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·综 述·

粪菌移植治疗神经系统疾病的研究进展

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摘 要：肠道微生物与中枢神经系统的功能密切相关，可通过神经途径、免疫途径及微生物代谢物等在肠-脑轴作用下影响宿主大脑。肠道微生物失调与抑郁症、阿尔兹海默症、帕金森病等神经系统疾病的发生发展密切相关，并且粪菌移植可以改善神经系统疾病动物模型或临床患者的症状。本文对人体肠道菌群的组成、功能以及菌群通过肠-脑轴与神经系统疾病的联系进行综述，并对粪菌移植在治疗神经系统疾病的研究进展和作用机制进行探讨，为临床治疗神经疾病提供了新思路。

关键词：肠道菌群；肠-脑轴；粪菌移植；神经系统疾病；临床治疗

Advances in the application of fecal microbiota transplantation for the treatment of nervous system diseases

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Abstract: The intestinal microbiota exhibits a strong correlation with the function of the central nervous system, exerting influence on the host brain through neural pathways, immune pathways, and microbial metabolites along the gut-brain axis. Disorders in the composition of the intestinal microbial are closely associated with the onset and progression of neurological disorders, such as depression, Alzheimer's disease, and Parkinson's disease. It has been proven that fecal microbiota transplantation can improve symptoms in animal models of neurological diseases and clinical patients. This paper provides a comprehensive review of the composition and function of the human intestinal microbiota, as well as the intricate the relationship between

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the human intestinal microbiota and nervous system diseases through the gut-brain axis. Additionally, it delves into the research advancements and underlying mechanism of fecal microbiota transplantation in the treatment of nervous system diseases. These findings offer novel insights and potential avenues for clinical interventions targeting nervous system diseases.

Keywords: intestinal microbiota; gut-brain axis; fecal microbiota transplantation; nervous system diseases; clinic treatment

人体的肠道微生物组成复杂，微生物数量超 100 万亿，在正常生理条件下，肠道菌群相互影响，对维持宿主肠道平衡和健康起着重要的作用[1]。肠道菌群和中枢神经系统之间存在双向交流，即菌群可以通过“肠-脑轴”作用于大脑进而影响神经系统的活动，神经系统受到刺激也会在菌群中有所反馈[2]。研究表明，抑郁症、阿尔茨海默病(Alzheimer’s disease, AD)、帕金森病(Parkinson’s disease, PD)和孤独症谱系障碍(autism spectrum disorder, ASD)等疾病的发生通常伴随着肠道菌群的失调。因此，除临床药物治疗外，研究人员一直致力于通过对肠道菌群的调节来改善神经系统疾病的症状。

粪菌移植(fecal microbiota transplantation, FMT)是临床上一种便捷、高效、副作用少的治疗方法，通过将健康人群粪便中的菌群移植给患者，使患者异常的肠道微生物群恢复，目前在肠易激综合征(irritable bowel syndrome, IBS)的治疗中得到广泛应用[3]。基于神经系统和肠道菌群间的相互作用，近年来科学家开始尝试将 FMT 作为其新的治疗手段。本文结合“肠道微生物-肠-脑轴”的功能，主要探讨了 FMT 在神经性疾病治疗中的应用和作用机制，并对未来神经性疾病治疗的研究思路做出了展望。

1 肠道微生物概述

肠道微生物由人体肠道内的全部生物群落组成，成年人肠道内微生物约 1 000 多种，超过 99%都是细菌，其余的为真菌和病毒。细菌包括拟杆菌门(Bacteroidetes)、双歧杆菌属(*Bifidobacterium*)等有益菌，以及金黄色葡萄球菌(*Staphylococcus aureus*)等有害菌，优势菌门有厚壁菌门(Firmicutes)、放线菌门(Actinobacteria)、变形菌门(Proteobacteria)和拟杆菌门。菌群的丰度与人类健康密切相关，如厚壁菌门和拟杆菌门的比值(F/B)可评估菌群稳态，预测疾病的发生，F/B 值在肥胖等代谢疾病中显著增加[4-6]。

肠道菌群在长期的进化过程中，通过个体的适应和自然选择，菌群始终处于动态平衡状态，在人体内发挥生理功能，例如影响体重和消化能力、抵御感染和自体免疫疾病的患病风险[7]。近来研究发现肠道菌群能合成多种人体生长发育所需的维生素，如 B 族维生素(维生素 B_1、B_2、B_6 和 B_{12})、维生素 K、烟酸和泛酸等。肠道菌群还能利用蛋白质残渣合成人体必需氨基酸，如苯丙氨酸、缬氨酸和苏氨酸等，参与糖类和蛋白质的代谢，同时还能促进铁、镁、锌等矿物元素的吸收，这些营养物质对人类的健康有着重要作用，一旦缺少会引起多种疾病[8-9]。另外肠道菌群还可以通过调节神经营养因子和相关蛋白等影响大脑行为和功能，在神经系统的生长发育过程中起到重要作用。以上证据表明，肠道菌群具有提供营养、影响发育、调节免疫功能和参与宿主代谢等重要作用。

2 肠道微生物对神经系统疾病的影响

肠道菌群与脑通过“肠-脑轴”进行双向直接或间接的联系[10](图 1)。一些肠道微生物可直接作用于肠神经系统并激活其支配的迷走神经，产生的局部信号可通过感觉神经回路传递到参与认知、情绪、恐惧和焦虑等的大脑区域[11]。研究发现，乳酸菌如鼠李糖乳杆菌以区域依赖的方式持续调节 γ-氨基丁酸受体 mRNA 的表达，同时可以降低应激诱导的皮质酮并减轻焦虑、抑郁相关行为。而切除小鼠的迷走神经阻止了鼠李糖乳杆菌的抗抑郁作用，表明迷走神经是暴露于肠道和大脑的细菌之间的主要调节组成通讯途径[12]。

肠道微生物也可以通过调节免疫功能来影响中枢神经系统[13-14]。菌群失调引起脂多糖(lipopolysaccharide, LPS)和肽聚糖等免疫激动剂增加，并穿过血脑屏障与小胶质细胞 Toll 样受体 4 (Toll-like receptor 4, TLR4)结合，激活小胶质细胞，引起促炎细胞因子如白细胞介素-6 (interleukin-6, IL-6)、γ-干扰素(interferon γ, IFN-γ)等的释放[15]，从而参与神经疾病的发生。肠道微生物的代谢产物短链脂肪酸(short chain fatty acid, SCFA)也可以调节肠道黏膜免疫应答，影响中性粒细胞、T 细胞等免疫细胞的分化和激活，通过影响外周免疫系统调节大脑功能[16-17]。

同时研究还发现，肠道微生物能够通过内分泌系统与大脑相互调节[18]。下丘脑-垂体-肾上腺(hypothalamic-pituitary-adrenal, HPA)轴能够通过调控神经内分泌系统来影响机体肠道菌群

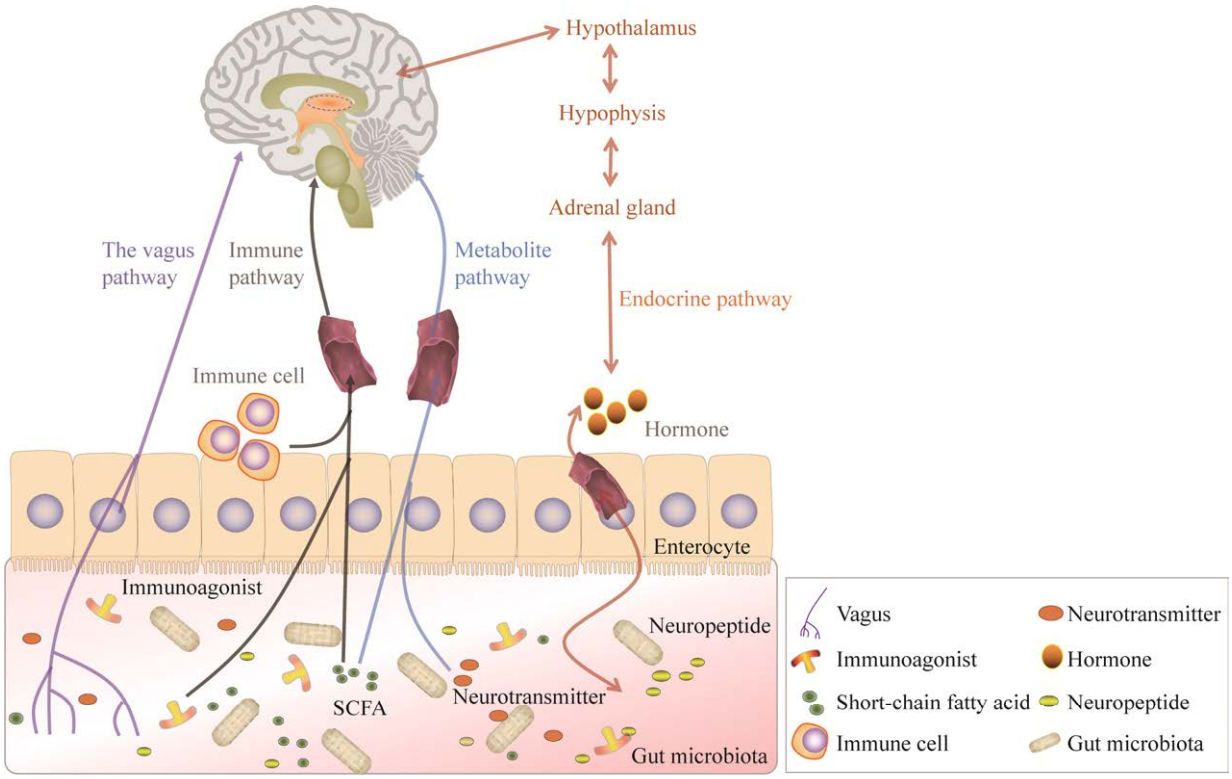

图 1 肠道菌群与中枢神经系统互作的方式

Figure 1 The way intestinal flora interacts with the central nervous system.

的组成，而改变肠道菌群则会刺激肠内分泌细胞释放多种神经肽等，影响神经系统功能[19]。例如慢性应激诱导的抑郁症模型大鼠会通过 HPA 轴导致 5-羟色胺和去甲肾上腺素水平下降，并引起肠道菌群的紊乱[20]；同时，将抑郁症患者的肠道菌群移植到无菌小鼠体内，发现小鼠血清中促肾上腺皮质激素释放激素、肾上腺皮质激素水平显著升高[21]，这表明肠道菌群可能通过引起 HPA 轴的异常而影响分泌系统，进而诱导大鼠的抑郁样行为造成神经功能的损伤。

研究发现，一些神经疾病患者肠道菌群的组成和多样性受到严重干扰，肠道微生物测定结果表明，厚壁菌门、拟杆菌门、放线菌门、变形菌门和疣微菌门(Verrucomicrobia)等都发生显著改变，其中脱硫弧菌属(*Desulfovibrio*)在抑郁症、AD 和 ASD 中均变化显著，阿克曼菌属(*Akkermansia*)为 AD、PD 和 ASD 中主要变化的属[22]，同时这些患者的消化功能严重减弱，并伴随着胃肠道功能紊乱的症状。有趣的是，比起普通小鼠，无菌小鼠的皮层和海马中的脑源性神经营养因子蛋白水平显著降低，且表现出记忆缺陷和神经损伤症状[23]。这意味着肠道菌群也能够影响大脑，参与神经系统疾病的病理和发生，说明稳定的肠道系统对正常中枢功能的维持至关重要，同时表明神经疾病与肠道菌群间存在相互作用关系(表 1)。

表 1　神经系统疾病患者肠道微生物变化

Table 1　Changes in gut microbiota in neurological diseases

Nervous system disease	Ascend	Descend	References
Depression			
Phylum	Firmicutes, Actinobacteria	Bacteroidetes	[24-25]
Family	Thermoanaerobacteriaceae	Prevotellaceae	
Genus	*Desulfovibrio*, *Oscillospira*, *Ruminococcus*, *Eggerthella*, *Holdemania*, *Turicibacte*, *Anaerofilum*, *Clostridium*, *Streptococcus*	*Prevotella*, *Dialister*	
AD			
Phylum	Proteobacteria, Verrucomicrobia	Bacteroidetes, Firmicutes	[26-27]
Family	Enterobacteriaceae, Veillonellaceae	Clostridiaceae, Lachnospiraceae	
Genus	*Desulfovibrio*, *Akkermansia*	*Alloprevotella*, *Blautia*, *Ruminococcus*	
PD			
Phylum	Verrucomicrobia, Proteobacteria	Firmicutes	[22,28]
Family	Ruminococcaceae, Enterobacteriacea,Odoribacter	Prevotellaceae, Lachnospiraceae, Peptostreptococcaceae	
Genus	*Proteus*, *Bilophila*, *Roseburia*, *Akkermansia*, *Veillonella*, *Enterococcus*	*Butyricicoccus*, *Prevotella*	
ASD			
Phylum	Bacteroidetes, Proteobacteria	Verrucomicrobia, Actinobacteria, Desulfobacterota, Firmicutes	[29-30]
Family	Lachnospiraceae	–	
Genus	*Turicibacter*, *Ruminococcus*, *Streptococcus*, *Bifidobacterium*, *Sutterella*, *Desulfovibrio*, *Lactobacillus*	*Faecalibacterium*, *Akkermansia*, *Dialister*, *Clostridium*	

–: Not mentioned.

3 粪菌移植在治疗神经系统疾病中的应用

基于肠道菌群通过“肠-脑轴”在神经系统疾病中的重要作用，对肠道菌群干预成为治疗神经疾病的潜在手段，例如施用抗生素、益生菌或粪便微生物群移植等。抗生素治疗一定程度上可以缓解神经病症，但动物实验中发现长期使用广谱抗生素会引发细菌的耐药，损伤肾脏肝脏等器官[31]；益生菌对脏器的损害较小，但会破坏免疫缺陷患者本就脆弱的免疫功能[32]。FMT 被证实是神经系统疾病的有效治疗手段，是将健康供体的粪便移植到患者胃肠道内，重建具有正常功能的肠道生态系统，实现肠道内外疾病的治疗[33]。FMT 补充了抗生素治疗失去微生物多样性的同时，还影响菌群代谢物 SCFA、吲哚衍生物、多糖等的生成，进一步改善肠屏障的功能，缓解神经损伤[34-35]。目前在神经疾病上的治疗主要有抑郁症、AD、PD 和 ASD 等。

3.1 抑郁症

抑郁症是一种常见且复发率高的神经精神疾病，表现为情绪低落、兴趣下降并且有轻微焦虑的症状[36]。抑郁症的发病机制复杂，其中“单胺缺乏假说”最为常见，但基于此治疗的相关药物并不能完全改善病症[37]。有研究表明，抑郁症患者肠道菌群组成发生了显著变化，尤其是粪杆菌属(*Faecalibacterium*)和粪球菌属(*Coprococcus*)的丰度降低[38]，小杆菌属(*Dialister*)在未经治疗的抑郁症患者中也显著减少。研究发现，将抑郁症患者的粪便移植到无菌大鼠一周后表现出抑郁症的行为和生理特征，以及色氨酸代谢异常，由此得出肠道菌群异常可能是引起抑郁症的重要原因之一[24]。

一些动物研究证实了 FMT 治疗抑郁症的可靠性。NOD 样受体热蛋白结构域相关蛋白 3 (nod-like receptor thermal protein domain associated protein 3, NLRP3)是固有免疫的重要组成因子，压力或应激等因素激活了静息态细胞中的 NLRP3 炎性小体，从而进一步裂解出成熟的白细胞介素-1β (interleukin-1β, IL-1β)，通过外周免疫系统参与介导了抑郁症的发生发展[39]，将 NLRP3-KO 小鼠的粪便转移到抑郁症小鼠肠道中会显著改善受体小鼠抑郁样行为[40]。Marcondes 等[41]发现，普通小鼠接受抑郁样动物的粪便后，小鼠表现出探索和运动活动减少、空间记忆缺陷、体重下降和神经活性物质的变化，如 IL-6、肿瘤坏死因子-α (tumour necrosis factor-α, TNF-α)水平和蛋白质氧化水平升高；而后又接受健康供体 FMT 后，这些因子和蛋白的水平都降低，FMT 可以增加小鼠对蔗糖溶液的消耗能力，有效恢复小鼠的抑郁样行为[42]。

临床上，Cai 等[43]首次将 FMT 应用于抑郁症患者治疗，发现对患者病情有显著的缓解作用，表现为便秘症状和精神状况改善；Yang 等[44]也在对患者进行 FMT 治疗中发现了类似的现象，患者的抑郁、焦虑和便秘症状都得到了改善，肠道乳酸菌增多。这说明 FMT 在抑郁症治疗中起到了重要作用，这为抑郁症的有效治疗提供了新的方向(表 2)。

3.2 AD

AD 是一种常见的神经退行性疾病，患病症状表现为记忆丧失、行为障碍[45]。AD 的发病机制与遗传和环境因素均有关，目前“β-淀粉样蛋白积聚假说”最为经典[46]，研究发现，AD 患者的大脑中 β-淀粉样蛋白发生聚积，且白细胞介素(IL-5、IL-6、IL-8、IL-1β)和 TNF-α 等神经炎症表达显著上调[47]，并伴随着肠道菌群的紊乱。由于肠道菌群与神经炎症的发生密切相关，通过调节肠道微生物降低这些促炎因子的

表 2 临床和动物实验抑郁症研究中的 FMT

Table 2 FMT in clinical and animal experimental studies of depression

Design	Follow-up after FMT	Number of transplants	Administration route	Microbiota effects of FMT	Neurological effects of FMT	Gut effects of FMT	References
Animal model (NLRP3-KO mice)	7 days	3	Oral gavage	Bacteroidete relative abundance decreased and *Desulfovibrio*, *Oscillospira*, and *Ruminococcus* increased after FMT	Astrocyte dysfunction decreased; the number of positive cells increased; the number, length, and volume of astrocyte branches increased significantly	Not mentioned	[40]
Animal model (depression)	1 day	5	Oral gavage	Not mentioned	The levels of IL-6 and TNF-α in the prefrontal cortex and hippocampus were decreased, and the levels of oxidative damage of proteins were decreased	Not mentioned	[41]
Human case series	6 months	4	Duodenum	The number of Firmicutes increased significantly, Bacteroidetes decreased significantly, and the number of Lachnospiraceae increased after FMT	Appetite improved, mental condition improved	Constipation symptoms improved and health questionnaire scores returned to normal	[43]

表达，这可能是预防或降低 AD 风险的有效策略(表 3)。

研究发现，将健康小鼠的粪便移植给 AD 小鼠，可以改善其肠道菌群及代谢物组成，上调粪便中 SCFA 的含量[48]。与此类似，Kim 等[49]研究发现，在小鼠中 FMT 治疗可以改善 AD 小鼠 β-淀粉样蛋白斑块沉积、tau 蛋白病理学特征和小胶质细胞激活等，并且逆转了 AD 小鼠的认知障碍表型。

临床上 FMT 治疗 AD 的报道迄今为止仅有一例，该病例显示一名 82 岁患者接受 FMT 后，记忆、认知、情绪等 AD 症状均得到了显著改善[50]。尽管目前 FMT 在 AD 的临床应用较少，但动物实验中的结果明确提出了 FMT 能够恢复肠道稳态的证据，表明 FMT 在 AD 治疗上具有很好的前景。

3.3 PD

PD 是一种多因素的神经退行性疾病，患者表现为步态障碍、运动受限及四肢震颤等，其主要特征是多巴胺能神经元的丧失，黑质和纹状体中的“α-突触核蛋白”表达积聚[52-53]。研究发现 PD 患者肠道菌群失调，从而引起肠上皮细胞损伤，激活 TNF-α/NF-κB 等促炎信号通路，通过肠-脑轴影响 α-突触核蛋白的表达[54]，因此，通过 FMT 调节肠道菌群可能对 PD 的治疗具有重要作用(表 4)。

FMT 处理对 PD 小鼠的病症具有明显的改善作用，一方面，FMT 减少 PD 小鼠肠道微生

表 3　临床试验和动物模型 AD 中的 FMT

Table 3　FMT in clinical trials and animal models of AD

Design	Follow-up after FMT	Number of transplants	Administration route	Microbiota effects of FMT	Neurological effects of FMT	Gut effects of FMT	References
Animal model (transgenosis AD mice)	4 weeks	28	Oral gavage	*Desulfovibrio* decreased and Bacteroidete increased after FMT	The mice stayed in the target quadrant much more frequently and much longer than the model	Not mentioned	[48]
Animal model (transgenosis AD mice)	16 days	16	Oral gavage	Not mentioned	The total plaque area of frontal cortex and hippocampus decreased significantly, and the levels of soluble and insoluble Aβ40 in cerebral cortex decreased significantly. Glial cell formation decreased	Intestinal permeability and intestinal barrier integrity were enhanced	[49]
Human case series	6 months	1	Not mentioned	Not mentioned	Cognitive function score increased from 20 points (cognitive impairment) to 26 points (normal function); after 6 months, mood improved and the score rose to 29	Not mentioned	[50]
Animal model (APPPS1-21 mice)	24 days	24	Oral gavage	There was no difference in alpha-diversity between donor and FMT, and the difference was significant in the control group without FMT	The cortical plaques and microglia body area increased, the total number of microglia cells did not change, the dendritic branch length of microglia shortened, and the dendritic branch points decreased	The cecum weight increased after FMT	[51]

物失调，缓解小鼠的体重减轻、运动及胃肠道功能障碍，恢复肠道菌群多样性，并增加厚壁菌门丰度等；另一方面，FMT 增加纹状体中神经递质含量，抑制黑质中小胶质细胞和星形胶质细胞的激活，降低炎症因子和 LPS 水平，并通过阻断 TLR4/TNF-α/NF-κB/MyD88 信号通路激活及下游促炎蛋白的产生来改善 PD 小鼠的症状[55-56]。

FMT 治疗 PD 在临床上也得到了一定的应用，科学家们对 27 名轻度至中度 PD 患者进行 FMT 治疗，随访期间未观察到严重不良反应，且患者的胃肠道疾病得到了改善，肠道微生态系统的复杂性显著增加[57]。另外，南京医科大学附属医院对一名 PD 患者进行 FMT 治疗后发现，在 4 周时患者情绪、睡眠质量均有所好转，但在 12 周时稍有恶化的趋势[58]。尽管 FMT 能够在一定程度上改善 PD 患者的症状，但结果也存在争议，还需更多的临床试验来支撑。

表 4 临床试验和动物模型 PD 中的 FMT

Table 4 FMT in clinical trials and animal models of PD

Design	Follow-up after FMT	Number of transplants	Administration route	Microbiota effects of FMT	Neurological effects of FMT	Gut effects of FMT	References
Animal model (MPTP induce PD mice)	8 days	7	Oral gavage	Firmicutes increased, Proteobacteria decreased; in the order level, Clostridiales decreased, Turicibacterales and Enterobacterales increased	Activated astrocytes and microglia decreased; reduce the expression of TLR4/TBK1/ NF-κB/TNF-α signaling pathway	Not mentioned	[55]
Animal model (rotenone induce PD mice)	6 weeks	14	Oral gavage	Increased alpha-diversity; there was no difference between FMT and control group	Restoring neuron loss, decreasing α-synuclein aggregation and decreasing astrocyte proliferation; inhibition of TLR4/MyD88/ NF-κB signaling pathway	Increased frequency of bowel movements; the blood-brain barrier connection and tissue structure were restored, the damage of endothelial cells was reduced	[56]
Human case series 1	12 weeks	27	Capsule	FMT alleviate the clinical symptoms of patients with PD by strengthening the correlation between the microbial genera	Not mentioned	Those participants had a significantly better quality of life regarding abdominal pain, flatulence, nausea, etc.	[57]
Human case series 2	12 months	1	Fibercolonoscopy, injected into the end of the ileum	*Ruminococcus*, *Blautia*, *Prevotella* and *Faecalibacterium* increased, Bacteroidete decresed	Constipation, mood and sleep quality were improved, and tremor and bradykinesia were significantly improved after 4 weeks	Not mentioned	[58]

3.4 ASD

ASD 是一种在儿童中常见的神经发育障碍，特征是社会交流和互动的改变以及重复的刻板行为，孤独症是其中的一种典型疾病[59-60]。免疫功能障碍是 ASD 发病的主要机制，在 ASD 模型中观察到与免疫相关的蛋白如接触蛋白相关样蛋白 4 (contactin associated protein-like 4, CNTNAP4)和脆性 X 智力低下蛋白(familial mental retardation protein, FMRP)的显著下调[61-62]，研究中常将 *CNTNAP4* 和 *FMRP* 基因敲除小鼠作为 ASD 模型。

肠道菌群可以通过调节免疫应答来影响神经系统的功能，近年来 ASD 的治疗多数集中在菌群改善方面(表 5)。Zhang 等[62]发现 *CNTNAP4*

表 5　临床试验和动物模型 ASD 中的 FMT

Table 5　FMT in clinical trials and animal models of ASD

Design	Follow-up after FMT	Number of transplants	Administration route	Microbiota effects of FMT	Neurological effects of FMT	Gut effects of FMT	References
Animal model (*FMRP*-KO mice)	Not mentioned	7	Oral gavage	*Akkermansia* and *Gordonibacter* increased	FMT significantly reduced the expression of TNF-α mRNA in the colon of recipient mice	Intestinal homeostasis improved after FMT, significantly increasing the expression level of ZO-3 in the colon of recipient mice	[61]
Animal model (*CNTNAP4*-KO mice)	15 days	7	Oral gavage	*Lactobacillus* increased colonisation in the colon	The time residence time in the open regional center area increased; the rate of social interaction in the interaction zone increased	Not mentioned	[62]
Human case series 1	8 weeks	10	Oral or rectal (upper digestive mixed drink, lower digestive enema)	*Bifidobacterium* increasing 4 times significantly, *Prevotella* and *Desulfovibrio* also increased	There was no difference between oral and rectal ingestion, and behavioral symptoms improved significantly	The gastrointestinal symptom score scale decreased, and the number of days with abnormal or no stool decreased significantly	[63]
Human case series 2	10 weeks	18	Not mentioned	Iignificant increases in levels of Bifidobacteria, Prevotella, and Desulfovibrio	Not mentioned	Levels of sulfuric acid against cresol were similarly reduced in healthy children	[64]

基因敲除小鼠表现出孤独症样行为，肠道菌群结构发生变化，乳杆菌属的丰度显著降低，而进行了正常小鼠的粪便移植后可缓解其恐惧和孤独症样行为。*FMRP* 基因敲除小鼠中也会观察到同样的表型，而喂养鱼油(fish oil, FO)提供多不饱和脂肪酸可以缓解小鼠出现的肠道炎症、菌群紊乱和孤独症行为。同时，在 *FMRP* 基因敲除小鼠中，将 FO 喂养组的粪便移植入无 FO 喂养组可以显著恢复小鼠肠道稳态，降低结肠中 TNF-α 和 ZO-3 的表达，从而改善小鼠的孤独症行为[61]。

FMT 临床试验发现，ASD 儿童的胃肠道症状得到了改善，腹痛、腹泻和便秘等症状显著减少，社交技能等行为症状也显著缓解，并且测序分析表明，细菌多样性得以提升[63]，同时还发现 FMT 推动了血浆中各种代谢特征的变化，包括烟酸/烟酰胺和嘌呤代谢[64]。综上所述，实验证明了 FMT 治疗 ASD 的可行性，为其提

供临床治疗的新方法，后续需要进一步地探究 ASD 的发病机制，为寻找 FMT 的靶点以便于更高效更快速的解决病症。

4 FMT 治疗神经性疾病的潜在机制

在神经系统疾病中，肠道微生态紊乱诱导了肠道炎症与氧化应激反应，减少了短链脂肪酸的产生，引起疾病标志性蛋白(如 β-淀粉样蛋白、tau 蛋白[46]、α-突触核蛋白[54])变化，并通过肠-脑轴的传递和转移，最终造成神经系统损伤。从该角度考虑，推测 FMT 治疗神经疾病可能参与减轻或抑制肠道炎症与氧化应激，进而保护神经系统[65](图 2)。

肠道中条件致病菌导致肠道通透性增加，提高了循环中细菌及细菌成分(如 LPS)水平，导致脑组织中炎症因子 IL-1、IL-6、TNF-α 及单核细胞趋化蛋白 1 的表达上升，引起宿主炎症及氧化应激。FMT 通过增加短链脂肪酸(乙酸、丙酸和丁酸)的含量[66]，调节炎症因子的释放，以游离脂肪酸受体(free fatty acid receptor 2, Ffar-2)依赖的方式保护肠道免受炎症的影响，从而减轻肠道炎症；同时 SCFA 还可以抑制小胶质细胞的激活和功能，保护血脑屏障，减少神经炎症[67]。也有研究报道，FMT 通过重塑肠

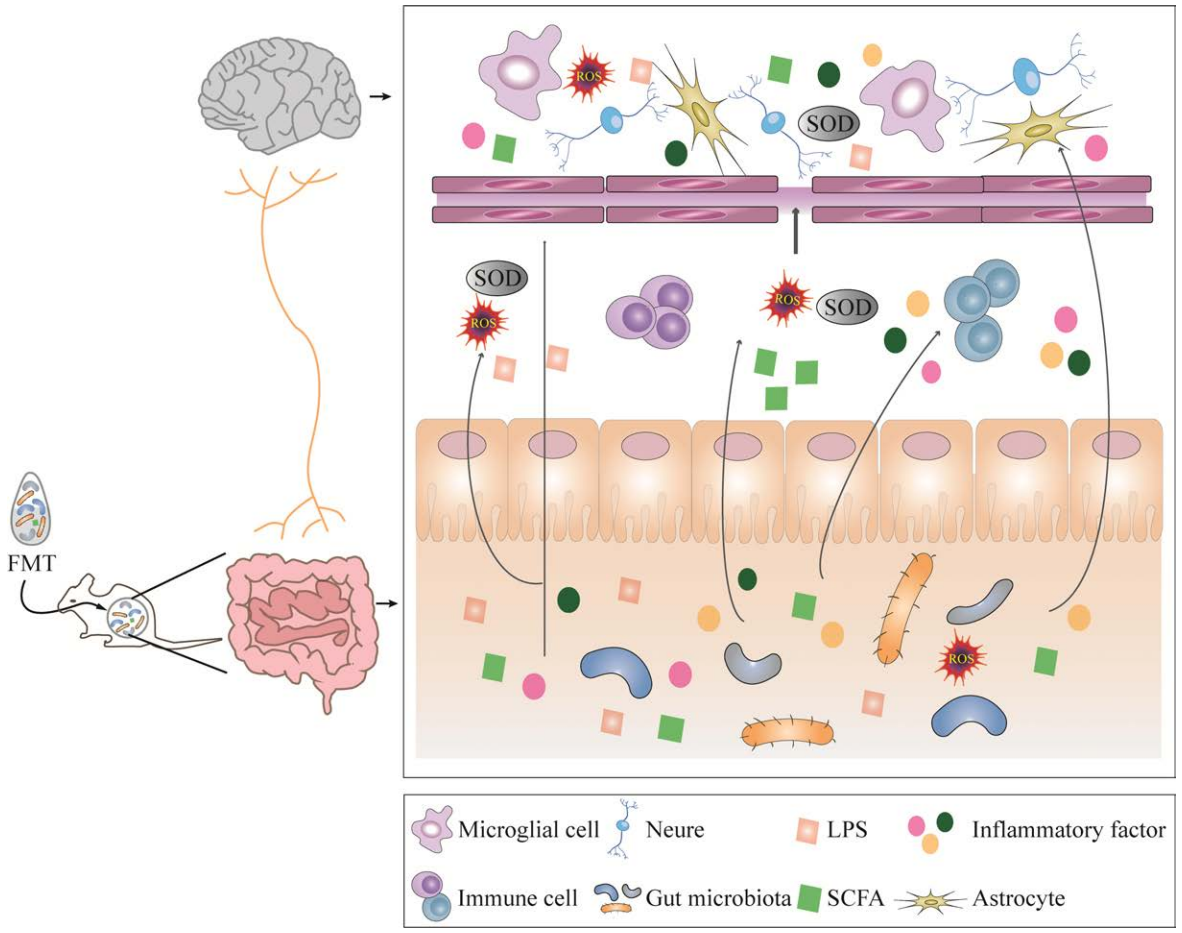

图 2 FMT 的潜在作用机制

Figure 2 Potential mechanism of the action of FMT.

道菌群，下调促炎因子，抑制神经系统疾病相关蛋白及信号通路，例如阻止 NLRP3 炎性小体聚集，下调 NF-κB 信号通路，抑制 α-突触核蛋白、β-淀粉样蛋白在大脑中的积聚，从而缓解炎症的发生[68]。FMT 可能通过影响菌群代谢物如 LPS 和肽聚糖等免疫激动剂，使其水平降低，并抑制它们穿过血脑屏障，可能通过调控免疫相关蛋白和信号通路，例如增加 CNTNAP4 和减少 TLR4 的表达，以及通过增加肠道菌群代谢物如色氨酸的代谢功能和途径，从而改善机体的免疫应答，对神经起到保护作用[69]。FMT 可以缓解机体内氧化应激的发生，降低活性氧(reactive oxygen species, ROS)和过氧化产物丙二醛等水平，增加还原性谷胱甘肽(glutathione, GSH)含量并提高抗氧化相关酶如过氧化物酶、超氧化物歧化酶(superoxide dismutase, SOD)等的活性[70]，并改善了 Nrf2、MAPK 等神经系统中与氧化应激相关的信号通路，从而减轻神经系统疾病的症状。

尽管 FMT 在神经疾病治疗上主要通过上述途径发挥神经保护的作用，但现阶段的研究较难在多种肠道菌群-肠-脑轴交流途径中区分出每种途径的直接影响程度，因此，未来将 FMT 与微生物组、代谢物、宏基因组等多组学结合进行研究，可能有利于阐释 FMT 对治疗神经疾病的机制。

5 总结与展望

本文对肠道微生物-肠-脑轴、FMT 的作用及其在不同的神经系统疾病中的应用进行了综述，FMT 通过重建肠道微生物组影响肠道微生态平衡，从而干预神经系统疾病患病体的紊乱肠道，使健康的肠道菌群在患病体中重新建立稳定的生态环境。许多动物实验和临床试验都证明 FMT 可以在一定程度上缓解抑郁症、AD、PD 和 ASD 患者的症状，改善其肠道菌群的构成，因此可以考虑作为一种治疗神经疾病的备选方式。另外还有一些神经性疾病，例如多发性硬化、肌萎缩性脊髓侧索硬化等与本文提到的神经系统疾病具有相似性，科学家们也在对其的发病机制及治疗途径进行探索。

按照现在研究的发展趋势，FMT 可能会作为治疗神经系统疾病的新方法，但是由于 FMT 对肠道无菌操作要求很高，利用抗生素处理较为困难，供体的选择以及移植菌体的处理都需要经过很严格的设计。另外，有研究报道两例炎症性肠病患者在进行 FMT 后出现严重腹泻，粪便检查结果为产气荚膜梭菌感染[71]，所以在进行 FMT 前需要对供体进行严格筛选，以减少 FMT 带来的负面作用。除此之外，不同的疾病对应的特异性菌株不同，FMT 这种治疗方法如果能够更加准确定位单菌株可能会提升其效果，还需进一步开展更多的工作，确保更有效地治疗对应病症。目前大多研究都集中于肠道菌群和各类神经疾病间的联系，以及饮食干预对疾病的影响，但是对具体的机制研究甚少，因此，未来需要采用多组学方法，深入探究通过肠道菌群治疗神经疾病的作用机制，筛选出更有针对性的菌株，为疾病的治疗提供理论依据。

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