肠道菌群与过敏性疾病

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[摘 要] 过敏性疾病的发病率持续上升，儿童期尤为常见，已成为重要的公共卫生问题。肠道菌群作为连接环境暴露、免疫发育与过敏易感性的关键环节，正成为相关研究的重要切入点。肠道菌群在生命早期免疫系统成熟、免疫耐受建立和黏膜屏障维持中发挥重要作用。菌群失衡可通过减少代谢物生成、促进Th2型免疫偏倚、削弱T细胞诱导并破坏上皮屏障功能，进一步经“肠-皮肤轴”“肠-鼻轴”“肠-肺轴”参与过敏性疾病的发生和发展。不同过敏表型虽临床表现各异，但在菌群多样性下降、关键共生菌减少及免疫耐受不足等方面具有一定共性。探讨过敏性疾病患者肠道菌群和代谢特征及其在发病机制中的作用和临床意义，有望为过敏性疾病的早期预防、风险识别和微生态精准干预提供理论依据。

[关键词] 肠道菌群；特应性皮炎；过敏性鼻炎；哮喘；微生态干预

Gut microbiota and allergic diseases

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ABSTRACT Incidence of allergic diseases continues to increase, particularly among children, and has become an important public health concern. As a key link connecting environmental exposure, immune development, and susceptibility to allergic diseases, the gut microbiota has emerged as an important focus of related research. The gut microbiota plays a crucial role in immune system maturation during early life, establishment of immune tolerance, and maintenance of mucosal barrier integrity. Gut dysbiosis may contribute to the occurrence and progression of allergic diseases through multiple mechanisms, including reduced metabolite production, promotion of Th2-type immune skewing, impaired T-cell induction, and disruption of epithelial barrier function. Furthermore, the gut microbiota participates in allergic disease development through the “gut-skin axis” “gut-nose axis”, and “gut-lung axis”. Although different allergic phenotypes exhibit distinct clinical manifestations, they share certain common characteristics, including reduced microbial diversity, depletion of key commensal bacteria, and insufficient immune tolerance.

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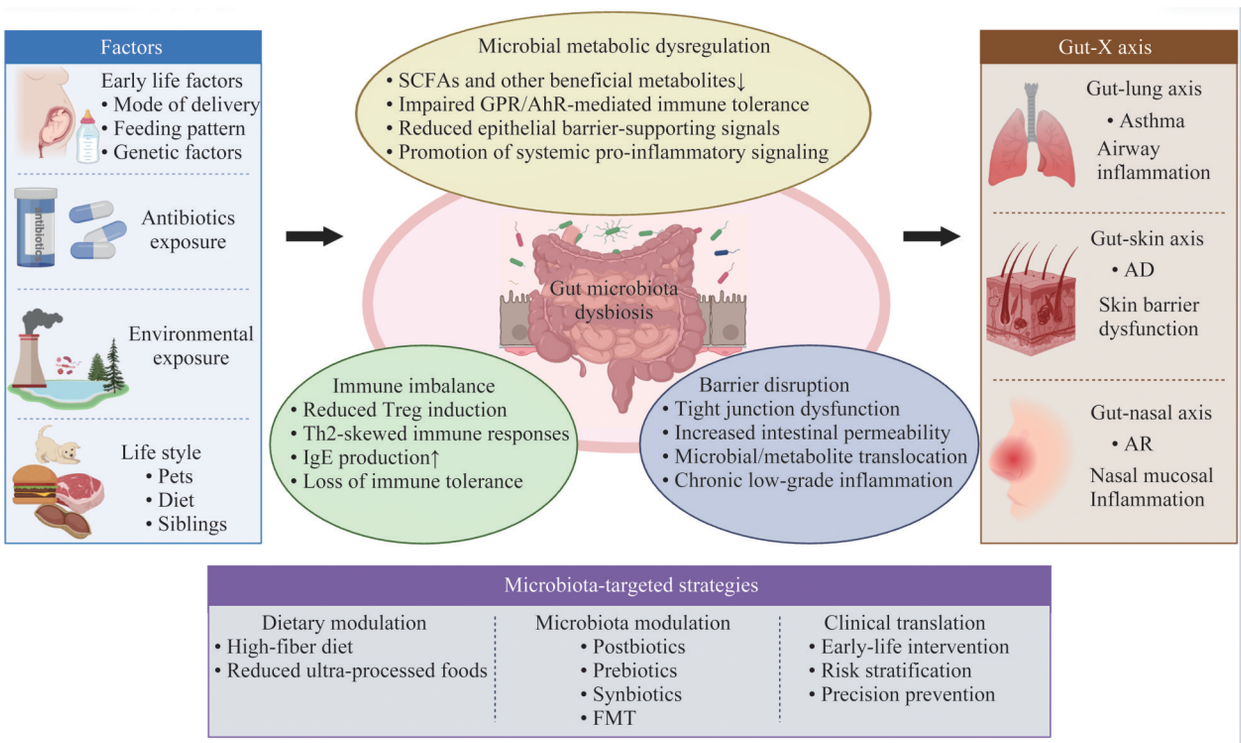
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Investigation of gut microbiota and metabolic characteristics in patients with allergic diseases, as well as their roles and clinical implications in disease pathogenesis, may provide a theoretical basis for early prevention, risk identification, and precision microbiome-based interventions for allergic diseases.

Graphical Abstract



Relationship between gut microbiota and allergic diseases. AD: Atopic dermatitis; AR: Allergic rhinitis; SCFAs: Short-chain fatty acids; Treg: Regulatory T cells; FMT: Fecal microbiota transplantation; GPR: G protein-coupled receptor; AhR: Aryl hydrocarbon receptor; Ig: Immunoglobulin.

KEY WORDS　gut microbiota; atopic dermatitis; allergic rhinitis; asthma; microbiome-based interventions

过敏性疾病是由免疫系统功能受损引起的全身性疾病，包括特应性皮炎(atopic dermatitis，AD)、过敏性鼻炎(allergic rhinitis，AR)、哮喘、食物和药物过敏等[1]。近年来，过敏性疾病的发病率持续上升，影响全球约20%的人口，尤其是儿童，世界卫生组织早已将过敏性疾病列为21世纪3大重点防治疾病之一[2-3]。既往观点认为过敏性疾病常遵循由婴儿期AD向儿童期AR和哮喘发生和发展的轨迹[4]。但随着出生队列和纵向研究的不断深入，更多证据[5-6]提示仅有部分患儿符合这一典型演变轨迹，过敏性疾病更可能是遗传背景、环境暴露和免疫调节异常共同作用下形成的多表型共病谱系[7]。这一认识对过敏性疾病共同通路的机制研究、诊断策略的更新及个体化预防有重要意义。

在过敏性疾病共同机制的探索中，肠道菌群逐渐成为重要切入点。作为人体最大的微生态系统，肠道菌群不仅是宿主与外界环境相互作用的重要中介，也在生命早期免疫发育和过敏易感性形成中发挥重要作用[8]。现代生活方式改变、微生物暴露减少及饮食结构转变等因素，均可能通过影响肠道菌群稳态参与过敏性疾病的发生和发展。本文通过检索PubMed、Web of Science和Elsevier ScienceDirect数据库，以肠道菌群、过敏性疾病、AD、AR、哮喘、免疫耐受及微生态干预等关键词进行组合检索，重

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点纳入近5年相关代表性文献，并辅以经典文献进行补充，综述肠道菌群在过敏性疾病中的研究进展，探讨其作用机制、应用现状和未来发展方向，以期为相关研究和临床实践提供参考。

1 肠道菌群的组成及其功能

肠道中栖息着超过100万亿个微生物，包含细菌、真菌、病毒、原生动物等，这些微生物共同组成人体重要的微生态系统，其组成和功能在生命历程中呈动态变化[8]。生命早期尤其是出生后1 000 d是肠道菌群建立和功能成熟的关键窗口[9-10]，遗传背景、分娩方式、饮食习惯、抗生素暴露等因素均可影响其组成、多样性和代谢特征[11-12]。这一时期同时也是免疫系统发育和免疫耐受建立的重要阶段，若肠道菌群发育异常，可能干扰免疫成熟，增加个体日后发生过敏及其他免疫炎症性疾病的风险[13]。除菌群组成外，短链脂肪酸(short-chain fatty acids，SCFAs)、胆汁酸、吲哚衍生物等菌群代谢产物也在宿主营养代谢、上皮屏障维持和免疫调节中发挥重要作用[14-15]。肠道菌群失调是指一系列环境和宿主因素(如感染、炎症、饮食、宿主遗传等)导致的菌群组成和功能改变，表现为共生菌减少、机会致病菌增多及微生态稳态破坏，并与过敏、炎症、自身免疫及代谢性疾病密切相关[16-17]。

2 从“卫生假说”到“屏障假说”：肠道菌群在过敏性疾病中的研究演进

对肠道菌群与过敏性疾病关系的认识经历了由“微生物暴露不足”向“菌群失调-免疫失衡-屏障损伤”逐步深入的过程。早期“卫生假说”认为生命早期微生物接触不足会影响免疫系统正常发育，增加过敏性疾病风险[18]。随后“肠道菌群假说”“老朋友假说”及“生物多样性假说”进一步强调与人类长期共存的共生微生物及其多样性对维持机体免疫稳态具有重要意义[19-21]。近年来，随着对黏膜免疫和上皮屏障研究的深入，“屏障假说”提出上皮屏障功能受损是过敏性疾病发生和发展的关键环节，肠道菌群失调及其代谢异常可通过削弱免疫耐受、破坏屏障完整性并促进炎症因子和微生物代谢产物易位，参与持续性炎症反应的形成[22]。因此，当前研究已不再局限于微生物接触减少这一现象层面，而是更加关注肠道菌群失调如何通过免疫调节异常和屏障功能障碍共同促进过敏性疾病的发生和发展。

3 肠道菌群参与过敏性疾病的共性机制

3.1 生命早期肠道菌群建立异常与过敏易感性

生命早期肠道菌群异常与过敏易感性的关联已由单纯菌群组成差异进展到菌群发育轨迹偏离和功能成熟不足的层面。出生队列研究[23]提示，婴儿期肠道菌群成熟延迟并非仅对应单一过敏表型，而与后续AD、食物过敏、AR及哮喘等多种儿童过敏结局相关；这种异常不仅表现为关键共生菌定植不足和菌群多样性下降，还伴随黏膜相关功能、代谢能力及微生态稳定性的整体失衡。进一步的纵向研究[24]表明，婴儿肠道菌群演替遵循可预测的发育轨迹，其中以双歧杆菌属和拟杆菌属为代表的早期优势定植，与更健康的后续轨迹相关。相反，偏离这一发育轨迹的婴儿，更容易进入一种与过敏不良结局相关的“发育迟滞型”菌群状态。值得注意的是，生命早期过敏易感性的形成并非由单一围产期暴露因素决定的，而与菌群扰动后的恢复能力也密切相关。以剖宫产为例，近期的研究[25]显示，部分婴儿虽存在早期菌群扰动，但若随后能够建立更接近阴道分娩婴儿的菌群恢复轨迹，其后续哮喘风险可明显降低。另外，关于食物过敏的研究[26]也提示出生后1月龄的肠道菌群分型较1周龄更能预测后续食物致敏和食物过敏风险，说明出生后最初数周可能是真正影响免疫耐受走向的关键阶段。总之，生命早期肠道菌群建立异常并非简单的“暂时失衡”，而更可能代表一种可持续影响免疫稳态的发育偏移，为后续多表型过敏性疾病奠定共同的易感基础。

3.2 肠道菌群与免疫耐受建立

生命早期是免疫系统发育和免疫耐受建立的关键阶段，其进程与肠道菌群定植和功能成熟基本同步[12]。这一时期，肠道菌群及其相关抗原是驱动外周调节性T细胞(peripherally induced regulatory T cells，pTreg)生成的重要外源因素[27]，而pTreg是免疫耐受建立的关键细胞基础[28]。研究[29]提示断奶期是pTreg大量诱导的关键窗口，随着食物抗原暴露和肠道菌群负荷增加，耐受相关免疫网络逐步建立。若该过程受到干扰，则可能削弱后续免疫耐受并增加过敏易感性。肠道菌群除提供抗原刺激外，其代谢产物也是耐受性免疫环境的重要组成部分，SCFAs可以通过抑制组蛋白去乙酰化酶(histone deacetylase，HDAC)促进叉头框蛋白P3(forkhead box P3，Foxp3)表达，从而诱导pTreg生成[30]；色氨酸代谢相关吲哚衍生物可以通过抑制哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin，mTOR)信号通路促

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进pTreg分化[31]，当菌群失衡导致这些代谢信号减少时，免疫耐受形成也随之受损。

近年来，随着单细胞测序技术的发展，有学者[32-34]鉴定出一类新的耐受性抗原呈递细胞——Thetis细胞。值得关注的是，这类细胞在断奶期达到发育高峰，并被认为与肠道菌群耐受与口服耐受建立密切相关[35]。与之相呼应的是，既往研究[36]发现杯状细胞相关抗原通道(goblet cell-associated antigen passages，GAPs)也在断奶期特异性开放，为肠腔抗原进入黏膜免疫系统提供了独特路径。二者在时间维度上的高度重叠提示其可能共同参与生命早期耐受微环境的构建。尽管目前尚缺乏证据证明二者之间存在直接功能联系，且其在过敏性疾病中的作用仍不清楚，但这一方向为揭示生命早期过敏易感性的形成机制提供了新的研究切入点。

3.3 上皮屏障破坏与Th2型免疫偏倚

过敏性疾病的致病机制通常涉及对常见过敏原的Th2型炎症反应增强。肠道菌群失衡可通过多条途径参与Th2型炎症反应的启动和放大，其中肠上皮屏障功能受损被认为是重要的上游环节[12, 37-38]。近年来研究[39]显示，上皮屏障并非单纯阻隔肠腔内容物的被动结构，而是整合微生物、代谢及环境刺激并主动调控黏膜免疫应答的重要界面。正常情况下，肠道菌群及其代谢产物有助于维持紧密连接、黏液层完整性和上皮细胞稳态。当菌群失调时，屏障破坏不仅增加抗原通透性，还可改变上皮细胞本身的免疫指令功能，使其由维持耐受转向释放促炎信号，从而为Th2型免疫偏倚奠定基础[22, 40]。肠道菌群失衡所致的代谢异常，是连接屏障损伤与免疫失衡的重要中介。SCFAs、吲哚衍生物及次级胆汁酸等有益代谢物分别参与上皮能量代谢、紧密连接维持、黏膜稳态保护及免疫调节功能，当这些代谢信号减少，而促炎相关代谢产物增加时，肠上皮屏障更易受损，受损上皮会释放胸腺基质淋巴细胞生成素(thymic stromal lymphopoietin，TSLP)、白细胞介素(interleukin，IL)-25和IL-33等“警报素”，驱动2型固有淋巴细胞(group 2 innate lymphoid cells，ILC2)、嗜酸性粒细胞和肥大细胞活化，并促进树突状细胞摄取抗原后迁移至次级淋巴器官，诱导初始T细胞向Th2细胞分化，继而推动B细胞发生免疫球蛋白(immunoglobulin，Ig)E类别转换。过敏原特异性IgE与肥大细胞表面高亲和力IgE受体(high affinity IgE receptor，FcεRI)结合后，使机体处于致敏状态；再次暴露于相同过敏原时，肥大细胞迅速脱颗粒并释放多种炎症介质，最终导致过敏性炎症持续放大[14, 37-38, 40-41]。因此，从“屏障假说”视角看，肠道菌群失衡所致的上皮功能障碍，可能先于明显的过敏性炎症发生，并通过抗原暴露增加、警报素释放、Th2型炎症反应放大等连续过程，推动慢性过敏性疾病的形成和维持。这一认识也提示，恢复屏障完整性和菌群代谢平衡或许是干预过敏性疾病共同机制的重要方向。

3.4 肠道菌群失衡与肠外器官炎症调控

肠道菌群可以调节肠外器官疾病的病理生理进程[42]。肠道菌群失衡可通过肠屏障受损、菌群代谢产物异常、全身低度炎症及免疫细胞功能重塑等多种途径，参与皮肤、鼻和肺等肠外器官的炎症调控[43-44]。与过敏性疾病关系密切的跨器官免疫调控主要体现在“肠-皮肤轴”“肠-鼻轴”和“肠-肺轴”。

AD患者的肠道菌群表现为金黄色葡萄球菌、梭菌、大肠杆菌定植增加，而双歧杆菌、肠球菌、拟杆菌、瘤胃球菌定植减少，特点是菌群多样性降低，有益菌减少及有害菌增加[45]。肠道菌群失衡及屏障受损可促进炎症信号和代谢产物进入循环，影响皮肤屏障稳态和局部免疫环境。Kim等[46]发现SCFAs中的丁酸缺乏可削弱pTreg介导的免疫调控，促进Th2型免疫偏倚和IgE介导致敏，从而加重皮肤炎症反应。动物实验[47]也提示，补充丁酸可改善小鼠皮肤屏障功能，促进角质形成细胞分化及结构蛋白和脂质生成。另外，肠道起源的系统性免疫失衡还可进一步改变皮肤局部微生态，促进金黄色葡萄球菌等致病菌过度定植，形成炎症持续和皮肤屏障受损的恶性循环[48]。

AR患者的肠道菌群α多样性明显低于健康对照，其中拟杆菌门的丰度增加，而放线菌门和变形菌门的丰度降低，大肠杆菌-志贺氏菌、普雷沃氏菌和副拟杆菌的丰度显著增加，梭菌属丰度下降[49]。虽然肠道菌群紊乱与AR之间存在关联，但其潜在机制尚不明确，肠道菌群紊乱可能导致胆汁酸代谢异常和NOD样受体热蛋白结构域相关蛋白3(NOD-like receptor family pyrin domain-containing 3，NLRP3)炎症小体活化，从而参与环境暴露导致的鼻黏膜上皮屏障损伤加剧，进而导致AR[50]。

哮喘患者肠道菌群组成失衡表现为菌群多样性降低，拟杆菌门/厚壁菌门比例升高，以及机会致病菌(如大肠杆菌)丰度增加[51]，且生命早期肠道菌群不成熟与后续哮喘风险增加密切相关[24, 52]。研究[53-54]显示肠道与肺通过共同黏膜免疫系统、微生物代谢物和炎症信号构成双向调控网络。肠道菌群失衡可通过免疫细胞迁移及微生物相关分子和代谢产物的循

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环运输，影响肺部免疫稳态并放大炎症反应。

综上，肠道菌群失衡可通过跨器官免疫调控影响肠外组织炎症，提示过敏性疾病虽表现于不同靶器官，但其病理基础可能源于共同的肠源性免疫失衡。

4 肠道菌群在过敏性疾病治疗中的潜在应用

4.1 益生菌与益生元

益生菌是指摄入足够数量后可对宿主产生健康益处的活性微生物[55]，益生元则是能够被肠道菌群选择性利用并带来健康效应的底物[56]。总体而言，益生菌在已患过敏性疾病中的治疗效果尚不稳定，但在生命早期用于过敏预防可能更有潜力。经典随机对照研究[57]显示，在过敏高危儿童中，围产期补充鼠李糖乳杆菌GG可降低早期过敏性疾病的发生风险。不同菌株、剂量、干预时机及研究人群差异较大，导致现有证据并不完全一致[58-60]。近年来，研究者逐渐从单一菌株转向多菌株组合、益生菌与益生元联用，以及基于菌群代谢物调控的新策略，以期更有效地提高肠道菌群稳定性并促进稳态恢复[61]。部分前沿研究提示，特定益生菌来源的细胞外囊泡[62]、人乳低聚糖与双歧杆菌联用[63]等策略可通过调节菌群和代谢物组成改善过敏表型，但其临床转化仍需进一步验证。

4.2 粪菌移植

粪菌移植(fecal microbiota transplantation，FMT)是将健康供体的肠道菌群移植至患者体内以重建健康微生态的治疗手段。在AD模型小鼠中，FMT可恢复肠道菌群至供体状态，提高体内SCFAs水平，恢复Th1/Th2平衡，上调pTreg细胞，并降低IgE水平，从而有效抑制过敏反应[64]。Dong等[65]也在AR模型小鼠中证实，FMT实验恢复了AR小鼠的肠道菌群，通过平衡$CD4^+$ T细胞群、抑制促炎性细胞因子释放、增强抗炎功能来减轻AR小鼠的炎症。临床个案报告[66]显示，在中重度AD患儿中观察到FMT后的症状改善和菌群重塑。尽管初步结果令人鼓舞，但FMT在过敏性疾病中的应用仍处于早期阶段，其有效性、安全性及标准化方案尚需更多研究证实。

4.3 其他

近年来调控肠道菌群的干预策略逐步由广泛调节菌群组成转向靶向菌群功能和免疫通路。工程菌借助合成生物学手段赋予特定菌群定向递送免疫调节分子或调控局部炎症微环境的能力，与传统益生菌相比体现出功能明确、靶向性更强等特点，是未来精准微生态治疗的重要方向[67]。其次，噬菌体治疗为精准清除致病菌提供了新思路，与抗生素相比，噬菌体可选择性裂解特定细菌，在尽量保证菌群结构的基础上纠正菌群失衡，具有较强的靶向性[68]。尽管目前这2种方法在过敏性疾病中的直接证据仍有限，但其作用机制提示其有望通过重塑肠道微生态、恢复免疫稳态而成为潜在的新型治疗策略。未来仍需进一步开展机制研究和临床验证，以明确其安全性、有效性及适用人群。

5 结 语

肠道菌群与过敏性疾病之间存在密切而复杂的相互作用。与现代生活方式相关的菌群多样性下降和稳态失衡，可能是近几十年来过敏性疾病发病率持续上升的重要因素。生命早期肠道菌群建立异常、免疫耐受受损、上皮屏障破坏及Th2型免疫偏倚共同构成过敏性疾病发生和发展的重要机制基础。尽管不同过敏表型在受累靶器官和临床表现上存在差异，但其可能共享肠道菌群失衡相关的病理机制，并可通过“肠-皮肤轴”“肠-鼻轴”和“肠-肺轴”等途径作用于不同肠外器官。

尽管该领域研究进展迅速，并为微生态干预提供了新的思路，但仍面临一些挑战。目前，该领域证据仍以相关性研究为主，菌群失调在过敏性疾病中的因果作用及关键作用环节尚需进一步明确。益生菌、益生元及FMT等微生态干预虽具有潜在应用前景，但其疗效一致性、长期安全性及标准化方案仍有待验证。未来应加强生命早期纵向队列和机制研究，推动微生态干预向早期预防和精准防治转化。

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