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Review

Akkermansia muciniphila and its role in regulating host functions

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ABSTRACT

Akkermansia muciniphila is an intestinal bacterium that was isolated a decade ago from a human fecal sample. Its specialization in mucin degradation makes it a key organism at the mucosal interface between the lumen and host cells. Although it was isolated quite recently, it has rapidly raised significant interest as *A. muciniphila* is the only cultivated intestinal representative of the Verrucomicrobia, one of the few phyla in the human gut that can be easily detected in phylogenetic and metagenome analyses. There has also been a growing interest in *A. muciniphila*, due to its association with health in animals and humans. Notably, reduced levels of *A. muciniphila* have been observed in patients with inflammatory bowel diseases (mainly ulcerative colitis) and metabolic disorders, which suggests it may have potential anti-inflammatory properties. The aims of this review are to summarize the existing data on the intestinal distribution of *A. muciniphila* in health and disease, to provide insight into its ecology and its role in founding microbial networks at the mucosal interface, as well as to discuss recent research on its role in regulating host functions that are disturbed in various diseases, with a specific focus on metabolic disorders in both animals and humans.

Contents

Abbreviations: DSS, dextran sulfate sodium; FISH, fluorescent *in situ* hybridization; HFD, high fat diet; FODMAP, fermentable oligosaccharides disaccharides; monosaccharides and polyols IBD, inflammatory bowel disease; LPS, Lipopolysaccharide; MGS, metagenomic species; qPCR, quantitative PCR; IgA, immunoglobulin A; T-RFLP, terminal-restriction fragment length polymorphism; T2D, type 2 diabetes.

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1. Culturability of the human gut microbiota

The human intestine is home to more than a thousand microbial species. A recent review pointed out that over 1000 microorganisms, belonging to Bacteria, Archaea and Eukarya, have been obtained in pure cultures [1]. In 1950, the study of intestinal bacteria was revolutionized by the development of an array of techniques for culturing strict anaerobes by Robert Hungate [2]. Prior to this, mostly only aerobic or facultative anaerobic bacteria could be isolated from intestinal samples. The use of strict anaerobic conditions according to the Hungate approach enabled the extensive characterization of the major intestinal microbes in the 1970s. Cultivation of most intestinal bacteria has been carried out using rich media, or semi-defined media with targeted carbon sources. In the late 1970s, Carl Woese discovered a third domain of life, Archaea, using a proposed universal phylogenetic marker, the 16S rRNA gene, that can be used as a signature of prokaryotic species [3]. This and the subsequent molecular revolution based on rapid sequencing methods have drastically changed the perception of microbial ecology, allowing for a more representative description of various ecosystems, and circumventing the need to cultivate bacteria in order to describe the community of a specific niche [3]. This has also emphasized that most of the sequences returned from profiling human intestinal microbiota samples are derived from microbes that have not yet been cultivated. In parallel, although there has been a decline in new cultivation approaches, there is an obvious renewal of interest in cultivating gut microbes. Indeed, obtaining bacteria in pure culture is complementary to molecular approaches since they provide information (e.g. physiology, interaction with host and other bacteria) that molecular approaches do not. However, the direct use of genome sequencing from intestinal samples to characterize as yet uncultivated microorganisms, can also provide information on their genetic capacity to use specific nutrients [4,5]. As a major fraction of the gut microbial ecosystem has not yet been cultured, it is often regarded as being refractory to cultivation in the laboratory. Although that is probably true for some microbes that are either too dependent on the host or on other bacteria to grow, the use of defined medium combined with novel isolation strategies (such as culturomics) has nevertheless, led to the successful isolation of an increasing number of intestinal bacterial species [6–8]. A recent example of an organism that was refractory to *in vitro* isolation is *Candidatus arthromitus* (also known as segmented filamentous bacteria, or SFB) that is found abundantly in the intestinal tract of mice although not, or not all, in humans. Using a strategy that combines an SFB–host cell co-culturing system, SFB was first isolated in pure culture in 2015 [9]. Some examples of currently uncultivable bacteria from human microbiota that are frequently detected in human samples by sequencing technologies include members of the Candidate TM7 phylum and Cyanobacteria [5], as well as some genera of Clostridiales such as *Oscillospira*, neither of which have been obtained in pure culture, although indications for the sequence of their genomes have been obtained. A species that was successfully isolated is *Akkermansia muciniphila* (Fig. 1). Interestingly it was, and still is, the first intestinal microbial isolate of the phylum Verrucomicrobia. With its isolation came the awareness that this phylum is represented in the intestine. It was originally isolated from a fecal sample from a healthy Caucasian female in a specific medium that contained purified mucin as the sole carbon source, using the most probable number approach [10]. Mucin was chosen as a selective carbon source since it was hypothesized that microbes capable of utilizing these host-produced glycans as carbon sources are those that are located at the interface between the luminal bacteria and the host, a prediction that materialized with the discovery of *A. muciniphila*.

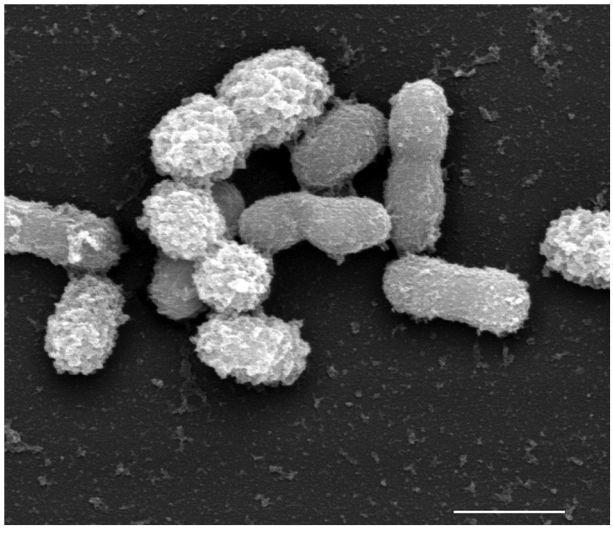

Fig. 1. Scanning electronic micrograph of *Akkermansia muciniphila* ATCC BAA-835 (Bar represents 1 μm.

2. Ecology of *A. muciniphila* in the intestine

2.1. Abundance in human samples

Once isolated, it was important to quantify the amount of *A. muciniphila* cells within human stool samples in order to evaluate whether it is commonly present. It was originally determined that *A. muciniphila* accounted for more than 1% of the total microbiota using fluorescent *in situ* hybridization (FISH) and quantitative PCR (qPCR) [11,12]. Notably, at that time, FISH was also commonly used to quantify major bacterial taxa. Interestingly, it was observed that *Akkermansia* spp. could not be targeted by the classical EUB-338 I universal bacterial probe. Later, the wider availability of 16S rRNA gene sequencing allowed for the detection of the genus *Akkermansia* in a large number of studies. When the