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肠道菌群调控抑郁症炎症反应和氧化应激的机制及应用前景

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摘要 抑郁症是一种常见的精神障碍, 具有高自杀、高致残风险, 对患者的生活和工作造成严重的负面影响, 加重了家庭和社会的经济负担. 在全球新型冠状病毒感染大流行期间, 抑郁症的复发率和患病率显著上升, 国家卫生和计划生育委员会等部门将抑郁症的防治列入我国精神卫生工作的重点. 抑郁症患者机体处于炎症和应激状态, 肠道菌群发生紊乱. 肠道菌群结构和组成的改变可能是抑郁症的潜在影响因素, 其可作为抗抑郁治疗的靶点, 在缓解和治疗抑郁症方面有一定的效果. 本文综述了肠道菌群基于"肠-脑"轴在抑郁症炎症反应、氧化应激中发挥的作用, 抗抑郁药与肠道菌群之间的相互作用以及其他通过调节肠道菌群抗抑郁的疗法, 如饮食疗法、益生菌、益生元、后生元、粪便移植等, 以期为促进以肠道菌群为靶点治疗抑郁症的精准医学发展提供参考.

关键词 肠道菌群, "肠-脑"轴, 抑郁症, 炎症, 氧化应激

抑郁症是一种常见的精神障碍. 在抑郁发作期间, 患者会感到悲伤、烦躁、过度内疚或自我认知低下, 重度抑郁症患者甚至会对未来感到绝望产生自杀的想法, 严重影响了患者的工作和生活[1]. 据世界卫生组织(World Health Organization, WHO)统计, 世界上大约有3亿抑郁症患者[2]. 青少年处于社会、情感和认知快速发展和人生转变的关键时期, 近年来青少年抑郁症患病率急剧上升[3]. 在人的一生中, 女性抑郁症的发病率大约是男性的2倍[4]. 全球7%~30%的女性和一些贫困地区约45%的女性会出现产后抑郁症状[5]. 而且, 近年来新型冠状病毒(corona virus disease 2019, COVID-19)在全球广泛传播, 扰乱了人们正常的生活和工作秩序, 使得抑郁症的患病率和复发率显著增加[6].

肠道菌群是寄居在人体消化道内的微生物[7], 被视为一个"动态器官", 在大脑功能和情绪调节中发挥重要作用. 一方面, Kelly等人[8]将抑郁症患者的肠道菌群移植到缺乏肠道菌群的大鼠身上, 诱导了大鼠产生抑郁样行为. 另一方面, Winter等人[9]研究发现, 诱导啮齿类动物出现抑郁样行为, 会导致其肠道菌群的丰度降低. 抗抑郁药是首选用于治疗中度至重度抑郁症患者的方法. Meißner等人[10]研究发现, 由于个体差异, 在服用抗抑郁药的患者中, 仅5%~20%的患者会得到完全而持久的缓解, 还有约30%的患者没有达到预期的治疗效果[11], 并且长期服用抗抑郁药物可能会出现发胖、大量出汗、性功能障碍等副作用, 其中50%以上的患者停止服用抗抑郁药后会发生戒断反应[12], 这可能会进

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一步加重抑郁程度. 因此, 可以联合副作用相对较小的中药与之优势互补产生更好的抗抑郁功效. 此外, 还有饮食干预、微生态制剂和粪便移植等基于肠道菌群辅助治疗抑郁症的安全、个性化措施.

1 肠道菌群与抑郁症的关系

1.1 抑郁症患者的肠道菌群变化特征

肠道菌群及其代谢产物在调控抑郁症患者生理反应中发挥重要作用, 关注肠道菌群的改变可为抑郁症的预防、诊断、治疗及预后提供思路. Mudimela等人[13]研究发现, 健康个体的肠道菌群环境主要由79%厚壁菌门(Firmicutes)、17%拟杆菌门(Bacteroidetes)、3%放线菌门(Actinobacteria)、0.9%变形菌门(Proteobacteria)和0.1%疣微菌门(Verrucomicrobia)组成. Nikolova等人[14]分析成年精神病患者肠道菌群后发现, 患者体内的微生物数量显著减少. 根据香农指数(Shannon Index)结果发现[15], 抑郁症患者肠道微生物区系中的Bacteroidetes、Actinobacteria和Proteobacteria的丰度高于健康人, 而Firmicutes的水平低于健康人. Liu等人[16]分析了抑郁症患者和抑郁老鼠模型肠道菌群在门水平和种水平发生的变化, 结果如图1所示.

随着宏基因组学、元转录组学和代谢组学等技术的发展, 宿主肠道菌群的代谢路径被逐渐揭示[17]. 肠道菌群主要的代谢产物之一是短链脂肪酸(short chain fatty acid, SCFAs), 其中包含乙酸、丙酸和丁酸, 它们在维持机体代谢、神经和免疫系统方面发挥着重要作用[18]. 与抑郁症病理生理学相关的肠道菌群及其代谢产物如表1所示. 例如, SCFAs能够通过调节神经可塑性、表观遗传和基因表达等方式作用于中枢神经系统(central nervous system, CNS)[25]. Rathour等人[26]研究发现, SCFAs穿过血脑屏障(blood-brain-barrier, BBB)后与各自的游离脂肪酸受体结合, 参与多种神经功能, 如影响情绪、认知、脑源性神经营养因子(brain derived neurotrophic factor, BDNF)的释放, 5-羟色胺(5-hydroxytryptamine, 5-HT)合成等. Skonieczna-Żydecka等人[27]在波兰抑郁症女性粪便样本中发现, 乙酸和丙酸的含量与贝克抑郁量表(Beck's depression inventory, BDI)呈负相关, 即表明抑郁症患者体内SCFAs含量降低.

1.2 肠道菌群与抑郁症炎症反应和氧化应激的关系

炎症的发展与精神疾病之间有着密切的联系[28]. Mac Giollabhui等人[29]通过Meta分析(Meta-analysis)发现, 较高的炎症生物标志物, 如C反应蛋白(C-reactive

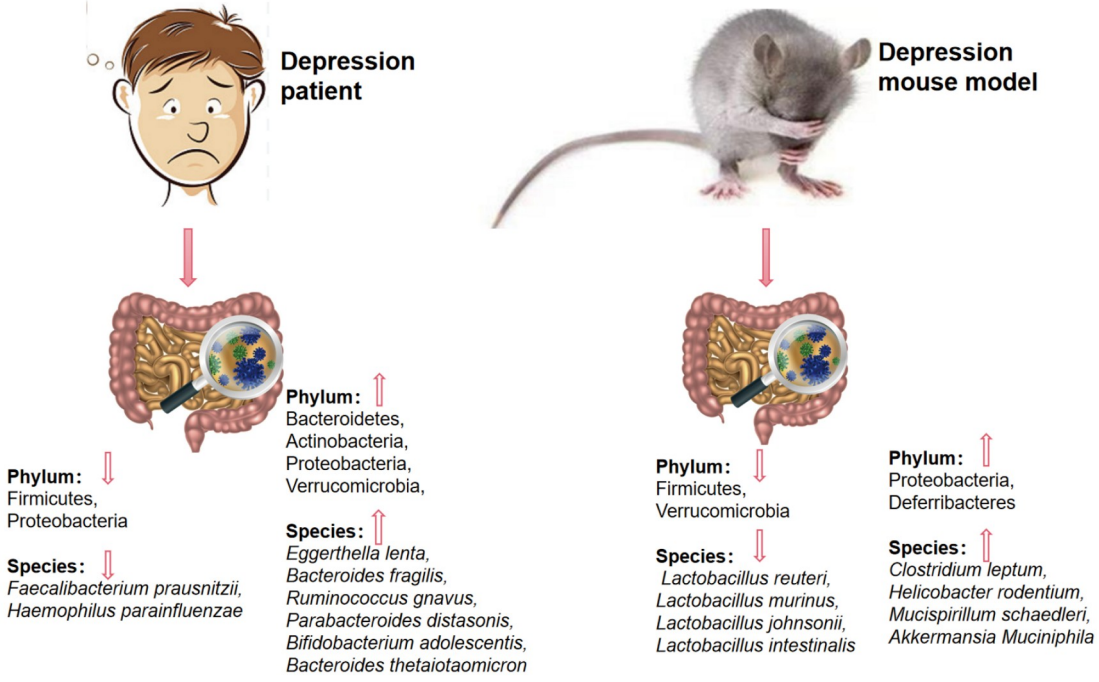

图 1 (网络版彩色)抑郁症患者和抑郁老鼠模型肠道菌群在门和种水平的变化[16]
Figure 1 (Color online) Changes of intestinal flora at phylum and species level in depressed patients and depressed mouse models[16]

表 1 肠道菌群相关代谢产物改善抑郁症

Tabel 1 Intestinal microbiota related metabolites improve depression

肠道菌群代谢产物	相关细菌	发挥的抗抑郁作用
短链脂肪酸, 如丁酸盐、丙酸盐	植物乳杆菌(*Lactobacillus plantarum*)[19]、普氏粪杆菌(*Faecalibacterium prausnitzii*)[20]	通过调节肠腔pH、黏液生成、上皮细胞活性和免疫系统来帮助维持肠道屏障的完整性; 在中枢神经系统中, SCFAs是小胶质细胞成熟和功能的主要介质. 通过减轻外周及中枢的炎症反应而起到抗抑郁作用
色氨酸代谢物, 如吲哚、犬尿氨酸和5-HT	梭菌属(*Clostridium*)、伯克氏菌属(*Burkholderia*)、链霉菌属(*Streptomyces*)、假单胞菌属(*Pseudomonas*)、芽孢杆菌属(*Bacillus*)	色氨酸代谢为吲哚、犬尿氨酸和5-HT, 能够调节神经内分泌和免疫系统, 如降低神经炎症、减少应激反应、调节脑源性神经影响因子的释放; 具有抗抑郁的功效[21]
乳酸	乳酸菌(*Lactic acid bacteria*)、双歧杆菌(*Bifidobacteria*)	可以穿过血脑屏障以满足大脑的能量需求, 影响许多神经元功能, 如兴奋性、可塑性和记忆巩固. 乳酸盐的外周给药有抗抑郁作用, 这种作用与海马乳酸盐水平升高以及改善星形胶质细胞功能、促进神经发生等变化有关[22]
神经递质, 如γ-氨基丁酸(GABA)	青春双歧杆菌(*Bifidobacterium adolescentis*)、植物乳杆菌(*Lactobacillus plantarum*)	GABA是运动和分泌活动的调节剂, 调节免疫细胞活动, 具有抗高血压、镇痛、抗抑郁和镇静作用[23]
其他代谢产物, 如胆汁酸	苏黎世杆菌属(*Turicibacter*)	肠道菌群或胆汁酸的失衡可能导致肠道屏障和完整性的损害. 胆汁酸可能通过代谢为具有抗炎作用的次级胆汁酸而发挥抗抑郁作用[24]

protein, CRP)和白细胞介素-6(Interleukin-6, IL-6)与抑郁症的发生相关, 而且抑郁症状的加重与血液中CRP和IL-6含量升高相关. Peirce和Alviña[30]发现, 抑郁症患者和抑郁动物模型的肠道菌群结构改变, 如与炎症相关的细菌门如Bacteroidetes丰度增加、与缓解炎症相关的细菌门如Firmicutes丰度减少. 向早期母性分离(Maternal Separation, MS)小鼠补充益生菌婴儿双歧杆菌(*Bifidobacterium infantis*)后其免疫反应趋于正常. 肠道菌群的代谢产物SCFAs如丁酸盐影响免疫细胞活性, 在免疫反应期间促进巨噬细胞和肠道树突状细胞中抗炎细胞因子IL-10的表达, 且增强调节性T细胞(Regulatory cells, Tregs)的抗炎活性, 使肠道防御能力增强, 限制了神经炎症, 从而有益于大脑活动和精神健康.

由于大脑需要较高的耗氧量, 而且抗氧化因子相对有限, 容易受到氧化应激的影响. 氧化应激主要是因活性氧(reactive oxygen species, ROS)增加和抗氧化防御功能减弱而触发促炎信号传导, 导致细胞、线粒体蛋白、脂质和DNA的氧化损伤[31]. 炎症和氧化应激介导的肠道菌群紊乱和抑郁症发生的过程如图2所示. Trzeciak和Herbet[32]研究发现, 抑郁症患者血浆中氧化应激标记物如丙二醛(malondialdehyde, MDA)浓度升高, 抗氧化酶如过氧化氢酶的活性降低, 表明抑郁症患者处于氧化应激状态. Mariani等人[33]研究发现, 抗抑郁药物能够减少抑郁小鼠模型的氧化应激, 选择性5-羟色胺再摄取抑制剂(selective serotonin reuptake inhibitors, SSRIs)类抗抑郁药, 如氟西汀、西酞普兰和舍曲林阻碍了诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)的产生, SSRIs如帕罗西汀、氟伏沙明和丙咪嗪阻碍了一氧化氮(nitrogen monoxide, NO)的产生. 这些结果表明, 抗抑郁药能够通过减轻氧化应激而发挥其抗抑郁特性. Dhaliwal等人研究[22]发现, 补充植物乳杆菌(*Lactobacillus plantarum*)可预防压力引起小鼠的抑郁样行为, 减少氧化应激标志物和促炎细胞因子的水平; 也可改善肠道菌群的结构和血脑屏障的通透性, 促进乳酸杆菌属(*Lactobacillus* sp.)的生长, 降低肠杆菌科(*Enterobacteriaceae*)的丰度. 长期补充*L. plantarum*可修复压力应激小鼠的行为缺陷, 并降低血浆皮质酮水平, 使过度激活的下丘脑-垂体-肾上腺轴(hypothalamic-pituitary-adrenal, HPA)趋于正常.

1.3 抑郁症中的“肠-脑”轴变化

“肠-脑”轴在维持体内平衡中发挥重要作用, 肠道菌群是肠道与大脑“交流”中不可或缺的组分, 由此“肠道菌群-肠-脑(Microbiota-Gut-Brain, MGB)”轴概念被提出. 肠道微生物通过神经元、内分泌和免疫信号途径与CNS“交流”. CNS可以通过自主神经系统(autonomic nervous system, ANS)调节肠道菌群的结构和功能[34]. Agirman等人[35]研究表明, 抑郁症患者的肠道通透性增加会使血浆中脂多糖(lipopolysaccharide, LPS)含量上升, 破坏了血脑屏障(Blood-Brain Barrier, BBB)

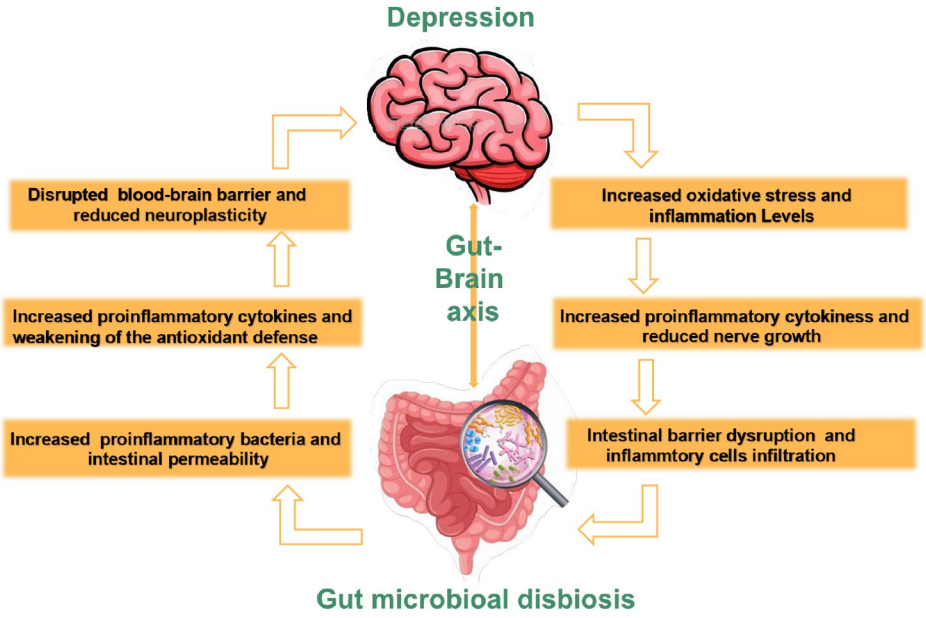

图 2 (网络版彩色)肠道微生物群紊乱与抑郁症的炎症和氧化应激反应流程
Figure 2 (Color online) Inflammatory and oxidative stress response processes in intestinal microbiota disturbances and depression

的完整性, 大量的炎症因子和神经毒素进入脑组织, 激活免疫细胞产生炎症反应, 从而导致抑郁症的发生[36]. 迷走神经、神经递质、下丘脑-垂体-肾上腺轴和免疫系统途径(如图3所示)可以改善抑郁症患者MGB轴的功能障碍.

1.3.1 迷走神经途径

迷走神经(vagus nerve, VN)支配消化系统的绝大多数器官, 是连接肠和脑的重要纽带. VN具有抗炎特性, 能够通过激活HPA轴和释放皮质醇以及VN反射来调节肠道功能、维持肠道稳态[37]. Pope和Wood[38]研究发现, VN能够改善炎症或氧化应激诱导的抑郁症. Siopi等人[39]研究发现, 切除VN修复了慢性不可预测性温和应激(chronic unpredictable mild stress, CUMS)小鼠海马神经发生缺陷, 降低了神经炎症即促炎细胞因子如肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)、白介素-1β(interleukin-1β, IL-1β)和白介素-6(interleukin-6, IL-6)的浓度以及改善了小鼠抑郁样行为.

1.3.2 神经递质

肠道内产生和释放多种神经递质, 如谷氨酸、γ-氨基丁酸(γ-aminobutyric acid, GABA)、5-HT和多种神经肽等. 神经递质为"肠-脑"轴双向"交流"的信使. 大脑可以通过下丘脑和脊髓神经元向肠道发送神经调节信号, 通过释放神经递质来调节肠道运动、黏膜屏障功能和肠道免疫反应, 肠道中的神经递质可以通过"肠-脑"轴向大脑传递信号, 影响情绪和认知等功能.

De Vadder等人[40]研究发现, 人体内约90%的5-HT是在肠道上皮产生, 其能够调节CNS和肠神经系统(enteric nervous system, ENS)的发育和功能. 神经元产生5-HT缺陷可能会导致脑和肠功能障碍[41]. 色氨酸羟化酶-2(TPH2)是CNS和ENS合成5-HT的限速酶, 该酶催化活性的缺失将导致5-HT合成及释放的减少, 如突变体(TPH2-R439H)小鼠CNS中5-HT水平降低60%~80%, 并表现出抑郁样行为. 通过直接向该小鼠喂养5-HT的前体物质5-羟基色氨酸(5-Hydroxytryptophan, 5-HTP)的缓释剂, 可以减少小鼠抑郁样行为.

谷氨酸是主要的兴奋性神经递质, 大脑中谷氨酸水平与情绪、精神障碍等有关. 谷氨酸释放、传递失调是抑郁症的主要原因之一. Cui等人[42]研究发现, 炎症环境下胶质细胞上谷氨酸转运体的表达减少, 致使突触外谷氨酸浓度升高且优先与N-甲基-D-天冬氨酸受体(N-methyl-D-aspartate, NMDA)结合, 这导致BDNF的合成和释放受到抑制、神经元功能障碍进而引发抑郁的发生. 而且, Kadriu等人[43]研究发现抗抑郁药氯胺酮(Ketamine)通过抑制NMDA受体等途径持续增强兴奋性突触, 增加了突触前谷氨酸释放, 从而起到抗抑郁的效果.

1.3.3 下丘脑-垂体-肾上腺轴

HPA轴是人体最重要的神经内分泌轴[44]. 大多数

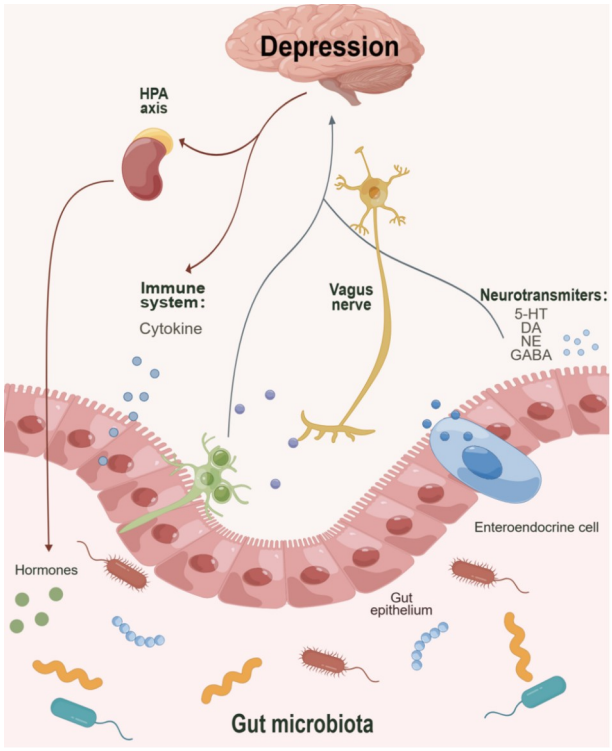

图 3 (网络版彩色)抑郁症患者MGB轴迷走神经、神经递质、下丘脑-垂体-肾上腺轴和免疫系统途径

Figure 3 (Color online) MGB axis vagus nerve, neurotransmitter, hypothalamic-pituitary-adrenal axis and immune system pathway in depressed patients

抑郁症患者HPA轴负反馈调节受损，处于过度激活状态，在临床上表现为对促肾上腺皮质激素释放激素(corticotropin releasing hormone, CRH)和肾上腺皮质激素(adrenocorticotropic hormone, ACTH)分泌增加以及血浆皮质醇含量升高[45]，由此激活了天然免疫系统产生促炎细胞因子和神经递质，影响肠道神经元的活性，并通过“肠-脑”轴传递信号到大脑. 另外，抑郁症患者肠道菌群失调和肠道黏膜屏障损伤可能会引发免疫炎症反应，激活免疫细胞，产生促炎细胞因子影响HPA轴的调节. Almeida等人[46]发现，GABA信号通路能够调节HPA轴对压力应激的反应. 其主要是通过激活γ-氨基丁酸A型受体(GABA type A receptors, GABAARs)以促进氯离子内流和突触后神经元的超极化，最终减轻HPA轴的功能紊乱. 抑郁症患者HPA轴变化显示了抑郁症患者在身体和心理层面上的应激反应异常，其中具体机制仍然需要深入研究.

1.3.4 免疫系统途径

免疫系统能够调节MGB轴的功能. 抑郁症患者肠道菌群失调，使其肠道屏障的通透性发生改变，细菌及其代谢产物向外周释放促炎细胞因子破坏BBB，致脑中促炎细胞因子如IL-6、IL-1β含量增加，激活NOD样受体热蛋白结构域相关蛋白(NOD-like Receptor Thermal Protein Domain Associated Protein 3, NLPR3)，该免疫过程可能是促使抑郁症发生的原因[47]. 抑郁症患者的先天免疫系统失调. Abdel-Haq等人[48]研究发现，小胶质细胞是大脑的先天免疫细胞，肠道菌群在小胶质细胞成熟和功能中发挥重要作用. 观察无特定病原体(specific pathogen free, SPF)小鼠和无菌(germ-free, GF)小鼠的小胶质细胞发现，两者小胶质细胞的结构和功能存在显著差异. 肠道菌群的变化也可能导致小胶质细胞表型的改变，从而介导其发挥“免疫监视”的作用. Walther等人[49]发现，抑郁症患者的外周血细胞更容易变形，其中淋巴细胞、单核细胞和中性粒细胞受到的影响最大，表明抑郁症患者的免疫细胞发生了力学变化，这可能是抑郁症发生持续免疫应激的原因.

2 肠道菌群与抗抑郁药相互作用

目前，药物干预仍然是抑郁症的主要治疗手段. 药物可以对肠道菌群产生直接作用，也可以通过其对宿主的药效学作用间接改变微生物的生长环境，从而影响肠道菌群的结构和功能；肠道菌群可以通过酶促反应改变抗抑郁药物的生物活性、生物利用度从而改变药物的疗效[50]. Klünemann等人[51]研究发现，唾液链球菌(*Streptococcus salivarius*)和大肠杆菌IAI1(*Escherichia coli* IAI1)等多种致病菌增加了5-羟色胺和去甲肾上腺素再摄取抑制剂(serotonin and noradrenaline reuptake inhibitiors, SNRIs)类抗抑郁药度洛西汀的生物蓄积，这可能降低了度洛西汀的生物利用度从而降低了其疗效. Vich Vila等人[52]研究发现抑郁症患者使用抗抑郁药后肠道菌群失调有所改善，如SSRIs治疗增加了肠道真杆菌(*Eubacterium*)的丰度，三环类抗抑郁药(tricyclic antidepressants, TCAs)增加了麻风梭菌(*Clostridium leptum*)的丰度. 这些细菌在代谢过程中会产生具有抗炎作用的丁酸盐，其含量的增加可能会提高抗抑郁药的疗效，对抗抑郁治疗有积极作用.

除此之外，一些中药基于其生物活性成分与作用靶点的多样性，具有抗抑郁的作用，还可以避免常规抗抑郁药治疗引起的副作用[53]. 《伤寒论》报道了用小柴胡汤(Xiaochaihutang, XCHT)、四逆散(Sinisan, SNS)、柴胡加龙骨牡蛎汤(Chaihujialonggumulitang,

CHJLGMLT)、栀子豉汤(Zhizichitang, ZZCT)、栀子厚朴汤(Zhizihoupotang, ZZHPT)治疗心烦[54]. 中药主要是通过调节神经递质及其受体[55]、HPA轴[56]、BDNF[57]、肠道菌群结构及其代谢[58]等途径发挥抗抑郁作用. Ma等人[59]对肉桂油研究发现, 肉桂油有效地提高了CUMS小鼠大脑中神经递质如多巴胺(dopamine, DA)、去甲肾上腺素(norepinephrine, NE)的水平, 并降低了血浆中皮质酮的含量, 抑制了HPA轴功能亢进和炎症因子的表达, 还能恢复肠道菌群的稳态, 从而发挥较强的抗抑郁作用. Dong等人[60]从莲子芯中提取出甲基莲心碱(neferine, Nef), 对其抗抑郁特性研究发现, Nef增加了抑郁小鼠肠道乳酸杆菌(*Lactobacillus*)丰度和抗抑郁神经递质DA、5-HT和NE的水平, 减轻了抑郁小鼠炎症反应和氧化应激, 从而改善了小鼠的抑郁样行为. 此外, 诸如开心散(Kai-Xin-San)、逍遥散(Xiaoyao Powder)和柴胡疏肝散(Chaihu Shugan Powder)等中药, 可以通过多组分协同调节肠道菌群平衡、发挥抗抑郁作用[50]. 中药在调节抑郁症患者的肠道菌群及其代谢产物方面展现出一定的潜力, 但其具体机制还需要进一步地研究, 在使用中药治疗抑郁症时, 应遵医嘱服用, 并结合其他方法联合治疗.

3 肠道菌群在抗抑郁症的应用前景

“肠-脑”轴的稳态有益于改善精神疾病、维持人们心理健康. 肠道菌群基于“肠-脑”轴辅助治疗抑郁症的措施主要有改善饮食模式, 摄入益生菌、益生元、合生素和后生元以及粪便移植(如图4所示).

3.1 饮食调节肠道菌群干预抑郁症

饮食可以通过调节肠道菌群、炎症反应、氧化应激、HPA轴等方式减轻抑郁症[61]. Firth等人[62]研究发现, 饮食干预在抑郁症治疗和自我疗愈中发挥辅助治疗作用, 有望成为一种新的干预抑郁症的措施. 高质量的饮食如地中海饮食, 是一种经典的抗炎饮食模式[63]. Krznarić等人[64]研究发现, 地中海饮食能减少肠道中致病菌如大肠杆菌(*Escherichia coli*, *E. coli*)的数量, 提高有益菌如双歧杆菌(*Bifidobacteria*)的比例, 产生更多的SCFAs. 而低质量的饮食如高脂饮食, 降低了肠道菌群的多样性, 增加了抑郁症的患病风险. Labban等人[65]研究发现, 喂食高脂饮食的大鼠大脑中的5-HT水平显著减少, 血液和大脑中促炎细胞因子增多, 并且小鼠肠道菌群失调如Firmicutes丰度显著降低而Bacteroidetes水平显著增加. 饮食干预对抑郁症的影响可能是多方面的. 在抑郁症的病理生理学中还有许多其他潜在的机制未被发现, 可能被饮食干预所调节.

3.2 微生态制剂辅助治疗抑郁症

微生态制剂(probioties)主要包括活菌、死菌及其代谢产物, 其中益生菌、益生元、合生素和后生元属于微生态制剂. 其能够促进正常微生物群生长、抑制致病菌繁殖, 维持肠道稳态, 因此能够用于调节抑郁症患者肠道菌群的平衡.

益生菌(probiotics)是最具潜力的微生物制剂之一, 其治疗潜力已在精神健康障碍、肥胖、肠易激综合征等疾病中得到验证[66]. 益生菌通过降低促炎细胞因子的水平、改善肠道屏障功能、调节HPA轴与VN活性等机制, 更好地改善抑郁症状[67]. 常使用的益生菌有嗜热链球菌(*Streptococcus thermophilus*)、保加利亚乳杆菌(*Lactobacillus bulgaricus*)、嗜酸乳杆菌(*Lactobacillus-acidophilus*)、两歧双歧杆菌(*Bifidobacterium-bifidum*)[68]等.

益生元(prebiotics)为一种被宿主微生物选择性利用的有益于健康的底物[69], 主要通过促进有益菌如*Bifidobacteria*和*Lactobacillus*的生长改善肠道菌群失衡[70]. Yang等人[71]研究发现, 低聚半乳糖(galacto-oligosaccharides, GOS)通过增加肠道SCFAs的水平、促进神经递质的合成以及降低血液中促炎细胞因子的浓度等途径有效地减轻了受试者抑郁症状.

合生素(synbiotics)又称合生元, 为益生菌和益生元两者优点的结合[72], 能够通过调节肠道菌群结构及其代谢产物如SCFA的产生、降低促炎细胞因子如TNF-α、减少氧化应激以及增加血清BDNF的水平等方式, 改善人们的心理状况[73]. Kleniewska和Pawliczak[74]研究发现, 使用合生素如干酪乳杆菌(*Lactobacillus casei*)联合菊粉(inulin)干预健康志愿者, 受试者的氧化应激参数如丙二醛、过氧化氢含量降低, 抗氧化酶如过氧化氢酶活性增加, 保护了人体免受氧化应激的损伤.

后生元(postbiotics)是一种对宿主有益的无生命的微生物和/或其组分的制剂[75]. Maehata等人[76]研究发现, 热灭活瑞士乳杆菌(*Lactobacillus helveticus* strain) MCC1848逆转了亚慢性和轻度社交失败应激(subchronic and mild social defeat stress, sCSDS)模型小鼠大脑中多巴胺受体D3(Dopamine receptor D3, Drd3)和5-羟色胺1A受体(serotonin 1A receptor, Htr1a)表达水平的降

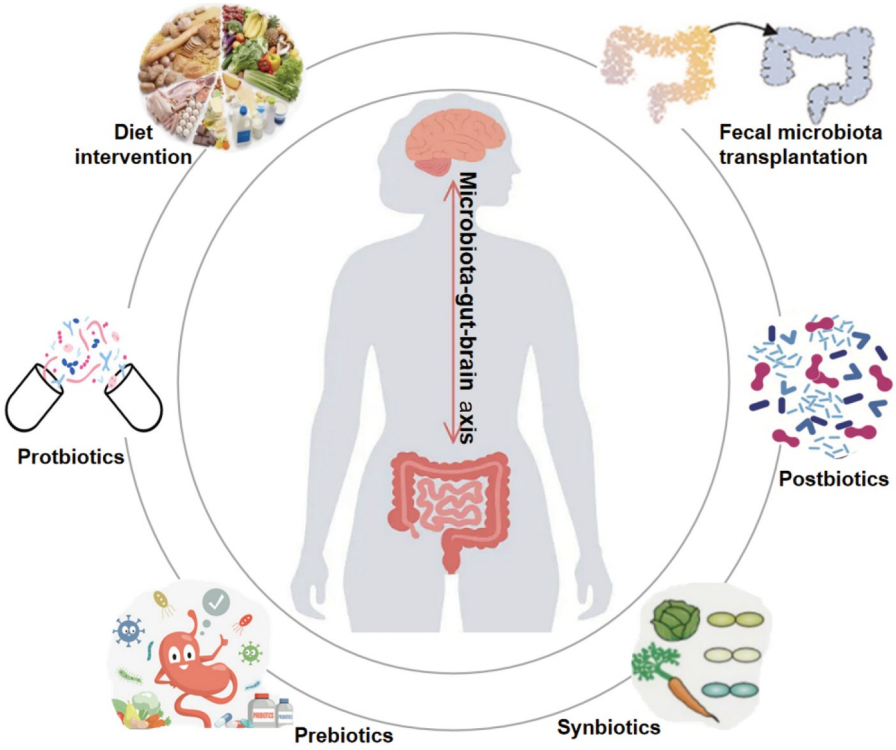

图 4 (网络版彩色)通过饮食干预, 补充益生菌、益生元、合生素和后生元, 以及粪便移植的方式辅助治疗抑郁症
Figure 4 (Color online) Dietary intervention, supplementation of probiotics, prebiotics, synbiotics and metabiotics, and fecal transplantation assisted the treatment of depression

低, 表明MCC1848有助于维持神经多巴胺能和5-羟色胺能系统稳定, 从而改善sCSDS小鼠抑郁样行为.

微生态制剂可能是神经精神药理学领域中新的治疗靶点, 然而未来仍需大量样本和前瞻性研究其对抑郁症治疗的真正益处及其背后的复杂机制.

3.3 粪便移植重塑抑郁症肠道菌群

粪便移植(fecal microbiota transplantation, FMT)是通过移植健康供体粪便中的功能菌群来重塑患者肠道菌群的方法. Rao等人[77]研究发现, FMT改善了CUMS大鼠抑郁样行为, 改善了肠道菌群失调, 缓解了大鼠肠道炎症、肠黏膜破坏和神经炎症. Lin等人[78]研究发现, FMT在治疗肠易激综合征(irritable bowel syndrome, IBS)时患者的焦虑和抑郁行为也逐渐改善. 高通量测序结果显示, FMT增加了有益菌双歧杆菌(*Bifidobacteria*)的数量, 降低了有害菌粪杆菌属(*Faecalibacterium*)、真杆菌属(*Eubacterium*)和埃希氏菌属(*Escherichia*)的丰度.

随着FMT临床试验和应用的增多, FMT的一些不良反应, 如腹泻、便秘、腹痛和短暂的低烧等也被发现, 但这些症状有可能在几天或几周内得到缓解[79]. 目前正在试验一种侵入性更小、更标准化的冻干粪菌胶囊, 集合了安全有效、方便使用等优势[80]. FMT抗抑郁作用机制涉及面广且复杂, 需要更多的临床试验评估这种疗法的副作用、供体的安全性, 最终实现能够在实验室中重建肠道菌群以维持人体肠道微生态的平衡.

4 讨论与展望

总之, 抑郁症患者肠道菌群的结构和功能发生改变, 肠道菌群失调又进一步加剧了抑郁症的严重程度. 通过补充相应的肠道菌群或其代谢产物可以降低抑郁症患者的炎症和氧化应激水平, 以维持机体代谢稳态. 目前抗抑郁药是治疗抑郁症的主要方式, 随着对肠道菌群以及MGB轴的不断探索, 中药在抗抑郁症中的应用也越来越受到人们的青睐. 而且通过调整饮食模式、补充微生态制剂和FMT等治疗方式, 有助于调控抑郁症患者的肠道稳态, 从而起到抗抑郁的作用.

随着宏基因组学、元转录组学等技术的不断发展, 对抑郁症患者肠道菌群及其代谢产物变化的认识将更加深入, 也将使微生物疗法的临床应用更加安

全、精准与高效. 然而目前还面临一些挑战, 诸如: (1) 探究抑郁症患者MGB轴的病理机制, 分离并鉴定关键菌株, 并建立基于抑郁症防治的菌株资源数据库; (2) 在分析抑郁症患者肠道菌群结构和功能变化时, 需要考虑细菌与细菌以及细菌与其代谢产物的相互作用等混杂因素的影响, 推动基于肠道菌群治疗抑郁症的精准医学发展; (3) 研究多种抗抑郁药物与肠道菌群之间的相互作用, 前人的研究多集中于单种药物与肠道菌群的相互作用, 然而重度抑郁症患者需要联合用药. 随着药物微生物组学发展, 人们将对两者关系有更深入的理解, 为提高抗抑郁药的疗效、降低其不良反应奠定理论基础.

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Summary for “肠道菌群调控抑郁症炎症反应和氧化应激的机制及应用前景”

The mechanism and application prospect of intestinal flora regulating inflammatory response and oxidative stress in depression

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Depression, a prevalent mental disorder, is characterized by feelings of sadness, irritability, excessive guilt, low self-esteem, and in severe cases, hopelessness and suicidal ideation. These symptoms significantly impact the quality of life and functioning of affected individuals. Approximately 300 million people worldwide suffer from depression, leading to substantial financial and social burdens. The COVID-19 pandemic has further exacerbated the recurrence rates and prevalence of depression, emphasizing the need for effective intervention strategies. Notably, National Health and Family Planning Commission of the People’s Republic of China and other relevant authorities have prioritized the prevention and treatment of depression. Multiple studies have demonstrated a strong association between inflammation and mental health. Patients with depression often exhibit elevated levels of pro-inflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor (TNF), etc. In addition, oxidative stress may be involved in the pathogenesis of depression. Patients with depression often exhibit an imbalance in oxidative stress levels. For instance, the concentration of oxidative stress markers, such as malondialdehyde, increases, whereas the activity of antioxidant enzymes, such as catalase, decreases, etc. These physiological changes compromise the integrity of the intestinal barrier and enhance the permeability of the blood-brain barrier, contributing to the occurrence and development of depression. Pharmaceutical interventions remain the cornerstone of depression management. These medications can directly impact the intestinal flora or indirectly modulate the microbial environment through their pharmacodynamic effects on the host. This modulation impacts the composition and functionality of the intestinal microbiota, ultimately affecting drug efficacy. However, long-term antidepressant use may lead to undesirable side effects, such as weight gain, excessive sweating, and sexual dysfunction. Advancements in metagenomics and metabolomics have revealed the metabolic pathways of host intestinal flora. Changes in the structure and composition of intestinal flora may play a pivotal role in the pathogenesis of depression. Experimental studies have demonstrated that in individuals with depression, there is an increase in the abundance of Bacteroidetes, which are associated with inflammation. Conversely, there is a decrease in the abundance of Firmicutes, which are associated with reducing inflammation. The intestinal flora, often referred to as “dynamic organ”, resides in the human digestive tract and significantly influences brain function and emotional well-being. The complex “gut-brain” axis maintains homeostasis and facilitates communication between the gut and the brain. Consequently, this microbiota becomes a potential target for antidepressant therapy, showing promise in alleviating and treating depression. This paper reviews the role of “gut-brain” axis in inflammation and oxidative stress in patients with depression. In addition, it emphasizes the association between antidepressants and the intestinal flora. Our study compiles various approaches for aiding in the intervention or treatment of depression through the “gut-brain” axis. These methods include dietary adjustments, probiotics, prebiotics, postbiotics, and fecal microbiota transplantation (FMT). These developments contribute to the advancement of precision medicine strategies targeting the intestinal flora in the treatment of depression.

intestinal flora, “gut-brain” axis, depression, inflammation, oxidative stress

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