

益生菌与宿主疾病关系的研究进展

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摘要 人类肠道中含有的多种微生物,称为肠道菌群,它们对宿主的健康起着至关重要的作用。肠道菌群的组成包括细菌、病毒和真核生物,已经被证明与宿主健康有密切的联系,尤其是其中的益生菌。益生菌通过多种途径发挥作用,包括与宿主微生物的相互作用、抵御病原菌的定殖、改善肠道屏障功能、调节免疫功能、产生相关代谢产物,在宿主的代谢、免疫和神经系统中发挥有益作用。综述益生菌的作用机制,讨论了近年来益生菌应用临床研究实例以更好地理解其对疾病风险和健康的可持续性的贡献,将为新的治疗干预和疾病预防策略提供参考。

关键词 肠道菌群; 益生菌; 失衡; 宿主疾病; 干预机制

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Advances in Relationship between Probiotics and Host Diseases

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Abstract In human intestines harbors diverse microbes, called intestinal microbial community (IMC), they play the most important role in the health of their host. The constituents of IMC includes bacteria, viruses, and eucaryotic organisms, they have been proved to have close relation with the host's health, especially probiotics. Probiotics play their role through many pathways, including the interaction with the host's microbes, to resist the setting of pathogen, to improve the function of preventive screen of intestines, to regulate the function of immunity, to produce correlated metabolites, they play beneficial role in host's metabolism, immunity, and nervous system. This paper summarizes the functional mechanism of probiotics, discusses the recent clinical study application cases of probiotics so as to better understand the distribution of probiotics on the risk of diseases and the sustainability of health, and will point out a road for new therapeutic interfering in and diseases prevention tactics.

Keywords intestinal microbial community (IMC); probiotic; dysbiosis; host disease; interfering mechanism

人类的肠道通常会容纳大约 10^{14} 个细菌有机体,多达 1 000 个不同的物种^[1]。这些微生物大部分都存在于结肠中,浓度为 $10^9 \sim 10^{12}$ cfu/mL^[2]。微生物多样性会随着饮食模式、外界因素的变化而发展。菌群之间通过共生和拮抗的关系

形成一种生态平衡。肠道菌群的紊乱将导致宿主系统稳态失衡,给致病菌的生长提供了机会。对于宿主来说,一系列的急性和慢性疾病可能是由于肠道微生物群落紊乱造成的^[3,4]。有研究表明,肠道菌群紊乱是导致抑郁症、帕金森病等心脑血管疾

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病的罪魁祸首^[5]。肠道菌群的失调与糖尿病^[6]、肥胖^[7]、炎症性疾病^[8]的发生都有密切联系。而益生菌的补充能够缓解代谢综合征,对抗肠道炎症,对抑郁症、阿尔茨海默症等神经系统疾病也起到调控作用。本文就益生菌对宿主疾病的干预机制及作用关系展开综述(图1)。

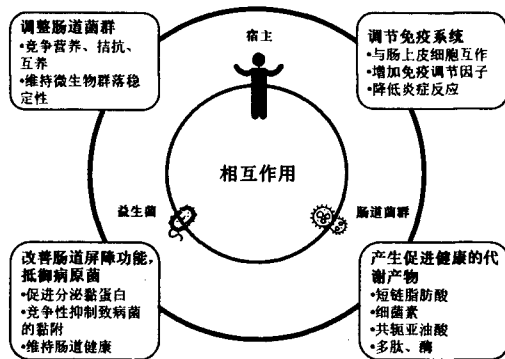


图1 益生菌的作用机制

Fig. 1 The mechanism of probiotics

1 益生菌与宿主的关系

益生菌是一类定殖于人体肠道、生殖系统内,对宿主有益的活性微生物。如乳酸菌和双歧杆菌,可以直接或与微生物产物的互动给宿主提供益处^[9]。目前研究的大多数益生菌来自乳杆菌属、双歧杆菌属和革兰阳性球菌属,包括罗伊氏乳杆菌(*Lactobacillus reuteri*)、干酪乳杆菌(*Lactobacillus casei*)、鼠李糖乳杆菌(*Lactobacillus rhamnosus*)、长双歧杆菌(*Bifidobacterium longum*)、嗜热双歧杆菌(*Bifidobacterium thermophilum*)、乳酸链球菌(*Streptococcus lactis*)、嗜热链球菌(*Streptococcus thermophilus*)等。乳酸菌是一类能利用可发酵碳水化合物产生大量乳酸的细菌的通称,其在体内的定殖程度会影响到宿主的健康水平。罗伊氏乳杆菌是目前已报道的几乎可存在于所有脊椎动物和哺乳动物肠道内的乳酸杆菌,是具有益生功效的肠道益生菌。罗伊氏乳杆菌产生的有机酸、罗氏菌素等抗菌分子可抑制病原微生物定殖,改变宿主的菌群结构^[10]。双歧杆菌具有互养活性,可作为初级降解者降解复杂的碳水化合物,产生的代谢产物又可作为其他细菌的发酵底物^[11]。宿主肠道内益生菌的比例含量会随着年龄、疾病

等变化而变化,例如双歧杆菌属在健康母乳喂养的婴儿肠道中较多,中长、短、两歧双歧杆菌占优势,成年人中,双歧杆菌属的比例会降低但相对稳定,链状、青春以及长双歧杆菌占优势^[12]。

人体肠道内的益生菌丰度会随着年龄的增长而逐渐降低,宿主体内益生菌充足稳定时,就会处于健康的状态,一旦菌群比例发生大幅变化或者偏离正常数值时,一系列疾病就会随之而来,例如经常使用抗生素会导致宿主共生菌群遭到破坏,使肠道菌群自我调节能力受损。而益生菌的补充能够改善宿主菌群的动态平衡,通过定殖抗性、抵御致病菌、维持微生物群的稳态、调节宿主免疫系统、促进黏膜完整性、减少细菌易位等多种机制来影响肠道菌群的生理功能,促进机体健康^[13-18]。

2 益生菌对宿主疾病的干预机制

2.1 调整宿主肠道菌群

益生菌的干预使宿主菌群组成产生差异,导致宿主菌群种属丰度和多样性的改变,通过调节菌群结构能够缓解和治愈宿主的疾病。益生菌可通过竞争营养、拮抗、互养等方式与肠道菌群相互作用从而维持微生物群落稳定性,增加肠道有益菌并降低有害菌的数量^[19-20]。Toscano等^[21]探讨了乳酸杆菌和双歧杆菌对肠道微生物群环境的影响,实验将20名健康成人随机分两组,于早餐前后分别口服鼠李糖乳杆菌 HN001 和长双歧杆菌 BB536,在服用及停用益生菌1个月后,两组人群肠道细菌中乳酸菌和双歧杆菌的丰度均增加,厚壁菌门和放线菌门丰度显著降低,活泼瘤胃球菌和 *Akkermansia muciniphila* 菌丰度增加。

在益生菌介导的肠道菌群调控改善代谢综合征的实验中也得到类似的结论。经益生菌介导后,肠道内15种与疾病指标负相关的细菌类群中,有13种能够产生短链脂肪酸、保护肠屏障的有益菌数量增加;34种与疾病指标负相关的细菌类群中,有26种能够致病的潜在有害菌数量降低^[22]。补充嗜酸乳杆菌 NCFM 及乳双歧杆菌 Bi-07(1:1)能使双歧杆菌属、乳杆菌属、不动杆菌属等6个菌属的水平显著升高,有助于促进肠道菌群群落的功能性成熟^[23]。有实验表明,小鼠结肠炎的恶化与黏膜相关共生细菌(*mucosa-associated commensal bacteria*, MACB)组成的变化相关,特别

是细菌种类多样性的减少和梭菌属比例的增加,而口服乳酸杆菌益生菌,可以保护 MACB 细菌种类的多样性,缓解肠道炎症^[24]。

2.2 改善肠道屏障功能

肠道屏障能够防止肠腔内的有害物质如病原菌和毒素等穿过肠黏膜进入体内其他组织器官和血液循环,对于宿主来说是一种直接的物理屏障。肠道屏障的损伤会增加肠道对细菌及其代谢产物的渗透性^[25]。肠道屏障功能主要是由肠黏膜屏障来实现的,当肠黏膜屏障受损时,肠道中的细菌及其衍生物便可突破肠黏膜屏障,进入血液引起细菌或内毒素移位,促进肠源性感染的发生^[26]。患有系统性红斑狼疮的 MRL/lpr 小鼠存在漏肠,乳酸杆菌的治疗能够增强这些小鼠的肠道屏障功能,降低其代谢内毒素血症。肠道通透性增大给致病菌的入侵和定殖提供机会,是肠道屏障受损的重要病理变化。Miele 等^[27]的研究表明,肠上皮细胞紧密连接的损伤可能导致肠通透性增加,从而引发大量细菌和细菌内毒素转位进入血液循环。有些乳酸菌和双歧杆菌能够上调紧密连接蛋白的表达,提高肠道的完整性,保护肠黏膜屏障^[28]。益生菌能够抵抗致病菌的入侵,与肠黏膜上皮细胞形成微生物膜,竞争性抑制致病菌的黏附定殖^[29]。

益生菌菌株提高屏障功能的另一个途径是通过上调黏液分泌基因的表达,减少病原体与上皮细胞的结合^[30]。在体外实验中,植物乳杆菌 299V 和鼠李糖乳杆菌能够促进肠上皮细胞分泌黏蛋白 MUC2 和 MUC3 来抑制病原微生物在肠黏膜的黏附^[31]。幽门螺旋杆菌感染是引起慢性胃炎和消化性溃疡的主要原因^[32]。而罗伊氏乳杆菌能与幽门螺旋杆菌竞争,并能抑制其与糖脂受体的结合,阻断幽门螺旋杆菌在胃黏膜表面的黏附,抑制其在宿主体内的定殖^[33-34]。

2.3 调节免疫系统

益生菌对宿主免疫系统的调节体现在与肠上皮细胞的相互作用上,产生特异性免疫调节因子来激发机体免疫功能产生抵御致病菌的免疫球蛋白。当抗原刺激时,激活巨噬细胞、B 淋巴细胞、NK 细胞诱导免疫反应,刺激肠黏膜产生抗炎细胞因子,增强宿主肠道内的免疫屏障作用,以提高肠道免疫性能。有些益生菌可以增加吞噬作用或自

然杀伤细胞的活性,并可直接与树突状细胞相互作用^[35]。Bharwani 等^[36]对小鼠进行 28 d 的口服鼠李糖乳杆菌(JB-1)治疗,结果表明,JB-1 的治疗能够增加 IL-10 + 调节性 T 细胞并减轻压力相关树突状细胞的激活,影响压力对宿主行为和免疫的调节。

CTLA-4 抗体等通过削弱免疫耐受来治疗癌症,但它们也能引发严重的自身免疫反应,造成更严重的结肠炎。双歧杆菌依赖于调节 T 细胞抑制炎症作用,可极大地抑制 CTLA-4 抗体造成的炎症表型及组织病理^[37]。Foxp3 是调节 T 细胞发育和功能相关的主要转录因子^[38]。转录因子 Foxp3 的突变一方面会破坏 T 细胞导致 CD4⁺ T 细胞驱动自身免疫性疾病如湿疹、I 型糖尿病^[39-40],另一方面 T 细胞缺陷也会通过肠道菌群的改变引起炎症和自身免疫性疾病,通过调节 Treg、Th1 和 Th2 细胞的分化和增殖可促使宿主免疫系统稳态^[41]。在自身免疫性疾病出现时, Foxp3 基因突变鼠的乳酸杆菌水平较低,给予罗伊氏乳酸杆菌 DSM17938 喂养小鼠后,结果发现它们能够重构 Foxp3⁺ Treg 细胞缺陷小鼠的肠道菌群,减轻多器官炎症反应,延长小鼠的寿命^[42]。

益生菌菌株不仅可以增加抗炎细胞因子(如 TNF)的水平,有些菌株还有提高抗体分泌的能力,能够增强免疫反应。如植物乳杆菌 P-8 可显著增加宿主肠道内的抗体水平^[43]。还有一些益生菌如干酪乳杆菌 CRL431 本身具有一定的抗炎能力,能有效减缓高脂诱导小鼠的肥胖并降低促炎细胞因子 IL-6、IL-17 和 TNF- α 的水平^[44]。

2.4 产生促进健康的代谢产物

益生菌的代谢产物在调节宿主与疾病的相互作用方面也起着重要的作用。益生菌有多种代谢产物如双歧杆菌可以参与许多潜在的健康代谢物的产生,包括短链脂肪酸、共轭亚油酸和细菌素^[45]。短链脂肪酸是肠道微生物发酵纤维的终产物,能够促进糖异生、降血糖素合成,增强肠道屏障功能^[46-47]。乳酸杆菌和双歧杆菌能够代谢肠道中不被人体吸收的低聚糖等物质,产生丙酸,使得肠道中的 pH 值降低,增加肠道的酸度,形成一个不利于有害菌生长的环境。研究表明,从婴儿的粪便中分离的 10 株益生菌(包括 5 株乳杆菌属菌株、5 株肠球菌属菌株)的组合,可调节小鼠和

人类便中的肠道菌群并增加短链脂肪酸(尤其是丙酸和丁酸)的产生^[48]。动物双歧杆菌如乳链球菌 GCL2505 能够通过增加醋酸盐等短链脂肪酸的水平来改善代谢紊乱^[49]。

除了短链脂肪酸,益生菌还会产生细菌素、胞外多糖等,这些产物对病原菌也会产生抑制作用。罗伊氏乳杆菌产生抗菌物质罗氏菌素,抑制肠道病原菌的生长繁殖^[10]。胞外多糖作为益生菌和致病菌的竞争结合对益生菌和致病菌的黏附起到调控作用^[50]。Ganesh 等^[51]发现人体肠道菌群中的罗伊氏乳杆菌 6475 也可以通过分泌一种称为甘油二酯激酶(Dgk)的可溶性细菌酶来减少由 1 型受体(H1R)引起的 PKC 磷酸化从而降低炎症反应。胆固醇的升高会导致心血管疾病的发生,乳酸菌产生胆盐水解酶(bile salt hydrolase, BSH)是降低胆固醇的一种重要机制^[52]。BSH 可结合胆盐水解为游离胆酸,游离胆酸在体内的溶解度很低从而随粪便排出体外^[53],促使部分胆固醇重新合成胆盐来弥补被排泄掉的部分,加快胆固醇的代谢,减少其进入血液的机会。益生菌(尤其是乳酸杆菌和双歧杆菌)可通过结合胆盐、胆固醇同化,催化胆固醇转化为不溶性的粪甾醇等方式,来降低血清胆固醇^[54]。

3 益生菌与宿主疾病的关系

3.1 益生菌与代谢性疾病

代谢性疾病是一类由于代谢物质缺乏或堆积而引起的疾病。肥胖是一个日益严重的国际健康问题,可能会导致胰岛素抵抗和其他代谢疾病^[55]。研究表明,在肥胖等代谢疾病中,肥胖人群的正常微生物平衡遭到破坏,拟杆菌门与厚壁菌门的比值明显下降^[56]。近年来,越来越多的结论证明了益生菌与肥胖等代谢疾病的关系。赵立平等^[22]进行了一项研究,将副干酪乳杆菌、鼠李糖乳杆菌、动物双歧杆菌等 3 株益生菌分别喂给高脂饮食鼠,结果发现益生菌能够改善高脂饮食诱导的代谢综合征的多种症状,不仅使小鼠的体重增加量减少,还对葡萄糖胰岛素稳态及肝脏脂肪变性有显著改善。益生菌在降低 2 型糖尿病患者的胰岛素抵抗方面也有积极作用,61 名 2 型糖尿病患者分为两组,补充双歧杆菌属及乳杆菌属中的多个菌株或安慰剂,结果发现与安慰剂组相

比,血糖、胰岛素、胰岛素抵抗指数、甘油三酯、总胆固醇等指标均有下降^[57]。乳杆菌和双歧杆菌复合剂可延缓高脂饮食诱导的非酒精性脂肪肝病变,益生菌的治疗改善了肝脏代谢环境^[58]。在非酒精性脂肪肝的发展过程中,肠源性细菌内毒素的核心成分脂多糖(lipopolysaccharide, LPS)通过门静脉循环进入肝脏与细胞表面 Toll 样受体 4(toll-like receptor-4, TLR-4)结合,激活 Kupffer 细胞,进而诱导炎症因子的产生^[59-60]。体内血清 LPS 和肝脏 TLR-4 水平的增加会使肠道菌群的多样性和定殖抗性下降。益生菌干预可以改善肝脏病理状态,降低血清 LPS 和肝脏 TLR-4 水平,延缓非酒精性脂肪肝的发展^[61]。

3.2 益生菌与免疫系统疾病

机体能够依靠自身的免疫力抵御多种疾病,而当宿主的免疫调节失去平衡时,其免疫应答就会受到影响。补充双歧杆菌不仅能够帮助宿主对抗感染,对肠道健康也具有有益作用。双歧杆菌可通过蛋白、多肽、胞外多糖、DNA 等各种分子与人体免疫细胞相互作用,调节先天性及适应性免疫相关的特定信号通路^[62]。Dini 等^[63]从类植物乳杆菌 BGCG11 分离出高分子量的胞外多糖(EPS CG11),这种物质能减轻大鼠的炎症性疼痛,降低促炎症因子的表达,同时增加抗炎因子 IL-10 和 IL-6,有很好的抗痛觉过敏和抗水肿作用。鼠李糖乳杆菌可以促进 T 淋巴细胞的转化,从而预防或者缓解过敏性大肠综合征和溃疡性结肠炎等疾病^[31]。Hou 等^[64]发现罗伊氏乳杆菌 D8 通过刺激细胞增殖,促进恢复炎症因子 TNF- α 诱导的肠损伤,从而改善病理变化。Arnbjerg 等^[65]进行一项试验,给 45 名 HIV 感染者每日服用 2 次鼠李糖乳杆菌 GG(LGG),持续 8 周,每次服用的剂量为 6×10^9 CFU,治疗后 HIV 感染者的肠道炎症显著缓解。系统性红斑狼疮(Systemic lupus erythematosus, SLE)是一种复杂的自身免疫性疾病,益生菌被认为是 SLE 发病中潜在的免疫调节物质^[66-67]。对于 SLE 的 MRL/lpr 小鼠,乳酸杆菌治疗可平衡其局部和全身的促炎抗炎系统,降低肠内的 IL-6,增加 IL-10,从而提供抗炎环境^[30]。

3.3 益生菌与神经系统疾病

越来越多的研究证明,肠道菌群的变化与神

经系统疾病密切相关,肠道菌群-肠-脑轴(Microbiota-Gut-Brain Axis, MGBA)的调控对神经系统疾病有良好的治疗作用,但相关研究结果是否适用于人体还需要进一步验证。有研究证明肠道菌群可能在抑郁症的发病机理中起着重要作用,双歧杆菌可以帮助小鼠抵抗慢性社会抗压能力,所以也有可能在对人体抑郁方面发挥积极作用^[68]。Bangshan 等^[69]评估了益生菌对焦虑患者的作用,将 660 名受试者分成两组,实验组每日服用 2 次包括干酪乳杆菌、德氏乳杆菌、鼠李糖乳杆菌、长双歧杆菌等,使用单个益生菌物种或多种益生菌剂,结果发现相比于对照组,益生菌可显著减少患者的焦虑,降低患者的抑郁焦虑和压力量表评分。口服罗伊氏乳杆菌可缓解抗生素氨苄青霉素诱导的焦虑和结肠炎^[70]。在 *Shank3* 基因敲除的自闭症小鼠模型中,补充罗伊氏乳杆菌可改善自闭症症状^[71]。

Friedrich 等^[72]进行了一项随机双盲临床试验,阿尔茨海默症(Alzheimer's disease, AD)患者连续 12 周每日补充益生菌后,血浆丙二醛、胰岛素代谢标志物、甘油三酯等代谢参数,相对于对照组都显著提高。益生菌的补充对 AD 患者的认知和代谢功能有良好的作用,益生菌或可用于阿尔茨海默症的防治。但有新的临床试验结果表明,对于严重 AD 患者,益生菌无法改善其认知及生化指标,这表明除了益生菌本身因素之外,疾病严重程度和给药时间对治疗效果也有重要影响^[73]。益生菌对防治阿尔茨海默症的作用仍然需要更深入的实验验证。Huiying 等^[74]进行了 25 项动物研究及 15 项人体研究,大多数研究使用的是双歧杆菌及乳酸菌,用剂量为 $10^9 \sim 10^{10}$ 个菌落单位分别处理动物 2 周,处理人体 4 周,结果发现,在 22 项动物研究中,益生菌对改善焦虑、抑郁、自闭、强迫症、记忆等有效;在 7 项人体研究中发现益生菌对焦虑、抑郁有效。益生菌对改善这些精神疾病有效果,因此这一结果可能会对进一步的临床研究提供方向。

3.4 益生菌与其他疾病

益生菌在预防结直肠癌方面的有益作用已经得到了证实,一项实验研究发现,干酪乳杆菌 BL23 对小鼠的结直肠癌发展有显著的保护作用,能够降低细胞因子 IL-22 的水平起到免疫调节作

用,以及通过上调 caspase-7、caspase-9 及 Bik 的表达调节抗增殖作用^[75]。Sivan 等^[76]用 16S 核糖体 RNA 的测序确定了双歧杆菌属的细菌与抗肿瘤效应有关。给小鼠口服双歧杆菌,能使肿瘤的控制达到与抗 PD-L1 免疫抑制剂同等程度的效果,双歧杆菌可增强肿瘤微环境中的树突细胞的功能、CD8⁺T 细胞的启动和积累,联合治疗几乎完全抑制肿瘤的生长^[77]。Li 等^[78]探索了益生菌对肝细胞肿瘤生长的影响。实验通过一种新型的益生菌混合物 Prohep (LGG、EcN、热灭活 VSL#3 1:1:1 混合)喂给肝癌小鼠,研究结果表明,它能降低 IL-17 表达和 Th17 的细胞数量,且肿瘤的生长速度显著降低,肝细胞瘤减小 40%。在治疗儿童急性腹泻方面,克劳氏芽胞杆菌作为益生菌对其能够进行有效的治疗。与对照组相比,益生菌干预显著降低了患者腹泻的持续时间(平均减少 9.12 h)和住院时间(平均减少 0.85 d)^[79]。服用嗜酸乳杆菌 CL1285、干酪乳杆菌 LBC80R、鼠李糖乳杆菌 CLR2 的益生菌组合胶囊,可改善肠易激综合征患者的腹痛、腹胀等症状^[80]。

4 展 望

益生菌对宿主的干预调节作用在代谢、免疫、神经系统等多种疾病领域不断拓展研究。益生菌被摄入体内后,会改变肠道菌群的结构,保护肠道屏障功能,其代谢产物也有抗炎、调节系统稳态的作用,但并不是所有的益生菌都对宿主疾病产生积极作用, Aoki 等^[49]评估了动物双歧杆菌 GCL2505 (BlaG) 与长双歧杆菌 JCM1217 (BloJ) 的抗代谢综合征效应,结果 BlaG 能够降低内脏脂肪堆积,并改善了葡萄糖耐受性,但 BloJ 则对上述指标没有影响。这两株双歧杆菌调节代谢效果的不同也说明了不是所有的益生菌都能对宿主疾病产生积极的作用。在防治阿尔茨海默症方面,除了益生菌本身作用,疾病严重程度和给药时间对治疗效果也有重要影响^[79]。益生菌在人肠黏膜的定殖情况,有明显的个体、部位和菌株特异性,这说明菌株是具有特异性的,所以仍需要进一步地研究来了解肠道微生物群的调控作用所涉及的具体机制^[81]。益生菌干预的效果可能存在个体间差异,支持益生菌功能的临床证据还很少,对益生菌机理的了解大多是基于体外、动物、细胞

培养或体外人体模型的研究,但并不是所有的机制都在人类身上得到了证实,也不是所有的益生菌株都有这种机制,每一个特定机制都受多种因素影响。因此,益生菌作用机制的研究不能只依赖体外或动物实验,还需要大规模的临床试验进一步证实益生菌对宿主疾病的疗效。益生菌对于宿主疾病的调控干预具有良好的前景,要继续研究益生菌与疾病作用所涉及的具体机制,同时要充分结合不同人群肠道菌群的特点进行新型益生菌的筛选,目标微生物将从典型的双歧杆菌和乳酸菌扩展到其他属,也许还包括更多的酵母菌种类^[82-83],从而探索更多益生菌与宿主疾病的相关性。

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