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肠道菌群与自身免疫性甲状腺疾病相关性的研究进展

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摘　要

肠道菌群是人体共生的重要组成部分，对宿主的营养、代谢、屏障、免疫至关重要，菌群稳态受损会引起胃肠道及全身疾病。自身免疫性甲状腺疾病(AITD)是一种器官特异性自身免疫性疾病，其发病机制尚不明确，目前认为与遗传易感性、环境因素、免疫失衡有关，其中免疫失衡是核心因素。近年研究表明，和健康人群相比，AITD患者的肠道菌群存在明显差异。本文通过探讨肠道菌群参与AITD发生发展的可能机制以及AITD患者肠道菌群的特征变化，以期为AITD的诊断及治疗提供新视角。

关键词

自身免疫性甲状腺疾病，肠道菌群，Graves病，桥本甲状腺炎，粪菌移植

Research Progress on the Relationship between Gut Microbiota and Autoimmune Thyroid Disease

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Abstract

The gut microbiota is an important component of human symbiosis, which is crucial for the host's

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nutrition, metabolism, barrier, and immunity. Impaired microbiota homeostasis can cause gastrointestinal and systemic diseases. Autoimmune Thyroid disease (AITD) is an organ specific autoimmune disease, and its pathogenesis is still unclear. At present, it is believed that it is related to genetic susceptibility, environmental factors, and immune imbalance, of which immune imbalance is the core factor. Recent studies have shown that the gut microbiota of AITD patients is significantly different from that of healthy people. This article discusses the possible mechanism of gut microbiota participating in the occurrence and development of AITD and the characteristic changes of gut microbiota in AITD patients, in order to provide a new perspective for the diagnosis and treatment of AITD.

Keywords

Autoimmune Thyroid Disease, Gut Microbiota, Graves Disease, Hashimoto Thyroiditis, Fecal Bacteria Transplantation

1. 引言

自身免疫性甲状腺疾病(Autoimmune thyroid disease, AITD)是最常见的器官特异性自身免疫性疾病，患病率在全球范围内高于 5%，且仍在增加[1]，临床常见类型包括 Graves 病(Graves desease, GD)和桥本甲状腺炎(Hashimoto’s thyroiditis, HT)，其特征为甲状腺自身抗原暴露激活、免疫耐受紊乱导致体内产生甲状腺特异性自身抗体，同时伴有甲状腺淋巴细胞的浸润。AITD 的病因和发病机制尚不明确，既往研究均提示遗传、环境、免疫等因素与该病相关。越来越多的研究表明，众多自身免疫性疾病具有肠道微生物组生态失调的特征模式，例如类风湿关节炎[2]、系统性红斑狼疮[3]、强直性脊柱炎[4]中均发现了肠道菌群失衡，肠道菌群与 AITD 的关系也相继被发现，但仍存在很大局限，现针对二者之间的关联做一简要综述。

2. 肠道菌群

肠道菌群是寄生在人体胃肠道内的庞大微生物群体，由大量细菌及少量的病毒、真菌、古菌、原生动物组成，约占人类微生物群的 66%。肠道菌群作为“人类第二个基因组”，所编码的基因总数是人体基因的 150 多倍[5]。肠道菌群在与人类的共生关系中保持着一种互惠互利的平衡状态，肠道菌群参与宿主营养物质的吸收和消化、维生素的合成[6]和淋巴系统的发育[7]、中枢神经系统活动[8]，以及防止病菌定植、免疫系统的发育成熟[9]，而宿主为微生物群提供生活场所和营养素。然而，当这种相互关系受到损害时，肠道菌群的功能和组成改变，这一过程称为生态失调，进而可能导致或有助于各种疾病的发生和发展。

3. 肠道菌群参与 AITD 发生发展的可能机制

3.1. 参与甲状腺激素的合成与代谢

目前认为，肠道菌群通过调节甲状腺激素所需微量元素来影响甲状腺激素的合成和代谢。碘是甲状腺激素合成不可或缺的微量元素，肠道菌群会影响碘的吸收及摄取。碘的摄取主要通过钠/碘同转运体

(sodium/iodine symporter, NIS)进行，功能性 NIS 蛋白在不仅在甲状腺细胞中表达，而且在唾液腺、胃和乳腺组织中表达[10]。此外，肠道中存在的 Na^+/多种维生素转运蛋白(SMVT)和囊性纤维化转运蛋白(CFTR)也参与碘的吸收，然而，仅在小范围内[11]。动物模型显示，缺乏微生物组的个体对碘的摄取有限。Vought RL 等人[12]通过放射性碘摄取分析得出，无菌大鼠或用卡那霉素处理的大鼠的放射性碘摄取较对照组在早期显著减少。然而，碘的排泄似乎没有受到影响。肠胃外喂养的短肠综合征[13]和吸收不良的减肥手术[14]都不会稳定的改变尿碘排泄。但支持这一发现的证据太弱，目前无法得出明确的结论。

硒参与调节甲状腺激素的代谢平衡。甲状腺是硒含量最高的器官。硒在甲状腺素(thyroxine, T4)转化为三碘甲状腺原氨酸(triiodothyronine, T3)的过程中发挥着重要作用，并能保护甲状腺细胞免受氧化应激和炎症的损伤。此外，补硒还能降低 AITD 患者甲状腺抗体水平，改善甲状腺结构、代谢及临床症状[15]。硒在人体内主要以硒蛋白的形式存在并发挥生物效应，如谷胱甘肽过氧化物酶、硫氧还蛋白还原酶和碘甲腺氨酸脱碘酶等。而细菌总数的 1/4 拥有硒蛋白编码基因，肠道菌群结构改变时将影响硒蛋白的表达[16]。此外，结肠可吸收小肠中未被吸收的硒，进而被肠道内的微生物代谢[17]。当硒不足时，细菌与宿主竞争硒，肠道菌群与硒的亲和力增加，进而导致硒蛋白的水平及活性降低。

3.2. 参与碘化甲腺原氨酸代谢

碘化甲腺原氨酸有多种代谢途径，其中脱碘和共轭最有效，后者包括硫共轭和葡萄糖醛酸共轭。肠道菌群可通过以下途径来影响碘化甲腺原氨酸的代谢：1) 脱碘酶活性：既往有学者在大鼠和人的肠道中发现了脱碘酶活性[18]，肠道常驻菌群抑制脱碘酶的活性。此外，肠道细菌细胞壁的脂多糖(LPS)可增加 2 型脱碘酶活性，影响甲状腺素和促甲状腺激素的血清水平[19]。2) 肠肝循环：在肝脏，硫共轭使脱碘酶失活，而葡萄糖醛酸化产生大量的共轭 T4，后者随胆汁分泌到肠道，在肠道微生物的作用下被重新吸收进入体循环。3) 葡糖醛酸酶活性：肠道菌群可以影响葡糖醛酸酶的活性。由于 β-葡糖醛酸酶的存在，肠道细菌，尤其是专性厌氧菌，能够水解碘化甲腺原氨酸共轭化合物[20]。4) 碘甲腺原氨酸的结合和摄取：Roche 等人[21]的体外研究表明，大肠杆菌对放射性碘甲腺原氨酸有较高的结合(T3 > T4)和摄取能力。后来 DiStefano III 等人[22]也证实，正常大鼠粪便和盲肠内容物中放射性标记的 T3 和 T4 存在可逆结合，而经抗生素处理大鼠后这种结合减少甚至消失，这表明肠道可能储存碘代甲腺原氨酸。

3.3. 参与免疫调节

肠道菌群通过自身组成、结构及其代谢产物(如 SCFA、多胺)来影响 Th17/Treg 轴，进而参与 AITD 的发病过程。许多免疫细胞亚群的增殖分化受菌群调控，如分段丝状杆菌(SFB)是肠黏膜固有层 Th17 的诱导剂[23]；脆弱芽孢杆菌 YCH46 是 Treg 细胞的天然激活剂和 Th17 细胞的抑制剂[24]。SCFA 主要包括乙酸、丙酸和丁酸。丁酸盐是直肠真杆菌的主要产物，在肠道中可诱导 Treg 细胞的产生及增殖，并促进其功能增强。丙酸可增加 Treg 细胞的数量，减少 Th17 细胞的数量，维持 Th17/Treg 轴平衡。Su 等人[25]的研究发现，肠道生物失调通过丙酸调节途径导致 Treg/Th17 失衡，且通过气相色谱－质谱(GC-MS)分析发现产生 SCFA 的细菌和 SCFAs(丙酸、丁酸)显著减少，证明了肠道菌群在 GD 免疫失衡中的作用。SCFA 可抑制组蛋白去乙酰化酶减少干扰素产生，增加幼稚的 $CD4^+$、Treg 细胞。此外，菌群可影响肠道树突状细胞和巨噬细胞，树突状细胞分泌 TGF-β 促进 Th17 和 Treg 细胞分化，或产生维甲酸促进 Treg 细胞发育、抑制 Th17 细胞；巨噬细胞产生 IL-2 和 IL-10 抑制 Th17 细胞发育[26]。

肠道菌群可能通过分子模拟机制引起交叉免疫反应，导致自身抗原的免疫耐受减退或丧失。Kiseleva 等人[27]发现，某些乳杆菌 B-01 和双歧杆菌 791 蛋白序列与甲状腺过氧化物酶(TPO)和甲状腺球蛋白(TG)具有结构相似性，它们可以通过分子模拟机制选择性结合 TPO 抗体(TPOAb)和 TG 抗体(TGAb)，从而诱

导 AITD。小肠结肠炎耶尔森菌和幽门螺杆菌可能通过与自身抗原发生交叉免疫在 AITD 中发挥作用也已被描述[28]。

4. 肠道菌群在 AITD 中的变化

大量证据表明，AITD 患者的肠道菌群与健康人存在显著差异，肠道细菌的过度生长在 AITD 的发生发展中起重要作用。研究表明，GD 患者的肠道菌群多样性显著降低，拟杆菌、普雷沃氏菌等的比例明显升高，厚壁菌、另枝菌等的比例明显降低[29]。此外，Cornejo-Pareja 等[30]通过核心微生物组分析发现 Prevotellaceae 家族和 *Prevotella* 属是 GD 组的特征菌群。普雷沃氏菌是丙酸盐的已知生产者，可以诱导调节性 T 细胞的分化并抑制 Th17 极化[31]，它还可能影响药物治疗 GD 的疗效[32]。Jiang 等提出乳杆菌在 GD 中发挥有害作用。尽管乳酸杆菌是一种益生菌，但研究表明某些乳酸杆菌菌株具有潜在的致病性，可能通过激活 NF-KB 信号通路在 GD 中发挥邪恶作用[33]。据报道，拟杆菌属、另枝杆菌属和普雷沃氏菌属 3 个菌属能够以 85%的准确率将 GD 患者与健康人区分开来[25]。

近年 Cayres 等[34]通过实时 PCR 分析 40 名 HT 患者和 53 名健康对照者的粪便样本，结果显示两组之间 27 个属存在显著差异。与健康人群相比，HT 患者真杆菌属、布劳特氏菌属、瘤胃球菌、罗氏菌属、毛螺菌属、普拉梭菌属和真细菌属的丰度增加，而粪杆菌属、拟杆菌属、普雷沃菌属和梭状芽孢杆菌属的丰度降低，这与 Zhao 等[35]的研究结果相似。该研究还发现，肠道菌群与 FT4、TSH 显著相关，与 TPOAb 和 TGAb 无相关性，而 Zhao 等人指出肠道菌群与临床参数(TPOAb 和 TGAb、FT4、TSH)强相关。此外，Liu 等[36]发现，HT 患者肠道菌群的组成与甲状腺功能状态相关。

由此表明，AITD 可显著影响肠道菌群的丰富度和多样性，研究之间存在差异可能是由于不同的方法，甚至是由于地理位置、疾病严重程度和饮食习惯等的影响。

5. 粪菌移植(Fecal Microbiota Transplantation, FMT)

粪菌移植是将健康人粪便中的功能菌群移植到患者肠道内，重建正常的肠道微生态系统。FMT 可直接证明菌群与许多疾病存在相互作用，目前已有多种疾病受益，如艰难梭菌感染、炎症性肠病、多发性硬化等。粪菌移植将逐步应用于神经精神、代谢系统、肿瘤免疫等疾病的治疗。因此，FMT 有望通过重塑肠道微环境，改善 AITD 患者的预后。

6. 总结与展望

综上所述，肠道菌群与 AITD 之间存在明显关联。尽管研究证实 AITD 患者肠道菌群发生变化，但研究结果并不一致，二者之间相互影响的机制尚不明确，其因果关系尚未得到证实，未来有待更深入的研究。

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