

菌群代谢物介导滋养细胞代谢重编程参与子痫前期

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摘要

子痫前期是妊娠期高发且严重威胁母婴安全的并发症, 胎盘滋养细胞功能异常与代谢紊乱是其核心病理环节。近年来, 肠道菌群及其代谢产物在妊娠相关疾病中的调控作用成为研究热点, 肠-胎盘轴机制为阐释子痫前期发病机理提供了全新视角。肠道菌群失调可引发短链脂肪酸、胆汁酸、色氨酸代谢物及三甲胺-N-氧化物等代谢物谱异常, 通过能量代谢调控、表观遗传修饰、免疫微环境重塑等通路, 诱导胎盘滋养细胞发生代谢重编程, 抑制滋养细胞侵袭与螺旋动脉重塑, 加剧胎盘氧化应激与炎症反应, 最终推动子痫前期发生发展。本文系统梳理肠道菌群代谢物的种类与功能、滋养细胞代谢异常特征, 阐明菌群代谢物介导滋养细胞代谢重编程的分子通路, 总结临床生物标志物开发与微生态干预的研究进展, 展望精准防治策略, 为子痫前期的早期预警与靶向治疗提供理论依据与新思路。

关键词

肠道菌群代谢物, 代谢重编程, 胎盘滋养细胞, 子痫前期

Gut Microbiota Metabolites Mediate Trophoblast Metabolic Reprogramming in Preeclampsia

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Abstract

Preeclampsia is a highly prevalent and life-threatening complication of pregnancy, with placental trophoblast dysfunction and metabolic disorders serving as its core pathological link. In recent years, the regulatory role of the gut microbiota and its metabolites in pregnancy-related diseases has become a research hotspot, and the “gut-placenta axis” mechanism provides a novel perspective for elucidating the pathogenesis of preeclampsia. Gut microbiota dysbiosis leads to abnormal profiles of metabolites such as short-chain fatty acids (SCFAs), bile acids, tryptophan metabolites, and trimethylamine-N-oxide (TMAO). These metabolites induce metabolic reprogramming in placental trophoblasts through pathways including energy metabolism regulation, epigenetic modification, and immune microenvironment remodeling. Such reprogramming inhibits trophoblast invasion and spiral artery remodeling, exacerbates placental oxidative stress and inflammatory responses, and ultimately promotes the development of preeclampsia. This paper systematically reviews the types and functions of gut microbiota metabolites, the characteristics of trophoblast metabolic abnormalities, clarifies the molecular pathways of microbiota metabolites mediating trophoblast metabolic reprogramming, summarizes research advances in clinical biomarker development and microecological interventions, and prospects precise prevention and treatment strategies. It provides theoretical basis and new ideas for early warning and targeted therapy of preeclampsia.

Keywords

Gut Microbiota Metabolites, Metabolic Reprogramming, Placental Trophoblasts, Preeclampsia

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1. 前言

子痫前期(Preeclampsia, PE)以妊娠20周后出现高血压、蛋白尿为核心临床表现,全球发病率达2%~8%,是造成孕产妇与围产儿死亡的重要诱因[1]。其发病机制复杂未明,学界普遍认可胎盘功能障碍是核心起始环节,具体表现为滋养细胞侵袭不足、子宫螺旋动脉重塑缺陷,进而引发胎盘缺血缺氧、系统性炎症与血管内皮损伤[2]。

随着微生物组学与代谢组学技术发展,肠道菌群及其代谢物在PE中的作用被逐步揭示,肠-胎盘轴理论为解析PE发病机制开辟新方向[3]。妊娠期肠道菌群稳态失衡,会导致短链脂肪酸(SCFAs)生成减少、三甲胺-N-氧化物(TMAO)等异常代谢物蓄积,通过循环系统作用于胎盘组织,调控滋养细胞代谢表型与功能[4][5]。研究证实,产SCFAs菌株如嗜黏蛋白阿克曼菌(*Akkermansia muciniphila*)丰度下降,会降低丙酸、丁酸水平,抑制滋养细胞侵袭与巨噬细胞M2型极化,加重胎盘炎症与血管功能异常[6]-[8]; TMAO则可干扰自噬-铁死亡平衡,参与胎盘损伤进程[5][9]。

上述发现不仅完善了PE的病理机制网络,也为早期诊断标志物筛选与微生态干预提供潜在靶点。本文围绕肠道菌群代谢物、滋养细胞代谢重编程与PE的关联展开综述,梳理核心机制与临床转化进展,为PE的精准防治提供参考。

2. 主体

2.1. 肠道菌群及其代谢物的组成与功能

2.1.1. 肠道菌群的主要分类及其代谢特征

肠道菌群是维持宿主代谢与免疫稳态的复杂微生态系统，其结构紊乱与 PE 密切相关[10][11]。健康孕妇肠道核心菌群包含双歧杆菌属、真杆菌属、普雷沃菌属、拟杆菌属等，参与营养代谢与免疫调节[12]。PE 患者呈现显著菌群失调特征：产 SCFAs 的 *Akkermansia muciniphila*、发酵乳杆菌(*Limosilactobacillus fermentum*)丰度显著降低，厚壁菌门/拟杆菌门比例失衡，导致 SCFAs 合成不足，同时鞭毛组装、精氨酸-脯氨酸代谢通路异常，进一步加剧病理进程[13][14]。粪菌移植实验证实，PE 患者肠道菌群可诱导模型动物出现高血压、胎盘炎症等典型表型，直接验证菌群失调在 PE 中的致病作用[4][15]。但现有动物模型多采用啮齿类，其肠道菌群结构、胎盘发育模式与人类存在明显差异，粪菌移植的表型重现性有限，相关结论尚不能完全等同于人类 PE 的真实病理过程，仍需在人群队列中进行验证。

2.1.2. 肠道菌群代谢物的种类及其生理功能

肠道菌群代谢物是介导肠-胎盘信号传递的关键介质，核心类型包括 SCFAs、TMAO、苯丙酸酯、胍基丁胺等[16]。SCFAs (乙酸、丙酸、丁酸)是膳食纤维发酵产物，既为宿主提供能量，也发挥抗炎、维持肠道屏障的作用；PE 患者体内丁酸、己酸水平降低，与血压升高、炎症激活呈正相关[8][16]。TMAO 由胆碱代谢生成，可通过调控自噬、氧化应激干扰胎盘发育[5][9]。苯丙酸酯、胍基丁胺在 PE 患者粪便中浓度升高，与乳酸杆菌丰度下降相关，影响精氨酸代谢与血管功能[13]。总体而言，多数代谢物与 PE 的关联仍停留在相关性证据层面，直接因果关系尚未在人体研究中得到充分证实，部分结论仅为基于动物实验的合理推测。

2.1.3. 肠道菌群代谢物与宿主代谢的相互作用

肠道菌群代谢物与宿主代谢的交互作用，通过免疫调节、自噬、血管重塑等通路参与 PE 发病[3]。SCFAs 中的丙酸、丁酸可促进胎盘巨噬细胞 M2 极化、激活滋养细胞自噬，改善螺旋动脉重塑；其缺乏则引发炎症失控、胎儿生长受限[4][6]。TMAO 及氨基酸衍生物通过破坏自噬-铁死亡平衡，影响胎盘发育与新生儿生长指标[5]。PE 患者体内苯丙酸酯升高与血压、尿素水平正相关，SCFAs 水平可作为 PE 风险评估的潜在代谢标志物，为非侵入性诊断提供依据[13][17]。不过，代谢物的组织特异性、胎盘穿透效率及妊娠窗口期效应等尚不明确，不同研究间的结果差异也提示菌群代谢物调控存在个体差异性。

2.2. 胎盘滋养细胞的功能及其在子痫前期中的作用

2.2.1. 胎盘滋养细胞的生物学特性

胎盘滋养细胞是维持胎盘功能的核心细胞，分为绒毛滋养细胞(CTB)与绒毛外滋养细胞(EVT)。CTB 融合形成合体滋养层，承担母胎物质交换与激素分泌功能；EVT 具备侵袭特性，主导子宫螺旋动脉重塑，保障胎盘血供[18]。TGF- β 超家族通过 Smad 通路调控 EVT 上皮-间质转化(EMT)，基质金属蛋白酶 MMP-2、MMP-9 降解细胞外基质，共同维持滋养细胞正常侵袭能力[18]。PE 状态下，上述信号通路失衡，导致滋养细胞生物学功能受损[14]。

2.2.2. 胎盘滋养细胞功能障碍与子痫前期的关系

滋养细胞侵袭不足、螺旋动脉重塑障碍是 PE 的核心病理特征[2]。PE 患者胎盘组织中 FKBPL、galectin-3 表达上调，提示血管功能损伤与炎症加剧；滋养细胞侧群基因 ELL2、HK2、CXCL8 异常表达，CXCL8 过表达抑制滋养细胞迁移，GATA6 下调阻碍 EVT 分化，共同导致滋养细胞功能紊乱[13]。上述异常共同造成胎盘灌注不足，触发系统性高血压、蛋白尿等 PE 临床表现[19][20]。

2.2.3. 胎盘滋养细胞代谢异常在子痫前期发病中的作用

代谢紊乱是 PE 滋养细胞功能障碍的重要机制。PE 胎盘中存在显著氧化应激, Sonic hedgehog (SHH) 高表达加剧线粒体 ROS 蓄积与滋养细胞凋亡[21]。维生素 D 信号通路异常同样参与致病: PE 胎盘维生素 D 受体(VDR)、miR-26b-5p 表达降低, 使环氧合酶-2 (COX-2)上调、PGE2 释放增加, 加重炎症与氧化损伤; 1,25(OH)₂D₃ 可通过 miR-26b-5p 抑制 COX-2, 缓解细胞损伤, 提示营养干预的潜在价值[22]。值得注意的是, 滋养细胞代谢异常相关数据多来自胎盘组织或细胞系研究, 尚未在 PE 早发型与晚发型、不同疾病程度等不同亚型中分层验证, 临床异质性问题突出, 一定程度上限制了结论的普适性。

2.3. 肠道菌群代谢物对胎盘滋养细胞功能的调控

2.3.1. 短链脂肪酸(SCFAs)对滋养细胞功能的调节

SCFAs 是调控滋养细胞功能的核心菌群代谢物。PE 患者产 SCFAs 菌群与代谢物水平显著下降, 与疾病严重程度相关[8] [13]。丙酸、丁酸可直接增强滋养细胞侵袭能力, 改善螺旋动脉重塑; 同时激活自噬通路、促进胎盘巨噬细胞 M2 极化, 抑制胎盘局部炎症, 维持微环境稳态[4] [6]。基于此, SCFAs 被视为 PE 治疗的潜在靶点, 补充 SCFAs 或产 SCFAs 益生菌可缓解 PE 病理表型[23] [24]。尽管 SCFAs 的保护作用已在动物模型中得到证实, 但人类胎盘的受体表达、信号强度及安全剂量范围仍为推测性结论, 缺乏大样本、前瞻性临床数据支撑。

2.3.2. 胆汁酸及其衍生物对滋养细胞代谢的影响

胆汁酸是肠道菌群重要代谢产物, 通过 FXR、TGR5 受体调控代谢与炎症[25]。目前胆汁酸对滋养细胞的直接作用研究较少, 但妊娠期肝内胆汁淤积症(ICP)中, 胆汁酸升高与胎盘功能障碍、不良妊娠结局相关[26]。据此推测, 胆汁酸可能通过影响滋养细胞能量代谢、氧化应激、侵袭能力参与胎盘调控, 有待后续研究验证[3]。但目前胆汁酸与 PE 的关联仅为间接相关证据, 其直接调控滋养细胞代谢重编程的分子机制尚属推测, 需通过靶向敲除/过表达等干预实验进一步明确因果关系。

2.3.3. 色氨酸代谢物与滋养细胞免疫调节

色氨酸代谢物(犬尿氨酸、吲哚衍生物)是肠道与宿主共代谢产物, 具备强免疫调节活性[27]。PE 患者色氨酸代谢通路紊乱, 犬尿氨酸通路过度激活释放促炎因子, 抑制滋养细胞功能; 吲哚-3-丙酸等衍生物可激活 AhR 通路, 诱导滋养细胞抗炎表型, 维持胎盘免疫耐受[3] [28]。色氨酸代谢物通过调控滋养细胞与巨噬细胞、T 细胞的交互作用, 影响妊娠免疫耐受建立, 是 PE 免疫干预的潜在方向[29]。但现有研究以相关性分析为主, 色氨酸代谢通路在 PE 中的具体作用、AhR 通路的胎盘特异性调控机制尚未完全证实, 仍需更精准的机制研究夯实理论基础。

2.4. 代谢重编程在子痫前期发病中的机制

2.4.1. 代谢重编程的概念及其在疾病中的作用

代谢重编程是细胞应对应激时, 改变糖酵解、氧化磷酸化、脂质代谢等途径的适应过程[30]。PE 胎盘中存在典型 Warburg 效应, 糖代谢向糖酵解偏移, 导致乳酸堆积、氧化应激加剧; 乳酸介导的组蛋白乙酰化修饰(如 Hsp60 乙酰化)促进线粒体分裂与 ROS 生成, 加速滋养细胞凋亡[21]。同时, 代谢重编程激活 NLRP3 炎症小体, 与滋养细胞侵袭不足形成恶性循环, 是 PE 多器官损伤的共性机制[31]。

2.4.2. 肠道菌群代谢物诱导滋养细胞代谢重编程的途径

肠道菌群代谢物通过受体 - 信号通路 - 代谢酶轴驱动滋养细胞代谢重编程[3] [14]。菌群失调导致 LPS 增加, 激活 TLR4/NF- κ B 通路上调糖酵解关键酶 PFKFB3, 使代谢向糖酵解偏移; 色氨酸代谢物吲哚

乙醛、嘌呤代谢物肌苷分别通过 PPAR γ 、A2AR 受体调节能量代谢与胎盘屏障[14]。肌苷可通过 A2AR/PPAR γ 轴增强紧密连接蛋白表达, 缓解氧化应激; 而 5-HIAA/5-HT 比例失衡则加重炎症, 共同塑造滋养细胞异常代谢表型[3] [30]。该通路在细胞与动物水平已获得部分证实, 但在人类胎盘中的直接证据仍不足, 通路中多数关键环节仅为基于现有结果的合理推测。

2.4.3. 代谢重编程与胎盘氧化应激和炎症反应的关联

代谢重编程、氧化应激、炎症反应形成致病恶性循环。糖酵解增强导致 NADH/NAD⁺失衡、线粒体 ROS 爆发, 激活 NF- κ B 释放 IL-1 β 、TNF- α ; 炎症信号又通过 TLR4/PFKFB3 轴进一步增强糖酵解, 形成正反馈[14] [31]。乳酸介导的 Hsp60 乙酰化直接损伤线粒体, 诱导 Drp1 磷酸化与细胞凋亡[21]。二甲双胍可抑制 TLR4/NF- κ B/PFKFB3 轴, 同步纠正代谢紊乱与炎症激活, 提示靶向代谢 - 炎症交互调控的治疗潜力[31]。PE 胎盘中甘油磷脂、鞘脂代谢紊乱与滋养细胞分化异常相关, 为脂质代谢干预提供新靶点[30] [32]。

2.5. 肠道菌群代谢物与子痫前期的临床研究进展

2.5.1. 子痫前期患者肠道菌群特征的变化

PE 患者肠道菌群呈现特异性失调: *Akkermansia muciniphila*、*Oscillibacter* 等有益菌丰度下降, SCFAs 合成能力降低[13] [15]。一项纳入 92 例 PE 患者与 86 例健康孕妇的研究显示, PE 患者粪便 SCFAs (丙酸、丁酸)水平显著降低, 且与菌群结构改变高度相关[13]。动物粪菌移植实验证实, PE 菌群可直接诱导高血压、胎盘炎症等表型, 明确菌群失调的致病作用[4] [15]。

2.5.2. 肠道菌群代谢物作为子痫前期生物标志物的潜力

SCFAs 及相关菌群具备 PE 非侵入性生物标志物潜力[8] [17]。PE 患者 SCFAs 水平降低与疾病严重程度正相关, 相较于稳定性有限的单一代谢物指标, 基于 *Akkermansia*、*Oscillibacter* 与 SCFAs 构建的多代谢物组合标志物, 具备更高诊断灵敏度与特异性, 可更好实现 PE 早期筛查与风险分层[13] [17]。这类代谢标志物直接反映肠 - 胎盘轴功能状态, 与胎盘功能障碍、炎症等核心病理高度关联, 整体效能优于传统单一指标[3]。不过, 目前相关研究仍缺乏外部验证队列、统一诊断阈值与标准化妊娠窗口期检测标准, 距离临床应用仍有差距。

2.5.3. 基于肠道菌群代谢物的干预策略

微生态干预为 PE 防治提供新策略[24] [33]。动物实验证实, 补充 *Akkermansia muciniphila*、丙酸、丁酸可降低 PE 模型血压、减轻胎盘炎症, 通过促进巨噬细胞 M2 极化、增强滋养细胞侵袭改善胎盘功能[4] [6]。健康孕妇粪菌移植可缓解 PE 病理表型, 验证菌群稳态的保护作用[15]。益生菌(如 *Limosilactobacillus reuteri*)、膳食纤维干预可调节菌群结构、提升 SCFAs 水平, 具备临床转化前景[23] [24]。动物实验已明确干预有效性, 但面向孕妇的微生态干预需严格设计临床试验, 明确血压控制、蛋白尿缓解、分娩孕周延长等主要终点, 建立感染、宫缩、胎儿窘迫等安全性监控体系, 并区分 PE 不同亚型实施分层干预, 以更好贴合精准医学理念。

3. 结论

肠道菌群代谢物通过介导胎盘滋养细胞代谢重编程, 在 PE 发病中发挥关键调控作用, 是肠-胎盘轴机制的核心环节。菌群失调引发 SCFAs、TMAO、色氨酸代谢物等谱式异常, 通过能量代谢重塑、表观遗传修饰、免疫炎症调控等通路, 导致滋养细胞侵袭不足、胎盘缺血缺氧、系统性炎症, 最终诱发 PE。综合现有证据, 动物模型与细胞实验结论多为已证实证据, 临床关联研究多为相关性证据, 而人类胎盘

直接机制与亚型差异相关结论多为推测性证据，证据强度存在明显层级差异。未来开发出菌群-代谢物联合诊断标志物，益生菌、代谢物补充等干预策略在实验中显示良好效果。

但该领域仍存在不足：不同代谢物的交叉调控机制未完全阐明，临床研究样本量有限、缺乏多中心验证，干预措施的安全性及有效性需进一步评估。未来研究应重点关注 PE 亚型差异，明确肠-胎盘轴在不同亚型中的特异性作用，应结合空间多组学、基因编辑等技术，解析代谢重编程的精准分子机制；开展大样本前瞻性队列研究，验证生物标志物的临床价值；优化微生态干预方案，推动 PE 从机制研究向精准防治转化，最终改善母婴健康结局。

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