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Review 综 述

黏质阿克曼菌及其代谢物短链脂肪酸与溃疡性结肠炎肠黏膜屏障的相关性研究

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摘　要：溃疡性结肠炎(ulcerative colitis, UC)已成为当今世界范围内的发病率高、患病人数多、病程缠绵的终身难治性疾病。而黏质阿克曼菌(*Akkermansia muciniphila*, *A. muciniphila*)及其代谢物短链脂肪酸(short chain fatty acid, SCFA)是近年来发现的对UC肠黏膜屏障具有保护作用的益生菌及代谢物，但其具体作用机制有待归纳和总结。因此本文从肠黏膜机械、化学、免疫及生物屏障这四个角度综合分析近年来的相关研究，试图探讨 *A. muciniphila* 和 SCFA 对肠黏膜屏障的具体作用机理，为研究 UC 的发病机制、治疗手段提供新视角和新思路。

关键词：黏质阿克曼菌；短链脂肪酸；溃疡性结肠炎；肠黏膜屏障

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Relationship of *Akkermansia muciniphila* and the metabolites short chain fatty acids with intestinal mucosal barrier in ulcerative colitis

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Abstract: Ulcerative colitis (UC) is a life-long refractory disease with high incidence worldwide. *Akkermansia muciniphila* (*A. muciniphila*) and the metabolites short chain fatty acids (SCFA) have been found to protect intestinal mucosal barrier in UC, but the specific mechanisms fail to be summarized. Therefore, we analyze the research on the mechanical, chemical, immune, and biological barriers of intestinal mucosa and discuss the mechanisms of *A. muciniphila* and SCFA on intestinal mucosal barrier, hoping to provide a new perspective and mindset for the study of the pathogenesis and therapy of UC.
Keywords: *Akkermansia muciniphila*; short chain fatty acids; ulcerative colitis; intestinal mucosal barrier

溃疡性结肠炎(ulcerative colitis, UC)作为炎性肠病(inflammatory bowel disease, IBD)的一种，病变以腹泻、黏液脓血便为主要特征，是以病程反复发作、缠绵难愈、终身治疗、预后不佳、癌变率高为主要致病特点的慢性非特异性疾病。流行病学研究表明中国 UC 的发病率为 1.18/100 000 人/年，虽低于西方发达国家，但其发病率也呈逐年上升的趋势，并且呈现南高北低的地域特点(其中华南地区发病最高)[1-2]。其患病人群在性别上以男性患病率高于女性为主，在年龄分布上以 40 岁以上的中老年人为易感人群，而 16 岁以下的青少年儿童为低危人群[1]。从临床特征来看，中国 UC 的病例具有诊断晚、病程更重、节段性病变多、肠外表现少等不同于西方 UC 的流行病学特点[1,3]。因此，在中国 UC 的危险因素、易感人群、病变特点及诊疗方式均与西方发达国家存在差异的基础上，明确 UC 发病机制，寻找影响 UC 进程的关键因素，结合中医学整体论治的治疗理念，探索中药保护肠黏膜屏障的机制，拓展治疗 UC 的新思路、新方向及新靶点成为目前的研究重点。

益生菌作为一类摄入后对宿主机体有益的活的微生物，对调节肠道微生态平衡，提高宿主免疫力具有重要作用[4]。传统一代益生菌常源于发酵食品，多以乳酸菌为主，但是第一代益生菌产品存在污染、菌株信息错误以及活菌数不足等质量问题，其作用未得到广泛认可[5-6]。而下一代益生菌(next-generationprobiotics, NGPs)作为一类在人或动物消化道内发现的具有很大益生潜力的细菌，其优点为菌株来源更广泛，对机体的调节作用更强，尤其是在糖和脂肪代谢异常、炎症反应等方面发挥重要作用，被称为活体生物治疗药品，但受制于分离、鉴定和培养技术的不完善，NGPs 不仅非常难培养而且尚处于研究阶段难以产业化[7-9]，如嗜黏蛋白阿克曼菌(*Akkermansia muciniphila*, *A. muciniphila*)。

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黏质阿克曼菌是2004年由荷兰瓦赫宁根大学研究者Derrien等首次通过严格厌氧手段从人类粪便中鉴定出的一种新的黏液降解菌，是属于疣微菌门的一种定植于肠道黏液层以黏蛋白为食物的革兰氏阴性菌(Gram-negative bacteria, G^- bacteria, G^-)，该菌占肠道微生物区系的1%−3%，呈椭圆形，不运动，不产芽孢，*A. muciniphil* 为该菌的唯一菌种，模式菌株为 MUCT 的耐氧厌氧菌[10-11]。肠道共生菌 *A. muciniphil* 与 UC 关系密切，研究发现 UC 模型小鼠疾病的严重程度与其肠道内的 *A. muciniphila* 的数量成反比，而补充 *A. muciniphila* 制剂后，可有效增加结肠长度、恢复体重、降低肠道通透性和促进抗炎细胞因子表达，从而减轻 UC 对肠道的损害[12-13]。并且 *A. muciniphila* 可以通过其外膜蛋白 *Amuc_1100*、细胞外囊泡 *Am*EV 及其代谢产物丙酸为宿主提供能量和调节肠道免疫应答以此保护肠黏膜屏障免受损伤[14-16]。因此，*A. muciniphila* 被认为是一种对肠道黏液层厚度和肠黏膜屏障完整性有益的且在改善宿主代谢功能和免疫应答方面具有重要价值的益生菌[17-18]。

1 *A. muciniphila* 与肠黏膜屏障的相互作用

肠黏膜屏障的损伤是 UC 的主要损伤机制，因此恢复肠黏膜屏障的完整性也是治疗 UC 的重中之重。具体而言，肠黏膜屏障是阻止肠腔内细菌、抗原等有害物质进入肠黏膜，进而激活固有层免疫细胞引起异常免疫反应的肠黏膜结构，主要由黏膜基底膜、上皮细胞层及其表面的黏液层构成[19-20]。具体包括含有肠上皮在内的机械屏障[21]；肠道抗菌因子构成的化学屏障[22-23]；肠黏膜淋巴组织构成的免疫屏障[24]；肠道共生菌组成的生物屏障[25]，这 4 个屏障在选择营养物质吸收，防止细菌和内毒素进入血液等方面起到了重要作用[26]。尽管，肠黏膜屏障根据功能分为 4 种，但当肠道受到损伤刺激时，其损伤不是单一的，往往是4个屏障共同受损而出现肠黏膜功能和完整性受损进而导致 UC 的发生。同时，肠黏膜屏障的物理防御及免疫防御功能也是由上述 4 个屏障协同配合、共同发挥作用的，主要由包括肠道菌群、抗菌肽(antimicrobial peptide, AMPs)和分泌型免疫球蛋白 A (secretory immunoglobulin A, sIgA)在内的肠黏膜黏液层和包含固有免疫细胞，如 T 细胞、B 淋巴细胞、巨噬细胞和树突状细胞构成的上皮细胞层相互配合共同防御[27-28]。正如，*A. muciniphila* 是定植于肠道黏液层的益生菌，它即属于肠黏膜生物屏障又能与包括肠黏膜生物屏障在内的 4 个屏障相互作用，共同维护肠黏膜屏障的结构和功能的完整性。

1.1 *A. muciniphila* 与肠黏膜机械屏障之间的作用关系

肠黏膜机械屏障主要由肠黏膜表面的肠上皮细胞及其紧密连接等组成[29]。其中肠上皮细胞作为机械屏障的核心部分具有选择性屏障功能，主要由吸收细胞、杯状细胞及潘氏细胞分工完成，既能有效选择营养物质从肠腔进入循环，又能限制内毒素、促炎因子等有害物质通过肠腔进入血液，从而维护肠道内稳态[30]。紧密连接是肠黏膜机械屏障的决定性因素，也是肠黏膜动能正常的保障，它能可逆地调节肠黏膜屏障的通透性[31-32]。紧密连接的核心结构为紧密连接蛋白，主要由咬合蛋白(occludin)、闭合蛋白(claudin)家族、带状闭合蛋白(zonula occludens, ZO)家族、钙黏蛋白(cadherin)和连接黏附分子(junctional adhesion molecule, JAM)等组成[33]。肠黏膜机械屏障作为肠腔内抵御机械、化学和微生物等损伤的第一道防线，在 UC 的发病机制中占据重要地位。在肠黏膜机械屏障中，肠上皮细胞主要通过分泌抗菌肽、黏蛋白等物

质激活肠黏膜免疫屏障和化学屏障进而发挥保护肠黏膜的作用，但当 UC 发生时，肠上皮细胞受损，导致上述物质分泌不足，不能正常激活肠黏膜免疫屏障和化学屏障，肠黏膜屏障的保护力降低，从而使内毒素、促炎因子等有害物质通过薄弱的屏障结构入血，同时又进一步反向破坏肠上皮细胞，形成肠黏膜损伤的恶性循环。如在结直肠中，黏液层由潘氏细胞分泌的抗菌肽、免疫球蛋白 A 和杯状细胞分泌的黏蛋白构成，这三者使黏液层成为具有预防感染、维护肠道微生物平衡和调节免疫稳态等作用的凝胶状结构[34-36]。但当 UC 发生时杯状细胞受损，其分泌的黏蛋白减少，肠黏膜黏液层变薄；肠上皮细胞紧密连接开放，肠道通透性增加造成肠黏膜机械屏障受损；同时肠道内 *A. muciniphila* 数量的减少扰乱肠道微生态的平衡，由此导致的肠道内环境紊乱又反向加重肠上皮细胞的损伤，成为破坏肠黏膜屏障的主要因素[37]。国内外研究表明，*A. muciniphila* 可以诱导包括 zona occludens protein-1 和 occludin 在内的紧密连接蛋白的表达，增加肠上皮的紧密连接，减少肠道通透性，并减少内毒素的内循环从而维护肠黏膜屏障的完整性。活动期的 UC 由于杯状细胞分化因子 Hath1 和 KLF4 缺乏，导致杯状细胞耗竭，黏蛋白分泌不足，造成黏液层变薄甚至部分剥脱，肠黏膜机械屏障崩溃，从而使管腔微生物侵入黏膜并引发炎症(图 1)。规范给予 *A. muciniphila* 制剂后可以有效增加杯状细胞的数量，提高黏蛋白的分泌量，使黏液层厚度正常化，进而缓解 UC 导致的肠道损伤[38-39]。进一步研究发现，*A. muciniphila* 细胞外囊泡(extracellular vesicle, EV)与 UC 的严重程度呈反比，给予 UC 小鼠灌服 *A. muciniphila* EV 制剂后能有效改善 DSS 诱导的 UC 表型(如体质量减轻、结肠长度缩短等)，通过实验研究发现 *A. muciniphila* EV 能通过激活 AMPK 信号通路促进肠黏膜机械屏障中紧密连接蛋白的表达，降低肠黏膜屏障的通透性，维护肠黏膜机械屏障的完整性，防止内毒素、促炎因子等有害物质进入体内[40-42](图 1)。而 *Amuc_1100* 则可以直接增加肠道内紧密连接蛋白(ZO-1 和 Occludin)的表达量，维护肠黏膜机械屏障的完整性，减轻肠道损伤[43]。因此，*A. muciniphila* 能针对 UC 肠黏膜机械屏障的损伤机制全面保护机械屏障结构和功能的完整性，进而减轻 UC 对肠道的损伤。

1.2 *A. muciniphila* 与肠黏膜化学屏障之间的作用关系

肠黏膜化学屏障与机械屏障在组成上相互交织，功能上相互配合。肠黏膜化学屏障主要由肠道的代谢产物以及肠上皮细胞分泌的黏液(黏蛋白)、抗菌肽和溶菌酶等先天性免疫分子构成，其中黏蛋白尤其是 Mucin-2 (MUC2)是构成肠黏膜化学屏障的重要骨架部分[44](图 1)。其主要功能是防止细菌与肠上皮细胞接触，避免由此造成的肠上皮细胞损伤[45]。其中肠黏膜屏障的黏液层分为内外 2 层，内层是由 MUC2 多聚体构成的无菌性屏障避免肠上皮细胞遭受细菌侵害，外层是密度较小，有孔适宜微生物居住的黏液层[46-47]。正常人的肠道黏液内层完整致密，细菌无法穿透，而活动期的 UC 患者和 UC 动物模型的结肠黏液内层被破坏，黏液层呈高度渗透状态，MUC2 表达减少使黏液内层的致密性降低，从而使肠上皮细胞接触到黏液外层的致病菌，继而诱发肠道损伤，引发炎症反应，加快 UC 进程[48-49]。同时，敲除或缺失 MUC2 基因小鼠的肠道内，致病菌与肠上皮细胞密切接触，引起严重的肠道损伤，导致肠道炎症和结肠癌的发生，由此证实 MUC2 是肠黏膜化学屏障损伤的关键因子[50]。在规范给予 *A. muciniphila* 治疗后，模型组小鼠肠道内的 MUC2 表达增加，黏液层变厚，这说明 *A. muciniphila*

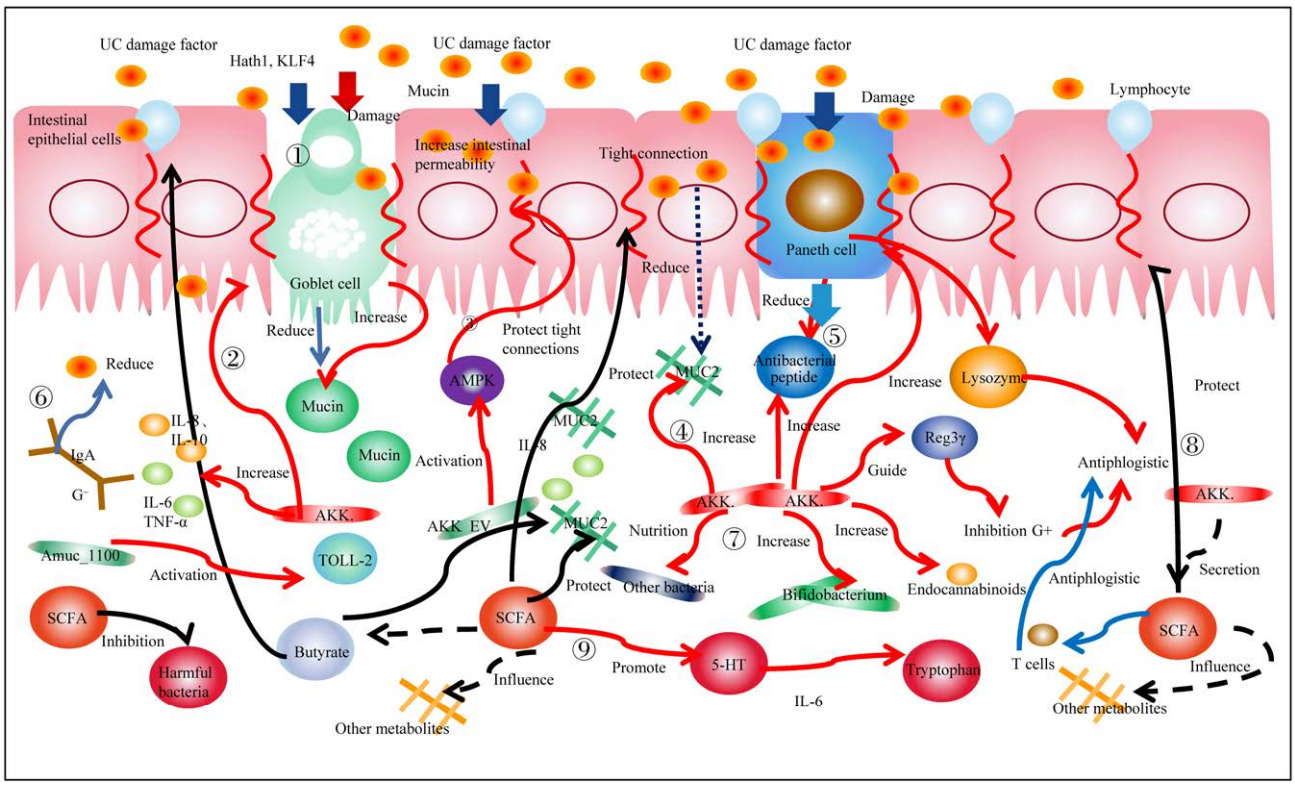

图 1　AKK 及其代谢物短链脂肪酸与肠黏膜屏障关系图

Figure 1　Relationship between akk and intestinal mucosal barrier. ①, ②: UC damage factors through Hath1, KLF4 or directly damage goblet cells lead to decreased mucin secretion and thinning of the mucus layer. AKK can effectively increase the number of goblet cells and increase the amount of mucin or by promoting the expression of IL-8 and IL-10, inhibiting expression of IL-6 and TNF-α, thereby regulating intestinal immunity. ③: *A. muciniphila* EV can further maintain the intestinal mucosal mechanical barrier by activating AMPK to promote the expression of tight junction proteins. ④: *A. muciniphila* maintains the intestinal mucosal barrier by increasing the intestinal mucosal chemical barrier skeleton Muc2. ⑤: UC damage factor destroys paneth cells, resulting in decreased secretion of antimicrobial peptides. *A. muciniphila* can not only directly increase antimicrobial peptides, but also increase antimicrobial peptides by increasing the number of paneth cells to reduce inflammation and protect the intestinal mucosal barrier. ⑥: IgA in the chemical barrier can effectively protect the intestinal mucosal barrier against Gram-negative bacteria (G^-). *Amuc_110* activates Toll-like receptor 2 to regulate immune response and maintain intestinal mucosal barrier. ⑦: *A. muciniphila* can protect the intestinal mucosal barrier by inducing the release of Reg3γ from Paneth cells and inhibiting G^+. *A. muciniphila* can nourish other bacteria or increase probiotics to maintain the microbial structure of the intestinal mucosa, or by increasing the level of endocannabinoids to control inflammation, Increase the thickness of the mucus layer and the secretion of intestinal antimicrobial peptides, thereby protecting the intestinal mucosal barrier. ⑧: Short-chain fatty acids (SCFA) promote the differentiation of regulatory T (Treg) cells and reduce the inflammatory response in the intestine. Up-regulate the expression of tight junction proteins and intestinal epithelial mucus, and improve the function of the intestinal mucosal mechanical barrier. ⑨: Short-chain fatty acids can affect the intestinal mucosal barrier by affecting other metabolites such as 5-HT.

能通过调节肠道黏液层 MUC2 的表达，维护肠道黏液内层的致密性进而避免由肠上皮细胞接触致病菌导致的肠道损伤[51-53]。与此同时，当 UC 发生时，肠黏膜化学屏障中分泌抗菌肽的潘氏细胞受损，数量减少，抗菌肽的分泌量不足，无法正常抵御细菌使其侵入黏液层内层，导致肠上皮细胞受损，造成肠道肠道损伤，加重 UC 的进程(图 1)。首先，抗菌肽主要通过选择性地吸附在病原菌外膜的结构上，与膜融合后产生跨膜通道，导致其内容物外泄致使细菌死亡。其次，抗菌肽也可以迅速进入细菌内部，在特定的靶细胞位点发生作用、阻碍其代谢和生长，有效地杀菌灭菌[54-55]。第三，抗菌肽通过诱导黏蛋白和紧密连接蛋白的表达来增强肠黏膜物理屏障功能，进而维护肠道健康[56]。研究表明，给予 UC 模型小鼠 *A. muciniphila* 治疗后既可以有效增加 UC 小鼠肠道内潘氏细胞的数量，使抗菌肽的分泌量恢复至正常水平，还可以增加黏液层的厚度，从而发挥保护肠黏膜的作用[57]。进一步研究发现，*A. muciniphila* 还可以通过诱导潘氏细胞释放抗菌肽再生胰岛源性 3γ (Reg3γ)进入肠腔，在抑制炎症反应的基础上，直接杀灭革兰阳性菌(Gram-positive bacteria, G^+)，协同维护肠道生态系统的抗炎环境[58-59](图 1)。同时，潘氏细胞分泌的特异性抗菌肽和 α-防御素等又能有效增加 UC 小鼠肠道内 *A. muciniphila* 的数量，由此可见 *A. muciniphila* 与肠黏膜化学屏障是相互影响、互为因果、协同配合、共同维护肠道健康的关系[60-62]。由肠上皮细胞分泌的溶菌酶则通过破坏细菌的细胞壁，使细菌裂解，发挥抗菌作用，但研究发现潘氏细胞分泌的溶菌酶具有双重调节作用，既可以平衡肠道炎症反应，维护肠道健康，又可以促进炎症反应，加重 IBD 进程，其双重调节机制原理尚未明确，需进一步研究[63-64]。目前，尚无明确研究表明 *A. muciniphila* 能直接刺激潘氏细胞分泌溶菌酶或者直接增加溶菌酶的分泌量，但有实验研究发现中药大黄牡丹汤中的大黄提取物既能刺激肠壁潘氏细胞分泌大量溶菌酶进入肠腔，也能提高肠腔内 *A. muciniphila* 丰度，从而发挥保护肠黏膜屏障的作用[65-66]。由此可见，*A. muciniphila* 与肠黏膜化学屏障既有相互影响互为因果的关系，也有将药物刺激作为中间物相互促进的间接关系。因此，肠黏膜化学屏障结构和功能的完整性需要肠道内 *A. muciniphila* 维护，而肠腔内 *A. muciniphila* 的数量也需要肠黏膜化学屏障的保护。

1.3 *A. muciniphila* 与肠黏膜免疫屏障之间的作用关系

肠黏膜免疫屏障是由肠道内所有的免疫细胞构成的，包括肠相关淋巴组织(gut-associated lymphoid tissue, GALT)、淋巴组织及分泌型免疫球蛋白 A[67]。GALT 主要有两种形式存在，一种是组织化的淋巴组织，主要负责摄取和转运抗原，如派氏结(peyer patch, PP)、肠系膜淋巴结(mesenteric lymph nodes, MLN)和较小的孤立淋巴滤泡，是免疫应答的诱导和活化部位；另一种是呈弥散分布的淋巴组织，即肠道黏膜固有层淋巴细胞(innate lymphoid cell, LPL)和上皮内淋巴细胞(intraepithelial lymphocyte, IEL)，是肠黏膜免疫应答的调节与效应位点[68]。分泌型免疫球蛋白是机体内分泌量最多的免疫球蛋白，主要附着于肠黏膜表面，是肠道防御致病菌在肠黏膜上黏附和定植的第一道防线[69]。研究表明，当肠黏膜屏障受损时，革兰氏阴性菌侵入肠黏膜，化学屏障中广泛分布的 IgA 能有效抵御革兰氏阴性菌的入侵及破坏，进而保护肠黏膜屏障的功能[70](图 1)。肠黏膜上皮内淋巴细胞是与外来抗原和微生物最先接触的免疫细胞，也是最先发生免疫反应的细胞，在抵御黏膜超敏反应，中和外源性细胞毒素等方面具有重要作用，也是

反映肠黏膜免疫屏障结构和功能完整性的重要指标[71]。研究发现，*A. muciniphila* 能将幼稚 $CD4^+$ T 细胞重新编程为 Treg 谱系，限制结肠炎 $CD4^+$ T 细胞转移从而减轻 UC 的免疫损伤[72]。同时，规范给予 *A. muciniphila* 制剂可有效减少巨噬细胞和 $CD8^+$ 细胞毒性 T 淋巴细胞(cytotoxic T lymphocyte, CTL)在 DSS 诱导的 UC 小鼠结肠中的炎性浸润，降低炎症细胞因子的表达，保护肠黏膜免疫屏障，维护肠道菌群的多样性[73]。在 UC 中 *A. muciniphila* 与肠上皮细胞相互作用以促进抗炎因子 IL-8 和 IL-10 的表达，抑制促炎因子 IL-6 和 TNF-α 的表达，从而调节肠道免疫，降低 UC 的炎性反应[74-75]。同时，研究证明 *A. muciniphila* 能与相关炎性信号转导通路相互作用减轻 UC 的肠道炎症反应，如 *A. muciniphila* 通过激活 NLRP3 上调 caspase-1 p20 和 IL-1βp17 的表达，进而减轻 DSS 诱导的急性结肠炎，维护肠黏膜免疫屏障稳态[76]。*A. muciniphila* 能降低肠道干扰素 γ (interferonγ, 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，维护肠黏膜免疫屏障平衡[77]。*A. muciniphila* 在通过刺激 TLR2 增强 AMPK 信号通路活化的同时抑制 NF-κB 信号通路，维持肠道黏膜免疫功能的平衡[78]。同样的，研究发现 *A. muciniphila* 菌鞭毛中的膜型毛样蛋白 *Amuc_1100* 是 Toll 样受体 2 的激活剂，可调节宿主免疫应答和肠道屏障功能，也能通过将宿主的肠黏液降解为短链脂肪酸(short chain fatty acid, SCFA)来抑制肠上皮细胞的免疫反应，进而保护肠黏膜屏障的结构和功能[79-80](图 1)。因此，*A. muciniphila* 可从抑制炎性因子、调节细胞信号转导通路等多方面维护肠黏膜免疫屏障，减轻 UC 肠道的免疫反应，维护肠黏膜屏障结构和功能的完整性。

1.4 *A. muciniphila* 与肠黏膜生物屏障之间的作用关系

肠黏膜生物屏障由肠道内的常驻菌群构成的，正常机体肠道内的常驻菌群会在肠道内形成一个稳定平衡的微生态系统，在病原体入侵肠道时发挥保护作用[81]。而当 UC 发生时，肠道内的菌群结构会出现紊乱，其主要表现为有害菌的数量和丰度增加，有益菌数量和丰度减少[82-83]。*A. muciniphila* 作为对机体有益的益生菌，主要的生长代谢基质为黏蛋白，是由胃肠道组织中的杯状细胞持续分泌。该菌将黏蛋白作为唯一的碳源和氮源，降解黏蛋白，因此 *A. muciniphila* 对其他降解黏蛋白的病原菌产生竞争抑制作用，如对变形菌门(*Proteobacteria*)、拟杆菌属(*Bacteroides*)、双歧杆菌属(*Bifidobacterium*)等造成生存压力，但这种生存压力从肠道菌群总体菌落结构上看无显著性破坏作用[10,84]。而且，在竞争抑制的同时 *A. muciniphila* 为其他常驻细菌提供营养物质，促进其生长，维护肠道菌群的多样性，如乳酸菌属(*Lactobacillus*)[10,85]。因此，当 UC 导致 *A. muciniphila* 菌群丰度及数量减少，无法为其他常驻菌群提供足量的营养物质，在导致肠道菌群紊乱的同时进一步造成内源性的肠道菌群失衡。所以，UC 是造成肠道菌群失衡的主要原因之一，而且它的严重程度与 *A. muciniphila* 丰度和数量呈反比[86-87]。与此同时，实验研究发现肠道菌群紊乱不仅是 UC 的结果也是诱发或者加重 UC 严重程度的原因之一，如小鼠肠道菌群紊乱，与炎症感染相关的致病菌增加，破坏肠黏膜结构，造成肠黏膜萎缩，上皮细胞脱落并伴有炎性渗出等导致结肠损伤[88]。因此，维护肠黏膜生物屏障的平衡及多样性是保护肠黏膜的关键，也是治疗 UC 的机制之一。研究发现通过优化肠道菌群比例如在增加 *A. muciniphila* 的基础上进一步增加双歧杆菌(*Bifidobacterium*)和 *Erysipelatoclostridium* 等益生菌的丰度可有效维

护肠黏膜生物屏障平衡，抑制炎症反应，保护肠黏膜免受损伤[89]。同时，*A. muciniphila* 作为肠黏膜生物屏障中的一员，其数量和丰度的变化会打破肠道内菌群结构的平衡性，加重肠黏膜损伤，尤其是当 *A. muciniphila* 数量减少时，UC 的肠道损伤进一步加重。而补充 *A. muciniphila* 后可以明显缓解 UC 症状和体征，其机理可能是提高小鼠肠道内源性大麻素的水平，从而控制炎症反应，增加黏液层厚度和肠道抗菌肽的分泌量，进而保护肠黏膜屏障[90]。而 *A. muciniphila* 的代谢物丁酸盐被认为可以通过抑制组蛋白去乙酰化酶，激活 G-偶联蛋白受体增强保护性免疫和改善肠道屏障来减轻肠道疾病[91-92]。同时，丁酸盐本身可以通过增加调节性 T 细胞进一步增加抗炎细胞因子 IL-10 的表达，减少结肠中促炎性 $CD4^+$ T 细胞的数量来降低肠道内的炎症反应[93]。研究发现，*A. muciniphila* 作为肠黏膜生物屏障的一部分，在调节其他菌群维护肠道菌群平衡的同时，也受其他菌群调控，如戊糖乳杆菌(*L. pentosus*)可以增加 DSS 诱导的 UC 小鼠肠道内 *A. muciniphila* 菌群的数量及丰度，进而提高血清中吲哚丙酮酸和泛酸的水平，调节肠道菌群紊乱的情况，抑制炎症反应，保护肠黏膜屏障，降低结肠损伤程度[74]。因此，*A. muciniphila* 作为一种对 UC 而言的有益菌，通过调节炎性因子，维护肠道微生物平衡等，综合调节肠黏膜各个屏障，从不同的层次保护肠黏膜屏障结构和功能的完整性，减轻 UC 导致的肠道损伤。

2 *A. muciniphila* 的代谢物短链脂肪酸与肠黏膜屏障之间的关系

A. muciniphila 不仅通过直接作用或联合细胞信号转导通路共同作用的方式保护肠黏膜屏障，其分泌的代谢产物(短链脂肪酸)也是维护肠黏膜屏障稳定的重要物质。研究发现 *A. muciniphila* 能特异性地降解黏蛋白和低聚糖，产生短链脂肪酸等代谢物，促进调节性 T (Treg)细胞的分化，减轻肠道内的炎症反应，尤其是产生的丙酸等代谢物不仅为宿主提供能量还能促进微生物定植，改变肠道微生物群的组成维护肠道内环境稳定[73,94](图 1)。

短链脂肪酸是可以直接被肠黏膜细胞吸收的小分子，能为肠上皮细胞提供能量并维持其正常的形态和功能，由此维护肠黏膜机械屏障的结构和功能的完整性[16,95]。短链脂肪酸中的丁酸盐还可以通过上调紧密连接蛋白和肠黏膜上皮黏液的表达，提高肠黏膜机械屏障的防御功能，防止乙醇、促炎细胞因子等有害因子进入肠黏膜，对维持肠黏膜屏障完整性具有重要作用[96](图 1)。

在肠上皮细胞中，刺激短链脂肪酸的关键受体 G 蛋白受体，能进一步促进肠上皮 MUC2 基因的表达，增加黏液内层的致密性，短链脂肪酸中的丁酸可以促进潘氏细胞分泌溶菌酶和防御素，有利于修复损伤的肠道黏膜，维护肠黏膜化学屏障结构的完整[97-98]。同时，短链脂肪酸中的丁酸还可以通过促进激活蛋白-1 (AP-1)转录因子并与 MUC2 启动子中相应位点结合，以及通过组蛋白乙酰化修饰上调 MUC2 mRNA 表达，诱导肠上皮细胞分泌多种抗菌肽，保护肠黏膜化学屏障正常发挥防御功能[99-100]。研究表明，UC 小鼠肠道内丁酸盐的含量明显减少，而丁酸盐作为结肠上皮细胞的主要能量来源，既能抑制组蛋白去乙酰化酶(histone deacetylase, HDAC)调节基因的表达，又能维持肠上皮细胞能量均势并阻止自噬，减轻黏膜损伤，延缓 UC 进程[101-102]。

对于肠黏膜免疫屏障而言，短链脂肪酸可以调节结肠上皮细胞和免疫细胞发挥抗炎作用[103]。短链脂肪酸中的丁酸不仅能参与肠黏膜局部免疫，还能参与肠外 T 淋巴细胞的分化，通过抑制组蛋白去乙酰化酶，调节肠巨噬细胞

及树突状细胞，减少促炎介质(如 IL-1、IL-12)释放，促进 Treg 细胞分化，抑制炎症反应[104-105]。丁酸还可以直接通过抑制 G 蛋白耦连受体传递信号调节宿主免疫反应，维持辅助性 T 淋巴细胞 Th1/Th2、Th17/Treg 平衡减轻炎症反应，维护肠黏膜免疫屏障的稳态[106-107]。短链脂肪酸中的丙酸，存在于靠近肠上皮细胞的黏液层，丙酸通过 G 蛋白偶联受体 43 作用于肠道组织对机体有明确的免疫调节作用[108-109]。

研究表明，短链脂肪酸可以抑制有害菌生长从而调整肠道微生态环境并达到动态平衡，如抑制大肠杆菌对肠上皮细胞的黏附作用和活力，同时改善因大肠杆菌所造成的细胞凋亡现象等，从而维护肠黏膜生物屏障的稳定[110-111]。同时，短链脂肪酸还可以通过影响其他菌代谢物的表达进而影响肠黏膜屏障的稳定性，如短链脂肪酸能够调节宿主肠嗜铬细胞瘤合成 5-羟色胺(5-hydroxytryptamine, 5-HT)使远端结肠管腔和血清中 5-HT 的水平增加，进而改变免疫细胞的功能，损害肠黏膜的完整性，尤其是通过 5-HT7R 激活 NF-κB 细胞信号通路，调节树突状细胞加剧炎性因子的释放，导致结肠溃疡的形成[112-114]。5-HT 作为色氨酸的主要代谢途径之一，在维护肠黏膜屏障稳态方面具有重要意义，研究发现肠道微生物可通过短链脂肪酸影响 5-HT 的分泌进而成为维护肠黏膜屏障稳态的重要因素[113](图 1)。

由此可见，*A. muciniphila* 的代谢物短链脂肪酸可以综合全面的影响肠黏膜屏障的结构和功能，其本身既可以与细胞信号转导通路相结合抑制炎性因子的表达，增加紧密连接蛋白的表达，抑制有害菌的定植等方式保护肠黏膜屏障，减轻 UC 带来的肠道损伤，也可以影响其他肠道代谢物(如 5-HT)的表达加重 UC 肠黏膜屏障的损伤，如短链脂肪酸可以增加色氨酸代谢物 5-HT 的表达量进而加重 UC 肠道炎症反应。因此，短链脂肪酸对肠黏膜屏障的调节可能是双向的、复杂的，有待于进一步研究探讨。

3 中医药能有效干预 *A. muciniphila* 及其代谢物短链脂肪酸的表达

中医药作为祖国传统医药在维护肠黏膜屏障的完整性、平衡性上具有疗效好、经济负担小等优点。尤其是能有效维护肠黏膜生物屏障的平衡性、多样性。本课题组研究发现[115] Treg/Th17 免疫轴失衡是脾肾阳虚型 UC 的重要发病基础，采用中医病证结合造模法成功复制脾肾阳虚型 UC 大鼠模型，运用蛋白、基因及生物信息学等技术发现脾肾阳虚型 UC 大鼠体内促炎因子表达量显著升高，结肠组织中 Th17 细胞比例显著升高，Treg/Th17 免疫轴明显失衡，肠道内厚壁菌门与拟杆菌门比例失衡，肠黏膜生物屏障受损。辨证给与温肾健脾代表方剂四神丸后发现，四神丸不仅能通过抑制 TLR2/IRAK4/NF-κB 信号通路中关键基因和蛋白的表达，抑制促炎因子 IL-1β 和 TNF-α 表达，同时还能抑制结肠组织中 Notch1、Jagged1 蛋白及基因的表达，进而纠正 Notch 信号通路，减轻肠道炎症反应，恢复 Treg/Th17 免疫轴的平衡，保护肠黏膜屏障[115-116]。在此基础上进一步研究表明四神丸高剂量组能有效调节肠道菌群的数量和丰度，恢复肠道菌群平衡，同时激活由丁酸介导的 PPARγ 信号转导通路，调节 Treg/Th17 免疫轴的平衡、恢复肠道内环境稳态，进而减少脾肾阳虚型 UC 大鼠的肠道损伤，达到治疗 UC 的效果[116]。同时，本课题组成员通过文献分析发现不同中医证型 UC 患者肠道内的菌种种类及丰富度不尽相同。*A. muciniphila* 在大肠湿热型 UC 患者肠道内分布尤为丰富，可作为

UC中医辨证分型的特征菌进行针对性研究[117]。中医药不仅能通过调节肠道免疫反应，抑制炎性因子，维护肠黏膜的完整性，还能通过增加有益菌的丰度，减少有害菌的丰度维护肠黏膜生物屏障的平衡[118]。因此，本文进一步探讨中医药对 *A. muciniphila* 及其代谢物短链脂肪酸的影响机制。

3.1 中药能有效调节 *A. muciniphila* 的表达

3.1.1 中药直接调节 *A. muciniphila* 的数量和丰度

基于中药能有效调节肠道菌群的数量和丰度，因此结合现代研究发现中药复方慢溃宁及痛泻要方能直接提高 UC 小鼠肠道内 *A. muciniphila* 菌属的丰度及多样性从而改善肠道菌群紊乱进而恢复肠道免疫平衡，达到促进结肠黏膜恢复的作用[118-119]。因中药复方组方药物种类多，组方比例复杂，所以研究者将目光投向单味药，如传统中药香加皮可有效纠正 IBD 小鼠失调的肠道微生物群结构,尤其是增加 IBD 小鼠肠道内 *A. muciniphila* 的数量和丰度，并以此作为调节 Th17 免疫的机制的基础，进而缓解肠黏膜损伤[120]。但研究者进一步研究发现中药增加 *A. muciniphila* 的数量和丰度受给药浓度及剂量的影响，一项研究表明黄芪花有效成分黄芪总黄酮(TFA)能增加 *A. muciniphila* 丰度从而维护肠道菌群的平衡性，尤其是黄芪总黄酮高剂量组(TFA-H, 125 mg/kg)的疗效最佳，同时体外研究证实 TFA (1 μg/mL)能直接促进培养基中 *A. muciniphila* 的生长，但 TFA (100 μg/mL)则抑制其生长，因此中药单体黄芪总黄酮(TFA)调控 *A. muciniphila* 的生长不仅呈剂量依赖性还受药物浓度影响[89](图 2)。综上所述，中药复方、单味中药及中药有效成分均能直接增加 *A. muciniphila* 数量和丰度但其增加程度与给药浓度及给药剂量高度相关，需要研究者进一步明确最佳给药浓度及给药剂量。

3.1.2 中药间接调节 *A. muciniphila* 的数量和丰度

同时，研究发现中药不仅能直接增加 *A. muciniphila* 的数量和丰度，还可以通过减轻肠黏膜损伤、调节黏蛋白表达、维护肠黏膜结构和功能完整性，间接增加 *A. muciniphila* 的数量和丰度，从而调控肠黏膜生物屏障结构的平衡性及完整性。如中医经典方剂戊己丸在促进结肠黏膜杯状细胞增殖，改善肠黏膜屏障损伤和结肠动力障碍的同时，通过维护肠道内环境稳态，改善肠道菌群生存环境，间接增加肠道内 *A. muciniphila* 的数量和丰度(较模型组提高 234 倍)进而维持肠黏膜黏液层的完整性，发挥保护肠黏膜屏障的作用[119,121](图 2)。同样的，单味中药黄柏作为四妙散的君药能通过其活性成分小檗碱激活杯状细胞增加黏蛋白的分泌量，补充 *A. muciniphila* 所需的碳源和氮源从而间接促进 *A. muciniphila* 的增殖，降低促炎因子的表达，抑制肠道炎症，减少巨噬细胞浸润和活化，减轻肠道损伤,降低肠道通透性,改善菌群结构，促进肠道微生态平衡[122-123](图 2)。同时，中药有效成分葛根素可以通过增加 MUC2 和抗菌肽基因 Reg3g 的表达来促进杯状细胞的生长和维护其功能的完整性，增加黏蛋白的分泌量从而提高 *A. muciniphila* 的数量和丰度，同时，充足的 *A. muciniphila* 可以为部分有益菌提供足量的营养物质间接增加其他益生菌的数量和丰度(如双歧杆菌属和乳酸杆菌属)，竞争性抑制病原菌的生长，优化肠道菌群的结构，维护肠道微生物稳态，从而发挥保护肠黏膜屏障的作用[119](图 2)。

综上所述，研究表明中药复方、单味中药及中药有效成分不仅能直接增加 *A. muciniphila* 的数量和丰度，还能通过增加杯状细胞的增殖、调节黏蛋白的表达、增加 MUC2 和抗菌肽的表

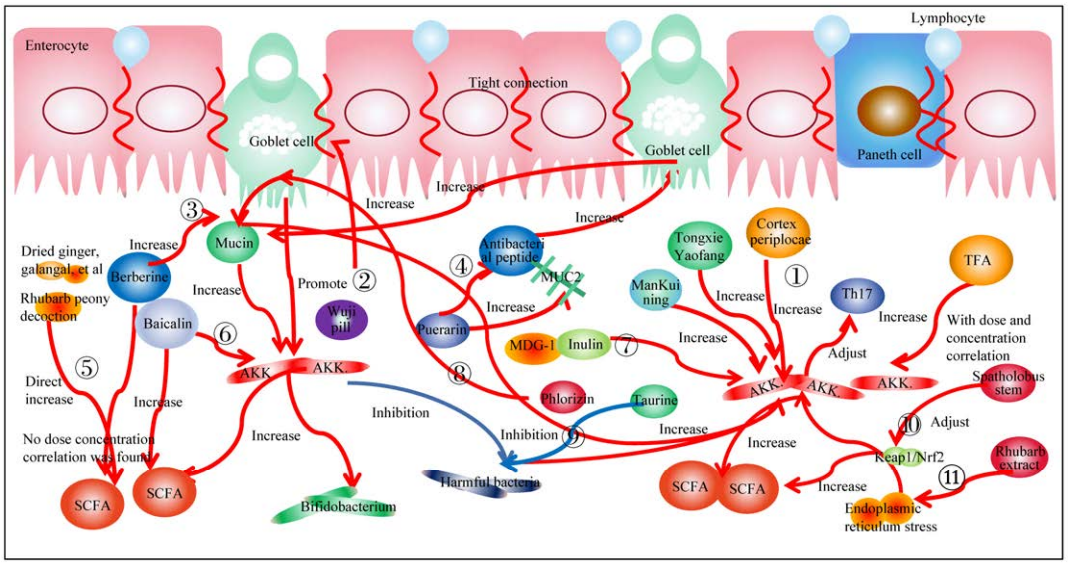

图 2　中医药干预 *Akkermansia* muciniphila 及其代谢物短链脂肪酸的关系图

Figure 2　Relationship diagram of TCM Intervention on *Akkermansia muciniphila* and its metabolite short chain fatty acids. ①: Directly increases the number and abundance of *A. muciniphila*. The traditional Chinese medicine compound Mankuining and Tongxie Yaofang can directly increase the quantity and abundance of *A. muciniphila*, and the traditional Chinese medicine Cortex Periplocae can directly increase the quantity and abundance of *A. muciniphila*, and use this as the basis for the mechanism of regulating Th17 immunity. Protect intestinal mucosa; Astragalus total flavonoids (TFA), the active ingredient of Astragalus flower, can increase the abundance of *A. muciniphila*, and it is related to the dosage and concentration. ②: Indirectly increase the quantity and abundance of *A. muciniphila*, Wuji Pill promotes the proliferation of goblet cells, improves the intestinal mucosal environment and increases the number and abundance of *A. muciniphila* in the intestinal tract. ③: Berberine, the active ingredient of *Phellodendron chinensis*, can activate the expression of mucin in intestinal cells, indirectly promote the proliferation of *A. muciniphila*, improve the structure of the flora, and promote the balance of intestinal microecology. ④: Puerarin, the monomer of traditional Chinese medicine, restores the growth and function of goblet cells by increasing Muc2 and antibacterial peptide, and increases the secretion of mucin, thereby improving *A. muciniphila*. And further increase the abundance of beneficial bacteria (such as *Bifidobacterium* and *Lactobacillus*), thereby inhibiting the growth of pathogenic bacteria, maintaining the balance of intestinal flora and protecting the intestinal mucosal barrier. ⑤: Traditional Chinese medicine directly increases the expression of short-chain fatty acids (SFCA): Chinese medicine compound rhubarb peony decoction, single-flavor Chinese medicine dried ginger, galangal and the active ingredients of traditional Chinese medicine such as baicalin and berberine can directly restore the number of short-chain fatty acids in the intestine, but they do not. Found dosing concentration, dose correlation. ⑥: The study found that baicalin, an active ingredient of traditional Chinese medicine, can not only directly increase the amount of short-chain fatty acids, but also further increase the amount of short-chain fatty acids by increasing the amount of *A. muciniphila* in the intestine. ⑦: The extract of *Ophiopogon japonicus* MDG-1 and the active ingredient inulin of *Jerusalem artichoke* family stimulate the colonization of *A. muciniphila*, increase its quantity and abundance, and then increase the quantity of short-chain fatty acids. ⑧: Phloridizin, the active ingredient of traditional Chinese medicine sweet tea, promotes the growth of intestinal mucosal goblet cells, increases the expression of mucin, increases the number and abundance of *A. muciniphila*, and increases the expression of short-chain fatty acids. ⑨: Taurine, an active ingredient of traditional Chinese medicine, can inhibit the growth of harmful intestinal bacteria, promote the growth of short-chain fatty acid-producing flora, and increase short-chain fatty acids. ⑩: The active ingredients of *S. chinensis* regulate the Keap1/Nrf2 signaling pathway to reduce oxidative stress, thereby increasing the amount of short-chain fatty acids. ⑪: Rhubarb extract recruits mast cells to increase short-chain fatty acid content by regulating endoplasmic reticulum stress.

达，改善肠道内环境从而维护肠黏膜结构和功能上的完整性，进而增加 *A. muciniphila* 的数量和丰度，维护肠道菌群的平衡，并通过维护肠黏膜生物屏障的稳定，发挥保护肠黏膜屏障的作用。因此，中医药能通过全面调节肠黏膜屏障的各个因素，综合、全面、协同调节肠黏膜机械、免疫及化学屏障，发挥增加 *A. muciniphila* 的数量和丰度保护肠黏膜生物屏障的作用。中医药还能将肠黏膜生物屏障作为沟通其他屏障的纽带，通过调节 *A. muciniphila* 菌群维护肠黏膜各个屏障的构和功能，降低 UC 引起的肠道损伤。

3.2 中药能有效调节短链脂肪酸的表达

3.2.1 中药能直接调节短链脂肪酸的表达

中药复方、单味中药及中药有效成分均能直接增加短链脂肪酸的数量，从而发挥保护肠黏膜屏障的作用。如《金匮要略》中的经典方剂大黄牡丹汤(rhubarb peony decoction)能有效恢复 UC 小鼠肠道内短链脂肪酸的数量[124]。同时作为药食两用的干姜、高良姜、红豆蔻、党参及枸杞等单味中药也可以通过促进短链脂肪酸的生成进而恢复肠道菌群平衡[125-126](图 2)。而黄芩的有效成分黄芩苷作为益生元制剂通过增加肠道内短链脂肪酸的数量逆转 UC 大鼠肠道菌群紊乱进而发挥保护肠黏膜屏障的作用[127](图 2)。因此，中药复方、单味药及药物有效成分均能直接增加短链脂肪酸在肠道内的表达量，发挥保护肠黏膜屏障的作用，但目前未发现短链脂肪酸的表达量与中药给药浓度及剂量的相关性，需进一步研究探讨。

3.2.2 中药能间接调节短链脂肪酸的表达

A. muciniphila 以黏蛋白为碳源和氮源，产生短链脂肪酸，为宿主提供能量，维护肠黏膜的完整性[128]。因此，中药能通过调节产生短链脂肪酸的上源细菌(如 *A. muciniphila*)的数量，进而调节短链脂肪酸的分泌，从而保护肠黏膜屏障。如一项机制研究表明，中药麦冬的提取物 MDG-1 及菊芋科有效成分菊粉能够刺激结肠中 *A. muciniphila* 的定植，增加 *A. muciniphila* 的相对丰度，从而增加短链脂肪酸中的乙酸、戊酸及丙酸得表达量，从而调节肠道炎症反应，促进肠道健康[129-130](图 2)。中药有效成分小檗碱及黄芩苷在增加 *A. muciniphila* 数量促进短链脂肪酸分泌的同时，能进一步调节肠道能量代谢，减轻炎症反映，保护肠黏膜屏障[127,131-132]。因此进一步研究发现，中药有效成分通过调整肠道内环境稳态，提高 *A. muciniphila* 的数量和丰度进而增加短链脂肪酸的表达。如中药甜茶的有效成分根皮苷可以通过促进肠黏膜杯状细胞的生长，提高黏蛋白的表达进而为 *A. muciniphila* 提供营养，促进其生长，由此提高短链脂肪酸的表达量，改善肠黏膜屏障功能，减轻肠道损伤[133](图 2)。中药有效成分牛磺酸能通过抑制肠道有害菌的生长，竞争性的促进产短链脂肪酸菌群生长，增加短链脂肪酸的表达量，调节肠道微生态，维护肠黏膜屏障健康[134](图 2)。

中药不仅能直接增加 *A. muciniphila* 的数量和丰度还能通过改善 *A. muciniphila* 的生长环境进一步促进其生长从而增加短链脂肪酸的表达。在此基础上研究发现，中药有效成分可以通过调节细胞信号转导及内质网应激间接增加短链脂肪酸的表达水平。如鸡血藤有效成分通过调节 Keap1/Nrf2 信号通路减轻氧化应激，进而增加短链脂肪酸的数量从而维护肠道菌群结构平衡，抑制 DSS 诱导的结肠炎[135]。大黄提取物通过调节内质网应激募集肥大细胞，提高小鼠结肠组胺和乙酰胆碱含量，促进结肠黏液的分泌，进而维护肠道菌群多样性和增加短链脂肪酸的含量[136](图 2)。因此，中药复方、单味中药及中药有效成分均能直接或间接调控产短链

脂肪酸上源菌的生长内环境促进其生长进而增加短链脂肪酸的表达量。

综上所述，在传统中医理论的指导下结合现代科研技术发现中药复方、单味药及中药有效成分可以直接或间接增加 *A. muciniphila* 的数量和丰度进而增加其相关代谢物短链脂肪酸的含量，从而维护肠道菌群的平衡，抑制炎性反应，保护肠黏膜屏障，达到治疗 UC 的目的。

4 结论及展望

UC 逐渐成为当今世界发病率高，波及人群广的终身难治性的疾病。肠黏膜屏障损伤既是 UC 重要的发病机制之一，也是当今治疗 UC 的主要研究方向。近年来，肠道菌群在保护肠黏膜屏障中的作用逐渐凸显出来，研究发现在治疗 UC 中益生菌制剂与传统药物治疗相比具有疗效可靠安全、副作用小等优点。因此，肠道 *A. muciniphila* 菌作为肠黏膜屏障的保护菌，其保护肠黏膜屏障的作用机制就显得尤为重要。本文结合临床需要，从肠黏膜机械、化学、免疫、生物屏障等四个角度综合分析 *A. muciniphila* 及其代谢物短链脂肪酸保护肠黏膜屏障的机理。*A. muciniphila* 及其代谢物短链脂肪酸均能保护肠黏膜杯状细胞、潘氏细胞，维护肠黏膜紧密连接，降低肠道炎症反应，维护肠道微生物平衡。但是短链脂肪酸也可以影响 5-HT 的表达进而加重肠道炎症反应。因此，*A. muciniphila* 及其代谢物短链脂肪酸对肠黏膜屏障的影响不是单向的，应是呈网状交错影响的；其次 *A. muciniphila* 及其代谢物短链脂肪酸可以与细胞信号转导通路相结合共同影响肠黏膜屏障的结构和功能；第三，同一菌或代谢物的功能复杂，正向作用与负性调节往往同时出现，这可能与肠道菌群功能的复杂性、肠道菌群内环境的多样性相关。

A. muciniphila 作为保护肠黏膜屏障的兼性厌氧菌具有对起始存在环境、培养条件和操作方法要求严格的特点，同时存在培养鉴定困难，生长情况不稳定等问题[10,137-138]。因此，目前常用经巴氏灭菌后的 *A. muciniphila* 及其外膜蛋白 *Amuc_1100* 作为研究对象。但目前科研研究仍然未明确 *A. muciniphila* 的毒理学特性研究，如剂量反应等。现阶段初步人体数据表明口服 *A. muciniphila* 是安全的，但其效果需更多的临床试验进一步验证。同时，研究发现 *A. muciniphila* 在 UC 的丰度降低但在结肠癌中的丰度升高，这表明 *A. muciniphila* 保护肠黏膜屏障的机制尚未明确，即 *A. muciniphila* 保护肠黏膜屏障的机制不是简单的通过增加其数量和丰度进行的，结合 *A. muciniphila* 不是肠道内唯一以黏蛋白为生长代谢基质的细菌，对其他以降解黏蛋白为主的细菌存在竞争抑制关系，由此可推论 *A. muciniphila* 保护肠黏膜屏障可能与调节肠道内部分菌群的比例相关，但因肠道菌群存在数量庞大，菌群种属未完全鉴别明确，各类菌群作用机制尚未明确，故导致无法探究出适合肠道健康的菌群比例。虽然，已有临床研究表明口服 *A. muciniphila* 对维护肠黏膜屏障完整性是安全的、有效的，但口服外源益生菌依然存在无法在患者体内长期定植的问题，这也成为发展 *A. muciniphila* 制剂的一大挑战。综上所述，*A. muciniphila* 及其代谢物短链脂肪酸作为 UC 的保护因素虽然面临许多研究困难但仍值得我们深入研究，成为明确 UC 的发病机制，拓展 UC 的治疗手段，研发治疗 UC 新药的新视角、新思路和新方向。

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