DOI: 10.11844/cjcb.2026.04.0025
中国细胞生物学学报 Chinese Journal of Cell Biology 2026, 48(4): 1202–1210 CSTR: 32200.14.cjcb.2026.04.0025

肠道菌群调控小胶质细胞极化在缺血性脑卒中炎症中的研究进展

石福楠[1] 于正道[1] 刘佳怡[1] 王潇苧[1] 刘骥飞[1] 苏刚[2] 张振昶[1]*
([1]兰州大学第二医院神经内科, 兰州 730030; [2]兰州大学基础医学院, 兰州 730030)

摘要 缺血性脑卒中(IS)后, 肠道菌群及其代谢谱可在短时间内发生重塑, 并经“肠–免疫–脑”多种通路影响中枢先天免疫反应, 其中小胶质细胞表型极化是连接外周炎症信号与脑内继发性损伤的重要环节。现有临床及动物研究提示, 卒中后常见短链脂肪酸(SCFAs)产生菌(如*Faecalibacterium*、*Roseburia*及*Lachnospiraceae*等)减少, 而条件致病菌或炎症相关菌(如*Enterobacteriaceae*、*Porphyromonadaceae*等)增加; 上述变化与卒中严重程度、不良预后及感染并发症风险密切相关。在机制上, 菌群失衡可通过多重途径协同促进神经炎症反应, 包括微生物代谢物和内毒素信号通路(如SCFAs-GPR41/43-HDAC轴、TMAO相关炎症信号通路及LPS-TLR4通路等)、外周免疫重塑(如Th17/Treg失衡、单核/中性粒细胞募集及细胞因子释放等)以及肠屏障破坏引发的全身炎症反应扩散, 在这些因素的共同作用下, 小胶质细胞由相对抗炎状态向促炎状态转变, 并进一步启动NF-κB信号通路、促进NLRP3炎症小体的组装与激活, 加重血脑屏障损伤和神经炎症反应。在干预方面, 围卒中期营养支持联合益生菌或合生元在部分临床研究中显示出改善肠屏障功能、减轻炎症反应及优化营养指标, 从而降低感染风险的潜力; 粪菌移植、后生元或SCFAs补充以及靶向TMAO等代谢通路的策略, 在动物实验中亦显示出减轻脑损伤、调节小胶质细胞极化的作用。总体来看, 肠道菌群失调是卒中后神经炎症的重要上游因素, 但“特征菌群–关键代谢物–小胶质细胞表型–临床结局”之间的因果链仍有待高质量临床研究进一步证实, 以推动菌群靶向策略在缺血性脑卒中炎症管理中的转化应用。

关键词 肠道菌群; 缺血性脑卒中; 小胶质细胞极化; 神经炎症; 肠–脑轴

Research Progress on the Regulation of Microglial Polarization by Gut Microbiota in Inflammatory Ischemic Stroke

SHI Funan[1], YU Zhengdao[1], LIU Jiayi[1], WANG Xiaoning[1], LIU Jifei[1], SU Gang[2], ZHANG Zhenchang[1]*
([1]*Department of Neurology, the Second Hospital of Lanzhou University, Lanzhou 730030, China*;
[2]*College of Basic Medical Sciences, Lanzhou University, Lanzhou 730030, China*)

收稿日期: 2025-11-20 接受日期: 2026-03-12
甘肃省自然科学基金(批准号: 25JRRA583)、甘肃卫生行业科技创新重大科研项目(批准号: GSWSZD2024-15)、甘肃省卫生行业科研计划(批准号: GSWSKY2021-017)、兰州市城关区科技计划(批准号: 2024SHFZ0021)、兰州大学第二医院“萃英科技创新”计划(批准号: CY2021-MS-B01)、癌症、心脑血管、呼吸和代谢性疾病防治研究国家科技重大专项课题(批准号: 2024ZD0527800)、甘肃省临床优势专科建设项目和兰州大学第二医院院士专家工作站(王陇德院士)资助的课题
*通信作者。Tel: 13893647595, E-mail: tougao13893647595@163.com
Received: November 20, 2025 Accepted: March 12, 2026
This work was supported by the Gansu Provincial Natural Science Foundation (Grant No.25JRRA583), the Major Project of Gansu Health Industry Science and Technology Innovation (Grant No.GSWSZD2024-15), the Gansu Health Industry Research Plan (Grant No.GSWSKY2021-017), the Lanzhou City Chengguan District Science and Technology Plan (Grant No.2024SHFZ0021), the “Cuiying Science and Technology Innovation” Plan of the Second Hospital of Lanzhou University (Grant No.CY2021-MS-B01), the National Key R&D Program on the Prevention and Treatment of Cancer, Cardiovascular Diseases, Respiratory Diseases, and Metabolic Diseases (Grant No.2024ZD0527800), and the Gansu Provincial Clinical Advantage Specialty Construction Project and the Academician Expert Workstation of the Second Hospital of Lanzhou University, Academician WANG Longde
*Corresponding author. Tel: +86-13893647595, E-mail: tougao13893647595@163.com

Abstract After ischemic stroke, the gut microbiota and its metabolic profile can be rapidly reshaped and influence central innate immune responses through multiple gut-immune-brain pathways. Among these processes, microglial polarization is a key step linking peripheral inflammatory cues to secondary brain injury. Available clinical and experimental evidence indicates that stroke-associated dysbiosis is commonly characterized by a decrease in SCFAs (short-chain fatty acids)-producing bacteria, such as *Faecalibacterium*, *Roseburia*, and *Lachnospiraceae*, together with an increase in opportunistic or inflammation-associated taxa, including *Enterobacteriaceae* and *Porphyromonadaceae*. These alterations are associated with stroke severity, poor functional outcome, and infectious complications. Mechanistically, gut microbiota dysbiosis can synergistically promote neuroinflammatory responses through multiple pathways, including microbial metabolites and endotoxin signaling (e.g., the SCFAs-GPR41/43-HDAC axis, the TMAO-related inflammatory signaling, and the LPS-TLR4 pathway), peripheral immune remodeling (e.g., Th17/Treg imbalance, monocyte/neutrophil recruitment, and cytokine release), and systemic inflammation triggered by intestinal barrier disruption. Under the combined influence of these factors, microglia shift from a relatively reparative state toward a pro-inflammatory phenotype, further activating the NF-κB signaling pathway and promoting the assembly and activation of the NLRP3 inflammasome, thereby exacerbating blood-brain barrier disruption and neuroinflammatory responses. In terms of intervention, peri-stroke nutritional support combined with probiotics or synbiotics has shown potential in some clinical studies to improve intestinal barrier function, alleviate inflammatory responses, and optimize nutritional parameters, thereby potentially reducing the risk of infection. In experimental studies, fecal microbiota transplantation, postbiotics or SCFAs supplementation, and targeted modulation of metabolic pathways such as the TMAO axis have also shown promise in alleviating brain injury and regulating microglial polarization. Overall, gut microbiota dysbiosis is an important upstream contributor to post-stroke neuroinflammation; however, the causal relationship among signature taxa, key metabolites, microglial phenotypes, and clinical outcomes still requires further confirmation by high-quality clinical studies before microbiota-targeted strategies can be translated into ischemic stroke management.

Keywords gut microbiota; ischemic stroke; microglial polarization; neuroinflammation; intestinal-brain axis

缺血性脑卒中(ischemic stroke, IS)后的继发性神经炎症是决定脑损伤扩展与功能结局的关键环节, 其核心在于小胶质细胞由静息态向不同功能表型的动态转换[1]。既往研究已从TLR4/MyD88/NF-κB、JAK/STAT、cGAS-STING等多条中枢信号通路方面解释了小胶质细胞促炎激活与抗炎修复的可塑性[2-3], 但仍难以回答一个临床上更具“上游意义”的问题, 即为何相似的缺血负荷在不同个体中呈现截然不同的炎症幅度与恢复轨迹。近年来的“肠–脑轴”研究提示, 卒中可快速引起肠道微生态失衡及肠屏障功能重构, 并通过代谢物信号、外周免疫应答与系统炎症反应将信号传递至中枢, 从而改变小胶质细胞极化阈值与炎症终点[4]。本综述围绕肠道菌群失调的特征性改变、其影响小胶质细胞极化的三条核心路径及现有干预证据进行系统整合, 旨在缩小基础机制与临床应用之间的证据缺口, 为卒中后炎症分层管理与精准干预提供可操作的研究框架。

1 IS后小胶质细胞的表型极化与神经炎症

1.1 小胶质细胞的双重角色

小胶质细胞是中枢神经系统的常驻免疫细胞, 兼具稳态监测与炎症效应调控功能[5-6]。在IS早期, 小胶质细胞迅速被激活, 偏向M1样促炎表型, 释放肿瘤坏死因子-α(tumor necrosis factor-alpha, TNF-α)、白细胞介素-1β(interleukin-1 beta, IL-1β)、活性氧(reactive oxygen species, ROS)等炎性介质, 参与坏死组织清除与病原防御, 但同时可加剧血脑屏障破坏与继发性神经元损伤[7-8]。随着病程进展, 部分小胶质细胞向M2样抗炎/修复表型转化, 分泌白细胞介素-10(interleukin-10, IL-10)、转化生长因子-β(transforming growth factor-beta, TGF-β)等因子并促进细胞碎片清除、血管与髓鞘修复, 从而有利于神经功能恢复[9]。

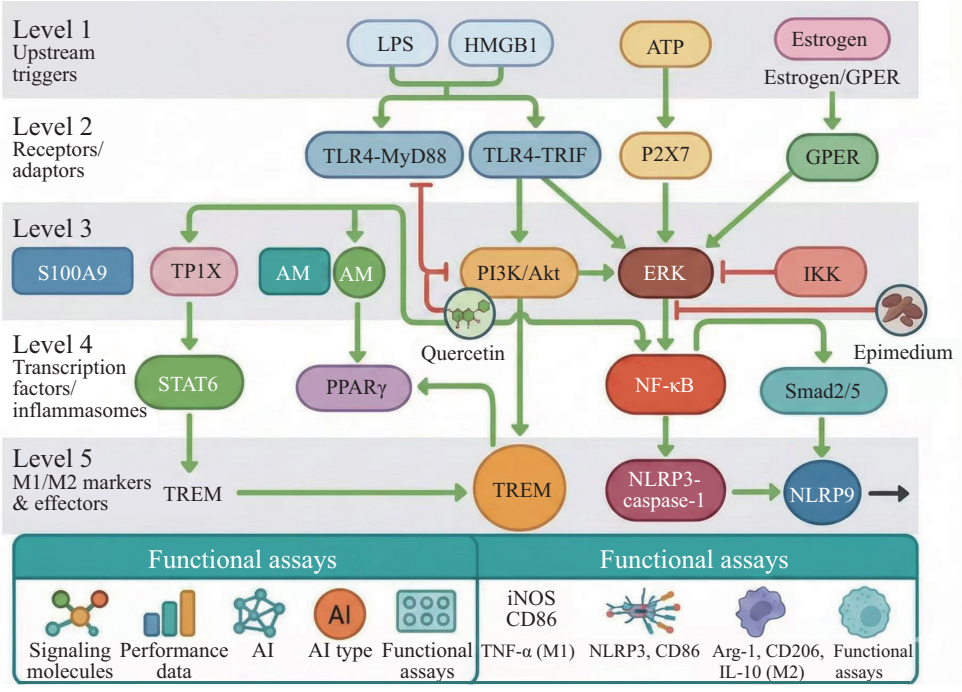
1.2 神经炎症的双重效应

神经炎症在IS的发生与发展中呈现阶段性“双重效应”。急性期炎症反应有助于清除坏死组织、抑制感染并启动修复; 但若促炎反应持续或过度, 则

可通过细胞因子瀑布、氧化应激与炎症小体激活等途径造成血脑屏障进一步破坏、脑水肿加重及神经网络重建受阻[10-11]。研究显示，卒中后数小时内活化的小胶质细胞及外周免疫细胞聚集于缺血半暗带，TNF-α和IL-1β等水平显著升高，血脑屏障通透性可增加约2~4倍，为外周免疫细胞进入脑组织创造了条件[12]。因此，精准把握炎症反应的“窗口期”与强度，是卒中后干预策略设计的关键。

1.3 调控小胶质细胞极化的关键信号通路

IS发生后，小胶质细胞极化受多条信号通路协同调控。需要说明的是，图1为卒中相关小胶质细胞极化调控通路的示意图，主要用于概括不同信号网络之间的联系，并非直接展示人小胶质细胞表型极化的原始实验结果。为便于理解不同信号通路的功能及相互关系，本文按促炎放大通路、抗炎修复通路及其他调节通路进行归纳。(1) 促炎放大通路在卒中后神经炎症早期占据重要地位。PI3K/Akt/NF-κB通路是影响小胶质细胞极化的重要节点，研究显示槲皮素可通过激活PI3K/Akt并抑制NF-κB核转位，促进小胶质细胞/巨噬细胞向M2样表型转化，减少炎症介质释放，并在脑缺血再灌注模型中减轻脑损伤[13]。TLR4/NF-κB/NLRP3信号轴则是连接缺血损伤与神经炎症放大的关键通路之一。脑卒中发生后，坏死细胞释放的损伤相关分子模式(damage-associated molecular patterns, DAMPs)以及肠屏障受损后入血的脂多糖(lipopolysaccharide, LPS)等可共同激活



该图系统展示了IS后，微环境分子通过五层级联反应调控小胶质细胞由M1型向M2型极化的分子机制。Level 1(上游诱导因子)：包含LPS、HMGB1及ATP等损伤相关分子模式(DAMPs)，以及雌激素等保护性因子。Level 2(受体/适配器)：TLR4-MyD88/TRIF、P2X7及GPER等跨膜转录识别受体。Level 3与Level 4(中间信号通路与转录因子网络)：以NF-κB、ERK和STAT6为核心的转录调控网络。Level 5(M1/M2表型标记物与效应器)：最终导向不同的小胶质细胞极化状态及其功能产物。绿色箭头：表示激活或促进作用，指示信号由上游向下游的正向传导。红色线条：表示抑制或拮抗作用，指示特定分子或药物(如槲皮素、淫羊藿苷)对通路传导的阻断。黑色箭头：表示结果导向或后续效应，如NLRP3活化导致后续的细胞因子释放或表型转化。

This figure illustrates the multi-level regulatory network governing the transition of microglia between M1and M2 phenotypes following IS. Level 1 (upstream triggers): includes DAMPs (e.g., LPS, HMGB1, ATP) and protective factors (e.g., estrogen). Level 2 (receptors/adaptors): highlights transmembrane receptors such as TLR4-MyD88/TRIF, P2X7, and GPER. Level 3 and level 4 (intermediate signalling pathways and transcription factor networks): depicts key regulatory hubs including NF-κB, ERK and STAT6. Level 5 (M1/M2 markers and effectors): represents the final polarization states and their downstream biological effectors. Green arrows: denote activation or promotion, indicating the positive transduction of signaling cascades. Red lines: denote inhibition or antagonism, indicating the blockage of specific pathways by molecular inhibitors or natural compounds (e.g., quercetin, epimedium). Dark arrows: represent downstream consequences or phenotypic transitions resulting from the activated cascades.

图1 缺血性脑卒中(IS)中调控小胶质细胞极化的主要信号通路示意图

Fig.1 Schematic diagram of the major signaling pathways regulating microglial polarization in ischemic stroke

TLR4, 继而启动NF-κB介导的炎症相关基因转录, 激活NLRP3炎症小体, 促进IL-1β、IL-18等炎症介质成熟和释放, 推动小胶质细胞向M1样促炎方向转变, 并促进血脑屏障破坏、神经元焦亡及缺血半暗带炎症扩展。LUO等[14]研究显示, 间歇性θ波爆发刺激(intermittent theta burst stimulation, iTBS)可抑制TLR4/NF-κB/NLRP3通路过度激活, 从而减轻神经元焦亡和小胶质细胞极化失衡并促进运动功能恢复。因此, 该信号轴不仅参与卒中后的炎症级联反应, 也是连接肠源性炎症刺激与脑内小胶质细胞异常激活的重要机制。(2) 抗炎与修复相关通路主要参与炎症缓解及组织修复。STAT6/PPARγ通路在抗炎极化中具有代表性, 缺失小胶质细胞/巨噬细胞中的S100钙结合蛋白A9(S100 calcium-binding protein A9, *S100A9*)基因可增强STAT6和PPARγ活性, 促进M2型极化, 减轻脑损伤并加快神经功能恢复[15]。脑泰方可通过BMP6/SMADs通路促进M2型极化, 降低氧糖剥夺/复氧(oxygen-glucose deprivation/reoxygenation, OGD/R)模型中的炎症反应程度及铁死亡水平[16-17]; 低氧预处理小胶质细胞来源外泌体可通过TGF-β/Smad2/3通路促进血管生成、抑制神经元凋亡, 从而促进卒中后组织修复[18]。(3) 其他调节通路同样参与IS后炎症微环境的塑造。GPER-ERK-NF-κB信号通路可影响炎症因子表达, 淫羊藿素通过激活GPER并抑制ERK-NF-κB信号, 能够降低TNF-α和IL-1β水平, 减轻脑组织炎症反应。总体来看, 不同信号通路并非孤立存在, 而是在卒中后不同阶段共同决定小胶质细胞促炎与修复程序的动态平衡。

2 IS后的肠道菌群失调及其对脑损伤的影响

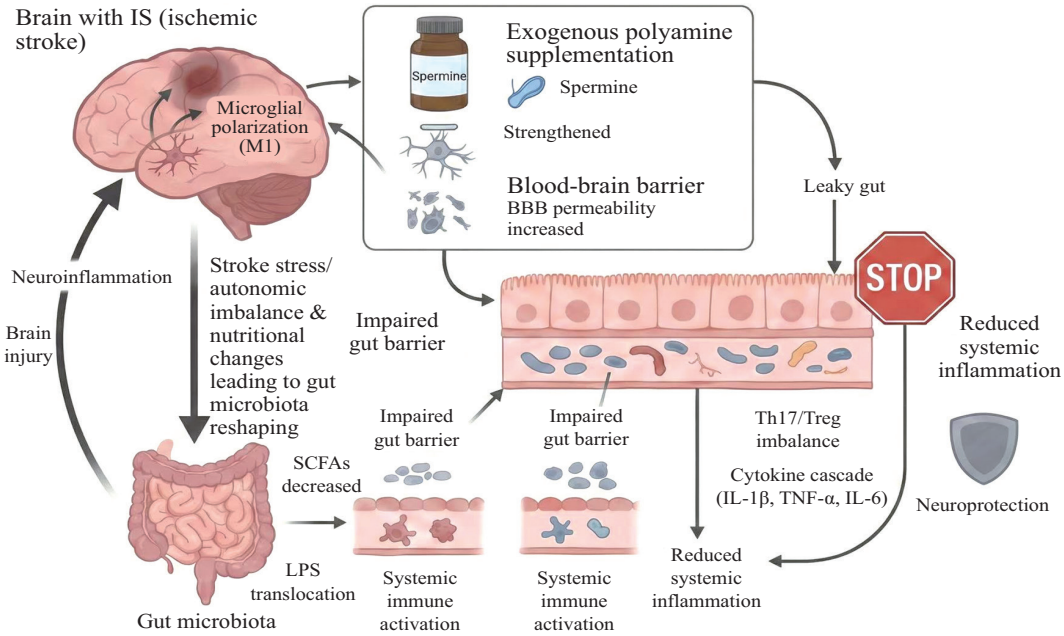
2.1 IS诱导的肠道菌群失调

IS不仅引发中枢急性损伤与炎症反应, 还可通过自主神经–肠神经系统失衡、应激激素释放、吞咽障碍与营养摄入改变等因素, 迅速重塑肠道微生态与屏障功能, 形成可量化的“卒中相关失衡”表型。多项临床研究显示, 急性期卒中患者肠道菌群α多样性下降, 短链脂肪酸(short-chain fatty acids, SCFAs)产生菌(如*Faecalibacterium*、*Roseburia*、*Lachnospiraceae*、*Ruminococcaceae*等)减少, 而机会致病菌或炎症相关菌(*Enterobacteriaceae*、*Porphyromonadaceae*等)增多, 并与美国国立卫生研究院卒中量表(national institutes of health stroke scale, NIHSS)评分、梗死体积及3个月功能结局相关。基于这些变化构建的脑卒中失调指数SDI(stroke dysbiosis index)可在一定程度上反映菌群失衡强度, 并与早期不良转归呈正相关[19-20]。肠道菌群紊乱会诱发肠屏障功能障碍, 即“肠漏”现象, 使肠道内的细菌及其代谢产物更容易进入循环系统, 激活免疫系统, 加剧脑组织炎症反应[21]。MA等[22]研究表明, 通过外源性补充多胺类物质(如精胺), 可显著改善高脂饮食小鼠的肠黏膜屏障功能, 降低肠上皮通透性, 并恢复菌群代谢平衡, 从而缓解系统性炎症反应。类似机制在脑卒中中同样存在, 即卒中后肠道菌群失衡及屏障破坏共同促进全身炎症放大和神经损伤(机制见图2)。因此, IS诱导的肠道菌群失调不仅是卒中病理反应的一个重要环节, 也是潜在的干预靶点。

2.2 菌群失调加剧脑损伤

肠道菌群失调不仅是IS后的伴随现象, 更可能通过可验证的因果链条加剧脑损伤并影响神经功能恢复[23]。动物实验表明, 来自高SDI卒中患者的粪便微生物群移植(fecal microbiota transplantation, FMT)可使受体小鼠梗死体积扩大、神经功能评分变低, 并伴随外周炎症细胞浸润增加与小胶质细胞促炎基因表达上调; 相反, 健康供体菌群或富含SCFAs产生菌的菌群可部分逆转上述改变。提示菌群失衡可以通过“可转移”的方式改变卒中后的炎症基线水平及功能恢复轨迹[24-25]。在机制层面, 菌群失调主要通过三类路径放大脑损伤。(1) 代谢物与内毒素信号: 丁酸等SCFAs缺乏会减弱G蛋白偶联受体41/43(G protein-coupled receptor 41/43, GPR41/43)介导的抗炎信号并解除对组蛋白去乙酰化酶(histone deacetylase, HDAC)的抑制, 促使NF-κB相关转录程序更易被激活[26-27]; 同时, 三甲胺-N-氧化物(trimethylamine N-oxide, TMAO)升高可促进血管内皮炎症并增加血栓形成风险, 加重缺血负荷。(2) 外周免疫重塑: 菌群紊乱可诱导Th17/Treg比例失衡、单核细胞“促炎化”及中性粒细胞募集, 从而导致细胞因子瀑布(IL-6、IL-1β、TNF-α等)产生, 并通过循环进入或作用于血脑屏障, 降低小胶质细胞极化阈值[28]。(3) 屏障破坏与系统炎症扩散: 肠漏使LPS等进入血液, 激活TLR4/NF-κB/NLRP3轴, 促进炎症小体成熟与IL-1β释放, 进一步导致血脑屏障通透性升高[29]。

综上, 卒中相关菌群失衡通过“代谢–免疫–屏



该图系统阐述了IS发生后脑部损伤与肠道微环境之间的双向调控网络: 脑卒中应激及自主神经失调导致肠道菌群重塑, 引发短链脂肪酸(SCFAs)减少、肠屏障受损及脂多糖(LPS)易位, 进而触发以Th17/Treg失衡和细胞因子风暴(IL-1β、TNF-α、IL-6)为特征的全身免疫激活, 最终通过神经炎症加重脑损伤; 而外源性精胺补充可增强血脑屏障与肠屏障完整性, 阻断肠道渗漏并抑制全身炎症, 从而发挥神经保护作用。黑色实线箭头: 病理状态下的正向驱动或诱导关系(如脑损伤诱发肠道功能障碍), 以及该水平下的特定生物学效应或产物输出。

This figure illustrates the reciprocal regulatory network between brain injury and the intestinal microenvironment post-IS: stroke-induced stress and autonomic dysfunction lead to gut microbiota reshaping, characterized by reduced SCFAs (short-chain fatty acids), impaired intestinal barrier integrity, and LPS (lipopolysaccharide) translocation. These alterations subsequently trigger systemic immune activation marked by Th17/Treg imbalance and a pro-inflammatory cytokine cascade (IL-1β, TNF-α, and IL-6), which ultimately exacerbates secondary brain injury via neuroinflammation. Conversely, exogenous spermine supplementation strengthens the integrity of both the blood-brain barrier and the intestinal barrier, effectively blocking "leaky gut" and suppressing systemic inflammation to exert neuroprotective effects. Black solid arrows: indicate positive driving forces or induction relationships under pathological conditions (e.g., brain injury-induced gut dysfunction), as well as specific biological effects or product outputs at each regulatory level.

图2 缺血性脑卒中(IS)诱导的肠道菌群失调机制

Fig.2 Mechanisms of IS-induced gut microbiota dysbiosis

障"三位一体的放大回路, 促使小胶质细胞由修复型向促炎型转变, 导致神经炎症持续、梗死扩展与功能恢复受限。与单一通路解释相比, 这一框架更能阐明临床上炎症异质性及其相关并发症(如卒中相关肺炎、营养不良)的共同上游机制, 也为后续靶向干预提供了明确的切入点。

2.3 干预肠道菌群改善IS预后的证据

现有证据提示, 围卒中期重塑肠道微生态具有一定可行性, 但干预方式、适用人群与终点差异较大。为提高临床可参考性, 可将菌群干预按"作用靶点–强度–风险"分为四类。(1) 以基础营养与膳食纤维/肠内营养为基础, 联合益生菌(probiotics)或合生元(synbiotics)的干预策略[30]: 多项临床研究/Meta分析提示, 该策略可改善营养指标与肠黏膜屏障功能, 并降低感染并发症与胃肠道不良事件发生率, 适用于吞咽障碍或需鼻饲的急性期患者; 其局限在于菌株、剂量与疗程不统一, 且对神经功能终点[如NIHSS评分、改良Rankin评分(modified Rankin scale, mRS)]方面的直接临床获益仍需更高质量临床研究进一步验证。(2) 后生元(postbiotics)/代谢物补充(如SCFAs): 可在不引入活菌的情况下提供抗炎与屏障支持, 理论上更安全, 但需要明确后生元/代谢物补充剂量–反应关系以及其对宿主肠道菌群结构的长期影响。(3) FMT与"下一代益生菌"定向补充: 在动物模型中可显著调控小胶质细胞极化并减轻脑损伤, 但临床推广需解决供体筛选、感染风险与监管合规等问题。(4) 靶向代谢通路的精确干预(如抑制TMAO轴、调节胆汁酸/色氨酸代谢): 具有明确的分子机制与治疗靶点, 适合与卒中分层(炎症型/代谢型)结合, 但目前以前临床证据为主[31]。

总体而言, 菌群干预从"广谱重塑"(饮食/益生菌)到"精准靶向"(代谢通路)呈阶梯式递进。未来研究应以卒中亚型、炎症表型与基线菌群特征为分层

依据，采用统一的菌群与代谢组评估指标，并将小胶质细胞极化相关生物标志物(如外周细胞因子谱、神经影像炎症指标)纳入研究终点指标，以构建可重复、可推广的临床证据链。

3 肠道菌群调控小胶质细胞表型极化的核心机制

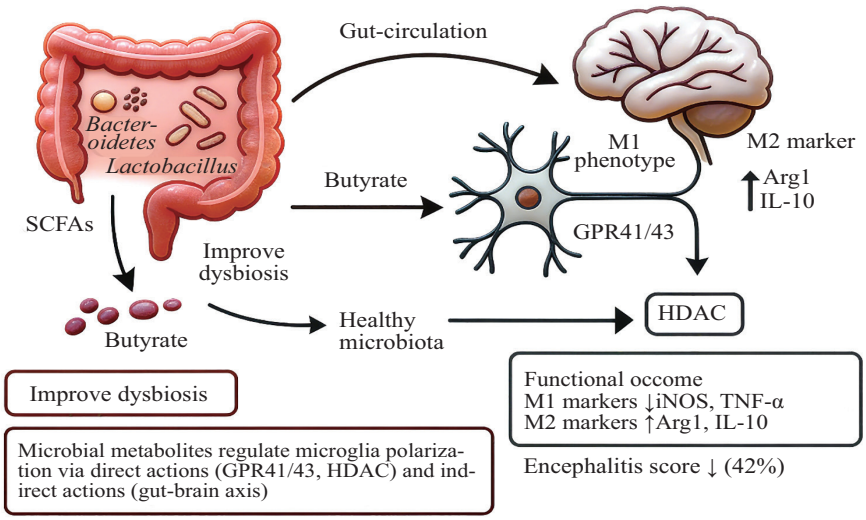
3.1 微生物代谢产物的直接调控作用

微生物代谢产物是肠道菌群调控小胶质细胞表型极化的重要介质，其中SCFAs尤其受到关注。研究表明，丁酸(butyrate)可通过多条信号途径直接影响小胶质细胞的功能与炎症状态。WEI等[32]在慢性酒精中枢神经损伤小鼠模型中发现，丁酸处理(300 mg·kg^{-1}·d^{-1}、14天)可显著抑制小胶质细胞的活化，使促炎M1表型标志物诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)和TNF-α表达水平分别下降约55%和48%，同时增加抗炎M2表型标志物精氨酸酶-1(arginase-1, Arg1)和IL-10的表达量，使脑组织炎症评分较模型组降低约42%。这一研究还显示，丁酸能够减轻酒精诱导的肠道菌群失调，增加拟杆菌门及乳杆菌属丰度，提示其通过肠–脑轴对小胶质细胞表型进行间接调控。

SCFAs通过结合G蛋白偶联受体(如GPR41/43)及抑制HDAC活性，调节小胶质细胞的炎症基因表达，促进M2极化和神经保护[33]。LIAPIS[34]的综述指出，肠道微生物代谢物不仅可作为能量底物，还能作为“伪神经递质”直接参与中枢神经系统信号转导，通过调节神经炎症和神经递质平衡影响宿主的认知与行为。综合来看，微生物代谢产物通过直接作用于小胶质细胞及通过肠–脑轴调节系统性免疫(图3)，为干预IS后神经炎症和促进神经修复提供了潜在的机制与治疗靶点。

3.2 免疫细胞介导的间接调控

肠道菌群通过免疫细胞间接作用于小胶质细胞，调控其极化状态和炎症活性，是调节卒中后神经炎症的重要机制之一。研究显示，肠道菌群代谢产物不仅可直接作用于小胶质细胞，还能通过外周



该图系统阐述了肠道益生菌(如*Lactobacillus*和*Bacteroidetes*)产生短链脂肪酸(SCFAs, 尤其是丁酸)对小胶质细胞极化的影响: 丁酸盐可通过“肠–脑轴”进入血液循环, 并直接作用于小胶质细胞表面的受体(GPR41/43)及抑制组蛋白去乙酰化酶(HDAC), 诱导小胶质细胞由促炎M1型向抗炎M2型转化。这一过程通过减轻肠道失调和增强代谢调控, 显著降低脑炎评分并改善功能预后。向下箭头: 水平降低或抑制。向上箭头: 水平升高或上调。黑色实线箭头: 表示信号转导或转化路径, 指示从代谢产物到受体激活及表型切换的过程。

This figure illustrates the impact of short-chain fatty acids (SCFAs, particularly butyrate) produced by gut probiotics (e.g., *Lactobacillus* and *Bacteroidetes*) on microglial polarization: butyrate can enter the bloodstream via the “gut-brain axis”, or through direct interaction with surface receptors (GPR41/43) and inhibition of HDAC (histone deacetylase), thereby inducing a phenotypic transition from the pro-inflammatory M1 type to the anti-inflammatory M2 type. This process significantly reduces encephalitis scores and improves functional outcomes by alleviating gut dysbiosis and enhancing metabolic regulation. Downward arrows: a decrease in levels or inhibition of specific parameters. Upward arrows: an increase in levels or up-regulation of factors. Solid black arrows: represent signal transduction or transformation pathways, tracing the process from metabolite production to receptor activation and subsequent phenotypic switching.

图3 微生物代谢产物的直接调控机制

Fig.3 Direct regulatory mechanisms of microbial metabolic products

免疫细胞影响中枢神经系统的炎症状态。ZHOU等[35]在脑出血小鼠模型中发现，小胶质细胞来源的极化外泌体可携带多种炎症相关蛋白，如IL-1β和TNF-α，通过与周围免疫细胞相互作用，改变小胶质细胞的表型及功能，从而影响神经损伤程度。SOARES等[36]指出，一氧化碳可通过调节小胶质细胞与神经元之间的通讯，促进神经营养因子分泌，同时抑制促炎细胞因子产生，实现间接的抗炎效应。在远端缺血预处理(remote ischemic conditioning, RIC)研究中，AKHTER等[37]发现，RIC通过激活外周髓系细胞中的腺苷酸活化蛋白激酶催化亚基α1(AMP-activated protein kinase catalytic subunit alpha-1, AMPKα1)信号通路，降低外周炎症介质水平，从而间接促进脑内小胶质细胞向M2型极化，改善神经功能。NLRP3炎症小体在小胶质细胞介导的脑损伤中发挥关键作用，同时也提示外周免疫细胞可通过调控小胶质细胞炎症反应产生间接影响。ZHANG等[38]报道，在放射性脑损伤模型中，NLRP3激活导致小胶质细胞焦亡水平增加，而通过调控外周免疫反应，可抑制小胶质细胞促炎表型的扩展，从而减轻脑组织损伤。综上，肠道菌群通过调节外周免疫细胞及其信号分子，间接影响小胶质细胞的表型极化与炎症反应。

3.3 肠道屏障与全身性炎症

肠道屏障功能的完整性在维持全身免疫稳态和中枢神经系统健康中发挥关键作用。IS及其他应激状态可导致肠道屏障受损，增加肠上皮通透性，使肠道内微生物及其代谢产物进入循环系统，引发系统性炎症反应[39]。DI VINCENZO等[39]指出，肠道屏障破坏与菌群失衡密切相关，在肠道高通透性状态下，血液中LPS水平可升高约2~3倍，进而激活外周免疫细胞，使其释放IL-6、TNF-α等促炎因子，从而间接加剧脑内神经炎症。肠道菌群可通过脑–肠轴介导的慢性系统性炎症反应，间接加剧脑内的神经炎症，并影响中枢神经系统功能。MOU等[40]指出，肠道微生物失衡可持续激活全身免疫反应，导致小胶质细胞长期处于促炎状态，促进神经退行性变化与认知功能下降。这一机制表明，肠道屏障受损不仅增加了炎症介质进入血液循环的机会，还可能通过血液–脑屏障影响脑组织炎症环境。饮食结构亦是影响肠道屏障和系统性炎症的重要因素。MALESZA等[41]指出，高脂西式饮食可显著降低肠道益生菌丰度，增加炎症相关菌群比例，并使血清C反应蛋白(C-reactive protein, CRP)和IL-1β水平升高约1.5~2倍，进一步诱发全身性低度炎症。因此，肠道屏障功能、菌群结构与全身性炎症之间的相互作用，是肠道微生态调控小胶质细胞表型极化和神经炎症的重要桥梁，为卒中后微生态干预提供了潜在靶点。

4 总结及展望

IS后神经炎症的核心在于小胶质细胞极化的方向与持续时间：急性期适度的M1样反应有助于清除坏死细胞及损伤相关危险信号，但小胶质细胞促炎表型持续激活可沿NF-κB/NLRP3轴放大炎症并加重血脑屏障损伤；M2样程序则更利于血管再生、髓鞘修复与突触重塑。仅用中枢内源性通路难以解释临床炎症强度与并发症的个体差异，本综述强调肠道菌群是影响卒中炎症阈值的重要上游调节器，可在代谢、免疫与屏障层面协同改变小胶质细胞极化的“起点与终点”。临床观察与粪菌移植实验提示菌群改变具有一定可转移性：SCFAs缺乏削弱了抗炎作用，并阻碍了其介导的表观遗传调控，LPS/TLR4与炎症小体提供了持续的促炎信号，TMAO可能通过血管炎症/血栓途径加重缺血负荷。在转化上，可将菌群干预纳入围卒中期综合管理：高感染风险者优先规范肠内营养联合益生菌/合生元；对SDI高、SCFAs低者探索后生元/靶向代谢干预。未来需以“特征菌/代谢物–极化标志–临床终点”三联终点开展分层多中心随机对照试验，并建立标准化、可复现的炎症评估体系。

参考文献 (References)

[1] JIANG Y X, WANG N, LIU J Y, et al. Evobrutinib mitigates neuroinflammation after ischemic stroke by targeting M1 microglial polarization via the TLR4/Myd88/NF-κB pathway [J]. Mol Med, 2025, 31(1): 148.

[2] JIWON KIM B, KIM J Y, LEE J E. Abstract TP399: modulation of cytotoxic T cells by poly-Glu/Tyr attenuates neuroinflammation after ischemic stroke [J]. Stroke, 2025, doi: 10.1161/str.56.suppl_1.TP399.

[3] LI Z R, WANG Y Y, WANG Z H, et al. The positive role of transforming growth factor-β1 in ischemic stroke [J]. Cell Signal, 2024, 121: 111301.

[4] HERNANDEZ V G, LECHTENBERG K J, PETERSON T, et al. Translatome analysis reveals microglia and astrocytes to be distinct regulators of inflammation in the hyperacute and acute phases after stroke [J]. Glia, 2023, 71: 1960-84.

[5] WROBLEWSKI V, WILLMANN M, ROSS T, et al. Molecular

imaging of the brain-heart axis after stroke: impact of regional microglia suppression on cardiac function [J]. J Nucl Med, 2023, 64(Sup): 1.

[6] ZENG J S, BAO T T, YANG K L, et al. The mechanism of microglia-mediated immune inflammation in ischemic stroke and the role of natural botanical components in regulating microglia: a review [J]. Front Immunol, 2023, 13: 1047550.

[7] FAN P L, WANG S S, CHU S F, et al. Time-dependent dual effect of microglia in ischemic stroke [J]. Neurochem Int, 2023, 169: 105584.

[8] WAN H X, HE M F, CHENG C, et al. Clec7a worsens long-term outcomes after ischemic stroke by aggravating microglia-mediated synapse elimination [J]. Adv Sci, 2024, 11(36): e2403064.

[9] ALSBROOK D L, DI NAPOLI M, BHATIA K, et al. Neuroinflammation in acute ischemic and hemorrhagic stroke [J]. Curr Neurol Neurosci Rep, 2023, 23(8): 407-31.

[10] GUAN X, ZHU S T, SONG J Q, et al. Microglial CMPK2 promotes neuroinflammation and brain injury after ischemic stroke [J]. Cell Rep Med, 2024, 5(5): 101522.

[11] DING R, LI H Y, LIU Y Q, et al. Activating cGAS-STING axis contributes to neuroinflammation in CVST mouse model and induces inflammasome activation and microglia pyroptosis [J]. J Neuroinflammation, 2022, 19(1): 137.

[12] CANDELARIO-JALIL E, DIJKHUIZEN R M, MAGNUS T. Neuroinflammation, stroke, blood-brain barrier dysfunction, and imaging modalities [J]. Stroke, 2022, 53(5): 1473-86.

[13] LI L, JIANG W F, YU B J, et al. Quercetin improves cerebral ischemia/reperfusion injury by promoting microglia/macrophages M2 polarization via regulating PI3K/Akt/NF-κB signaling pathway [J]. Biomed Pharmacother, 2023, 168: 115653.

[14] LUO L, LIU M X, FAN Y H, et al. Intermittent theta-burst stimulation improves motor function by inhibiting neuronal pyroptosis and regulating microglial polarization via TLR4/NFκB/NLRP3 signaling pathway in cerebral ischemic mice [J]. J Neuroinflammation, 2022, 19(1): 141.

[15] LIU X, WANG J M, JIN J, et al. S100A9 deletion in microglia/macrophages ameliorates brain injury through the STAT6/PPARγ pathway in ischemic stroke [J]. CNS Neurosci Ther, 2024, 30(8): e14881.

[16] YU Z N, SU G J, ZHANG L M, et al. Icaritin inhibits neuroinflammation in a rat cerebral ischemia model by regulating microglial polarization through the GPER-ERK-NF-κB signaling pathway [J]. Mol Med, 2022, 28(1): 142.

[17] LIAO J, WEI M Z, WANG J J, et al. Naotaifang formula attenuates OGD/R-induced inflammation and ferroptosis by regulating microglial M1/M2 polarization through BMP6/SMADs signaling pathway [J]. Biomed Pharmacother, 2023, 167: 115465.

[18] ZHANG L, WEI W, AI X Y, et al. Extracellular vesicles from hypoxia-preconditioned microglia promote angiogenesis and repress apoptosis in stroke mice via the TGF-β/Smad2/3 pathway [J]. Cell Death Dis, 2021, 12(11): 1068.

[19] BAI X W, WEI H, LIU W X, et al. Cigarette smoke promotes colorectal cancer through modulation of gut microbiota and related metabolites [J]. Gut, 2022, 71(12): 2439-50.

[20] CHAE Y R, LEE Y R, KIM Y S, et al. Diet-induced gut dysbiosis and leaky gut syndrome [J]. J Microbiol Biotechnol, 2024, 34(4): 747-56.

[21] ANAND N, GORANTLA V R, CHIDAMBARAM S B. The role of gut dysbiosis in the pathophysiology of neuropsychiatric disorders [J]. Cells, 2022, 12(1): 54.

[22] MA L Y, NI Y H, WANG Z, et al. Spermidine improves gut barrier integrity and gut microbiota function in diet-induced obese mice [J]. Gut Microbes, 2020, 12(1): 1-19.

[23] JING Y L, YU Y, BAI F, et al. Effect of fecal microbiota transplantation on neurological restoration in a spinal cord injury mouse model: involvement of brain-gut axis [J]. Microbiome, 2021, 9(1): 59.

[24] PAN C L, ZHANG H W, ZHANG L Y, et al. Surgery-induced gut microbial dysbiosis promotes cognitive impairment via regulation of intestinal function and the metabolite palmitic amide [J]. Microbiome, 2023, 11(1): 248.

[25] LIANG B X, DENG Y H, HUANG Y J, et al. Fragile guts make fragile brains: intestinal epithelial Nrf2 deficiency exacerbates neurotoxicity induced by polystyrene nanoplastics [J]. ACS Nano, 2024, 18(35): 24044-59.

[26] CHEN A D, TENG C Q, WEI J J, et al. Gut microbial dysbiosis exacerbates long-term cognitive impairments by promoting intestinal dysfunction and neuroinflammation following neonatal hypoxia-ischemia [J]. Gut Microbes, 2025, 17(1): 2471015.

[27] SPENCER C N, MCQUADE J L, GOPALAKRISHNAN V, et al. Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response [J]. Science, 2021, 374(6575): 1632-40.

[28] PORCARI S, BENECH N, VALLES-COLOMER M, et al. Key determinants of success in fecal microbiota transplantation: from microbiome to clinic [J]. Cell Host Microbe, 2023, 31(5): 712-33.

[29] KIM J, LEE H K. Potential role of the gut microbiome in colorectal cancer progression [J]. Front Immunol, 2022, 12: 807648.

[30] TANG Y X, CHEN L Q, YANG J, et al. Gut microbes improve prognosis of *Klebsiella pneumoniae* pulmonary infection through the lung-gut axis [J]. Front Cell Infect Microbiol, 2024, 14: 1392376.

[31] GUO Y, LUO S Y, YE Y X, et al. Intermittent fasting improves cardiometabolic risk factors and alters gut microbiota in metabolic syndrome patients [J]. J Clin Endocrinol Metab, 2021, 106(1): 64-79.

[32] WEI H L, YU C Y, ZHANG C, et al. Butyrate ameliorates chronic alcoholic central nervous damage by suppressing microglia-mediated neuroinflammation and modulating the microbiome-gut-brain axis [J]. Biomed Pharmacother, 2023, 160: 114308.

[33] YAN X L, SHI L B, ZHU X L, et al. From microbial homeostasis to systemic pathogenesis: a narrative review on gut flora's role in neuropsychiatric, metabolic, and cancer disorders [J]. J Inflamm Res, 2025, 18: 8851-73.

[34] LIAPIS C C. "Pseudoneurotransmission" and gut microbiome-brain communication in neuropsychiatric disorders [J]. Psychiatriki, 2024, doi: 10.22365/jpsych.2024.024.

[35] ZHOU Y N, ZHANG Y, XU D C, et al. Exosomes from polarized microglia: proteomic insights into potential mechanisms affecting intracerebral hemorrhage [J]. Gene, 2025, 935: 149080.

[36] SOARES N L, PAIVA I, BRAVO J, et al. Carbon monoxide modulation of microglia-neuron communication: anti-neuroinflammatory and neurotrophic role [J]. Mol Neurobiol, 2022, 59(2): 872-

89.

[37] AKHTER N, CONTRERAS J, ANSARI M A, et al. Remote ischemic post-conditioning (RIC) mediates anti-inflammatory signaling via myeloid AMPKα1 in murine traumatic optic neuropathy (TON) [J]. Int J Mol Sci, 2024, 25(24): 13626.

[38] ZHANG W, WU Q H, ZHANG X N, et al. NLRP3 promotes radiation-induced brain injury by regulating microglial pyroptosis [J]. Neuropathol Appl Neurobiol, 2024, 50(3): e12992.

[39] DI VINCENZO F, DEL GAUDIO A, PETITO V, et al. Gut microbiota, intestinal permeability, and systemic inflammation: anarrative review [J]. Intern Emerg Med, 2024, 19(2): 275-93.

[40] MOU Y, DU Y, ZHOU L X, et al. Gut microbiota interact with the brain through systemic chronic inflammation: implications on neuroinflammation, neurodegeneration, and aging [J]. Front Immunol, 2022, 13: 796288.

[41] MALESZA I J, MALESZA M, WALKOWIAK J, et al. High-fat, western-style diet, systemic inflammation, and gut microbiota: a narrative review [J]. Cells, 2021, 10(11): 3164.

[42] WANG T T, CHEN B D, LUO M C, et al. Microbiota-indole 3-propionic acid-brain axis mediates abnormal synaptic pruning of hippocampal microglia and susceptibility to ASD in IUGR offspring [J]. Microbiome, 2023, 11(1): 245.

[43] CHEN C, LIAO J M, XIA Y Y, et al. Gut microbiota regulate Alzheimer's disease pathologies and cognitive disorders via PUFA-associated neuroinflammation [J]. Gut, 2022, 71(11): 2233-52.

[44] LI H N, XIANG Y J, ZHU Z M, et al. Rifaximin-mediated gut microbiota regulation modulates the function of microglia and protects against CUMS-induced depression-like behaviors in adolescent rat [J]. J Neuroinflammation, 2021, 18(1): 254.

[45] BANO N, KHAN S, AHAMAD S, et al. Microglia and gut microbiota: a double-edged sword in Alzheimer's disease [J]. Ageing Res Rev, 2024, 101: 102515.

[46] MOSSAD O, BATUT B, YILMAZ B, et al. Gut microbiota drives age-related oxidative stress and mitochondrial damage in microglia via the metabolite N^6-carboxymethyllysine [J]. Nat Neurosci, 2022, 25(3): 295-305.

[47] ZENG X L, GAO X X, PENG Y, et al. Higher risk of stroke is correlated with increased opportunistic pathogen load and reduced levels of butyrate-producing bacteria in the gut [J]. Front Cell Infect Microbiol, 2019, 9: 4.

[48] XIA G H, YOU C, GAO X X, et al. Stroke dysbiosis index (SDI) in gut microbiome are associated with brain injury and prognosis of stroke [J]. Front Neurol, 2019, 10: 397.

[49] TAN C H, WU Q H, WANG H D, et al. Dysbiosis of gut microbiota and short-chain fatty acids in acute ischemic stroke and the subsequent risk for poor functional outcomes [J]. JPEN J Parenter Enteral Nutr, 2021, 45(3): 518-29.

[50] ZHU W F, ROMANO K A, LI L, et al. Gut microbes impact stroke severity via the trimethylamine N-oxide pathway [J]. Cell Host Microbe, 2021, 29(7): 1199-208,e5.

[51] LIU X M, ZHANG Y S, CHU J H, et al. Effect of probiotics on the nutritional status of severe stroke patients with nasal feeding that receive enteral nutrition: a protocol for systematic review and meta-analysis of randomized controlled trials [J]. Medicine, 2021, 100(17): e25657.

[52] ZHONG D Y, LI L, MA R M, et al. The effect of probiotics in stroke treatment [J]. Evid Based Complement Alternat Med, 2021, 2021: 4877311.