Akkermansia muciniphila

Subjects: Microbiology

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Akkermansia muciniphila is one of the early occupants (in first year of life) of the intestinal tract with 108 cell/gm or more than 1% of total faecal microbes.

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1. Introduction

Disparity in energy consumption and energy expenditure is manifested as weight gain and adiposity [1]. Obesity has been recognized as one of the most severe public-health issues in the 21st century due to its detrimental impact on overall quality of life [2]. Obesity is associated with the prevalence of many chronic diseases, such as cardiovascular disorders, certain tumors, type 2 diabetes, elevated blood pressure, stroke, osteoarthritis, gallbladder disease, and psychosocial issues [3]. Overweight and obesity were estimated to cause 3.4 million deaths globally in 2010 [4], and have affected more than 671 million in 2016 [5]. Obesity has recently been shown to be a progressive phenomenon in both developed and developing countries [6], and the prevalence of obesity has tripled between 1975 and 2016 according to the WHO [7]. Rural areas have the highest increase compared to cities, meaning that dramatic changes have happened in the lifestyle [8]. The main culprit of such changes was overconsumption of animal products, refined grains and added sugars, especially in forms of sweetened beverages [9]. On the other hand, macronutrients including carbohydrates and proteins have been demonstrated to be the most influential in restructuring the gut microbiota [10]. Simply put, the variations in the gut microbiota rely on the variations presented in the carbohydrates (i.e., sugars) [10].

In both human and animal studies, gut microbes have been reported to play a pivotal role in regulating host metabolism [11]. Tens of trillions of microorganisms and more than 1000 different species of bacteria, with at least 3 million genes, have been identified in the microbiota of the human intestine. The classification of species among members of the gut community is enormous because the distribution and composition of gut microbiota differs at different anatomical sites of the intestine and is likely to be affected by intrinsic and extrinsic factors, including lifestyle, diet, and health status [12]. The colon was reported to be the most inhabited site, with approximately 10^7 to 10^8 cells of *Clostridium* Type IV and XIV, *Bacteroidetes*, *Bifidobacterium* and *Enterobacteriaceae* [13]. *Firmicutes* and *Bacteroidetes* represent 64% and 23%, respectively, of the microbiota.

Not only the gut microbiota composition has been reported to exhibit strong pathological and physiological associations with obesity and metabolic syndrome [14], but also the ratio of Firmicutes to Bacteroides was found to be crucial [15]. Accordingly, the ratio of Firmicutes to Bacteroides in adults was found to increase as the BMI increased [16]. However, in conflict with these results, several studies did not observe any modifications of the Firmicutes/Bacteroidetes ratio, or even reported a decreased value in obese animals and humans [17].

Mucin, a protective barrier against xenobiotics in the intestine, plays a great role in the microbiota adhesion to the intestinal layers. The bacteria that have the ability to degrade mucin are more advantageous to survive the changing microenvironment of the intestine [18]. In this term, probiotics, to be effective, should adhere to and interact with mucin layers, while pathogenicity of harmful microbes would increase if they were mucin-degrading microorganisms [19].

Akkermansia muciniphila is one of the early occupants (in first year of life) of the intestinal tract with 10^8 cell/gm [19] or more than 1% of total faecal microbes [20]. *Akkermansia muciniphila* can use mucin as its sole source of carbon and nitrogen. It is considered one of the “next-generation probiotics”, and the knowledge about it has grown exponentially since its first isolation in 2004 [20]. Since it is the only member of *Verrucomicrobia* (phylum) in the gut of mammals, it is easier to be detected using 16S rRNA gene sequence. A large number of studies has shown that the abundance of *Akkermansia* in the gut was correlated with host health and disease status [21] and its number as a beneficial microorganism is decreasing by aging [19]. As a matter of fact, one study showed that *A. muciniphila* has modulated the endocannabinoid (eCB) system. In the context of obesity, type 2 diabetes and inflammation, eCB is an essential

regulatory system reported to include glucose and energy metabolism [22]. Human and animal trials showed a positive correlation between *A. muciniphila* intervention and obesity and metabolic disorders [23]. Moreover, it has been demonstrated that *A. muciniphila* can be involved in anti-cancer immune therapy [24] and may prevent from atherosclerosis [25].

Cross-talk between *A. muciniphila* and the host epithelial cell in the intestine is well documented. Supplementation with *A. muciniphila* and the use of other strategies such as prebiotics or food components that increase the abundance of this bacterium in the population of gut microbiota may be a beneficial novel approach to obesity management [26].

2. *A. muciniphila* in the Improvement of Obesity Parameters

Ten studies have investigated the effect of *A. muciniphila* supplementation on the vital obesity parameters and metabolic disorder in C57BL/6J mice models [27][28][29][30][31][32][33][34][35][36]. In 2020, Yang et al. [27] found that the body weight gain, caloric intake, mesenteric fat weight, subcutaneous fat weight, epididymal fat weight, total fat and energy efficiency significantly decreased in high fat diet (HFD)-fed mice after treatment with pasteurized culture of *A. muciniphila*. Furthermore, authors examined the effects of bacterial supplementation on the colonic gene expression of Glucagon-like peptide-1 (GLP-1) and Peptide YY(PYY), which are the intestinal hormones with appetite suppressing and anti-diabetic plus anti-obesity properties. The treatment with *A. muciniphila* has increased PYY's mRNA level, and significantly upregulated GLP-1 gene expression.

To further demonstrate whether *A. muciniphila* has to be alive to exert its metabolic effects, Everard et al. [28] have compared the effect of viable *A. muciniphila* administration with that of heat-killed *A. muciniphila* and found that viable *A. muciniphila* normalized metabolic endotoxemia caused by diet, fat storage, adipose tissue metabolism, and CD11c adipose tissue marker. Similarly, *A. muciniphila* treatment decreased body weight and improved body composition without changes of food intake. Notably, these effects were not observed after administration of heat-killed *A. muciniphila*.

Interestingly, other trials [29][30] observed that without affecting the accumulated food intake in the HFD-fed group, pasteurized *A. muciniphila* significantly decreased body weight gain, total adiposity index, and fat mass gain; additionally, the fecal caloric content significantly increased. Finally, transcript levels of the main glucose transporters GLUT2 and SGLT1 mRNA were significantly lower than in the normal diet (ND) fed group.

Depommier et al. [29] reported that five weeks of supplementation with *A. muciniphila* at a dosage of 10^8 CFU decreased body weight gain and significantly reduced fat mass as well as increased lean mass in mice fed with a ND. Moreover, the visceral fat weight, which was more closely related to insulin resistance pathogenesis, was more clearly reduced. Furthermore, supplementation with *A. muciniphila* was unaltered in food intake and fecal triglyceride content. Shen et al. [19] showed that treatment with *A. muciniphila* maintained body weight and food intake compared to control group.

Plovier et al. [32] found that daily treatment of 2×10^8 CFU of *A. muciniphila* live cells reduced HFD-induced weight gain and fat mass gain (by about 40–50%). Additionally, they observed that the same dose of pasteurized *A. muciniphila* gave a greater effect than unpasteurized culture regardless of food consumption. Furthermore, the mean adipocyte diameter is normalized, and plasma leptin is significantly lower in mice treated with pasteurized *A. muciniphila* compared to control HFD fed mice. Notably, same results were not detected in mice treated with the unpasteurized culture. The same study revealed that mice fed with pasteurized *A. muciniphila* had a higher fecal caloric content than the other groups, implying that pasteurized culture administration reduces caloric absorption. This could play a significant role in the body weight decrease and fat mass gain shown in this group. Corresponding to what was observed with the pasteurized microorganism, the treatment with Amuc_1100*, the outer membrane protein of *A. muciniphila* produced in *E. coli*, resulted in lower body weight and fat mass gain as compared to untreated HFD fed mice, regardless of food consumption. It also helped to correct the higher adipocyte diameter caused by the HFD.

Wu et al. [33] demonstrated that in both HFD and ND groups, *A. muciniphila* GP01 treatment reduced food intake and body weight. Accordingly, in the HFD group, mice ingested about 20.9 g of food daily, which was marginally higher than the amount ingested by the mice in HFD with GP01 gavage group. Comparably, the mice on the ND group ingested about 18.2 g of food per day, which was marginally more than the mice on the ND with GP01 group ingested. Moreover, after 30 weeks, the HFD mice had significantly higher body weights than the HFD-GP01 mice, and ND fed mice had a significantly higher body weight than the ND plus GP01 fed group.

Ashrafian et al. [34] reported that the HFD-mice group revealed an increase in body weight after 3 months. Obese mice were treated with *A. muciniphila*-derived extracellular vehicles (EVs) and demonstrated a substantial reduction in food consumption as well as a low level of body weight gain. As a result, obese mice feeding with *A. muciniphila* live cells

caused body and epididymal adipose tissue (EAT) weight loss, but had a lower impact on body weight and adipose weight than its EVs. Notably, both interventions showed a substantial impact on body weight in ND mice, while food intake does not change. Furthermore, both the bacterium and EVs significantly reduced adipocyte size in HFD-fed mice, with the results of EVs being more observable. Finally, in comparison to the other groups, the ND group treated with *A. muciniphila* and its EVs had the smallest adipocytes.

Contradictory, Kim et al. [35] and Deng et al. [36] reported that no difference in weight gain was observed between groups treated and not non-treated group with *A. muciniphila*. Deng et al. [36] showed that the size of adipocytes in inguinal white adipose tissue (iWAT) and epididymal white adipose tissue (eWAT) was significantly increased by HFD. However, treatment with cells of strains GP01 and GP25 alleviate the effect. The diameter of inguinal adipocytes was reduced more with cells of the strain GP01, but browning was not observed in iWAT or eWAT. They also noticed that HFD mice's scapular brown adipocytes changed from multilocular to unilocular adipocytes, a process known as brown adipose tissue (BAT) whitening. Interestingly, *A. muciniphila* treatment greatly decreased the amount of unilocular adipocytes in HFD mice, which alleviating the whitening of BAT.

3. *A. muciniphila* in the Improvement of Insulin Sensitivity and Glucose Homeostasis

The results of one study [27] showed that in the HFD group, the fasting blood glucose level, determined by oral glucose tolerance test (OGTT) immediately before glucose intake (0 min), was significantly higher than in the normal fed group. However, this parameter was substantially depleted by the treatment of HFD-fed mice with *A. muciniphila*. The same authors found that in the HFD group, the OGTT area under the curve (AUC), serum insulin level, homeostatic model assessment for Insulin Resistance (HOMA-IR), and hepatic gene expression of G6Pase (an enzyme involved in glucose production) were significantly higher than in the normal group. However, the HFD group treated with *A. muciniphila* significantly reduced the levels of these four parameters. These results also showed that A. muciniphila significantly increased the hepatic GLUT2 gene expression, improving regulation of glucose transport in the liver. Moreover, this new generation probiotic significantly upregulated the expression of two important gut hormone genes, GLP-1 and PYY, involved in the appetite suppressing and anti-diabetic plus anti-obesity properties, respectively.

Everard et al. [28] demonstrated that the treatment with *A. muciniphila* completely reversed diet-induced fasting hyperglycemia and regulate the homeostasis of glucose. These effects were associated with a dramatic reduction in the expression of the hepatic glucose-6-phosphatase and the consequent drop in gluconeogenesis; insulin resistance index was also decreased after treatment. Moreover, after OGTT, viable *A. muciniphila* was found to significantly reduce plasma glucose levels, whereas heat-killed *A. muciniphila* exhibited glucose intolerance similar to that of HFD mice. On the contrary, Zhao et al. [30] found *A. muciniphila* treatment did not significantly affect the fasting blood glucose level in fed NCD mice. However, the authors reported that glucose tolerance, as reflected by the intraperitoneal glucose tolerance test (IPGTT) and the corresponding reduction of AUC, were greatly improved by *A. muciniphila* supplementation in ND fed mice. Although fasting plasma insulin levels were comparable between the two groups, a large change in liver and muscle phospho AKT Ser473 levels in the *A. muciniphila* group was detected, indicating an increased insulin sensitivity in the liver and muscles. Consequently, enhanced insulin sensitivity in the liver led to decreased hepatic G6P and Pepck expression. All these findings have demonstrated that *A. muciniphila* supplementation in ND fed mice improved energy homeostasis and glucose tolerance.

Plovier et al. [32] observed that mice given pasteurized *A. muciniphila* had significantly lower glucose intolerance and insulin concentrations than mice given the HFD, resulting in a lower insulin resistance (IR) index in the treated mice. Additionally, Amuc_1100* had the same potency as the live and pasteurized bacterium in improving glucose tolerance. The authors investigated the effects of A. muciniphila on insulin sensitivity by analyzing insulin-induced phosphorylation of the insulin receptor (IR) and its downstream mediator Akt at the threonine and serine sites in the liver. They found that HFD-fed mice got lower phosphorylation of all analyzed proteins when compared to ND-fed mice, in particular for Akt at the threonine. Interestingly, these effects were counteracted by the A. muciniphila or Amuc_1100* treatment. In particular, a significant higher phosphorylation level of IR and Akt at the threonine or Akt at the serine, when compared to untreated HFD-fed mice, was registered in mice treated with Amuc_1100* and live bacterium, respectively.

Wu et al. [33] found that mice on the HFD had significantly higher fasting blood glucose levels than mice in the other groups. Furthermore, the HFD-GP01 group's fasting blood glucose levels were not substantially different from the ND groups. Consequently, the ND mice had significantly higher fasting blood glucose levels than the ND-GP01 fed mice. Moreover, they observe only a slight decrease in the HOMA-IR and a slight increase in the HOMA-%B in the HFD-GP01 group compared to the HFD one. The area under the oral glucose tolerance test curve showed that the HFD impaired

blood glucose regulation and that GP01 significantly eased this impairment. Another study [34] showed that using EVs resulted in substantially lower plasma glucose levels in both the HFD and ND groups.

According to Deng et al. [36], *A. muciniphila* treatment reduced fasting blood glucose levels in HFD mice as compared to the HFD group. OGTT tests revealed that *A. muciniphila* intervention significantly enhanced HFD mice's impaired glucose tolerance. They compared serum insulin levels between HFD groups and found that it was higher after *A. muciniphila* gavage, implying that the microorganisms might be able to stimulate insulin release to lower blood glucose levels. However, only the treatment with the strain GP01 was found to be significantly involved in these results.

4. *A. muciniphila* in Improvement of Anti-Inflammatory Effects

In addition to the role of *A. muciniphila* on obesity and glucose metabolism, it was thought to be involved in inflammation modulation. The results of Yang et al. [27] showed that in the HFD group, TNF-a, IL-6, MCP-1, TLR2 and TLR4 colonic mRNA levels were significantly higher than in the normal group. Conversely, the colonic expression of the IL-10 gene was significantly lower. The HFD group's exposure to *A. muciniphila* has substantially depleted the TLR2 mRNA level and downregulated the expression of the TNF-a and MCP-1 genes.

Zhao et al. [30] found that the supplementation with *A. muciniphila* significantly decreased the phospho-JNK level and increased the level of the NF-KB protein inhibitor and IKBA protein in the liver, indicating that inactivation of these two pathways in the supplementation of the *A. muciniphila* group has enhanced metabolic endotoxemia and subsequent local inflammatory cascades, which could mediate the beneficial metabolic effects.

Plovier et al. [32] reported that HFD-fed mice had higher portal LPS levels than ND-fed mice, but intervention with *A. muciniphila* (live or pasteurized) or Amuc_1100* protein completely restored LPS levels to those of ND group.

Wu et al. [33] found that the mice in the ND-GP01 group had significantly higher IL-10 levels than the mice in the other groups. The HFD-GP01 group's IL-10 levels were significantly higher than those of the HFD and ND groups. This result showed that intervention with *A. muciniphila* GP01 improved the expression of the anti-inflammatory factor IL-10.

Ashrafian et al. [34] showed that the treatment with *A. muciniphila* decreased the mRNA expression of TLR-4 and IL-6 genes in EAT in both HFD and ND fed mice, but had no effect on TNF-α expression in HFD mice, whereas it increased in ND mice. In HFD mice, however, EVs caused a greater reduction in inflammatory cytokines (TNF-a and IL-6) and TLR-4 expression. However, when compared to the bacterium, EVs reduced more TNF-a and TLR-4 expression in ND mice.

In HFD mice, Deng et al. [36] found that *A. muciniphila* GP01 administration significantly reduced the mRNA expression of macrophage inflammation markers (Itgax and Emr1), immune cell recruitment (Ccl2), and LPS-binding protein (Lbp), while *A. muciniphila* GP25 gavage only significantly reduced *Emr1* and *Lbp* transcript expression. Furthermore, in ND mice, the strain GP01 significantly decreased Lbp mRNA expression. These findings suggested that *A. muciniphila* gavage could reduce inflammation in BAT and that GP01 intervention improved gene regulation.

5. *A. muciniphila* in Lipid Levels and Metabolism

Oral gavage of *A. muciniphila* in three studies has shown that plasma triglycerides levels were unaltered [29][30][31][35]. Shen et al. [31] also found that there was no significant change in the cholesterol contents after treatment.

Another study [32] showed that *A. muciniphila* administration or its protein extract substantially reduced plasma HDL cholesterol concentrations and reversed HFD-induced hypercholesterolemia. Pasteurized *A. muciniphila* also showed lower plasma triglyceride levels than both untreated mice or HFD-fed mice treated with live *A. muciniphila*.

Ashrafian et al. [34] showed that the EVs corrected HFD-induced hypercholesterolemia with significantly lower plasma TC, but TG levels did not change. On the other hand, obese mice and normal group treated with *A. muciniphila* reported significantly lower plasma TG.

Deng et al. [36] demonstrated that the *A. muciniphila* GP01 intervention improved both TG and TC, while *A. muciniphila* GP25 only improved TC. When TC levels between the HFD groups were compared, GP25 showed a more substantial difference.

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