DOI:10.16781/j.0258-879x.2019.02.0203

·综　述·

嗜黏蛋白阿克曼菌与肥胖的关系

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[摘要]　嗜黏蛋白阿克曼菌（*A. muciniphila*）是一种人类肠道的正常菌群，肥胖患者肠道菌群中的 *A. muciniphila* 丰度明显降低。许多证据表明 *A. muciniphila* 与肥胖、糖尿病、心血管疾病和低度炎症呈负相关。*A. muciniphila* 不仅可以保护肠道上皮细胞及黏液层的完整性发挥代谢保护作用，在炎症反应过程中 *A. muciniphila* 也能通过调节性 T 细胞、内源性大麻素系统以及非经典 Toll 样受体发挥抗炎作用。本文就 *A. muciniphila* 与肥胖的相关性及分子机制、临床应用等作一综述。

[关键词]　嗜黏蛋白阿克曼菌；肥胖症；代谢综合征；肠道菌群
[中图分类号]　R 589.2　　**[文献标志码]**　A　　**[文章编号]**　0258-879X(2019)02-0203-06

Relationship between *Akkermansia muciniphila* and obesity

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[Abstract]　*Akkermansia muciniphila* (*A. muciniphila*) is a normal flora of human gastrointestinal tract. The *A. muciniphila* abundance of intestinal flora in obese patients is significantly decreased. Many evidences suggest that *A. muciniphila* is negatively related to obesity, diabetes, cardiovascular diseases and low-grade inflammation. *A. muciniphila* not only plays a metabolic protective role by protecting the integrity of intestinal epithelial cells and mucus layer, but also plays an anti-inflammatory role by regulatory T cells, endogenous cannabinoid system and non-classical Toll-like receptor in the process of inflammatory reaction. This article reviews the relationship between *A. muciniphila* and obesity, and the molecular mechanism and application of *A. muciniphila* in obesity.

[Key words]　*Akkermansia muciniphila*; obesity; metabolic syndrome; intestinal bacteria
[Acad J Sec Mil Med Univ, 2019, 40(2): 203-208]

2015 年全球有超过 6 亿成年人和 1 亿儿童罹患肥胖症[1]。肥胖是心血管疾病、糖尿病、慢性肾病、肿瘤等许多疾病的危险因素，其不仅和食物摄入量、基础代谢、能量消耗的不平衡有关，与肠道菌群的组成也关系密切[2]。研究发现肥胖小鼠肠道菌群中厚壁菌/拟杆菌的比例明显高于瘦小鼠，并且用来自肥胖小鼠或肥胖人群的肠道菌群定植在无菌小鼠体内后均能引起小鼠总体脂肪的显著增加[3-4]。抗生素对肠道菌群产生影响从而引起肥胖在许多研究[5-7]中也得到证实。因此，肠道菌群在肥胖的发病机制中具有重要的作用[8]。嗜黏蛋白阿克曼菌（*Akkermansia muciniphila*，*A. muciniphila*）是人类肠道的正常定植菌，近年来越来越多的研究发现 *A. muciniphila* 与肥胖之间关系密切，本文现就 *A. muciniphila* 与肥胖的相关性及分子机制、临床应用等作一综述。

1　*A. muciniphila* 及其生物学特性

2004 年 Derrien 等[9]首次从人类肠道菌群中分离出 *A. muciniphila*。*A. muciniphila* 是一种椭

[收稿日期]　2018-06-02　　**[接受日期]**　2019-01-02
[基金项目]　国家自然科学基金(81670741). Supported by National Natural Science Foundation of China (81670741).
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圆形革兰阴性厌氧菌，无动力，属于疣微菌门，细胞长轴为 0.6～1.0 mm，适合在 20～40 ℃ 和 pH 5.5～8.0 条件下生长（最适温度 37 ℃，最适 pH 6.5）。*A. muciniphila* 对氧气相对敏感，能在微需氧条件下呼吸产生额外的能量[10]，这使得它在与其他肠道严格厌氧菌的竞争中处于更有利地位。*A. muciniphila* 在肠道菌群中的比例并不高，占健康成人粪便中细菌总数的 1%～3%[11]，在 6 个月和 12 个月大的婴儿中也仅占细菌总数的 0.9%和 1.6%[12]，但 *A. muciniphila* 在新生儿体内增长迅速，1 年内细菌量就可达到成人水平[13]。*A. muciniphila* 主要利用肠道黏蛋白作为碳源、氮源和能源，分解黏蛋白产生乙酸盐和丙酸盐[9]。*A. muciniphila* 能通过保护上皮细胞层的完整性增强肠道上皮屏障功能[14]，其在黏膜层的定植能够和其他益生菌共同维护肠道黏膜稳态[15]。

2　*A. muciniphila* 与肥胖及代谢性疾病

目前有临床研究发现 *A. muciniphila* 与肥胖呈负相关[16]。双胞胎具有相同遗传基因，环境因素引起的肠道菌群改变是其肥胖差异的原因之一，一项有关双胞胎的研究证实双胞胎人群的体质量指数与 *A. muciniphila* 的丰度呈负相关[17]。针对学龄前儿童和孕妇两类人群的研究同样也发现，正常体质量组的 *A. muciniphila* 丰度明显高于肥胖组[18-19]。低聚果糖可以通过调节肠道菌群改善机体代谢紊乱和肥胖，许多研究发现低聚果糖能显著增加 *A. muciniphila* 丰度[20-23]，而高脂饮食却能降低 *A. muciniphila* 丰度到不足原来的 1/16[24]，低聚果糖是否通过 *A. muciniphila* 途径改善高脂饮食诱发的肥胖尚需进一步研究证实。伦理的限制使得临床研究难以通过前瞻性实验明确变量之间的因果关系，但在动物实验中已经证实 *A. muciniphila* 与机体代谢状况存在明确的因果关系[24-26]。*A. muciniphila* 与肥胖呈负相关在新型药物靶点的研究中也获得证实，如龙舌兰中提取的皂苷通过增加 *A. muciniphila* 丰度改善肥胖相关的代谢异常[27]，蔓越莓提取物多酚、绿茶提取物低聚异麦芽在增加 *A. muciniphila* 丰度的同时伴有改善肥胖、胰岛素抵抗以及肠道炎症的作用[25,28]。

A. muciniphila 还可改善糖尿病、脂代谢及相关的心血管疾病[29]。研究发现 *A. muciniphila* 丰度与胰岛素敏感性及代谢状况呈正相关[30]，而 *A. muciniphila* 丰度的减少与糖代谢功能的恶化有关[31]。二甲双胍一直是 2 型糖尿病治疗的一线用药，具有减轻体质量、改善胰岛素敏感性等作用，二甲双胍治疗和减肥手术能引起 *A. muciniphila* 丰度的显著增加[24,32-34]，表明肠道菌群在一定程度上参与介导二甲双胍对糖代谢的有益作用。有趣的是，一项人群研究显示，与正常人群相比，*A. muciniphila* 在 2 型糖尿病患者中丰度更高[35]，这也可能与服用二甲双胍的治疗有关。糖代谢、脂代谢、肥胖、动脉粥样硬化之间密切相关，*A. muciniphila* 不仅能改善肥胖与糖代谢，对脂代谢及动脉粥样硬化也有改善作用[36-37]，说明 *A. muciniphila* 同时具有改善多种代谢性疾病的治疗潜力，其中涉及的分子机制的共同通路有待研究。

3　*A. muciniphila* 影响肥胖的分子机制

3.1　*A. muciniphila* 增强肠道黏膜的屏障作用　目前许多动物实验研究证实，低聚果糖能显著恢复肥胖小鼠肠道 *A. muciniphila* 的丰度[38-40]，通过胰高血糖素样肽 2（glucagon-like peptide 2，GLP-2）依赖性机制保护肠道屏障功能，改善小鼠代谢性内毒素血症和代谢紊乱[41]。另一项研究也发现口服 *A. muciniphila* 能通过增加肠道屏障功能来降低血浆脂多糖（lipopolysaccharide，LPS）水平，从而逆转高脂饮食诱导的小鼠肥胖和糖代谢紊乱，而加热灭活的 *A. muciniphila* 却没有这种保护作用[38]，有趣的是经过巴氏消毒（70 ℃，30 min）的 *A. muciniphila* 反而对高脂饮食喂养小鼠的体质量增加、脂肪增加和葡萄糖不耐受具有更强的改善作用[42]。细胞实验同样证实 *A. muciniphila* 增强肠道黏膜的屏障作用，*A. muciniphila* 与大肠杆菌相比能显著增加细胞的跨膜电阻、增强体外细胞屏障功能[14]。但 Shin 等[24]发现尽管 *A. muciniphila* 丰度与维护肠道黏液层完整性的过碘酸雪夫染色（periodic acid-Schiff stain，PAS）阳性杯状细胞数量呈正相关，口服 *A. muciniphila* 的高脂饮食小鼠与对照组相比肠道通透性差异却无统计学意义，因此 *A. muciniphila* 除了具有改变肠道屏障功能以外，还存在改善小鼠的能量代谢的其他机制，值得进一步研究。

3.2 *A. muciniphila* 与炎症的关系 调节性 T 细胞在控制肥胖诱导的与慢性炎症有关的免疫反应中发挥关键作用[43]，*A. muciniphila* 可以恢复 $CD4^+$ T 细胞群体中调节性 T 细胞的百分比和绝对数量，*A. muciniphila* 的增加通过内脏脂肪组织中调节性 T 细胞的抗炎活性介导白细胞介素（interleukin，IL）-1β、IL-6 水平的降低，从而改善肥胖患者的能量代谢[24]，这与 *A. muciniphila* 在炎症性肠病中的研究结论[44]一致。*A. muciniphila* 也能降低肠道干扰素 γ（interferon γ，INF-γ）、IL-15 表达水平，下调肠上皮细胞中自然杀伤细胞 2 族成员 D（natural killer group 2 member D，NKG2D）配体表达[45]。*A. muciniphila* 与调节性 T 细胞及相关炎症因子关系密切，可以针对其与调节性 T 细胞关系及上下游分子机制开展更深入的研究。

内源性大麻素系统在肠和脂肪组织生理学中具有重要作用。内源性大麻素通过过氧化物酶体增殖物激活受体（peroxisome proliferator-activated receptor，PPAR）-α 和 PPAR-γ 以及 G 蛋白偶联受体调节机体能量平衡，肥胖患者肠道微生物群组成的变化可导致免疫细胞产生内源性大麻素[46]。而 *A. muciniphila* 引起内源性大麻素家族的改变[花生四烯酸乙醇胺（arachidonoylethanolamine，AEA）水平降低，2-花生四烯酸甘油（2-arachidonoylglycerol，2-AG）、2-油酰甘油（2-oleoylglycerol，2-OG）、2-棕榈酰甘油（2-palmitoylglycerol，2-PG）等水平升高] 有助于增加脂肪氧化，减少炎症因子产生并维持胰岛素敏感性[47]。*A. muciniphila* 可能在内源性大麻素系统中起着重要作用，然而这方面的相关研究仍较少。

肠道产生的脂多糖（lipopolysaccharide，LPS）是引起慢性内毒素血症的重要原因，研究发现 *A. muciniphila* 基因组也编码 LPS[48]，但与大肠杆菌相比，*A. muciniphila* 编码的 LPS 并不诱导细胞强烈释放 IL-8，*A. muciniphila* 产生的 LPS 与大肠杆菌 LPS 在结构上的不同体现在它不能激活 Toll 样受体（Toll-like receptor，TLR）4 产生瀑布样炎症反应[14]。有研究证实人体的益生菌属中的脆弱拟杆菌产生的 LPS 通过 TLR2 发出信号[49]。因此提示 *A. muciniphila* 和大肠杆菌的 LPS 之间存在的结构和抗原性差异使其通过 TLR4 之外的途径维持肠道黏膜的免疫功能处于合适的水平。另有研究发现 *A. muciniphila* 的外膜蛋白 Amuc_1100* 通过 TLR2 信号通路参与 *A. muciniphila* 与宿主之间的相互作用，并且 Amuc_1100* 能够起到与活菌或经过巴氏灭菌法的 *A. muciniphila* 相同的改善高脂饮食诱导的代谢紊乱作用[42]。*A. muciniphila* 的非经典的 TLR 作用在影响局部和全身的炎症反应中起到重要的作用。

总之，动物实验显示 *A. muciniphila* 的定植上调了免疫应答相关基因的表达，其中涉及到 B 细胞受体、T 细胞受体、核因子 κB（nuclear factor κB，NF-κB）、细胞外调节蛋白激酶/丝裂原活化蛋白激酶（extracellular regulated protein kinase/mitogen-activated protein kinase，ERK/MAPK）、IL-4、自然杀伤细胞、硫酸角质素代谢等多通路的参与[50]，各通路之间的具体分子机制及上下游关系尚待进一步研究。

4 *A. muciniphila* 制剂的临床应用研究

Plovier 等[42]选取肥胖患者（每组 5 例）分别服用活菌（剂量为 10^{10} 及 10^9）及巴氏灭菌（剂量为 10^{10}）后的 *A. muciniphila*，2 周后，患者血液中 C 反应蛋白、白细胞、凝血酶原时间、丙氨酸转氨酶、天冬氨酸转氨酶、γ-谷氨酰转移酶、尿素氮、肌酐、肾小球滤过率、肌酸激酶、乳酸脱氢酶等指标较前无明显变化，恶心、腹胀、腹痛、胃反流等不良反应与安慰剂组相比差异也无统计学意义，结果表明肥胖患者对口服 *A. muciniphila* 具有良好的耐受性和安全性。

目前关于 *A. muciniphila* 对肥胖的改善仅有细胞实验、动物实验以及人群观察性研究的证据，尚缺乏能够证明 *A. muciniphila* 治疗肥胖有效性的临床随机对照研究结果。

5 小结与展望

肥胖的患病率及疾病负担在全球范围内不断增加，寻求更加高效的措施来预防和干预十分必要。*A. muciniphila* 对肥胖的改善作用在细胞实验及动物实验中普遍得到证实，*A. muciniphila* 及其制剂非常有潜力成为改善糖脂代谢紊乱的一种新型食品或药品。*A. muciniphila* 的使用需要考虑安全性问题。*A. muciniphila* 是人体正常的菌群，在不超剂量的情况下使用是安全的，现有的证据

也初步表明了其安全性，但 *A. muciniphila* 的安全性和有效性仍需要更大样本的人群研究证实。使用 *A. muciniphila* 的另一个障碍是制剂问题，*A. muciniphila* 活菌对氧气的敏感性高，而巴氏灭菌后的 *A. muciniphila* 及其外膜蛋白 Amuc_1100* 能起到相同的改善代谢的作用，有望成为新型制剂的有效成分。在解决好安全性问题和制剂问题后，*A. muciniphila* 有望被广泛用于预防和治疗肥胖人群的代谢紊乱。而 *A. muciniphila* 的起效的机制可能涉及到肠道屏障功能、免疫应答、炎症因子及抗炎因子等，其具体的分子通路及上下游蛋白尚待更多的实验予以证实。

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