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Microbe Profile: *Akkermansia muciniphila*: a conserved intestinal symbiont that acts as the gatekeeper of our mucosa

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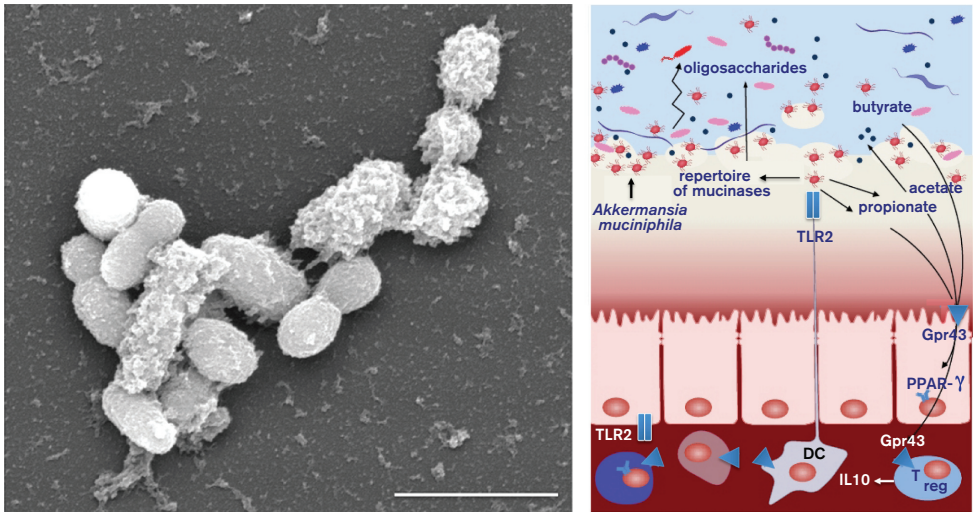

Graphical abstract

Ultrastructure of *Akkermansia muciniphila* and model for its interaction with the host. Left: scanning microscopy of *A. muciniphila* cells revealing extracellular and outer membrane structures that are the subject of intense research (Ottman N, Huuskonen L, Reunanen J, Boeren S, Klievink J *et al.Front Microbiol* 2016;7:1157). Scale bar, 2 µm. Right: model for the interaction of *A. muciniphila* and its host [after (Belzer C, de Vos WM. *ISME J* 2012;6:1449–1458)]. The production of the short-chain fatty acids acetate, propionate and butyrate from mucus by *A. muciniphila* in syntrophy with other intestinal microbes as well as the interaction with the immune system and regulatory T cells have been experimentally verified in *in vitro* and mouse models (Plovier H, Everard A, Druart C, Depommier C, van Hul M *et al. Nat Med* 2017;23:107–113).

Abstract

Akkermansia muciniphila is an abundant inhabitant of the intestinal tract of humans and many other animals. It is the sole intestinal representative of the verrucomicrobia in human stools and depleted in adults suffering from obesity, diabetes and several other diseases. *A. muciniphila* degrades intestinal mucin into mainly propionic and acetic acid, and lives in symbiosis with its host, marked by signalling to immune and metabolic pathways, priming trophic chains and likely providing competitive exclusion at the host–microbe interface. Since its recent discovery, *A. muciniphila* has increasingly been studied and recognized as a true intestinal symbiont promoting beneficial interactions in the intestinal tract.

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Keyword: microbe profile.

TAXONOMY

Domain *Bacteria*, phylum *Verrucomicrobia*, class *Verrucomicrobiae*, order *Verrucomicrobiales*, family *Verrucomicrobiaceae*, genus *Akkermansia*, species *A. muciniphila*, strain Muc^T. Presently, *A. muciniphila* strain Muc^T is the only cultured and deposited human representative of the genus *Akkermansia*.

PROPERTIES

The type strain of *A. muciniphila*, strain Muc^T, has been isolated under strict anaerobic conditions from a faecal sample of a healthy adult by using purified mucin as the sole carbon, nitrogen and energy source. It is an obligate chemoorganotroph optimally growing at 37 °C in anaerobic conditions with a preference for mucus as substrate, yielding doubling times of approximately 1 h. Mucus is degraded by a large set of secreted mucolytic enzymes and its major sugar components, including *N*-acetyl galactosamine and *N*-acetyl glucosamine, are converted into the major end products propionate and acetate [1].

GENOME

The complete 2 664 102 bp genome of *A. muciniphila* Muc^T has been determined and found to encode a large secretome that included over 25 % of all predicted proteins, 61 of which were predicted to be involved in mucin [2]. The availability of the genome of strain Muc^T has sparked various studies into its evolution, distribution and function. Metaproteome analysis revealed *A. muciniphila* to be highly active in a subject carrying a high level (12 %) of *Akkermansia*, revealing a set of hundreds of proteins, some of which are present in the outer membrane, including a 33 kD protein that partly recapitulates the beneficial effects of *A. muciniphila* in a preclinical model (see below; [3–5]).

PHYLOGENY

Comparison with genomes of other Verrucomicrobia (sizes from 2.2 to 8.2 Mb) revealed *A. muciniphila* Muc^T to share only very little similarity, indicating a deep rooting. Detailed analysis of human metagenomic datasets suggested the presence of other *Akkermansia* genomes that have less than 88 % average nucleotide identity with the *A. muciniphila* genome, suggesting the existence of other human species [2]. However, misassembly of short reads, sequence errors and co-occurrence of multiple strains in a single subject cannot be ruled out. The ubiquitous presence of a single species with limited genomic variation in a range of mammals testifies a high level of specialized adaptation to the mucosal environment and is indicative of a conserved symbiosis between *A. muciniphila* and its hosts [4].

KEY FEATURES AND DISCOVERIES

While mucus degradation has been associated with a potential pathogenic lifestyle, it should be considered that this glycoprotein is highly abundant in the colon and may represent approximately half of the carbon that is found in the human colon. Hence, specialized microbes have been selected that can degrade this complex glycoprotein and live in symbiosis with the host, notably in the mucosal layer that protects the intestinal cells. *A. muciniphila* is a prime example of the symbiosis that is conserved in many mammalian species and is capable of priming trophic chains (graphical abstract figure).

In a healthy human, *A. muciniphila* is present in high levels (approximately 3 %) in the adult colon, rendering it one of the most abundant intestinal species and testifying its apparent safety. Moreover, *A. muciniphila* can be found in all age groups and its capacity to grow on human milk supports its close association with the intestinal tract. Remarkably, *A. muciniphila* is depleted in faecal samples from adults suffering from a variety of diseases, including obesity, metabolic syndrome and diabetes. Evidence for its impact on the host originated from analysing the transcriptional response of germ-free mice mono-associated with *A. muciniphila* that showed increased immune and metabolic signalling, indicating specific host–microbe cross-talk [4, 5].

A landmark discovery has been the finding that *A. muciniphila* or a specific 33 kDa outer membrane protein protected mice from diet-induced obesity, increased the mucosal barrier function and reduced insulin resistance as well as intestinal and systemic inflammation [5]. Moreover, recent studies revealed that *A. muciniphila* binds human intestinal cells and increases barrier function, while human dietary intervention studies indicated *A. muciniphila* to be an indicator of a healthy metabolic status [5].

Since the isolation of *A. muciniphila* a dozen years ago, the research on this intestinal symbiont has come of age and attracted considerable interest for its physiology, genomics and ecology. Its impact in model animals and intestinal model systems has to be further confirmed and extended. Presently, a human safety and dose-finding trial is ongoing to provide causal relations and may result in the development of *A. muciniphila* as a next-generation therapeutic microbe with a wide spectrum of applications ([5]; see www.clinicaltrials.gov).

KEY QUESTIONS

- How widely spread is the conserved symbiosis between *A. muciniphila* and the mammalian host?
- What other *Akkermansia* species exist and how do they differ at the genomic, physiological and symbiotic level from *A. muciniphila*?
- What are the signalling mechanisms by which *A. muciniphila* interacts with human and other hosts?
- What trophic chains are induced by *A. muciniphila* and its degradation of mucus?
- Can delivery of *A. muciniphila* alone or in combination with other microbes be used in therapies to increase barrier function, reduce inflammation and cure diseases?

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Conflicts of interest
The author declares that there are no conflicts of interest.

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