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Akkermansia muciniphila – multifunctional bacteria

Alicja Wosińska

Marshal Józef Piłsudski Memorial Hospital in Płońsk, Henryka Sienkiewicza 7, 09-100 Płońsk

https://orcid.org/0009-0000-8712-6148

Dorota Pazik

Orłowski Hospital, ul. Czerniakowska 231, 00-416 Warszawa

https://orcid.org/0009-0008-6826-0083

Inga Łopuszyńska

The National Institute of Medicine of the Ministry of Interior and Administration, Wołoska 137, 02-507 Warszawa

https://orcid.org/0000-0002-0002-9917

Katarzyna Kosecka

The National Institute of Medicine of the Ministry of Interior and Administration, Wołoska 137, 02-507 Warszawa

https://orcid.org/0009-0001-8434-7030

Patryk Rudziński

Orłowski Hospital, ul. Czerniakowska 231, 00-416 Warszawa

https://orcid.org/0000-0003-4709-2187

Aleksandra Cieślik

Praski Hospital in Warsaw, Aleja Solidarności 67, 03-401 Warszawa

https://orcid.org/0009-0007-0272-8045

Anna Jargieło
Military Institute of Medicine - National Research Institute, ul. Szaserów 128, 04-141 Warszawa
https://orcid.org/0009-0008-9300-4655
Karolina Kosieradzka
Praski Hospital, Aleja Solidarności 67, 03-401 Warszawa
https://orcid.org/0000-0002-2446-6396
Dominik Adamowicz
University Clinical Centre of the Medical University of Warsaw, Banacha 1a, 02-097 Warszawa
https://orcid.org/0009-0007-0386-9392
Justyna Stańczyk
National Geriatrics, Rheumatology and Rehabilitation Institute, name of prof. Eleonora Reicher in Warsaw, Spartańska 1, 02-637 Warszawa
https://orcid.org/0000-0002-6004-4406

ABSTRACT

Introduction: The complex symbiotic connection between the host and the gut microbiome, which has many important functions in the organism, provides an opportunity for dysbiosis to potentially serve as a catalyst for various health disorders. Akkermancia muciniphila, a bacterium that degadates mucin, is a noteworthy element of the human gut microbiome and has captured the attention of researchers due to its correlation with numerous diseases.

Aim of the study: The purpose of this research was to review literature and determine the impact of Akkermansia muciniphila in selected diseases. A systematic review was conducted using PubMed database.

State of knowledge: Studies have shown that reduced numbers of Akkermansia muciniphila have been associated with many diseases, including obesity, type 2 diabetes, atherosclerosis, fatty liver, some neurological conditions, inflammation, and response to cancer immunotherapies. Furthermore, the administration of this bacterium has been shown to have a positive impact on reducing obesity-related parameters, improving insulin sensitivity and

glucose homeostasis, mitigating inflammation, and enhancing the prognosis of immune checkpoint inhibitor treatment.

Conclusions: The condition and composition of the intestinal microbiome play a significant role in the development and progression of numerous diseases. Akkermansia muciniphila, as demonstrated in various studies, is an example of a bacterium associated with beneficial effects in multiple diseases. It is regarded as a promising candidate for probiotic use.

Keywords: gut microbiota; Akkermansia muciniphila; probiotic; dysbiosis; metabolic diseases.

INTRODUCTION

The collection of microorganisms that colonize the gastrointestinal tract, known as the "gut microbiome" exceeds 10^{14} microorganisms and performs specific functions in the nutrient, xenobiotics and drugs metabolism, the synthesis of certain vitamins, immunomodulation, maintaining the structural integrity of the intestinal mucosal barrier and protection against pathogens.[1,2] The intricate symbiotic relationship between the host and the microbiota makes taxonomic or functional dysbiosis a potential trigger for various health disorders, including inflammatory bowel disease (IBD), malnutrition, metabolic disorders, asthma, and neurodegenerative diseases.[3]

One of the bacteria that constitutes 1-3% of the fecal microflora and is present in most of the human population is Akkermansia muciniphila.[4] It is a strictly anaerobic, oval-shaped gram-negative bacterium that is able to use mucin as the only source of carbon, nitrogen and energy.[1] Mucin, which is a protective barrier in the intestine, plays an important role in the adhesion of the microbiota to the intestinal layers. Bacteria with the capability to degrade mucin exhibit a greater propensity to thrive in the dynamic microenvironment of the gut.[5] A.muciniphila colonizes the intestines in the first year of life and its incidence may decrease with age or disease states.[6] Since this bacterium was discovered and characterized two decades ago, numerous studies have consistently demonstrated that its absence or diminished abundance is linked to many diseases, including obesity, diabetes, fatty liver disease, inflammation, and altered responses to cancer immunotherapies.[7]

STATE OF KNOWLEDGE

Obesity

Obesity has been identified as one of the most serious public health issues of the 21st century due to its association with the occurrence of many chronic diseases, such as high blood pressure, cardiovascular disorders, stroke, diabetes mellitus type 2, osteoarthritis and some cancers. [8,9] Gut microbes have been found to play a key role in regulating host metabolism in both human and animal studies and this is why controlling the gut microbiology may be a therapeutic strategy in the prevention and treatment of obesity.[10]

Wu et al. sought to examine the enduring impact of a specific subtype of A. muciniphila on obesity and diabetes induced by a high-fat diet (HFD), while also exploring its potential in alleviating complex psychiatric disorders. The administration of this subtype of A. muciniphila led to a significant reduction in body weight gain, enhanced spatial memory in mice on a high-fat diet, and improved blood glucose regulation.[12]

Other researchers have also shown a growing interest in investigating the impact of Akkermansia muciniphila on mice that have developed obesity due to a HFD.

In a study conducted by Depommier et al. in the same year, the utilization of pasteurized Akkermansia muciniphila demonstrated a notable decrease in weight gain and fat accumulation caused by a HFD in mice used for experimentation. Notably, this effect was observed without any significant impact on cumulative food intake. At the conclusion of the study, the treated group exhibited significantly lower deposits of yellow adipose tissue in various regions, resulting in a significantly lower overall obesity rate among the treated mice.[11] Another report shows that supplementation of the selected A.muciniphila strains prevented weight gain, calorie intake, and reduced body fat mass. In addition, they improved glucose homeostasis and insulin sensitivity and had the effect of inhibiting low-grade intestinal inflammation, restoring damaged intestinal integrity and improving liver function.[13]

However, the pivotal research was a human, randomized, double-blind, placebo-controlled pilot study conducted by Depomier et al. in overweight or obese insulin-resistant volunteers. The investigation demonstrated that the oral administration of 10^{10} live or pasteurized A. muciniphila for a duration of three months was deemed safe and well-tolerated. Additionally, supplementation with pasteurized A. muciniphila slightly reduced body weight, body fat mass, and hip circumference compared to baseline.[14]

Diabetes mellitus type 2 (DMT2)

Another common metabolic disease, very often associated with obesity, is diabetes mellitus type 2. Diabetes is a disease characterized by high blood glucose levels, insulin resistance and relative insulin deficiency.[15] In studies on the association of the gut microbiome and DMT2, Akkermansia was shown to be negatively correlated with this disease.[16]

A 2021 study by Yun et. al showed that A. muciniphila decreased in mice with type 2 diabetes, and that feeding with prebiotics normalized the amount of this bacteria, which correlated with an improvement in the metabolic profile. In addition, treatment with alive A. muciniphila has been shown to reverse metabolic disorders induced by a high-fat diet (HFD), including fat mass gain, metabolic endotoxemia, adipose tissue inflammation, and insulin resistance.[17] The findings of the study conducted by Depomier et al. demonstrate that A. muciniphila improved insulin sensitivity, decreased insulinemia and total plasma cholesterol, lowered the levels of relevant blood markers for liver dysfunction and inflammation, while the overall structure of the gut microbiome remained unchanged.[14] Different study in which diabetic patients were given a probiotic formulation containing A. muciniphila the supplementation improved postprandial glucose control.[18] Recent evidence also suggests that the gut microbiota is the site of metformin's action, and A. muciniphila alteration is involved in the anti-diabetic effect of metformin, a widely used first-line drug for type 2 diabetes.[19] Diabetic participants taking metformin had a higher relative abundance of Akkermansia muciniphila, supporting the hypothesis that metformin alters the composition of the gut microbiota by enriching this the mucin-degrading bacteria.[20] Metformin treatment also improved the glycemic profile of the HFD-fed mice and showed a greater abundance of Akkermansia bacteria. Oral administration of Akkermansia muciniphila to HFD-fed mice without metformin significantly increased glucose tolerance, suggesting that pharmacological manipulation of the gut microbiota could be a potential treatment for DMT2.[21]

Cardiovascular diseases (CVD)

Cardiovascular diseases are one of the leading causes of death and disability in developed countries.[22] Also in this case the relationship between the occurrence of CVD and the composition of the intestinal microbiota has been noticed.[23] The gut microbiota and its metabolites play a role in the origin and development of cardiovascular diseases including atherosclerosis, hypertension, heart failure, atrial fibrillation, and myocardial fibrosis.[24] In a study on the effect of A. muciniphila on atherosclerotic lesions in mice, it was determined that this bacterium attenuates atherosclerotic lesions by alleviating the

inflammation caused by metabolic endotoxemia by restoring the intestinal barrier.[25] Different study shown that administration of A. muciniphila improved damage of the elastic fibers in the vascular wall, inhibited the infiltration of inflammatory cells and protected the integrity of the medial septum in the abdominal aorta of mice, indicating that A. muciniphila can inhibit the formation of aortic aneurysms in mice.[26]

Nonalcoholic fatty liver disease (NAFLD)

NAFLD is a chronic liver disease and a hepatic manifestation of the metabolic syndrome. The exact cause of NAFLD is unidentified, but it is thought to be linked with abnormal lipid metabolism associated with obesity and metabolic syndrome.[27] Preliminary findings from obesity research indicate that the intestinal microbiota (IM) might contribute to the onset of obesity and metabolic syndrome. These results suggest that IM could potentially be involved in the development of non-alcoholic fatty liver disease (NAFLD).[28]

An animal model study investigated that differences in the composition of the microbiome can determine the response to high-fat diet in mice. These results further demonstrate that IM contributes to the development of NAFLD independently of obesity.[29] A. muciniphila also prevents hepatic steatosis by regulating the expression of genes that regulate fat synthesis and inflammation in the liver.[30] Human studies do not link the development of NAFLD to any particular bacterium but suggest that a dysbiotic environment exists in NAFLD patients.[31]

Inflammatory bowel diseases (IBD)

Despite being recognized as "foreign" by the host's immune system, the presence of bacteria in the mammalian intestine typically results in a state of immune homeostasis, characterized by a balanced and non-inflammatory interaction between pro- and anti-inflammatory immune responses in healthy individuals. This phenomenon is referred to as intestinal immune homeostasis. Derrien et al. conducted a study in which they colonized the gut of microbe-free mice with different types of bacteria. This colonization resulted in changes in the host transcriptomes, with a tendency towards balanced immune responses, indicating the development of tolerance to A. muciniphila. Based on the absence of microscopic signs of intestinal disease, stress, or any discomfort in germ-free mice following microbial colonization, it can be inferred that the colonization of A. muciniphila resulted in a non-inflammatory commensal interaction and intestinal tolerance.[31]

These findings prompted researchers to investigate the connections between the gut microbiota's composition and inflammatory bowel diseases (IBD). They discovered that the

microbiome linked to ulcerative colitis (UC) remained consistent during periods of remission and exhibited similarity among all UC patients.[32] Akkermansia muciniphila, the most prevalent mucolytic bacterium found in the control group, exhibited reductions in both Crohn's disease and ulcerative colitis cases.[33] Additionally, the results indicated that lower levels of A. muciniphila were correlated with higher inflammatory scores.[34]

Neurological disorders

Recent studies have established a correlation between A. muciniphila and various neurological disorders, in addition to its positive impact on the gut. The bidirectional relationship between the brain and the gut, known as the brain-gut axis, plays a significant role in the connection between risk factors for depression and the exacerbation of inflammatory bowel disease (IBD), according to emerging evidence.[35]

Study by Chen et. al revealed that dysbiosis of the gut microbiota caused by chronic restraint stress (CRS), a credible procedure for establishing a model of depression in mice, led to colonic mucus impairment and the subsequent onset of colitis. Supplementation of A. muciniphila was found to safeguard colonic mucus and prevent the worsening of colitis. Moreover, the presence of Akkermansia muciniphila was notably diminished in mice experiencing CRS and in patients with ulcerative colitis, who also had depression.[36]

Several cross-sectional studies have indicated alterations in the gut microbiota of individuals with Autism Spectrum Disorder (ASD), including a reduced abundance of Akkermansia. This suggests that a combination of decreased levels of beneficial bacteria and increased levels of detrimental bacteria potentially plays a role in contributing to ASD symptoms.[37]

Another neurological disease that has been demonstrated to have a connection with the gut microbiota is amyotrophic lateral sclerosis (ALS). It is multifaceted neurodegenerative condition characterized by clinical manifestations that can be influenced by a combination of genetic and unidentified environmental factors. The administration of Akkermansia muciniphila to transgenic mice (Sod1) susceptible to ALS, demonstrated alleviation of ALS symptoms in the presence of this particular bacterium.[38]

Emerging research has highlighted the significant implications of gut microbes in Alzheimer's disease (AD)[39], a progressive neurodegenerative disorder affecting the central nervous system. AD is primarily characterized by cognitive impairment, memory dysfunction, diminished self-care capacity, and behavioral decline. Substantial disparities in the composition of gut microbiota have been observed between individuals with AD and healthy controls, implying that microbial composition may contribute to the progression of cerebral

amyloidosis, a hallmark feature of AD.[40] A study in transgenic mice (APP/PS1) showed that the overall abundance of A. muciniphila decreased with age. After a 6-month treatment period with this bacterium, the mice demonstrated a considerably reduced learning time, suggesting that Akkermansia has the potential to alleviate learning and memory impairments in AD mice. Furthermore, the intervention led to a decrease in Aβ plaque deposits and Aβ levels in the brains of mice, independent of any changes in brain structure.[41]

Cancer treatment

In recent years, there has been a growing focus on understanding the impact of the microbiota, which refers to the community of microorganisms residing on the body surfaces and in the cavities of the host, on the development of cancer. The microbiota creates a microenvironment for host cells that can either foster or inhibit the formation of cancer. The intestinal microbiota, in particular, plays a pivotal role in host physiology, and its composition and activity are directly influenced by established cancer risk factors such as lifestyle, diet, and inflammation.[42]

Routy et al. found that immune checkpoint inhibitor (ICI) resistance in the treatment of lung and kidney cancer can be attributed to an aberrant composition of the gut microbiome. The study reached a conclusion that the administration of antibiotics impeded the clinical benefits of ICI in patients with advanced cancer. Furthermore, when fecal microbiota transplantation (FMT) was performed from cancer patients who exhibited a positive response to ICI to germ-free or antibiotic-treated mice, it resulted in a reduction of the antitumor effects of PD-1 blockade. Conversely, FMT from non-responders did not have the same effect. Analysis of stool samples collected from patients at the time of diagnosis unveiled significant correlations between clinical responses to ICI and the relative abundance of Akkermansia muciniphila. Notably, oral supplementation of A. muciniphila subsequent to FMT using non-responsive fecal samples reinstated the efficacy of PD-1 blockade.[44]

The prognostic importance of Akkermansia muciniphila has been also validated through multivariate analyses and interaction studies, demonstrating a strong association with the prognosis of advanced non-small cell lung cancer (NSCLC) patients undergoing treatment with PD-1 blockade. The abundance of this bacteria showed a correlation with clinical benefit, as indicated by an increase in objective response rate and overall survival. Furthermore, a study conducted on mice revealed that the absence of Akkermansia muciniphila in their fecal samples resulted in resistance to PD-1 blockade treatment.[43]

CONCLUSIONS

The condition and composition of the intestinal microbiome play a significant role in the development and progression of numerous diseases. Akkermansia muciniphila, a promising probiotic that effectively utilizes gastrointestinal mucin, is intricately intertwined with host metabolism and immune response. Research has consistently demonstrated that diminished levels of Akkermansia muciniphila have been linked to a range of diseases, such as obesity, type 2 diabetes, atherosclerosis, fatty liver disease, certain neurological disorders, inflammation, and altered responses to cancer immunotherapies. The administration of this bacterium holds great promise as a therapeutic target for this microbiota-related disorders. This comprehensive review provides compelling evidence supporting the effectiveness of A. muciniphila as a beneficial bacterium in reducing obesity-related parameters, enhancing insulin sensitivity and glucose homeostasis, mitigating inflammation, and enhance the prognosis of immune checkpoint inhibitor treatment. It can be confidently stated that A. muciniphila holds potential as a probiotic candidate, nevertheless, further research is required, particularly in human subjects.

Author's contribution

Conceptualization, AW, DP, IŁ; methodology, AW, KK; check, AW, PR, AC; resources, AW, AJ, KK; writing - rough preparation, AW, DA; writing - review and editing, AW, JS, DA, IŁ. All authors have read and agreed with the published version of the manuscript.

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