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肠道菌群与矮小症相关性研究进展

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摘　要

矮小症是指身高在同一种族、年龄和性别中比平均值低两个标准差。严重的身材矮小将会影响青少年儿童的心理健康和生活质量，密切关注儿童身高变化，及时明确病因并进行有效干预，对儿童青少年的健康成长具有重要意义。肠道菌群在调节免疫、维持肠上皮稳态、调节营养代谢以及激素水平中发挥着重要作用。菌群组成和功能异常将直接影响宿主健康，严重者可出现生长发育迟滞。近年来，部分临床研究探讨了肠道菌群在矮小症儿童中的调节作用，引起了人们广泛关注。本文结合课题组研究结果，对肠道菌群与矮小症的相关研究进行系统综述。

关键词

肠道菌群，矮小症，生长激素缺乏症，特发性矮小

Progress in the Study of the Correlation Between Gut Microbiota and Short Stature

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Abstract

Short stature refers to individuals who are more than two standard deviations below the average

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height for the same race, age, and sex. Severe short stature will affect the mental health and quality of life of children and adolescents. It is important to pay close attention to the changes in children's height, identify the causes of the disease in time and make effective interventions for the healthy growth of children and adolescents. Gut microbiota plays an important role in regulating immunity, maintaining intestinal epithelial homeostasis, regulating nutritional metabolism and hormone levels. Abnormalities in the composition and function of gut microbiota will directly affect the health of the host, and growth retardation may occur in severe cases. In recent years, some clinical studies have explored the regulatory role of gut microbiota in children with short stature, which has attracted widespread attention. In this paper, we combine the research results of our group to provide a systematic review of the studies related to gut microbiota and short stature.

Keywords

Gut Microbiota, Short Stature, Growth Hormone Deficiency, Idiopathic Short Stature

1. 引言

矮小症是指身高在同一种族、年龄和性别中比平均值低两个标准差[1]。矮小症的病因包括特发性矮小(ISS)、生长激素缺乏症(GHD)、家族性身材矮小、青春期发育迟缓、小于胎龄儿、甲状腺功能减退、特纳综合征和慢性肾脏疾病等[2]-[4]。严重的身材矮小将会影响儿童青少年的心理健康和生活质量[5][6]，因此，密切关注儿童身高变化，及时明确病因，并进行有效干预对儿童青少年的健康成长具有重要意义。

肠道菌群是指肠道内的一组微生物，主要包括细菌、病毒和真菌等，在机体免疫调节、维持肠上皮稳态、调节营养物质代谢以及激素水平中发挥着至关重要作用[7]。研究显示，肠道菌群对生长激素/胰岛素样生长因素(IGF)-1 轴的影响可通过其产生 SCFAs 和微生物模拟物直接介导，也可能通过其对生长激素调节激素、肠道环境和免疫系统的影响间接介导[8]-[10]。肠道菌群的组成和功能异常将导致宿主生长发育迟滞。例如，与常规小鼠相比，幼龄无菌小鼠的生长性能(身长、体重)显著降低，同时伴有生长激素和 IGF-1 水平下降[11]。近年来，部分临床研究进一步探讨了肠道菌群在矮小症儿童中的调节作用，引起了人们广泛关注[12]-[18]。本文结合课题组的研究结果(尚未发表)，对肠道菌群与矮小症的相关研究进行系统综述。

2. 肠道菌群对生长发育的影响

在青霉素被发现后，G.J. Martin 等人[19]发现在饲料中添加低剂量抗生素可以促进大鼠的生长速度和食物利用率。随后，这种效应在许多动物及人类中都得到了验证[20]，并且抗生素对生长代谢的作用可能与消除肠道中的某些微生物及其代谢产物有关[21]。肠道菌群影响宿主生长的早期证据来自无脊椎动物－黑腹果蝇的两项互补研究。研究发现常规饲养果蝇的生长和发育超过了无菌果蝇[22]，而在营养缺乏时，植物乳杆菌可通过激活宿主额外的生长途径(营养传感系统)来促进果蝇生长[23]。随后，在小鼠中也发现，植物乳杆菌具有相似程度的促生长作用[24]。随着研究深入，人们发现多种肠道微生物与宿主生长密切相关，包括植物芽孢杆菌、芽孢杆菌和肠球菌等，并且生长激素/IGF-1 轴可能是肠道菌群影响宿主生长和发育的重要潜在机制[25]-[27]。

3. ISS 菌群特征

目前关于矮小症的菌群研究主要集中在两种最常见的矮小症人群，ISS 和 GHD 儿童[28] [29]。与健康儿童相比，ISS 儿童的菌群结构主要表现为较低丰度的产短链脂肪酸(SCFAs)菌群(瘤胃球菌科、粪杆菌属、真杆菌属、双歧杆菌属以及罕见小杆菌属)和较高丰度的炎症相关菌群(拟杆菌属和普雷沃氏菌属) [12]-[14]。SCFAs 是肠道微生物分解不可消化纤维产生的代谢产物，主要包括丁酸、乙酸和丙酸，对宿主的能量代谢、免疫和炎症、骨形成及生长发育具有重要的调控作用[30]。对粪便进行 SCFAs 定量分析，ISS 儿童粪便的总 SCFAs、丁酸和戊酸浓度显著低于健康儿童，且总 SCFAs 和丁酸的水平与血清 IGF-1 标准差积分显著正相关[13]。在上述差异菌群中，瘤胃球菌科丰度降低与低水平促生长因子 NTproCNP 显著相关，瘤胃球菌科、粪杆菌属和真杆菌属的相对丰度与身高和 BMI 标准差积分呈显著正相关[13]。

通过对粪便中代谢产物进行通路富集分析，发现 ISS 儿童可能存在氨基酸和脂质代谢异常。与健康儿童相比，ISS 儿童粪便促进生长与能量代谢物质的水平显著下降，包括亚精胺、精氨酸、亮氨酸、异亮氨酸、谷氨酸、苏氨酸、腺苷和 L-5-羟色氨酸等，而具有抑制生长作用的芥酸水平升高[12] [16]。此外，在 Li 等人的研究中，ISS 和健康儿童粪便中的二羟丙酮和部分 SCFAs (醋酸盐、苏氨酸、丁酸盐、琥珀酸盐和丙酸盐)具有显著差异，然而该研究并未详细介绍组间具体变化[15]。此外，ISS 儿童菌群中参与嘧啶和嘌呤以及黄素、硫胺素合成的基因编码酶表达增加，目前尚不清楚这些菌群功能变化对 ISS 儿童的临床意义[16]。

4. GHD 患者菌群特征

Li 等人[15]比较了 GHD、ISS 与正常健康儿童的肠道菌群组成和代谢产物，与正常健康儿童相比，GHD 和 ISS 组的肠道菌群厚壁菌门/拟杆菌门比率及双歧杆菌丰度显著下降。值得注意的是，厚壁菌门/拟杆菌门比率及双歧杆菌丰度下降与 SCFAs，尤其是丁酸减少有关，这与生长激素基因敲除小鼠的研究结果相一致[31]。此外，与健康儿童相比，GHD 儿童肠道炎症及肠道吸收能力减低相关的菌群的丰度明显增加，包括普雷沃氏菌、梭杆菌、克雷伯氏菌和另枝菌，而与能量代谢相关的益生菌水平出现下降，比如毛螺杆菌、巨单胞菌和双歧杆菌[17]。

代谢组学分析显示，GHD 与健康儿童之间粪便中缬氨酸、苯乙酸、乙酸、丁酸盐、尿嘧啶、醋酸盐、丙酸盐、甲酸盐和烟酸盐存在显著差异[15]。与健康儿童及 ISS 儿童相比，GHD 儿童粪便缬氨酸和苯乙酸水平降低，两种菌群代谢产物均与生长激素峰值呈正相关[15]。缬氨酸具有促进生长，增强免疫及维持肠道健康的重要作用，而苯乙酸在维持氧化还原稳态中发挥着重要作用。因此，GHD 儿童菌群可能通过诱导氨基酸代谢的特定改变，特别是缬氨酸，来损害生理生长。苯乙酸水平降低会导致氧化应激增强，可能会导致心血管风险增加。

5. GHD 与 ISS 菌群组分及功能差异

为了消除身高及体重的干扰，并明确儿童生长激素水平与肠道菌群的关系，部分研究对比分析了 GHD 与 ISS 儿童之间的菌群组分及功能差异。在 Li 等人的研究，GHD 儿童的梭杆菌属丰度显著高于 ISS 儿童，并且梭杆菌属丰度与生长激素峰值呈负相关[15]。值得注意的是，在高水平生长激素的垂体腺瘤患者中，枯草梭杆菌丰度显著降低，进一步提示生长激素水平与枯草梭杆菌丰度存在相关性[32]。此外，与健康儿童相比，GHD 及 ISS 儿童的双歧杆菌比例均明显降低，这可能提示参与了矮小症儿童代谢紊乱。

在本课题组研究中，GHD 儿童与 ISS 儿童相比，部分具有抗炎及改善胰岛素抵抗作用的益生菌丰度显著升高，包括肠道罗斯氏菌、小杆菌属、韦氏非渗透杆菌和青春双歧杆菌，这可能解释为什么 GHD 患者具有较低的糖尿病发生风险。与健康儿童相比，GHD 及 ISS 儿童均存在菌群功能变化，主要表现为糖

酵解/糖异生功能增强，丙酮酸和嘧啶代谢功能减弱[15]，这与 GHD 患者血清代谢物异常结果一致[33]。在我们的研究中，进一步对比了 GHD 与 ISS 儿童间的菌群功能差异，发现 GHD 儿童菌群的多聚糖降解能力，氮类及维生素 B6 的代谢能力显著下降。多聚糖降解是 SCFAs 的主要来源[34]，而氮类代谢是蛋白质利用的重要环节[35]，因此，GHD 儿童菌群功能异常可能导致生长激素/IGF-1 轴及能量代谢受损。

6. 生长激素治疗对菌群影响

Miao 等人研究发现，ISS 儿童在生长激素治疗后，普雷沃氏菌丰度显著下降并接近健康儿童，而其它菌属组成及菌群多样性无显著变化[14]。这一研究结果与 GHD 儿童普雷沃氏菌丰度远高于健康儿童相一致[17]。普雷沃氏菌丰度的增加与代谢紊乱、发育迟缓和消化系统炎症密切相关[36]-[38]，因此，生长激素治疗导致的普雷沃氏菌丰度下降可能在促进宿主身高增长过程中发挥着重要作用。此外，Navas 等人研究发现，生长激素缺乏和 IGF-1 低水平与细菌移位有关[18]，而生长激素治疗逆转了这种移位增加。综上所述，生长激素治疗可能会减少部分有害菌属丰度，逆转肠道菌群异位，然而，生长激素治疗对菌群功能及代谢组学的影响有待进一步研究。

7. 研究进展总结

整体而言，GHD 及 ISS 儿童均存在肠道菌群组分及功能异常，主要表现为产 SCFAs 及促生长菌群丰度及代谢功能下降、肠道炎症相关菌群丰度升高。与 ISS 相比，GHD 儿童炎症相关菌群有所改善，但代谢能力进一步减弱，而生长激素治疗可纠正部分菌群组分异常及菌群移位。然而，关于矮小症儿童肠道菌群的研究相对较少，且研究样本量小，目前结果的可靠性需要大样本研究进一步证实。

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