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Review article

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Akkermansia muciniphila: biology, microbial ecology, host interactions and therapeutic potential

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Abstract

Akkermansia muciniphila is a gut bacterium that colonizes the gut mucosa, has a role in maintaining gut health and shows promise for potential therapeutic applications. The discovery of *A. muciniphila* as an important member of our gut microbiome, occupying an extraordinary niche in the human gut, has led to new hypotheses on gut health, beneficial microorganisms and host–microbiota interactions. This microorganism has established a unique position in human microbiome research, similar to its role in the gut ecosystem. Its unique traits in using mucin sugars and mechanisms of action that can modify host health have made *A. muciniphila* a subject of enormous attention from multiple research fields. *A. muciniphila* is becoming a model organism studied for its ability to modulate human health and gut microbiome structure, leading to commercial products, a genetic model and possible probiotic formulations. This Review provides an overview of *A. muciniphila* and *Akkermansia* genus phylogeny, ecophysiology and diversity. Furthermore, the Review discusses perspectives on ecology, strategies for harnessing beneficial effects of *A. muciniphila* for human mucosal metabolic and gut health, and its potential as a biomarker for diagnostics and prognostics.

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Introduction

The human gut harbours a complex community of trillions of microorganisms, including bacteria, archaea, eukaryotes and viruses, collectively termed the human gut microbiota[1,2]. The human gut microbiota has co-evolved with its host[3] and is influenced by factors such as host genetics, birth mode, diet, environment and medication[4–7]. Its functions include digestion of dietary compounds, production of beneficial metabolites and vitamins, prevention of infection, immunomodulation, protection of gut barrier integrity and communication within the gut–brain axis[8,9]. Numerous diseases are associated with compositional characteristics of the gut microbiota, including inflammatory bowel disease[10], autoimmune diseases[11], metabolic syndrome[12], cancer[13], allergies[14], neurological diseases[15] and infectious diseases[16]. Therefore, understanding the framework of a health-associated gut microbiota and the individual roles that gut microorganisms play in health and disease is crucial for microbiome-based personalized treatment. In this Review, we highlight findings on the gut bacterium *Akkermansia muciniphila*, which is associated with host health and has potential for multiple applications.

Its intricate relationship with the host and correlation with host health have made *A. muciniphila* an interesting study subject since its discovery in 2004 (ref. 17). *A. muciniphila* was isolated by enrichment from human faeces with mucin as the only carbon and energy source. The genus *Akkermansia* was named after Dr Antoon Akkermans, who was leading the Microbial Ecology group within the Laboratory of Microbiology of Wageningen University, the Netherlands, where *A. muciniphila* was isolated. Its species name refers to its mucin-degrading abilities[17]. Whole genome sequencing revealed that this organism is a specialist with a remarkable number of mucin-targeting enzymes[18,19]. From an ecological perspective, *A. muciniphila* is a frequent inhabitant of the vertebrate mucosal layer, where it cross-feeds other residents[20–22]. *A. muciniphila* is mostly associated with host health and is negatively correlated with various diseases[21]. *A. muciniphila* interacts with its host and stimulates host immune and metabolic responses, host mucus production and gut barrier function[21–24]. The described host interactions of *A. muciniphila* suggests that this organism could be a useful biotic for improving mucosal health, weight management and metabolic syndrome. It also has potential as a biomarker for diagnostics of response to dietary interventions. As such, *A. muciniphila* is proposed as a promising candidate next-generation probiotic[25]. In this Review, we summarize two decades of science on *A. muciniphila*. We explore recent insights into the diversity of *A. muciniphila*, its biological functions, its interactions with the host, diet and other members of the microbiota, its association with health and disease, and its potential in various applications. We envision a future in which *A. muciniphila* is applied for several purposes, including biotechnological application and as a therapeutic agent.

Akkermansia species and strain diversity

Before the discovery of *A. muciniphila* in 2004, it was not known that members of the phylum Verrucomicrobiota (formerly Verrucomicrobia) inhabited gut systems. This was because the ribosomal RNA gene primers used for fluorescence in situ hybridization did not detect this phylum[17]. Thereafter, *A. muciniphila* sequences were found in gut samples of many vertebrate species[26–33]. Only recently have the occurrence and diversity of the genus and species been appreciated (Table 1 and Box 1), which we discuss in this section.

A. muciniphila throughout life and the gastrointestinal tract

A. muciniphila is prevalent and abundant in the human gastrointestinal tract throughout all stages of life[18,34–38]. Although most often studied in faecal and mucosal samples, the bacterium has also been identified in the mouth and the small intestine[38]. *A. muciniphila* can colonize the gastrointestinal tract from the first month and increases in prevalence and abundance within the first year of life[34,36]. In adults, its relative abundance varies between 0 and 4%, whereas its prevalence varies per study depending on age, geographic location, diet and health status[18,34–37,39]. Metagenomes from humans of various ages and backgrounds showed that 1,159 out of the 3,810 samples collected produced metagenome-assembled genomes identified as *A. muciniphila*[40]. In centenarians and super-centenarians, *Akkermansia* spp. sequences are abundant among the shrunken core of gut microorganisms found in these groups, and are hypothesized to be a marker for healthy ageing[41–45]. A decrease of *Akkermansia* spp. in late life is also reported[46,47]. It is still unclear whether inflammation in the gut of centenarians is prompted by mucin-degrading bacteria or whether it creates a less beneficial environment for *A. muciniphila*; however, the presence of *A. muciniphila* can benefit mucosal and metabolic health[47]. The presence and abundance of *A. muciniphila* also depends on geography. Colonization incidence differs between Chinese and Western populations[37], and different stains are more often associated with certain geographical locations[48]. This could be due to the host genotype or the environment, or due to food habits. The effect of low-fibre diets, dietary emulsifiers[49] and other compounds known to adversely alter the microbiota[49] should be studied in more detail for their effects on the presence or absence of strains and species of *Akkermansia*. As *A. muciniphila* is present in some humans but absent in others, it remains to be answered whether the mucosal niche is occupied by other microorganisms in its absence and what the possible reasons and consequences could be. Furthermore, improvement of sampling and DNA isolation from mucus would provide a more accurate representation of *Akkermansia* spp. in the gut, as its main niche is the mucosal layer and current data are mostly based on faecal samples.

Akkermansia species and strain occurrence and functionality

For a long time, *A. muciniphila* was the only isolated representative of the Verrucomicrobiota in the human gut. Recent efforts estimate four to seven phylogroups[48]. Genomic analysis of the *Akkermansia* genus suggests the presence of more than 25 *Akkermansia* spp. in the human gut[35,50–52]. The concept of hosting multiple species within one individual has recently been confirmed by bioinformatics analysis of multiple *Akkermansia* genomes[51]. On the strain level, human guts are not exclusively colonized by a single strain of *A. muciniphila* (Box 1) but, rather, by a collection of strains, where usually one strain dominates[53]. This richness on the strain level indicates that strains can compete; however, the suppression of strains can also be the result of host environmental conditions. Isolated strains from different mammals have low genomic and physiologic divergence based on their genomes, their growth on mucin, and short-chain fatty acid (SCFA) production[54]. This suggests optimization to and co-evolution with the mucosal environment[31] (Table 1), a characteristic that is embedded in the pangenome of the genus[51]. Despite the genus-wide association with mucus, *Akkermansia* spp. demonstrate differences in physiology (Table 1). *Akkermansia biwaensis* showed significantly increased growth in human milk oligosaccharides (HMOs) 2′-fucosyllactose (2′-FL), 3′-FL and 6′-sialyllactose (6′-SL) compared with *A. muciniphila* Muc^T, probably because of its diverse glycoside hydrolase profile[55]. Nonetheless, *A. muciniphila* grows on fucose, whereas *Akkermansia massiliensis* and *Akkermansia glycaniphila* can grow on galactose[56,57]. *A. muciniphila* also exhibits strain-specific functional profiles[52,55,58–60]. Examples include the utilization efficiency of HMOs[55], as well as the ability to synthesize

Table 1 | *Akkermansia* species that have been characterized and proposed

Parameter	*Akkermansia muciniphila*[17]	*Akkermansia biwaensis*[205]	*Akkermansia massiliensis* strain DSM 33459 (ref. 57)	*Akkermansia timonensis*[57]	*Akkermansia glycaniphila*[56]	*Akkermansia intestinavium*[206]	*Akkermansia intestinigallinarum*[206]
Isolation source	Human faeces	Human faeces	Human faeces	Human faeces	Python faeces[56,48]	Chicken faeces	Chicken faeces
Mucin substrates	Mucin, fucose, GlcNAc, GalNAc, mannose[81,205]	Mucin, GlcNAc, GalNAc, mannose[55,205]	Mucin, galactose, glucose, mannose, GlcNAc	Not characterized	Mucin, glucose, galactose, GlcNAc, GalNAc, mannose[205]	Not characterized	Not characterized
HMO substrates	Glucose, HMOs (2′-FL, 3′-SL, LNnT and others)[76]	Glucose, lactose, HMOs (2′-FL, 3′-FL, LNT and others)[55]	Lactose	Not characterized	Lactose, glucose	Not characterized	Not characterized
Growth temperature	20–40 °C (optimum, 37 °C)	25–45 °C (optimum, 30–37 °C)	(optimum 37–42 °C)	Not characterized	15–40 °C (optimum 25–30 °C)	Not characterized	Not characterized
pH	5.5–8.0 (optimum 6.5)	5.5–9.5 (optimum 6.5–8.0)	6.0–7.5	Not characterized	5.0–7.5 (optimum 6.0)	Not characterized	Not characterized
Phylogroup	AmI, AmII, AmIII[50,59]	AmIV	AmII	AmIII[57]	Agy[48]	Not characterized	Not characterized
Similarity to Amuc 16S rRNA gene	100%	98.0%	Not characterized	Not characterized	94.4%	Not characterized	Not characterized
ANI to Amuc	100%	84.5%	88.0%	82.0%	79.7%	Not characterized	Not characterized
Confirmed species name	Yes	Yes	Yes	*Candidatus*	Yes	*Candidatus*	*Candidatus*

ANI, average nucleotide identity; 2′-FL, 2′-fucosyllactose; GalNAc, *N*-acetylgalactosamine; GlcNAc, *N*-acetylglucosamine; HMO, human milk oligosaccharide; 3′-SL, 3′-sialyllactose.

vitamin B_{12} (presence in phylogroup AmII versus absence in phylogroup AmI), which leads to distinct fermentation products[59]. Strain characteristics can lead to different host responses. Strain-specific effects have been reported for gut integrity[58,60] and host metabolism[52] in mice models of ulcerative and chronic colitis, and in preclinical obesity mice models, respectively. This functional diversity between species and strains stresses the importance of isolation and thorough characterization of new isolates to evaluate strain–strain interactions and strain-specific applications.

Biological features of *A. muciniphila*

In this section, we describe key features of *A. muciniphila* and summarize essential features of its metabolism and physiology.

Morphology and outer membrane structure

A. muciniphila is Gram-negative, oval-shaped and 0.6–1.0 µm long when grown in vitro[17]. The first electron microscopy images revealed pili-like filaments, which turned out to be involved in immune stimulation and attachment to other cells and mucus[17]. Extraction of *A. muciniphila* membrane proteins identified PilQ (Amuc_1098) as a prominent outer membrane protein[61]. The *A. muciniphila* genome possesses several type IV pili proteins[62] and the products of this gene cluster were enriched in a fraction of membrane and cell-envelope proteins[63]. Amuc_1098 was annotated as PilQ from a type IV pilus and was confirmed to localize in the outer membrane[61]. Furthermore, the outer membrane protein Amuc_1100 is structurally similar to PilO of the type IV pilus system, and the *A. muciniphila* protein Amuc_1102 displayed structural similarity to an archaeal type IV pilus[64]. Type IV pili are implicated in a broad variety of cell functions, including adherence, motility and biofilm formation (reviewed in ref. 62) (Fig. 1). The outer membrane protein Amuc_1100 is immunostimulatory and induces Toll-like receptor 2 (TLR2) activation and cytokine production[63]. *A. muciniphila* is known to adhere to in vitro cultured colonic epithelial cells[65]. Furthermore, *A. muciniphila* specifically binds mucin O-glycans through recognition of LacNAc (*N*-acetyllactosamine; Galβ_{1-4}GlcNAc), which often occurs in human colonic mucin[66]. However, further studies are needed to understand the structure and function of pili in *A. muciniphila* and other possible mechanisms that it applies to attach. Apart from the pili proteins, host interaction has been described through *A. muciniphila* lipopolysaccharide (LPS), which induces the production of NF-κB and cytokines in the host through TLR4 (refs. 18,63,65). Furthermore, in response to cocultivation with *Bacteroides thetaiotaomicron*, *A. muciniphila* upregulated its LPS biosynthesis genes, which was hypothesized to increase resistance to antimicrobial peptides[67]. Moreover, the peptidoglycan layer of *A. muciniphila* contains non-acetylated glucosamine residues, which are not commonly observed in Gram-negative bacteria[68]. Indeed, muropeptides from *A. muciniphila* are recognized by host receptors NOD1 and NOD2.

Physiology and essential metabolism

The preferred substrate of *A. muciniphila* is mucin, and it can utilize fucose, glucose, *N*-acetylgalactosamine (GalNAc) and *N*-acetylglucosamine (GlcNAc), but only in the presence of GlcNAc[17,69]. It is also auxotrophic for L-threonine (that is, it is unable to synthesize L-threonine)[69]. After transport inside the cell, GlcNAc is phosphorylated

Box 1 | Challenges in isolation of new *Akkermansia* species and strains

There is a noteworthy genetic characteristic that has posed a major bottleneck in identifying more *Akkermansia* spp. An example is the newly isolated *Akkermansia* sp. DSM 33459 from human faeces. This strain has 99.2% identity of the 16S rRNA gene with type strain Muc^T, but merely 87.5% average nucleotide identity (ANI) with *Akkermansia muciniphila* Muc^T. A study indicates that *Akkermansia* sp. DSM 33459 belongs to the AmII cluster, and therefore it is most likely that this isolate is an *Akkermansia massiliensis*[57]. In either case, *Akkermansia* sp. DSM 33459 has a different fatty acid profile and substrate utilization preferences[52]. Furthermore, *Akkermansia* spp. feature an open pangenome with many unique genes, especially in the cluster of *A. muciniphila*. This could explain the high 16S rRNA identities and the relatively low ANI, which further suggests that use of the 16S rRNA gene may have hindered the isolation of new species. Studies including metagenomics analysis have investigated this specifically for the *A. muciniphila* cluster.

A study enrolling Chinese individuals isolated 33 new *A. muciniphila* strains (assigned to AmI, AmII and AmIII) from human faeces[50]. Additionally, the ANI between the groups was 86.8–91.5%, which is below the threshold of 96% that defines a distinct prokaryotic species[207]. However, the 16S rRNA genes are highly similar between the phylogroups (>99%), which could be explained by the pangenome hypothesis as discussed above. Furthermore, the phylogroups are similar in phenotype and habitat[50]. Another extensive genomic analysis that combined isolate genomes and metagenome-assembled genomes of the *Akkermansia* genus grouped the *A. muciniphila* strains of the human gut into five different candidate subspecies (Amuc1–Amuc4 and AmucU (unassigned))[35]. Interestingly, these subspecies display ecological co-exclusion within the host and have distinct associations with host body mass. Furthermore, they have distinct functional profiles[35] and differ in prevalence globally[48]. Also, recently, six new strains were isolated from human donors that were found to belong to subspecies Amuc1 and AmucU[88]. Similar to the study that isolated 33 new *A. muciniphila* strains, the whole genome similarity was relatively low (<90%), whereas the 16S rRNA genes were highly similar (>98%)[35]. A third study that enrolled children and adolescents who were being treated for obesity isolated and characterized 71 new *A. muciniphila* strains[208]. This effort led to the classification of *Akkermansia* into four phylogroups (AmI–AmIV).

Future studies should attempt to better understand the species richness of *Akkermansia* in the gut. In this context, metagenomics is a valuable tool to analyse faecal and mucosal samples. The draft genomes will also help design isolation strategies. Advanced techniques for single-cell isolation and characterization should further aid the isolation of new *Akkermansia* strains. New isolates will give better insight into genome composition as well as different physiological characteristics. It is of interest to know the importance of *Akkermansia* spp. richness and diversity in the gut to better understand the role of different species in gut ecology and host physiology.

and enters the glycolysis pathway or the peptidoglycan synthesis pathway. Mucin glycan fermentation by *A. muciniphila* results in the production of acetate, propionate, succinate and 1,2-propanediol[70], and the release of sulfate[17]. When grown on monosaccharides, acetate and propionate are the main secondary metabolites, but their ratio varies depending on whether GlcNAc or GalNAc, or the deacetylated D-glucosamine (GlcN) and glucose are used as a carbon source[69]. In the latter case, more propionate is produced. This could be because acetate produced by glucose is transformed into acetyl-CoA to enable the acetylation of GlcN. The utilization of fucose upregulates the deoxyhexose pathway in *A. muciniphila* and leads to the production of 1,2-propanediol. These metabolites are produced during anaerobic fermentation, but tolerably low oxygen concentrations increase the acetate to propionate ratio[31].

The metabolites that result from mucin fermentation beneficially affect both host epithelial and immune cells, as well as having a systemic effect[71]. Acetate and propionate are instrumental in the process of glucose regulation, the metabolism of food components, and energy regulation. These processes involve regulation of gut hormones, such as peptide YY and glucagon-like peptide 1 (GLP1), as well as other hormones such as insulin and glucagon, and also the regulation of appetite and gastric emptying[72–74]. In addition, propionate and succinate can be used in the liver for glucose production[75]. Lastly, evidence suggests that propionate exerts an antiproliferative effect on colon cancer cells[74].

A. muciniphila adaptation to the gut environment

In this section, we discuss findings that report specific adaptations of *A. muciniphila* to the gut mucosa.

Carbon sources used for growth by *A. muciniphila*

Degradation of mucus glycans and associated metabolite production. The *A. muciniphila* genome encodes all enzymes necessary to collectively degrade mucin glycans (Fig. 2). Fucose, sialic acid and sulfate groups, which occupy the terminal positions of mucin glycans, are hypothesized to hinder access to the underlying glycans, and therefore their release is essential for mucin glycan degradation[76,77]. *A. muciniphila* encodes 12 sulfatases, six of which were upregulated during growth on mucin[70]. These sulfatases have varying specificities, targeting 4S-Gal, 4S-GalNAc and/or 6S-GalNAc sulfations that occur in mucin, as suggested by a recent preprint[78]. Even though *A. muciniphila* cannot metabolize sialic acid, it encodes three sialidases[18,79]. Two sialidases are from family GH33 and act on $\alpha_{2,3}$-sialic acid and $\alpha_{2,6}$-sialic acid linkages as suggested by a recent preprint, and one from family GH181 which specifically acts on the sialylated Tn antigen[78,80]. The *A. muciniphila* fucosidases from families GH29 (four in number) and GH95 (two in number) are active during growth on mucin[81] and target a broad range of fucosylated substrates with different specificities as suggested by a recent preprint[78,80]. Mutagenesis revealed that one GH33 sialidase, one GH29 fucosidase and one GH95 fucosidase are important for mucin glycan degradation by *A. muciniphila*, and proteomics analysis confirmed that this GH95 enzyme is highly abundant during growth on mucin[82,83].

To cleave galactose, GlcNAc and GalNAc from mucin, *A. muciniphila* encodes galactosidases and hexosaminidases[81,84] (Fig. 2). *A. muciniphila* encodes α-galactosidases from families GH27, GH36, GH97 and GH110, and β-galactosidases from families GH2, GH16 and GH35 with varying specificity as suggested by a recent preprint[78,84–86]. In particular, an outer membrane-associated GH16 β-galactosidase

cleaves the poly-LacNAc chain[82,85]. One of the GH110 α-galactosidases was abundant during growth on mucin[83]. Furthermore, *A. muciniphila* encodes hexosaminidases from families GH18, GH20, GH36, GH84, GH89 and GH109 (ref. 87). More specifically, *A. muciniphila* encodes α-*N*-acetylgalactosaminidases from families GH36 and GH109. A recent preprint suggests that one GH36 enzyme from *A. muciniphila* can cleave a broad range of α-GalNAc substrates including the Tn antigen that forms the base of the mucin glycan[78]. Interestingly, the preprint reported that two GH31 enzymes can cleave GalNAc from the mucin peptide backbone, but not the Tn antigen[78]. Both α-*N*-acetylglucosaminidases (GH89) that *A. muciniphila* encodes are abundant during growth on mucin, whereas mutation of one of these enzymes impaired growth[82,83]. Finally, *A. muciniphila* encodes β-*N*-acetylglucosaminidases from families GH18, GH20 and GH84 (ref. 87). The GH20 enzymes of *A. muciniphila* are mainly exo-acting β-*N*-acetyl-glucosaminidases with varying specificities, with some also demonstrating activity against GalNAc, whereas the GH84 β-*N*-acetylglucosaminidase showed a preference for disaccharides in a recent preprint[78]. Interestingly, this GH84 was abundant during growth on mucin[83]. The GH18 β-*N*-acetylglucosaminidase has not been characterized, but mutation of this enzyme did not lead to growth impairment on mucin, and not all *A. muciniphila* strains encode GH18, suggesting that this enzyme may not be essential for mucin degradation by *A. muciniphila*[82,88].

A. muciniphila can ferment fucose, glucose, GalNAc and GlcNAc, but requires the presence of GlcNAc for growth[69]. During mucin degradation, the complete glycans or their degradation products accumulate in *A. muciniphila* internal compartments. Mucin degradation is facilitated by a cluster of genes which was termed the mucin utilization locus (MUL) and includes genes encoding pili and a periplasmic protein complex[82]. It is expected that the success of *A. muciniphila* lies in the high mucin specificity of its enzymes, which have been extensively characterized in a recent preprint[78]. This is an important feature, as mucin degradation will occur in a network of cooperating microorganisms[87,89] and will rarely, if ever, be carried out by a single microorganism.

Degradation of human milk glycans and establishment in early life. *A. muciniphila* appears in the gut in early life and is also detected in breast milk samples[36,90]. Approximately one in ten breastfed infants harbour *A. muciniphila*, and cessation of breastfeeding is associated with elevated levels[91]. The effect of infant feeding is not fully established, as there is evidence of both an increased relative abundance of *A. muciniphila* in formula-fed infants[92,93] and no differences[91]. Work on mice colonized with synthetic microbial communities showed that mothers fed a low-fibre diet nursed pups with a delayed increase of *A. muciniphila* and several altered parameters of the immune system[94]. Moreover, mice colonized with organisms from faeces of infants breastfed by non-secretor mothers had significantly higher *Akkermansia* spp. abundance than those fed by secretor mothers[95]. Secretor mothers possess a functional secretor gene (*FUT2*) which allows for $\alpha_{1,2}$-linked fucose at the backbone of HMOs. However, it would also be relevant to investigate the association of *Akkermansia* spp. levels with the secretor status of pups, as this affects mucosal fucosylation patterns available to mucolytic bacteria. Accumulating evidence suggests that *A. muciniphila* colonization in early life may be evolutionarily orchestrated due to its ability to degrade and grow both on mucin and on HMOs[81]. HMOs contain glycosidic structures that are similar to mucin glycans[81]. *A. muciniphila* employs its mucin glycan-degrading enzymatic machinery for the degradation of HMOs. This machinery includes a GH29 α-fucosidase, GH33 α-sialidases, GH35 β-galactosidases and GH20 β-hexosaminidases[55,81,96]. Another component of human milk, namely betaine, influences the abundance of *Akkermansia* spp. and can modulate long-term metabolic health[97]. Possibly, the abundance of *A. muciniphila* in early life is maintained low enough to protect the developing mucosal layer, but high enough to interact with the developing immune system.

Protein degradation and amino acid synthesis

A. muciniphila possesses proteases that cleave the peptide backbone of mucins[18]. For some proteases, in vitro mucin protein degradation was proven. Amuc_1434 and Amuc_0627 can degrade MUC2 (refs. 98,99). Amuc_0627, Amuc_0908 and Amuc_1514 belong to the M60-like/PF13402 family, which recognizes and hydrolyses O-linked glycoproteins, and cleave O-glycosylated serine or threonine residues from mucin[100]. Furthermore, Amuc_1438 and Amuc_1119 (OgpA) were identified as O-glycopeptidases that specifically cleave the peptide backbone amino terminus to an O-glycosylated serine or threonine[101,102]. *A. muciniphila* depends on the threonine of host mucin for a nitrogen source in vitro[70]. Mutagenesis experiments showed that it needs to synthesize the other amino acids de novo when grown on mucin, most likely because of their growth-rate limiting abundances in the protein backbone[82].

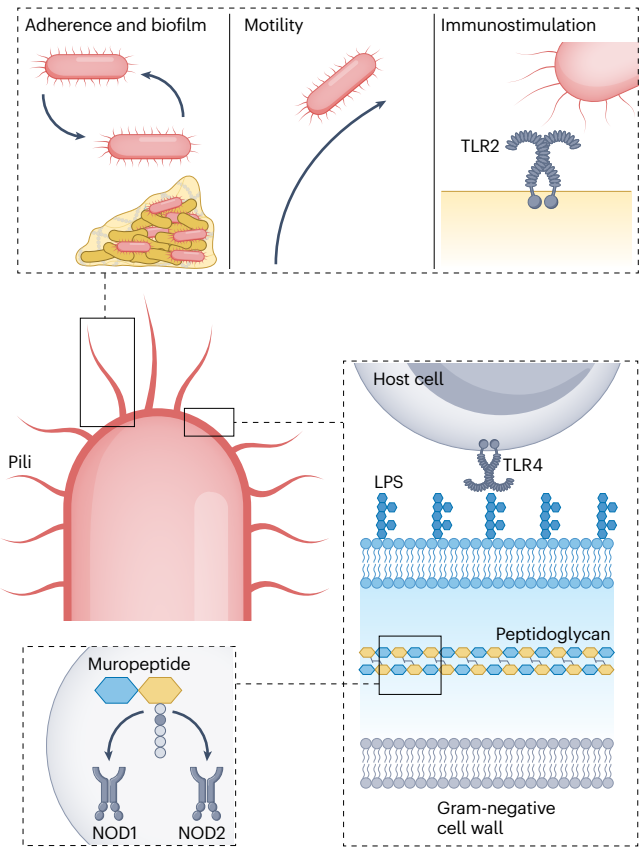
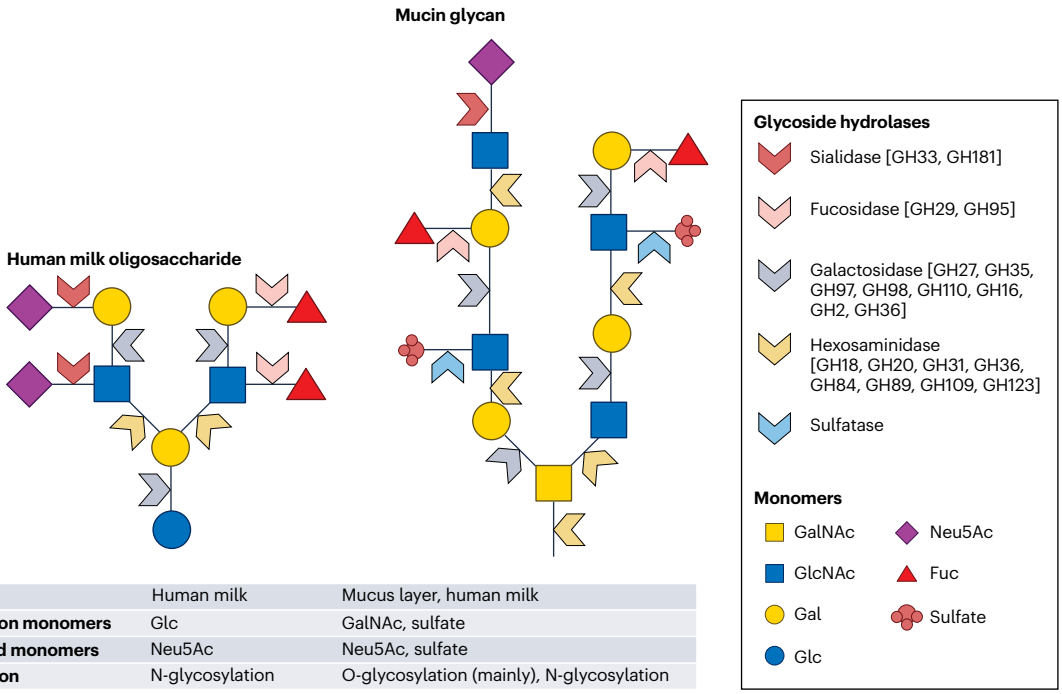


Fig. 1 | Biological features of *A. muciniphila*. Pili and cell membrane components are key biological features of *Akkermansia muciniphila*. The pili are involved in adherence and biofilm formation, cell motility and immunostimulation through Toll-like receptor 2 (TLR2). *A. muciniphila* has a Gram-negative type cell wall with lipopolysaccharide (LPS) in the outer layer, and an inner peptidoglycan layer composed of muropeptides. These muropeptides are recognized by host receptors NOD1 and NOD2.



Source	Human milk	Mucus layer, human milk
Non-common monomers	Glc	GalNAc, sulfate
Non-utilized monomers	Neu5Ac	Neu5Ac, sulfate
Glycosylation	N-glycosylation	O-glycosylation (mainly), N-glycosylation

Fig. 2 | Enzymatic arsenal of *A. muciniphila* for the degradation of mucin glycans and human milk oligosaccharides. *Akkermansia muciniphila* produces sialidases, fucosidases, galactosidases, hexosaminidases and sulfatases that target both mucin glycans and human milk oligosaccharides (HMOs). These glycans share common structures, but also have differences regarding their source, certain monomers and utilization as well as their glycosylation type. The gut mucus layer is composed of mucins, which are highly glycosylated proteins. These mucin glycans consist of *N*-acetylgalactosamine (GalNAc), *N*-acetylglucosamine (GlcNAc) and galactose, and are decorated with sialic acid (Neu5Ac), fucose and/or sulfate. By contrast, HMOs are free oligosaccharides in breast milk that consist of glucose, galactose, GlcNAc and GalNAc, and are decorated with sialic acid or fucose. Due to these structural similarities, *A. muciniphila* is able to degrade both substrates with similar enzymes.

Oxygen tolerance

Even though the intestines are considered an anoxic environment, the submucosa has an oxygen level of 80–100 mmHg. This gradient ends with near anoxia at the midpoint of the lumen, deeming it the steepest in the human body[103]. Therefore, bacteria in the mucosal layer should be adapted to oxygen presence. *A. muciniphila* survives aerobic conditions at a rate of 90% for 1 h[65] and grows faster and to a higher yield in nanomolar amounts of oxygen, with evidence of oxygen reduction[31]. *A. muciniphila* can also perform respiration in the presence of oxygen by using the cytochrome bd complex (Amuc_1694–Amuc_1965) as a terminal oxidase. More recently, *A. muciniphila* cells were collected with a high survival rate after 72 h at 4 °C and 22 °C[104]. Another restriction related to aerobic growth that *A. muciniphila* overcomes is the handling of reactive oxygen species (ROS). Upregulation of catalase HPII, alkyl hydroperoxide reductase and superoxide dismutase signify transformation of ROS to non-toxic forms of oxygen[31]. The survival of *A. muciniphila* for 24 h within macrophages and monocytes[105] further exemplifies its ability to handle ROS.

Bile acid resistance

Bile acids are involved in lipid digestion and, despite reabsorption in the ileum, around 5% reach the large intestine[106]. *A. muciniphila* resists different concentrations of bile acids in vitro, but this is dependent on the bile acid source. Porcine bile extract of 0.1%, 0.5% and 1% led to increased growth[107], whereas 0.5% of purified bile salt inhibited growth[69]. The composition plays a role, as deoxycholic acid promoted *A. muciniphila* growth whereas other bile acids had an inhibitory effect or no effect[108]. In rodent models, the relative abundance of *A. muciniphila* in the caecum and faeces was positively associated with circulating primary bile acids[109,110]. In the presence of bile acids, *A. muciniphila* altered extracellular polymeric substances (EPS) biosynthesis-related and export-related enzyme expression, suggesting a possible change in membrane structure[108]. Alteration of EPS in bifidobacteria[111] directly protected against bile acids[112]. Therefore, it is possible that a similar protective effect of EPS from *A. muciniphila* could contribute to increased growth in bile acids[111,112], along with squalene-associated membrane structures[108]. However, intracellular bile acids could be exported by a putative bile acid transporter (Amuc_0139) which is continuously expressed, along with other transporters that have been shown to be upregulated by ox bile[108]. Additional research is needed to clarify the association between EPS and bile resistance in *A. muciniphila*. This includes better characterization of its EPS, gene knockouts and heterologous expression of EPS-related genes, as well as in vivo supplementation of *A. muciniphila* with variable bile acid compositions.

Polyphenols as prebiotic supplement

The consumption of food affects the gut environment, and food rich in polyphenols is correlated with an increase of *A. muciniphila*. Mice fed a high-fat diet supplemented with either cranberry extract[113] or

concord grape polyphenols[114] had improved metabolic and immunological markers together with an increase in *A. muciniphila*. Moreover, colitis-induced mice that were supplemented with diosmin in their diets showed an increase in *A. muciniphila*, reduced inflammation markers and increased MUC2 expression[115]. In a human cohort supplemented with 600 mg black elderberry extract, *Akkermansia* spp. were significantly associated with the consumption and this association persisted after the supplementation[116]. The possible mechanism through which different polyphenols boost *Akkermansia* spp. has not been completely resolved, but possible modes of action have been extensively reviewed[117,118]. These include a direct effect on *A. muciniphila* through utilization or an indirect effect either by altering the surrounding environment[119] or by affecting bacteria interacting with *A. muciniphila*. There is no experimental evidence of its growth on polyphenols through degradation and utilization; the only indication comes from computationally inferred enzymes[117,118]. However, polyphenol administration to mice increased mucus thickness[120] and the production of MUC2 (ref. 121), and this could result in more substrate for growth of *A. muciniphila*.

Role in host response and health

In this section, we summarize the mechanistic evidence for the cross-talk between *A. muciniphila* and the immune system. We also showcase the mechanisms through which *A. muciniphila* promotes metabolic health and improves gut barrier, as well as its role in the gut–brain axis (Fig. 3).

A. muciniphila interaction with the immune system

A. muciniphila is recognized by the immune system through TLRs. Incubation of HEK-Blue cells expressing single receptors with *A. muciniphila* or its supernatant stimulated TLR2 and TLR4, but not TLR5 and TLR9 (ref. 63). The pili of *A. muciniphila* are recognized by TLR2 and the LPS of its cell wall is recognized by TLR4 (refs. 63,122). The extracellular vesicles (EVs) of *A. muciniphila* could also stimulate TLR2 and TLR4, and subsequent signalling molecules[123]. This is highly relevant as most Gram-negative bacteria can only stimulate TLR4 (refs. 124,125). The TLR2–TLR1 heterodimer can be activated by the diacyl phosphatidylethanolamine found in the cell membrane of *A. muciniphila*[126], leading to responses including the production of cytokines and chemokines, and activation of other immune cells through NF-κB, mitogen-activated protein kinases (MAPKs) and phosphoinositide 3-kinases (PI3K)[127]. The molecular mechanisms have been reviewed extensively[127]. However, we would like to note that *A. muciniphila* seems to train the immune system and this in vitro and ex vivo observation paves the way for future research on early establishment of microorganisms in the gut. More specifically, a second administration of live *A. muciniphila* cells on macrophages and monocytes after a first administration, of either live or dead cells, resulted in a significant downregulation of cytokines in vitro, namely TNF and IL-10 (ref. 105).

Other *A. muciniphila* epitopes and host receptors are also involved in recognition. The peptide RKH, for example, binds to TLR4, and probably blocks its LPS-induced activation, which was tested both in vitro and in mice and piglet models, and was found to reduce inflammation in septic hosts[128]. Another peptide, p9, directly binds to ICAM2, an immunoglobulin-like adhesion peptide, and induces GLP1 and the respective peptide secretion[129]. p9 is also involved in IL-6 production, as shown in macrophages. Knocking out IL-6 production in mice also confirms its importance for GLP1 production[129]. *A. muciniphila* aminoacyl tRNA synthases (AmTARS), unlike TARS of other tested bacteria, are mainly secreted and are not transferred through EVs. Through TLR2 activation, they triggered IL-10 production in bone marrow-derived macrophages[130]. Ornithine lipids (OL) produced by *A. muciniphila*, found to be present in growth medium and its EVs, regulated inflammatory and anti-inflammatory cytokine production, including an increase in IL-10 that is also induced by LPS[131]. OL were not produced by the Gram-negative bacteria, *B. thetaiotaomicron* and *Escherichia coli*[131]. In the presence of *A. muciniphila*, bone marrow-derived macrophages presented increased expression of Tlr1, Tlr2 and Tlr4 and other receptors associated with bacterial recognition, including Nod1, Nod2 and Clec4 (ref. 105).

A. muciniphila promotes metabolic health

A. muciniphila has gained attention for its negative association with metabolic diseases including diabetes, obesity and fatty liver disease[132,133], and is positively correlated with lean phenotypes[32,134–136]. In mice, a high-fat diet had a detrimental effect on metabolic markers and diminished the level of *A. muciniphila* in the gut[137]. Even in individuals without obesity, those with type 2 diabetes had a significantly lower abundance of *A. muciniphila*[138]. However, *A. muciniphila* is also positively correlated with the use of metformin, the drug used by individuals with type 2 diabetes, and as such this should be considered as a confounder in such studies[139].

Live *A. muciniphila* supplementation in mice diminished some major effects of a high-fat diet such as weight gain, metabolic inflammation, insulin resistance and memory loss[122,140,141]. Furthermore, pasteurized *A. muciniphila* cells were more effective in suppressing weight gain in mice, which was also retained by sole administration of the Amuc_1100 pili. These effects have been replicated in several studies and one of the mechanisms reported is that *A. muciniphila* reduced serum triglycerides and alanine aminotransferase compared with the control in adult mice on a high-fat diet[142]. A proof-of-concept study that administered live and heat-inactivated *A. muciniphila* to humans yielded similar results with significantly lessened insulin and cholesterol levels in the blood compared with the untreated control group of individuals with a high body mass index[143].

The possible mechanisms through which *A. muciniphila* affects metabolism have been studied, mainly in models. An organoid study indicated that *A. muciniphila* specifically regulates metabolism-related gene transcription[144]. The observed protection from fat accumulation in the liver was proposed to relate to reduced transcription of sterol regulatory element-binding protein and IL-6 (ref. 142). The former is a transcription regulator that is important for fatty acid regulation and the latter is an interleukin that controls inflammation. Further evidence of how *A. muciniphila* can control fat accumulation comes from a study on *A. muciniphila*-treated mice. These mice showed restored levels of oxidation marker genes (*Cpt1a*, *Acox1*, *Pgc1a* and *Ppara*) after a high-fat diet[22]. The mechanism by which the immune system, *A. muciniphila* and glucose homeostasis are interconnected in mice has been elucidated. Interferon-γ (IFNγ), which can control IL-6 expression[145], affects the levels of *A. muciniphila* in mice via the *Irgm1* gene through direct binding[146], and subsequently the bacterium affects glucose regulation. In the same study, a negative correlation was found between *A. muciniphila* and glucose levels in humans, and between IFNγ-regulated genes in human duodenal biopsies. IL-6 induction from p9 was also found to regulate GPL-1 production, leading to a reduction in adipose tissue volume and glucose intolerance in mice fed a high-fat diet[129]. The relative abundance of *A. muciniphila* was also associated with genetic marks in the *PLD1*

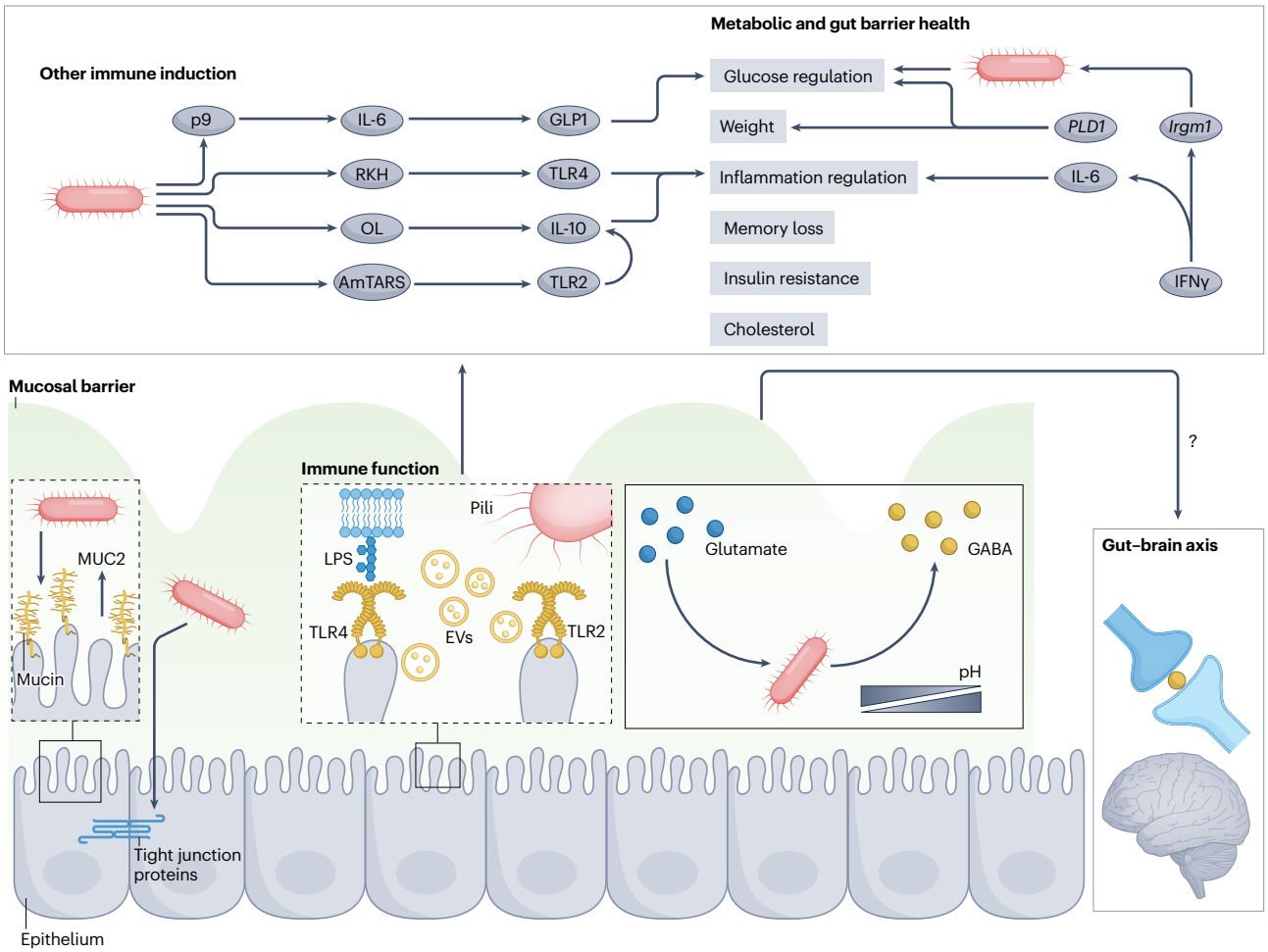


Fig. 3 | *A. muciniphila* and its interaction with the host. *Akkermansia muciniphila* has a direct interaction with the immune system via cell structures and excreted products. The recognition is mediated by Toll-like receptor 2 (TLR2) and TLR4 receptors, mainly, but more receptors may be implicated in the recognition such as glucagon-like peptide 1 (GLP1). *A. muciniphila* interacts with the host via its pili, lipopolysaccharide (LPS) and extracellular vesicles (EVs), and through other products such as p9, RKH, ornithine lipids (OL) and aminoacyl tRNA synthases (AmTARS). The recognition triggers cytokine-mediated immunological response as well as an improvement of various metabolic health markers. Multiple studies have researched the beneficial effects of live *A. muciniphila* supplementation in mice fed a high-fat diet. Among others, supplementation restricted weight gain, metabolic inflammation, insulin resistance and memory loss. A direct causal relationship has been found specifically between *A. muciniphila* and glucose levels. The interferon-γ (IFNγ) cytokine regulates the IL-6 cytokine and, through its binding to the *Irgm1* gene, the abundance of *A. muciniphila*, leading to glucose regulation. Association of *Akkermansia* spp. abundance with SNPs in the phosphatidylcholine phospholipase *PLD1* gene, which is important for appetite, weight, glucose and fatty acid regulation, further adds to evidence of metabolism regulation by the bacterium. The promising *A. muciniphila*-induced upregulation of the Marco receptor, which binds to low-density lipoprotein cholesterol, still needs to be researched in vivo. Regulation of anti-inflammatory cytokine production, such as IL-6 and IL-10, by the bacterium is suggested to be pivotal for hindering chronic inflammation in the gut. Moreover, *A. muciniphila* improves the gut barrier function by increasing mucin production by goblet cells and the tight junction proteins. *A. muciniphila* is also involved in the gut–brain axis communication through γ-aminobutyric acid (GABA), a neurotransmitter that it produces via glutamate in low pH.

gene, which encodes for a phosphatidylcholine phospholipase in humans[147]. Later studies showed that mice lacking this gene demonstrated increased weight and appetite, free fatty acid levels and glucose in the bloodstream[148]. *A. muciniphila* may also have a direct effect on cholesterol regulation; it was found to upregulate the Marco receptor of bone marrow-derived macrophages[105], which is known to bind to low-density lipoprotein cholesterol[149]. However, further in vivo research is needed to determine whether this has a direct effect on blood cholesterol regulation.

A. muciniphila and gut barrier integrity

The beneficial role of *A. muciniphila* in intestinal health encompasses gut barrier function, anti-inflammatory properties[22,23,63,139,150] and the physiology of mucus and the underlying epithelial layer. In vitro experiments of *A. muciniphila* on Caco-2 cell lines demonstrated its potential to strengthen enterocyte monolayer integrity, as evidenced by increased transepithelial resistance[65]. In mice fed a high-fat diet, *A. muciniphila* administration resulted in increased acylglycerol (endocannabinoid), mucus thickness and goblet cells. In specific

pathogen-free mice, *A. muciniphila* administration reduced plasma LPS levels[22,139,151]. In fast-ageing *Ercc1*-deletion mice, supplementation of *A. muciniphila* prevented the age-related decline of mucus layer thickness[24]. *A. muciniphila* also induces mucin production by goblet cells, thus contributing to mucus layer thickness and structure[152].

In vitro experiments in Caco-2 cells showed that both the sole pili protein and EVs increase gut permeability[23,63]. Inactivated cells and the pili protein had an anti-inflammatory and tumour-suppressive effect in mice, where the production of neoplasia-related cytokines, such as IL-6, and lymphocytes was reduced[153]. EVs isolated from *A. muciniphila* could halt the increase of IL-6 in mice with induced colitis[154]. Products from *A. muciniphila* significantly lessened the levels of IL-8 from TNF-stimulated human HT-29 cells in vitro and facilitated the in vivo restoration of gut microbiota diversity in mice with induced colitis[60]. Additionally, *A. muciniphila* promoted the differentiation of T helper cells and the production of SCFAs[60]. In a study including individuals with ulcerative colitis, a positive association was found between *A. muciniphila* abundance and the mucin sulfation, whereas lower abundances of *A. muciniphila* correlated with higher inflammation[155]. Recently, protein Amuc_1409 was found to promote intestinal stem cell differentiation in organoids and in mice, presumably through triggering Wnt/β-catenin signalling[156]. Other possible mechanisms could include TLR2-activated mucosal repair. Both in vitro and in vivo experiments with TLR2 knockouts showed a direct upregulation of TFF3, important for mucosal restoration, but no effect on MUC2, KLF4 and Math1 (ref. 157). Additionally, ex vivo experiments with TLR2 knockouts and in vitro experiments showed that TLR2 activation is a determinant for MyD88-dependent phosphorylation of Akt leading to tight junction-associated barrier integrity[158]. Future research could employ experiments with *A. muciniphila* to investigate whether the bacterium, its pili or its EVs can confer the same TFF3 regulatory effect.

Conversely, some studies associate *A. muciniphila* with impaired mucosa and the occurrence of allergies. Mice colonized with minimal microbiomes and fed a diet without fibre had an elevated relative abundance of *A. muciniphila*, presumably due to mucin degradation resulting from the lack of other complex glycans[159–162]. One such study showed that, depending on the absence or presence of fibre, *A. muciniphila* either aggravated or protected against infection by *Citrobacter rodentium*[162]. Other experiments in ovalbumin and cholera toxin-sensitized mice showed that, in the absence of fibre, a synthetic community including *A. muciniphila* led to a lower amount of ovalbumin-specific antibodies despite a more severe allergic reaction[161]. Mucus erosion was also suggested to modulate graft-versus-host disease in mice treated with imipenem–cilastatin[163]. In these mice, *A. muciniphila* relative abundance was increased together with reads mapped to genes involved in mucus degradation[163]. Further studies with microbial consortia will provide more clarity on the cross-talk between the microbiome, including *A. muciniphila*, external factors such as diet and medicines, and the immune system. However, such results should be critically interpreted using absolute abundances, as an altered gut microbiota biomass can skew relative abundances of certain bacteria. It remains imperative to further investigate this in studies for its relevance to human health, as the bacterium has not been associated with these diseases in humans.

A. muciniphila and the gut–brain axis

A. muciniphila might play a key role in the gut–brain axis. *A. muciniphila* produces γ-aminobutyric acid (GABA) in acidic conditions (pH < 5.5) in the presence of mucin[164]. The synthesis of GABA from glutamate by *Akkermansia* spp. occurs through glutamate decarboxylase[165]. The GABA produced by *A. muciniphila* can directly serve as a neurotransmitter. However, the translocation of GABA from the gut to blood is not yet clear. In mouse models, an increased relative abundance of *A. muciniphila* led to a decrease in γ-glutamylated amino acid levels in both the lumen and serum. This increased the levels of GABA and glutamate in the gut, and raised the GABA to glutamate ratio in the brain, which is protective against seizures[166]. In an observational study, *A. muciniphila* was enriched in healthy controls compared with individuals with bipolar disease and showed a positive correlation with serum GABA levels[166,167]. Additionally, in children with tic disorder, *A. muciniphila* was negatively correlated with tic severity[168]. *Akkermansia* spp. are also enriched in individuals with Parkinson disease. It is hypothesized that this is a consequence of the altered sulphuration in individuals with Parkinson disease, as *A. muciniphila* plays a role in gut sulfur metabolism[169]. Furthermore, *Akkermansia* spp. were increased in individuals with multiple sclerosis. However, the same study showed that *Akkermansia* spp. were negatively associated with disability and lesion size, and positively associated with brain volume, suggesting that increased *Akkermansia* spp. in multiple sclerosis could be a beneficial compensating response[170]. In an amyotrophic lateral sclerosis mouse model, *A. muciniphila* gradually decreased during disease progression, and supplementation of *A. muciniphila* in these mice ameliorated symptoms[171]. Overall, these studies suggest that *A. muciniphila* may play a role in the gut–brain axis, although more research is required to further elucidate the mechanisms of action and to establish causality.

A. muciniphila as a member of the gut microbiome

A. muciniphila plays a role in the complex microbial networks of the human gut and the mucosal layer. The species builds interactions with other human gut commensals through cross-feeding (Fig. 4). More specifically, through cross-feeding, *A. muciniphila* can sustain other microorganisms during in vitro growth on mucin glycans and HMOs[20,80,172,173]. The availability of degraded glycans and metabolites can support butyrate production by butyrate producers *Anaerostipes caccae*, *Anaerobutyricum hallii*, *Faecalibacterium duncaniae*, *Roseburia inulinivorans* and *Roseburia hominis* in co-culture[20,173]. *A. muciniphila* and *A. hallii* demonstrate bidirectional cross-feeding by trading mucin-derived sugars and 1,2-propanediol for a vitamin B_{12} analogue[20]. *A. caccae* stimulates the expression of mucin degradation genes in *A. muciniphila*[172]. Furthermore, *R. inulinivorans* and *R. hominis* both cross-feed on the sugars liberated from mucin by *A. muciniphila*[173]. More complex ecological interactions of *A. muciniphila* have been studied in a synthetic community, which was constantly supplied with mucin and regularly fed with dietary fibres[174]. *A. muciniphila* was among the most abundant microorganisms and contributed to two trophic guilds: the degradation of complex substrates and the degradation of simpler carbohydrates[174].

In human adults, the genus *Akkermansia* was enriched in the enterotype that is named after the *Ruminococcus* genus. In this cluster, *Akkermansia* spp. are positively correlated with *Ruminococcus*, Ruminococcaceae and *Gordonibacter* spp. Conversely, for the *Prevotella*-named enterotype, a negative correlation between *Akkermansia* and *Prevotella* spp. was found[175,176]. Other studies found several positive correlations between *A. muciniphila* and other species such as the saccharolytic *Bacteroides caccae*, the butyrate producer *A. hallii* and the methane-producing archaeon *Methanobrevibacter smithii*[133]. Faecal virome transfer from mice with >6% of *A. muciniphila* resulted in mice with higher relative abundances of *A. muciniphila*[177]. This paves new avenues for the investigation of *A. muciniphila* cross-kingdom interactions.

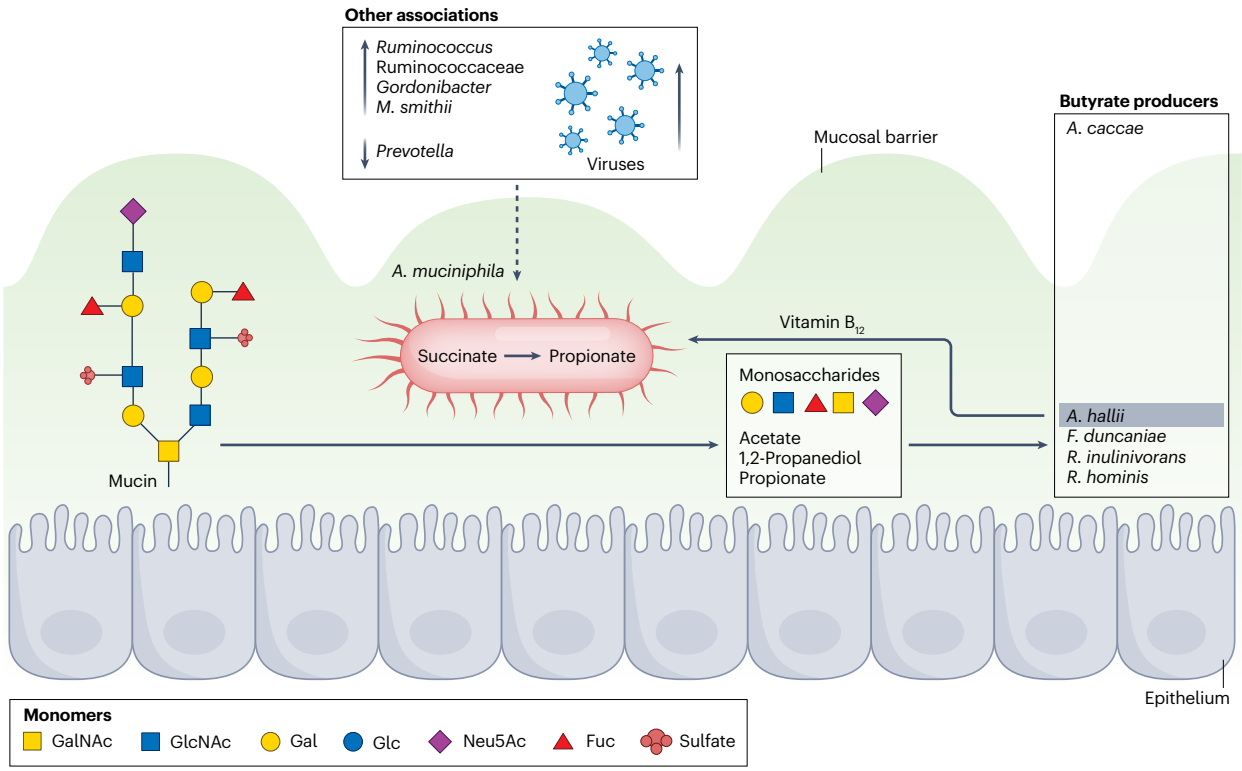


Fig. 4 | Ecological interactions between *A. muciniphila* and other members of the human gut microbiota. Mucin glycan degradation by *Akkermansia muciniphila* liberates saccharides and metabolites that become available for cross-feeding by other members of the mucosal microbiota. During growth on mucin, *A. muciniphila* releases monosaccharides and produces acetate, 1,2-propanediol and propionate. Through cross-feeding, *A. muciniphila* fosters the growth of butyrate-producing bacteria, such as *Anaerostipes caccae*, *Anaerobutyricum hallii*, *Faecalibacterium duncaniae*, *Roseburia inulinivorans* and *Roseburia hominis*, resulting in the production of the beneficial compound butyrate. A bidirectional cross-feeding relationship exists between *A. muciniphila* and *A. hallii* because a vitamin B_{12} analogue is used by *A. muciniphila* to produce propionate from succinate. More positive and negative associations with other bacteria, archaea and viruses have been identified, but the complete mechanism of their possible interactions has not been fully characterized. *A. muciniphila* is positively associated with *Ruminococcus*, Ruminococcaceae, *Gordonibacter* and *Methanobrevibacter smithii*, whereas it was negatively associated with *Prevotella*. GalNAc, *N*-acetylgalactosamine; GlcNAc, *N*-acetylglucosamine; Neu5Ac, *N*-acetylneuraminic acid (also known as sialic acid).

Potential future applications of *A. muciniphila*

In the previous sections, we summarized two decades of science on *A. muciniphila*. In this section, we look forward by discussing its ecological function, how *A. muciniphila* genetic models could enhance our knowledge of this bacterium, how we could exploit the enzymes that it produces for biotechnological and biopharmaceutical applications and how *A. muciniphila* could be applied as a therapeutic (Fig. 5).

Ecology

The current understanding that multiple strains of *A. muciniphila* colonize host systems and that different species exist should be further explored to understand their distinct patterns of associations with host health, diversified functional capabilities, strain suppression and ecological structure. Genome diversity indicates a large phylogenetic and functional diversity of the *Akkermansia* genus[35]. New isolates will help understand subspecies-level genetic stratification and why certain species dominate over others, why some strains are human-specific, why strains are related to human geographical location and their health-inducing properties or connection with animal species. Such insight will also be necessary to predict the effectiveness of strains for therapeutic applications and possible engraftment in ecological structures. The finding of *Akkermansia*-associated bacteriophages in relation to relative abundance of *Akkermansia* spp. could also lead to targeted suppression of *Akkermansia* spp. and explain possible strain–strain competition[35].

Genetic model

A robust system for the genetic manipulation of *A. muciniphila* is lacking. A patent for genetic engineering of *A. muciniphila* through random transposon mutagenesis has been published and applied[82]. The study retrieved valuable results on *A. muciniphila* colonization strategy and mucin utilization mechanisms. However, it is less suitable for targeted mutagenesis and the field awaits a more robust system. Being able to genetically manipulate *A. muciniphila* will identify the functions that this bacterium exhibits. The lack of genetic tools for manipulation of *A. muciniphila* suggests that it is not straightforward for this organism. Its features that belong to the Verrucomicrobiota phylum, anaerobic nature, sensitivity to oxygen, outer membrane structure and restriction–modification systems can hamper traditional protocols using vectors, electroporation, the bacteriophage-λ recombination system and CRISPR–Cas. More in-depth knowledge about these features and accessibility of different strains with various features can lead to progress in this field of study.

Enzyme production

The discovery of *A. muciniphila* OgpA led to the establishment of an analytical workflow to study O-glycosylation of proteins with potential biotechnological and biopharmaceutical applications. *A. muciniphila* *O*-glycopeptidase OgpA exclusively cleaves the peptide bond that is N-terminal to O-glycosylated serine or threonine residues. Therefore, OgpA can be applied to map O-glycosylation sites on a protein by generating a digestion pattern with only O-glycans[101,178,179]. Applications of OgpA in glycomics so far included mapping the O-glycosylation patterns of human plasma, platelets and endothelial cells[180], human coagulation factor V[181], cancer tissue[178] and Zika virus antigens[179]. The arsenal of *A. muciniphila* contains many more enzymatic activities, such as galactosidases, fucosidases, *N*-acetylglucosaminidases, *N*-acetylgalactosaminidases, sialidases, glucosidases and mannosidases[18,182], which can be studied on O-glycosylated proteins.

Biotic concepts

Pasteurized *A. muciniphila* cells have been determined to be a safe food ingredient by the European Food Safety Authority (EFSA)[183]. Therefore, this bacterium may now be applied as paraprobiotic and postbiotic. Future studies should focus on understanding the differences in effects between the administration of paraprobiotics or postbiotics and live cells. *Akkermansia* spp. EVs are reported to enhance intestinal tight junction function, to reduce weight gain and to improve glucose tolerance[23]. Another application is the use of specific proteins, as a biotic ingredient. Amuc_1100 has a regulatory effect on host metabolism and the mucus barrier[70]. Furthermore, the prebiotics inulin, polyphenols, linoleic acids, oat bran, betacyanins and non-digestible feruloylated oligosaccharides and polysaccharides[184–188] increase the abundance and activity of *A. muciniphila* in the gut. Prebiotics can stimulate strains and species that are already present and are most effective in their current host, providing an alternative to expensive living probiotic formulations. One interesting application could be HMOs, as HMO catabolism is described to be strain-specific for *Akkermansia* spp. Two mechanisms are proposed for the host metabolic changes that *A. muciniphila* induces. One is through strengthening of the mucus barrier that can be damaged by a high-fat diet or inflammation[22]. The second proposed mechanism is through modulation of the intestinal endocannabinoid system, which comprises lipid mediators that control barrier function, gut inflammation and glucose homeostasis[22]. Altogether, the current findings are important steps towards the application of *A. muciniphila* as a biotic or therapeutic agent to improve human health. Furthermore, the hypothesis that *A. muciniphila* improves health needs much more evidence regarding the mechanistic insights

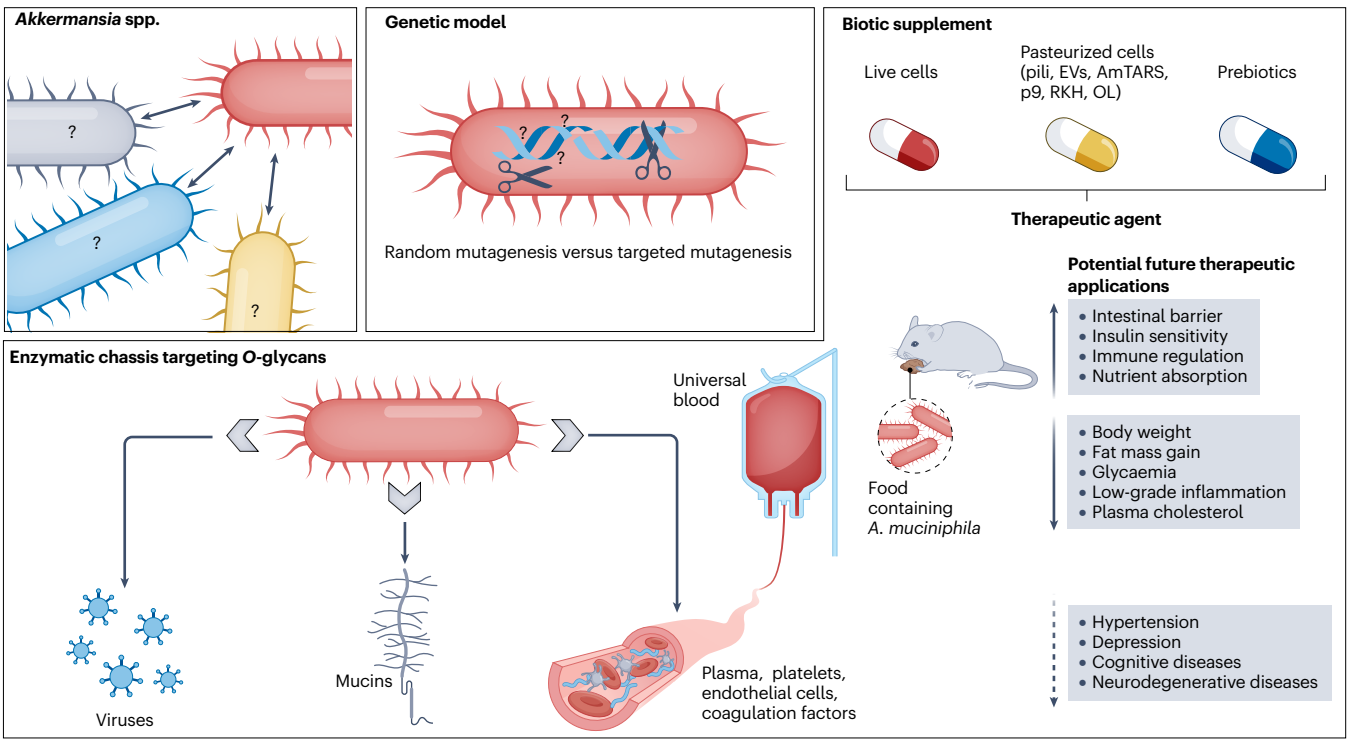


Fig. 5 | Current and future potential applications of *A. muciniphila*. More research on identifying other *Akkermansia* spp. and more *Akkermansia muciniphila* strains will increase our understanding of their ecological roles in the gut. Currently, a genetic model for random mutagenesis is patented, and there are efforts for the establishment of a targeted mutagenesis method. This would allow the enhanced production of its numerous enzymes, which include an *O*-glycopeptidase and many other enzymes that target glycans for various applications. *A. muciniphila* enzymes can target O-glycans from viruses, mucins and human blood components, thus potentially providing a means for creating universal blood for transfusions. There are multiple ways of inducing the beneficial effects of *A. muciniphila*, including administration of live cells, pasteurized cells and its components (pili, extracellular vesicles (EVs), p9, aminoacyl tRNA synthases (AmTARS), RKH, ornithine lipids (OL)) as well as prebiotics that boost *A. muciniphila* such as polyphenols. Clinical trials in humans and in vivo supplementation in mice showed that *A. muciniphila* can confer many metabolic, immunological and intestinal positive effects such as the improvement of the intestinal barrier and the lowering of plasma cholesterol. Its association with protection or treatment of certain diseases needs further corroboration in human trials, but also highlights the possibility of future therapeutic applications.

of microbial functional components and the pathways of the host response. The field should focus on the engraftment of *A. muciniphila* in the ecosystem, characterization of host–microorganism interaction pathways and the direct role in metabolic and immune health. Another important consideration in probiotic application is antibiotic resistance and the transferability risk of resistance genes within the *Akkermansia* genus. There is much uncertainty around this topic, as summarized previously[35,189].

Therapeutic concepts

Administering *A. muciniphila* cells, either living, pasteurized or derivatives, is hypothesized to improve intestinal barrier with a direct effect on insulin sensitivity, immune regulation and nutrient absorption. Preclinical studies report decreases in body weight, fat mass gain and lower glycaemia for both live cells and pasteurized cells of *A. muciniphila* Muc^T and *Akkermansia* sp. DSM 33459 (*A. massiliensis*)[22,52,122]. A reduction in low-grade inflammation, a decrease in plasma cholesterol and an improvement of intestinal barrier function are reported for *A. muciniphila* Muc^T (refs. 52,190,191). The immune-related application of *A. muciniphila* is proposed for secreted *Am*TARS as a therapeutic agent against inflammatory bowel disease because of its function in improving immune homeostasis through the TLR2 pathway[130]. For immune therapy and oncotherapy, it functions through immune modulation, leading to a more stable clinical response[192,193]. Another interesting application involves the mucin-degrading enzymes of *A. muciniphila* to create more potent enzyme variants for a universal blood type for blood transfusions[194]. For instance, *A. muciniphila* fucosidase can convert universal O-type blood into the rare Bombay-type blood[195]. The list of diseases in which *A. muciniphila* could be used as potential therapy is growing[171,196–203]. Most of the hypotheses are based on relative abundances in faecal matter, mouse studies and strong or weaker correlations with disease states[171,196–203]. One should be careful drawing direct conclusions from such studies, as this could lead to unsuccessful intervention studies with a burden and risk for critically ill patients undergoing immune therapy or suffering from cancer, mental or neurological disorders and chronic inflammatory diseases. For each disease, a thorough investigation, causative evidence and mechanistic evidence are needed. However, from the number of clinical trials registered up to now we can expect exciting results in the field of *A. muciniphila* as a therapeutic agent in the future.

Conclusions and outlook

A. muciniphila is an extraordinary bacterium characterized by its affinity for gut mucus and its effects on human metabolic and mucosal health. The discovery of this organism has contributed to new insight that a mucin-foraging bacterium can, instead of being pathogenic, have beneficial effects by stimulating host mucin production and improving the gut barrier. Research on *A. muciniphila* has also shown how correlations can be transformed into causal relationships with health and that fundamental research can be transformed into usable applications. Over the past two decades, research in the field of *A. muciniphila* has expanded and resulted in robust evidence for its role in health, including maintenance of body weight and insulin sensitivity. Because the organism was proven to be safe for human consumption and is currently available as an over-the-counter product in many countries, we can expect results on the consumption of *A. muciniphila* in its living or pasteurized form in the near future. The new *Akkermansia* spp. and strains that have been reported also open the possibility of additional functions for host health.

Big questions that still remain concern evolutionary adaptation of the organism to the gut and interactions with the host. It remains unanswered why *A. muciniphila* is so omnipresent throughout vertebrate gut systems and why the genus remains so low in genomic diversity. The low genome diversity could mean high adaptation but also points towards a more recent colonization of the gut systems by this organism. Furthermore, another question is why the *Akkermansia* genus is the only representative of the Verrucomicrobiota phylum in the gut. This question asks for fundamental science projects that aim to understand the evolutionary adaptation of *A. muciniphila* to the host mucosal environment. A follow-up question is why the host tolerates *A. muciniphila* in the mucosal layer. This could suggest evolutionary 'addiction', where hosts need this microbial symbiont to perform an essential function[204]. However, before understanding the dependencies, more insight is needed into the molecular level of the host–*A. muciniphila* interaction. Therefore, future research should focus more on the molecular mechanisms by which the bacterium stimulates a healthy gut and how it regulates host metabolic, immune and mucosal responses. The discovery that the Amuc_1100 protein binds host TLR2 and other receptors, leading to improved gut barrier, is a breakthrough that deserves more attention and exploration. This is one of the few disease-relevant human gut bacterial protein–protein interactions that have been identified to regulate the gut barrier. We envision that the interaction of Amuc_1100 with host cells extends much further, and that other components of *A. muciniphila* play an important role in host–microorganism interactions that improve metabolic and gut barrier responses. In the long run, advanced methods to manipulate *A. muciniphila* should enable mechanistic insight into its physiology and possible health effects. Mechanistic insights such as these will improve the design of clinical trials and intervention studies, helping move the field towards more targeted and possible new applications of gut-associated microorganisms such as *A. muciniphila*.

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References

1. Matijašić, M. et al. Gut microbiota beyond bacteria—mycobiome, virome, archaeome, and eukaryotic parasites in IBD. *Int. J. Mol. Sci.* **21**, 2668 (2020).
2. Sender, R., Fuchs, S. & Milo, R. Revised estimates for the number of human and bacteria cells in the body. *PLoS Biol.* **14**, e1002533 (2016).
3. Davenport, E. R. et al. The human microbiome in evolution. *BMC Biol.* **15**, 127 (2017).
4. Goodrich, J. K. et al. Human genetics shape the gut microbiome. *Cell* **159**, 789–799 (2014).
5. Lange, K., Buerger, M., Stallmach, A. & Bruns, T. Effects of antibiotics on gut microbiota. *Dig. Dis.* **34**, 260–268 (2016).
6. Bokulich, N. A. et al. Antibiotics, birth mode, and diet shape microbiome maturation during early life. *Sci. Transl. Med.* **8**, 343ra82 (2016).
7. Perler, B. K., Friedman, E. S. & Wu, G. D. The role of the gut microbiota in the relationship between diet and human health. *Annu. Rev. Physiol.* **85**, 449–468 (2023).
8. Adak, A. & Khan, M. R. An insight into gut microbiota and its functionalities. *Cell. Mol. Life Sci.* **76**, 473–493 (2019).
9. Jandhyala, S. M. et al. Role of the normal gut microbiota. *World J. Gastroenterol.* **21**, 8836–8847 (2015).
10. Haneishi, Y. et al. Inflammatory bowel diseases and gut microbiota. *Int. J. Mol. Sci.* **24**, 3817 (2023).
11. Christovich, A. & Luo, X. M. Gut microbiota, leaky gut, and autoimmune diseases. *Front. Immunol.* **13**, 946248 (2022).
12. Wang, P. X., Deng, X. R., Zhang, C. H. & Yuan, H. J. Gut microbiota and metabolic syndrome. *Chin. Med. J.* **133**, 808–816 (2020).
13. Bagheri, Z., Moeinzadeh, L. & Razmkhah, M. Roles of microbiota in cancer: from tumor development to treatment. *J. Oncol.* **2022**, 3845104 (2022).
14. Akagawa, S. & Kaneko, K. Gut microbiota and allergic diseases in children. *Allergol. Int.* **71**, 301–309 (2022).
15. Sorboni, S. G., Moghaddam, H. S., Jafarzadeh-Esfehani, R. & Soleimanpour, S. A comprehensive review on the role of the gut microbiome in human neurological disorders. *Clin. Microbiol. Rev.* **35**, e0033820 (2022).
16. Maciel-Fiuza, M. F. et al. Role of gut microbiota in infectious and inflammatory diseases. *Front. Microbiol.* **14**, 1098386 (2023).

17. Derrien, M., Vaughan, E. E., Plugge, C. M. & de Vos, W. M. *Akkermansia muciniphila* gen. nov., sp. nov., a human intestinal mucin-degrading bacterium. *Int. J. Syst. Evol. Microbiol.* **54**, 1469–1476 (2004).
This paper describes the discovery and basic characterization of *A. muciniphila*.
18. van Passel, M. W. J. et al. The genome of *Akkermansia muciniphila*, a dedicated intestinal mucin degrader, and its use in exploring intestinal metagenomes. *PLoS ONE* **6**, e16876 (2011).
19. Derrien, M. et al. Mucin–bacterial interactions in the human oral cavity and digestive tract. *Gut Microbes* **1**, 254–268 (2010).
20. Belzer, C. et al. Microbial metabolic networks at the mucus layer lead to diet-independent butyrate and vitamin B_{12} production by intestinal symbionts. *mBio* **8**, 1–14 (2017).
This in vitro study is a proof-of-principle study demonstrating that *A. muciniphila* cross-feeds other bacteria within the microbiome.
21. Ottman, N., Geerlings, S. Y., Aalvink, S., de Vos, W. M. & Belzer, C. Action and function of *Akkermansia muciniphila* in microbiome ecology, health and disease. *Best. Pract. Res. Clin. Gastroenterol.* **31**, 637–642 (2017).
22. Everard, A. et al. Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. *Proc. Natl Acad. Sci. USA* **110**, 9066–9071 (2013).
This mouse study provides insights into the role of *A. muciniphila* in the context of obesity and type 2 diabetes.
23. Chelakkot, C. et al. *Akkermansia muciniphila*-derived extracellular vesicles influence gut permeability through the regulation of tight junctions. *Exp. Mol. Med.* **50**, e450 (2018).
24. Van Der Lugt, B. et al. *Akkermansia muciniphila* ameliorates the age-related decline in colonic mucus thickness and attenuates immune activation in accelerated aging $Ercc1^{-/\Delta 7}$ mice. *Immun. Ageing* **16**, 1–17 (2019).
25. Cani, P. D., Depommier, C., Derrien, M., Everard, A. & de Vos, W. M. *Akkermansia muciniphila*: paradigm for next-generation beneficial microorganisms. *Nat. Rev. Gastroenterol. Hepatol.* **19**, 625–637 (2022).
26. Ley, R. E. et al. Evolution of mammals and their gut microbes. *Science* **320**, 1647–1651 (2008).
27. Sommer, F. et al. The gut microbiota modulates energy metabolism in the hibernating brown bear *Ursus arctos*. *Cell Rep.* **14**, 1655–1661 (2016).
28. Carey, H. V., Walters, W. A. & Knight, R. Seasonal restructuring of the ground squirrel gut microbiota over the annual hibernation cycle. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **304**, R33–R42 (2013).
29. Sonoyama, K. et al. Response of gut microbiota to fasting and hibernation in Syrian hamsters. *Appl. Env. Microbiol.* **75**, 6451–6456 (2009).
30. Costello, E. K., Gordon, J. I., Secor, S. M. & Knight, R. Postprandial remodeling of the gut microbiota in Burmese pythons. *ISME J.* **4**, 1375–1385 (2010).
31. Ouwerkerk, J. P. et al. Adaptation of *Akkermansia muciniphila* to the oxic–anoxic interface of the mucus layer. *Appl. Env. Microbiol.* **82**, 6983–6993 (2016).
This work shows the unique adaptation of *A. muciniphila* to the oxygen gradient of the mucus layer.
32. Belzer, C. & de Vos, W. M. Microbes inside—from diversity to function: the case of *Akkermansia*. *ISME J.* **6**, 1449–1458 (2012).
33. Green, T. J., Smullen, R. & Barnes, A. C. Dietary soybean protein concentrate-induced intestinal disorder in marine farmed Atlantic salmon, *Salmo salar* is associated with alterations in gut microbiota. *Vet. Microbiol.* **166**, 286–292 (2013).
34. Derrien, M., Collado, M. C., Ben-Amor, K., Salminen, S. & De Vos, W. M. The mucin degrader *Akkermansia muciniphila* is an abundant resident of the human intestinal tract. *Appl. Env. Microbiol.* **74**, 1646–1648 (2008).
35. Karcher, N. et al. Genomic diversity and ecology of human-associated *Akkermansia* species in the gut microbiome revealed by extensive metagenomic assembly. *Genome Biol.* **22**, 1–24 (2021).
This research describes a large-scale population genomics dataset of the genus *Akkermansia* and reveals a large phylogenetic and functional diversity of this genus.
36. Collado, M. C., Derrien, M., Isolauri, E., De Vos, W. M. & Salminen, S. Intestinal integrity and *Akkermansia muciniphila*, a mucin-degrading member of the intestinal microbiota present in infants, adults, and the elderly. *Appl. Env. Microbiol.* **73**, 7767–7770 (2007).
37. Guo, X. et al. Different subtype strains of *Akkermansia muciniphila* abundantly colonize in southern China. *J. Appl. Microbiol.* **120**, 452–459 (2016).
38. Geerlings, S. Y., Kostopoulos, I., de Vos, W. M. & Belzer, C. *Akkermansia muciniphila* in the human gastrointestinal tract: when, where, and how? *Microorganisms* **6**, 75 (2018).
39. Momozawa, Y., Deffontaine, V., Louis, E. & Medrano, J. F. Characterization of bacteria in biopsies of colon and stools by high throughput sequencing of the V2 region of bacterial 16S rRNA gene in human. *PLoS ONE* **6**, e16952 (2011).
40. Nayfach, S., Shi, Z. J., Seshadri, R., Pollard, K. S. & Kyrpides, N. C. New insights from uncultivated genomes of the global human gut microbiome. *Nature* **568**, 505–510 (2019).
41. Palmas, V. et al. Gut microbiota markers and dietary habits associated with extreme longevity in healthy Sardinian centenarians. *Nutrients* **14**, 2436 (2022).
42. Biagi, E. et al. Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians. *PLoS ONE* **5**, e10667 (2010).
43. Biagi, E. et al. Gut microbiota and extreme longevity. *Curr. Biol.* **26**, 1480–1485 (2016).
44. Wu, L. et al. Gut microbiota as an antioxidant system in centenarians associated with high antioxidant activities of gut-resident *Lactobacillus*. *NPJ Biofilms Microbiomes* **8**, 102 (2022).
45. Kim, B.-S. et al. Comparison of the gut microbiota of centenarians in longevity villages of South Korea with those of other age groups. *J. Microbiol. Biotechnol.* **29**, 429–440 (2019).
46. Wang, F. et al. Gut microbiota community and its assembly associated with age and diet in Chinese centenarians. *J. Microbiol. Biotechnol.* **25**, 1195–1204 (2015).
47. Cătoi, A. F. et al. Gut microbiota and aging—a focus on centenarians. *Biochim. Biophys. Acta, Mol. Cell Res.* **1866**, 165765 (2020).
48. Lv, Q.-B. et al. A thousand metagenome-assembled genomes of *Akkermansia* reveal phylogroups and geographical and functional variations in the human gut. *Front. Cell Infect. Microbiol.* **12**, 957439 (2022).
49. Daniel, N., Gewirtz, A. T. & Chassaing, B. *Akkermansia muciniphila* counteracts the deleterious effects of dietary emulsifiers on microbiota and host metabolism. *Gut* **72**, 906–917 (2023).
50. Guo, X. et al. Genome sequencing of 39 *Akkermansia muciniphila* isolates reveals its population structure, genomic and functional diversity, and global distribution in mammalian gut microbiotas. *BMC Genomics* **18**, 800 (2017).
51. González, D., Morales-Olavarria, M., Vidal-Veuthey, B. & Cárdenas, J. P. Insights into early evolutionary adaptations of the *Akkermansia* genus to the vertebrate gut. *Front. Microbiol.* **14**, 1238580 (2023).
This paper reports the genomic potential of *Akkermansia* spp. in relation to environmental conditions that have led to traits important for colonization of the gut.
52. Kumar, R. et al. Identification and characterization of a novel species of genus *Akkermansia* with metabolic health effects in a diet-induced obesity mouse model. *Cells* **11**, 2084 (2022).
53. Truong, D. T., Tett, A., Pasolli, E., Huttenhower, C. & Segata, N. Microbial strain-level population structure and genetic diversity from metagenomes. *Genome Res.* **27**, 626–638 (2017).
54. Geerlings, S. Y. et al. Genomic convergence between *Akkermansia muciniphila* in different mammalian hosts. *BMC Microbiol.* **21**, 298 (2021).
55. Luna, E. et al. Utilization efficiency of human milk oligosaccharides by human-associated *Akkermansia* is strain dependent. *Appl. Env. Microbiol.* **88**, e0148721 (2022).
56. Ouwerkerk, J. P., Aalvink, S., Belzer, C. & de Vos, W. M. *Akkermansia glycaniphila* sp. nov., an anaerobic mucin-degrading bacterium isolated from reticulated python faeces. *Int. J. Syst. Evol. Microbiol.* **66**, 4614–4620 (2016).
57. Ndongo, S., Armstrong, N., Raoult, D. & Fournier, P. E. Reclassification of eight *Akkermansia muciniphila* strains and description of *Akkermansia massiliensis* sp. nov. and Candidatus *Akkermansia timonensis*, isolated from human feces. *Sci. Rep.* **12**, 21747 (2022).
58. Liu, Q. et al. *Akkermansia muciniphila* exerts strain-specific effects on DSS-induced ulcerative colitis in mice. *Front. Cell Infect. Microbiol.* **11**, 698914 (2021).
59. Kirmiz, N. et al. Comparative genomics guides elucidation of Vitamin B_{12} biosynthesis in novel human-associated *Akkermansia* strains. *Appl. Env. Microbiol.* **86**, e02117–e02119 (2020).
60. Zhai, R. et al. Strain-specific anti-inflammatory properties of two *Akkermansia muciniphila* strains on chronic colitis in mice. *Front. Cell Infect. Microbiol.* **9**, 239 (2019).
61. Ottman, N. et al. Characterization of outer membrane proteome of *Akkermansia muciniphila* reveals sets of novel proteins exposed to the human intestine. *Front. Microbiol.* **7**, 1157 (2016).
62. Ligthart, K., Belzer, C., de Vos, W. M. & Tytgat, H. L. P. Bridging bacteria and the gut: functional aspects of type IV pili. *Trends Microbiol.* **28**, 340–348 (2020).
63. Ottman, N. et al. Pili-like proteins of *Akkermansia muciniphila* modulate host immune responses and gut barrier function. *PLoS ONE* **12**, 1–18 (2017).
This study discovers the pili-like protein Amuc_1100, and describes its effect on host immune response and gut barrier function.
64. Xiang, R., Wang, J., Xu, W., Zhang, M. & Wang, M. Amuc_1102 from *Akkermansia muciniphila* adopts an immunoglobulin-like fold related to archaeal type IV pilus. *Biochem. Biophys. Res. Commun.* **547**, 59–64 (2021).
65. Reunanen, J. et al. *Akkermansia muciniphila* adheres to enterocytes and strengthens the integrity of the epithelial cell layer. *Appl. Env. Microbiol.* **81**, 3655–3662 (2015).
This paper shows that *A. muciniphila* adheres to human colonic cell lines and increases cell layer integrity.
66. Elzinga, J. et al. Binding of *Akkermansia muciniphila* to mucin is *O*-glycan specific. *Nat. Commun.* **15**, 4582 (2024).
67. Kostopoulos, I. et al. A continuous battle for host-derived glycans between a mucus specialist and a glycan generalist in vitro and in vivo. *Front. Microbiol.* **12**, 1–14 (2021).
68. Garcia-Vello, P. et al. Peptidoglycan from *Akkermansia muciniphila* MucT: chemical structure and immunostimulatory properties of muropeptides. *Glycobiology* **32**, 712–719 (2022).
69. van der Ark, K. C. H. et al. Model-driven design of a minimal medium for *Akkermansia muciniphila* confirms mucus adaptation. *Microb. Biotechnol.* **11**, 476–485 (2018).
70. Ottman, N. et al. Genome-scale model and omics analysis of metabolic capacities of *Akkermansia muciniphila* reveal a preferential mucin-degrading lifestyle. *Appl. Env. Microbiol.* **83**, e01014–e01017 (2017).
71. Parada Venegas, D. et al. Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. *Front. Immunol.* **10**, 277 (2019).
72. Hernández, M. A. G., Canfora, E. E., Jocken, J. W. E. & Blaak, E. E. The short-chain fatty acid acetate in body weight control and insulin sensitivity. *Nutrients* **11**, 1943 (2019).
73. Bridgeman, S. C. et al. Butyrate generated by gut microbiota and its therapeutic role in metabolic syndrome. *Pharmacol. Res.* **160**, 105174 (2020).
74. Hosseini, E., Grootaert, C., Verstraete, W. & Van de Wiele, T. Propionate as a health-promoting microbial metabolite in the human gut. *Nutr. Rev.* **69**, 245–258 (2011).

75. De Vadder, F. et al. Microbiota-generated metabolites promote metabolic benefits via gut–brain neural circuits. *Cell* **156**, 84–96 (2014).
76. Corfield, A. P., Wagner, S. A., Clamp, J. R., Kriaris, M. S. & Hoskins, L. C. Mucin degradation in the human colon: production of sialidase, sialate *O*-acetylesterase, *N*-acetylneuraminate lyase, arylesterase, and glycosulfatase activities by strains of fecal bacteria. *Infect. Immun.* **60**, 3971–3978 (1992).
77. Tailford, L. E., Crost, E. H., Kavanaugh, D. & Juge, N. Mucin glycan foraging in the human gut microbiome. *Front. Genet.* **6**, 81 (2015).
78. Bakshani, C. R. et al. Carbohydrate-active enzymes from *Akkermansia muciniphila*. Preprint at *bioRxiv* https://doi.org/10.1101/2024.03.27.586211 (2024).
79. Huang, K. et al. Biochemical characterisation of the neuraminidase pool of the human gut symbiont *Akkermansia muciniphila*. *Carbohydr. Res.* **415**, 60–65 (2015).
80. Shuoker, B. et al. Sialidases and fucosidases of *Akkermansia muciniphila* are crucial for growth on mucin and nutrient sharing with mucus-associated gut bacteria. *Nat. Commun.* **14**, 1833 (2023).
81. Kostopoulos, I. et al. *Akkermansia muciniphila* uses human milk oligosaccharides to thrive in the early life conditions in vitro. *Sci. Rep.* **10**, 14330 (2020).
82. Davey, L. E. et al. A genetic system for *Akkermansia muciniphila* reveals a role for mucin foraging in gut colonization and host sterol biosynthesis gene expression. *Nat. Microbiol.* **8**, 1450–1467 (2023).
This study reports a genetic system for *A. muciniphila*, applies transposon mutagenesis to *A. muciniphila* and gives insight into the importance of mucin-degrading enzymes for gut colonization.
83. Lee, J. Y. et al. Nutrient-specific proteomic analysis of the mucin degrading bacterium *Akkermansia muciniphila*. *Proteomics* **22**, 2100125 (2022).
84. Kosciow, K. & Deppenmeier, U. Characterization of three novel β-galactosidases from *Akkermansia muciniphila* involved in mucin degradation. *Int. J. Biol. Macromol.* **149**, 331–340 (2020).
85. Crouch, L. I. et al. Prominent members of the human gut microbiota express endo-acting *O*-glycanases to initiate mucin breakdown. *Nat. Commun.* **11**, 4017 (2020).
86. Kosciow, K. & Deppenmeier, U. Characterization of a phospholipid-regulated β-galactosidase from *Akkermansia muciniphila* involved in mucin degradation. *Microbiologyopen* **8**, 1–11 (2019).
87. Berkhout, M. D., Plugge, C. M. & Belzer, C. How microbial glycosyl hydrolase activity in the gut mucosa initiates microbial cross-feeding. *Glycobiology* **32**, 182–200 (2022).
88. Ouwerkerk, J. P. et al. Comparative genomics and physiology of *Akkermansia muciniphila* isolates from human intestine reveal specialized mucosal adaptation. *Microorganisms* **10**, 1605 (2022).
89. Belzer, C. Nutritional strategies for mucosal health: the interplay between microbes and mucin glycans. *Trends Microbiol.* **30**, 13–21 (2021).
90. Aakko, J. et al. Human milk oligosaccharide categories define the microbiota composition in human colostrum. *Benef. Microbes* **8**, 563–567 (2017).
91. Bäckhed, F. et al. Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell Host Microbe* **17**, 690–703 (2015).
92. Bergström, A. et al. Establishment of intestinal microbiota during early life: a longitudinal, explorative study of a large cohort of Danish infants. *Appl. Env. Microbiol.* **80**, 2889–2900 (2014).
93. Azad, M. B. et al. Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. *CMAJ* **185**, 385–394 (2013).
94. Grant, E. T., Boudaud, M., Muller, A., Macpherson, A. J. & Desai, M. S. Maternal diet and gut microbiome composition modulate early-life immune development. *EMBO Mol. Med.* **15**, e17241 (2023).
95. Gurung, M. et al. Microbiota from human infants consuming secretors or non-secretors mothers' milk impacts the gut and immune system in mice. *mSystems* **9**, e0029424 (2024).
96. Padilla, L. et al. Mechanism of 2′-fucosyllactose degradation by human-associated *Akkermansia*. *J. Bacteriol.* **206**, e0033423 (2024).
97. Ribo, S. et al. Increasing breast milk betaine modulates *Akkermansia* abundance in mammalian neonates and improves long-term metabolic health. *Sci. Transl. Med.* **13**, eabb0322 (2021).
98. Meng, X. et al. A purified aspartic protease from *Akkermansia muciniphila* plays an important role in degrading Muc2. *Int. J. Mol. Sci.* **21**, 72 (2021).
99. Shon, D. J., Fernandez, D., Riley, N. M., Ferracane, M. J. & Bertozzi, C. R. Structure-guided mutagenesis of a mucin-selective metalloprotease from *Akkermansia muciniphila* alters substrate preferences. *J. Biol. Chem.* **298**, 101917 (2022).
100. Shon, D. J. et al. An enzymatic toolkit for selective proteolysis, detection, and visualization of mucin-domain glycoproteins. *Proc. Natl Acad. Sci. USA* **117**, 21299–21307 (2020).
101. Trastoy, B., Naegeli, A., Anso, I., Sjögren, J. & Guerin, M. E. Structural basis of mammalian mucin processing by the human gut *O*-glycopeptidase OgpA from *Akkermansia muciniphila*. *Nat. Commun.* **11**, 4844 (2020).
This paper characterizes the *A. muciniphila O*-glycopeptidase OgpA and describes its possible application to map O-glycosylation sites on a protein.
102. Medley, B. J. et al. A previously uncharacterized *O*-glycopeptidase from *Akkermansia muciniphila* requires the Tn-antigen for cleavage of the peptide bond. *J. Biol. Chem.* **298**, 102439 (2022).
103. Espey, M. G. Role of oxygen gradients in shaping redox relationships between the human intestine and its microbiota. *Free. Radic. Biol. Med.* **55**, 130–140 (2013).
104. Machado, D. et al. Uncovering *Akkermansia muciniphila* resilience or susceptibility to different temperatures, atmospheres and gastrointestinal conditions. *Anaerobe* **61**, 102135 (2020).
105. Peña-Cearra, A. et al. *Akkermansia muciniphila*-induced trained immune phenotype increases bacterial intracellular survival and attenuates inflammation. *Commun. Biol.* **7**, 192 (2024).
106. Dawson, P. A. & Karpen, S. J. Intestinal transport and metabolism of bile acids. *J. Lipid Res.* **56**, 1085–1099 (2015).
107. van der Ark, K. C. H. et al. Encapsulation of the therapeutic microbe *Akkermansia muciniphila* in a double emulsion enhances survival in simulated gastric conditions. *Food Res. Int.* **102**, 372–379 (2017).
108. Hagi, T., Geerlings, S. Y., Nijsse, B. & Belzer, C. The effect of bile acids on the growth and global gene expression profiles in *Akkermansia muciniphila*. *Appl. Microbiol. Biotechnol.* **104**, 10641–10653 (2020).
109. Juárez-Fernández, M. et al. The synbiotic combination of *Akkermansia muciniphila* and quercetin ameliorates early obesity and NAFLD through gut microbiota reshaping and bile acid metabolism modulation. *Antioxidants* **10**, 2001 (2021).
110. Pierre, J. F. et al. Activation of bile acid signaling improves metabolic phenotypes in high-fat diet-induced obese mice. *Am. J. Physiol. Gastrointest. Liver Physiol.* **311**, G286–G304 (2016).
111. Ruas-Madiedo, P., Gueimonde, M., Arigoni, F., de los Reyes-Gavilán, C. G. & Margolles, A. Bile affects the synthesis of exopolysaccharides by *Bifidobacterium animalis*. *Appl. Env. Microbiol.* **75**, 1204–1207 (2009).
112. Fanning, S. et al. Bifidobacterial surface-exopolysaccharide facilitates commensal–host interaction through immune modulation and pathogen protection. *Proc. Natl Acad. Sci. USA* **109**, 2108–2113 (2012).
113. Anhê, F. F. et al. A polyphenol-rich cranberry extract protects from diet-induced obesity, insulin resistance and intestinal inflammation in association with increased *Akkermansia* spp. population in the gut microbiota of mice. *Gut* **64**, 872–883 (2015).
114. Roopchand, D. E. et al. Dietary polyphenols promote growth of the gut bacterium *Akkermansia muciniphila* and attenuate high-fat diet-induced metabolic syndrome. *Diabetes* **64**, 2847–2858 (2015).
115. Salem, M. B., El-Lakkany, N. M., Seif el-Din, S. H., Hammam, O. A. & Samir, S. Diosmin alleviates ulcerative colitis in mice by increasing *Akkermansia muciniphila* abundance, improving intestinal barrier function, and modulating the NF-κB and Nrf2 pathways. *Heliyon* **10**, e27527 (2024).
116. Reider, S. et al. Short- and long-term effects of a prebiotic intervention with polyphenols extracted from European black elderberry—sustained expansion of *Akkermansia* spp. *J. Pers. Med.* **12**, 1479 (2022).
117. Rodríguez-Daza, M. C. et al. Polyphenol-mediated gut microbiota modulation: toward prebiotics and further. *Front. Nutr.* **8**, 689456 (2021).
118. Rodríguez-Daza, M. C. & de Vos, W. M. Polyphenols as drivers of a homeostatic gut microecology and immuno-metabolic traits of *Akkermansia muciniphila*: from mouse to man. *Int. J. Mol. Sci.* **24**, 45 (2022).
119. Van Buiten, C. B., Seitz, V. A., Metcalf, J. L. & Raskin, I. Dietary polyphenols support *Akkermansia muciniphila* growth via mediation of the gastrointestinal redox environment. *Antioxidants* **13**, 304 (2024).
120. Rodríguez-Daza, M.-C. et al. Wild blueberry proanthocyanidins shape distinct gut microbiota profile and influence glucose homeostasis and intestinal phenotypes in high-fat high-sucrose fed mice. *Sci. Rep.* **10**, 2217 (2020).
121. Lu, F. et al. Early-life polyphenol intake promotes *Akkermansia* growth and increase of host goblet cells in association with the potential synergistic effect of *Lactobacillus*. *Food Res. Int.* **149**, 110648 (2021).
122. Plovier, H. et al. A purified membrane protein from *Akkermansia muciniphila* or the pasteurized bacterium improves metabolism in obese and diabetic mice. *Nat. Med.* **23**, 107–113 (2016).
This study shows that pasteurized *A. muciniphila* and purified Amuc_1100 induce beneficial metabolic effects in mice.
123. Gao, X. et al. *Akkermansia muciniphila*-derived small extracellular vesicles attenuate intestinal ischemia–reperfusion-induced postoperative cognitive dysfunction by suppressing microglia activation via the TLR2/4 signaling. *Biochim. Biophys. Acta, Mol. Cell Res.* **1871**, 119630 (2024).
124. Kikkert, R., Laine, M. L., Aarden, L. A. & Van Winkelhoff, A. J. Activation of Toll-like receptors 2 and 4 by Gram-negative periodontal bacteria. *Oral. Microbiol. Immunol.* **22**, 145–151 (2007).
125. Mandell, L. et al. Intact Gram-negative *Helicobacter pylori*, *Helicobacter felis*, and *Helicobacter hepaticus* bacteria activate innate immunity via Toll-like receptor 2 but not Toll-like receptor 4. *Infect. Immun.* **72**, 6446–6454 (2004).
126. Bae, M. et al. *Akkermansia muciniphila* phospholipid induces homeostatic immune responses. *Nature* **608**, 168–173 (2022).
127. Akira, S. & Takeda, K. Toll-like receptor signalling. *Nat. Rev. Immunol.* **4**, 499–511 (2004).
128. Xie, S. et al. Novel tripeptide RKH derived from *Akkermansia muciniphila* protects against lethal sepsis. *Gut* **73**, 78–91 (2024).
129. Yoon, H. S. et al. *Akkermansia muciniphila* secretes a glucagon-like peptide-1-inducing protein that improves glucose homeostasis and ameliorates metabolic disease in mice. *Nat. Microbiol.* **6**, 563–573 (2021).
130. Kim, S.-M. et al. Secreted *Akkermansia muciniphila* threonyl-tRNA synthetase functions to monitor and modulate immune homeostasis. *Cell Host Microbe* **31**, 1021–1037 (2023).

131. Zhang, Q. et al. Genetic mapping of microbial and host traits reveals production of immunomodulatory lipids by *Akkermansia muciniphila* in the murine gut. *Nat. Microbiol.* **8**, 424–440 (2023).
132. Seck, E. H. et al. Salt in stools is associated with obesity, gut halophilic microbiota and *Akkermansia muciniphila* depletion in humans. *Int. J. Obes.* **43**, 862–871 (2019).
133. Dao, M. C. et al. *Akkermansia muciniphila* and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. *Gut* **65**, 426–436 (2016).
134. Santacruz, A. et al. Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. *Br. J. Nutr.* **104**, 83–92 (2010).
135. Dao, X. M. C. et al. *Akkermansia muciniphila* abundance is lower in severe obesity, but its increased level after bariatric surgery is not associated with metabolic health improvement. *Am. J. Physiol. Endocrinol. Metab.* **317**, E446–E459 (2019).
136. Ouwerkerk, J. P., De Vos, W. M. & Belzer, C. Glycobiome: bacteria and mucus at the epithelial interface. *Best. Pract. Res. Clin. Gastroenterol.* **27**, 25–38 (2013).
137. Schneeberger, M. et al. *Akkermansia muciniphila* inversely correlates with the onset of inflammation, altered adipose tissue metabolism and metabolic disorders during obesity in mice. *Sci. Rep.* **5**, 16643 (2015).
138. Zhang, J. et al. Decreased abundance of *Akkermansia muciniphila* leads to the impairment of insulin secretion and glucose homeostasis in lean type 2 diabetes. *Adv. Sci.* **8**, 2100536 (2021).
139. Shin, N. R. et al. An increase in the *Akkermansia spp*. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. *Gut* **63**, 727–735 (2014).
140. Zhao, S. et al. *Akkermansia muciniphila* improves metabolic profiles by reducing inflammation in chow diet-fed mice. *J. Mol. Endocrinol.* **58**, 1–14 (2017).
141. Wu, F. et al. An *Akkermansia muciniphila* subtype alleviates high-fat diet-induced metabolic disorders and inhibits the neurodegenerative process in mice. *Anaerobe* **61**, 102138 (2020).
142. Kim, S. et al. *Akkermansia muciniphila* prevents fatty liver disease, decreases serum triglycerides, and maintains gut homeostasis. *Appl. Env. Microbiol.* **86**, e03004–e03019 (2020).
143. Depommier, C. et al. Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers: a proof-of-concept exploratory study. *Nat. Med.* **25**, 1096–1103 (2019).
This study shows that pasteurized *A. muciniphila* is safe and tolerated by human subjects.
144. Lukovac, S. et al. Differential modulation by *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* of host peripheral lipid metabolism and histone acetylation in mouse gut organoids. *mBio* **5**, e01438–14 (2014).
145. McLoughlin, R. M. et al. Interplay between IFN-γ and IL-6 signaling governs neutrophil trafficking and apoptosis during acute inflammation. *J. Clin. Investig.* **112**, 598 (2003).
146. Greer, R. L. et al. *Akkermansia muciniphila* mediates negative effects of IFNγ on glucose metabolism. *Nat. Commun.* **7**, 1–13 (2016).
147. Davenport, E. R. et al. Genome-wide association studies of the human gut microbiota. *PLoS ONE* **10**, e0140301 (2015).
148. Viera, J. T., El-Merahbi, R., Nieswandt, B., Stegner, D. & Sumara, G. Phospholipases D_1 and D_2 suppress appetite and protect against overweight. *PLoS ONE* **11**, e0157607 (2016).
149. Alberts, A. et al. Binding of macrophage receptor MARCO, LDL, and LDLR to disease-associated crystalline structures. *Front. Immunol.* **11**, 596103 (2020).
150. Ansaldo, E. et al. *Akkermansia muciniphila* induces intestinal adaptive immune responses during homeostasis. *Science* **364**, 1179–1184 (2019).
151. Wu, W. et al. Protective effect of *Akkermansia muciniphila* against immune-mediated liver injury in a mouse model. *Front. Microbiol.* **8**, 1804 (2017).
152. Kim, S. et al. Mucin degrader *Akkermansia muciniphila* accelerates intestinal stem cell-mediated epithelial development. *Gut Microbes* **13**, 1892441 (2021).
153. Wang, L. et al. A purified membrane protein from *Akkermansia muciniphila* or the pasteurised bacterium blunts colitis associated tumourigenesis by modulation of $CD8^+$ T cells in mice. *Gut* **69**, 1988–1997 (2020).
154. Kang, C. S. et al. Extracellular vesicles derived from gut microbiota, especially *Akkermansia muciniphila*, protect the progression of dextran sulfate sodium-induced colitis. *PLoS ONE* **8**, e76520 (2013).
155. Earley, H. et al. The abundance of *Akkermansia muciniphila* and its relationship with sulphated colonic mucins in health and ulcerative colitis. *Sci. Rep.* **9**, 15683 (2019).
156. Kang, E.-J. et al. The secreted protein Amuc_1409 from *Akkermansia muciniphila* improves gut health through intestinal stem cell regulation. *Nat. Commun.* **15**, 2983 (2024).
157. Podolsky, D. K., Gerken, G., Eyking, A. & Cario, E. Colitis-associated variant of TLR2 causes impaired mucosal repair because of TFF3 deficiency. *Gastroenterology* **137**, 209–220 (2009).
158. Cario, E., Gerken, G. & Podolsky, D. K. Toll-like receptor 2 controls mucosal inflammation by regulating epithelial barrier function. *Gastroenterology* **132**, 1359–1374 (2007).
159. Desai, M. S. et al. A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. *Cell* **167**, 1339–1353 (2016).
160. Kuffa, P. et al. Fiber-deficient diet inhibits colitis through the regulation of the niche and metabolism of a gut pathobiont. *Cell Host Microbe* **31**, 2007–2022 (2023).
161. Parrish, A. et al. *Akkermansia muciniphila* exacerbates food allergy in fibre-deprived mice. *Nat. Microbiol.* **8**, 1863–1879 (2023).
162. Wolter, M. et al. Diet-driven differential response of *Akkermansia muciniphila* modulates pathogen susceptibility. *Mol. Syst. Biol.* **20**, 596–625 (2024).
163. Shono, Y. et al. Increased GVHD-related mortality with broad-spectrum antibiotic use after allogeneic hematopoietic stem cell transplantation in human patients and mice. *Sci. Transl. Med.* **8**, 339ra71 (2016).
164. Konstanti, P. et al. Physiology of γ-aminobutyric acid production by *Akkermansia muciniphila*. *Appl. Env. Microbiol.* **90**, e0112123 (2024).
165. Yunes, R. A. et al. GABA production and structure of gadB/gadC genes in *Lactobacillus* and *Bifidobacterium* strains from human microbiota. *Anaerobe* **42**, 197–204 (2016).
166. Olson, C. A. et al. The gut microbiota mediates the anti-seizure effects of the ketogenic diet. *Cell* **173**, 1728–1741 (2018).
167. Li, Z. et al. Multi-omics analyses of serum metabolome, gut microbiome and brain function reveal dysregulated microbiota–gut–brain axis in bipolar depression. *Mol. Psychiatry* **27**, 4123–4135 (2022).
168. Xi, W. et al. Depicting the composition of gut microbiota in children with tic disorders: an exploratory study. *J. Child. Psychol. Psychiatry* **62**, 1246–1254 (2021).
169. Fang, X., Li, F. J. & Hong, D. J. Potential role of *Akkermansia muciniphila* in Parkinson's disease and other neurological/autoimmune diseases. *Curr. Med. Sci.* **41**, 1172–1177 (2021).
170. Cox, L. M. et al. The gut microbiome in progressive multiple sclerosis. *Ann. Neurol.* **89**, 1195–1211 (2021).
171. Blacher, E. et al. Potential roles of gut microbiome and metabolites in modulating ALS in mice. *Nature* **572**, 474–480 (2019).
172. Chia, L. W. et al. Deciphering the trophic interaction between *Akkermansia muciniphila* and the butyrogenic gut commensal *Anaerostipes caccae* using a metatranscriptomic approach. *Antonie Van. Leeuwenhoek* **111**, 859–873 (2018).
173. Pichler, M. J. et al. Butyrate producing colonic clostridiales metabolise human milk oligosaccharides and cross feed on mucin via conserved pathways. *Nat. Commun.* **11**, 3285 (2020).
174. Shetty, S. A. et al. Dynamic metabolic interactions and trophic roles of human gut microbes identified using a minimal microbiome exhibiting ecological properties. *ISME J.* **16**, 2144–2159 (2022).
175. Arumugam, M. et al. Enterotypes of the human gut microbiome. *Nature* **473**, 174–180 (2011).
176. Derrien, M., Belzer, C. & de Vos, W. M. *Akkermansia muciniphila* and its role in regulating host functions. *Microb. Pathog.* **106**, 171–181 (2017).
177. Rasmussen, T. S. et al. Fecal virome transfer improves proliferation of commensal gut *Akkermansia muciniphila* and unexpectedly enhances the fertility rate in laboratory mice. *Gut Microbes* **15**, 2208504 (2023).
178. Yang, W., Ao, M., Hu, Y., Li, Q. K. & Zhang, H. Mapping the *O*-glycoproteome using site-specific extraction of O-linked glycopeptides (EXoO). *Mol. Syst. Biol.* **14**, e8486 (2018).
179. Yang, S. et al. Deciphering protein O-glycosylation: solid-phase chemoenzymatic cleavage and enrichment. *Anal. Chem.* **90**, 8261–8269 (2018).
180. King, S. L. et al. Characterizing the O-glycosylation landscape of human plasma, platelets, and endothelial cells. *Blood Adv.* **1**, 429–442 (2017).
181. Ma, C. et al. Comprehensive N- and O-glycosylation mapping of human coagulation factor V. *J. Thromb. Haemost.* **18**, 1884–1892 (2020).
182. Lombard, V., Golaconda Ramulu, H., Drula, E., Coutinho, P. M. & Henrissat, B. The carbohydrate-active enzymes database (CAZy) in 2013. *Nucleic Acids Res.* **42**, 490–495 (2014).
183. Turck, D. et al. Safety of pasteurised *Akkermansia muciniphila* as a novel food pursuant to Regulation (EU) 2015/2283. *EFSA J.* **19**, e06780 (2021).
184. Yang, J. et al. Disparate metabolic responses in mice fed a high-fat diet supplemented with maize-derived non-digestible feruloylated oligo and polysaccharides are linked to changes in the gut microbiota. *PLoS ONE* **11**, e0146144 (2016).
185. Song, H. et al. Red pitaya betacyanins protects from diet-induced obesity, liver steatosiaand insulin resistance in association with modulation of gut microbiota in mice. *J. Gastroenterol. Hepatol.* **31**, 1462–1469 (2016).
186. Gómez-Gallego, C. et al. Infant formula supplemented with polyamines alters the intestinal microbiota in neonatal BALB/cOlaHsd mice. *J. Nutr. Biochem.* **23**, 1508–1513 (2012).
187. Andersson, K. E. et al. Diverse effects of oats on cholesterol metabolism in C57BL/6 mice correlate with expression of hepatic bile acid-producing enzymes. *Eur. J. Nutr.* **52**, 1755–1769 (2013).
188. Everard, A. et al. Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. *Diabetes* **60**, 2775–2786 (2011).
189. Li, L. et al. Function and therapeutic prospects of next-generation probiotic *Akkermansia muciniphila* in infectious diseases. *Front. Microbiol.* **15**, 1354447 (2024).
190. Jia, B., Zou, Y., Han, X., Bae, J.-W. & Jeon, C. O. Gut microbiome-mediated mechanisms for reducing cholesterol levels: implications for ameliorating cardiovascular disease. *Trends Microbiol.* **31**, 76–91 (2023).
191. Hasani, A. et al. The role of *Akkermansia muciniphila* in obesity, diabetes and atherosclerosis. *J. Med. Microbiol.* **70**, 001435 (2021).
192. Wang, L. & Tang, D. *Akkermania muciniphila*: a rising star in tumor immunology. *Clin. Transl. Oncol.* https://doi.org/10.1007/s12094-024-03493-6 (2024).
193. Pellegrino, A., Coppola, G., Santopaolo, F., Gasbarrini, A. & Ponziani, F. R. Role of *Akkermansia* in human diseases: from causation to therapeutic properties. *Nutrients* **15**, 1815 (2023).

194. Jensen, M. et al. *Akkermansia muciniphila* exoglycosidases target extended blood group antigens to generate ABO-universal blood. *Nat. Microbiol.* **9**, 1176–1188 (2024).
195. Anso, I. et al. Turning universal O into rare Bombay type blood. *Nat. Commun.* **14**, 1765 (2023).
196. Chua, H.-H. et al. Antagonism between gut *Ruminococcus gnavus* and *Akkermansia muciniphila* modulates the progression of chronic hepatitis B. *Cell Mol. Gastroenterol. Hepatol.* **17**, 361–381 (2024).
197. Liu, Y.-F. et al. Astaxanthin alleviates chronic prostatitis/chronic pelvic pain syndrome by increasing colonization of *Akkermansia muciniphila* in the intestine. *Phytomedicine* **123**, 155249 (2024).
198. Qiao, C.-M. et al. *Akkermansia muciniphila* is beneficial to a mouse model of Parkinson's disease, via alleviated neuroinflammation and promoted neurogenesis, with involvement of SCFAs. *Brain Sci.* **14**, 238 (2024).
199. Guo, H., Liu, X., Chen, T., Wang, X. & Zhang, X. *Akkermansia muciniphila* improves depressive-like symptoms by modulating the level of 5-HT neurotransmitters in the gut and brain of mice. *Mol. Neurobiol.* **61**, 821–834 (2024).
200. Kim, J. Y. et al. *Akkermansia muciniphila* extracellular vesicles have a protective effect against hypertension. *Hypertens. Res.* **47**, 1642–1653 (2024).
201. Ou, Z. et al. Protective effects of *Akkermansia muciniphila* on cognitive deficits and amyloid pathology in a mouse model of Alzheimer's disease. *Nutr. Diabetes* **10**, 12 (2020).
202. Ding, Y. et al. A next-generation probiotic: *Akkermansia muciniphila* ameliorates chronic stress-induced depressive-like behavior in mice by regulating gut microbiota and metabolites. *Appl. Microbiol. Biotechnol.* **105**, 8411–8426 (2021).
203. DeSana, A. J., Estus, S., Barrett, T. A. & Saatman, K. E. Acute gastrointestinal permeability after traumatic brain injury in mice precedes a bloom in *Akkermansia muciniphila* supported by intestinal hypoxia. *Sci. Rep.* **14**, 2990 (2024).
204. Hammer, T. J. Why do hosts malfunction without microbes? Missing benefits versus evolutionary addiction. *Trends Microbiol.* **32**, 132–141 (2024).
205. Kobayashi, Y., Kawahara, T., Inoue, S. & Kohda, N. *Akkermansia biwaensis* sp. nov., an anaerobic mucin-degrading bacterium isolated from human faeces. *Int. J. Syst. Evol. Microbiol.* **73**, https://doi.org/10.1099/ijsem.0.005697 (2023).
206. Gilroy, R. et al. Extensive microbial diversity within the chicken gut microbiome revealed by metagenomics and culture. *PeerJ* **9**, e10941 (2021).
207. Richter, M. & Rosselló-Móra, R. Shifting the genomic gold standard for the prokaryotic species definition. *Proc. Natl Acad. Sci. USA* **106**, 19126–19131 (2009).
208. Becken, B. et al. Genotypic and phenotypic diversity among human isolates of *Akkermansia muciniphila*. *mBio* **12**, 00478–21 (2021).

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