数和Shannon指数均显著低于AL组(*P*<0.000 1,图2C、D),说明其物种丰富度与多样性均受到显著抑制。β多样性分析使用基于Bray-Curtis距离与Jaccard距离的PCoA,二者均显示AL组与GMD组的样本点各自聚集且完全分离,表明2组间肠道菌群的整体结构存在显著差异(图2E、F)。在科水平上看,与AL组相比,GMD组*Bacteroidaceae*、*Peptostreptococcaceae*、*Clostridiaceae* 1、*Lachnospiraceae*等菌群相对丰度均显著降低(*P*<0.05,图2G、H),几近耗竭。以上结果显示,连续14 d的联合抗生素饮水干预能够有效、显著地降低大鼠肠道菌群的多样性,并改变其群落结构,表明成功构建了GMD大鼠模型。

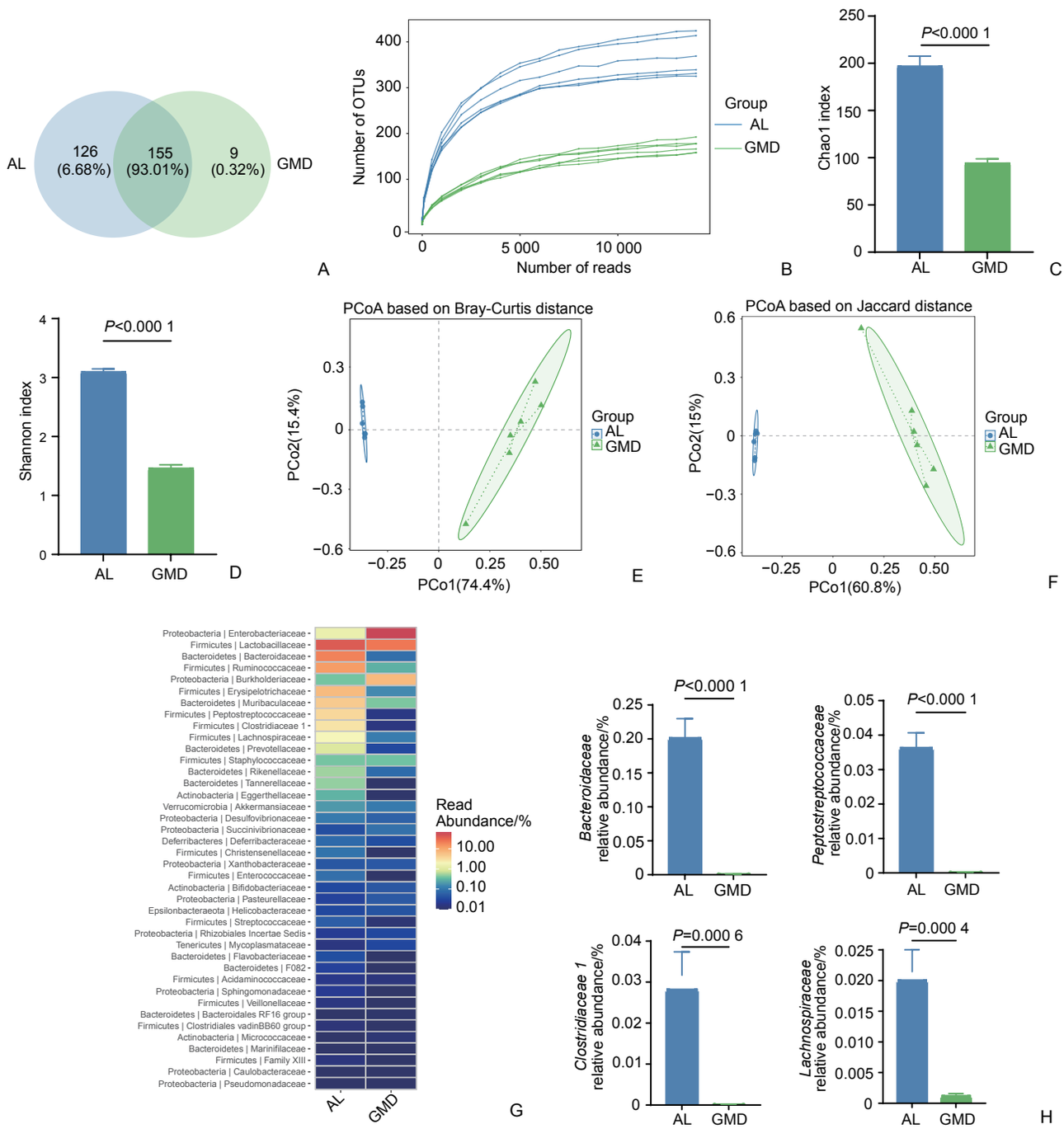
2.2 EODF-FMT对SCI后肠道菌群的重塑作用

各组大鼠粪便16S rDNA测序分析结果如图3所示。稀释曲线分析表明,各组菌群丰度相似,各组测序深度充足(图3A)。PCoA图结果显示,EODF-FMT-SCI组、AL-FMT-SCI组与Sham组的样本点聚集更为紧密,表明其菌群结构相似度较高(图3B)。在科水平上(图3C、D),与AL-SCI组相比,EODF-FMT-SCI组中*LachnosPiraceae*、*Prevotellaceae*、*Rikenellaceae*等菌群相对丰度显著增加(*P*<0.05);同时,EODF-FMT-SCI组中*Bacteroidaceae*丰度也显著高于AL-FMT-SCI组及EODF-SCI组(*P*<0.05,图3E、F)。在种水平上,与AL-SCI组相比,EODF-FMT-SCI组中*Lactobacillus gasseri*显著增加,而*Helicobacter apodemus*显著减少(*P*<0.05);此外,EODF-FMT-SCI组*Lactobacillus gasseri*丰度也显著高于AL-FMT-SCI组(*P*<0.05)。以上结果表明,移植经EODF干预的肠道菌群,能够有效富集有益菌群,并减少潜在致病菌,从而正向调控SCI后的肠道微生态紊乱。

2.3 EODF-FMT可以通过调整摄食量控制体质量

在摄食量结果中,分组与时间存在显著交互作用(*F*=4.117,*P*<0.000 1),进一步分析显示:在术后7 d,除Sham组外其余4组摄食量均显著低于术前(*P*<0.05,图4A);EODF-SCI组在术后7、14 d均显著低于其余4组(*P*<0.05),随着实验进程发展,EODF-SCI组在进食日的摄食量逐渐增加,在21 d显著低于除EODF-FMT-SCI组外的其余3组(*P*<0.05),至术后28 d,该组摄食量仍显著低于Sham组(*P*<0.05)。

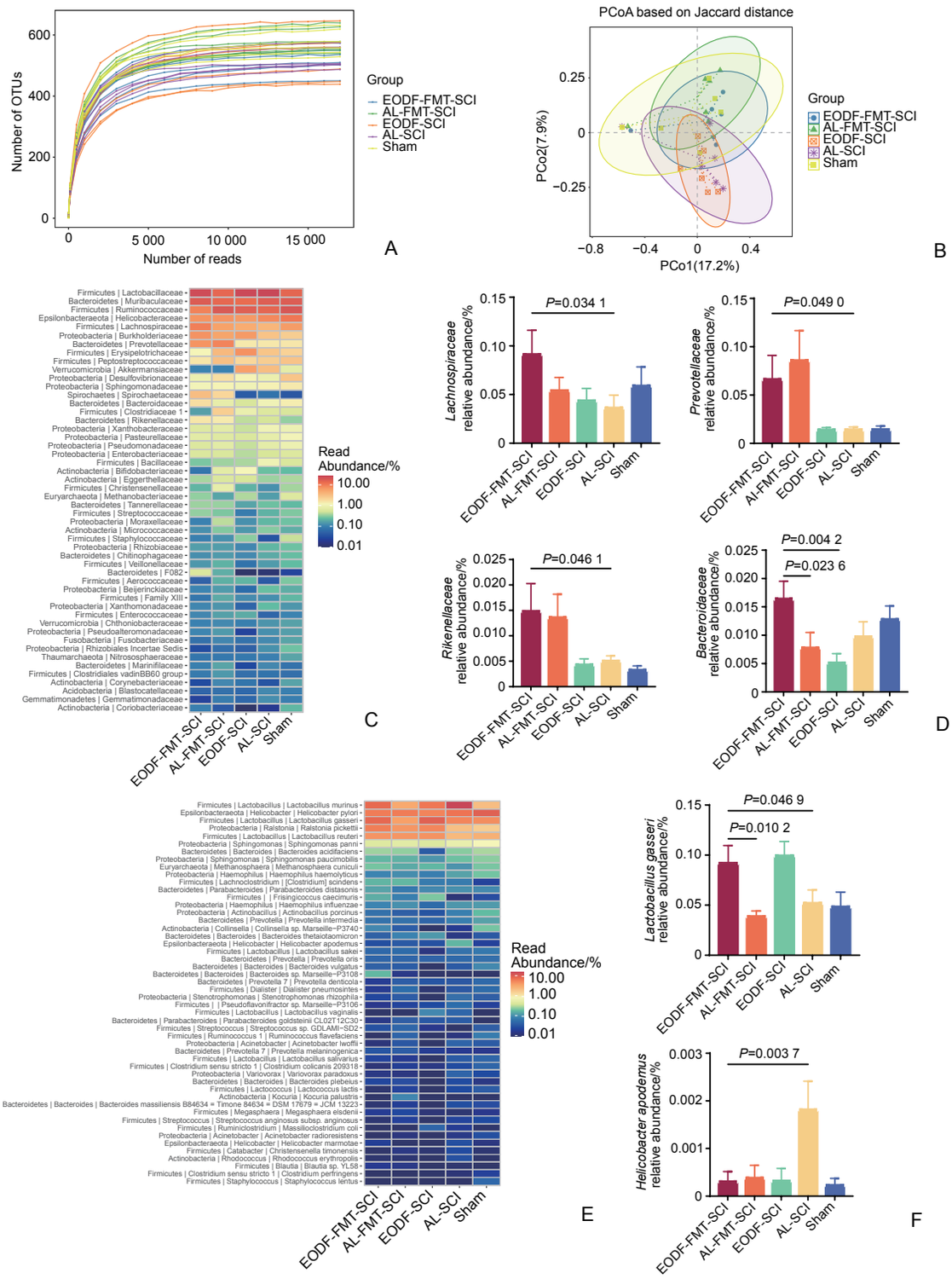
在体质量结果中,分组与时间不存在交互作用[*F*=1.844,*P*=0.145,*F*(时间)=61.509,*P*<0.000 1,*F*(分组)=0.795,*P*=0.555],进一步分析显示:各组大鼠体质量术后7 d与术前相比,EODF-SCI组明显降低(*P*<0.05,图4B),其余4组体质量变化差异无统计学意义。随时间进展各组体质量均逐渐增加,EODF-FMT-SCI组术后14 d体质量先与术后7 d形成显著差异(*P*<0.05),术后28 d各组体质量均与术后7 d形成显著差异(*P*<0.05)。以上结果表明,EODF及EODF-FMT均可以调整进食节奏从而改善代谢和控制体质量,且不会导致营养不良。



A: Venn diagram showing shared and unique operational taxonomic units (OTUs) between the 2 groups; B: Rarefaction curve reflecting sequencing depth and species richness between the 2 groups; C: Box plot of the Chao1 index evaluating gut microbiota richness between the 2 groups; D: Box plot of the Shannon index evaluating gut microbiota evenness between the 2 groups; E: Scatter plot of principal coordinates analysis (PCoA) based on Bray-Curtis distance displaying β-diversity of gut microbiota between the 2 groups; F: Scatter plot of PCoA based on Jaccard distance displaying β-diversity of gut microbiota among groups; G: Stacked bar chart of mean family-level abundance among groups using 16S rDNA sequencing; H: Relative abundance of *Bacteroidaceae*, *Peptostreptococcaceae*, *Clostridiaceae* 1, *Lachnospiraceae*

图2 联合抗生素饮水成功建立伪无菌大鼠模型(n=6,$\bar{x}\pm s$)

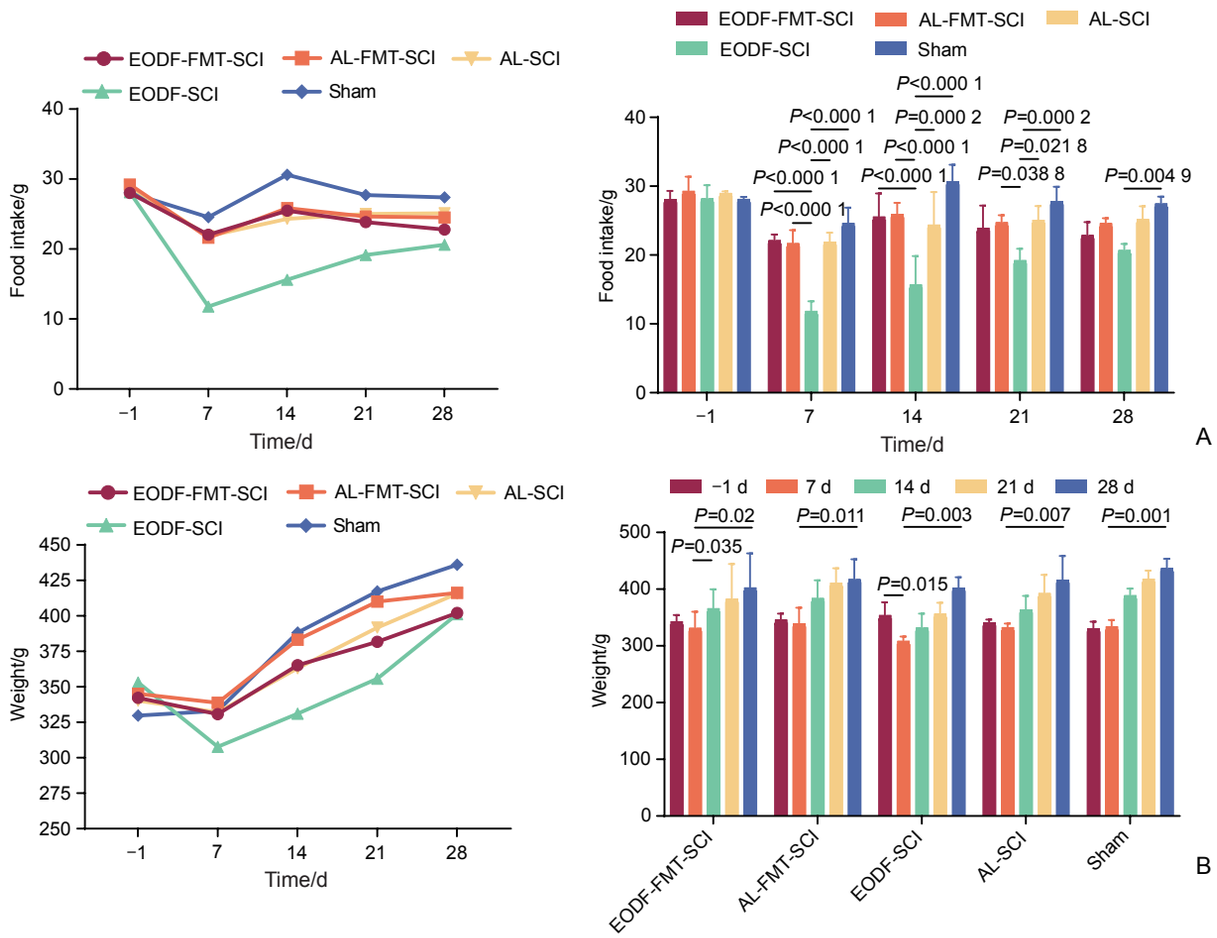
Figure 2 Establish of a rat model of pseudo-germ-free (gut microbiota depletion, GMD) by drinking antibiotic cocktail (n=6,$\bar{x}\pm s$)



A: Rarefaction curve reflecting sequencing depth and species richness among groups; B: Scatter plot of PCoA based on Jaccard distance displaying β-diversity of gut microbiota among groups; C: Stacked bar chart of mean family-level abundance among groups using 16S rDNA sequencing; D: Comparison of relative abundances of *Lachnospiraceae*, *Prevotellaceae*, *Rikenellaceae* and *Bacteroidaceae* in each group at the family level; E: Stacked bar chart of mean species-level abundances among groups using 16S rDNA sequencing; F: Comparison of relative abundances of *Lactobacillus gasseri* and *Helicobacter apodemus* in each group at the species level

图3 隔日限食粪菌移植重塑脊髓损伤后大鼠肠道菌群结构(n=6,$\bar{x}\pm s$)

Figure 3 Fecal microbiota transplantation (FMT) from every-other-day fasting (EODF) rats reshapes gut microbiota structure after spinal cord injury (SCI) (n=6,$\bar{x}\pm s$)



A: Food intake changes in each group; B: Body weight changes in each group

图4 隔日限食粪菌移植可以调整摄食量与体质量(n=3,$\bar{x}\pm s$)

Figure 4 EODF-FMT regulates food intake and body weight in rats(n=3,$\bar{x}\pm s$)

2.4 EODF-FMT可改善运动功能

各组大鼠前肢运动功能分析时间与分组存在显著交互作用(F=18.47,P<0.000 1),进一步分析显示:在术后3、7、14、28 d,与Sham组相比,其余4组大鼠患侧前肢运动功能均显著下降(P<0.05),提示C5半钳夹SCI模型构建成功。在术后7 d,EODF-FMT-SCI组梳理实验评分显著高于AL-SCI组(P<0.05);在术后14、28 d,EODF-FMT-SCI组梳理实验评分显著高于EODF-SCI组与AL-SCI组(P<0.05)。从时间维度看,各组前肢运动功能均随时间逐渐提高,在术后14 d,EODF-FMT-SCI组与AL-FMT-SCI组的梳理实验评分已较各自术后第3天显著提高(P<0.05,图5)。以上结果表明,接受EODF-FMT的大鼠,其SCI后前肢运动功能恢复更早、更显著。

2.5 EODF-FMT改善全身及局部炎症反应

各组大鼠血清及脊髓组织的炎症相关指标结果如图6所示。与sham组相比,AL-SCI组大鼠血清BDNF含量显著降低,而LPS含量显著升高(P<0.05);同时,其脊髓组织中促炎因子IL-1β与TNF-α的蛋白表达显著上调(P<0.05),表明SCI后全身及局部炎症反应均被激活。与EODF-SCI组及AL-SCI组相比,EODF-FMT-SCI组的大鼠表现出全面的抗炎与神经营养效果:血清中抗炎因子IL-4与BDNF的含量显著增加,而LPS水平显著降低(P<0.05);同时,脊髓组织中IL-1β与TNF-α的蛋白表达也显著下调(P<0.05)。上述结果表明,EODF-FMT能有效调控SCI后的异常免疫反应,减轻全身内毒素负荷与局部脊髓炎症。

2.6 EODF-FMT促进小胶质细胞向M2表型活化

各组大鼠脊髓组织中M1型标志物iNOS与M2型标志物Arg-1的表达如图7所示。结果显示,与Sham组相比,AL-SCI组脊髓组织iNOS、Arg-1蛋白表达显著增高(P<0.05),提示SCI后小胶质细胞被广泛激活。在脊髓损伤各组中,与EODF-SCI组及AL-SCI组相比,EODF-FMT-SCI组与AL-FMT-SCI组均表现出显著的

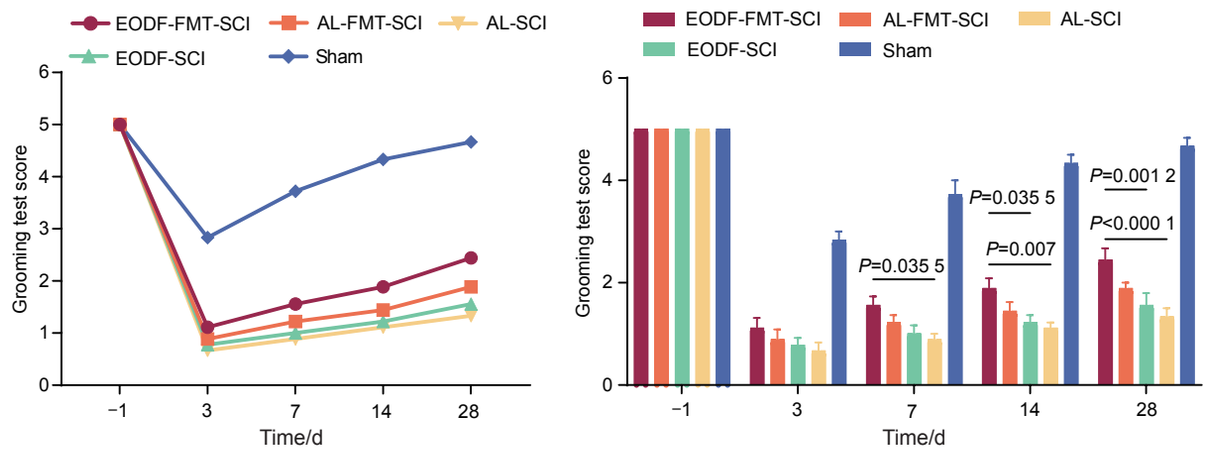
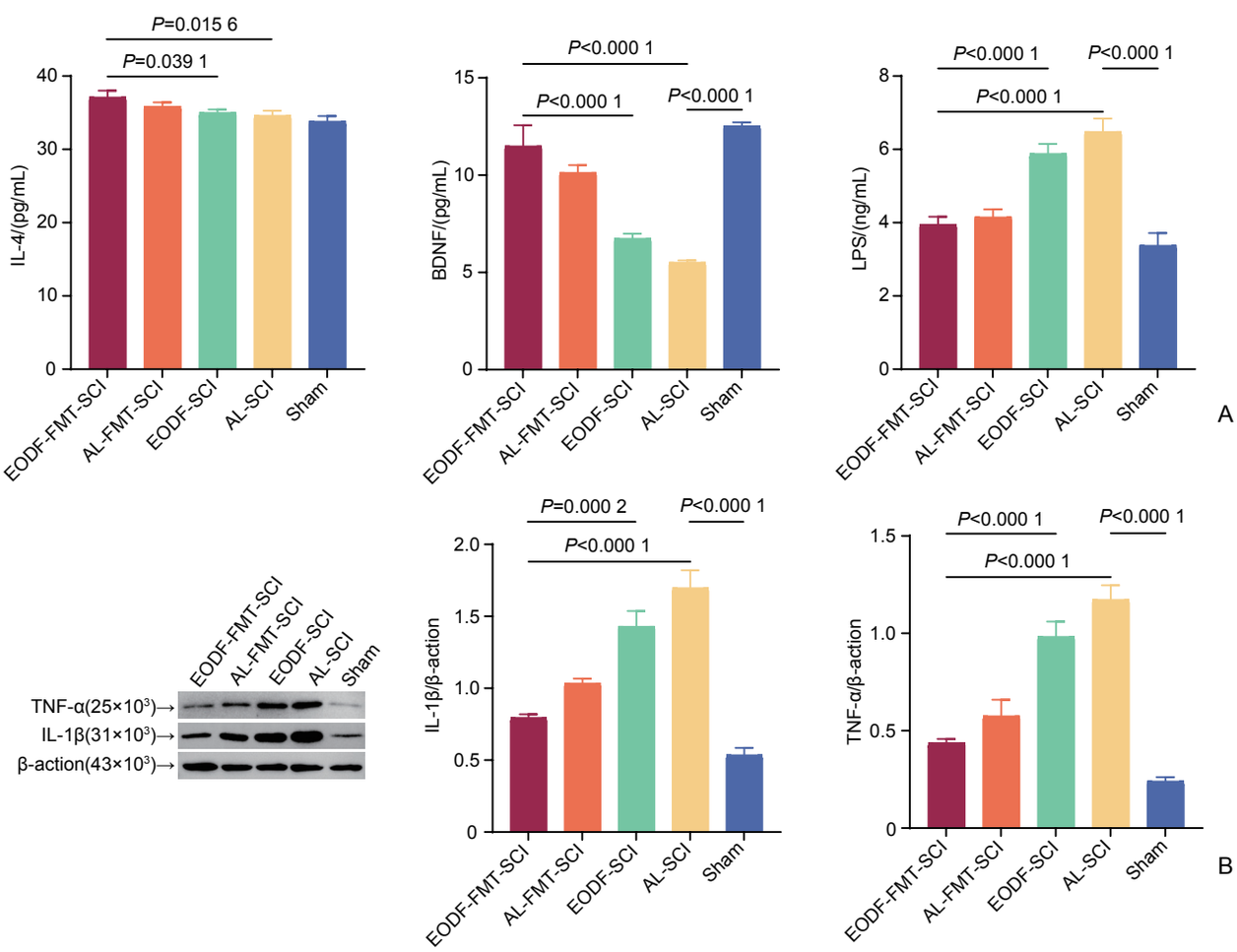


图5　隔日限食粪菌移植改善脊髓损伤大鼠的运动功能(n=9,$\bar{x}\pm s$)

Figure 5　EODF-FMT improves the motor function of SCI rats(n=9,$\bar{x}\pm s$)



A: Serum contents of IL-4, LPS and BDNF in rats of each group by ELISA (n=6,$\bar{x}\pm s$); B: Relative expression levels of TNF-α and IL-1β in spinal cord tissues in rats of each group by Western blotting(n=3,$\bar{x}\pm s$)

图6　隔日限食粪菌移植改善全身及局部的炎症反应

Figure 6　EODF-FMT ameliorates systemic and local inflammatory responses

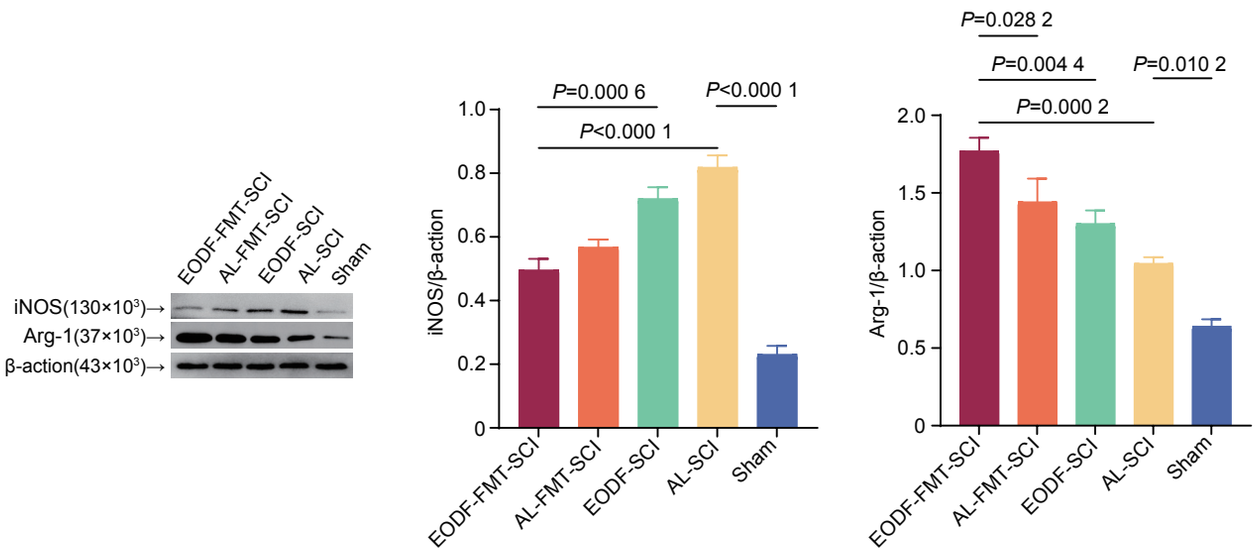


图7 隔日限食粪菌移植促进小胶质细胞M2型活化(n=3,$\bar{x}\pm s$)

Figure 7 EODF-FMT promotes microglial M2 activation (n=3,$\bar{x}\pm s$)

活化调控作用:其iNOS蛋白表达明显下调,而Arg-1蛋白表达显著增加(P<0.05);尤为重要的是,EODF-FMT-SCI组脊髓组织Arg-1蛋白表达水平显著高于AL-FMT-SCI组(P<0.05)。以上结果表明,FMT,特别是EODF-FMT,能有效促进SCI后小胶质细胞由促炎的M1表型向抑炎的M2表型活化。

3 讨论

SCI后继发性神经炎症是导致神经功能持续恶化的重要病理环节,如何减轻继发性损害是目前治疗的重点。越来越多的研究发现,紊乱的肠道菌群影响了SCI后的功能恢复[18],肠道菌群的调节干预成为干预SCI的新靶点[9, 18-19]。本研究创新性地在GMD大鼠模型中发现,EODF的神经保护作用与完整的肠道菌群非常相关;移植经EODF干预后的肠道菌群可重塑受损的肠道微生态,促进小胶质细胞向抑炎的M2表型活化,进而减轻炎症反应并促进运动功能恢复。

3.1 EODF改善SCI预后依赖一些重要的肠道菌群

本研究中,GMD大鼠菌群检测结果显示:与AL组相比,GMD组的OTU总数减少了117个。在科水平上,*Lactobacillaceae*、*Ruminococcaceae*、*Erysipelotrichaceae*、*Peptostreptococcaceae*、*Clostridiaceae* 1、*Lachnospiraceae*等菌群相对丰度明显减少,濒临耗竭,以上菌群均属于厚壁菌门,是肠道菌群的核心菌群,是短链脂肪酸(short-chain fatty acids,SCFAs),特别是丁酸的重要生产者[20]。前期研究报道EODF可以促进SCI后的运动功能恢复、减轻继发性炎症,而本研究中,在GMD模型基础上,EODF-SCI组在行为学、血清IL-4、BDNF和LPS含量、小胶质细胞活化情况上与AL-SCI组无明显统计学差异。这表明,在大部分肠道菌群被清除的情况下,EODF对SCI的改善作用十分有限,进一步支持EODF的神经保护效应主要依赖于完整的肠道菌群来实现。本研究与前人研究结果一致,LI等[21]在EODF干预饮食性肥胖小鼠的研究中发现,EODF显著改善了其肥胖与肝脂肪变性,但在微生物消耗的小鼠中并未发挥作用,使用EODF-FMT后,在微生物消耗的小鼠中再次展示出EODF在代谢中的有益作用;再次表明EODF发挥作用的关键是依赖一些重要的肠道菌群。

3.2 EODF-FMT重塑肠道菌群并复现了神经保护作用

本研究结果显示,EODF-FMT干预28 d后,GMD大鼠SCI后的肠道菌群紊乱得到重塑,产生SCFAs的菌群如*Lachnospiraceae*、*Prevotellaceae*、益生菌如*Lactobacillus gasseri*等有益菌相对丰度增加,*Helicobacter apodemus*显著减少(P<0.05)。*Lachnospiraceae*属于厚壁菌门,具有改善肠道健康、调节黏膜屏障等作用,可以减轻炎症、改善代谢综合征与糖尿病等[22-23]。*Lactobacillus gasseri*作为一种常见的乳杆益生菌,具备拮抗致病菌、缓解便秘与腹痛等作用[24-25]。*Helicobacter apodemus*是革兰阴性菌,其外膜产生LPS,在免疫或屏障受损时与胃肠道炎症与肿瘤相关,具有跨胃-肠多部位定植和潜在致病能力[26]。在本研究中,移植EODF-FMT比移植AL-FMT显著增加了*Bacteroidaceae*、*Lactobacillus gasseri*等有益菌的相对丰度。*Bacteroidaceae*可以维持肠道屏障稳定,发挥抗炎及调节免疫稳态的作用[20]。

以上结果表明,EODF-FMT可以重塑肠道菌群。

本研究结果显示,EODF-FMT-SCI组大鼠在上肢运动功能恢复更早更显著,且EODF-FMT-SCI组脊髓组织Arg-1蛋白表达水平显著高于AL-FMT-SCI组、EODF-SCI组及AL-SCI组(P<0.05)。在改善炎症方面,EODF-FMT-SCI组与AF-FMT-SCI组未表现出明显差异。这可能与样本量较少有关,但这也与既往研究一致,移植AL-FMT也可以改善SCI预后[9,27]。EODF-FMT不仅重塑了SCI大鼠的肠道菌群,还增加了*Bacteroidaceae*、*Lactobacillus gasseri*等有益菌的相对丰度,这可能也是EODF-FMT-SCI组在SCI后的恢复优于AL-FMT-SCI组的原因。以上结果表明,EODF-FMT可以复现EODF在SCI大鼠中的神经保护作用。

3.3 潜在机制:肠道菌群通过"菌群-代谢物-小胶质细胞"轴调控小胶质细胞活化

本研究中,EODF-FMT显著富集产SCFAs的菌群:*Lachnospiraceae*是醋酸盐、丙酸盐、丁酸盐的主要生产者之一,*Prevotellaceae*可生成乙酸与琥珀酸,*Bacteroidaceae*可产生醋酸和丙酸,三者还能通过菌群间"交叉喂养"网络协同生成丁酸盐[20,28-30]。SCFAs可通过多途径直接调控小胶质细胞向M2型活化:一是结合肠黏膜神经末梢FFAR2受体,经迷走神经调控小胶质细胞激活[31];二是通过血脑屏障或MCT1、MCT4转运体被小胶质细胞摄取,促进抗炎基因转录、上调M2型表型[31-33]。LPS作为革兰阴性菌细胞壁主要成分,可激活TLR4信号通路,调控NF-κB、MyD88等相关因子,诱导小胶质细胞向M1型活化[34]。而SCFAs可通过促进黏液分泌、收紧上皮紧密连接等方式增强肠屏障,减少LPS入血[35],与本研究EODF FMT-SCI组血清LPS显著降低的结果一致;此外,LPS可破坏BBB及PVB屏障完整性,直接作用于中枢,进一步促进小胶质细胞M1型活化。SCFAs可重塑血脑屏障紧密连接及肌动蛋白细胞骨架(claudin-5、ZO-1等)[36],间接抑制小胶质细胞M1型活化。综上,EODF-FMT富集的特定菌群可升高SCFAs、降低LPS,SCFAs直接促进小胶质细胞M2型活化,同时通过减少LPS间接抑制其M1型活化,实现对小胶质细胞表型的调控。

在本研究中,EODF-FMT增加了产生SCFAs的菌群相对丰度,通过"菌群-代谢物-小胶质细胞"轴调控小胶质细胞活化,这可能也是EODF-FMT改善SCI预后的机制之一。

3.4 本研究的局限性与未来展望

本研究亦存在以下局限:首先,本研究虽然观察到了菌群结构的改变与小胶质细胞活化表型及神经行为改善的相关性,但对菌群如何调控脊髓小胶质细胞活化以及小胶质细胞如何通过具体的分子机制或神经环路影响下游行为的机制阐释仍不够充分;其次,未直接检测肠道及中枢神经系统中SCFAs等关键菌群代谢物水平,未能明确介导该效应的具体关键菌株或关键代谢产物;最后,样本量相对有限,可能影响部分组间比较的统计效力。

未来的研究应扩大样本量,并整合宏基因组、代谢组和转录组等多组学技术,系统筛选EODF干预后产生的关键有益菌株及其特征性代谢产物。进一步通过菌株定植、代谢物补充或特异性受体拮抗等实验,在体内外验证其作用及具体分子机制。最终,推动基于EODF调控的个性化菌群制剂走向临床转化研究,为SCI患者继发性炎症治疗提供新的治疗策略。

综上所述,本研究证实了肠道菌群在介导EODF神经保护效应中的重要地位。通过FMT技术,EODF调控后的肠道菌群可作为一个"功能单元",在受体中发挥其促进修复的多重效益。这为将饮食干预转化为易于临床应用的菌群制剂提供了强有力的实验依据,具有重要的转化潜力。

利益冲突 本文所有作者声明不存在利益冲突

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