



The Emerging Biotherapeutic Agent: *Akkermansia*

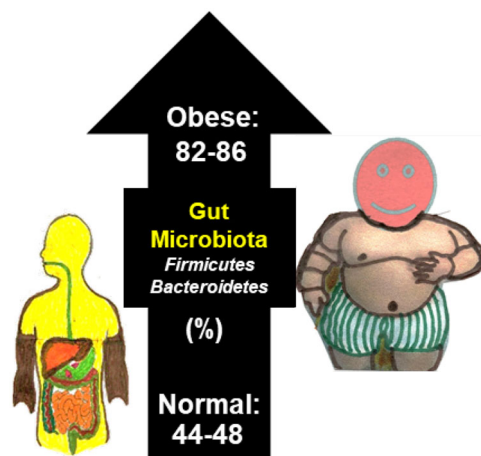
Vipin Chandra Kalia¹ · Chunjie Gong² · Ramasamy Shanmugam¹ ·
Hui Lin³ · Liaoyuan Zhang³ · Jung-Kul Lee¹

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Abstract The human gastrointestinal tract (GIT) is a well-recognized hub of microbial activities. The microbiota harboring the mucus layer of the GIT act as a defense against noxious substances, and pathogens including *Clostridium difficile*, *Enterococcus faecium*, *Escherichia coli*, *Salmonella* Typhimurium. Toxins, pathogens, and antibiotics perturb the commensal floral composition within the GIT. Imbalanced gut microbiota leads to dysbiosis, manifested as diseases ranging from obesity, diabetes, and cancer to reduced lifespan. Among the bacteria present in the gut microbiome, the most beneficial are those representing Firmicutes and Bacteroidetes. Recent studies have revealed the emergence of a novel biotherapeutic agent, *Akkermansia*, which is instrumental in regaining eubiosis and conferring various health benefits.

Keywords *Akkermansia* · Biotherapy · Microbiota · Dysbiosis · Eubiosis · Obesity · Diabetes · Cancer · Aging

Graphical abstract



Introduction

Prokaryotes interact with human beings on their skin surface and within their body [1]. Together these microbial populations constitute the microbiome [2]. The distribution of bacterial populations varies significantly throughout the human body [3, 4]. The estimated bacterial population present in the colon is around two orders of magnitude higher than those present in all other organs. Interestingly, within the gastrointestinal tract (GIT), the stomach and the small intestine harbor a negligible proportion of the total bacterial population, while the colon makes substantial contributions [2]. The diversity of gut microbiota (GM) is manifested by around 1500 different species [5]. This

✉ Vipin Chandra Kalia
vckaliaku@gmail.com

✉ Liaoyuan Zhang
zliaoyuan@126.com

✉ Jung-Kul Lee
jkrhee@konkuk.ac.kr

¹ Department of Chemical Engineering, Konkuk University, 1 Hwayang-Dong, Gwangjin-Gu, Seoul 05029, Republic of Korea

² National “111” Center for Cellular Regulation and Molecular Pharmaceutics, Key Laboratory of Fermentation Engineering (Ministry of Education), Hubei University of Technology, Wuhan 430068, People’s Republic of China

³ College of Life Sciences, Gutian Edible Fungi Research Institute, Fujian Agriculture and Forestry University, Fuzhou 350002, People’s Republic of China

ecosystem performs various metabolic activities [6–8]. Among the diverse bacteria which inhabit our gut, the categorization into beneficial and harmful bacteria is not very distinct. Many factors such as age, genotype, diet, nutrition, and environmental components regulate our GM [9, 10]. A few most prevalent factors which damage our microbiomes are pharmaceutical and personal care products, especially antibiotics and pollutants, including pesticides and insecticides [11, 12]. The dysbiosis of the GM seems to be responsible for various metabolic disorders, such as inflammatory diseases, auto-immune diseases, cancers, mental disorders, ocular diseases, and diabetes [13, 14]. Comparing microbiomes from healthy individuals with those manifesting metabolic disorders or diseased conditions established their role in regaining eubiosis and maintaining health [15–20]. The major problem is to establish a correlation between bacterial population dynamics and disease conditions. This paper aims to identify bacteria that are critical for maintaining health and how to enrich them in the GIT. The future prospects are the development of strategies for overcoming dysbiosis and regaining health.

This article provides insights into the role of GM in maintaining health based on the studies on germ-free animal models. These works provided the necessary information that the mucus layer in the GIT and its associated microbiota is critical for preventing the proliferation of pathogens and promoting the growth and metabolism of the probiotic bacteria. Comparative genomics revealed the changes in various bacterial population densities in the GM and multiple diseases such as obesity, diabetes, cancer, and aging. Further, prebiotics, which promote the abundance of *Akkermansia*, is critical in preventing diseased conditions.

The Hub of Microbiota

Human GIT is the hub of microbial activities. GIT has a mucous lining that produces mucus, which is composed of glucoproteins called mucins. The mucus layer and microbiota harboring it act as a defense system against noxious substances, cytokines, and pathogens. Toxins and pathogens inhibit mucin production, which leads to diverse pathological conditions, especially chronic inflammatory diseases. It is thus imperative to identify the factors, which modulate the mucus barrier and accordingly develop innovative strategies to circumvent these disorders [21]. The consumption of antibiotics perturbs the commensal floral composition within the GIT. This interaction supports the epithelial colonization with the enteric pathogen (*Salmonella* Typhimurium and *Clostridium*) [22]. Germ-free mice models furnished further information regarding the effects of microbial composition and mucus layer.

The addition of probiotics induces the expression of mucins—MUC2 and MUC3, which prevent the adherence of Enteropathogenic *Escherichia coli* (EPEC) to the epithelial lining [23]. Recent works have highlighted the role of *Akkermansia muciniphila* in various health benefits [24, 25]. *A. muciniphila*, a gram-negative bacteria, was isolated from human feces [26], and it accounts for up to 4% of the total bacterial population in the large intestine [27] (Fig. 1). This article elucidates the role of *A. muciniphila* in improving health by regulating various metabolic disorders.

Microbiome and Human Health

Diet

Diet is a principal constituent, which significantly impacts our GM composition (Fig. 2). A high-fat, low-fiber diet, largely burgers, potato chips, cake, ice cream, and cheese fed to African-Americans for two weeks, increased the colon's inflammation. It also resulted in lower butyrate production, which is otherwise essential for reducing colon cancer. Rural Africans eating low-fat, high-fiber content did not show any ill effects. It implied that low-fiber processed foods result in lower availability of feed for gut bacteria. In the long run, the population density of commensal bacteria reduced drastically, and their contribution became insignificant. The absence of these bacteria provides an opportunity for the other group of non-short-chain fatty acids (SCFA) producers to feed on the mucus layer, making the gut lining susceptible to invasion by pathogenic bacteria [28]. The information generated from mice fed on a high-fat diet further supports the beneficial aspects of *A. muciniphila*. (Fig. 3). Here, a negative correlation between the abundance of this specific bacterium and inflammation and metabolic syndromes such as fatty acid oxidation and browning of white adipocytes was recorded [29]. GM also regulates the host metabolic activities essential for obtaining vitamin K, folate, and SCFAs. GM is instrumental in the metabolism of non-digestible carbohydrates into SCFAs, which increase mucus production and its secretion. Here, butyrate plays a critical role in inhibiting inflammation and tumor growth. Low concentrations of SCFAs induce the expression of MUC2, which can be reversed by increasing the availability of the same [21]. Dietary SCFAs contribute towards conferring mucosal immunity and preventing inflammation [30]. These nutrients help the immune system prevent the proliferation of the pathogenic microbe [31, 32].

Fig. 1 Role of *Akkermansia* in preventing proliferation of bacterial pathogens in human gut

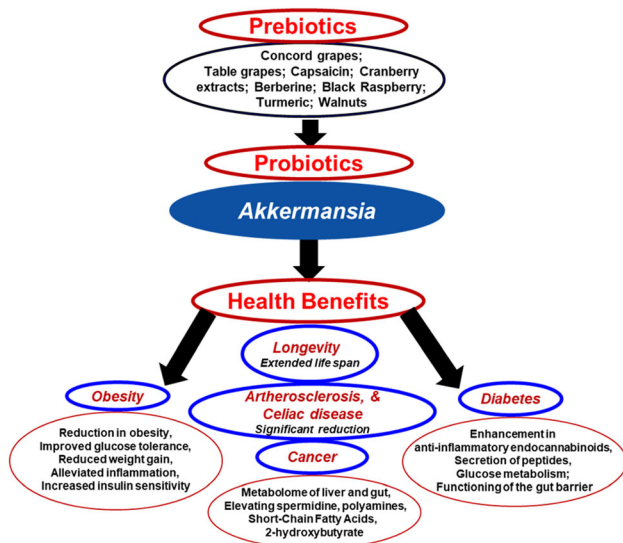
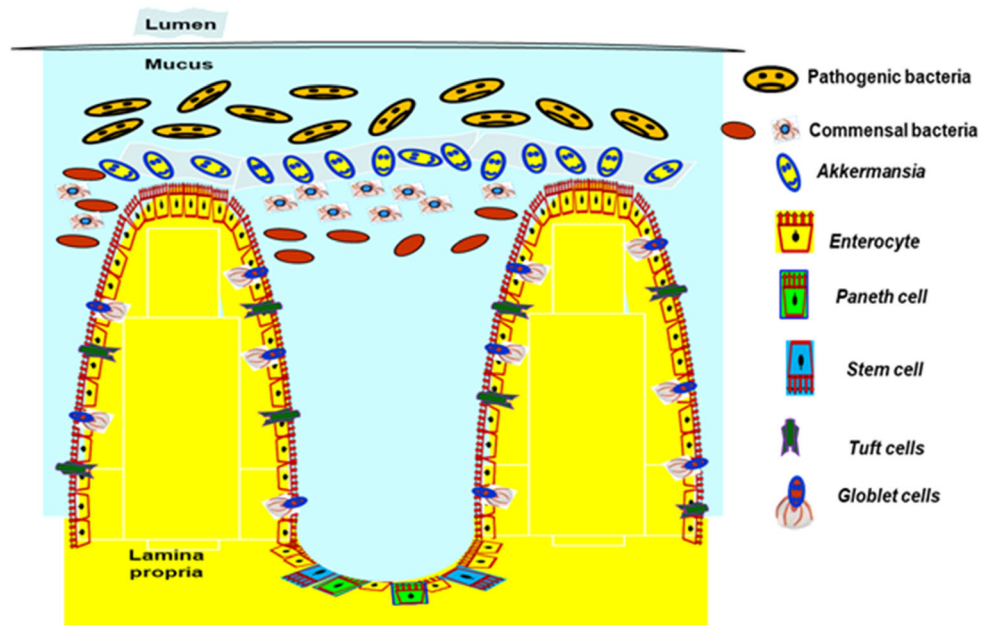


Fig. 2 Beneficial effects of *Akkermansia* to human beings

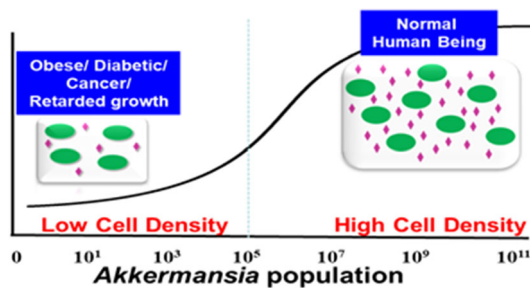


Fig. 3 Abundance of *Akkermansia* in human gut microbiota prevents diseases

Obesity

Mice (C57BL/6J) fed with a high-fat diet supplemented with 3–5% table grapes significantly altered the gut microbial population. At 3% grape supplementation, the significant changes were in reducing *Bilophila wadsworthia* (a dissimilatory sulphite reducer) and a *Desulfobacter* spp. (sulidogenic bacteria). The most important part of the dietary treatment was increasing *A. muciniphila* population, which reduced obesity (Table 1) [33]. A similar effect on supplementing a high-fat diet with capsaicin to mice improved its glucose tolerance and reduced weight gain. These changes were linked to an abundance of *A. muciniphila* bacterial population and a decrease in genera representing Proteobacteria [34]. Direct response to oral supplementation of *A. muciniphila* alleviated the inflammation (reduced hyperlipidemia) and endoplasmic reticulum stress [35]. A few other studies have shown a shift towards the abundance of *A. muciniphila* accompanied by a decline in Bacteroidetes and Firmicutes, *B. wadsworthia*, *Desulfobacter* spp. in C57BL/6J mice models fed with polyphenol-rich feed such as concord grapes, cranberry extracts, and table grapes, berberine and walnuts (Fig. 2). Among the various health benefits recorded in the animals were: reduced weight gain, reduced adiposity, reduced visceral fat, suppression of inflammation and oxidative stress, increased insulin sensitivity (Table 1) [36–40]. A diet rich in black raspberry resulted in the abundance of *A. muciniphila* in the GM of C57BL/6J mice. It regulated the metabolic pathways related to vitamin synthesis, oxidative stress, and those responsible for amino acid and carbohydrate biosynthesis [41].

Table 1 Diversity of therapeutic potentials of *Akkermansia*

Metabolic disorder	Host	Treatment	Metabolic changes	Impact in gut microbiota	References
Obesity	Mice (C57BL/6J)	High-fat diet with 3–5% Table grapes	<i>Akkermansia muciniphila</i> induced reduction in obesity	Abundance of <i>A. muciniphila</i> ; Reduction in <i>Bilophila wadsworthia</i> and <i>Desulfobacter</i> spp.	[33]
Obesity	Mice	High-fat diet with capsaicin	Improved glucose tolerance and reduced weight gain	Abundance of <i>A. muciniphila</i> ; decrease in genera representing Proteobacteria	[34]
Obesity	Mice	Chow diet-fed and oral supplementation of <i>A. muciniphila</i>	Alleviated the inflammation (reduced hyperlipidemia) and endoplasmic reticulum stress	Abundance of <i>A. muciniphila</i>	[35]
Obesity	Mice (C57BL/6J)	Polyphenol-rich feed such as concord grapes, cranberry extracts, and table grapes, berberine and walnuts.	Reduced weight gain, reduced adiposity, reduced visceral fat, suppression of inflammation and oxidative stress, increased insulin sensitivity	Abundance of <i>A. muciniphila</i> accompanied by a decrease in Firmicutes and Bacteroidetes, <i>Bilophila wadsworthia</i> , <i>Desulfobacter</i> spp	[36–40]
Obesity	Mice (C57BL/6J)	Diet rich in black raspberry	Metabolic pathways related to vitamin synthesis, oxidative stress, and carbohydrate and amino acid biosynthesis	Abundance of <i>A. muciniphila</i>	[41]
Diabetes	Type 2 diabetic (T2DM) mice	Administration of <i>A. muciniphila</i>	Enhanced the concentration of anti-inflammatory endocannabinoids, secretion of peptides	Abundance of <i>A. muciniphila</i>	[42]
Diabetes	Human Colombian T2DMs	Undergoing drug treatment - metformin	–	Higher population density <i>A. muciniphila</i> and SCFA-producing bacteria: <i>Butyrivibri</i> , <i>Bifidobacteria</i> , and <i>Megasphaera</i> ,	[43, 44]
Diabetes	Mice	Fed with a high-fat diet in live as well as the pasteurized form	Expression of Amuc_1100 (an outer membrane protein); enhances the glucose metabolism and functioning of the gut barrier	Abundance of <i>A. muciniphila</i>	[45]
Diabetes	Human patients	Diabetics: prediabetics, newly diagnosed and undergoing treatment	Negatively correlated with HbA1c and showed a positive correlation with total antioxidants	Abundance of <i>Megasphaera</i> , <i>Escherichia</i> , <i>Acidaminococcus</i> , <i>Sutterella</i> , and <i>Akkermansia</i>	[19]
Diabetes	Human	Patients with T2DM and diabetic retinopathy	Healthy individuals benefited	Interactions of two hubs (<i>Akkermansia</i> and <i>Barnesiella</i>) with four pathogenic hubs (<i>Gardnerella</i> , <i>Cloacibacillus</i> , <i>Leptotrichia</i> , and <i>Anaerobiospirillum</i>)	[14]
Cancer	Human	Patients with colorectal carcinoma	Marked reduction in butyrate and acetate concentration	Lower butyrate-producing bacteria and a 4-fold increase in <i>A. muciniphila</i>	[46]
Cancer	Human	Treated with various immune checkpoint inhibitors (ICIs)	Patient undergoing antibiotics treatment has a poorer response to ICI PD-1 antibody.	An increased abundance of <i>Akkermansia</i> in the intestine of those who responded positively to the ICI.	[47]

Table 1 continued

Metabolic disorder	Host	Treatment	Metabolic changes	Impact in gut microbiota	References
Cancer	Mice	Employing extracellular vesicles derived from <i>A. muciniphila</i> into immune-competent mice	Suppressed the proliferation and invasion of prostate cells No toxicity to normal tissues	–	[48]
Cancer	Mice	Oral administration of live or pasteurized <i>Akkermansia</i>	Significantly affected the metabolome in the liver and gut: elevating the intestinal concentrations of spermidine, polyamines, Short-chain fatty acids, and 2-hydroxybutyrate	Pasteurized <i>Akkermansia</i> were more effective than live <i>Akkermansia</i>	[49]
Longevity	Human	Gut microbiota analysis	Showed association with longevity	highest diversity of Ruminococcaceae; lower prevalence of Prevotellaceae members (in centenarians): <i>Alistipes</i> , <i>Akkermansia</i> , and <i>Ruminococcoaceae</i>	[18]
Longevity	Mice	FMT and transplantation with <i>A. muciniphila</i> into short-lived mouse	Extended life span	enhancement in Verrucomicrobia and a decline in the Proteobacterial species	[50]
Atherosclerosis	Human	Diet free of fat, sugars and cholesterol, and alkaloid, berberine, (grapes, barberry, and turmeric)	Reduced the high-fat diet-induced atherosclerosis in ApoE ^{-/-}	Abundance of <i>Akkermansia</i> spp. in the gut	[51]
Celiac disease	Human	Characterization of amplicon sequence variants (ASVs)	A dramatic reduction in the quantity of ASVs	<i>Dorea</i> and <i>Akkermansia</i> in the fecal microbiomes	[17]

Diabetes

Gut microbiota participate actively in intestinal physiology. The altered composition of GM, inflammation and disruption of the gut barrier are significant symptoms of type 2 diabetes (T2D) and obesity. In rodents and humans, *A. muciniphila*, a mucin degrader harboring in the mucus layer, is negatively correlated with body weight. Feeding *A. muciniphila* reversed metabolic disorders, including insulin resistance and adipose tissue inflammation induced by the high-fat diet. The administration of *A. muciniphila* enhanced the concentration of anti-inflammatory compounds—endocannabinoids, the gut barrier, and the secretion of peptides. It showed that the cross-talk between

the microbiota and the host could assist in overcoming these metabolic disorders [42]. Patients undergoing treatment for Colombian T2DMs using the drug—metformin had a significantly higher population density of *A. muciniphila* and SCFA-producers, such as *Butyrivibri*, *Bifidobacteria*, and *Megasphaera*, compared to controls (Table 1) [43, 44]. The role of this bacterium in improving the metabolic activities of T2DM in mice fed with a high-fat diet in live as well as the pasteurized form was reported to be due to the expression of Amuc_1100 (an outer membrane protein). This protein activates insulin and toll-like receptor 2 signaling, which enhances the glucose metabolism and functioning of the gut barrier [45]. A change in the GM of freshly diagnosed T2D patients

compared to healthy non-diabetic individuals showed an abundance of Firmicutes and Proteobacteria, especially *Lactobacillus*. It was accompanied by a significant decrease in Bacteroidetes and Verrucomicrobia represented by *Prevotella*, *Akkermansia*, *Blautia*, and *Ruminococcus*. Patients undergoing diabetic treatment compared to those who had been recently diagnosed were observed to have an abundance of *Acidaminococcus*, *Escherichia*, *Megasphaera*, *Sutterella*, and *Akkermansia*. The proportion of *Akkermansia* showed a negative correlation with HbA1c and a positive relationship with total antioxidant content [19]. A more complicated scenario was present in the gut of patients with T2DM and diabetic retinopathy (DR) and compared with healthy subjects. The microbiome of healthy individuals shared *Coprobacillus* and *Gardnerella* with T2DM and *Cloacibacillus* and *Synergistes* with DR. The five hub genera unique to healthy individuals were: *Akkermansia*, *Leptotrichia*, *Barnesiella*, *Anaerovibrio*, and *Anaerobiospirillum*. Among the nine networks, healthy individuals benefited from the interactions of two hubs (*Akkermansia* and *Barnesiella*) with four pathogenic hubs (*Leptotrichia*, *Cloacibacillus*, *Gardnerella*, and *Anaerobiospirillum*) [14].

Cancer

Efforts to manage cancer have been constantly made primarily through the use of food components. Studies showing the role of *Akkermansia* in colorectal carcinoma have been quite limited. The fecal analysis revealed a marked reduction in butyrate and acetate concentration in CRC patients in comparison to normal subjects. The entire bacterial communities were the same in CRC and controls. However, a correlation was established between lower butyrate-producing bacteria and a fourfold increase in *A. muciniphila* (Table 1) [46]. Based on observation on 249 cancer patients which treated with various immune checkpoint inhibitors (ICIs), a linkage was seen between *Akkermansia* and the drugs. The two major observations were as follows: (1) patient undergoing antibiotics treatment has a poorer response to ICI PD-1 antibody, and (2) an enhanced abundance of *Akkermansia* in the intestine of those who responded positively to the ICI. The potential application of these findings was supported by the positive response to ICI PD1 in the case of fecal microbial transplantation (FMT) from the patient to a sterile mouse [47]. The efficacy of human prostate cancer (PCa) drug was improved by employing extracellular vesicles derived from *A. muciniphila* (Akk-EVs). Intravenously injected Akk-EVs into immune-competent mice led to a significant reduction in the tumor stress of PCa. It did not cause any toxicity to normal tissues. Under *in vitro* conditions, these vesicles enhanced the number of M1-like macrophages,

GZMB⁺CD8⁺ cells, and IFN- γ ⁺CD8⁺ T cells. These expressions suppressed the invasion and proliferation of prostate cells [48]. Oral administration of pasteurized or live *Akkermansia* to mice brought in significant changes in the metabolome of the liver and gut. Here, the pasteurized *Akkermansia* were more effective than live *Akkermansia* in reducing the intestinal concentrations of spermidine, polyamines, SCFAs, and 2-hydroxybutyrate. These metabolites provided information regarding the functioning of *Akkermansia* [49].

Longevity

Gut microbiota in centenarians from geographically diverse populations provided clues for identifying signature microbial species. The highest diversity of Ruminococcaceae members were the most prevalent bacteria among these individuals. A distinctly lower prevalence of Prevotellaceae members was present in the GM of Indian centenarians. The signature taxa identified to contribute towards longevity were *Akkermansia*, *Alistipes*, and *Ruminococcoaceae* D16. The role of sulphur compounds in longevity was reported in promoting *Akkermansia* and *Alistipes*. The lower population density of *Prevotella* species in centenarians is justified since these bacteria have inherently low SCFA producing capacity and reduced carbohydrate-active enzymes. Chronic inflammation is associated with their abundance. The study did not show any positive correlation in the population densities of Christensenellaceae and *Bifidobacterium*, and *Faecalibacterium*. However, their association with longevity had been reported previously (Table 1) [18]. Based on the information that mouse dysbiosis is related to increased abundance of Proteobacteria and cyanobacteria on the one hand and reduced quantity of Verrucomicrobia, GM of human progeria patients was also analyzed. These patients displayed similar variations in their GM. Centenarians exhibited a significant enhancement in Verrucomicrobia and a decline in the Proteobacterial species. FMT and transplantation with *A. muciniphila* into short-lived mouse strains extended their lifespan, supporting the observation that *A. muciniphila* has an antiaging impact [50].

Other Disorders

Another disorder where arteries get blocked due to high cholesterol levels is atherosclerosis. A diet free of sugars, cholesterol, and fat has been recommended for managing this metabolic disorder. Plants containing high concentrations of an alkaloid, berberine, such as grapes, barberry, and turmeric, have been used for medicinal purposes. Berberine mixed with drinking water resulted in enhancing the population of *Akkermansia* spp. in the gut and reduced

the high-fat diet-induced atherosclerosis in ApoE^{-/-} (Table 1) [51]. Duodenal microbiomes of celiac disease (CeD) and their first-degree relatives (FDRs) were characterized by the significant presence of amplicon sequence variants (ASVs) of different genera. In contrast, CeD had a significantly higher abundance of ASVs belonging to *Helicobacter* and *Megasphaera* species. In contrast, FDRs were distinguished by an abundance of ASVs representing *Actinomyces*, *Anaerostipes*, *Bifidobacterium*, *Gemella*, *Granulicatella*, and *Parvimonas* genera. A dramatic reduction in the quantity of ASVs from *Dorea* and *Akkermansia* in the fecal microbiomes of FDRs and CeD was observed compared to the microbiota of the control group [17].

Childbirth and Growth

Another relatively new insight has been provided by microbiome analysis of babies delivered through vaginal and cesarean procedures. The baby delivery process influences the gut microbial diversity in children. The dominant bacterial populations in Indian and Finnish children were *Bacteroides*, and *Streptococcus* species in vaginally born subjects. In contrast, children delivered through the cesarean system had a predominance of *Escherichia*, and *Akkermansia*. Vaginally delivered children had a high abundance of *Clostridium*, *Collinsella*, *Megamonas*, *Megasphaera*, *Rummeliibacillus*, and *Veillonella*, while higher *Lactobacillus* was present in the children born through the cesarean operation. Microbial community analysis to predict the predominant metabolic activities revealed that Indian children's microbial genes were involved in glycan biosynthesis and metabolisms of glycan and proteins for the biosynthesis of lipopolysaccharide. Finnish children's gut microbiota possessed genes responsible for carbohydrate and methane metabolisms. The study also showed that mucin degrading *Akkermansia* spp. was in significantly higher abundance in Finnish children. It showed a negative correlation with a high-fat diet [52]. Children having stunted growth expressed a decrease in Actinobacteria and a marked increase in the abundance of Bacteroidetes with age. *Akkermansia* (2.65%) were among the ten most abundant genera, whose contribution to the manifestation of the abnormality was observed to fluctuate as follows: significant decrease at 3 and 18 months, a substantial increase in the cases at 6, 8, and 21-month stage compared to their respective controls [53].

Improving Health via FMT

A strategy to regain and maintain health has been developed by manipulating GM through FMT from healthy individuals. FMT from humans to mice has shown significant improvements in reversing diseased (dysbiosis) conditions to normal (eubiosis). Various potential benefits of FMT strategy in restoring health have been reported: (a) enhances insulin sensitivity in patients with metabolic syndrome [54]; (b) obesity and general metabolism in mice and humans [55, 56]; (c) diabetes [57]; (d) treating individuals for refractory ICI-associated colitis [58]; (e) preventing recurrent *Clostridium difficile* infections [59–61]; (f) restoring metabolic homeostasis [62]; (g) lifespan [50]. Rodents receiving FMT from cancer patients acquired their inability to respond to immunotherapeutic treatments using ICIs [47, 63].

Interestingly, in contrast to FMT, application of a single bacterium (*A. muciniphila*) has also proved beneficial in treating various disorders: (a) the lifespan in progeria, (b) the health of mammals and aged mice [29, 42, 45, 64]; (c) activation of bile acid metabolism in mice [65, 66]. A clinical trial has validated the anti-obesity and antidiabetic effects of *Akkermansia* [45, 67].

By regulating the food items, we consume and their quantities, it is possible to manipulate the population densities of the different bacteria (Fig. 2). The consumption of fibers can proportionately increase the diversity of these probiotic bacterial species in the gut. Bacteria metabolize these fibers, and the fermentation results in the production of SCFAs, which nourish the gut barrier, enhance immunity and reduce inflammation [68]. Vegetables, herbal tea, fruits, red wine, and dark chocolate can come in handy in regaining the lost bacterial diversity. The essential components in these food items are the polyphenols—which have unique properties—the most important being their antioxidant characteristic [69]. Prebiotics, probiotics, and phytobiotics have chemical components such as dietary fibers (Fruits, vegetables, nuts, legumes, whole grains), which are beneficial for maintaining a healthy microbiota within the gut [32, 70–72]. Together these reduce the risk of metabolic, endocrine, and immune functions and cancer [73–75]. It was suggested that a healthy diet might be instrumental in better prognosis of infected with COVID-19 patients during the lockdown [76, 77]. We must remember that maintaining a healthy microbiome is imperative to ensure health [78].

Knowledge Gaps and Perspectives

Efforts to establish an unambiguous correlation between the microbial diversity and population dynamic of GM, and the health status of human beings and animals, are being made globally. Similar studies have elucidated the role of microbes in the rhizosphere and phyllosphere and the plant growth and yield. The need is to study if these probiotics can prove effective individually or as consortia. Secondly, it is also necessary to identify prebiotics, which will help the probiotics increase and maintain the desired cell density. Further, information is lacking on the potential side effects of the transfer of these bacterial species to unhealthy individuals on a large scale and at high frequency. A clear idea is yet to be made available about the additional features introduced into these probiotic bacteria through genetic engineering to enhance their sustainability and robustness, especially for industrial production. These studies will enable human beings to gain health and remain healthy without synthetic chemical drugs.

Conclusions

The microbe *Akkermansia* is proving instrumental in regaining eubiosis and consequently conferring various health benefits. A two-prong strategy is necessary to achieve and maintain good health. A diet rich in prebiotics and FMT from healthy individuals can help us achieve an abundance of probiotic bacteria. A low-fat, high-fiber diet is perhaps an ultimate option to ensure a healthy life.

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