

肠道菌群在抑郁障碍中的作用机制的研究进展

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摘 要

抑郁障碍是常见的精神疾病, 发病率常年居高, 进行有针对性的治疗干预十分迫切。越来越多的研究证据证明肠道菌群在抑郁障碍的发生发展中有关键作用, 肠道菌群可能通过多种方式改善抑郁症状及认知功能。本文介绍了肠道菌群影响抑郁障碍的可能机制, 总结最新研究进展, 旨在为肠道菌群抗抑郁治疗的研究提供新见解。

关键词

抑郁障碍, 肠道菌群, 炎症因子, 肠道通透性, 神经递质, 综述

Advances in the Study of Mechanisms Underlying the Role of Gut Microbiota in Depressive Disorders

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Abstract

Depressive disorder is a common mental illness with a persistently high morbidity rate, making targeted therapeutic intervention extremely urgent. A growing body of research evidence confirms

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that gut microbiota plays a critical role in the occurrence and development of depressive disorder, and may alleviate depressive symptoms and improve cognitive function through multiple pathways. This paper elaborates on the potential mechanisms by which gut microbiota influences depressive disorder and summarizes the latest research progress, aiming to provide new insights for research on gut microbiota-based antidepressant therapies.

Keywords

Depressive Disorder, Gut Microbiota, Inflammatory Factors, Intestinal Permeability, Neurotransmitters, Review

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1. 引言

抑郁障碍是全球范围内致残和致死的重要原因,严重影响患者的社会功能及生活质量。据世界卫生组织(WHO)统计,2019 年全球有 9.7 亿人患有精神障碍,其中以焦虑障碍和抑郁障碍最为常见[1]。抑郁障碍不同于日常生活中常见的短暂情绪波动和对挑战的短暂情绪反应,在抑郁发作期间,患者会持续至少两周,几乎每天大部分时间都感到情绪低落(悲伤、易怒、空虚)或对活动失去兴趣和乐趣[2]。此外,还可能出现其他症状,包括注意力不集中、过度内疚或自我价值感低、对未来感到绝望、有死亡或自杀的想法、睡眠紊乱、食欲或体重变化以及感到极度疲倦或精力不足[2]。

近年来,越来越多的研究发现,微生物-脑-肠轴在抑郁障碍的发生发展过程中起重要作用。抑郁障碍患者通常伴有肠道菌群的失调,大多数证据来自临床前模型[3];肠道微生物群的缺失诱导了小鼠的抑郁样行为,将抑郁障碍患者的粪菌移植给无菌(germ-free, GF)小鼠,亦可导致抑郁样行为[4]。

人类研究发现,抑郁患者与健康人群的肠道微生物组成存在显著差异[5][6]。与健康人群相比,抑郁障碍患者肠道中变形菌门、拟杆菌门丰度增加,厚壁菌门的丰度减少,在属水平上,粪球菌属(Coprococcus)、粪杆菌属(Faecalibacterium)、戴阿利斯特杆菌属(Dialister)和萨特氏菌属(Sutterella)水平显著降低[7][8]。

肠道菌群与脑通过肠-脑轴(gut-brain axis, GBA)进行双向联系,微生物-脑-肠轴通过多种途径维持机体平衡[9]。GBA 主要由脑、迷走神经等自主神经、下丘脑-垂体-肾上腺轴(hypothalamic-pituitary-adrenal axis, HPA)、肠神经等几部分组成,通过迷走神经、内分泌、免疫等多种途径将肠道菌群和脑连接起来,彼此调控,共同维持机体生理功能的稳定[10]。本文阐述了肠道菌群在抑郁障碍中的作用机制的研究进展,并分析了基于肠道菌群的干预策略的现状、面临的挑战及发展前景。

2. 肠道菌群抑郁障碍中的作用机制

2.1. 炎症假说

大量证据表明肠道菌群及其代谢产物会引发宿主神经系统的炎症反应进而影响到宿主中枢神经系统的功能[11]。肠道来源的 $\text{TNF-}\alpha$ 、 $\text{IL-1}\beta$ 和 IL-6 等炎性细胞因子能够激活外周免疫,引起神经内分泌和免疫系统的过度激活,进一步导致功能障碍,最终导致抑郁[12]。肠道菌群失调导致肠道通透性增加和细菌移位,进而激活循环免疫细胞,导致细胞因子产生和系统性炎症[13]。

研究报道抑郁障碍患者血清和脑脊液中循环 C 反应蛋白、 IL-6 、 IL-1 、 $\text{IL-1}\beta$ 及肿瘤坏死因子- α (tumor

necrosis factor- α , TNF- α)浓度增加, 抗炎性细胞因子 IL-10 及 IL-4 浓度显著减少[12]。炎症假说认为, 机体释放炎症细胞因子激活外周免疫, 引起神经内分泌和免疫系统的过度激活, 进一步导致功能障碍, 增加抑郁患病风险[14]。中枢神经系统炎症也已被证实, 在抑郁障碍患者死后的大脑中发现了异常神经炎症, 包括小胶质细胞的激活, 并且在抑郁障碍患者的脑脊液(CSF)中检测到促炎细胞因子(包括 TNF- α 和 IL-6)水平的增加[15]。目前对于炎症反应影响抑郁障碍发病的机制, 许多研究集中在 NLRP3 炎症小体的激活、Toll 样受体 4 (Toll-like receptor 4, TLR4)对神经元炎症的影响以及吲哚胺-2,3-双加氧酶(Indoleamine 2,3-dioxygenase, IDO)的过度表达等方面。

NLRP3 炎症小体是参与固有免疫的重要因子, 它也是 IL-1 β 相关的中枢神经系统(Central Nervous System, CNS)中的炎症因子的介质, NLRP3 的激活在抑郁障碍的发病机制中起重要作用, NLRP3 小体被认为是抑郁障碍的潜在炎症指标之一[16] [17]。NLRP3 的激活促进胱天蛋白酶原-1 的裂解, 激活效应蛋白 Caspase-1, 裂解并激活 IL-1 β 和 IL-18, 进而激活下游信号转导通路, 产生大量炎症介质[18]。NLRP3 的激活还可诱导小胶质细胞合成和释放炎症介质, 介导炎症反应, 诱导海马神经元的凋亡, 进而导致脑内抑郁样行为的发生[18]。有研究者提出, 应激诱导的炎症反应能够引起肠道菌群的紊乱, 并导致其代谢产物的失衡, 从而引起中枢和外周神经系统 NLRP3 介导的促炎信号的传导增多, 影响大脑的功能, 最终加重抑郁样行为[19]。在抑郁障碍的发生发展过程中, NLRP3 与肠道菌群的相互作用是重要的环节。Zhang 等证明了 NLRP3 缺陷小鼠的肠道微生物群通过 circHIPK2 调节星形胶质细胞功能障碍, 从而改善抑郁样行为[20]。Li 等将来自慢性应激诱导的抑郁小鼠的微生物群注射到无菌小鼠体内, 进一步证实了肠道菌群的紊乱影响了促炎因子的表达, 并加剧了抑郁样行为[4]。综上所述, 肠道菌群与炎症反应具有较强的相关性。与抑郁障碍相关的炎症因子, 如 ILs、IFN、TNF 等可以刺激肠道影响肠道菌群, 肠道菌群反过来通过 NLRP3 通路加重炎症反应, 最终加剧抑郁。然而, 这两种途径导致抑郁的具体机制还需要进一步的研究。

Toll 样受体 4 是一种存在于细胞膜表面的自身免疫识别受体, 能够识别各种内源性损伤相关分子模式、微生物相关分子模式和病原体相关分子模式, 它可以通过神经炎症信号通路影响抑郁障碍的发病。有研究发现, TLR4 通过促进核转录因子 Kappa B (NF- κ B)、干扰素调节因子 3 等转录因子的表达, 诱导 IL-1 β 、IL-6、TNF- α 等炎症因子的产生和释放, 同时上调环氧化物酶 2 (COX-2)等蛋白的表达, 最终参与神经炎症反应[21]。通过动物实验发现, 在动物体内通过脂多糖刺激 TLR4 受体会导致快感缺失、兴趣减退、食欲不振等抑郁样行为[22]。此外, TLR4 在抑郁大鼠脑内过度表达, 脑内 TLR4 的激活参与了抑郁障碍的发病机制。Huang 等利用正电子发射计算机断层扫描技术(Positron Emission Tomography, PET)发现, 抑郁障碍患者海马内小胶质细胞过度激活, TLR4 在脑内主要表达于这些细胞[23]。肠道菌群失调, 特别是脂多糖(lipopolysaccharide, LPSs)水平升高, 可激活 TLR4, 引发与抑郁障碍相关的炎症通路, 有研究显示, 肠道菌群可通过抑制 TLR4/MYD88/NF- κ B 炎症通路相关信号, 激活抗炎因子 I κ B- α , 减轻大鼠抑郁样行为[24]。

IDO 作为一种限速酶, 广泛存在于人体组织中, 促进色氨酸(TRP)和犬尿氨酸的代谢和分解, 近年来研究发现, IDO 与细胞因子、神经元可塑性等密切相关, 在抑郁障碍的发病机制和治疗中发挥重要作用[25]。当 IDO 被过度激活时, 犬尿氨酸的代谢途径增强, 产生犬尿氨酸和喹啉酸等细胞毒性产物, 从而产生神经毒性, 最终导致神经疾病[25]。研究表明, IDO 水平在大脑的前额叶、海马等区域最高, 促炎因子可增加这些区域小胶质细胞中 IDO mRNA 的表达[26]。一些促炎因子的受体基因也可以被敲除来阻断 IDO 的过度激活, 调节色氨酸代谢途径, 从而阻断抑郁样行为的产生[27]。综上, 可以通过抑制促炎因子的活性或促进抗炎因子的激活来降低 IDO 的过表达, 最终减少抑郁样行为的发生。肠道菌群与色氨酸代

谢之间有双向作用,色氨酸代谢途径可调节肠道菌群的组成,介导调节肠-脑信号传导,同时肠道菌群直接参与色氨酸代谢,产生具有生物活性的代谢物,如吲哚-3-丙酸(IPA)和吲哚-3-醛(IAld),调节酶活性,如降低IDO1活性调整上游代谢[28]。因此,肠道菌群可能通过调节IDO酶活性,影响色氨酸代谢从而改善抑郁症状。

2.2. 调节神经元的结构和功能

调节肠道菌群一方面能够改善神经系统炎症反应从而改善抑郁症状,另一方面健康的肠道菌群对于神经元的生长发育有重要作用。慢性应激可导致脑结构改变,表现为海马体积缩小及神经元凋亡,脑结构的改变和情绪可相互影响[29][30]。肠道菌群可以影响神经元的再生、结构和功能。有研究发现,将衰老小鼠(24月龄)的肠道菌群移植到GF年轻小鼠(5~6周龄)肠道,可以促进GF小鼠的神经元再生,进一步研究发现这种作用主要是产生丁酸盐的微生物介导的,说明丁酸盐有刺激神经再生的作用[31]。丁酸盐是短链脂肪酸(SCFAs)的一种,由结肠微生物进行纤维发酵产生,参与维持肠道屏障完整性、神经递质合成和免疫炎症调节[32]。小鼠缺乏肠道菌群后其神经元基因表达、放电模式、连接方式发生了改变,突触的修剪受到干扰,树突棘的数量被减少,小鼠表现出了恐惧行为和学习能力的下降[33]。无特定病原体(specific pathogen free, SPF)小鼠在4周龄或12周龄时比GF小鼠表现出较好的认知功能,主要灰质和白质区体积和髓鞘化增加,显示出更好的大脑成熟度,这表明肠道菌群对大脑灰质和白质的正常形态发育和成熟是必要的[34]。与正常对照组小鼠相比,GF小鼠的杏仁核和海马显著扩张,这些发现表明肠道菌群是维持杏仁核和海马正常形态和超微结构所必需的,这种神经重塑可能有助于GF小鼠应对不良的应激反应,调节抑郁情绪。

海马的突触损伤被认为是抑郁障碍的重要病理基础[35][36],先前有研究已经证实过度自噬在突触损伤中发挥重要作用[37]。进一步的动物实验发现,在慢性随机应激(Chronic Unpredictable Mild Stress, CUMS)和皮质酮(cortisol, CORT)诱导的抑郁小鼠模型中给予高香草酸(HVA)、长双歧杆菌可显著改善抑郁症状[38]。HVA是多巴胺的非生理活性终末代谢产物,该研究发现,长双歧杆菌可以产生HVA, HVA通过阻止微管相关蛋白1轻链3(LC3)和SQSTM1/p62蛋白的过度降解,保护海马神经元突触前膜,从而抑制突触自噬性死亡[38]。该研究揭示了代谢物HVA和产生HVA的肠道细菌具有治疗抑郁障碍的潜力,这种治疗主要是通过调节自噬过程来增强突触完整性,以利于细胞存活。

2.3. 迷走神经途径

肠道菌群还能够直接或间接地调控迷走神经功能调节宿主的情绪反应,从而改善抑郁症状。迷走神经是副交感神经系统的主要组成部分,是肠道与大脑交流的重要方式之一[10]。迷走神经介导了肠道菌群与中枢神经系统之间抑制和兴奋两种效应。迷走神经传入纤维位于胃肠道壁,但不穿过上皮,因此与肠道菌群不直接接触[39]。然而,电生理实验已经证明,细胞因子、营养物质、肠肽和激素等可以穿过上皮细胞层,直接作用于迷走神经传入纤维,肠道菌群可以通过改变这些因子的浓度来改变迷走神经信号传导[40]。此外,一些菌株还能产生神经递质,如血清素,这些神经递质被吸收后可直接作用于迷走神经末梢或通过激活肠神经元间接发挥作用[40]。肠腔壁也受肠神经系统(enteric nervous system, ENS)支配,主要负责肠道运动,并可被短链脂肪酸(short chain fatty acid, SCFAs)和神经递质靶向调节[10]。

迷走神经刺激(VNS)是一种被批准的治疗难治性抑郁障碍(TRD)的辅助疗法。有研究表明,迷走神经刺激后患者的平均抑郁严重程度评分降低59.9%,缓解率为87%,焦虑水平也大大降低,表明迷走神经刺激存在改善抑郁症状的作用,这种作用可能与血脑屏障完整性的增加和炎症细胞募集减少有关,为难治性抑郁障碍的治疗提供了新途径[41]。

2.4. 内分泌途径

广泛的研究已经强调了抑郁障碍中肠道微生物群和代谢物的紊乱[42][43]。肠道菌群自身能够合成多种神经递质,乳酸菌和双歧杆菌可以产生 γ -氨基丁酸(γ -aminobutyric acid, GABA);大肠杆菌、芽孢杆菌能产生去甲肾上腺素(noradrenaline, NE);芽孢杆菌能产生多巴胺(dopamine, DA);乳酸菌能产生乙酰胆碱(acetylcholine, Ach);念珠菌、链球菌和肠球菌可产生5-羟色胺[44]。

1965年Coppen等首次提出,中枢神经系统中5-羟色胺含量减少会导致抑郁障碍的发生[45];1972年Schildkraut等首次提出单胺类神经递质假说,认为大脑中单胺类神经递质(去甲肾上腺素、多巴胺、5-羟色胺等)水平的下降会导致抑郁障碍发生[46]。5-HT是一种重要的兴奋性神经递质,由色氨酸分解代谢生成,色氨酸代谢也可生成犬尿氨酸,而犬尿氨酸的代谢产物喹啉酸具有神经毒性。色氨酸代谢途径被认为是抑郁障碍的发病机制之一,5-HT水平下降或功能异常可能是导致抑郁障碍的关键因素之一[28]。大量临床及临床前研究表明,神经炎症导致色氨酸代谢过程向犬尿氨酸方向倾斜,使犬尿氨酸生成增多,犬尿氨酸最终分解成喹啉酸损害神经元导致抑郁症状[47][48]。肠道菌群可能通过提升5-HT水平参与情绪调控,改善抑郁症状[49]。有研究发现,将健康小鼠的粪菌微生物群移植给酒精诱导的抑郁小鼠后,抑郁小鼠的抑郁行为明显缓解,进一步研究发现经过粪菌移植的抑郁小鼠肠道和脑组织中的5-HT含量显著增加,肠道通透性也得到了改善[50]。Sun等[51]研究表明,植物乳杆菌WLPL04可改善小鼠慢性应激诱导的5-HT、BDNF和TrkB水平降低从而改善小鼠焦虑或抑郁样行为及认知功能。乳酸乳球菌E001-B-8可能通过调节肠道菌群和增加5-HT来改善慢性应激诱导的抑郁小鼠的抑郁症状及认知功能障碍[52]。肠道菌群也可直接参与色氨酸代谢,产生吲哚-3-丙酸(IPA)和吲哚-3-醛(IAld),这些活性产物能够降低与犬尿氨酸生成相关的酶IDO1的活性,调节上游代谢,促进5-HT的生成,改善抑郁症状[28]。

γ -氨基丁酸(γ -aminobutyric acid, GABA)是神经组织中重要的抑制性神经递质,研究表明, γ -氨基丁酸功能改变对潜在的抑制性精神疾病(包括重度抑郁等)起主导作用,且抑郁障碍患者的脑脊液和血浆 γ -氨基丁酸水平均下降[53]。GABA是人体内重要的神经递质,由谷氨酸产生,在调节大脑功能过程中发挥重要作用。有大量证据支持GABA能够改善抑郁和焦虑症状[54]。近年来多篇报道表明,多种肠道菌群均能产生GABA,例如植物乳杆菌[55]-[57]、短乳杆菌(*Lactobacillus brevis*) [58]、发酵黏液乳杆菌(*Limosilactobacillus fermentum*)、乳酸乳球菌(*Lactococcus lactis*) [59]、鼠李糖乳杆菌[60]、罗伊特氏乳杆菌[61]、鼠乳杆菌(*Lactobacillus murine*) [61]、齿双歧杆菌(*Bifidobacterium dentium*) [62]、青春双歧杆菌(*Bifidobacterium adolescentis*) [63]以及嗜热链球菌(*Streptococcus thermophilus*) [64]等。多项动物实验发现,这些菌株可能通过改善GABA水平从而改善抑郁情绪。发酵黏液乳杆菌(*Limosilactobacillus fermentum*) L18可产生高水平的GABA,可提高肠上皮细胞进行紧密连接所必须的连接蛋白的浓度,调节肠道微生物群,进而增强肠道上皮屏障,可能通过调节肠-脑轴以达到调节情绪的作用[65]。另有研究表明,能产生GABA的鼠李糖乳杆菌JB-1能够减少小鼠的焦虑样行为,降低炎症因子水平,机制可能与鼠李糖乳杆菌JB-1能够调节情绪相关脑区(如海马体和杏仁核)中GABA-A受体亚基的表达有关[66]。

慢性应激刺激会导致HPA轴功能持续亢进,导致促肾上腺皮质激素释放激素和糖皮质激素(glucocorticoids, GCs)的分泌增加,GCs持续处于较高水平会进一步刺激HPA轴功能持续亢进,形成恶性循环,最终诱发或加重抑郁症状[67]。肠道菌群与脑的交流中也有下丘脑-垂体-肾上腺轴的参与,在应激状态下,GF小鼠的下丘脑-垂体-肾上腺轴反应比SPF小鼠更加强烈,同时也伴随着促肾上腺皮质激素(adrenocorticotrophic hormone, ACTH)和皮质酮水平的增加,将SPF级小鼠的肠道菌群移植给GF小鼠后该现象消失,证明肠道菌群能够改善HPA轴亢进,降低促肾上腺皮质激素和皮质酮水平,改善应激反应,调节抑郁症状[68]。

脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)是神经营养因子家族中的一员,广泛分布于大脑,由神经细胞、小胶质细胞和星形胶质细胞产生,有助于神经元的存活、生长和维持[69]。最近的研究表明,以 BDNF 为介质能够调节中枢神经系统的功能和结构,影响海马体中神经元的成熟[70],海马的神经损伤被认为是抑郁障碍的重要病理基础[35]。有动物研究发现,干酪乳杆菌(*Lactobacillus casei*) HY2782 和乳双歧杆菌(*Bifidobacterium lactis*) HY8002 可抑制肠道微生物群介导的 NF- κ B 激活和诱导 BDNF 表达,从而增加大脑中的 BDNF、5-HT 水平和 BDNF 相关的神经元细胞数量,最终达到缓解压力引起的抑郁和焦虑样行为的效果[71]。一项为期 8 周的临床试验显示,抑郁障碍患者持续补充长双歧杆菌(*Bifidobacterium longum*) R0175 和瑞士乳杆菌(*Lactobacillus helveticus*) R0052 可显著提高血清 BDNF 水平,进而改善抑郁症状[72]。以上证据均可证明肠道菌群可能通过提升 BDNF 水平改善抑郁症状。

2.5. 改善肠道通透性

肠道能够选择性地吸收有益的营养物质及细胞因子,并将有害物质及炎症因子等拒之门外,依赖的就是完整的肠道屏障功能,肠道上皮细胞通过紧密连接(tight junction, TJ)组成肠上皮屏障的结构基础,肠道屏障的破坏会导致各种有害物质入血,甚至通过血-脑屏障进入大脑影响神经系统功能导致多种疾病[73]。研究者们通过研究肠道通透性标志物,在抑郁障碍患者中也发现了肠道通透性的改变[73]。已有多项动物研究表明,肠道菌群可改善肠道屏障通透性,从而改善小鼠的抑郁及焦虑样行为。在一项研究副肠膜状魏斯氏菌(*Weissella paramesenteroides*) WpK4 在溃疡性结肠炎小鼠模型和慢性应激小鼠模型中的作用的实验中,副肠膜状魏斯氏菌 WpK4 改善了结肠炎小鼠的健康状况,降低了肠道通透性,改善了结肠组织病理学外观。在应激小鼠中,副肠膜状魏斯氏菌 WpK4 通过免疫调节作用减少海马中炎症细胞因子的表达,从而改善动物行为,减少焦虑样和抑郁样行为[74]。另一项研究表明,普通拟杆菌(*Bacteroides vulgatus*)通过增加血脑屏障血管内皮细胞紧密连接蛋白 claudin-5 的表达,减轻了肠道炎症,缓解了脂多糖诱导的小鼠抑郁样行为[75]。

另外,有最新理论强调了肠上皮细胞(intestinal epithelial cell, IEC)线粒体对肠道微生物群的调节作用[76],该理论认为,IEC 线粒体功能障碍改变肠道微生物群组成,介导氧化应激,激活外周免疫系统引起外周炎症,并通过迷走神经和肠神经系统传递外周信号导致大脑炎症,激活下丘脑-垂体-肾上腺轴,激活小胶质细胞和星形胶质细胞,诱导神经元损伤,最终导致抑郁障碍[76]。该研究提出了一种炎症性肠病(Inflammatory Bowel Disease, IBD)与精神疾病共病的治疗策略,建议将压力管理作为 IBD 护理的重点。

综上所述,肠道菌群可能通过改善中枢及外周神经系统炎症、降低炎症因子水平、调节神经元的结构和功能、调节迷走神经功能、调节多种神经递质及神经营养因子、降低 HPA 轴激活程度降低炎症反应、修复肠道通透性减少有害物质入血等多种途径改善抑郁情绪。但对于肠道菌群的研究结果大多来源于基础实验或动物实验,临床试验数据较少,对于肠道菌群的治疗效果也褒贬不一,仍需进一步深入探索。

3. 基于肠道菌群的干预策略:现状、挑战与未来

当前针对抑郁障碍的肠道菌群相关的治疗方法主要分为三大层级:食品级干预(益生菌/益生元)、生物制品级干预(特定菌株组合的活体生物药)以及生态重建级干预(粪菌移植)。表 1 汇总了近年来具有重要意义随机对照试验(RCT)及高质量前瞻性研究。

尽管上述试验提供了乐观的初步信号,但微生态干预在临床应用中仍面临着标准化、个体化、安全性等重大核心挑战。与传统化学药分子式明确不同,微生态制剂的活性成分(活菌)具有高度动态性,益生菌的功效具有严格的菌株特异性,即同一菌种不同菌株效果截然相反,且在生产、储存和通过胃肠道的过程中活菌数量的损耗程度难以一致化,使得微生物制剂治疗难以达到标准化。其次,微生态干预的

Table 1. Representative clinical trials on gut microbiota in depressive disorders**表 1.** 基于肠道菌群的抑郁障碍代表性临床试验

研究者	研究对象	干预策略	关键结果
Akkasheh <i>et al.</i> [77]	重度抑郁患者	益生菌(嗜酸乳杆菌 + 干酪乳杆菌 + 双歧杆菌)	贝克抑郁量表评分显著下降(-5.7 vs. -1.5, $P = 0.001$), 响应率提高
Slykerman <i>et al.</i> [78]	产后抑郁高风险孕妇	益生菌(鼠李糖乳杆菌 HN001)	产后抑郁发生率降低约 50% ($HR = 0.50$, $P = 0.04$)
Kazemi <i>et al.</i> [79]	慢性应激诱导的抑郁小鼠模型	益生菌(植物乳杆菌 R6-3)	益生菌组的平均贝克抑郁量表评分在 8 周内显著降低
Schaub <i>et al.</i> [80]	抑郁障碍患者	生物制品(嗜热链球菌 + 短双歧杆菌 + 长双歧杆菌 + 婴儿双歧杆菌 + 嗜酸乳杆菌 + 植物乳杆菌 + 副干酪乳杆菌 + 德氏乳杆菌亚种 + 瑞士乳杆菌)	益生菌组汉密尔顿抑郁量表分值较安慰剂组显著下降($t(40.55) = 2.11$, $P < 0.05$)
Lin <i>et al.</i> [81]	合并轻度 - 中度焦虑和抑郁行为的肠易激综合征患者	粪菌移植	粪菌移植治疗可在短期治疗后缓解焦虑、抑郁情绪, 且时间越长效果越好

疗效高度依赖于人体原有的菌群生态网络, 干预效果容易被个体的饮食习惯和宿主基因影响, 使得常规的剂量方案注定在部分人群中无效。另外, 微生态制剂及粪菌移植并非“绝对安全”, 对于免疫功能低下、肠黏膜屏障受损(如炎症性肠病)的共病抑郁患者, 活菌制剂存在易位至血液的潜在致命风险, 目前尚无针对高危人群的筛查标准。粪菌移植供体粪便中潜藏的耐药基因、病毒组(噬菌体)及致肥胖菌群可能随移植长期定植, 其表型效应可能数年才显现。

靶向肠道菌群为抑郁障碍的治疗带来了新的方案, 但它并非简单的“补充细菌”或“移植粪便”。在临床实践中, 标准化是基石, 个体化是灵魂, 安全性是底线。我们必须严谨地探索肠道菌群与人脑之间的双向调控机制, 不断地验证微生态干预疗法的安全性, 并开发出相对完善的个体化治疗方案, 微生态干预才能真正用于抑郁障碍治疗。

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