

Akkermansia muciniphila in inflammatory bowel disease and colorectal cancer

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Akkermansia muciniphila (*A. muciniphila*), a type of Gram-negative anaerobe, was first isolated and identified from the feces of a healthy Caucasian woman at Wageningen University in 2004.^[1] It can stably colonize the human gut 1 year after birth and accounts for 1%–4% of the total gut microbiota. *A. muciniphila* specializes in the degradation of mucin (the glycoprotein in mucus) and uses the mucin as the sole source of carbon and nitrogen. *A. muciniphila* is abundant in the host intestinal mucosal layer, with the greatest abundance in the cecum, where most mucin is produced.^[2] Although degradation of mucin is a pathogen-like behavior; *A. muciniphila* does not show any pathogenicity, it resides only in the outer mucosal layer and does not reach the inner mucosal layer. Recently, several studies have revealed that *A. muciniphila* has important regulatory effects on gut homeostasis.

Dysbiosis of the gut microbiota has been associated with the development and progression of inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD). Colorectal cancer (CRC), including colitis-associated colorectal cancer (CAC), is inseparably associated with IBD, which is an important influencing factor for the occurrence of CRC. The abundance of *A. muciniphila* is inversely associated with metabolic disorders, which could increase the risk of CRC. Interestingly, supplementation with *A. muciniphila*, specific proteins from the outer membrane (Amuc_1100), secreted proteins (glucagon-like peptide-1-inducing protein), or extracellular vesicles could alleviate metabolic disease in humans and mice.^[3,4] These results indicate that *A. muciniphila* is a member of beneficial microbiota in terms of modulating disorders. However, the role of *A. muciniphila* in IBD and CRC remains inconclusive. Environmental factors, such as diet, probiotics, and medications, play a substantial role in shaping the gut microbiome composition. Therefore, we explored the association between *A. muciniphila* and IBD and CRC and addressed the important role of *A. muciniphila* in the anti-inflammatory and anti-cancer effects of dietary agents, probiotics, and medications.

Richness of *A. muciniphila* in intestinal inflammation and tumor: Lower colonization and abundance of *A. muciniphila* were also observed in patients with UC and CD.^[5] In agreement with data regarding humans, the abundance of *A. muciniphila* was also decreased in experimental colitis induced by dextran sulfate sodium (DSS) or 2,4,6 trinitrobenzenesulfonic acid (TNBS).^[6] Moreover, disruption of the gut microbiota was observed in azoxymethane (AOM)/DSS-induced CAC, reflected by a higher abundance of harmful bacteria (such as *Desulfovibrio* and *Helicobacter*) and a lower abundance of beneficial bacteria (such as *Lactobacillus*, *Bifidobacterium*, *A. muciniphila*, and *Faecalibaculum*). Moreover, the abundance of *A. muciniphila* in colon biopsies was modestly and inversely correlated with baseline trimethylamine *N*-oxide content that has been identified as a risk factor for CRC.^[7] Our previous study revealed that *A. muciniphila* could distinguish CRC and AOM/DSS-induced CAC from healthy controls due to a reduced abundance.^[8] However, several studies on the effects of *A. muciniphila* in IBD and CRC have drawn opposite conclusions. Limited human studies have revealed an increased abundance of *A. muciniphila* in patients with CRC [Supplementary Table 1, <http://links.lww.com/CM9/A808>]. In addition, the abundance of *A. muciniphila* has been found to be significantly increased in colitis-prone mice with certain gene mutations (*muc2*) or knockouts, such as interleukin (IL)-10.^[6] This discrepancy could be partly explained by health state, disease activity, and gene functions. Consequently, large-scale human studies, animal studies, and clinical trials are needed to verify the causality between *A. muciniphila* and IBD and CRC.

***A. muciniphila*, dietary target for the treatment of IBD and CRC:** Diet may have a role in the modulation of the microbiota, the metabolome, and gut immunity. Ketogenic diets have been found to alleviate colitis by reducing the number of colonic group 3 innate lymphoid cells through altering the gut microbiome, with a reproducible increase in *A. muciniphila* abundance. Fermented foods could protect against colitis induced by pathogenic bacteria or

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DSS by increasing the abundance of *A. muciniphila*. Extracts from various fruits, vegetables, and meat exhibit inhibitory effects on colitis and augment the abundance of *A. muciniphila* [Supplementary Table 2, <http://links.lww.com/CM9/A808>]. Moreover, enrichment of *A. muciniphila* in association with beneficial effects was observed in colitis mice treated with phytochemicals, such as caffeic acid derivatives, myricetin, resveratrol, teasaponin, and polysaccharides. Barley leaf insoluble dietary fiber and egg white peptides ameliorated colitis, while they inhibited the expansion of *A. muciniphila* [Supplementary Table 2, <http://links.lww.com/CM9/A808>]. Host-derived substances, such as primary bile acids, secondary bile acids, vitamin D, and α -ketoglutarate, could boost the abundance of *A. muciniphila*. They have been proven to protect against DSS-induced colitis or inhibit the occurrence and development of CRC by regulating *A. muciniphila*-mediated colon barrier integrity and immunomodulatory effects [Supplementary Table 3, <http://links.lww.com/CM9/A808>].

An increasing number of probiotics are being used to improve IBD and CRC by regulating the immune response and altering the gut microbiota. Single probiotic treatments, such as *Lactobacillus pentosus* could alleviate the colitis symptoms via modulation of the immune response, accompanied by increased *A. muciniphila* abundance and short-chain fatty acid (SCFA) [Supplementary Table 2, <http://links.lww.com/CM9/A808>]. Moreover, probiotic mixtures of *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Enterococcus faecalis*, and *Bacillus cereus* have been found to improve DSS-induced colitis by rebuilding the structure of the gut microbiota, especially increased abundances of *Bifidobacterium*, *Akkermansia*, and *Lactobacillus*.^[9] In addition, several studies have revealed that probiotics alone or in combination with therapeutic proteins or plant extracts reduced tumor volume, inhibited tumor growth, and increased the abundance of *A. muciniphila* in CAC mice [Supplementary Table 3, <http://links.lww.com/CM9/A808>]. However, several probiotics exert anti-inflammatory activities, while their administration significantly decreases the abundance of *A. muciniphila*.^[10] These results indicate that probiotic effectiveness can be species- and disease-specific. The underlying mechanism involved in direct interaction with intestinal epithelial cells and immune cells has been proposed. In addition, they may also interact with other gut microbiota constituents, such as *A. muciniphila*, to support gut homeostasis by producing beneficial metabolites.

***A. muciniphila* is a potential target for pharmaceutical interventions:** A major known stressor of the intestinal microbiota is exposure to antibiotics, which significantly modulate the relative abundance of *A. muciniphila*.^[6] The interaction between gut microbes and commonly used non-antibiotic drugs is complex and bidirectional. Enrichment of *A. muciniphila* following metformin treatment has been found to frequently coincide with alleviated colonic inflammation in colitis mice.^[11] TAK-242 (resatorvid), an inhibitor of Toll-like receptor 4 (TLR4), was reported to exhibit therapeutic potential in UC by regulating the gut microbiota and promoting the growth of *A. muciniphila*.

Hyaluronic acid-bilirubin nanomedicine has been found to be associated with enrichment of *A. muciniphila*, regulate innate immune responses, and exert potent therapeutic efficacy against colitis. HuR inhibition of human antigen R by MS-444 could increase the abundance of *A. muciniphila* and attenuate tumorigenesis in APC^{Min/+} mice, a model of familial adenomatous polyposis and CRC. Expansion of *A. muciniphila* is associated with the anti-inflammatory and anti-tumor effects of various traditional Chinese medicines [Supplementary Table 2, <http://links.lww.com/CM9/A808>]. Berberine and alisol B 23-acetate prevented the development of CAC, whereas they decreased the relative abundance of *A. muciniphila*. Although these results support the positive or negative influences of medication on the gut microbiota in hosts with IBD and CRC, *A. muciniphila* can serve as an intermediary for pharmaceutical interventions of IBD and CRC.

Intervention of *A. muciniphila* in IBD and CRC: Emerging evidence indicates that *A. muciniphila* may be a potential probiotic agent for ameliorating colitis and CRC. Gavage of *A. muciniphila* (strain DSM 22959) accelerated the recovery from colitis in the mice fed the casein diet by decreasing the disease activity index and increasing the mucus thickness and *muc2* mRNA level.^[12] *A. muciniphila* type strain ATCC BAA-835 has been shown to alleviate DSS-induced colitis via microbe-host interactions and improving the microbial community.^[13] Both the murine *A. muciniphila* strain (designated 139) and the *A. muciniphila* type strain ATCC BAA-835 have been reported to exert anti-inflammatory effects on chronic colitis.^[14] However, the anti-inflammatory effects of strain ATCC BAA-835 were stronger than those of strain 139, emphasizing the importance of the further study of the function of *A. muciniphila* at the strain level. Oral administration of *A. muciniphila* to low-cellulose diet-fed mice elevated crypt length, increased goblet cell numbers, and ameliorated colitis induced by DSS.^[15] *A. muciniphila*-derived extracellular vesicles, Amuc_1100, and pasteurized bacteria (strain ATCC BAA-835) could improve colitis via regulation of intestinal barrier integrity and the immune response.^[8,16] Oral administration of *A. muciniphila* elevated systemic anti-aging and anti-cancer metabolite levels, such as SCFAs, polyamines, and multiple bile acids. These effects were more pronounced after pasteurized *A. muciniphila* treatment than after live bacterium treatment. Our previous study showed that pasteurized *A. muciniphila* and Amuc_1100 could blunt AOM/DSS-induced CAC by expanding CD8⁺ T cells and enhancing their cytotoxic effects.^[8] Targeted regulation of the intestinal flora, especially *A. muciniphila*, might be a novel and promising therapeutic strategy for preventing and curing IBD and CRC. However, *A. muciniphila* (strain ATCC BAA-835) failed to promote short-term intestinal inflammation in gnotobiotic *IL10*-deficient mice. Moreover, repeated oral gavage of *A. muciniphila* could induce spontaneous colitis in germ-free *IL10*-deficient mice, suggesting that *A. muciniphila* can act as a pathobiont to promote colitis in a genetically susceptible host.^[17] Thus, genotypes and disease states should be considered to evaluate the validity and feasibility of microbiota-based therapies for IBD or CRC.

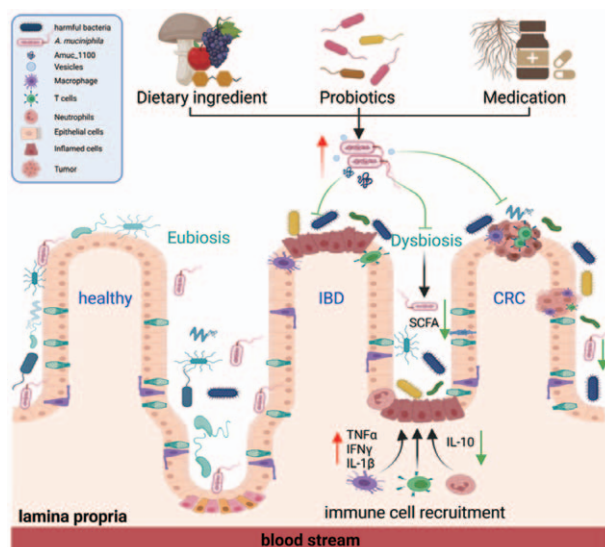


Figure 1: The role of *A. muciniphila* in IBD and CRC. Decreased abundance of *A. muciniphila* was observed in patients and animal models with IBD or CRC. Increased level of *A. muciniphila* was associated with the prevention and protection in IBD and CRC following dietary ingredients, nutrients, probiotics, and medication intervention. Supplementation with *A. muciniphila*, *A. muciniphila*-derived extracellular vesicles, and the therapeutic protein Amuc_1100 could also protect against IBD and CRC by increasing the production of SCFA and modulation of an immune response. *A. muciniphila*: *Akkermansia muciniphila*; CRC: Colorectal cancer; IBD: Inflammatory bowel disease; SCFA: Short-chain fatty acid; TNF α : Tumor necrosis factor α ; IFN γ : Interferon γ ; IL: Interleukin.

Conclusions and outlook: Dysbiosis of the gut microbiota is a hallmark of intestinal disorders, and the host-*A. muciniphila* symbiotic equilibrium is disrupted in IBD and CRC [Figure 1]. Increased levels of *A. muciniphila* are associated with the prevention of and protection against IBD and CRC following dietary ingredients, nutrients, probiotics, and medication intervention. Despite these impressive therapeutic advantages, a negative correlation between their beneficial effects and *A. muciniphila* has also been observed in some animal studies. Thus, it would be best to propose *A. muciniphila* as both a “friend and foe” until additional research and clinical data have emerged. However, the application of *A. muciniphila*, *A. muciniphila*-derived extracellular vesicles, and the therapeutic protein Amuc_1100 has been revealed to effectively protect against IBD and CRC, and the cellular and molecular mechanism needs extensive further investigation. In addition, the discovery of new strains or derivatives of *A. muciniphila* will reveal new approaches for biomolecule isolated probiotics to treat intestinal disorders. Overall, *A. muciniphila* has brought new hope for the use of probiotics for the prevention and treatment of intestinal diseases.

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Conflicts of interest

None.

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