Role of Akkermansia in IBD and Cancer

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Akkermansia muciniphila (*A. muciniphila*) represents approximately 1–3% of the total gut microbiota in healthy people; it is a non-motile, Gram-negative, non-spore-forming, oval-shaped bacterium belonging to the *Verrucomicrobia* phylum, and it is the first and only member of the phylum *Verrucomicrobia* found in the human gut. Its key features are the ability to produce short-chain fatty acids (SCFAs, energy source for colonocytes and anti-inflammatory molecules), to promote mucin turnover and thickening thereby reinforcing the intestinal barrier and to interact with host receptors with its exposed active molecules thus influencing inflammation and metabolism. *A. muciniphila* can be used as a biomarker of a healthy host metabolic profile and that its depletion represents a signature of intestinal dysbiosis across different gastrointestinal and extraintestinal diseases as inflammatory bowel disease and some cancer types. The molecular mechanism beneath the action of this bacteria in the abovementioned diseases and how *A. Muciniphila* can modulate the response to both conventional and targeted cancer therapy are explored.

Keywords: gut ; IBD ; Akkermansia muciniphila ; cancer ; cancer therapy ; immunotherapy

1. Introduction

Akkermansia muciniphila (*A. muciniphila*) represents approximately 1–3% of the total gut microbiota in healthy people; it is a non-motile, Gram-negative, non-spore-forming, oval-shaped bacterium belonging to the *Verrucomicrobia* phylum, and it is the first and only member of the phylum *Verrucomicrobia* found in the human gut [1][2][3]. *A. muciniphila* was originally considered a strict anaerobe, but it was recently proved to tolerate small amounts of oxygen and was therefore reclassified as an aerotolerant anaerobe [4].One of the distinguishing features of *A. muciniphila* is its ability to degrade intestinal mucin glycoproteins via various enzymes and to use them as a sole source of carbon and nitrogen; this process leads to the production of short-chain fatty acids (SCFAs). Due to this process of degradation, *A. muciniphila* promotes mucin turnover and thickening, thereby reinforcing the intestinal barrier and reducing gut permeability to microbial products. A further barrier-reinforcing mechanism is the *A. muciniphila*-induced production of antimicrobial peptides from Paneth cells. SCFAs derived from gut mucin glycoproteins are absorbed in the colon and serve as an energy source for colonocytes, inducing regulatory T cells and exerting anti-inflammatory effects [4][5][6][7][8].

SCFAs are subsequently used by other bacteria in the gut microbial community, such as *Anaerostipes caccae*, *Anaerobutyricum hallii*, and *Faecalibacterium prausnitzii*, to further produce butyrate and propionate [1][6][9][10][11].

In addition to metabolites, the effects of *A. muciniphila* are mediated by exposed active molecules; among these, Amuc_1100 (an outer membrane protein involved in pili formation) can replicate almost all of the effects of live *A. muciniphila* through Toll-like receptor 2 (TLR2) sensing [12][13][14]. TLRs are expressed by a wide range of immune, epithelial, and endothelial cells whose main role is the recognition of microbial structures, capable of stimulating pro- and anti-inflammatory responses with further implications in the regulation of host metabolism [14][15]. The heat stability of these proteins explains why *A. muciniphila* retains most of its effects even after pasteurization. In 2021, the safety of pasteurized *A. muciniphila* was positively assessed by the European Food Safety Authority (EFSA) and the Panel on Nutrition, Novel Foods and Food Allergens (NDA) [16], and its production represents the beginning of the new generation of probiotics [17].

Due to its many beneficial effects, it is not surprising that *A. muciniphila* can be used as a biomarker of a healthy host metabolic profile, and that its depletion represents a signature of intestinal dysbiosis across different gastrointestinal and extraintestinal diseases. A reduced abundance of *A. muciniphila* in the gut microbial community has been related in fact to several diseases, such as obesity, type 2 diabetes, inflammatory bowel disease and some cancer types; conversely, the administration of live *A. muciniphila* has shown a protective role even in the pathogenesis of cardiovascular disease in mice [18][19][20][21].

2. *Akkermansia muciniphila* and Inflammatory Bowel Diseases

The gut microbiota plays an undeniable role in the pathogenesis of inflammatory bowel diseases (IBD), and the modulation of the gut microbiota represents one of the most promising challenges in IBD therapy [22][23][24][25][26].

Many case–control studies have documented a significant decrease in the relative abundance of *A. muciniphila* both in ulcerative colitis (UC) and Crohn's disease (CD) compared to healthy controls [27][28][29][30], with only one study showing an opposite trend in a group of patients affected by CD [31].

As previously mentioned, *A. muciniphila* exerts an anti-inflammatory effect within the intestinal microecology. Among the underlying mechanisms proposed, the production of SCFAs is the most deeply investigated; the production of SCFAs has been demonstrated to protect against colitis by increasing the number of forkhead box P3 (Foxp3+) regulatory T cells in the colon and through the activation of the G-protein coupled receptor 43 (GPR43) expressed by immune cells and colonic epithelium [32][33][34]. Wang et al. observed that the administration of *A. muciniphila* could improve dextran sulfate sodium (DSS)-induced colitis in mice by reducing macrophage and CD8+ cytotoxic T lymphocyte levels in the colon [35], while Bian et al. reported a downregulation of pro-inflammatory cytokines and chemokines [36]. Additionally, the administration of *A. muciniphila* enhances intestinal stem cell proliferation and Paneth and goblet cell differentiation in the small intestine and colon of both healthy mice and mice with gut damage [37].

A. muciniphila also restored the mRNA expression of tight junction proteins such as zonulin-1, occludin, and claudin-1 in mouse models of DSS-induced colitis, thereby reducing gut permeability and reshaping the intestinal microbiota, leading it toward eubiosis; these effects are related to the administration of Amuc:2109, a β-acetylaminohexosidase secreted by this microorganism [38].

However, an increased abundance of *A. muciniphila* was reported in some preclinical models of gut inflammation [39][40][41]. Interestingly, when administered to mice with non-DSS-induced colitis, *A. muciniphila* was associated with symptoms worsening; *A. muciniphila* administration also exacerbated the symptoms of *Salmonella-typhimurium*-induced gut inflammation in a mouse model with a background microbiota of eight bacterial species [42], and it was possibly implicated in the worsening of colitis in IL10 −/− mice.

The discrepancy in the effects of this bacterial species could allow for several interpretations, being possibly biased by the different mouse models used; moreover, it can be speculated that the increased abundance of *A. muciniphila* in colitis models could represent a causative factor or rather, a reactive response. When *A. muciniphila* was administered in the IL-10 −/− mice colonized with a simplified human gut microbiota, it did not promote inflammation, suggesting that other environmental conditions could be involved [43][44].

Finally, there are few studies on the predictive effect of *Akkermansia* after FMT in patients with IBD. Zhang et al. demonstrated that washed microbiota transplantation (WMT) significantly increased the colonization rate of *Akkermansia* and that there was a positive correlation between the abundance of patient's and donor's *Akkermansia* abundance after WMT, speculating its possible role as a predictive factor of WMT efficacy [27]. Similar results were obtained by Kump et al. in treatment-refractory patients with UC; indeed, the stool of donors with a higher bacterial richness and a higher relative abundance of *A. muciniphila*, *Ruminococcaceae*, and *Ruminococcus spp*. were more likely to induce remission in these patients. In particular, *A. muciniphila* was nearly absent in baseline samples but was significantly increased the day after FMT in patients achieving remission [45].

In conclusion, current evidence, although conflicting to some degree, paves the way for a potential role of *A. muciniphila* in IBD treatment [46].

3. *Akkermansia muciniphila* and Cancer

Colorectal cancer (CRC) is one of the most common and lethal cancers in the world. Although obesity, Western dietary habits, smoking, and heavy alcohol consumption are the better-known risk factors for CRC, the intestinal environment has also received widespread attention in this field. It has been demonstrated in humans and in animal models that gut dysbiosis may promote colon carcinogenesis via multiple mechanisms, including the development of chronic inflammation and the production of genotoxins and other microbial products [47][48][49][50].

A. muciniphila depletion is a feature of CRC-associated dysbiosis. In models of colitis-associated CRC (CAC), the administration of pasteurized *A. muciniphila* or Amuc_1100 alone improved symptoms, delayed tumor development, and decreased the number and area of tumor lesions by attenuating DNA damage, cell apoptosis, and abnormal proliferation;

the beneficial effects of *A. muciniphila* were associated with the expansion of cytotoxic T-lymphocytes in the colon and mesenteric lymph nodes and with the modulation of macrophages subpopulations, thus explaining how *A. muciniphila* influences inflammation-associated tumorigenesis [35].

Another study further confirmed that the abundance of *A. muciniphila* is significantly reduced in humans with CRC and that its supplementation can inhibit colonic tumorigenesis in ApcMin/+ mice via the expansion of M1-like macrophages in colonic tissue. Tumor-associated macrophages (TAMs) can assume a pro-inflammatory polarization (M1) or an anti-inflammatory polarization (M2), with only the former helping to suppress cancer cells. Even this effect is mediated by the interaction between *A. muciniphila* and the TLR2 expressed by macrophages [51][52][53].

Apart from its immunomodulatory effects, *A. muciniphila* can also directly interfere with colon carcinogenesis through the production of Amuc_1434, an enzyme that can degrade Mucin2, the main component of the intestinal mucus layer, which is highly expressed in mucinous CRC. Amuc_1434 showed a protective effect on tumor protein 53 (p53) expression in vitro, resulting in the blockade of the G0/G1 cell cycle phase and the promotion of CRC cells apoptosis [54][55].

Conversely, it was observed that *A. muciniphila* abundance was increased in two different cohorts of patients affected by CRC, as well as in a cohort of patients with esophageal and gastric cancers compared with healthy controls [56][57]. However, according to Weil et al., this observation can be related to an increased substrate availability rather than to a detrimental role of this bacterium, considering the overexpression of MUC1 and MUC5AC in CRCs [57].

Besides CRC, *A. muciniphila* was found to be more abundant in patients with non-small-cell lung cancer (NSCLC) and to gradually decrease during the progression from cirrhosis to hepatocellular carcinoma [58][59][60].

In recent years, gut microbiota modulation applied to cancer therapy is certainly a topic of growing interest in either treatment efficacy or tolerability [61][62][63].

There are some data regarding the possible role of *A. muciniphila* in both conventional and targeted anticancer therapy. For instance, *A. muciniphila* could improve the antitumor effect of cisplatin; in mouse models of lung cancer, the administration of *A. muciniphila* in combination with cis-diamminedichloroplatinum (CDDP) was associated with reduced tumor growth, the downregulation of ki-67, p53, factor-associated suicide (Fas) ligand proteins, and the upregulation of Fas proteins [61]. Moreover, the administration of *A. muciniphila* in this setting increased the production of pro-inflammatory cytokines and suppressed the development of T-reg lymphocytes, thus suggesting that it could modulate the immune microenvironment toward an inflammatory response, counteracting tumor immune escape. *A. muciniphila* has been proven to enhance the antitumor efficacy of interleukin (IL)-2; in murine models of melanoma and CRC, the combined administration of IL-2 and *A. muciniphila* reduced the tumor burden and improved survival compared with IL-2 treatment alone, primarily by stimulating the response of CD4+ and CD8+ T cells against cancer cells and by decreasing the number and the activity of T-regs. These beneficial effects were at least partially mediated by the interaction between a specific membrane protein and TLR2 [64]. The current literature also shows a peculiar interplay between *A. muciniphila* and abiraterone acetate (AA), an inhibitor of androgen biosynthesis for the treatment of prostate cancer (PCa) refractory to androgen deprivation therapy (ADT). In a cohort of PCa patients, AA administration increased the abundance of *A. muciniphila,* with this effect probably resulting from the interaction between the conjugated acetate portion of AA and *A. muciniphila* [65][66][67]. Unfortunately, the authors did not explore the contribution of *A. muciniphila* to the efficacy of AA. In a later study, the intravenous administration of *A. muciniphila*-derived extracellular vesicles in PCa-bearing, immune-competent mice operated as an immune modulator; it was associated with the increased activation of CD8+ T cells and tumor-killing M1 macrophages, resulting in a reduced tumor mass [68].

To further clarify the role of *Akkermansia* in cancer immunotherapy, Xu et al. evaluated the effects of the modulation of the gut microbiome on the response to immune checkpoint inhibitors (ICIs). In CRC mouse models, the exposure to several broad-spectrum antibiotics interfered with the efficacy of programmed cell death protein 1 (PD-1) antibodies, depending on the type of antibiotic and the resulting changes in the gut microbiota composition. *A. muciniphila* was found to be enriched in the vancomycin-treated group and associated with a better outcome; according to the authors, *Akkermansia* could preserve the efficacy of anti-PD-1 therapy by modulating the metabolism of glycerophospholipids, which influence the expression of immune-related cytokines IFN-γ and IL-2 in the tumor microenvironment [69]. Other published studies in patients with hepatocellular carcinoma and melanoma highlighted the contribution of the gut microbiome to the response to immunotherapy, and *A. muciniphila* emerged as a key element associated with treatment efficacy [70][71][72][73][74].

Finally, in patients with NSCLC and renal cell carcinoma (RCC) undergoing immunotherapy with ICIs, FMT from treatment responders to germ-free mice resulted in increased efficacy of immunotherapy. *A. muciniphila* was found to be more abundant and associated with treatment response, and the oral administration of *A. muciniphila* improved PD-1 blockade

effectiveness, once again through the modulation of the immune response, specifically by promoting the recruitment of CD4+ T cells [70].

In conclusion, even in the setting of the modulation of the response to cancer therapy, current evidence, although limited, shows a promising role for *A. muciniphila*. Further studies are needed to clarify its potential in this field.

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