肠道菌群及其代谢物在抑郁症诊断和治疗中的作用研究进展

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摘要:肠道菌群及其代谢物在抑郁症的诊断与治疗中展现出重要价值。本文总结了抑郁症患者在不同阶段肠道菌群及代谢物的变化特征,探讨其作为早期诊断生物标志物和指导个体化治疗依据的可行性。同时,分析了多种干预方式对肠道菌群的调节机制及其对抑郁症状的影响。还阐述了基于肠道菌群的治疗策略,并提出需加强多模式联合干预与精准医学应用,以提高抑郁症的诊疗疗效。

关键词:抑郁症;肠道菌群;肠道菌群代谢物;菌群调节;药物治疗;物理治疗

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Research progress on the role of gut microbiota and its metabolites in the diagnosis and treatment of depression

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Abstract: The gut microbiota and its metabolites have shown significant value in the diagnosis and treatment of depression. This paper summarizes the changes in gut microbiota and metabolites in patients with depression at different stages, and explores their feasibility as early diagnostic biomarkers and the basis for personalized treatment. Meanwhile, the article analyzes various interventions that regulate the gut microbiota and their impact on depressive symptoms. The paper also discusses gut microbiota-based therapeutic strategies and suggests the need for enhanced multimodal combined interventions and the development of precision medicine to improve the effectiveness of depression diagnosis and treatment.

Key words: depression; gut microbiota; gut microbiota metabolites; microbiota regulation; drug treatment; physical therapy

抑郁症作为全球最常见的精神障碍疾病之一,也是导致长期致残的主要精神障碍疾病[1]。其病因复杂,涉及遗传、环境、心理社会和生物学等多种因素[2-3]。尽管近年来相关研究持续深入,但抑郁症的病理机制尚未完全明确,临床仍缺乏可靠的生物学诊断标志物和精准的机制解释。

近年来,肠道菌群在心理健康中的作用受到广泛关注。研究发现,抑郁症患者常伴有肠道菌群多样性和丰度下降,且特定菌群比例异常[4]。目前尚无充分证据明确抑郁症与肠道菌群紊乱之间的因果关系,但二者可能通过“脑-肠轴”相互作用。一方面,肠道菌群失衡可促进炎症因子释放,影响神经递质代谢、血脑屏障功能及神经网络活动,从而干扰脑功能,诱发抑郁[5]。另一方面,抑郁状态亦可通过神经内分泌等途径反向改变肠道菌群结构[6],形成双向调节机制。此外,研究显示,长期心理压力可破坏肠道屏障,诱发“肠漏”,使脂多糖等有害代谢产物进入血液,引发系统性炎症,损伤中枢神经系统,进而加重抑郁病情[7]。在此背景下,系统探讨肠道菌群及其代谢产物在抑郁症的诊断与治疗中的作用就显得尤为重要。

1　肠道菌群及其代谢物作为抑郁症诊断生物标志物的价值

目前,抑郁症的诊断主要依赖临床评估,依据《精神障碍诊断与统计手册》第5版(DSM-5)及《国际疾病分类》第11版(ICD-11)标准进行判定[8-9]。这些主观评估工具存在一定局限,缺乏客观的生物

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标志物,不仅增加诊断难度,也影响开展早期干预。抑郁症患者的肠道菌群及其代谢物在疾病的不同阶段均表现出特征性变化,不仅菌群组成发生改变,其丰度也随病程进展而波动。因此,探索其在抑郁症早期诊断中的应用价值具有重要意义。

1.1 阈下抑郁阶段肠道菌群微变化　在阈下抑郁阶段,患者可能尚未表现出典型的抑郁症状;但肠道菌群已开始出现微妙的变化。研究表明,阈下抑郁症患者的多样性指数已经发生变化[10-11],主要表现为菌群结构紊乱:有害菌或潜在致病菌(如大肠埃希菌-志贺菌属)相对丰度升高,有益菌(如霍氏真杆菌属、瘤胃球菌属、克里斯滕森菌属、副普雷沃菌属)相对丰度降低[12-13]。这些变化提示,肠道菌群失衡可能早于临床症状的出现,为抑郁症的早期识别和干预提供了潜在的生物学标志物,具有重要的诊断价值。

1.2 典型抑郁阶段肠道菌群变化　研究证实,随着病情进展,抑郁症患者在不同阶段均表现出肠道菌群及其代谢物的紊乱[14]。双歧杆菌和乳酸杆菌等抗炎益生菌在抑郁症患者中的丰度出现显著性下降,这些益生菌的减少会削弱肠道屏障功能,增加肠道通透性,使炎症因子更容易进入全身循环,从而通过肠-脑轴影响神经递质代谢,导致大脑微环境改变从而诱发抑郁症[15-16]。拟杆菌和普雷沃菌等促炎菌在抑郁症患者中的丰度增加,其代谢产物(如脂多糖)会激活炎症反应,增加促炎性细胞因子的释放,例如白细胞介素-6(IL-6)和肿瘤坏死因子-α(TNF-α);这些炎症因子进一步干扰中枢神经系统功能,加重抑郁症状[17-18]。此外,短链脂肪酸(SCFAs)和色氨酸代谢紊乱是抑郁症患者肠道代谢物的特异性变化。SCFAs 含量的降低削弱了抗炎和神经保护功能,而色氨酸代谢的改变可能影响血清素等关键神经递质的合成,干扰情绪调节平衡[15-16,18]。肠道菌群失调通过炎症反应和神经递质代谢紊乱加重抑郁症状,提示调节肠道菌群可能是抑郁症治疗的新方向。

因此,肠道菌群及其代谢物具有作为抑郁症疾病发生、发展生物标志物的潜质,尤其有望成为抑郁症患者早期诊断的生物学标志物。

2 肠道菌群及其代谢物在传统抗抑郁症治疗过程中的变化

2.1 抗抑郁治疗对患者肠道菌群及代谢物的改变　传统的治疗方法主要包括药物治疗[如选择性5-羟色胺再摄取抑制剂(SSRIs)]和物理治疗(如经颅磁刺激和运动干预)等,可通过直接或者间接方式影响抑郁症患者肠道菌群及其代谢物。

药物治疗是抑郁症管理的主要手段之一,具有情绪调节作用及症状改善效果[19]。常用药物如 SSRIs 和去甲肾上腺素再摄取抑制剂(SNRIs),通过调节 5-羟色胺(5-HT)和去甲肾上腺素水平,缓解情绪低落、焦虑等症状,并促进脑源性神经营养因子(BDNF)表达,改善海马萎缩及前额叶功能障碍[20-21]。同时,抗抑郁药物可通过脑-肠轴多途径调节肠道菌群及其代谢产物。一方面,5-HT 等神经递质在调控中枢功能的同时也可影响肠道微生态,提升双歧杆菌和乳酸杆菌等益生菌丰度[22];另一方面,部分药物如阿米替林具有抗菌活性,可直接抑制致病菌生长[23-24];此外,抗抑郁药还可通过抑制炎症因子(如 IL-6、TNF-α),改善肠屏障功能,优化菌群结构[25-26]。例如,氟西汀和度洛西汀不仅调节 5-HT 通路,还可促进有益菌增殖和 SCFAs 如乙酸、丁酸的生成,维护肠道屏障完整性,降低炎症水平,增强抗抑郁作用[27-28];N-甲基-D-天冬氨酸受体拮抗剂(NMDA)氯胺酮可通过重塑菌群结构、增强免疫调节功能、增加 SCFAs 生成,以及减少拟杆菌和脱硫弧菌等有害菌,实现快速抗抑郁效应[29-30];褪黑素受体激动剂阿戈美拉汀则可促进褪黑素与 SCFAs 合成,改善昼夜节律,提高双歧杆菌丰度,减少炎性菌群(如 脱硫弧菌科、肽球菌科、毛螺菌科),并降低脂多糖水平[31-32]。综上,传统抗抑郁药物不仅通过中枢机制缓解症状,还可通过调节肠道菌群及其代谢功能增强疗效。

运动干预是研究最为广泛的物理治疗方式之一,其通过多种机制改善抑郁症患者的肠道菌群,并最终缓解抑郁症状。首先,运动能够通过影响海马和下丘脑中的谷氨酸(Glu)和 γ-氨基丁酸(GABA)受体的表达来调节下丘脑-垂体-肾上腺轴(HPA 轴)的激活状态,降低慢性应激引发的皮质醇分泌,改善肠道屏障功能,减少炎症反应[33-34]。研究表明,运动干预可以提高 BDNF 水平和神经递质(如多巴胺和 5-HT)的生成,间接调节肠道菌群结构及其代谢物变化,从而进一步改善患者情绪状态[35];同时,研究表明,运动对肠道菌群的直接影响包括增加菌群多样性,提升有益菌(如双歧杆菌、乳酸杆菌)丰度,并促进短链脂肪酸(如丁酸、丙酸)的生成,从而发挥抗炎作用[36]。研究报道,为期 12 周的中等强度有氧运动干预后,具有阈下抑郁特征的青少年

的微生物组中与神经退行性疾病相关的 KEGG 通路丰度减少,以及抑郁症状得到改善[37]。综上所述,运动疗法可能通过调节肠道菌群及其代谢物变化,进而影响抑郁症状的发生、发展。

重复经颅磁刺激(rTMS)是一种非侵入性技术,对抑郁症患者具有显著的临床疗效,特别是对于难治性抑郁症患者[38],通过电磁刺激大脑特定区域(如前额叶皮质),调节脑-肠轴的信号传递,间接影响肠道菌群的组成;rTMS 增加多巴胺、5-HT 和 BDNF 水平,并通过脑-肠轴影响肠道菌群,调节情绪并改善抑郁症状[39-40]。研究表明,rTMS 可通过减少中枢和外周炎症因子,改善肠道微生态环境异常,从而缓解抑郁效应[41]。在慢性不可预测性应激模型中,应用 rTMS 治疗的小鼠肠道菌群结构显著改善,乳杆菌属和粪杆菌属比例上升,同时抑郁样行为显著减轻[39]。整合大鼠粪便代谢组学和 16S rRNA 测序技术研究发现,rTMS 可通过调节肠道菌群,增加 SCFAs 生成,改善炎症和肠道屏障功能,减轻抑郁样行为,揭示其通过脑-肠轴调节抑郁的潜力[42]。因此,肠道菌群变化可能成为评估抗抑郁治疗效果的潜在生物标志物。

2.2　*抗抑郁治疗效应与肠道菌群变化密切相关*　抑郁症的治疗仍面临疗效不足、复发率高等挑战,30%~40%的患者对常见的抗抑郁药物(如 SSRIs 类药物)没有明显反应,进入难治性抑郁症的范畴[43];即使在初次治疗中有效的患者,多数也会在几年内经历疾病的复发[44]。还伴随有治疗反应的显著个体差异。虽然许多患者能够从抗抑郁药物中获益,但仍有相当一部分人群未能得到有效治疗或出现了药物耐受性问题。研究表明,肠道微生物群可能是重要的影响因素。Xie 等[45]发现,抑郁症患者的肠道微生物群基线特征在一定程度上决定了他们对抗抑郁药物(特别是 SSRI 类药物)的治疗反应。这一发现为基于肠道微生物群的个性化治疗提供了理论依据。因此,探索和识别哪些肠道菌群谱能够预测药物疗效,成为当前抑郁症研究的重要方向之一。Borgiani 等[46]则进一步探讨了抗抑郁药物与肠道微生物群之间的双向互动;他们提出,抗抑郁药物不仅能够通过改变肠道微生物群的组成来增强治疗效果,如厚壁菌门中 *Roseburia* 和 *Faecalibacterium* 属的基线 α 多样性和丰度增加与抗抑郁反应有关,有希望成为生物标志物。Gao 等[47]发现,SSRIs 类药物的疗效与患者肠道微生物群的组成有显著相关性。研究表明,益生菌(如双歧杆菌、乳酸菌)在某些患者中占主导地位时,治疗效果显著改善;而在肠道内病原菌占优势的患者中,SSRIs 的效果则可能不佳。Lin 等[48]的研究表明,肠道内的某些菌群特征(如双歧杆菌的增加)与抗抑郁药物的疗效相关联,这意味着通过监测肠道微生物群的变化,可能预测患者对不同抗抑郁药物的反应。因此,干预肠道菌群、补充益生菌、调整饮食等措施,可能有助于减少药物的不良反应并提升治疗效果。这一观点为未来抑郁症的个性化治疗方案提供了新的方向。

3　基于肠道微生物群的特异性抗抑郁治疗措施

3.1　*饮食干预*　饮食是肠道微生物组成和功能的关键决定因素。饮食、肠道微生物群和抑郁症之间的关联已被越来越多地探索[49]。其中,地中海饮食以其丰富的 omega-3 脂肪酸、多酚和抗氧化剂,通过减少炎症标志物(如 IL-6、TNF-α),显著改善抑郁症状[50]。随机对照试验如支持情绪低落人群的生活方式调整研究(SMILES 试验)和地中海饮食与健康生活研究(HELFIMED 试验)均证实,改善饮食结构可显著缓解重度抑郁症患者的症状,且疗效可持续数月[50-51]。此外,生酮饮食通过调节肠道菌群,增强 GABA 等神经递质的生成与释放,减轻神经炎症反应[52]。这些发现表明,饮食干预通过调节肠道菌群及其代谢产物发挥抗抑郁效应。

3.2　*粪便微生物群移植(FMT)*　FMT 是一种通过移植健康供体粪便中的肠道菌群,以重塑患者肠道微生态的创新治疗方法。动物实验为 FMT 在抑郁症中的应用提供了机制依据。将抑郁症患者的粪便移植至无菌小鼠体内,可诱导其出现抑郁样行为(如兴趣减退、活动减少及焦虑水平升高),并伴随海马神经发生受损和肠道炎症标志物升高[53-54]。类似地,慢性应激模型小鼠的粪便移植至无菌小鼠后,亦可诱发类似的行为异常与生物学改变[55]。上述结果提示,肠道菌群失调可能是抑郁样症状的重要诱因,而 FMT 通过恢复菌群稳态为抑郁治疗提供了新方向。进一步研究发现,将健康供体的粪便移植至表现抑郁样行为的小鼠,可显著改善行为异常,恢复神经递质平衡,并降低炎症水平[53]。尽管目前大多数证据来自动物实验,但初步临床研究也显示积极信号。一项随机对照试验显示,接受冷冻干燥 FMT 胶囊治疗的重度抑郁症患者在治疗 4 周后抑郁症状(如汉密尔顿量表评分)显著减轻,肠道菌群多样性及代谢功能亦明显改善[56]。综上,通过 FMT 调节肠道微生态,可能成为抑郁症治疗中具有转化

潜力的新型治疗策略。

3.3 益生菌和益生元　益生菌与益生元作为肠道微生物群调节剂,在抑郁症的干预中显示出良好前景。益生菌可通过抑制慢性应激诱发的神经炎症、调节下丘脑-垂体-肾上腺轴功能、增强免疫调控等机制,有效缓解抑郁症状[57]。研究表明,干酪乳杆菌和嗜酸乳杆菌可上调 BDNF 表达,改善应激引起的海马神经元损伤[58]。益生元通过为益生菌提供代谢底物,间接增强其抗抑郁效应。主要机制包括促进 SCFAs 生成、改善肠道屏障功能、抑制炎症反应[59]。动物实验显示,半乳糖与低聚果糖联合可减轻小鼠的抑郁和焦虑行为,并逆转慢性应激带来的影响[60]。然而,亦有研究发现,肥胖伴重度抑郁女性在 8 周内补充 10 g 低聚果糖并实施热量限制,对抑郁症状的改善作用有限,提示其更适合作为辅助干预手段[61]。

益生菌与益生元联合应用(即合生元)通过多途径协同作用,展现更显著的抗抑郁效果[62]。例如,一项研究表明,由低聚半乳糖与瑞士乳杆菌、长双歧杆菌等多菌株复合合生元制剂,能够有效缓解抑郁症状,并改善重度抑郁障碍患者的色氨酸代谢通路[63]。此外,益生元、益生菌和合生元在大多数研究中都是辅助治疗措施;因此,其是否可以替代抗抑郁药物作为一线治疗仍然缺乏支持性证据。

4 总结与展望

研究表明,肠道菌群及其代谢物在抑郁症各阶段均发生显著变化,有望成为潜在的诊断生物标志物。通过药物、物理治疗、饮食和益生菌等手段调节菌群,可有效改善抑郁症状,为精准医疗提供新方向。然而,现有研究仍缺乏大规模临床验证和机制探讨,需开展多中心纵向研究以明确因果关联,并优化干预策略。同时,应加强多种干预手段的协同研究,探索联合治疗的效果与机制,全面提升患者生活质量。

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