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REVIEW

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The role of *Akkermansia muciniphila* in obesity, diabetes and atherosclerosis

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Abstract

Alteration in the composition of the gut microbiota can lead to a number of chronic clinical diseases. *Akkermansia muciniphila* is an anaerobic bacteria constituting 3–5% of the gut microbial community in healthy adults. This bacterium is responsible for degenerating mucin in the gut; its scarcity leads to diverse clinical disorders. In this review, we focus on the role of *A. muciniphila* in diabetes, obesity and atherosclerosis, as well as the use of this bacterium as a next-generation probiotic. In regard to obesity and diabetes, human and animal trials have shown that *A. muciniphila* controls the essential regulatory system of glucose and energy metabolism. However, the underlying mechanisms by which *A. muciniphila* alleviates the complications of obesity, diabetes and atherosclerosis are unclear. At the same time, its abundance suggests improved metabolic disorders, such as metabolic endotoxemia, adiposity insulin resistance and glucose tolerance. The role of *A. muciniphila* is implicated in declining aortic lesions and atherosclerosis. Well-characterized virulence factors, antigens and cell wall extracts of *A. muciniphila* may act as effector molecules in these diseases. These molecules may provide novel mechanisms and strategies by which this bacterium could be used as a probiotic for the treatment of obesity, diabetes and atherosclerosis.

INTRODUCTION

Specific consortia of gut microflora can serve protective, metabolic and trophic functions; however, when germ-free animals (animals raised without any exposure to microorganisms) are compared with conventional animals (animals raised with an undetermined microbiological status), a commonly asked question is whether the bacteria are a friend or a foe [1]? The concept of the metagenome has established a strong correlation between the gut microbiota and dysbiosis of them. Perturbation of the normal microbiome content often leads to the emergence of such chronic diseases as colon cancer, colitis, irritable bowel syndrome, diabetes, obesity and atherosclerosis [2, 3]. *Akkermansia muciniphila* is a Gram-negative, elliptical, obligate anaerobe, chemo-organotroph, non-motile and non-spore-forming bacterium that has the ability to grow on gastric mucin and use mucin as a carbon, nitrogen and energy source [4, 5]. The epithet *Akkermansia* is attributed to the microbial ecologist Antoon D. L. Akkermans and this was combined with 'preferring mucin', eventually making the bacterium popular as *A. muciniphila*; it has been classified under the phylum *Verrucomicrobia* [5]. In genomic terms, *A. muciniphila* is a member of *Verrucomicrobia*, in respect to both the GC percentage of the genome and the number of protein-coding genes. Approximately a quarter of the proteins encoded in the genome of *A. muciniphila* contain a signal peptide, which is potentially secreted [2]. The colonization of *A. muciniphila* starts from childhood and similar levels have been shown in adults; however, it is reduced in the elderly (80–82 years old) [6–8]. Furthermore, its colonization depends on several host factors, such as metabolic syndromes (e.g. diabetes and obesity) [9, 10], body metabolic status (including the adipocyte distribution, serum lipids and glucose homeostasis) [11] and the severity of intestinal inflammations (e.g. inflammatory bowel disease and appendicitis) [2, 12, 13].

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Abbreviations: BACON, bacteroidetes-associated carbohydrate-binding often N-terminal; CRISPR, clustered regularly interspaced palindromic repeats; DIO, diet-induced obesity; GI, gastrointestinal; HFD, high-fat-diet; IBD, inflammatory bowel disease; LPS, lipopolysaccharide; MGWAS, metagenome-wide association study; ND, normal diet; NGS, next-generation sequencing; SCFA, short-chain fatty acid; T2D, type 2 diabetes.

Mucin, a protective barrier against xenobiotics in the intestine, plays a great role in the adhesion of the microbiota to the intestinal layers. Bacteria that have the ability to degrade mucin are more likely to survive the changing microenvironment of the intestine [14]. While *A. muciniphila* harbours several candidate genes encoding mucinase, no recognized mucus-binding domains have been deciphered. However, Mello *et al.* [15] found a novel module termed BACON (*Bacteroidetes*-associated carbohydrate-binding often N-terminal) in two candidate mucinases of *A. muciniphila* (encoded by Amuc_2164, a glycosyl hydrolase, and Amuc_0953, a sulfatase). BACON is thought to be involved in the mucin binding of *A. muciniphila*. A C-terminal Pro–Glu–Pro motif found in *A. muciniphila* proteins, along with exosortase EpsH, forms a protein that is a sorting system associated with exopolysaccharides expression [2].

The genomic analysis of *A. muciniphila* has shown the presence of clustered regularly interspaced palindromic repeats (CRISPR) loci 1 and 2 in *A. muciniphila*, which contain nine phage-related sequences, suggesting that this bacterium has experienced frequent infections by bacteriophages [2]. CRISPR loci indicate heritable and adaptive immune systems in archae and eubacteria against invading genetic elements such as plasmids and bacteriophages [16–18]. The presence of numerous presumably phage-derived sequences and two distinct CRISPR loci in the genome of *A. muciniphila* suggests that phage infections play a critical role in the evolutionary history and, perhaps, speciation. There is, however, not much information regarding the diversity of *Akkermansia* strains and species colonization. Despite this, these studies suggest that eight different species of *Akkermansia* colonize the human gastrointestinal (GI) tracts; so, it seems that the human gut is simultaneously colonized by different species [2, 19]. However, it is not known whether different mucin-degrader bacteria exist in the GI tract or different *Akkermansia* species continuously infect humans, leading to discontinuous (co-) colonization [2, 8].

Recently, the genomic architecture of *A. muciniphila* based on whole-genome sequencing has unveiled a flexible open pangenome consisting of 5644 unique proteins. Phylogenetic analysis led to the identification of three species-level *A. muciniphila* phylogroups exhibiting distinct metabolic and functional features [20].

The gut microbiota shapes intestinal architecture during health and disease. The commensal bacteria in the colon live and thrive in the outer loose layer of mucosa; however, they cannot permeate the inner layers. These bacteria can penetrate into the mucin network (after the expanding Muc2 mucin network in volume) and expend their glycan-degrading enzymes, releasing one monosaccharide at a time from mucin glycans. The bacterial enzymes reach and expose themselves to the mucin protein core for proteolysis, paving the way for a relatively thick outer mucus layer [21]. The mucosal immune system, including epithelial cells and paneth cells, which are specialized cells in the epithelium of the small intestine, is an important source of antimicrobial peptides in the intestine, maintaining a homeostatic relationship between a host and its colonizing microbes. Innate immunity helps to maintain the immune barrier. Several studies have presented good evidence suggesting that inflammatory bowel disease (IBD) arises from dysregulated control of host–micro-organism interactions [22–27].

Several proteins of *A. muciniphila*, such as Am0868 (a β-N-acetylhexosaminidase) [28], Amuc_0771, Amuc_0824 and Amuc_1666 (three extracellular β-galactosidases) [29], and Amuc_1686 (a extracellular β-galactosidase) [30], have been predicted to be involved in different steps of mucin degradation, whereas the numerous genes encoding signal peptide bearing hypothetical proteins suggest that this organism may have a large undiscovered capacity to break down extracellular polymeric substrates, including mucin.

The role of *A. muciniphila* in humans is not well understood. Several studies have demonstrated different roles of *A. muciniphila* in obese and diabetic humans [31–34]. It has been shown that *A. muciniphila* may be used to treat type 2 diabetes and obesity, but some other studies have suggested that *A. muciniphila* may contribute to health; despite this, the underlying mechanisms of *A. muciniphila* are unclear [35, 36]. In this review, we aimed to assess the roles of *A. muciniphila* in human health, as well as its role in obesity, diabetes and atherosclerosis. We searched some data sources, including Google Scholar, Web of Science, PubMed and Medline, to understand the role of *A. muciniphila* in obesity, diabetes and atherosclerosis; the literature published during the last two decades up to 2021 was considered. During the search, no filters or limitations were used. The following search words were used, '*Akkermansia muciniphila*', 'obesity', 'diabetes', 'atherosclerosis' 'probiotics' and 'health'.

A. MUCINIPHILA IN OBESITY AND DIABETES

Obesity is a heterogeneous condition correlated with several pathological dysfunctions [37]. Almost a decade ago, several studies proposed an innovative hypothesis holding that microbial ecology could play an important role in energy homeostasis, i.e. individuals predisposed to obesity may have gut microbial communities that would favour the occurrence of metabolic diseases [11, 26, 38–43]. *A. muciniphila* is consistently correlated with obesity, diabetes and atherosclerosis. Gut microbiota may influence the whole body metabolism [44, 45] by affecting gut permeability, metabolic inflammation [38, 46–48], serum lipopolysaccharides (LPSs), such as metabolic endotoxemia [38], and the energy balance [45], which can be associated with obesity, diabetes and cardiovascular diseases [31, 32, 40, 44]. Gut microbiota-derived LPSs (mimicking metabolic endotoxemia) have been involved in the onset and progression of inflammation and metabolic diseases; therefore, the conclusion is that the involvement of bacteria retains its putative role in managing metabolic disorders [38, 40, 45]. A metagenome-wide association study (MGWAS) also indicated that patients with type 2 diabetes (T2D) could be characterized by altered microbial flora, an increment in opportunistic pathogens, a decrease of some

universal butyrate-producing bacteria, and the enrichment of other microbial functions involving sulphate reduction and the development of oxidative stress resistance [31]. Metformin (1, 1-dimethylbiguanide hydrochloride) has been widely used to treat T2D for more than 50 years. Metformin has been shown to enhance the relative abundance of *A. muciniphila* in the gut, which is associated with its therapeutic efficacy for glucose metabolism, as well as its anti-obesity and anti-inflammatory efficacy [49–51]. Transition of the gut microbiota was specifically enhanced in *A. muciniphila* by metformin treatment, showing that this modulation could lead to the improvement of metabolic parameters, including those of obesity and insulin resistance [52]. As mentioned earlier, an unhealthy state in high-fat-diet (HFD) fed mice reduced the abundance of *Akkermansia* spp. [53]. Therefore, an increase in the cecum mucin level was suggested to enhance the abundance of *Akkermansia* spp. in the HFD–metformin mice, as compared with HFD-fed control ones [54]. Shin *et al*. [53] also demonstrated that metformin treatment increased the number of mucin-producing goblet cells in both normal-chew and HFD-fed mice. In addition, *Akkermansia* spp. administration resulted in an increase of goblet cells and the reduction of LPS translocation across the intestinal barrier; these may lead to attenuation of glucose intolerance [53, 55, 56]. Further, attenuation of adipose tissue inflammation and enhancement of glucose tolerance have been shown to be significantly induced by regulatory T cells (Treg cells) (FoxP3 – the natural regulatory T cells) in the visceral adipose tissue [53]. *A. muciniphila* has been proved to have a robust correlation with inflammatory markers and adipose tissue homeostasis and with insulin and glycaemia at the onset of obesity [57]. The indirect alteration evoked by *A. muciniphila* in obesity also involves the stimulation of Treg cell proliferation [53]. Metformin increases the abundance of *Akkermansia* spp. in the gut. Progressive mechanistic insights showing how the gut microflora could modulate metabolic diseases have paved the way for the identification of innovative microbiota-based diagnostics and/or therapeutics [33], providing a new mechanism for metformin in type 2 diabetes.

Furthermore, it has been demonstrated that oral administration of short-chain fatty acid (SCFA)-producing bacteria, in return, could protect against obesity and enhance glucose tolerance in mice [34, 58]. The role of *A. muciniphila* in glucose and lipid metabolism regulation has been elucidated by the fact that mucin fermentation induces the production of acetate and propionate [4], and the interaction with butyrate-producing bacteria activates GPR43 or GPR41, the pair of mammalian G protein-coupled receptors (GPCRs) expressed in human adipocytes, colon epithelial cells and peripheral blood mononuclear cells Fig. 1 [59, 60].

Patients with prediabetes have also been shown to harbour low concentrations of *Clostridium* spp. and mucin-degrading *A. muciniphila* [61, 62]. Karlsson *et al*. [63] demonstrated that the abundance of *A. muciniphila* in patients with prediabetes was not different from that in the control group. However, Zhang *et al*. [64] showed that it was decreased in prediabetes patients. Further, Qin *et al*. [31] revealed that its abundance was increased in patients with T2D. The reasons for these differences could be related to the different approaches used to calculate the abundance, such as next-generation sequencing (NGS), 16S rDNA gene amplicon sequencing or quantitative PCR. There is a need to combine different approaches. In addition, many other confounding factors could also affect the gut microbiota, such as pharmaceutical treatment or diet [65, 66]. Further study is needed to explore this issue. Overall, these results and the decrease of *A. muciniphila* in the prediabetes patients indicate that the abundance of *A. muciniphila* is meaningful for risk estimation and diagnosis of T2D.

In a HFD and a normal diet (ND) mice model, the influence of metformin-induced changes on the composition and metabolic functions of the gut microbiota was studied, showing that *A. muciniphila* consistently decreased under the HFD regimen [53, 58, 67, 68]. The results of these studies also demonstrated that the progression of obesity is negatively associated with *A. muciniphila*, while inflammation is positively associated with adipose tissue browning process markers [67, 69]. Research studies have also documented that *A. muciniphila* declines before the onset of metabolic alterations, and its levels are inversely associated with several plasma markers of insulin resistance, lipid synthesis, adiposity, cardiovascular risks and inflammatory markers [41, 53, 57, 69–71]. Lack of a putative link between calorie intake and the abundance of *A. muciniphila* was another notable feature of this investigation [67].

Everard *et al*. [69] also demonstrated that the abundance of *A. muciniphila* was lower in type 2 diabetic and obese mice. Their results showed that treatment with *A. muciniphila* reversed HFD-induced disorders such as metabolic endotoxemia, fat mass gain, insulin resistance and adipose tissue inflammation. Other studies have demonstrated that *A. muciniphila* can regulate the gut barrier and intestinal permeability by tight-junction proteins such as cannabinoid receptor-1 and -2 (CB1 and CB2), occluding and claudin-3 [70, 72–75]. The enhancement of *A. muciniphila* could reverse the high expression of flavin-containing monooxygenase 3 (FMO3) in the liver, modulating trimethylamine (TMA) conversion into trimethylamine N-oxide (TMAO) [13, 70]. These findings thus establish that the physiological abundance of *A. muciniphila* may play a key role in the physiopathology of T2D, obesity and metabolic inflammation.

Gut microflora can play an important role in the pathophysiology of obesity; the experimental model (HFD mice), in comparison to control diet mice, provides evidence that *Bifidobacterium* spp. and *A. muciniphila* are inversely correlated with the onset of inflammation, altered adipose tissue metabolism and metabolic disorders during the HFD regimen [57]. In obesity states, the pathological massive expansion of adipose tissue is associated with the development of low-grade inflammation, which is reflected in the enhanced production of pro-inflammatory fatty acids, chemokines and cytokines. This causes an imbalance between pro- and anti-inflammatory factors produced by leukocytes, further promoting inflammation and adipose tissue dysfunction (e.g. β-oxidation, browning processes

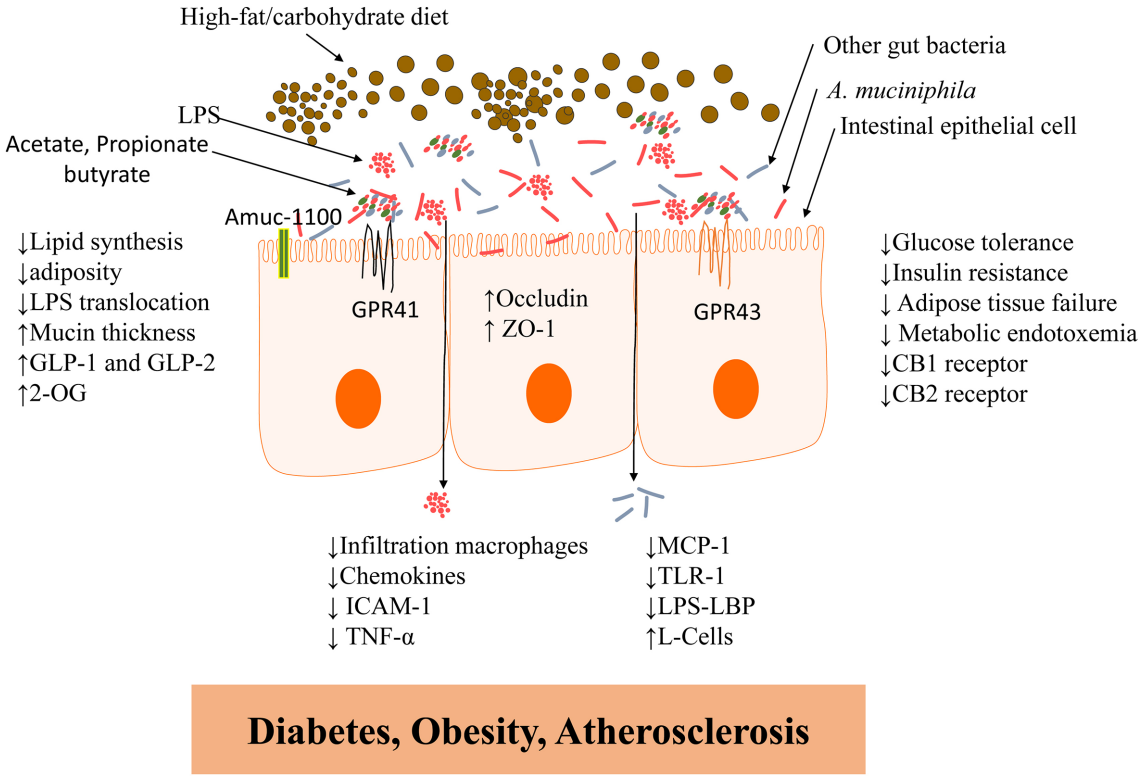

Fig. 1. The role of *A. muciniphila* in diabetes, obesity and atherosclerosis. Acetate and propionate produced by *A. muciniphila*, combined with butyrate produced by other bacteria, can bind to GPR41 or GPR43; this is followed by the activation of the downstream signal pathway to regulate the metabolism of the lipid and glucose in the peripheral organ. Enhancement of the activity of L-cells by *A. muciniphila* stimulates the release of GLP-1 and GLP-2 from L-cells. Production of Reg3γ is increased by the oral administration of *A. muciniphila*. Regulation of glucose metabolism and activation of TLR2 can be induced by the outer membrane Amuc_1100 of *A. muciniphila*. *A. muciniphila* can induce the upregulation of the expression of tight junction proteins, such as ZO-1, ZO-2, ZO-3, claudins and occludin, increasing the number of goblet cells and normalizing the mucus thickness of the inner layer. In addition, *A. muciniphila* can induce the reduction of circulating endotoxin levels, thus improving the gut barrier function and inhibiting the inflammatory responses; these, in turn, could have beneficial effects on the regulation of lipid and glucose metabolism in the peripheral tissues.

and adipogenesis) [48, 76–78]. It is also well established that there is a direct correlation between gut microbiota alterations and diet-induced obesity (DIO) [57]. However, it is not known whether this remains during obesity development and related adipose tissue metabolic alterations or changes when preceded by the abundance of specific bacteria. When this potential interconnection was studied during obesity and T2D development following chronic HFD in mice, it was observed that levels of *A. muciniphila* were strongly and positively correlated with those of almost all parameters involved in fatty acid oxidation and fat browning [57]. HFD also strongly influenced the adipose tissue profile and intestinal microbiota, in a way mimicking ageing, particularly in older mice [11].

The presence of extracellular vesicles (EVs) is another mechanism proposed for the communication between bacteria and the host [79, 80]. These configurations include proteins, lipids, nucleic acids, lipopolysaccharides and other virulence factors documented to play a role in the transfer of genetic material, interacting with immune and epithelial cells to initiate several signalling pathways. Chelakkot *et al.* [79] also demonstrated that the administration of *A. muciniphila*-derived extracellular vesicles (AmEVs) led to improved glucose tolerance, reduced body weight gain and enhanced tight junction function in HFD-induced diabetic mice. Everard *et al.* [69] also showed that the administration of *A. muciniphila* could improve glucose homeostasis, restore the mucus layer and contribute to the reduction of metabolic endotoxemia, thereby inhibiting diet-induced obesity and associated disorders in mice.

The involvement of enteroendocrine L-cells (EL-cells), which are primarily in the colon and ileum, is the other aspect suggested for the interaction of gut microflora with the host. Prebiotics can act on the EL-cells, stimulating the secretion of glucagon-like peptide-1 and -2 (GLP-1 and GLP-2) [45]. The gut microbiome manages gut peptides such as GLP-2, which can regulate the proliferation of epithelial cells and functions of the gut barrier [47, 69]. *A. muciniphila* increases the tricarboxylic acid (TCA) cycle intermediate 2-oxoglutarate (2-OG) level in the intestine to stimulate the secretion of glucagon-like peptide from the intestinal L-cells [81]; these, in return, help *A. muciniphila*

to control metabolic endotoxemia, metabolism and the gut barrier function. Administration of live *A. muciniphila* has also been implicated in the endogenous restoration of antimicrobial peptides [82] and increased production of specific bioactive lipids [41]. These compounds, which belong to the endocannabinoid family, have anti-inflammatory activities; they are known to regulate the endogenous production of the gut peptides involved in the gut barrier and glucose regulation. These responses are observed in other specific disorders, such as hypercholesterolemia, hepatic inflammation and atherosclerosis [53, 70, 71, 83, 84].

In general, it is known that the accumulation of adipose tissue causes obesity. However, the expansion of this tissue produces a number of bioactive substances known as adipocytokines or adipokines. These substances trigger chronic low-grade inflammation and interact with a range of processes in many different organs [85, 86]. Dysregulation of these adipokines is proposed as a cause of metabolic diseases in obesity, which is elucidated as increased adipose tissue mass and a major driving force in insulin resistance and pathogenesis of T2D and metabolic syndrome [87, 88]. Bacterial LPSs are the triggering factor for the above phenomenon [37]. Lipogenesis and adipose tissue differentiation are inhibited by higher circulating LPS levels [48]. Muccioli *et al.* [48] and Cani *et al.* [38] also demonstrated that that the LPS-dependent mechanism of gut microbiota can improve lipid and glucose metabolism; the composition of the gut microbiota could also be influenced by the HFD [38, 89]; however, the administration of *A. muciniphila* does not affect this profile [69]. Increased levels of *A. muciniphila* have been associated with a lower control of adipose tissue inflammation and a better gut barrier function [69, 90]. Several studies do not support a simple linear relationship between the levels of *A. muciniphila* and the inflammation stage [11, 43, 53, 57, 69], while other bacterial studies have confirmed a putative association between the abundance of *A. muciniphila* and caloric intake [9, 91]. Schneeberger *et al.* [57] also found a link between *A. muciniphila* gut abundance and adipose tissue homeostasis on the onset of obesity, reinforcing the beneficial effect of this bacterium on metabolism. In an animal experiment, during HFD feeding, the gut microbiota could influence the expression of neuropeptides in the hypothalamic arcuate nucleus of mice. The expression of orexigenic NPY (neuropeptide Y) and AgRP (agouti-related protein) was decreased, while levels of anorexigenic peptides such as POMC (proopiomelanocortin) were enhanced [57, 92]. Overall, *A. muciniphila* is strongly correlated with adipose tissue metabolic parameters [39, 93]. Recently, *A. muciniphila* administration has been proved to improve cardiometabolic risk factors; it is given as a probiotic to humans who are overweight or obese; the safer looking bacteria are associated with a healthier metabolic status and better clinical outcomes after calorie restriction in overweight/obese adults [11, 94].

A. MUCINIPHILA IN ATHEROSCLEROSIS

Atherosclerosis is a chronic inflammatory disease and the main contributor to cardiovascular mortality [95]. Considering the infectious aspect of disease, bacterial infection has been suggested as one of the triggering signals for the development of inflammation in atherosclerosis [74]. Interestingly, bacterial DNA has been detected in atherosclerotic lesions. Pyrosequencing revealed that the bacteria in the lesions are derived from the gut and oral cavity, suggesting the possible involvement of the gut microbiota in the development of the disease. Cardiovascular risk is inversely associated with levels of *A. muciniphila* [57]. Kasahara *et al.* [96], in a mice model, showed that the gut microbiota significantly decreased the atherosclerotic plaque area despite unfavourable high plasma cholesterol levels. Their investigation also revealed that although metabolic endotoxemia could be considered as an initiating factor for cardiometabolic diseases, *A. muciniphila* could attenuate atherosclerosis lesions by ameliorating metabolic endotoxemia-induced inflammation [74, 96]. Activation of the fibroblast growth factor receptor-4 axis and enterohepatic fibroblast growth factor-15 by the gut microbiota could reduce hepatic bile acid synthesis and cholesterol 7α-hydroxylase, leading to accumulation of the liver cholesterol content and the reduction of atherosclerotic lesion formation. The antiatherogenic effect of *A. muciniphila* is mediated by limiting the lipopolysaccharide level in the bloodstream and ameliorating metabolic endotoxemia [74].

In an animal model, *A. muciniphila* administration has been shown to prevent the thinning of the mucus layer in mice with diet-induced obesity [97]. However, primary control of the gut barrier relies on an intact epithelium where tight junctions, including occludin, claudins and zona occludens (ZOs) protein, seal the space between individual epithelial cells, maintaining epithelial integrity [98]. Loss of occludin has been shown to increase gut permeability, whereas a deficiency of ZO-1 interrupts the assembly of the tight junction by inhibiting the recruitment of other components. The expression of the two tight junction proteins, occludin and ZO-1, has been shown to increase in the ileum of apolipoprotein-deficient mice after the administration of *A. muciniphila*, suggesting an additional mechanism of preserving the gut barrier by the organism [74, 97].

The alleviation of atherosclerotic lesion in the apoprotein E-deficient mice showed that the presence of *A. muciniphila* in the gut led to the reduction of the infiltration of macrophages and adhesion of several molecules, chemokines, intercellular adhesion molecule-1 (ICAM-1), tumour necrosis factor-alpha (TNF-α) and monocyte chemo-attractant protein (MCP-1) [74]. In addition, metabolic endotoxemia has been suggested to be an initiating factor of obesity-associated cardiometabolic dysfunction [38]. As is known, LPS binding to Toll-like receptor (TLR)-4 is a strong stimulus of inflammation [99]. This reinforces systematic inflammation by stimulating the production of pro-inflammatory adipokines [100]. Furthermore, in vascular inflammation and atherosclerosis, LPS-induced inflammatory cytokines can act in a paracrine

manner in the perivascular adipose tissue. Deletion of the downstream cytosolic adaptor, TLR4 or myeloid differentiation factor-88 can prevent LPS transport by inhibiting LBP (LPS-binding protein). This inactivates the LPS pathway, reducing aortic lesions in low-density lipoprotein receptor-deficient or ApoE-deficient mice [101, 102], suggesting that the anti-inflammatory activity of *A. muciniphila* is an important mechanism in the anti-atherosclerotic effect.

A. MUCINIPHILA AS A PROBIOTIC

Probiotics are live and non-pathogenic micro-organisms administered to improve the microbial balance of the gastrointestinal microflora composition, ensuring beneficial effects through various mechanisms. Probiotics increase the L-cell number and such associated parameters as plasma glucagon-like peptide-1 levels and intestinal proglucagon mRNA expression, as well as improving glucose tolerance, lipid metabolism and gut barrier functions. In addition, probiotics can reduce oxidase stress, plasma LPSs, fat mass development and low-grade inflammation [43]. Li *et al.* [74] demonstrated that after the administration of *A. muciniphila*, the expression of zona occludens protein-1 (ZO-1) and occludin was increased in the ileum of ApoE-deficient mice. These results suggest the *A. muciniphila* mechanism for preserving the gut barrier. Everard *et al.* [43] also demonstrated that the probiotic treatment could improve metabolic parameters and leptin sensitivity in high-fat fed mice. Opportunities for direct contact between probiotics and the mucosa are far fewer, but *A. muciniphila* have more intensive contact with the host mucus layer, inducing differential host responses [103]. Everard *et al.* [69] also showed that administration of *Lactobacillus plantarum*, as a control species, did not change the adipose tissue metabolism, fat mass development, mucus layer thickness, metabolic endotoxemia and colon Reg3g mRNA. However, *A. muciniphila* can induce specific host responses. *A. muciniphila* regulates antimicrobial peptides (e.g. RegIIIγ) of the intestine in the colon, with a low-level effect on the production of antimicrobial peptides in the ileum [69]. RegIIIγ expressed via *A. muciniphila* exposure can have bactericidal activity against Gram-positive bacteria in the intestine, promoting host–bacterial mutualism through immune mechanisms [104]. Derrien *et al.* [103] also demonstrated modulations of gene expression in the colon (442 genes) of germ-free mice mono-associated with *A. muciniphila*, followed by 243 genes in the ileum and 211 genes in the cecum. Meanwhile, in germ-free mice mono-associated with by *L. plantarum*, as a control, there were 1243 modulated genes in the ileum, followed by 608 in the colon and 449 in the cecum. Colonization of the intestine with *A. muciniphila* increases the expression of the genes involved in cell fate determination and immune response, while colonization by *L. plantarum* increases the expression of the genes involved in lipid metabolism [103]. In addition, Ganesh *et al.* [12] demonstrated that the presence of *A. muciniphila* in *S. typhimurium*-infected SIHUMI mice (a gnotobiotic C3H mouse model with a background gut microbiota of eight bacterial species) caused a significant increase in histopathology scores and elevated mRNA levels of IFN-c, IP-10, TNF-a, IL-12, IL-17 and IL-6 in the cecal and colonic tissue. This revealed the role of *A. muciniphila* in disturbing host mucus homeostasis and exacerbating the inflammation caused by pathogenic bacteria. The keratin sulphate biosynthesis pathway is involved in the production of mucin, a feature of the epithelial tissue response due to physical alterations such as those resulting from wounding and development [105]. This pathway is the main regulated pathway following colonization by *A. muciniphila* in the mouse cecal pathway [103]. The genome of *A. muciniphila* contains various genes encoding secreted sulfatases [2, 106], showing that *A. muciniphila* uses mucin as a carbon, sulphur and nitrogen source. These results demonstrated that *A. muciniphila* can modulate the expression of the genes involved in establishing homeostasis for the immune response and basal metabolism toward commensal microbiota. It may be potentially regarded as a next-generation probiotic for the production of novel dietary and pharmaceutical supplements with beneficial effects.

CONCLUSION

Akkermansia muciniphila is implicated in improving metabolic disorders such as metabolic endotoxemia, adiposity, insulin resistance and low-grade inflammation. Feeding the bacteria in an animal model has been shown to improve the intestinal expression of endocannabinoids that control the gut barrier functions, gut hormone secretion and inflammation. However, its probiotic role cannot be denied. There is not yet enough evidence recommending this bacterium for patients. There is some uncertainty and there are some limitations regarding the mechanisms of *A. muciniphila* in obesity, diabetes and atherosclerosis. Virulence factors, antigens and cell wall extracts of *A. muciniphila* may act as the effector molecules in these diseases. *A. muciniphila* induces specific host responses, showing a low-level effect on the production of antimicrobial peptides in the intestine. Therefore, the bacterium may be a possible candidate feature to prevent the onset of many metabolic and inflammatory diseases; however, more *in vivo* studies should be carried out in future.

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Conflicts of interest
The authors declare that there are no conflicts of interest.

Ethical statement
This is a literature review study and therefore ethical approval was not required. For this type of study, formal consent was not required.

References

1. Canny GO, McCormick BA. Bacteria in the intestine, helpful residents or enemies from within? *Infect Immun* 2008;76:3360–3373.
2. Van Passel MW, Kant R, Zoetendal EG, Plugge CM, Derrien M. The genome of *Akkermansia muciniphila*, a dedicated intestinal mucin degrader, and its use in exploring intestinal metagenomes. *PLoS One* 2011;6:e16876.
3. Belzer C, De Vos WM. Microbes inside—from diversity to function: the case of *Akkermansia*. *ISME J* 2012;6:1449–1458.

4. Derrien M, Vaughan EE, Plugge CM, de Vos WM. *Akkermansia muciniphila* gen. nov., sp. nov., a human intestinal mucin-degrading bacterium. *Int J Syst Evol Microbiol* 2004;54:1469–1476.
5. Naito Y, Uchiyama K, Takagi T. A next-generation beneficial microbe: *Akkermansia muciniphila*. *J Clin Biochem Nutr* 2018;63:33–35.
6. Wang L, Christophersen CT, Sorich MJ, Gerber JP, Angley MT. Low relative abundances of the mucolytic bacterium *Akkermansia muciniphila* and *Bifidobacterium* spp. in feces of children with autism. *Appl Environ Microbiol* 2011;77:6718–6721.
7. Collado MC, Isolauri E, Laitinen K, Salminen S. Distinct composition of gut microbiota during pregnancy in overweight and normal-weight women. *Am J Clin Nutr* 2008;88:894–899.
8. Collado MC, Derrien M, Isolauri E, de Vos WM, Salminen S. Intestinal integrity and *Akkermansia muciniphila*, a mucin-degrading member of the intestinal microbiota present in infants, adults, and the elderly. *Appl Environ Microbiol* 2007;73:7767–7770.
9. Remely M, Hippe B, Geretschlaeger I, Stegmayer S, Hoefinger I. Increased gut microbiota diversity and abundance of *Faecalibacterium prausnitzii* and *Akkermansia* after fasting: a pilot study. *Wien Klin Wochenschr* 2015;127:394–398.
10. Seregin SS, Golovchenko N, Schaf B, Chen J, Pudlo NA. NLRP6 protects Il10−/− mice from colitis by limiting colonization of *Akkermansia muciniphila*. *Cell Rep* 2017;19:S2211-1247(17)30457-6:733–745.:.
11. Dao MC, Everard A, Aron-Wisnewsky J, Sokolovska N, Prifti E. *Akkermansia muciniphila* and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. *Gut* 2016;65:426–436.
12. Ganesh BP, Klopfleisch R, Loh G, Blaut M. Commensal *Akkermansia muciniphila* exacerbates gut inflammation in Salmonella Typhimurium-infected gnotobiotic mice. *PLoS One* 2013;8:e74963.
13. Xu Y, Wang N, Tan H-Y, Li S, Zhang C, *et al*. Function of *Akkermansia muciniphila* in obesity: interactions with lipid metabolism, immune response and gut systems. *Front Microbiol* 2020;11:219.
14. Abuqwider JN, Mauriello G, Altamimi M. *Akkermansia muciniphila*, a new generation of beneficial microbiota in modulating obesity: a systematic review. *Microorganisms* 2021;9:1098.
15. Mello LV, Chen X, Rigden DJ. Mining metagenomic data for novel domains: BACON, a new carbohydrate-binding module. *FEBS Lett* 2010;584:2421–2426.
16. Suau A, Bonnet R, Sutren M, Godon J-J, Gibson GR. Direct analysis of genes encoding 16S rRNA from complex communities reveals many novel molecular species within the human gut. *Appl Environ Microbiol* 1999;65:4799–4807.
17. Van der Oost J, Jore MM, Westra ER, Lundgren M, Brouns SJ. CRISPR-based adaptive and heritable immunity in prokaryotes. *Trends Biochem Sci* 2009;34:401–407.
18. Gholizadeh P, Aghazadeh M, Asgharzadeh M, Samadi Kafil H. Suppressing the CRISPR/CAS adaptive immune system in bacterial infections. *Eur J Clin Microbiol Infect Dis* 2017:1–9.
19. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A. A core gut microbiome in obese and lean twins. *Nature* 2009;457:480–484.
20. Guo X, Li S, Zhang J, Wu F, Li X, *et al*. Genome sequencing of 39 *Akkermansia muciniphila* isolates reveals its population structure, genomic and functional diverisity, and global distribution in mammalian gut microbiotas. *BMC Genomics* 2017;18:1–12.
21. Johansson ME, Larsson JMH, Hansson GC. The two mucus layers of colon are organized by the MUC2 mucin, whereas the outer layer is a legislator of host–microbial interactions. *Proc Natl Acad Sci* 2011;108:4659–4665.
22. Bevins CL, Salzman NH. Paneth cells, antimicrobial peptides and maintenance of intestinal homeostasis. *Nat Rev Microbiol* 2011;9:356–368.
23. Pott J, Hornef M. Innate immune signalling at the intestinal epithelium in homeostasis and disease. *EMBO Rep* 2012;13:684–698.
24. Hooper LV, Macpherson AJ. Immune adaptations that maintain homeostasis with the intestinal microbiota. *Nat Rev Immunol* 2010;10:159–169.
25. Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and the future ahead. *Gastroenterology* 2014;146:S0016-5085(14)00220-0:1489–1499.:.
26. Koboziev I, Webb CR, Furr KL, Grisham MB. Role of the enteric microbiota in intestinal homeostasis and inflammation. *Free Radic Biol Med* 2014;68:S0891-5849(13)01497-4:122–133.:.
27. Maslowski KM, Mackay CR. Diet, gut microbiota and immune responses. *Nat Immunol* 2011;12:5–9.
28. Xu W, Yang W, Wang Y, Wang M, Zhang M. Structural and biochemical analyses of β-N-acetylhexosaminidase Am0868 from *Akkermansia muciniphila* involved in mucin degradation. *Biochem Biophys Res Commun* 2020;529:S0006-291X(20)31334-6:876–881.:.
29. Kosciow K, Deppenmeier U. Characterization of three novel β-galactosidases from *Akkermansia muciniphila* involved in mucin degradation. *Int J Biol Macromol* 2020;149:S0141-8130(19)40011-1:331–340.:.
30. Kosciow K, Deppenmeier U. Characterization of a phospholipid-regulated β-galactosidase from *Akkermansia muciniphila* involved in mucin degradation. *MicrobiologyOpen* 2019;8:e00796.
31. Qin J, Li Y, Cai Z, Li S, Zhu J. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 2012;490:55–60.
32. Karlsson FH, Tremaroli V, Nookaew I, Bergström G, Behre CJ, *et al*. Gut metagenome in european women with normal, impaired and diabetic glucose control. *Nature* 2013;498:99:99–103.:.
33. Khan MT, Nieuwdorp M, Bäckhed F. Microbial modulation of insulin sensitivity. *Cell Metab* 2014;20:S1550-4131(14)00314-3:753–760.:.
34. Dao MC, Everard A, Aron-Wisnewsky J, Sokolovska N, Prifti E, *et al*. *Akkermansia muciniphila* and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. *Gut* 2015:gutjnl-2014
35. Zheng H, Liang H, Wang Y, Miao M, Shi T, *et al*. Altered gut microbiota composition associated with eczema in infants. *PLoS One* 2016;11:e0166026.
36. Zhang L, Wang Y, Xiayu X, Shi C, Chen W. Altered gut microbiota in a mouse model of Alzheimer's disease. *J Alzheimers Dis* 2017;60:1241–1257.
37. Zatterale F, Longo M, Naderi J, Raciti GA, Desiderio A. Chronic adipose tissue inflammation linking obesity to insulin resistance and type 2 diabetes. *Front Physiol* 2020;10:1607.
38. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* 2007;56:1761–1772.
39. Vallianou N, Stratigou T, Christodoulatos GS, Dalamaga M. Understanding the role of the gut microbiome and microbial metabolites in obesity and obesity-associated metabolic disorders: current evidence and perspectives. *Curr Obes Rep* 2019;8:317–332.
40. Gholizadeh P, Mahallei M, Pormohammad A, Varshochi M, Ganbarov K. Microbial balance in the intestinal microbiota and its association with diabetes, obesity and allergic disease. *Microb Pathog* 2019;127:S0882-4010(18)31695-4:48–55.:.
41. Cani PD, Plovier H, Van Hul M, Geurts L, Delzenne NM, *et al*. Endocannabinoids--at the crossroads between the gut microbiota and host metabolism. *Nat Rev Endocrinol* 2016;12:133–143.
42. Everard A, Cani PD. Diabetes, obesity and gut microbiota. *Best Pract Res Clin Gastroenterol* 2013;27:73–83.
43. Everard A, Lazarevic V, Derrien M, Girard M, Muccioli GG. Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. *Diabetes* 2011;60:2775–2786.
44. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 2006;444:1027–1131.

45. Cani PD, Osto M, Geurts L, Everard A. Involvement of gut microbiota in the development of low-grade inflammation and type 2 diabetes associated with obesity. *Gut microbes* 2012;3:279–288.
46. Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* 2008;57:1470–1481.
47. Cani PD, Possemiers S, Van de Wiele T, Guiot Y, Everard A. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut* 2009;58:1091–1103.
48. Muccioli GG, Naslain D, Bäckhed F, Reigstad CS, Lambert DM. The endocannabinoid system links gut microbiota to adipogenesis. *Mol Syst Biol* 2010;6:392.
49. Lee H, Ko G, Griffiths MW. Effect of metformin on metabolic improvement and gut microbiota. *Appl Environ Microbiol* 2014;80:5935–5943.
50. Shin N-R, Lee J-C, Lee H-Y, Kim M-S, Whon TW, *et al*. An increase in the *Akkermansia* spp. Population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. *Gut* 2014;63:727–735.
51. Zhou Z-Y, Ren L-W, Zhan P, Yang H-Y, Chai D-D, *et al*. Metformin exerts glucose-lowering action in high-fat fed mice via attenuating endotoxemia and enhancing insulin signaling. *Acta Pharmacol Sin* 2016;37:1063–1075.
52. Lee H, Lee Y, Kim J, An J, Lee S. Modulation of the gut microbiota by metformin improves metabolic profiles in aged obese mice. *Gut Microbes* 2018;9:155–165.
53. Shin N-R, Lee J-C, Lee H-Y, Kim M-S, Whon TW. An increase in the *Akkermansia* spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. *Gut* 2014;63:727–735.
54. Van den Abbeele P, Gérard P, Rabot S, Bruneau A, El Aidy S. Arabinoxylans and inulin differentially modulate the mucosal and luminal gut microbiota and mucin-degradation in humanized rats. *Environ Microbiol* 2011;13:2667–2680.
55. Artis D, Wang ML, Keilbaugh SA, He W, Brenes M. RELM*β*/FIZZ2 is a goblet cell-specific immune-effector molecule in the gastrointestinal tract. *Proc Natl Acad Sci U S A* 2004;101:13596–13600.
56. Suemori S, Lynch-Devaney K, Podolsky D. Identification and characterization of rat intestinal trefoil factor: tissue-and cell-specific member of the trefoil protein family. *Proceed National Acad Sci* 1991;88:11017–11021.
57. Schneeberger M, Everard A, Gomez-Valades AG, Matamoros S, Ramirez S. *Akkermansia muciniphila* inversely correlates with the onset of inflammation, altered adipose tissue metabolism and metabolic disorders during obesity in mice. *Sci Rep* 2015;5:16643.
58. De La Cuesta-Zuluaga J, Mueller NT, Corrales-Agudelo V, Velásquez-Mejía EP, Carmona JA. Metformin is associated with higher relative abundance of mucin-degrading *Akkermansia muciniphila* and several short-chain fatty acid–producing microbiota in the gut. *Diabetes Care* 2017;40:54–62.
59. Zhai Q, Feng S, Arjan N, Chen W. A next generation probiotic, *Akkermansia muciniphila*. *Crit Rev Food Sci Nutr* 2019;59:3227–3236.
60. Ang Z, Ding JL. GPR41 and GPR43 in obesity and inflammation–protective or causative? *Front Immunol* 2016;7:28.
61. Allin KH, Tremaroli V, Caesar R, Jensen BA, Damgaard MT. Aberrant intestinal microbiota in individuals with prediabetes. *Diabetologia* 2018;61:810–820.
62. Li W-Z, Stirling K, Yang J-J, Zhang L. Gut microbiota and diabetes: From correlation to causality and mechanism. *World J Diabetes* 2020;11:293.
63. Karlsson FH, Tremaroli V, Nookaew I, Bergström G, Behre CJ. Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature* 2013;498:99–103.
64. Zhang X, Shen D, Fang Z, Jie Z, Qiu X, *et al*. Human gut microbiota changes reveal the progression of glucose intolerance. *PLoS One* 2013;8:e71108.
65. Yan H, Potu R, Lu H, Almeida V de, Stewart T, *et al*. Dietary fat content and fiber type modulate hind gut microbial community and metabolic markers in the pig. *PLoS One* 2013;8:e59581.
66. Davis LM, Martínez I, Walter J, Goin C, Hutkins RW. Barcoded pyrosequencing reveals that consumption of galactooligosaccharides results in a highly specific bifidogenic response in humans. *PLoS One* 2011;6:e25200.
67. Lee H, Ko G. Effect of metformin on metabolic improvement and gut microbiota. *Appl Environ Microbiol* 2014;80:5935–5943.
68. Forslund K, Hildebrand F, Nielsen T, Falony G, Le Chatelier E. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. *Nature* 2015;528:262–266.
69. Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C. Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci* 2013;110:9066–9071.
70. Plovier H, Everard A, Druart C, Depommier C, Van Hul M. A purified membrane protein from *Akkermansia muciniphila* or the pasteurized bacterium improves metabolism in obese and diabetic mice. *Nat Med* 2017;23:107–113.
71. Shen J, Tong X, Sud N, Khound R, Song Y. Low-density lipoprotein receptor signaling mediates the triglyceride-lowering action of *Akkermansia muciniphila* in genetic-induced hyperlipidemia. *Arterioscler Thromb Vasc Biol* 2016;36:1448–1456.
72. Cario E, Gerken G, Podolsky D. Toll-like receptor 2 controls mucosal inflammation by regulating epithelial barrier function. *Gastroenterology* 2007;132:1359–1374.
73. MJ G, Song SK, Lee IK, Ko S, Han SE, *et al*. Barrier protection via Toll-like receptor 2 signaling in porcine intestinal epithelial cells damaged by deoxynivalnol. *Vet Res* 2016;47:1–11.
74. Li J, Lin S, Vanhoutte PM, Woo CW, Xu A. *Akkermansia muciniphila* protects against atherosclerosis by preventing metabolic endotoxemia-induced inflammation in Apoe-/- mice. *Circulation* 2016;CIRCULATIONAHA. 115.019645.
75. Bian X, Wu W, Yang L, Lv L, Wang Q, *et al*. Administration of *Akkermansia muciniphila* ameliorates dextran sulfate sodium-induced ulcerative colitis in mice. *Front Microbiol* 2019;10:2259.
76. Qiu Y, Nguyen KD, Odegaard JI, Cui X, Tian X. Eosinophils and type 2 cytokine signaling in macrophages orchestrate development of functional beige fat. *Cell* 2014;157:S0092-8674(14)00601-1:1292–1308.:.
77. Rao RR, Long JZ, White JP, Svensson KJ, Lou J. Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis. *Cell* 2014;157:S0092-8674(14)00600-X:1279–1291.:.
78. Geurts L, Everard A, Van Hul M, Essaghir A, Duparc T, *et al*. Adipose tissue NAPE-PLD controls fat mass development by altering the browning process and gut microbiota. *Nat Commun* 2015;6:1–15.
79. Chelakkot C, Choi Y, Kim D-K, Park HT, Ghim J, *et al*. Akkermansia muciniphila-derived extracellular vesicles influence gut permeability through the regulation of tight junctions. *Exp Mol Med* 2018;50:e450.
80. Cuesta CM, Guerri C, Ureña J, Pascual M. Role of microbiota-derived extracellular vesicles in gut-brain communication. *Int J Mol Sci* 2021;22:4235.
81. Hansen KB, Rosenkilde MM, Knop FK, Wellner N, Diep TA, *et al*. 2-Oleoyl glycerol is a GPR119 agonist and signals GLP-1 release in humans. *J Clin Endocrinol Metab* 2011;96:E1409–E1417.
82. Cani PD, de Vos WM. Next-generation beneficial microbes: the case of *Akkermansia muciniphila*. *Front Microbiol* 2017;8:1765.
83. Grander C, Adolph TE, Wieser V, Lowe P, Wrzosek L. Recovery of ethanol-induced *Akkermansia muciniphila* depletion ameliorates alcoholic liver disease. *Gut* 2018;67:891–901.

84. Li J, Zhao F, Wang Y, Chen J, Tao J, *et al*. Gut microbiota dysbiosis contributes to the development of hypertension. *Microbiome* 2017;5:1–19.
85. Guzik T, Mangalat D, Korbut R. Adipocytokines novel link between inflammation. *J Physiol Pharmacol* 2006;4:505–528.
86. Piya MK, McTernan PG, Kumar S. Adipokine inflammation and insulin resistance: the role of glucose, lipids and endotoxin. *J Endocrinol* 2013;216:T1–T15.
87. Jung UJ, Choi M-S. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. *Int J Mol Sci* 2014;15:6184–6223.
88. Kahn CR, Wang G, Lee KY. Altered adipose tissue and adipocyte function in the pathogenesis of metabolic syndrome. *J Clin Invest* 2019;129:129187:3990–4000.:.
89. Cani PD, Neyrinck A, Fava F, Knauf C, Burcelin R. Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. *Diabetologia* 2007;50:2374–2383.
90. Schneeberger M, Everard A, Gómez-Valadés AG, Matamoros S, Ramírez S, *et al*. *Akkermansia muciniphila* inversely correlates with the onset of inflammation, altered adipose tissue metabolism and metabolic disorders during obesity in mice. *Sci Rep* 2015;5:1–14.
91. Sonoyama K, Fujiwara R, Takemura N, Ogasawara T, Watanabe J. Response of gut microbiota to fasting and hibernation in Syrian hamsters. *Appl Environ Microbiol* 2009;75:6451–6456.
92. Briggs DI, Enriori PJ, Lemus MB, Cowley MA, Andrews ZB. Diet-induced obesity causes ghrelin resistance in arcuate NPY/AgRP neurons. *Endocrinology* 2010;151:4745–4755.
93. Kyriachenko Y, Falalyeyeva T, Korotkyi O, Molochek N, Kobyliak N. Crosstalk between gut microbiota and antidiabetic drug action. *World J Diabetes* 2019;10:154:154–168.:.
94. Van Hul M, Le Roy T, Prifti E, Dao MC, Paquot A. From correlation to causality: the case of Subdoligranulum. *Gut Microbes* 2020;12:1–13.
95. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002;105:1135–1143.
96. Kasahara K, Tanoue T, Yamashita T, Yodoi K, Matsumoto T. Commensal bacteria at the crossroad between cholesterol homeostasis and chronic inflammation in atherosclerosis. *J Lipid Res* 2017;58:519–528.
97. Santacruz A, Collado MC, Garcia-Valdes L, Segura M, Martin-Lagos J. Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. *Br J Nutr* 2010;104:83–92.
98. Turner JR. Intestinal mucosal barrier function in health and disease. *Nat Rev Immunol* 2009;9:799:799–809.:.
99. Stoll LL, Denning GM, Weintraub NL. Potential role of endotoxin as a proinflammatory mediator of atherosclerosis. *Arterioscler Thromb Vasc Biol* 2004;24:2227–2236.
100. Schäffler A, Schölmerich J. Innate immunity and adipose tissue biology. *Trends Immunol* 2010;31:228–235.
101. Sallam T, Ito A, Rong X, Kim J, van Stijn C. The macrophage LBP gene is an LXR target that promotes macrophage survival and atherosclerosis. *J Lipid Res* 2014;55:1120–1130.
102. Curtiss LK, Tobias PS. Emerging role of Toll-like receptors in atherosclerosis. *J Lipid Res* 2009;50:S340–S345.
103. Derrien M, Van Baarlen P, Hooiveld G, Norin E, Müller M, *et al*. Modulation of mucosal immune response, tolerance, and proliferation in mice colonized by the mucin-degrader *Akkermansia muciniphila*. *Front Microbiol* 2011;2.
104. Vaishnava S, Yamamoto M, Severson KM, Ruhn KA, Yu X. The antibacterial lectin RegIIIγ promotes the spatial segregation of microbiota and host in the intestine. *Science* 2011;334:255–258.
105. Funderburgh JL. MINI REVIEW Keratan sulfate: structure, biosynthesis, and function. *Glycobiology* 2000;10:951–958.
106. Derrien M, van Passel MW, van de Bovenkamp JH, Schipper R, de Vos W. Mucin-bacterial interactions in the human oral cavity and digestive tract. *Gut microbes* 2010;1:254–268.