AKKERMANSIA MUCINIPHILA; FUNCTIONAL AND PROBIOTIC PROPERTIES IN THE GASTROINTESTINAL TRACT

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Abstract

The development of microbial communities in the human gastrointestinal tract begins immediately after birth. Human gut microbiota is comprised of the millions of bacterial microbial communities that are effective in protecting the health of the host organism and share the common site with the host. At the same time, the mucus layer formed by the epithelial cells surrounding the intestinal surface protects intestines against intestinal external factors and meets the microbiota's need for nutrition. It was found recently that one of the intestinal bacteria isolated from human fecal samples, *Akkermansia muciniphila,* meets the need for nutrition of itself and other bacteria by grafting to the mucus layer and providing the monomer by degrading mucin which is the main component of mucus. *Akkermansia muciniphila,* which has positive effects on human gut microbiota, decreases in microbiota in the presence of certain chronic diseases. Recent studies have shown that decreasing amounts of *Akkermansia muciniphila* was also found in the feces samples of individuals with chronic diseases such as obesity and diabetes, and as well as found in the gastrointestinal tract, too.

Keywords: *Akkermansia muciniphila, gut microbiota, probiotic properties, obesity, diabetes*

INTRODUCTION

The early stages of development in vertebrates are usually seen in chorion, a sterile medium that does not contain any microorganisms. From birth, the microbial ecosystem quickly develops in the gastrointestinal tract and develops specifically with the influence of environmental factors. The evolving intestinal microbiology allows for the provision of energy to the host and the absorption of nutrients, the trophic effect of the intestinal epithelium, the maintenance of the integrity and completeness of the intestinal tract, the maintenance of intestinal homeostasis, and the defense against pathogenic bacteria [1].

The primary function of the intestinal tract is to provide ready-to-use nutrients to the host. The lubricant and protective mucus layer in the intestinal lumen, which develops during the development of the intestinal tract, provides protection of the intestinal lumen as well as host-microbial interactions. Various bacteria attach themselves to the mucus layer and use it as energy and carbon source. So, these bacteria do not have to compete with other bacteria in the intestinal lumen, and they do not need the nutrients that will come from the host [2]. In addition, these bacteria that are mucous-colonized help to restore the microbiota while protecting the host from intestinal microbes [3].

Mucin, a major component of the mucus, is composed of amino acids and oligosaccharides and is a food source for intestinal bacteria. Some bacteria have an enzyme system that breaks down the mucin and prepare the environment for use by other bacteria in microbiota by converting the oligosaccharide chain found in its structure into fucose, galactose, N-acetyl-glucosamine, N-acetyl-galactosamine, sialic acid, sulphate and

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disaccharides [4]. Mucin degradation seems to be a pathogenic event for the gastrointestinal system, but it is used as an energy source in the intestinal microbiota. Only 1% of the colonic microbiota results in mucin degradation. In this way, the source of energy and nutrients are produced for the bacteria that are found in intestinal microbiota and can only use monomers [5]. Mucin degradation provides competition advantage and survival advantages to the host in the absence of nutrients such as starvation, malnutrition and total parenteral nutrition. [6].

Human Gut Microbiota

The concept of human microbiota was first described by Joshua Lederberg in the scientific world. In the definition by Lederberg, microbiota is an ecological community containing commensal, symbiotic and pathogenic microorganisms that are ignored but the determinants of both disease and health conditions, which share a common body area with the host [7].

Colonization of the human intestine with bacteria begins immediately after birth. After a birth canal, a complex population of bacteria begins to form in newborns [8]. Evidence that immediate contact with microbes during labor can affect the development of intestinal microbiota is due to the similarity between infant intestinal microbiota and the vaginal microbiota of their mothers [9].

Intestinal (gut) microbiota is a complex environment that affects the normal structural and functional development of the mucosal immune system in a significant and positive manner and functions like the organ system [10]. The intestinal microbiota consists of trillions of commensal microorganisms that maintain the integrity of the mucosal barrier function in the human intestines. Microbiota is required for the maturation of gut-associated lymphoid tissues (GALT), the secretion of IgA and the production of antimicrobial peptides, which are necessary for immunity. The normal intestinal microbial population varies from 500 to 1000 different species depending on the distal or proximal parts of the intestine, the outer layers from the inner layers, age, dietary habits, geographical origin, delivery pattern, antibiotic therapy and environmental stimuli [11].

The intestinal microbiota maintains a symbiotic relationship with the intestinal mucosa and has important metabolic, immunological and intestinal protective functions in healthy individuals [12]. The intestinal microbiota is active on host living physiology from nutritional status to behavior and stress response. Under normal conditions, the commensal bacteria and the main living organism have many common advantages that protect the intestinal barrier integrity [11]. Bacteria in the microbiota protect the host organisms from outbreaks pathogenic microorganisms. Thus, the host is protected against the outbreak of infections.

Intestinal Ecology of *A. muciniphila*

Akkermansia muciniphila is one of the important bacteria found in the intestinal flora that provides mucin degradation. Metagenome data demonstrate that at least eight different species of *Akkermansia gonorrhoeae* have colonized human intestines other than A. *muciniphila* and that even simultaneous colonization of different species can occur [6]. Subsequent studies based on the cloning and sequencing of the 16S rRNA gene revealed that A. *muciniphila* is also present in stool specimens as well as in different parts of the human mucosa.

A. muciniphila has received the name of Dr. Antoon Akkermans, a Dutch microbiologist recognized for his many contributions to microbial ecology. In 2004, it was isolated in search of the identification of new mucinous bacteria from human feces [6]. It was first found in a fecal sample taken from a Caucasian woman. Later on, in animal studies, they observed the presence of *A. muciniphila* in the feces of animals such as rodents, rabbits, donkeys, pigs and horses, and therefore in intestinal microbiota. This bacterium is the first bacterial species obtained from man that belongs to the *Verrucomicrobia* phylum. *A. municiphila* is an anaerobe belonging to the upper branch of *Planctomycetes-Verrucomicrobia-Chlamydiae*, a gram-negative bacterium present in the intestinal

microbiota [5]. During the isolation phase of *A. muciniphila* the mucin, which is the only carbon source in the environment, is used [13].

A. municiphila uses carbon and nitrogen in mucin as a source of energy. A healthy person has 3-5% of the intestinal flora. The presence of *A. mucinicipila* is greater in colon than the ileum [2]. Factors such as eating habits, race and environmental factors may cause the ratio in the dominant flora to be different. The presence of *A. muciniphila* is inversely proportional to body weight and diabetes rate [14]. The presence of *A. muciniphila* in the microbiota may vary depending on the body weight, the thickness of the mucus layer and the immunity status of the host. These factors also vary in different phases of life and in the presence of any disease that can be seen in the host [15].

A. muciniphila acts as a protective against type 1 Diabetes Mellitus, inflammatory bowel diseases, atopic dermatitis and autism by protecting the body against inflammation through its anti-inflammatory properties which are thought to be possessed. The amount of *A. muciniphila* in intestinal microbiota is inversely proportional to the aging process. In a study on obese mice with leptin deficiency, which were aged 16 and 8 weeks; it was observed that the amount of *A. muciniphila* was lower in 16-week-old mice compared to 8-week-old mice. In the present study, it was observed that as the amount of *A. muciniphila* decreased, the glucose clearance and tolerance decreased, too. The subjects, which were in the study, also had impaired glucose tolerance [16].

A. muciniphila as a Probiotic

Probiotics have been described by the World Health Organization (WHO) and the United Nations Food and Agriculture Organization (FAO) as living microorganisms that have healthy effects on the host organism when given in sufficient quantities [7].

Probiotics may improve the functionality of the microbial community found in the intestines, or may provide useful functions in the gastrointestinal tract. Probiotics can also influence the composition and function of microbial communities through competition for nutrients, production of growth substrates or inhibitors, and modulation of intestinal immunity [7].

Probiotics may inhibit the growth of other microorganisms by producing antimicrobial agents or metabolic compounds, or they may be of interest for the receptor and binding regions of other microbes found in the intestinal mucosa [17].

While there is no adequate study of the use of *A. muciniphila* as a probiotic; however, experimental studies may be developed since it is likely to be a potential probiotic [18]. Experimental studies have demonstrated that prebiotic consumption has a positive effect on the presence of *A. muciniphila,* although there is insufficient evidence to use it as a probiotic. In one study, the presence of oligofructose, which is a prebiotic, was restored with the presence of *A. muciniphila,* and improvement in intestinal barrier and metabolic parameters was observed. In fact, *A. muciniphila* does not evolve only in the presence of oligofructose in vitro. This indicates that the complex cross-nutritional interactions contribute to bacterial growth. In studies on oligo-fructose-consumed rats, it was observed that the number of goblet cells increased, resulting in increased mucus production and mucus layer thickening [14]. The amount of *A. muciniphila* that provides mucus layer degradation also increases due to mucus increase.

Interaction of *A. muciniphila* with diet

It has been debated since the 1960s by the scientific community that the diet directly affects intestinal microbiota. Recently, the distributions of intestinal microbiota and gene content have been examined using animal models to determine the relationship between composition and function of diet and intestinal microbiota. The nutrients consumed during the studies may have direct effects on the microbiota, leading to changes in the biochemical reactions in the intestinal lumen. In studies on mice that do not harbor any microorganisms, mice were transplanted with human feces microbiota and the mice were fed a Western-style diet with high fat

and high sugar content. As a result of the study, it was observed that the intestinal microbiota changes in terms of structure and distribution of species [7].

Different dietary practices and pharmaceutical treatments may have an impact on the amount of *A. muciniphila* in the microbiota. Individuals' eating habits also affect the amount of *A. muciniphila.* Consumption of nutrients and food groups, including polyphenols, fructooligosaccharides, conjugated linoleic acid, oatmeal, resistant starch, fermentable oligosaccharides, disaccharides, monosaccharides and polyols, affects *A. muciniphila* development and amount positively [15].

Contrary to this situation, consumption of high fat diets affects microbiota in the negative direction. The consumption of high-fat diets decreases the amount of *Bacteriodetes* in the intestines and increases the amount of F*irmicutes* and *Protebacteria* bacteria by affecting the intestinal microbiota as well as the formation of obesity. This change in the intestinal flora causes the development of obesity and other chronic diseases. As a result of this change, the energy use and storage capacity increases while the risk of intestinal permeability and inflammation increases. High-fat dietary consumption decreases the amount of *Akkermansia muciniphila* in the intestinal flora, whereas the amount of *Lactoococcus* from the *Firmicutes* bacterial arm increases, contrary to the percentage of increased fat in the body [19]. Gut disbodies, increased levels of fasting glucose and glucose intolerance are seen as a result of this type of dietary intake.

Through the treatment of *A. muciniphila,* the increase in body fat mass, metabolic endotoxemia, adipose tissue inflammation, and insulin resistance caused by consumption of high-fat diets are alleviated by the mechanisms involved in the restoration of adequate intestinal mucus production by the goblet cells. At this point, the barrier function in the intestines is improved. This mucus barrier produced by the goblet cells is supported with antimicrobial peptides that are associated with innate immunity and produced by the Paneth cells.

According to the work done by Elleilde and colleagues, the presence of *A. muciniphila* bacteria in intestinal microbiota has been observed to increase in caloric restriction in humans, mice, hamsters and snakes. As a result of the mucosal analysis, it was observed that the amount of *A. muciniphila* was higher in healthy subjects, and conversely, the amount was lower in subjects with inflammatory bowel disease [16].

Studies have shown that the amount of *A. muciniphila* increased in intestinal microbiota when the fermented or non-fermented form of Flos Lonicera which is used as a traditional herbal treatment in East Asia, was given to rats. An increase in the amount of *A. muciniphila* was observed with the Flos Lonicera supplement, which was fermented or not fermented, although the rats were fed a high fat diet [20].

Beneficial effects of *A. muciniphila* on health (obesity, diabetes etc.)

While healthy intestinal microbiota is important for human health, changes in intestinal microbiota cause chronic and / or non-chronic diseases. Exact evidence shows that intestinal microbiota affects whole-body metabolism by affecting energy balance, intestinal permeability, serum lipopolysaccharides, and metabolic inflammation. This interaction is thought to be related to obesity and related disorders. Obesity and diabetes, which are common worldwide, are characterized by inflammation, intestinal microbiota exchange and intestinal barrier impairment [14]. Therefore, intestinal microbiota is directly related to obesity, type 2 diabetes mellitus and insulin resistance [21].

There are also studies in which *A. muciniphila* bacteria are given as supplements from the outside. In a study of obesity-prone mice, *A. muciniphila* supplements were administered orally to subjects at defined ratios and at specified time intervals. After 1-week supplementation, the experiment was continued for 5 weeks by applying a diet containing high amount of fat and high amount of sucrose. At the end of the study, metabolic parameters of the subjects were improved despite high fat and

high sucrose diets consumed. At the same time, when the body weight and total fat amount of the subjects were examined, it was seen that there was a significant decrease. Biochemical values were found to have significant improvement especially in total cholesterol and triglyceride levels. It has also been shown that insulin resistance, which is also present, is ineffective due to the decrease in glucose and insulin levels [22]. In another study done, *A. muciniphila* supplements did not show any decrease in the amount of *A. muciniphila,* which normally declines in aging process and intestinal flora. At the same time, goblet cells in the intestines and in the villi were observed in terms of both number and density in terms of unit surface area. Compared with subjects with diabetes mellitus supplemented with *A. muciniphila* and subjects with diabetes treated with metformin, the glucose tolerance level was found to be close to each other. However, the same bacterium did not show the same metabolic activity when given at low doses or when the heat treatment reduced the viability [23].

The use of metformin in the Biguanide drug group, which is effective in insulin receptor sensitivity, promotes the growth of this bacterium in vitro, while increasing the percentage of *A. muciniphila* in microbiota in mice [13]. The amount of metformin in the intestinal mucosa was found to be higher than that of other tissues in the body tissues examined in the performed studies. These findings increase the likelihood of metformin having direct and indirect effects on intestinal microbiota and contribute to the antidiabetic effects of the drug. In studies conducted on mice, intestinal microbiota was found to be similar to that of mice fed a normal diet, due to the use of metformin in diabetic mice which are fed a high fat diet (60% fat, 20% protein, 20% carbohydrate, kcal / 100 gr). This decrease was minimized by metformin treatment despite the reduction of *A. muciniphila* in the microbiota of mice that did not receive metformin treatment under normal conditions and were fed a high fat diet. Metformin has been observed to remove the adverse effects of high fat diet on microbiota at this point. At the same time, metformin treatment increased goblet cells that produced intestinal mucosa, and the increase in goblet cells was found to be directly proportional to the presence of *A. muciniphila* [23].

It has been shown that the development of atherosclerosis, one of the main components of cardiovascular mortality, is associated with bacterial infections and intestinal microbiota. When atherosclerotic lesions were examined, it was determined that there are some bacterial species in the lesions or some bacterial DNA strains were found. Pyrosequencing technique has also shown that the lesions are from the oral cavity and the connective microbiota of the bacteria in the lesions. With this finding, it is thought that the direct effect of on the development of the disease [24].

Functional Properties of *A. muciniphila*

A. muciniphila is a bacterium found in intestinal microbiota that provides mucin degradation. The presence of this bacterium in the microbiota is reduced in bowel diseases such as Crohn's disease and ulcerative colitis as well as with aging [14].

A. muciniphila produces energy and nutrients for other bacteria in the intestinal microbiota by producing fucose, galactose, N-acetylglucosamine, N-acetylgalactosamine, sialic acid, sulfate, disaccharides and monomers with mucin degradation. In addition to the benefits provided by the bacteria, mucin degradation provides the opportunity to live for the host when it is not possible to reach the food directly, such as starvation, total parenteral nutrition and malnutrition [5].

Studies have shown that the restoration of the amount of *A. muciniphila* in the intestines led to a reduction in dietary weight gain, a decrease in fat mass and an improvement in fasting hyperglycemia. This effect is due to the fact that in the process of energy metabolism, especially in adipogenesis and fatty acid oxidation in the adipose tissue become proper as it is supposed to be. This effect of *A. muciniphila* bacteria is thought to restore metabolic endotoxemia and adipose tissue metabolism by restoring the intestinal barrier function [14].

CONCLUSION

A. muciniphila is a mucin degrading bacterium that is related to colonic health. By doing mucin degradation, *A. muciniphila* creates an appropriate environment to the other living bacteria. Apart from creating medium for other living organisms, *A. muciniphila* is also linked to chronic diseases such as diabetes, obesity etc. Especially in the chronic disease stage, the ratio of this bacterium decreases and gut flora is destroyed. According to the result of studies, replacement of *A. muciniphila* via supplements provides better prognosis for chronic diseases, like especially obesity and diabetes. Tests that are conducted on animals are promising for the new treatment method for certain chronic diseases. More animal and human based studies may elucidate to the use of *A. muciniphila* as a treatment way.

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