Disease-associated dysbiosis and potential therapeutic role of *Akkermansia muciniphila*, a mucus degrading bacteria of gut microbiome

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Abstract
The unique functionality of *Akkermansia muciniphila* in gut microbiota indicates it to be an indispensable microbe for human welfare. The importance of *A. muciniphila* lies in its potential to convert mucin into beneficial by-products, regulate intestinal homeostasis and maintain gut barrier integrity. It is also known to competitively inhibit other mucin-degrading bacteria and improve metabolic functions and immunity responses in the host. It finds a pivotal perspective in various diseases and their treatment. It has future as a promising probiotic, disease biomarker and therapeutic agent for chronic diseases. Disease-associated dysbiosis of *A. muciniphila* in the gut microbiome makes it a potential candidate as a biomarker for some diseases and can provide future theranostics by suggesting ways of diagnosis for the patients and best treatment method based on the screening results. Manipulation of *A. muciniphila* in gut microbiome may help in developing a novel personalized therapeutic action and can be a suitable next generation medicine. However, the actual pathway governing *A. muciniphila* interaction with hosts remains to be investigated. Also, due to the limited availability of products containing *A. muciniphila*, it is not exploited to its full potential. The present review aims at highlighting the potential of *A. muciniphila* in mucin degradation, contribution towards the gut health and host immunity and management of metabolic diseases such as obesity and type 2 diabetes, and respiratory diseases such as cystic fibrosis and COVID-19.

Keywords *Akkermansia muciniphila* · Biomarker · COVID-19 · Gut microbiome · Host immunity · Mucus degradation · Obesity · Probiotic · Therapeutic · Type 2 diabetes

Introduction

*Akkermansia muciniphila* (*A. muciniphila*) is a recently discovered member of commensal gut microbiota and constitutes a new genus of the phylum *Verrucomicrobia* (Derrien et al. 2004). It is oval, strictly anaerobic, non-motile and Gram-negative bacteria that do not form endospores. It has circular genome of 2,664,102 base pairs, sharing 29% gene similarity with phylum *Verrucomicrobia* (van Passel et al. 2011). As unveiled by whole-genome sequencing, its proteome consists of 5644 unique proteins (Guo et al. 2017). *A. muciniphila* colonizes the gastrointestinal tracts at an early stage through human milk and accounts for 1–4% of total gut microbiota (Collado et al. 2008). The abundance of *A. muciniphila* in caecum is ubiquitous in infants and healthy adults. Besides the large intestine, it is also found in the lining of the lungs and saliva.

The importance of *A. muciniphila* lies in its potential to degrade mucin, the significant component in mucus. It consumes mucin as a carbon and nitrogen source during its life cycle and metabolism. The optimum temperature and pH for its growth are 37 °C and 6.5 respectively. A recent study showed that despite being a strict anaerobe, it could sustain lower amounts of oxygen (Ouwerkerk et al. 2016). This property is quite similar to other microbes in the intestine, especially anaerobes, such as *Bifidobacterium adolescentis* and *Bacteroides fragilis*, which can tolerate ambient amounts of oxygen for 48 h (Ouwerkerk et al. 2016). *A. muciniphila* is known to competitively inhibit other mucin-degrading bacteria and improve metabolic functions and immunity responses in the host, making it a suitable candidate as a probiotic (Belzer and de Vos 2012).
was even found to be effective in treatment of inflammatory bowel diseases and cancer (Png et al. 2010; Chen et al. 2020a). The present review aims at studying the potential of A. muciniphila in mucin degradation, contribution towards the gut health and host immunity, and management of metabolic diseases such as obesity and type 2 diabetes, and respiratory diseases such as cystic fibrosis and COVID-19.

**A. muciniphila in gut microbiome**

The prevalence of A. muciniphila has been connected with a healthy gut, and therefore, its richness is inversely linked to numerous disease conditions (Jakobsson et al. 2015). An investigation of its relationships with the hosts revealed A. muciniphila to enhance the intestinal barrier function in mice (Shin et al. 2014). Colonization by A. muciniphila culminated in transcriptome alterations, leading to a rise in the genetic expression linked with immunogenicity. Outer membrane proteins of A. muciniphila were discovered to play a function in controlling immunological responses. One of the outer membrane proteins was recently discovered (Amuc-1100) (Ottman et al. 2017b). The work demonstrated that the outer membrane pili-like protein is essential in immunological modulation and the increase of trans-epithelial resistance. A. muciniphila performed a function in regulating metabolic endotoxemia and adipose tissue metabolism. Several investigations have consciously or inadvertently discovered the existence of Akkermansia-like spp. in regions of the human body other than the colon, where A. muciniphila could also have vital activities. The physiology and environmental factors of Akkermansia-like spp. in distinct anatomic locations of the digestive tract allow us to evaluate the ability of A. muciniphila to colonize and be productive at all these niches. Various beneficial effects of A. muciniphila in the human microbiome are presented in Fig. 1.

**Mucin-degrading activity of A. muciniphila**

Mucus consists of heavily glycosylated mucin-2 (MUC2), an oligosaccharide composed of various amino sugars and monosaccharide sugars, including N-acetyl-D-galactosamine (GalNAc), N-acetyl-D-glucosamine (GlcNAc), D-galactose...
and L-fucose (Ottman et al. 2017a). In many cases, these sugars are further substituted with acetate, phosphate and sulfate groups. Mucin has defining roles like a lubricant for food transport over membranes and provides selective permeability that allows the flow of nutrients to epithelial cells. It also acts as the first line of defence against mechanical damage, pathogens, and toxins and provides a surface layer to bacteria for its growth, adhesion and protection (Cone 2009; Johansson et al. 2013). However, some bacterial species of human microbiota release inflammatory toxins, which increase the permeability of the mucus layer and ultimately decrease its barrier property (Jakobsson et al. 2015). It has been concluded that bacterial colonies reside only at the outer layer of the intestinal tract. In contrast, the inner layer intends to keep the bacteria at bay from the epithelial cells to enforce immune tolerance to the guts by transporting IgA and antimicrobial proteins (Johansson et al. 2008, 2011).

It is observed that A. muciniphila can maintain an exciting microbial relationship in the host intestine by converting mucin into beneficial by-products (Ottman et al. 2017a, b). Recent studies showed that A. muciniphila could be grown on a synthetic medium where mucin can be replaced with media containing glucose, threonine, peptone and GlcNAc (Plovier et al. 2016). The amino group of sugars promotes the growth of bacteria in the presence of casitone, tryptone, yeast extract and peptone. One of the essential factors that account for the proliferation of A. muciniphila is glucose-6-phosphate, one of the constituents of mucin known to promote the adaptation of mucosal niche (van der Ark et al. 2018). In order to study substrate uptake abilities of A. muciniphila, few studies were conducted on a genome-scale metabolic model to demonstrate amino acids auxotrophy, sugar degrading capacities and vitamin biosynthesis (Ottman et al. 2017a). These experiments have also been validated through in vivo experiments in which A. muciniphila has been shown to proficiently utilize mucin-derived monosaccharide sugars and amino sugars. It has been found that the uptake of mucin-derived sugars and non-mucin sugar glucose by A. muciniphila is enhanced in a mucin-rich environment which indicates the need of mucin-derived components for the optimal growth of bacteria. In vivo experiments have also suggested that A. muciniphila may have galactose metabolism; however, mucin-derived components are necessary for its growth.

Transcriptomic analysis of A. muciniphila under mucin-rich and mucin-depleted conditions showed differential gene expression suggesting a global change in cellular functions (Shin et al. 2019). Out of 1126 differentially expressed genes (DEGs), 583 genes were upregulated while 543 were downregulated in mucin-rich conditions as compared to mucin-depleted conditions. The upregulated genes were significantly related to hydrolase activity acting on glycosidic bonds and their transporters, thereby confirming the activity of mucin-degrading genes under mucin-rich conditions. Thus, the genes that encode mucin-degrading enzymes, such as sulfatases, galactosidases, acetyl-glucosaminidase, neuraminidases and L-fucosidase transporters were upregulated in mucin-rich conditions. Furthermore, their downregulation in mucin-depleted medium determined the importance of its role in mucin-degradation. The catabolic glycolysis pathway is also correlated with mucin-degradation pathways (Shin et al. 2019). Thus, under mucin-depleted conditions, genes involved in glycolysis and energy metabolism, such as NADH dehydrogenase, succinate dehydrogenase and ATP synthase, either showed similar expression levels or were upregulated significantly. At the same time, there were few exceptions, including one ATP-dependent 6-phosphofructokinase gene (Amuc_1481), two enolase genes (Amuc_844, Amuc_1184) and one dihydrolipoyl dehydrogenase gene (Amuc_1689).

**A. muciniphila in host immunity and probiotic nature**

The symbiotic relationship between the gut microbiota and host determines the normal physiology, immunity and pathogen susceptibility of an individual. The interplay between host and gut microbiome that helps in pathogen displacement, regulating immune response and anti-inflammatory pathways, is a vital phenomenon. There is abundant evidence in the literature on mucin-utilizing A. muciniphila conferring immunity (Tummler and Puchelle 1997; Plovier et al. 2016; Ottman et al. 2017a). Many mucin degradation pathways regulate the host pathway by signalling through tumour necrosis factor α (TNF-α), interferon γ, interleukins-10 (IL-10) and interleukins-4 (IL-4) (Derrien et al. 2011; Andersson et al. 2012; Collado et al. 2012). Decreased levels of anti-inflammatory cytokines (IL-10 and IL-4) induced interleukins, while increased proinflammatory cytokines (TNF-α and IFN-γ) causing rapid proliferation of A. muciniphila. An increase in 2-arachidonoylglycerol levels was noted post A. muciniphila treatment, reducing inflammation (Gunderson and Kopito 1994; Everard et al. 2013). The secreted proteins from bacteria interact with host immune cells to induce signalling pathways that exhibit anti-inflammatory and immunomodulatory activity (Sánchez et al. 2008, 2010; Bernardo et al. 2012; Ruiz et al. 2014). The extracellular material secreted from it activates the downstream signalling pathway like toll-like receptors 2 (TLR2) (Ottman et al. 2017b). Amuc_110, a specific protein in the outer membrane, recapitulates the effect of bacteria on TLR2 activation and improves the barrier integrity of intestines (Dean and Annilo 2005; Belzer and de Vos 2012; Plovier et al. 2016; Ottman et al. 2017b). However, it is still unknown how Amuc_110 protein is regulated in the presence of a dynamic mucosal environment. The gene encoding
Amuc_110 protein is highly regulated in a mucin-depleted environment (Plovier et al. 2016). Amuc_110 has also shown its ability to exert a probiotic effect on diet-induced obesity and was present in the extracellular proteins of A. muciniphila as well (Plovier et al. 2016). To conclude, A. muciniphila is inversely correlated with inflammatory conditions and helps in epithelial barrier integrity by stimulating anti-inflammatory pathways (Gunderson and Kopito 1994; Shin et al. 2014; Cantarel et al. 2015; Caesar et al. 2015; Schneeberger et al. 2015).

The composition and functioning of the human gut microbiota are primarily proportional to nutritional accessibility of microbiota either obtained from a host or food (Zoetendal et al. 2012; Nicholson et al. 2012; Salonen and de Vos 2014). A. muciniphila is one of the good bacteria of the human gut microbiota. The presence of A. muciniphila in the intestinal mucus layer indicates it to be involved in gut regulation and host metabolism. It exists in a symbiotic relationship with the mucosal layer, and its abundance is greatly affected by the nutrients present in the mucin layer located around the intestinal epithelial cells. Its presence also supports other beneficial bacteria in the gut microbiome. A. muciniphila catabolizes mucins and turns them into short-chain fatty acids (SCFAs), including acetate, which other beneficial bacteria exploit, such as Firmicutes, to produce butyrate, a vital source of energy for the cells lining the gut. The production of SCFAs from the breakdown of mucin supplies energy to the goblet cells, which are responsible for secreting mucins. Furthermore, the consumption of specific dietary fibres can increase the abundance of this friendly bacteria, which helps thicken the mucus lining the gut. This strengthens the gut lining and improves gut barrier function and may, in turn, help in preventing weight gain. Chelakkot et al. demonstrated the role of Amuc_1100, isolated from A. muciniphila, in AMP-activated protein kinase (AMPK) activation mechanism, thereby improving gut integrity (Chelakkot et al. 2018). Amuc_1100 has been implicated in enhancing the expression of tight junction protein-1 (Tjp-1) and occludin (Li et al. 2016), thereby contributing to the gut barrier function. Thus, the presence of A. muciniphila in the mucus of the intestine regulates intestinal homeostasis and its integrity barrier through host signalling pathways (Derrien et al. 2004; Ottman et al. 2017a).

**A. muciniphila dysbiosis associated with disease states and its management**

The gut microbiome of healthy people is quite diverse. Gut microflora through microbial antigens and metabolites is the master regulator of innate and adaptive immunity. Disease-associated dysbiosis results in induction, training and function of immune system. The disturbance of the mucus layer by any means may lead to inflammation and increase the risk of infection. Even slight variance in intestinal flora may be associated with sensitivity and severity of a disease. Therefore, gut microbes find use as potential diagnostic biomarkers by studying their abundance in different diseases.

A. muciniphila has been linked with wide range of diseases and disorders such as type 2 diabetes (Tilg and Moschen 2014), alcoholic steatohepatitis (ASH) (Grander et al. 2018), appendicitis (Swidsinski et al. 2011), obesity (Dao et al. 2016), atopic diseases (Drell et al. 2015), colorectal cancer (Weir et al. 2013), autism (Wang et al. 2011), inflammatory bowel disease (Png et al. 2010), cystic fibrosis (Hayden et al. 2019), and COVID-19 (Yeoh et al. 2021) (Table 1). Various studies demonstrated A. muciniphila to be negatively correlated with inflammatory bowel diseases (Png et al. 2010; Rajilić-Stojanović et al. 2013), appendicitis (Swidsinski et al. 2011), obesity (Karlsson et al. 2012; Dao et al. 2016) and type 2 diabetes (Tilg and Moschen 2014). Lower abundance of A. muciniphila is commonly observed in the majority of metabolic disorders while higher abundance is seen in few cases like colorectal cancer (Yu et al. 2017).

Recently, an association between A. muciniphila and metastasis of lymph nodes in lung adenocarcinoma was reported (Chen et al. 2020a). The relative abundance of A. muciniphila was observed to be greater in metastasis cohort (0.057) than the non-metastasis cohort (0.023) pointing towards its potential as a promising biomarker to predict lymph node metastasis. Likewise, a study to investigate whether A. muciniphila could enhance the antitumor effect of cisplatin (cis-diamminedichloroplatinum; CDDP) was conducted (Chen et al. 2020b). It was found that when A. muciniphila was combined with cisplatin, the growth of tumour volume slowed and the changes of tumour pathomorphology significantly improved. At molecular level, upregulation of factor-associated suicide (Fas) proteins and downregulation of p53, ki-67 and Fas ligand (FasL) proteins were also observed. Several proinflammatory factors (TNF-α, IFN-γ and IL-6) were induced while the expression of CD4+CD25+Foxp3+ Treg was suppressed indicating the role of A. muciniphila in regulating immune inflammatory microenvironment in reversion of tumour growth and tumour immune escape. Also, the levels of IFI27/12 and IGFBP7, two most differentially expressed genes in lung cancer, were found to be increased because of the combined treatment with A. muciniphila and CDDP. Signalling pathways such as JAK-STAT, FOXO, cytokine-cytokine receptor interaction, PI3K-Akt, Th17 and cell differentiation were associated with the antitumor effect of A. muciniphila and CDDP. The study suggested that A. muciniphila combined with CDDP provides good symbiotic environment to achieve maximum therapeutic efficacy of antitumor drugs. The human gut microbiome could
therefore, be responsible for differences in drug response of individuals paving way for personalized therapeutics to significantly improve human health care. Thus, by regulating the abundance of *A. muciniphila* in the gut microbiome in a personalized manner, early treatment of related diseases may be facilitated. The microbiome in general, and *A. muciniphila* in particular, can act as a biomarker of these diseased states and provide future theranostics by suggesting ways of disease diagnosis and treatment (Morgan and Huttenhower 2012).

### Table 1 Altered abundance of *A. muciniphila* in various disease states in humans

| Disease                          | *A. muciniphila* abundance | Detection method               | Sample type       | References                                                                 |
|----------------------------------|-----------------------------|--------------------------------|-------------------|---------------------------------------------------------------------------|
| Allergic asthma                  | Reduced                     | qPCR                           | Faeces            | (Demirci et al. 2019)                                                    |
| Asthma                           | Reduced                     | 16S rRNA sequencing            | Faeces            | (Michalovich et al. 2019)                                                |
| Alcoholic steatohepatitis (ASH)  | Reduced                     | 16S rRNA sequencing            | Faeces            | (Grander et al. 2018)                                                    |
| Atopy                            | Reduced                     | 16S rRNA sequencing            | Faeces            | (Candela et al. 2012)                                                    |
| Atopy                            | Reduced                     | Pyrosequencing                 | Faeces            | (Drell et al. 2010)                                                      |
| Autism                           | Elevated                    | bTEFAP                         | Faeces            | (De Angelis et al. 2013)                                                 |
| Autism                           | Reduced                     | qPCR                           | Faeces            | (Wang et al. 2011)                                                       |
| *Clostridium difficile* infection| Elevated                    | qPCR                           | Faeces            | (Vakili et al. 2020)                                                     |
| Colorectal cancer                | Elevated                    | 16S rRNA sequencing            | Faeces            | (Weir et al. 2013)                                                       |
| Colorectal cancer                | Elevated                    | qPCR                           | Tissue biopsy     | (Mira-Pascual et al. 2015)                                               |
| Crohn’s disease                  | Reduced                     | qPCR                           | Tissue biopsy     | (Png et al. 2010)                                                       |
| Crohn’s disease                  | Reduced                     | 16S rDNA pyrosequencing        | Faeces            | (Opstelten et al. 2016; Malham et al. 2019)                               |
| Cystic fibrosis                  | Reduced                     | 16S-based tag-encoded FLX amplicon pyrosequencing (bTEFAP) | Faeces            | (Hoffman et al. 2014)                                                    |
| Cystic fibrosis                  | Reduced                     | Metagenomic sequencing         | Faeces            | (Hayden et al. 2019)                                                     |
| COVID-19                         | Elevated                    | Shotgun sequencing             | Faeces            | (Yeoh et al. 2021)                                                       |
| Oesophageal cancer               | Elevated                    | 16S rRNA sequencing            | Tissue biopsy     | (Snider et al. 2019)                                                    |
| Hyperlipidaemia                  | Reduced                     | 16S rRNA sequencing            | Faeces            | (Gargari et al. 2018)                                                   |
| Microscopic colitis              | Reduced                     | 16S rDNA pyrosequencing        | Faeces            | (Fischer et al. 2015)                                                   |
| Multiple system atrophy          | Elevated                    | Metagenomic sequencing         | Faeces            | (Wan et al. 2019)                                                       |
| Obesity                          | Reduced                     | qPCR                           | Faeces            | (Marvasti et al. 2020)                                                   |
| Obesity                          | Elevated                    | qPCR                           | Faeces            | (Remely et al. 2015)                                                     |
| Parkinson’s disease              | Elevated                    | qPCR                           | Faeces            | (Unger et al. 2016)                                                     |
| Parkinson’s disease              | Elevated                    | Shotgun sequencing             | Faeces            | (Bedarf et al. 2017)                                                    |
| Prediabetes                      | Reduced                     | 16S rRNA sequencing            | Faeces            | (Allin et al. 2018)                                                     |
| Psoriasis                        | Reduced                     | 16S rDNA pyrosequencing        | Faeces            | (Tan et al. 2018)                                                       |
| Pulmonary arterial hypertension  | Reduced                     | Shotgun sequencing             | Faeces            | (Kim et al. 2020)                                                       |
| Pulmonary tuberculosis           | Reduced                     | Metagenomic sequencing         | Faeces            | (Hu et al. 2019)                                                        |
| Schizophrenia                    | Elevated                    | 16S rRNA sequencing            | Faeces            | (Xu et al. 2020a)                                                       |
| Schizophrenia                    | Elevated                    | Shotgun sequencing             | Faeces            | (Zhu et al. 2020)                                                       |
| Spleen deficiency syndrome       | Reduced                     | qPCR                           | Faeces            | (Peng et al. 2020)                                                      |
| Type 1 diabetes                  | Reduced                     | qPCR                           | Faeces            | (Fassatou et al. 2019)                                                   |
| Type 2 diabetes                  | Elevated                    | Metagenomic sequencing         | Faeces            | (Chelakkot et al. 2018)                                                 |
| Type 2 diabetes                  | Elevated                    | Shotgun sequencing             | Faeces            | (Qin et al. 2012)                                                       |
| Type 2 diabetes                  | Reduced                     | 16S rRNA sequencing            | Urine             | (Liu et al. 2017)                                                        |
| Type 2 diabetes                  | Reduced                     | Metagenomic sequencing         | Faeces            | (Zhong et al. 2019)                                                     |
| Type 2 diabetes                  | Reduced                     | qPCR                           | Faeces            | (Fassatou et al. 2019)                                                   |
| Ulcerative colitis               | Reduced                     | qPCR                           | Tissue biopsy     | (Png et al. 2010)                                                       |
| Ulcerative colitis               | Reduced                     | MiSeq sequencing               | Faeces            | (Bajer et al. 2017)                                                     |
| Ulcerative colitis               | Reduced                     | 16S rRNA sequencing            | Faeces            | (Malham et al. 2019)                                                    |
**A. muciniphila and metabolic diseases**

**Decreased abundance of A. muciniphila in obesity**

World Health Organization (WHO) defines obesity as abnormal fat accumulation leading to health implications like type 2 diabetes, fatty liver disease and hypertension. Being a multifactorial disorder, not only does it result in fatal complications like cardiovascular diseases and psychological effects but also challenges one to perform everyday tasks with ease. It is a low-grade inflammatory metabolic disorder resulting in higher levels of inflammatory cytokines such as IL-6, TNF-α and hypersensitive C-reactive protein (hs-CRP). Inflammation in obesity leads to significant changes in gut microbiota, for example, increase in the abundance of *Firmicutes*, *Bifidobacterium* spp. and *Lactobacillus gasseri* while decrease in the abundance of *Bacteroidetes* (Ley et al. 2005; Wang and Jia 2016). *A. muciniphila* was inversely associated with obesity and found to be more abundant in lean individuals than overweight individuals (Remely et al. 2016). The various mechanisms by which *A. muciniphila* helps in obesity management are shown in Fig. 2. *A. muciniphila* maintains the intestinal immunity, gut barrier integrity and permeability by reducing inflammatory cytokines, thereby achieving metabolic homeostasis (Ottman et al. 2017b). Also, lipopolysaccharide (LPS) found in cell wall of Gram-negative bacteria is a potential proinflammatory molecule and is associated with onset of inflammation. Imbalance in LPS levels leads to activation of proinflammatory signalling pathways causing increased secretion of IL-6 and TNF-α. The inherent property of *A. muciniphila* of SCFAs production signals G-protein coupled receptor (GPCR) activation and histone deacetylase (HDAC) inhibition to maintain energy homeostasis and appetite sensation (Lukovac et al. 2014). SCFAs production facilitate increased production of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulin tropic polypeptide (GIP) upon binding to GPR41/GPR43 receptors present in L-cells in the intestinal mucosa. This results in improvement in insulin resistance and glucose tolerance thereby, suppressing appetite through metabolic signalling. Furthermore, *A. muciniphila* decreases inflammation by increasing the levels of oleoylthanolamide (OEA), 2-palmitoylglycerol (2-PG), 2-acylglycerol (2-AG) and 2-oleylglycerol (2-OG) which bind to GPR119 receptors, stimulating release of GLP-1 (Everard et al. 2013). In a recent study, oral supplementation of *A. muciniphila* in obese mice through high fat diet (HFD) has been demonstrated to reduce the intestinal endotoxin levels, hence reducing inflammation (Cani and de Vos 2017; Fuke et al. 2019). It helped restore gut barrier dysfunction through symbiotic relationships with other beneficial microbes like *Bacteroidetes*, *Euryarchaeota*, *Firmicutes* and *Actinobacteria* and improved intestinal permeability through the inhibition of claudin 3 (Cldn3), cannabinoid receptor 1 (Cnr1) and occludin like tight junction proteins or lowering of flavin-containing monoxygenase 3 (FMO3) expression (Dao et al. 2016).

In humans, both live and pasteurized *A. muciniphila* were found to be safe for oral consumption by heavy body weight individuals (Plovier et al. 2016). In a clinical trial (NCT02637115), oral administration of *A. muciniphila* in obese patients for 3 months was found to be an effective and safe treatment. Similarly, in a randomized, double-blind human study based on *A. muciniphila* supplementation, a decrease in body weight along with improvement in liver dysfunction and inflammation in patients was observed (Depommier et al. 2019). Also, supplementation with prebiotic containing oligofructose helped restore *A. muciniphila* abundance. But since *A. muciniphila* does not grow in vitro

![Fig. 2 Role of A. muciniphila in obesity management](image-url)
on oligofructose-enriched media, it can be concluded that complex cross-feeding interactions might be involved. While it is clear that the human mucus colonizer maintains gut barrier integrity and homeostasis during obesity, the role of human gut microbiome on etiology of obesity remains to be investigated. The study of *Akkermansia*-obesity relationship could provide better insights to microbe-based treatments. Since *A. muciniphila* regulates the energy metabolism of host, its therapeutic intervention in obesity could be explored (Xu et al. 2020b). The reduction in fat-mass ratio in obesity can be studied by urinary metabolomics profile of *A. muciniphila*, making it a suitable biomarker for obesity (Png et al. 2010). Furthermore, the risk of obesity and associated metabolic diseases can be reduced by proper management of gut microbial profile.

**Decreased abundance of *A. muciniphila* in type 2 diabetes**

According to WHO, 1 out of 11 people suffer from diabetes with over 1.5 million deaths globally. Type 2 diabetes is a silent killer marked by the body’s inability to utilize insulin produced by pancreatic β-cells. A study conducted by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) suggests that factors such as sedentary lifestyle and genetic conditions may contribute to early onset of type 2 diabetes. The increased levels of blood sugar, i.e. hyperglycaemia results in nervous, circulatory and immune system-related complications. Insulin resistance as a result of type 2 diabetes affects the gut microbial diversity and metabolite production. Alterations in the abundance of various gut microbes during the onset and progression of type 2 diabetes have also been observed. Many studies have reported negative correlation of genus *Akkermansia*, *Bacteroides*, *Faecalibacterium*, *Roseburia* and *Bifidobacterium*, while positive correlation of genus *Ruminococcus*, *Blautia* and *Fusobacterium* with type 2 diabetes (Sedighi et al. 2017; Gao et al. 2018). Patients with normal glucose tolerance exhibited higher abundance of *A. muciniphila* as compared to pre-diabetic or type 2 diabetes patients. Interestingly, several anti-diabetic drugs like metformin, dapagliflozin and liraglutide were found to favour the abundance of *A. muciniphila* (Shin et al. 2014; Wang et al. 2018; Lee et al. 2018). Furthermore, a study conducted on the administration of an antidiabetic drug, metformin revealed that *A. muciniphila* further enhanced its anti-diabetic effects (Shin et al. 2014). Mice fed on HFD, when treated with metformin, showed increased abundance of *A. muciniphila* and improved blood sugar levels. Moreover, improved tolerance to glucose was observed upon oral administration of *A. muciniphila* but not metformin.

*A. muciniphila* is known to protect the intestinal barrier function by maintaining normal blood sugar levels. The intrinsic ability of *A. muciniphila* to catabolize complex carbohydrates further assists in inhibition of α-glucosidase and reduction of postprandial hyperglycaemia (Everard et al. 2013). Both obesity and type 2 diabetes may be ameliorated by increasing fatty acid oxidation and energy expenditure but reducing fatty acid biosynthesis (Everard et al. 2013; Gurung et al. 2020). Thus, fatty acid oxidation in adipose tissues and adipocyte differentiation may be promoted by administration of *A. muciniphila*, and other bacteria such as *Lactobacillus gasseri*, *Bacteroides acidifiaciens* and thus SCFAs. This is correlated to increased levels of 2-PG, 2-AG and 2-OG in the adipose tissue. Furthermore, *A. muciniphila* can be regulated by increasing circulation of tryptophan metabolites through dietary intake (Cronin et al. 2021). Interestingly, *A. muciniphila* positively influences the host’s glucose metabolism by inducing IL-10, thus protecting from ageing-related insulin resistance (Wang et al. 2015; Greer et al. 2016). It fights against diabetic oxidative damage and improves resistance to gluco/lipotoxicity by decreasing hepatic glycogen levels and increasing HDL-C levels (Zhang et al. 2018). Moreover, it reduces inflammation by inhibiting the expression of TNF-α and lipid oxidative damage by lowering malondialdehyde levels in diabetic animals (Zhang et al. 2018). Increased paracellular gut permeability and gut barrier disruptions result in inflammation and metabolic diseases by increased absorption of LPS. *A. muciniphila* maintains glucose homeostasis and fat mass storage by controlling host mucus turnover and higher L-cell activity. Therefore, probiotic treatment could help restore *A. muciniphila* abundance and counter metabolic endotoxemia in type 2 diabetes and obesity. Therefore, it becomes necessary to study the host-gut microbe interactions for better understanding of governing mechanisms in development of type 2 diabetes. *A. muciniphila*, through the alteration of the gut microbiota, could help to control and manage type 2 diabetes in the near future.

**A. muciniphila and respiratory diseases**

**Decreased abundance of *A. muciniphila* in cystic fibrosis**

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene located on chromosome 7. CFTR protein functions as an important anion-selective ion channel responsible for epithelial fluid secretion and intra-luminal hydration (Welsh and Smith 1993). Defective CFTR protein leads to accumulation of mucus in the lungs and intestine largely affecting the pulmonary and intestinal microbiota (Price and O’Toole 2021). As the mucus gets more and more viscous, the mucociliary clearance mechanism (MCC) becomes unable to clear the mucus resulting in manifestation of opportunistic microbial infections. Dysfunctional CFTR results in an altered intestinal condition including dysbiosis of gut
microbiota due to physiological and biochemical imbalance. It includes changes in intestinal pH, inflammation, malabsorption and gut barrier disruptions (Meeker et al. 2020). Various factors such as prolonged antibiotics intake, immunosuppressive medications and high-calorie diet further shape the CFTR microbiome. Specifically, in delF508 mutations, bacteria such as *E. coli* and *Eubacterium biforme* were found in higher abundance while *Bifidobacterium* and *Faecalibacterium* species were in lower abundance (Schippa et al. 2013). Recent studies on the gut microbiota of CFTR-deficient mice reported an increase in abundance of *Enterobacteriaceae, Mycobacteria* and *Bacteroides* while a decrease in abundance of *Lactobacilli, Acinetobacter lwoffii* and *A. muciniphila* (Thomsson et al. 2002; Bazett et al. 2016). Through integrated metagenomics and metabolomics study on CFTR gut microbiota, an increase in the expression of associated metabolites such as propylbutyrate, 3-aminobutyric acid (GABA), ethanol, choline and pyridine was observed while there was reduction in expression levels of 4-methylphenol, methylacetate, uracil, sarcosine, acetate, phenol, benzoaldehyde and glucose (Vernocchi et al. 2018). The multi-omics-based model pointed out the correlation of microbial and metabolite variations caused by CFTR functional defects. Therefore, it becomes important to study the relationship between host gut, microbes and associated metabolites to investigate CF and its biomarkers. Major evidence of their relationship is the study on the administration of CFTR potentiator Ivacaftor which resulted in an increase in *A. muciniphila*. It could be explained by the release of bicarbonates from CFTR post Ivacaftor treatment that provided the optimal environment for mucin degraders (Ambort et al. 2012; Schütte et al. 2014). Post treatment with Ivacaftor, a significant reduction in stool calprotectin, a protein released by neutrophils, but no change in M2 pyruvate kinase (M2-PK) was observed. The reduction of calprotectin indicated that intestinal inflammation could be improved in CF patients upon restoration of intestinal milieu. Also, there was selective loss of pathogens like those of *Enterobacteriaceae* family which was positively correlated with stool calprotectin level (Manor et al. 2016). It led to an increase in the expression of an antimicrobial peptide (Reg III), which has direct metabolic activity in the intestine against Gram positive bacteria. In CF, *A. muciniphila* accounted for normal stool M2-PK concentration and decreased amount of *Enterobacter*. Thus, the increased abundance of *A. muciniphila* supports its potential as a biomarker for the gut and it may be used for the microbe based therapy in CF (Pang et al. 2014). Many gut microbes including *A. muciniphila* could be associated with CF and hold future as its promising therapeutic intervention. By regulating the gut profile of *A. muciniphila* through personalized nutrition and supplementation, host immunity can be improved, which could serve as one of the prophylactic ways by which the severity of CF could be minimized.

**Increased abundance of *A. muciniphila* in COVID-19**

On 11th March 2020, COVID-19 caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) was declared as a pandemic. Over 180 countries were affected globally leading to nationwide lockdowns. The virus primarily attacked the respiratory system causing high-grade fever, severe cough, shortness of breath and pneumonia in severe cases. Several people infected with the virus experienced neurological and gastrointestinal (GI) manifestations with or without respiratory symptoms. On the other hand, some people were asymptomatic or symptom-free. The viral infection was also correlated with gut-lung-brain axis and microbiome imbalance. Significant reduction in the abundance of beneficial microbes was associated with inflammation and pathogenesis in COVID-19 (Hussain et al. 2021). Altered microbiome composition could further weaken body’s immunity and may play a role in SARS-CoV-2 infection. Recent studies have elucidated the relationship between gut and lung microbiota in COVID-19 and potential as prognostic markers (Wang et al. 2021). Although there is no direct evidence of specific interaction between resident gut microbe and COVID-19, some studies suggest that the gut microbiome in COVID-19 could be a key player in modulating host response and disease severity (Hussain et al. 2021; Yamamoto et al. 2021; Yeoh et al. 2021). GI symptoms were accompanied by gut dysbiosis during the early phase causing changes in gut microbiome and increase in inflammatory cytokines. Recently, proinflammatory cytokine storm due to significant increase in levels of IL-6 and IL-10 was reported to be predictive of COVID-19 severity (Han et al. 2020). Moreover, the presence of SARS-CoV-2 RNA was reported in faecal samples suggesting gut to be a viral replication site (Xiao et al. 2020). According to a study performed on SARS-CoV-2 recovered patients, *A. muciniphila* along with *B. dorei* was found to be elevated in the COVID-19 patients (Yeoh et al. 2021). Moreover, these bacteria were positively correlated with inflammatory cytokines, namely IL-1β and IL-6 and proinflammatory cytokine C-X-C motif ligand 8 (CXCL8). On the other hand, *Faecalibacterium prausnitzii, Eubacterium rectale* and some species of *Bifidobacteria* were found in lower abundance. A recent faecal metabolomics studies through machine learning approach suggested that particular set of gut microbiota could be used to predict proteomic risk score based on 20 blood proteomic biomarkers for COVID-19 severity (Gou et al. 2021). The gut microbial profile was used as a tool for prediction of the blood molecular signatures, indicating amino acid related pathways such as aminoacyl-tRNA biosynthesis, arginine biosynthesis.

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and valine, leucine and isoleucine biosynthesis to be a possible link between inflammation and gut microbiota. It is well known that the gut microbiome renders beneficial effects on pulmonary mucosal immunity and host defence, thus safeguarding against respiratory infections (Gray et al. 2017). Downregulation of angiotensin-converting enzyme II (ACE2) involved in amino acid transport, tryptophan and antimicrobial peptide metabolism upon binding with viral spike protein might affect gut microbial ecology leading to dysbiosis in COVID-19 (Kuba et al. 2005). The possible factors contributing to A. muciniphila dysbiosis in COVID-19 along with strategies to restore its normal abundance are shown in Fig. 3. Co-morbidities such as diabetes, obesity and cardiovascular diseases largely influence the risk of infection and severity of disease. A lot of stress and consumption of fat and carbohydrate rich foods during the quarantine period was observed, leading to reduced CD8+ T cell response which could be linked to higher risk of infection (Mattioli et al. 2020). On the contrary, non-pharmacological measure such as reduction in consumption of fast food and increased emphasis on a healthy balanced diet also helped mitigate severe health conditions. Lifestyle habits, including diet and physical exercise, can profoundly influence the composition of the microbiome and consequently host metabolism and well-being. With the regulation of dietary habits, the optimum abundance of this friendly bacteria can be achieved in COVID-19 (Dhar and Mohanty 2020). Food supplements rich in polyphenols, omega-3 and FODMAP (Fermentable oligosaccharides, disaccharides, monosaccharides and polyols) are well known to increase A. muciniphila. Thus, by consuming polyphenol-rich foods, like fruits and vegetables, the abundance of A. muciniphila in the gut can be enhanced. Probiotic supplementations along with standard therapies as a prophylactic measure could also help mitigate the increased risk of comorbidities and move towards effective treatment. It becomes necessary to manage gut microbiome during and post disease recovery. The gut microbiome is asserted to critically impact the severity of infection as well as host immunity in COVID-19. By monitoring the GI symptoms, early diagnosis and treatment of COVID-19 can be facilitated. Therefore, it becomes important to study interaction between coronavirus and intestinal microbiome to develop novel treatment approaches.

Fig. 3 Possible factors contributing to A. muciniphila dysbiosis in COVID-19 along with strategies to restore its normal abundance

## Conclusion and future perspectives

A. muciniphila is a key mucus degrading bacteria in host immunity and infection response. The correlated metabolites and pathways are closely associated with inflammation, post-infection severity and recovery. A. muciniphila fortifying the intestinal mucus layer promotes several health-mediating effects. It regulates intestinal homeostasis and helps in maintaining epithelial barrier integrity by stimulating anti-inflammatory pathways. A. muciniphila presents itself as a powerful gut microbe having many metabolic interventions and as a promising therapeutic agent. The close relation of intestinal anti-inflammatory and protective effects of A. muciniphila emphasizes on its promising probiotic role (Neef and Sanz 2013). On the basis of
cross-talk elucidated across gut-lung axis, alterations in the gut microbiota through administration of SCFAs, probiotics or micronutrients could act as potential therapeutic strategies. A specific protein in the outer membrane of \textit{A. muciniphila}, Amuc-110, which recapitulates the effect of bacteria on TLR2 activation and improves the barrier integrity of intestines, could serve as a strong candidate for drug production in future. Thus, by unveiling the interrelationships between host factors such as diet, lifestyle habits, clinical markers and \textit{A. muciniphila} in the human gut microbiome, interventions and clinical trials may be designed. Through extensive investigation, new dimensions of the impact of \textit{A. muciniphila} in the microbiome on human health may be explored in obesity, type 2 diabetes, cystic fibrosis and COVID-19 by examining its dysbiosis in patients as compared to healthy individuals and adopting suitable strategies for its restoration (Fig. 4). The study of the relationship between \textit{A. muciniphila} in gut microbiome and personalized medicine can be one of the most attractive aspects of future research, which can provide significant perspectives for the treatment of metabolic diseases like type 2 diabetes and obesity, and even respiratory diseases such as cystic fibrosis and COVID-19. To conclude, potential opportunities exist for targeted interventions to modify the composition of \textit{A. muciniphila} in the gut microbiome to improve host health.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig4.png}
\caption{Dysbiosis and restoration of \textit{A. muciniphila} in obesity, type 2 diabetes, cystic fibrosis and COVID-19}
\end{figure}
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Declarations

Ethics approval Not applicable.

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References

Allin KH, Tremaroli V, Caesar R et al (2018) Aberrant intestinal microbiota in individuals with prediabetes. Diabetologia 61:810–820. https://doi.org/10.1007/s00125-018-4550-1

Ambort D, Johansson MEV, Gustafsson JK et al (2012) Calcium and pH-dependent packing and release of the gel-forming MUC2 mucin. Proc Natl Acad Sci 109:5645–5650. https://doi.org/10.1073/pnas.1120269109

Andersson KE, Axling U, Xu J et al (2012) Diverse effects of oats on cholesterol metabolism in C57BL/6 mice correlate with expression of hepatic bile acid-degrading enzymes. Eur J Nutr 52:1755–1769. https://doi.org/10.1007/s00394-012-0479-1

Bajer L, Kverka M, Kostovicik M et al (2017) Distinct gut microbiota profiles in patients with primary sclerosing cholangitis and ulcerative colitis. World J Gastroenterol 23:4548. https://doi.org/10.3748/wjg.v23.i25.4548

Bazett M, Bergeron ME, Haston CK (2016) Streptomyacin treatment alters the intestinal microbiome, pulmonary T cell profile and airway hyperresponsiveness in a cystic fibrosis mouse model. Sci Rep 6:1–13. https://doi.org/10.1038/srep19189

Bedarf JR, Hildebrand F, Coelho LP et al (2017) Erratum to: functional implications of microbial and viral gut metagenome changes in early stage L-DOPA-naïve Parkinson’s disease patients. Genome Med 9:61. https://doi.org/10.1186/s13073-017-0451-z

Belzer C, de Vos WM (2012) Microbes inside—diversity and function of the gut microbiota. ISME J 6:1449–1458. https://doi.org/10.1038/ismej.2012.6

Bernardo D, Sánchez B, Al-Hassi HO et al (2012) Microbiota/host crosstalk biomarkers: regulatory response of human intestinal dendritic cells exposed to Lactobacillus extracellular encrypted peptide. PLoS ONE 7:e36262. https://doi.org/10.1371/journal.pone.0036262

Cesare R, Tremaroli V, Kvatatcheva-Datchary P et al (2015) Cross-talk between gut microbiota and dietary lipids aggravates WAT inflammation through TLR signaling. Cell Metab 22:658–668. https://doi.org/10.1016/j.cmet.2015.07.026

Candela M, Rampelli S, Turroni S et al (2012) Unbalance of intestinal microbiota in atopic children. BMC Microbiol 12:95. https://doi.org/10.1186/1471-2180-12-95

Cani PD, de Vos WM (2017) Next-generation beneficial microbes: the case of Akkermansia muciniphila. Front Microbiol. https://doi.org/10.3389/fmicb.2017.01765

Cantarel BL, Waubant E, Chehoud C et al (2015) Gut microbiota in multiple sclerosis. J Investig Med 63:729–734. https://doi.org/10.1097/JIM.0000000000000192

Chelakkot C, Choi Y, Kim D-K et al (2018) Akkermansia muciniphila-derived extracellular vesicles influence gut permeability through the regulation of tight junctions. Exp Mol Med 50:e450–e450. https://doi.org/10.1038/emm.2017.282

Chen X, Song S, Zhao Y et al (2020a) 146P A new biomarker of microbe: Akkermansia muciniphila in lung adenocarcinoma tissues may predict lymph node metastasis in lung adenocarcinoma. Ann Oncol 31:S297–S298. https://doi.org/10.1016/j.annonc.2020.08.267

Chen Z, Qian X, Chen S et al (2020b) Akkermansia muciniphila enhances the antitumor effect of cisplatin in Lewis lung cancer mice. J Immunol Res 2020:1–13. https://doi.org/10.1155/2020/2969287

Collado MC, Isolauri E, Laitinen K, Salminen S (2008) Distinct composition of gut microbiota during pregnancy in overweight and normal-weight women. Am J Clin Nutr 88:894–899. https://doi.org/10.1093/ajcn/88.4.894

Collado MC, Laitinen K, Salminen S, Isolauri E (2012) Maternal weight and excessive weight gain during pregnancy modify the immunomodulatory potential of breast milk. Pediatr Res 72:77–85. https://doi.org/10.1038/pr.2012.42

Cone RA (2009) Barrier properties of oats. Adv Drug Deliv Rev 61:75–85

Cronin P, Joyce SA, O’Toole PW, O’Connor EM (2021) Dietary fibre modulates the gut microbiota. Nutrients 13:1655. https://doi.org/10.3390/nu13051655

Dao MC, Everard A, Aron-Wisnewsky J et al (2016) Akkermansia muciniphila and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. Gut 65:426–436. https://doi.org/10.1136/gutjnl-2014-308778

De Angelis M, Piccolo M, Vannini I et al (2013) Fecal microbiota and metabolome of children with autism and pervasive developmental disorder not otherwise specified. PLoS ONE 8:e76993. https://doi.org/10.1371/journal.pone.0076993

Dean M, Annilo T (2005) Evolution of the atp-binding cassette (ABC) transporter superfamily in vertebrates. Annu Rev Genomics Hum Genet 6:123–142. https://doi.org/10.1146/annurev.genom.6.080604.162122

Derrien M, Tokman HB, Uysal HK et al (2019) Reduced Akkermansia muciniphila and Faecalibacterium prausnitzii levels in the gut microbiota of children with allergic asthma. Allergol Immunopathol (Madr) 47:365–371. https://doi.org/10.1016/j.aller.2018.12.009

Depommier C, Everard A, Druart C et al (2019) Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. Nat Med 25:1096–1103. https://doi.org/10.1038/s41591-019-0495-2

Derrien M, Van Baarlen P, Hooiveld G et al (2011) Modulation of mucosal immune response, tolerance, and proliferation in mice colonized by the mucin-degrader Akkermansia muciniphila. Front Microbiol. https://doi.org/10.3389/fmicb.2011.00166

Derrien M, Vaughan EE, Plugge CM, de Vos WM (2004) Akkermansia muciniphila gen. nov., sp. nov., a human intestinal mucin-degrading bacterium. Int J Syst Evol Microbiol 54:1469–1476. https://doi.org/10.1099/ijs.0.02873-0

Dhar D, Mohanty A (2020) Gut microbiota and COVID-19- possible link and implications. Virus Res 285:198018. https://doi.org/10.1016/j.virusres.2020.198018

Dreil T, Larionova A, Voor T et al (2015) Differences in gut microbiota between atopic and healthy children. Curr Microbiol 71:177–183. https://doi.org/10.1007/s00284-015-0815-9
Everard A, Belzer C, Geurts L et al (2013) Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. Proc Natl Acad Sci 110:9066–9071. https://doi.org/10.1073/pnas.1219451110

Fassatou M, Lopez-Siles M, Díaz-Rizzolo DA et al (2019) Gut microbiota imbalances in Tunisian patients with type 1 and type 2 diabetes mellitus. Biosci Rep. https://doi.org/10.1042/BSR20182348

Fischer H, Holst E, Karlsson F et al (2015) Altered microbiota in microscopic colitis. Gut 64:1185–1186. https://doi.org/10.1136/gutjnl-2014-308956

Fuke N, Nagata N, Suganuma H, Ota T (2019) Regulation of gut microbiota and metabolic endotoxemia with dietary factors. Nutrients 11:2277. https://doi.org/10.3390/nu11022277

Gao R, Zhu C, Li H et al (2018) Dysbiosis signatures of gut microbiota along the sequence from healthy, young patients to those with overweight and obesity. Obesity 26:351–361. https://doi.org/10.1002/oby.22088

Gargari G, Deon V, Tavenini V et al (2018) Evidence of dysbiosis in the intestinal microbial ecosystem of children and adolescents with primary hyperlipidemia and the potential role of regular hazelnut intake. FEMS Microbiol Ecol. https://doi.org/10.1093/femsec/fhy045

Gou W, Fu Y, Yue L et al (2021) Gut microbiota, inflammation, and molecular signatures of host response to infection. J Genet Genomics 48:792–802. https://doi.org/10.1016/j.jgg.2021.04.002

Grander C, Adolph TE, Wieser V et al (2018) Recovery of ethanol-induced *Akkermansia muciniphila* depletion ameliorates alcoholic liver disease. Gut 67:891–901. https://doi.org/10.1136/gutjnl-2016-313433

Gray J, Oehrle K, Worthen G et al (2017) Intestinal commensal bacteria mediate lung mucosal immunity and promote resistance of newborn mice to infection. Sci Transl Med 9:eaaf9412. https://doi.org/10.1126/scitranslmed.aaf9412

Greer RL, Dong X, Moraes ACF et al (2016) *Akkermansia muciniphila* mediates negative effects of IFNγ on glucose metabolism. Nat Commun 7:13329. https://doi.org/10.1038/ncomms13329

Gunderson KL, Kopito RR (1994) Effects of pyrophosphate and nucleotide analogs suggest a role for ATP hydrolysis in cystic fibrosis transmembrane regulator channel gating. J Biol Chem 269:19349–19355. https://doi.org/10.1016/0021-9258(94)91274-9

Guo X, Li S, Zhang J et al (2017) Genome sequencing of 39 *Akkermansia muciniphila* isolates reveals its population structure, genomic and functional diversity, and global distribution in mammalian gut microbiotas. BMC Genomics. https://doi.org/10.1186/s12864-017-4195-3

Gurung M, Li Z, You H et al (2020) Role of gut microbiota in type 2 diabetes pathophysiology. EBioMedicine 51:102590. https://doi.org/10.1016/j.ebiom.2019.11.051

Han H, Ma Q, Li C et al (2020) Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerg Microbes Infect 9:1123–1130. https://doi.org/10.1080/22221751.2020.1770129

Hayden H, Eng A, Pope C et al (2019) P314 Fecal dysbiosis is associated with growth failure in infants with cystic fibrosis: a multicentre study. J Cyst Fibros 18:S146. https://doi.org/10.1016/S1569-9939(19)30607-1

Hoffman LR, Pope CE, Hayden HS et al (2014) *Escherichia coli* dysbiosis correlates with gastrointestinal dysfunction in children with cystic fibrosis. Clin Infect Dis 58:396–399. https://doi.org/10.1093/cid/cit715

Hu Y, Feng Y, Wu J et al (2019) The gut microbiome signatures discriminate healthy from pulmonary tuberculosis patients. Front Cell Infect Microbiol. https://doi.org/10.3389/fcimb.2019.00090

Hussain I, Cher GLY, Abid MA, Abid MB (2021) Role of gut microbiome in COVID-19: an insight into pathogenesis and therapeutic potential. Front Immunol. https://doi.org/10.3389/fimmu.2021.765965

Jakobsson HE, Rodríguez-Piñeiro AM, Schütte A et al (2015) The composition of the gut microbiota shapes the colon mucus barrier. EMBO Rep 16:164–177. https://doi.org/10.15252/embr.2014439263

Johansson MEV, Holmén Larsson JM, Hansson GC (2011) The two mucus layers of colon are organized by the MUC2 mucin, whereas the outer layer is a legislator of host-microbial interactions. Proc Natl Acad Sci U S A 108:4659–4665. https://doi.org/10.1073/pnas.1006451107

Johansson MEV, Philippson M, Petersson J et al (2008) The inner of the two Muc2 mucin-dependent mucus layers in colon is devoid of bacteria. Proc Natl Acad Sci U S A 105:15064–15069. https://doi.org/10.1073/pnas.0803124105

Johansson MEV, Sjövall H, Hansson GC (2013) The gastrointestinal mucus system in health and disease. Nat Rev Gastroenterol Hepatol 10:352–361

Karlsson CLJ, Önnerfält J, Xu J et al (2012) The microbiota of the gut in preschool children with normal and excessive body weight. Obesity 20:2257–2261. https://doi.org/10.1038/oby.2012.110

Kim S, Rigatto K, Gazzana MB et al (2020) Altered gut microbiome profile in patients with pulmonary arterial hypertension. Hypertension 75:1063–1071. https://doi.org/10.1161/HYPERTENSIONAHA.119.14294

Kuba K, Imai Y, Rao S et al (2005) A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. Nat Med 11:875–879. https://doi.org/10.1097/00001161-200504090-00365

Lee DM, Battson ML, Jarrell DK et al (2018) SGLT2 inhibition via dapagliflozin improves generalized vascular dysfunction and alters the gut microbiota in type 2 diabetic mice. Cardiovasc Diabetol 17:62. https://doi.org/10.1186/s12933-018-0708-x

Ley RE, Bäckhed F, Turnbaugh P et al (2005) Obesity alters gut microbiota ecology. Proc Natl Acad Sci 102:11070–11075. https://doi.org/10.1073/pnas.0504978102

Li J, Lin S, Vanhoutte PM et al (2016) *Akkermansia muciniphila* protects against atherosclerosis by preventing metabolic endotoxemia-induced inflammation in apoe−/− mice. Circulation 133:2434–2446. https://doi.org/10.1161/CIRCULATIONAHA.115.019645

Liu F, Ling Z, Xiao Y et al (2017) Dysbiosis of urinary microbiota is positively correlated with Type 2 diabetes mellitus. Oncotarget 8:3798–3810. https://doi.org/10.18632/oncotarget.14028

Lukovac S, Belzer C, Pellis L et al (2014) Differential modulation by *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* of host peripheral lipid metabolism and histone acetylation in mouse gut organoids. Mbio. https://doi.org/10.1128/mBio.01438-14

Malham M, Lilje B, Houen G et al (2019) The microbiome reflects diagnosis and predicts disease severity in paediatric onlaymatory bowel disease. Scand J Gastroenterol 54:969–975. https://doi.org/10.1080/00365521.2019.1644368

Manor O, Levy R, Pope CE et al (2016) Metagenomic evidence for taxonomic dysbiosis and functional imbalance in the gastrointestinal tracts of children with cystic fibrosis. Sci Rep 6:22493. https://doi.org/10.1038/srep22493

Marvasti FE, Moshiri A, Sadat Taghavi M et al (2020) The first report of differences in gut microbiota composition between obese and normal weight iranian subjects, Iran Biomed J 24:148–154. https://doi.org/10.29252/jbj.24.3.148

Mattioli AV, Scimmer S, Cocchi C et al (2020) Quarantine during COVID-19 outbreak: changes in diet and physical activity increase the risk of cardiovascular disease. Nutr Metab Cardiovasc Dis 30:1409–1417. https://doi.org/10.1016/j.numecd.2020.05.020

Meeker SM, Mears KS, Songwan N et al (2020) CFTR dysregulation drives active selection of the gut microbiome. PLoS Pathog 16:e1008251. https://doi.org/10.1371/journal.ppat.1008251
van der Ark KCH, Aalvink S, Suarez-Diez M et al (2018) Model-driven design of a minimal medium for *Akkermansia muciniphila* confirms mucus adaptation. Microb Biotechnol 11:476–485. https://doi.org/10.1111/1751-7915.13033

van Passel MWJ, Kant R, Zoetendal EG et al (2011) The genome of *Akkermansia muciniphila*, a dedicated intestinal mucin degrader, and its use in exploring intestinal metagenomes. PLoS ONE. https://doi.org/10.1371/journal.pone.0016876

Vernocchi P, Del CF, Russo A et al (2018) Gut microbiota signatures in cystic fibrosis: Loss of host CFTR function drives the microbiota enterophenotype. PLoS ONE 13:e0208171. https://doi.org/10.1371/journal.pone.0208171

Wan L, Zhou X, Wang C et al (2019) Alterations of the gut microbiota in multiple system atrophy patients. Front Neurosci. https://doi.org/10.3389/fnins.2019.01102

Wang H, Wang H, Sun Y et al (2021) Potential associations between microbiome and COVID-19. Front Med. https://doi.org/10.3389/fmed.2021.785496

Wang J, Jia H (2016) Metagenomewide association studies: fine-mining the microbiome. Nat Rev Microbiol 14:508–522. https://doi.org/10.1038/nrmicro.2016.83

Wang J, Tang H, Zhang C et al (2015) Modulation of gut microbiota during probiotic-mediated attenuation of metabolic syndrome in high fat diet-fed mice. ISME J 9:1–15. https://doi.org/10.1038/ismej.2014.99

Wang L, Christensen CT, Sorich MJ et al (2011) Low relative abundances of the mucolytic bacterium *Akkermansia muciniphila* and *Bifidobacterium spp.* in feces of children with autism. Appl Environ Microbiol 77:6718–6721. https://doi.org/10.1128/AEM.05212-11

Wang Z, Saha S, Van Horn S et al (2018) Gut microbiome differences between metformin- and liraglutide-treated T2DM subjects. Endocrinol Diabetes Metab 1:e00009. https://doi.org/10.1002/edm2.9

Weir TL, Manter DK, Sheflin AM et al (2013) Stool microbiome and metabolome differences between colorectal cancer patients and healthy adults. PLoS ONE 8:e70803. https://doi.org/10.1371/journal.pone.0070803

Wang L, Christophersen A, Asadzadeh Aghdaei H et al (2020) Characterization of gut microbiota in hospitalized patients with clostridioides difficile infection. Curr Microbiol 77:1673–1680. https://doi.org/10.1007/s00284-020-01980-x

Yu J, Feng Q, Wong SH et al (2017) Metagenomic analysis of faecal microbiota composition in multiple system atrophy patients with severe COVID-19. Emerg Infect Dis 26:1920–1922. https://doi.org/10.3201/eid2608.200681

Yu R, Wu B, Liang J et al (2020a) Altered gut microbiota and mucosal immunity in patients with schizophrenia. Brain Behav Immun 85:120–127. https://doi.org/10.1016/j.bbi.2019.06.039

Yu Y, Wang N, Tan H-Y et al (2020b) Function of *Akkermansia muciniphila* in obesity: interactions with lipid metabolism, immune response and gut systems. Front Microbiol. https://doi.org/10.3389/fmicb.2020.00219

Yeoh YK, Zuo T, Lui GC-Y et al (2021) Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. Gut 70:698–706. https://doi.org/10.1136/gutjnl-2020-323020

Yanamoto S, Saito M, Tamura A, Prawisud S, Mizutani T, Yotsuyanagi H (2021) The human microbiome and COVID-19: a systematic review. PLoS ONE 16(6):e0253293. https://doi.org/10.1371/journal.pone.0253293

Yeoh YK, Zuo T, Lui GC-Y et al (2021) Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. Gut 70:698–706. https://doi.org/10.1136/gutjnl-2021-309800

Zhang L, Qin Q, Liu M et al (2018) *Akkermansia muciniphila* can reduce the damage of gluco/lipotoxicity, oxidative stress and inflammation, and normalize intestine microbiota in streptozotocin-induced diabetic rats. Pathog Dis. https://doi.org/10.1093/femsdp/fty028

Zhong H, Ren H, Lu Y et al (2019) Distinct gut metagenomics and metaproteomics signatures in prediabetics and treatment-naïve biomers for colorectal cancer. Gut 66:70–78. https://doi.org/10.1136/gutjnl-2015-309800

Zhong H, Ren H, Lu Y et al (2019) Distinct gut metagenomics and proteomics signatures in prediabetes and treatment-naïve type 2 diabetics. EBioMedicine 47:373–383. https://doi.org/10.1016/j.ebiom.2019.08.048

Zhu F, Ju Y, Wang W et al (2020) Metagenome-wide association of gut microbiota features for schizophrenia. Nat Commun 11:1612. https://doi.org/10.1038/s41467-020-15457-9

Zoetendal EG, Raes J, van den Bogert B et al (2012) The human small intestine microbiota as a tool towards targeted non-invasive biomarkers for colorectal cancer. Gut 66:70–78. https://doi.org/10.1136/gutjnl-2015-309800

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