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肠道菌群在造血干细胞移植中的研究进展

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摘　要

造血干细胞移植(Hematopoietic stem cell transplantation, HSCT)作为治疗恶性血液病的重要手段，其临床疗效与患者免疫重建及并发症管理密切相关。近年来，肠道菌群在HSCT中的作用逐渐成为研究热点。本文系统综述了肠道菌群构成与HSCT预后的关联，通过分析HSCT前后患者肠道菌群的特征，为临床预防和治疗策略提供依据。而基于调节肠道菌群组成和功能的干预措施，有望重建肠道微生态平衡，降低移植相关并发症的发生率和严重程度，为HSCT患者的治疗开辟了新途径。通过研究肠道菌群如何通过调节免疫细胞的分化和功能，为新型治疗靶点提供思路，最终提高HSCT患者的生存率和生活质量。然而，当前研究仍面临菌群调控标准化方案缺乏、个体差异显著及长期安全性评估不足等挑战。未来需结合多组学技术及临床队列研究，深入解析肠道菌群与宿主免疫系统的相互作用，为HSCT精准诊疗提供新策略。

关键词

肠道菌群，造血干细胞移植，移植物抗宿主病，粪便微生物移植，益生菌

Advances in Gut Microbiota Research during Hematopoietic Stem Cell Transplantation

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Abstract

Hematopoietic stem cell transplantation (HSCT) is a critical treatment for malignant hematological

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disorders, with its clinical outcomes closely intertwined with immune reconstitution and complication management. Recent advances have highlighted the gut microbiota as a focal point in HSCT research. This review evaluates the association between gut microbiota composition and HSCT outcomes, analyzing pre- and post-transplant microbial profiles to inform clinical prevention and intervention strategies. Modulating gut microbiota composition and function shows promise in restoring intestinal homeostasis, reducing transplant-related complications, and paving novel therapeutic avenues for HSCT patients. Mechanistic insights into microbiota-mediated regulation of immune cell differentiation further identify potential therapeutic targets, ultimately improving survival and quality of life. However, current challenges include the absence of standardized microbiota modulation protocols, significant interpatient variability, and limited long-term safety assessments. Future investigations integrating multi-omics approaches and large-scale clinical cohorts are essential to elucidate host-microbiota interactions, thereby advancing precision medicine strategies for HSCT.

Keywords

Gut Microbiota, Hematopoietic Stem Cell Transplantation, Graft-versus-Host Disease, Fecal Microbiota Transplantation, Probiotics

1. 引言

造血干细胞移植于 1957 年由 E. Donnell Thomas 首次进行尝试实施，是治疗多种血液系统疾病的有效手段，目前主要用于血液系统恶性肿瘤的治疗[1]。然而，移植后感染和移植物抗宿主病(graft-versus-host disease, GVHD)等危及生命的主要并发症，仍影响着 HSCT 的预后及生存质量[2]。新一代测序技术的进步揭示了菌群与疾病风险之间以前被低估的关联，深入研究肠道菌群在 HSCT 中的作用机制，对于改善 HSCT 患者预后具有重要意义。本综述系统梳理了近年来肠道菌群在 HSCT 中的作用机制及诊疗进展，重点分析菌群失调与 GVHD、感染的因果关联，总结粪便微生物群移植(Fecal microbiota transplantation, FMT)、益生菌等新型策略的临床证据，探讨基于多组学技术的精准诊疗方向，旨在为建立菌群导向的 HSCT 优化方案提供理论依据。

2. 肠道菌群的构成与 HSCT 的关系

接受 HSCT 的患者由于暴露于广泛的化疗和全身性抗生素、饮食改变等多种因素的综合作用，导致肠道菌群受到严重损伤[3] [4]。一项纵向分析接受异基因 HSCT 的患者肠道菌群的大型多中心国际队列研究证实，在不同国家(美国、德国、日本)的移植中心患者菌群失调模式具有相似性，均表现为多样性的丧失和单个分类单元的支配，并且中性粒细胞植入时较高的肠道菌群多样性与较低的死亡率相关[5]。Han 等人的研究表明 allo-HSCT 期间中性粒细胞植入时肠道微生物群的构成和评分可以预测清髓型异基因 HSCT 后 aGVHD 的发展[6] [7]。Masetti 等人开展的一项针对接受 HSCT 的患儿的研究发现，移植前儿童肠道菌群的多样性和组成与生存率和发生 aGVHD 的可能性相关[8]。特定细菌类群的相对丰度也与临床结局相关，例如肠球菌是 HSCT 后总死亡率和 GVHD 相关死亡率增加的重要危险因素[9]，而 Blautia 丰度(梭状芽胞杆菌纲中的一个属)增加与降低致死性 GVHD 和提高总生存率有关[10]。产生细菌素的能力使 Blautia 具有抑制病原菌在肠道定植的潜力，并且还可以影响肠道微生物群的组成[11]。将来有希望开

展通过保存 Blautia 菌等特定菌群防止肠道微生物群损伤，进而影响 HSCT 患者的临床结果的临床研究，如避免使用抑制共生菌群中厌氧菌的抗生素，或鼓励口服营养支持治疗[10]。

研究报道，中性粒细胞缺乏的血液病患者血流感染的总发生率为住院时间的 7.48/1000，其中 30 天内的总病死率达 12.1% [12]。HSCT 过程中常通过预防性抗生素治疗和全身使用广谱抗生素来防治中性粒细胞缺乏患者的感染[13]。但在 HSCT 期间，某些抗生素的应用等因素会使肠道菌群的多样性和稳定性被破坏，导致与随后的血流感染相关的细菌占据主导地位[14]。Montassier 等人的研究发现，微生物组的多样性是发生血流感染的保护因素，并且有希望通过观察患者在治疗前的肠道菌群组成来识别可能易受感染的人群[15]。随着微生物群测序平台的发展，微生物群分析将越来越多地指导相关人群尤其是感染高风险人群的治疗。

3. 肠道菌群与免疫调节的机制研究

免疫系统构成性功能的很大一部分是为了控制我们与微生物群的关系，所以机体内数量最多的免疫细胞驻留在共生菌定植的部位，如皮肤或胃肠道。同时，健康微生物群对免疫系统的主导作用是为了增强屏障免疫，从而加强对自身的遏制[16]。宿主用于维持其与微生物群之间的稳态关系的主要策略是尽量减少微生物与上皮细胞表面之间的接触，从而限制组织炎症和微生物易位。在胃肠道中，这种分离是通过上皮细胞、黏液、IgA、抗菌肽和免疫细胞的共同作用完成的，这些结构和免疫成分统称为“黏膜防火墙”[17]。黏液是限制微生物群和宿主组织之间接触并防止微生物易位的主要屏障。除了杯状细胞产生黏液外，所有肠上皮细胞谱系都可以产生抗菌肽，这些抗菌肽通过酶攻击细菌细胞壁或破坏细菌内膜而发挥抗菌功能，在限制肠道共生菌的暴露中发挥重要作用[18]。肠道树突状细胞通过与上皮相关的共生细胞进行采样，并与 Peyer’s 结中的 B 细胞和 T 细胞相互作用，产生共生衍生抗原特异性 IgA [19]。黏膜 IgA 反应缺乏经典的记忆特性，并能够对共生微生物群组成的变化做出应答。事实上，已建立的产生 IgA 的克隆被新的抗菌反应所取代，使黏膜免疫系统能够对不断变化的微生物群做出反应[20]。在稳态下，大多数 IL-17 (Th17)和 IFN γ (Th1) T 细胞存在于胃肠道中，并由微生物群产生的信号发展而来[21] [22]。同时，微生物群可通过竞争特定的代谢产物[23]、改变营养物质的可利用性[24]、产生直接影响病原菌生长或存活的抗菌肽[25]来限制病原菌的定植。

共生菌是调控反应的关键和活跃的诱导物。耐受的建立，即对食物和其他经口摄入抗原的炎症反应的主动抑制在没有肠道菌群来源信号的情况下不能被诱导[26]。其中，Foxp3+ Treg 在免疫耐受机制中占据了核心地位。目前普遍认为，对共生抗原和环境抗原耐受性的最佳维持需要胸腺和胃肠道诱导的 Treg 的共同作用[27] [28]。这些细胞在宿主的整个生命周期中维持外周和黏膜的稳态，其稳态的破坏导致了口服耐受的丧失和肠道中异常效应因子反应的产生[28]。Treg 的诱导被认为是益生菌的作用机制之一，研究发现益生菌在炎症性疾病中的一些调节作用被认为与 Treg 的诱导或扩增有关[29] [30]。婴儿双歧杆菌可增加结肠组织中 Treg 相关的 IL-10 和 TGF-β，其中 IL-10 是一种有效的抗炎细胞因子，TGF-β 则是一种有效的调节细胞因子，可抑制 Th 细胞增殖、分化和活化，并减少有害细胞因子的分泌[31]。双歧杆菌、乳酸菌和肠球菌联合制剂通过增加 Foxp3+ Treg 和调节结肠粘膜中 Th1/Th2 细胞因子的平衡，可以有效减轻结肠炎症损伤[32]。除了微生物群对诱导口服耐受相关的免疫机制的直接影响外，共生特异性 Treg 还可以通过抗原特异性的方式促进 IgA 的类别转换，从而通过多种机制控制宿主与微生物群的关系[33]。研究表明凝结芽孢杆菌可促进免疫蛋白(IgA、IgE、IgG、IgM)的表达，上调回肠 IFN-γ、IL-2、IL-4 和 IL-10 水平，并且可以通过上调 ZO-1 通路和下调 TLR4/MyD88/NF-κB 通路的表达来改善环磷酰胺诱导的肠黏膜损伤和炎症[34]。哺乳动物依靠细菌来分解难以消化的膳食成分，在此过程中产生的一个主要代谢产物是短链脂肪酸(short-chain fatty acids, SCFAs)，其通过促进结肠环境中 Treg 细胞的诱导和适合性来调节

Treg 细胞网络的大小和功能[35] [36]。Blautia 作为共生专性厌氧菌属，通过上调肠道 Treg 和产生 SCFAs 在维持肠道环境平衡和预防炎症方面发挥着重要作用[37]。在急性黏膜感染期间，炎性单核细胞与胃肠道中的微生物群相遇，促进其产生脂质介质 PGE2，进而限制组织损伤中性粒细胞的活化水平[38]。

4. 肠道菌群调节在 HSCT 中的应用

研究表明，肠道菌群对 HSCT 具有显著影响[39]。基于多项临床试验的结果，提出了通过调控肠道菌群组成以改善临床结果的建议。针对微生物群以改善 HSCT 的策略可归纳为三大类：FMT、益生菌和益生元。

4.1. 粪便微生物群移植

FMT 是指将健康供者的粪菌输注到菌群失调患者的胃肠道内，已被欧洲微生物学和传染病学会(European Society for Microbiology and Infectious Disease)和美国胃肠病学会(American College of Gastroenterology)推荐作为复发性艰难梭菌感染的治疗方法[40]。临床研究结果表明，FMT 可通过植入有益的供体细菌，特别是产生抗炎代谢物的细菌，恢复共生和肠道稳态来改善 GVHD 相关结局[41] [42]。对于肠道类固醇耐药的 GVHD 患者采用 FMT 治疗的有效性和安全性也已经得到评估，研究显示患者的临床症状可以得到缓解，但病例的数量均较少[43]-[45]。已有报道在行异体造血细胞移植期间，预防性口服 FMT 胶囊后发生了产广谱 β-内酰胺酶的大肠杆菌菌血症[46]。这项病例报告强调了加强供体筛查以限制可能导致不良感染事件的必要性，并需警惕评估 FMT 在不同患者群体中的益处和风险。需要采取更好的措施来确保防止 FMT 介导的感染性并发症，比如确定一个具体的最小的 FMT 菌群，可以有效地恢复微生物群和减少 GVHD 但不引起感染[47]。另外还需制定标准化供体筛查和监测不良事件的明确方案，同时建立 FMT 登记处以收集长期数据以及随访结果和并发症。

4.2. 益生菌

益生菌被定义为：当摄入足够量时，对宿主的健康有益的活微生物[48]。益生菌的作用机制包括重塑微生物群落和抑制病原体，通过上调抗炎因子或抑制促炎因子的免疫调节作用，影响上皮细胞分化，以及增殖和促进肠道屏障功能[49]。Hart 等的研究发现[50]，包含八种不同细菌菌株(四种乳酸杆菌、三种双歧杆菌和一种嗜热链球菌唾液亚种)的益生菌混合物-VSL#3 (VSL#3 Pharmaceuticals, Fort Lauderdale, FL, USA)，是肠道和血液 DC 对 IL-10 的有效诱导剂，可抑制促炎性 Th1 细胞的产生，其中双歧杆菌通过树突状细胞上调 IL-10 的产生并降低共刺激分子 CD80 和 CD40 的表达，发挥显着的抗炎作用。本中心既往开展的一项回顾性临床研究也表明，活双歧杆菌片剂可以有效降低 HSCT 过程中 OM 的发生率和持续时间，并且不影响细胞植入[51]。在早期的一项动物实验中已证实，HSCT 前后口服鼠李糖乳杆菌可显著提高生存率并减少 aGVHD [52]。Sadanand 等开展的一项小型病例研究[53]，为肠黏膜完整性受损的儿童 HSCT 患者的高风险人群使用鼠李糖乳杆菌的安全性提供证据。一项单臂 II 期临床研究发现，预防性使用短乳杆菌 CD2 锭剂似乎可以降低口腔黏膜炎的发生率和严重程度[54]。通过调查行 HSCT 的患儿移植前的营养习惯与临床结局之间的关系，Tavil 等人发现发热性中性粒细胞减少症的持续时间与酸奶的摄入量之间呈负相关($r = -0.422$, $p = 0.009$) [55]。

益生菌种类繁多，但主要的医疗监管机构，如欧洲食品安全局(European Food Safety Authority)和美国食品药品监督管理局(US Food and Drug Administration)，尚未批准任何益生菌制剂作为治疗模式[56]。尤其对于肠壁完整性受损的免疫功能低下的患者，人们对益生菌给药的安全性仍存在担忧。例如，Koyama 等人报道了一例因酸奶来源的乳酸杆菌引起感染性休克的病例[57]，该中年男性 AML 患者在

进行 HSCT 过程中出现严重腹泻后摄入了富含益生菌的酸奶，但 1 周后出现了感染性休克。Mehta 等人也报道了一例接受 HSCT 的套细胞淋巴瘤患者因过量食用富含益生菌的酸奶而引起嗜酸乳杆菌败血症的案例[58]。未来还需要更多大规模、高质量随机对照研究证实不同益生菌菌株在 HSCT 患者中的确切有效性和安全性。

4.3. 益生元

益生元被定义为“被宿主微生物选择性利用并赋予健康益处的底物”，是一种无活性但可作为宿主所携带的有益微生物的营养物质，可以促进各种肠道微生物的生长[59]。目前在益生元类别中占主导地位的是低聚果糖和低聚半乳糖，它们的作用是通过富集乳酸杆菌和/或双歧杆菌发挥作用[60]。益生元通过肠道微生物代谢、发酵可产生包括丁酸盐、乙酸盐和丙酸盐等多种化合物，其代谢产生的有机酸可降低肠道 pH 值，并对微生物病原体和矿物质吸收产生伴随影响。对益生元摄入有反应的细菌可以通过抗菌药物和竞争性相互作用来影响微生物群组成，从而可能减少感染[60]。一项前瞻性评估益生元作用的研究发现，患者在行 HSCT 前后摄入抗性淀粉(可增加 SCFAs 的含量)和益生元混合物 GFO(包含谷氨酰胺、纤维和低聚糖)可以缩短患者 HSCT 后中重度 OM 和腹泻的持续时间，降低 II~IV 级 aGVHD 的发生率，并且维持肠道微生物的多样性[61]。Andermann 等人的研究观察到，在行 HSCT 当天，摄入低聚果糖的患者与空白对照组患者在肠道微生物群组成上有显著差异，但这种差异在 HSCT 后没有持续[62]，未来可能需要进一步研究来探讨益生元在 HSCT 患者中的应用。尽管个体的肠道微生物组中可能存在巨大的个体分类群多样性，但存在高水平的功能性冗余，特定的生态功能由不同个体的一系列细菌提供[63] [64]。目前的关联性研究往往只是研究特定微生物在疾病中的作用的起点，测序研究并不能提供对肠道微生物群成员之间功能相互作用的理解，因此需要对功能生态学进行更详细的研究。

5. 总结与展望

肠道菌群在 HSCT 中的关键作用日渐突显，其失衡与 GVHD、感染等严重并发症密切相关，进而影响患者预后。通过对肠道菌群组成、功能及其与宿主免疫相互作用的研究，我们认识到维持肠道菌群多样性、调节特定菌群丰度及代谢产物水平对改善 HSCT 疗效的重要性，并总结了目前相关干预手段。然而，目前在更确切的机制研究、临床干预指南、个体差异以及安全性等方面仍存在诸多问题，限制了肠道菌群相关诊疗策略在 HSCT 中的广泛应用。

未来可能需要借助宏基因组学、代谢组学、转录组学及蛋白质组学等多组学技术，通过对特定菌群－代谢物－宿主通路的研究，全面解析肠道菌群在 HSCT 中的作用机制。深入研究肠道菌群与宿主免疫系统的相互作用，如进一步开展动物实验研究 SCFA-Treg 轴等关键通路，明确关键功能菌群、代谢产物及相关信号通路，为精准靶向治疗提供坚实的理论基础。进一步进行大规模前瞻性随机对照研究评估不同干预方案的疗效和安全性，标准化菌群干预流程和剂量，同时结合患者临床特征、肠道菌群基线数据及 HSCT 后的动态变化，定制个性化肠道菌群调节策略，明确在不同患者群体中的最佳应用方案。

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