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Review 综述

丁酸产生菌在神经退行性变性疾病演进中的作用

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摘　要：神经退行性变性疾病是全球高发的中枢神经系统退行性变性疾病，其病理进程与肠道微生态失衡、肠-脑轴功能紊乱密切相关。新兴的肠-脑轴理论为阐释微生物跨器官调控中枢神经功能提供了新视角。近期研究表明，丁酸产生菌作为肠道微生态的核心功能类群，其异常变化与神经退行性变性疾病的发生发展在时间和空间维度上均存在关联，可能通过肠-脑轴途径调控中枢神经微环境及疾病病理进程。本文系统回顾了肠道微生态与脑之间的双向信号交流机制，分析了丁酸产生菌与神经退行性变性疾病之间的多维关联，包括其在不同临床特征患者中呈现的群体异质性，以及在疾病进展阶段的动态演变规律；总结了丁酸产生菌通过屏障保护、免疫调节、代谢调控及表观遗传修饰等途径调控疾病进程的作用机制，并进一步探讨了其作为疾病预测标志物及治疗靶点的临床应用潜力，提出未来可重点发展肠道源性丁酸产生菌的靶向干预策略，为推动丁酸产生菌在神经退行性变性疾病中的深入研究与临床转化提供理论依据和新思路。

关键词：肠-脑轴；神经退行性变性疾病；丁酸产生菌；作用机制；生物标志物

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Role of butyrate-producing bacteria in the progression of neurodegenerative diseases

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Abstract: Neurodegenerative diseases, a group of highly prevalent central nervous system disorders, are closely linked to gut microbiota dysbiosis and impaired gut-brain axis function. The emerging gut-brain axis theory offers a novel perspective to explain how microbes exert remote, cross-organ regulation over the central nervous system. Recent studies have indicated that butyrate-producing bacteria, a core functional component of the gut microbiota, exhibit dynamic changes temporally and spatially correlated with the onset and progression of these diseases. These bacteria are thought to modulate the central nervous system microenvironment and disease pathology *via* the gut-brain axis. This article systematically reviews the bidirectional signaling mechanisms between the gut microbiota and the brain, analyzing the complex, multidimensional relationship between butyrate-producing bacteria and neurodegenerative diseases. This analysis encompasses population heterogeneity in patients with diverse clinical features and the dynamic evolution of these bacterial communities across different disease stages. We summarize the key mechanisms by which butyrate-producing bacteria regulate disease progression, including barrier protection, immunomodulation, metabolic regulation, and epigenetic modification. Furthermore, we explore their clinical potential as predictive biomarkers and therapeutic targets. We propose that future research should prioritize the development of targeted intervention strategies for gut-derived butyrate-producing bacteria. This review aims to provide a theoretical foundation and novel insights to advance both the fundamental investigation and clinical translation of these bacteria in the context of neurodegenerative diseases.

Keywords: gut-brain axis; neurodegenerative disease; butyrate-producing bacteria; mechanisms of action; biomarkers

神经退行性变性疾病现已成为全球老龄化社会的重大健康挑战，其发病率随年龄增长显著升高，且缺乏根治性治疗手段，给患者家庭及社会带来沉重负担。传统研究多聚焦于中枢神经系统(central nervous system, CNS)局部病理改变，如神经元进行性凋亡、异常蛋白沉积及神经炎症激活等，难以全面揭示疾病的始动机制与演进规律[1]。近年来，“肠-脑轴”理论的发展打破了这一局限，证实肠道微生态可通过代谢、免疫、神经及内分泌等多条通路与中枢神经形成双向调控网络，为阐释神经退行性变性疾病的发病机制提供了新的研究思路。丁酸产

生菌作为肠道微生态的关键功能类群，其代谢产物丁酸不仅是肠道上皮细胞的主要能量来源，更可穿越血脑屏障参与中枢神经稳态调控，其丰度异常与神经退行性变性疾病的关联已被多项研究证实[2]。然而，当前关于丁酸产生菌在神经退行性变性疾病演进中的具体作用模式、分子调控通路及临床转化价值仍缺乏系统梳理。基于此，本文以“肠-脑轴”为核心框架，系统梳理丁酸产生菌与神经退行性变性疾病的关联证据，深入阐释其作用机制，并探讨其作为生物标志物及治疗靶点的应用潜力，以期为该领域的基础研究与临床干预提供理论支撑。

1 “肠-脑轴”的微生态对话

肠道微生物及其代谢产物与中枢神经系统的双向调控是肠道-微生物-脑之间功能关联的重要体现，也是理解机体跨器官功能调控的重要视角[3]。目前已鉴定出肠道含 1 000 余种微生物，主要由拟杆菌门、芽孢杆菌门和放线菌门的厌氧菌组成，在黏液层、肠上皮屏障及适宜 pH 值构成的独特微环境中，肠道微生物与宿主相互作用，参与营养代谢、免疫调节及神经信号传导等核心生理过程[4]。2022 年，Wang 等[5]发现了以丁酸为关键靶点的“肠-脑轴”表观遗传调控途径。此外，本课题组 Cheng 等[6]在 APP/PS1 转基因阿尔茨海默病(Alzheimer’s disease, AD)小鼠模型研究中发现，经加味七福饮干预后，与正常小鼠相比，AD 模型组小鼠丁酸产生菌丰度回升，菌群多样性改善，芽孢杆菌门丰度相对提升，拟杆菌门丰度趋于正常化，肠道内丁酸等短链脂肪酸(short-chain fatty acids, SCFAs)含量显著升高；同时，干预组小鼠脑内 β-淀粉样蛋白(amyloid-beta, Aβ)沉积减少，白细胞介素-1β (interleukin-1β, IL-1β)、白细胞介素-6 (interleukin-6, IL-6)、肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)等促炎因子及炎症通路关键基因表达下调，神经炎症减轻，认知功能显著提升；尽管研究未直接测定脑内丁酸浓度及其受体表达，但肠道丁酸水平的升高与中枢神经炎症的减轻呈现出显著的相关性，提示丁酸可能作为“肠-脑轴”通讯的关键介质参与加味七福饮的神经保护作用。

肠道丁酸产生菌主要包括梭菌属(*Clostridium*)、罗斯拜瑞氏菌属(*Roseburia*)、真杆菌属(*Eubacterium*)及栖粪杆菌属(*Faecalibacterium*)等，在健康成年人肠道菌群中，含有丁酸合成通路的细菌约占肠道总菌群的 26%；这些细菌主要定殖于结肠，其中以近端结肠分布最为丰富，其重要功能是通过发酵膳食纤维、抗性淀粉等底物产生丁酸[7]。丁酸不仅是肠道上皮细胞的主要能量来源，还具有调控肠道屏障完整性、抑制炎症反应及调节神经递质合成等多重生理活性。中枢神经系统作为机体的核心调控中枢，主要通过 4 个传导通路与肠道发生关联。(1) 代谢通路：丁酸等肠道微生物代谢产物经肠黏膜吸收进入血液循环，突破血脑屏障直接作用于中枢神经细胞[8]；(2) 免疫通路：肠道作为人体最大免疫器官，丁酸产生菌调控肠道免疫稳态，抑制异常炎症因子入血，减少中枢神经炎症浸润[9]；(3) 神经通路：迷走神经是肠-脑之间的直接纽带，肠道菌群及丁酸通过迷走神经末梢将信号传递至脑干、海马体等关键脑区[10]；(4) 内分泌通路：丁酸调节肠道内分泌细胞分泌 5-羟色胺(5-hydroxytryptamine, 5-HT)前体或脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)前体，间接调控中枢神经功能[11]。

在正常生理状态下，“肠-脑轴”维持着肠道与中枢神经系统之间的稳态平衡。丁酸产生菌维持肠道屏障完整性，抑制致病菌增殖及内毒素释放，通过迷走神经向大脑传递稳态信号；而中枢神经系统则通过调节肠道蠕动、黏液分泌及免疫状态反向调控肠道微生态[12]。当“肠-脑轴”功能紊乱，丁酸产生菌丰度下降及丁酸分泌减少会打破这一平衡，通过肠-脑间的病理信号传递，促进神经退行性变性疾病的发生与发展。

2 丁酸产生菌与神经退行性变性疾病的关联

2.1 不同疾病中丁酸产生菌的丰度特征与群体异质性

丁酸产生菌的丰度变化与神经退行性变性疾病的发生发展密切相关，且呈现显著的疾病特异性与群体异质性(图 1A)。在阿尔茨海默病(AD)、帕金森病(Parkinson's disease, PD)、肌萎缩侧索硬化(amyotrophic lateral sclerosis, ALS)、亨廷顿舞蹈病(Huntington's disease, HD)等神经退行性变性疾病中普遍观察到丁酸产生菌丰度降低。临床研究证实，AD 患者肠道内 *Roseburia*、*Faecalibacterium* 和 *E. rectum* 丰度较健康人群下降 30%–60%，且丰度降低程度与认知障碍评分呈正相关[13]。PD 患者发病前常伴随便秘等肠道症状，其肠道内人粪丁酸球菌(*Butyricicoccus faecihominis*)、*Roseburia* 丰度显著降低，且肠道内丁酸水平下降幅度与运动功能障碍程度相关。ALS 患者肠道中 *Clostridium* cluster XIVa 丰度下降，同时伴随肠道炎症水平升高[14]。HD 患者肠道内 *Roseburia*、*Faecalibacterium* 丰度显著降低，且肠道屏障通透性增加。本课题组 Zhu 等[15]发现，在免疫低下及神经退行性变性疾病相关模型中，陕北的槐桑黄 YASH1 的干预对肠道丁酸产生菌的调控呈现显著的菌属特异性和剂量依赖性；低剂量黄酮可显著促进 *Faecalibacterium*、*Eubacterium* 等丁酸产生菌的丰度恢复，并伴随肠道丁酸含量升高；桑黄多糖对 *Roseburia*、毛螺菌科(*Lachnospiraceae*)等丁酸产生菌的调控作用也呈现剂量依赖性差异。Hu 等[16]证实了发酵黏液乳杆菌(*Limosilactobacillus fermentum*) J2-5、J2-9 凭借高疏水性和强自凝集能力更易附着在肠道内形成有益生物膜；同时，这类乳杆菌分泌的丁酸等代谢产物具有抗氧化活性，能够显著提升过氧化氢损伤细胞的超氧化物歧化酶(superoxide dismutase, SOD)、过氧化氢酶(catalase, CAT)及总抗氧化能力(total antioxidant capacity, T-AOC)活性，进而发挥细胞保护作用。相关研究汇总如表 1 所示。

丁酸产生菌的群体异质性主要体现在(图 1A)：(1) 年龄差异：健康老年人 *Lachnospiraceae*、梭菌目(*Clostridiales*)等肠道丁酸产生菌丰度维持在较高水平时，AD 发病风险降低 40% 以上，而老年衰弱人群中丁酸产生菌丰度显著下降，神经退行性变性疾病发病风险升高[25]；(2) 性别差异：男性 PD 患者肠道 *C. butyricum* 丰度下降幅度显著大于女性，可能与性激素对肠道菌群的调控作用相关；(3) 并发症关联：合并糖尿病的 AD 患者肠道 *Roseburia* 丰度进一步降低，提示代谢紊乱与肠道菌群失衡的协同作用；(4) 治疗响应差异：对 PD 药物治疗敏感的患者，补充丁酸产生菌后肠道菌群恢复程度显著高于耐药患者。

2.2 疾病进程中的时序演变规律

丁酸产生菌的动态变化贯穿神经退行性变性疾病的全程，呈现明确的时序演变特征(图 1A)。在疾病早期，*Faecalibacterium*、*Roseburia* 等主要丁酸产生菌丰度开始下降；随着疾病进展，*Eubacterium*、*Lachnospiraceae* 等多类产丁酸菌群相继减少；至疾病晚期，丁酸产生菌的整体丰度显著耗竭，与认知功能下降程度呈正相关。机制研究表明，丁酸通过抑制 BACE1 表达减少 Aβ 生成，同时调节小胶质细胞功能、抑制神经炎症。研究发现，AD 模型小鼠血液和脑内丁酸水平分别降至野生型小鼠的 53.99% 和 28.92%，提示中枢丁酸缺乏较外周更为严重，产丁酸酿酒酵母(butyrate-producing *Saccharomyces cerevisiae*) J17 能缓解丁酸盐缺乏和认知缺陷，减轻 APP/PS1 小鼠的 Aβ 沉积、小胶质细胞过度激活和神经炎症[26]。宿主遗传因素、饮食模式及疾病状态均可导致丁酸产生菌丰度出现变化，而"肠-脑轴"是一个双向通信网络，可使微生物代谢物和免疫信号影响情绪、

表1　产丁酸菌与神经退行性变性疾病关联性研究汇总

Table 1　Growing evidence links butyrate-producing bacteria to the pathogenesis of neurodegene-rative diseases

Participants	Techniques	Samples	Key findings	References
Ten patients with AD and ten healthy controls	16S rRNA gene sequencing; real-time quantitative polymerase chain reaction (RT-qPCR)	Fecal samples	AD patients: pro-inflammatory genera ↑ *C. butyricum*→ acetate-producing bacteria ↑; pro-inflammatory genera ↓; LPS level ↓	[17]
100 patients with AD and 71 healthy controls	16S rRNA gene sequencing and targeted metabolomics	Fecal and blood samples	AD patients: *Faecalibacterium* ↓; blood BA levels positively correlate with cognitive scores	[18]
40 patients with prodromal Alzheimer's disease (pAD), 58 with subjective cognitive decline (SCD), and 37 with amnestic mild cognitive impairmenta (MCI)	16S rRNA gene sequencing	Fecal and blood samples	SCFAs-producing bacteria ↓ correlates with intestinal barrier disruption	[19]
28 AD patients and 29 healthy controls	Gas chromatography-mass spectrometry (GC-MS)	blood samples	AD patients: acetate ↑; bile acids ↓	[20]
223 PD patients and 137 healthy controls	Metagenomic sequencing and SCFAs analysis	Fecal samples	PD patients: *Akkermansia* ↑; *Roseburia*, *Faecalibacterium* ↓	[21]
96 PD patients and 85 healthy controls	Chromatography and mass spectrometry	Fecal and blood samples	PD: pro-inflammatory microbes ↔; fecal SCFAs ↓; plasma SCFAs ↑	[22]
19 HD patients and 36 healthy controls	16S rRNA gene sequencing	Fecal samples	HD patients: *Bacillota*, *Lachnospiraceae*, *Akkermansiaceae* ↓	[23]
66 ALS patients, 61 healthy controls, and 12 NDC participants	16S rRNA gene sequencing	Fecal samples	ALS: butyrate-producing bacteria (e.g., *Roseburia*, *Faecalibacterium*, *Eubacterium*) ↓	[24]

This table summarizes the detection results of intestinal flora and related metabolites in patients with different neurodegenerative diseases and healthy controls, including detection techniques, sample types and key research findings. ↑: Increased abundance/relative expression level; ↓: Decreased abundance/relative expression level; →: Promote; ↔: No significant change.

认知和神经健康，同时压力激素和神经信号相互影响肠道生理[27]。

2.3　中枢与肠道的空间分布关联

丁酸产生菌主要定殖于肠道，可通过"肠-脑轴"信号传递对中枢神经系统功能的影响呈现明确的空间分布特征(图 1A)。AD 患者脑内海马体、前额叶皮层等认知相关脑区的丁酸水平显著降低，降低区域与 Aβ 沉积区域高度重叠[17]。PD 患者黑质致密部等多巴胺能神经元富集区域的丁酸浓度下降最为明显，且与神经元凋亡程度呈正相关[21]。ALS 患者的脊髓前角运动神经元区域出现丁酸介导的抗炎信号减弱及促炎因子富集现象[24]。HD 患者纹状体作为亨廷顿蛋白异常聚集的核心区域，丁酸对组蛋白去乙酰化酶(histone deacetylase, HDAC)的抑制作用减弱，进而导致神经变性进程加重[23]。在肠道内，丁

酸产生菌主要富集于结肠黏膜，其在黏膜层富集程度越高、越靠近肠神经节，调控作用越显著。这种以结肠黏膜为主要作用点的分布模式有利于其通过神经通路向中枢传递信号。

3 丁酸产生菌在神经退行性变性疾病发展进程中的作用机制

3.1 屏障联动调控：肠道与血脑屏障的双重保护机制

肠道屏障与血脑屏障结构和功能的完整性可阻断肠漏-全身炎症-神经炎症的级联传递，从而发挥神经保护作用，丁酸产生菌通过肠道屏障与血脑屏障的双重保护作用实现神经保护。肠道内的丁酸产生菌通过定殖促进肠黏膜紧密连接蛋白(zonula occludens-1, ZO-1)、occludin 和 claudin-1 的表达，增强肠道屏障完整性，减少脂多糖(lipopolysaccharide, LPS)等肠源性内毒素及促炎因子入血；同时，丁酸作为肠道上皮细胞的能量底物，可改善肠黏膜细胞代谢，增强黏膜修复能力[28] (图 1B)。AD 患者肠道紧密连接蛋白表达降低，丁酸产生菌丰度下降会进一步加剧肠道屏障渗漏，导致 LPS 入血后通过循环系统破坏血脑屏障[29]；而补充 *C. butyricum* 可显著上调肠道 ZO-1 和 occludin 表达，降低血脑屏障通透性，减少外周炎症因子进入中枢[17]。在血脑屏障层面，丁酸经肠道吸收进入血液循环后，可穿越血脑屏障，增强血脑屏障内皮细胞的紧密连接，抑制基质金属蛋白酶(matrix metalloproteinase-9, MMP-9)活性，减轻血脑屏障渗漏[30]；并可调节星形胶质细胞和小胶质细胞的活化状态，维持血脑屏障微环境稳态[31]。PD 模型小鼠研究表明，补充 *R. intestinalis* 可通过提高丁酸生成水平，降低血脑屏障通透性，抑制 α-突触核蛋白从肠道向脑的传递[21]。ALS 患者中，丁酸产生菌丰度降低导致血脑屏障完整性受损，促炎因子浸润脊髓前角，加速运动神经元凋亡[32]。本课题组伍小衡[33]发现植物乳杆菌(*Lactobacillus plantarum*) L9 具备良好的肠道定殖能力，其联合中药(白术、黄芪)干预硫酸葡聚糖钠(dextran sulfate sodium, DSS)诱导的急性溃疡性结肠炎(ulcerative colitis, UC)小鼠时，不仅能通过代谢产生丁酸等短链脂肪酸，还可减少肠道来源的促炎因子，降低全身炎症负荷，进而间接减轻炎症对血脑屏障的损伤风险。

3.2 肠道与中枢免疫协同调控机制

神经退行性变性疾病常伴随着全身慢性低度炎症，而肠道是这类炎症的主要源头之一。丁酸产生菌可通过肠道-中枢免疫协同调控有效抑制神经炎症的发展(图 1B)。在肠道免疫层面，丁酸产生菌能够促进调节性 T 细胞增殖，上调白细胞介素-10 (interleukin-10, IL-10)和转化生长因子-β (transforming growth factor-beta, TGF-β)等抗炎因子的分泌，抑制辅助性 T 细胞 17 (thelper 17 cell, Th17)的活化，并减少 TNF-α、IL-6、IL-1β 等促炎因子的释放；同时，丁酸可直接作用于肠道巨噬细胞，抑制其向促炎表型极化[34]。本课题组 Cheng 等[35]使用益生菌发酵发芽谷物复合物干预对氯苯丙氨酸(p-chlorophenylalanine, PCPA)诱导的睡眠剥夺小鼠模型，结果显示，小鼠肠道丁酸产生菌相对丰度显著升高，下丘脑 5-羟色胺、γ-氨基丁酸(gamma-aminobutyric acid, GABA)和谷氨酸(glutamate, Glu)等神经递质的含量显著增加，血清中 IL-6、IL-1β 和 TNF-α 等炎症因子水平降低，肠道菌群结构得到改善，丁酸含量显著上升。

在中枢免疫层面，丁酸进入大脑后能够有效抑制神经炎症核心效应细胞(小胶质细胞)的过度激活，减少促炎因子与活性氧(reactive oxygen species, ROS)释放，减轻神经元损伤[36]；同时，丁酸可调节星形胶质细胞功能，促进脑源性神经营养因子和胶质细胞源性神经营养因子(glial cell line-derived neurotrophic factor, GDNF)等神经营养因子的分泌[37]。本课题组 Wang 等[38]的研究显示，zunyimycin C 介导的丁酸升高更能进一步增加 AD 小鼠脑组织中成熟星形胶质细胞数

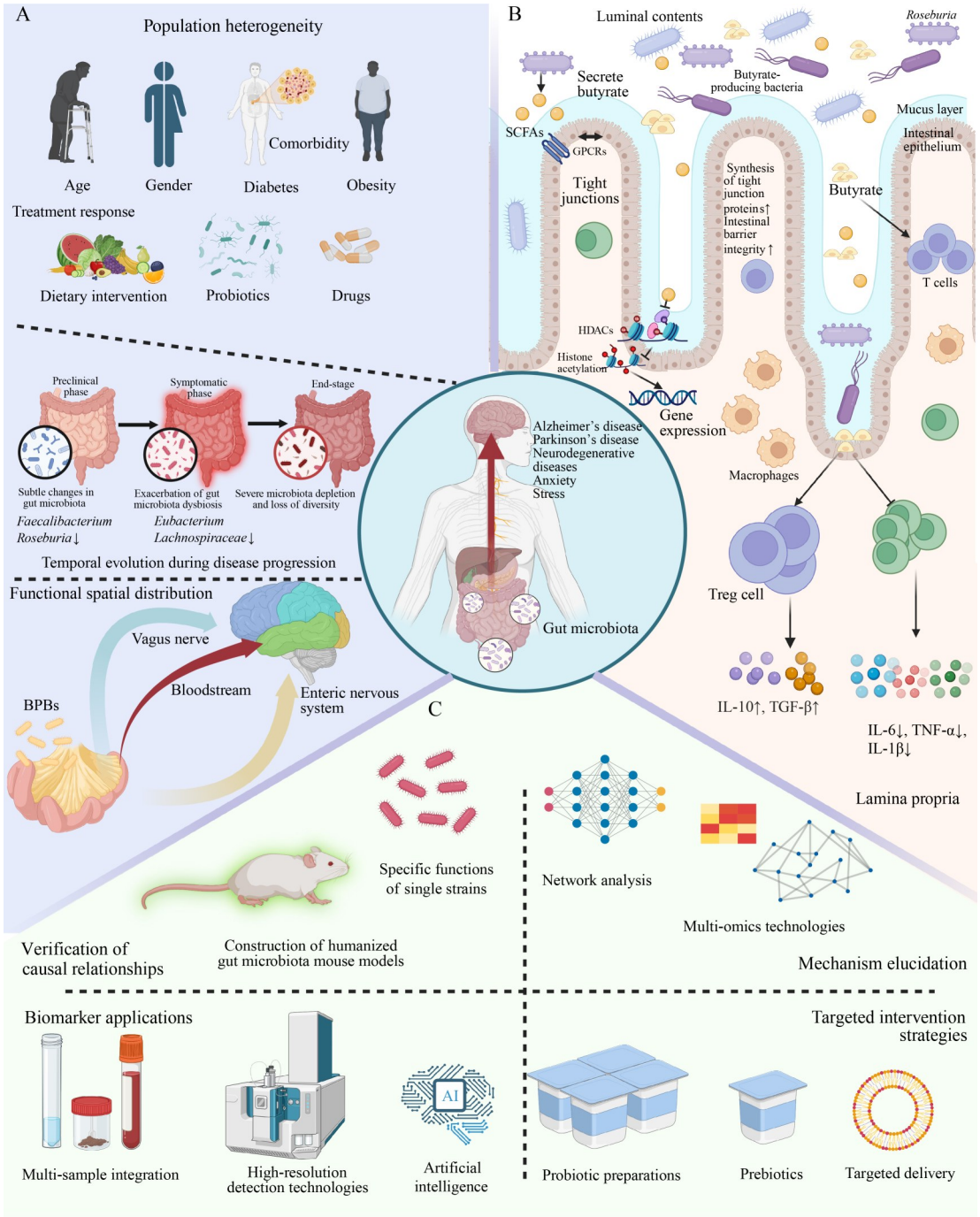

图1　肠道产丁酸菌与神经退行性变性疾病的关联

Figure 1　Association between butyrate-producing gut bacteria and neurodegenerative diseases. A: Population heterogeneity of butyrate-producing bacteria, temporal evolution of during disease progression, and intestinal mucosal colonization and association with central target brain regions; B: The action mechanisms of butyrate-producing bacteria (including intestinal barrier protection, immune regulation, metabolic modulation, and epigenetic modification); C: Prospect (investigating the causal relationship between butyrate-producing bacteria and diseases, strain specificity and signaling networks, expanding biomarkers and targeted intervention strategies). BPBs: Bile acid-binding proteins; GPCRs: G protein-coupled receptors.

量，最终改善模型小鼠的长期记忆。PD 患者黑质区小胶质细胞异常活化，补充可通过抑制 Toll 样受体 4 (Toll-like receptor 4, TLR4)/核因子 κB (nuclear factor kappa-light-chain-enhancer of activated b cells, NF-κB)通路激活，减轻多巴胺能神经元损伤[30]；在 ALS 模型小鼠中，丁酸产生菌通过抑制星形胶质细胞活化，延缓运动神经元凋亡[39]；HD 患者纹状体中，丁酸能够抑制小胶质细胞介导的炎症反应，缓解神经变性进程[40]。

3.3 丁酸的中枢代谢调控介导机制

丁酸作为丁酸产生菌的核心代谢产物，可通过代谢介导机制直接调控中枢神经功能。中枢神经细胞对能量需求极高，丁酸可通过血脑屏障为神经元提供能量，改善神经退行性变性疾病中的能量代谢紊乱[41]。AD 患者脑内葡萄糖代谢水平降低，丁酸可作为替代能量底物，缓解海马体神经元能量匮乏；ALS 患者运动神经元能量代谢异常，丁酸可通过增强线粒体功能改善能量供给。

在神经递质调控方面，丁酸可调节中枢神经递质的合成与释放：促进 5-羟色胺、多巴胺及 γ-氨基丁酸等神经递质的合成，其中 5-羟色胺参与情绪调节，多巴胺调控运动与认知功能，γ-氨基丁酸是重要的抑制性神经递质，同时减少具有兴奋性毒性作用的谷氨酸释放[42]。PD 患者脑内多巴胺水平显著降低，丁酸可通过促进肠道多巴胺前体酪氨酸的吸收与转运，增加脑内多巴胺合成；丁酸梭菌通过代谢产生丁酸，激活结肠 G protein-coupled receptor (GPR)41/GPR43 受体，进而通过“肠-脑轴”发挥信号传导作用，抑制小胶质细胞过度活化，最终减轻 1-甲基-4-苯基-1,2,3,6-四氢吡啶(1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP)诱导小鼠的 PD 相关病理损伤[43]。本课题组杨甜等[44]发现，在 APP/PS1 AD 小鼠模型中，经微生物发酵中药 YA3D3-MHF 干预后，模型小鼠丁酸产生菌丰度显著上调，肠道丁酸含量同步大幅增加；同时丁酸可作为神经元能量底物促进代谢，协同恢复脑内 5-羟色胺、γ-氨基丁酸、谷氨酸等神经递质平衡，最终改善模型小鼠认知功能障碍，为神经退行性变性疾病的肠道菌群-丁酸-肠-脑轴靶向干预提供了关键实验依据。

3.4 HDAC 抑制介导的神经保护表观遗传调控机制

丁酸作为组蛋白去乙酰化酶的特异性抑制剂，可通过表观遗传调控影响神经相关基因的表达(图 1B)。HDAC 异常激活会抑制神经保护基因的表达、促凋亡基因异常活化，加剧神经退行性变。AD 患者脑内 HDAC1、HDAC2 活性升高，丁酸进入脑组织后可抑制其活性，促进脑源性神经营养因子、B 细胞淋巴瘤-2 (B-cell lymphoma 2, Bcl-2)等神经保护基因表达，减少 Aβ 沉积和 tau 蛋白(tau protein)过度磷酸化[45]；HD 患者纹状体中，丁酸可通过抑制 HDAC6 活性，减轻突变亨廷顿蛋白的毒性聚集；PD 模型小鼠中，丁酸介导的 HDAC 抑制作用可促进多巴胺能神经元存活。

4 挑战与展望

4.1 明确丁酸产生菌与疾病的因果关系

尽管丁酸产生菌与神经退行性变性疾病的关联已得到大量证实，但二者之间的因果关系仍需深入验证(图 1C)。当前研究多为相关性分析，缺乏直接的因果证据：(1) 现有动物模型难以完全模拟人类“肠-脑轴”的复杂性，可通过构建定殖人类丁酸产生菌的人源化菌群小鼠模型，并结合 APP/PS1、MPTP 诱导的帕金森病等神经退行性变性疾病模型，验证丁酸产生菌丰度变化对疾病发生发展的直接影响；(2) 可借助宏基因组测序结合系统发育树等方法，在菌群水平开展追踪分析，明确肠道丁酸产生菌与中枢病理改变之间的时序关系；(3) “Driver-Passenger”模型提示，丁酸产生菌丰度下降可能是疾病发生后的伴随结果，而非致病原因。因此需要开

展纵向队列研究，判断其丰度变化是否早于疾病临床症状的出现[46]。

4.2 深入解析作用机制的菌株特异性与信号网络

现有研究多聚焦于丁酸产生菌的整体功能，缺乏菌株特异性机制解析：(1) 不同丁酸产生菌在产丁酸效率、肠道定殖能力及信号传导通路等方面存在显著差异，需进一步明确单一菌株对“肠-脑轴”的特异性调控作用；(2) 丁酸产生菌与其他肠道微生物的互作及其对“肠-脑轴”的影响尚不明确，可通过共培养体系和微生物网络分析揭示菌群间的协同调控作用；(3) 丁酸介导的肠-脑信号通路存在相互串扰，例如 GPR41/GPR43 受体通路与 HDAC 抑制通路之间可能存在交互作用，需结合转录组、蛋白质组及代谢组等多组学技术构建完整系统的信号调控网络。

4.3 拓展生物标志物的临床应用

丁酸产生菌作为神经退行性变性疾病的潜在生物标志物，在实际应用中仍面临样本选择、检测技术与数据分析等多方面挑战(图 1C)：(1) 样本选择方面，粪便样本虽易于获得，但稳定性差，而口腔拭子、血液样本的丁酸产生菌标志物尚未明确，需建立多类型样本联合检测策略以提高诊断准确性；(2) 在检测技术方面，当前研究多集中于菌属水平，未来应发展单细胞测序、数字 PCR 等高分辨率技术实现菌群水平的精准检测，提升标志物的特异性与临床实用性；(3) 数据分析方面，可结合人工智能和大数据融合分析方法，构建整合丁酸产生菌丰度、丁酸含量及临床指标的综合预测模型，用于疾病早期筛查与预后评估[47]。

4.4 开发靶向干预策略

针对丁酸产生菌的干预策略已展现出潜在临床应用价值，但目前仍存在诸多不足，需进一步优化完善(图 1C)：(1) 益生菌制剂方面，*F. prausnitzii* 等多数核心丁酸产生菌为严格厌氧菌，体外培养难度大且制剂稳定性差，需借助微囊化、芽孢包埋等技术改进，提升其在肠道内的定殖效率；(2) 合生元制剂方面，需筛选可选择性促进丁酸产生菌增殖与代谢的抗性淀粉、低聚果糖等经典益生元，构建“益生菌+益生元”复合体系以提高产丁酸效率；(3) 靶向递送技术方面，应研发诸如 pH 敏感微球和肠黏膜黏附制剂等新型递送系统，实现丁酸在肠道内的精准释放，从而提高其生物利用度；(4) 联合干预方面，可探索肠道菌群调控与中枢靶向治疗相结合的综合策略，以克服单一治疗方式的局限性。此外，传统中药对丁酸产生菌的调控作用也具有深入研究价值，可为神经退行性变性疾病的中西医结合干预提供新思路[48]。

5 总结

“肠-脑轴”作为连接肠道微生态与中枢神经的关键调控轴，为神经退行性变性疾病的研究提供了全新视角。丁酸产生菌作为肠道固有重要功能类群，可在肠道黏膜与肠腔生理性定殖，并通过“肠道定殖+丁酸介导调控”的双重模式，经屏障保护、免疫调控、代谢介导及表观遗传调控四大机制，参与神经退行性变性疾病的演进。其丰度下降不仅是疾病发生的重要诱因，还可作为疾病早期预警的生物标志物，而恢复其在肠道内的正常丰度则是疾病干预的关键靶点。目前研究虽已证实丁酸产生菌与神经退行性变性疾病的关联及部分作用机制，但仍面临因果关系不明确、菌株特异性机制不足、临床干预策略有待优化等问题。未来需结合多组学技术、人源化动物模型及前瞻性临床研究，进一步解析丁酸产生菌调控“肠-脑轴”的分子机制，研发安全、精准的微生态干预策略，为神经退行性变性疾病的预防、诊断、治疗及预后提供新的切入点。

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