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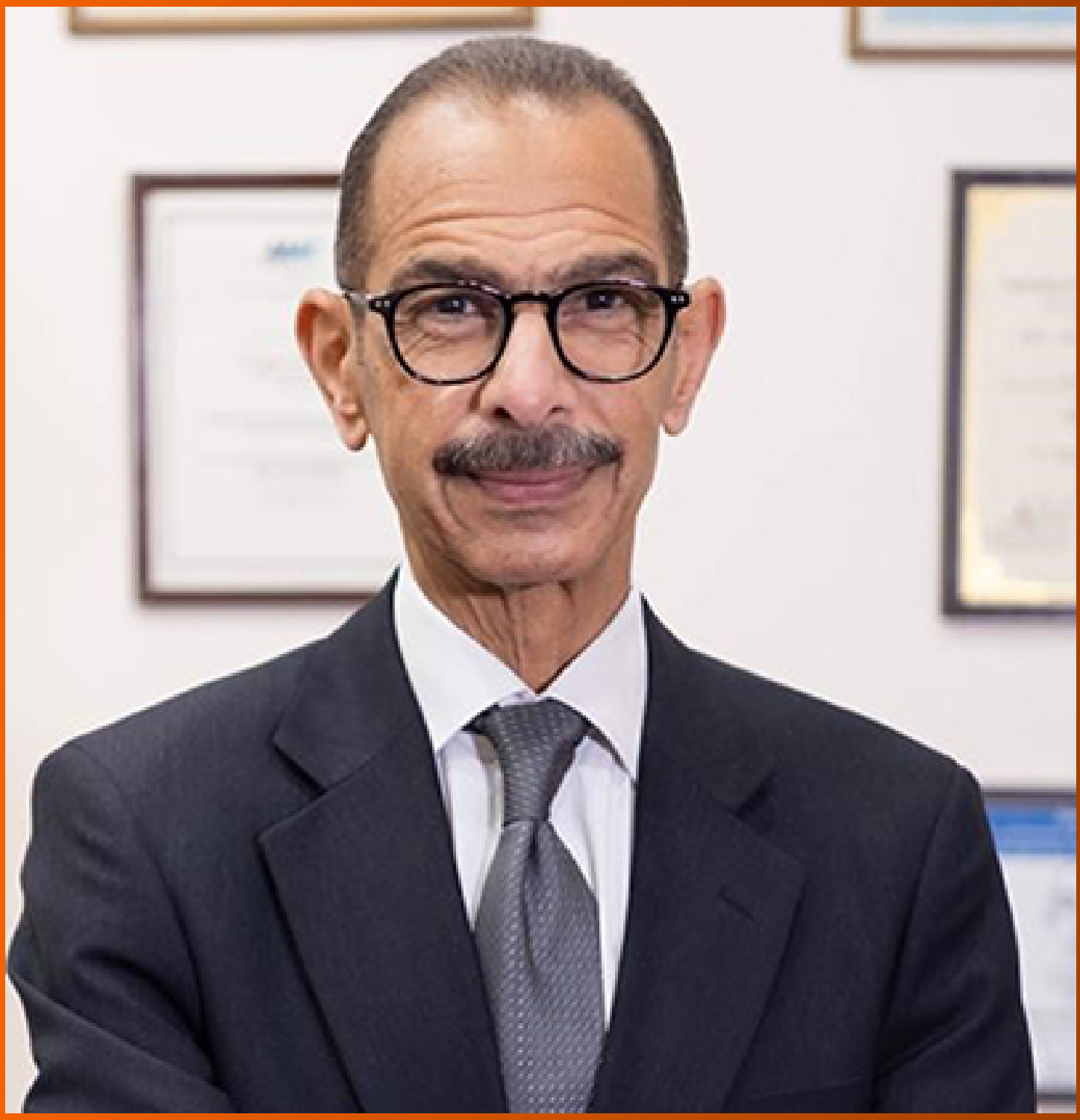

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MINIREVIEWS

Exploring the relationship between gut microbial ecology and inflammatory disease: An insight into health and immune function

Akashlina Marik, Saheli Biswas, Ena Ray Banerjee

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Akashlina Marik, Saheli Biswas, Ena Ray Banerjee, Department of Zoology, University of Calcutta, Kolkata 700019, West Bengal, India

Co-first authors: Akashlina Marik and Saheli Biswas.

Corresponding author: Ena Ray Banerjee, DSc, Professor, Department of Zoology, University of Calcutta, 35, Ballygunge Circular Road, Kolkata 700019, West Bengal, India.
enarb1@gmail.com

Abstract

The immune system, host brain development, and general metabolism are all influenced by the gut bacteria. Bacteria make up the majority of the gut microbiota in mammals. The mouse has been the most often used animal model in preclinical biological research. In mice, *Firmicutes* and *Clostridiales* are prominent. On the other hand, *Bacteroidaceae*, *Prevotellaceae*, and *Firmicutes* are commonly found in humans. In this review, we performed a detailed study by focusing on a comparison between human and murine gut microbiomes, role of the microbiome and their secreted metabolites in regulating gut immunity to maintain homeostasis, and changes in the microbial composition in the dysbiotic state.

Key Words: Gut microbiome; Immunity; Inflammatory Bowel disease; Diabetes; Dysbiosis

Core Tip: The gut microbiome is a complex assemblage of microorganisms consisting of bacteria, archaea, fungi which inhabits the gut and are responsible for carrying out various functions like digestion of complex food components, synthesis of vitamins, stimulation of immune response and strengthening of gut barrier and protection from pathogens. Metabolites secreted by these bacteria play an important role in homeostasis and in maintaining a healthy state in the host. Dysbiosis of the intricately woven ecological networks in the gut microbiome plays a critical role in various health-related disorders like diabetes, obesity, and inflammatory bowel disease.

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INTRODUCTION

The microbiome of an organism is considered as the collection of microbes that colonize the body since birth, their genes, and their products[1]. The total number of bacteria in a 70 kg human is estimated at around 3.8×10^{13}[2]. The greatest number of microbes are in gut colonies. From the stomach to the colon, there is a longitudinal rise in the variety and density of microbial species. The intricate communities of microorganisms that inhabit the gastrointestinal tract perform a vital role in the host, such as the conversion of indigestible food components into easily absorbed metabolites, the production of vital vitamins, elimination of harmful substances, inhibition of pathogens, fortification of the intestinal barrier, and the induction and modulation of the immune system through the release of diverse fermentation products such as short-chain fatty acids. Therefore, gut microbiome is an important factor in governing human health and disease [3]. The composition of the gut microbiota varies throughout the development of an individual and is dependent on the host genotype along with environmental factors like diet, early microbial exposure, age, geography, and antibiotic exposure. Ninety-eight percent of the gut microbiome in healthy people is made up of four phyla, Firmicutes, Bacteroides, Proteobacteria, and Actinobacteria. The most common bacterial species in the microbiota are members of phylum Firmicutes (60%-80%) and phylum Bacteroides (15%-25%)[4].

In addition to sharing 70% of their protein-coding genes, humans and mice share 90% of the phyla and 89% of the genera of their gut microbiomes. This means that everything from morphology and physiology to metabolism, pathophysiological illness manifestations, and the gut microbiome are similar across the two species. Abundant genetic resources, a short lifecycle, small size, and ease of maintenance make mice one of the most important preclinical disease models for biomedical research. Hence understanding the both the similarities and dissimilarities of the human and murine gut microbiomes is an important area of consideration.

ECOLOGY OF THE GUT MICROBIOME

The gut microbiome's ecological traits of stability, resistance, and resilience are crucial. When the gut microbial community is not perturbed, it displays a dynamic equilibrium that revolves around a stable ecological state. Although the relative abundance of each microbe varies over time and within individuals throughout their lives, the composition of the gut microbiota in healthy adults can remain stable for years at a time. Additionally, the gut microbiota is highly resilient to perturbation, allowing a host to retain important species for an extended period of time[4]. This intricate web of microorganisms is always open to threats from the outside world, and is capable of reestablishing homeostasis following a disturbance, like a. viral infection or the use of antibiotics. The ability to regenerate itself is referred to as the resilience phenomenon. On the other hand, when the microbial ecology experiences a compositional or functional imbalance that surpasses its capacity for resistance and resilience, the result is referred to as dysbiosis. Dysbiosis can lead to a decrease in alpha diversity, a rise in disease abundance, or the extinction of keystone taxa. Obesity has a phylum level imbalance, with a higher proportion of Firmicutes than another dominating phylum Bacteroidetes. The Firmicutes genome is enhanced with an ability to obtain energy from food sources resulting in obesity. Dysbiosis may result from varying levels of microbial metabolites in the blood or intestine between healthy individuals and patients, as in celiac disease. While there is not a continuous microbial imbalance in the gut microbiota, there are notable differences between the gut microbiotas of healthy individuals and those with Crohn's disease (CD) in the levels of short-chain fatty acids (SCFAs) and glutamine[5]. A number of inherent traits appear to control the resilience of the gut microbiome, influencing the makeup of microorganisms and, in turn, the properties of the gut environment. These qualities can be divided into two groups. A stable ecosystem is maintained in the gut by the microbiome's characteristics, which include biofilm formation, metabolic adaptability, functional redundancy, microbial interactions, and persistence in colonization. The variety of microbes is maintained by host controls, which involve selection pressure including nutrient provision, immune tolerance, mucus layer protection, host-microbe interactions, peristaltic movement, and oxygen level control. Various interactions like competition, mutualism, commensalism, ammensalism, parasitism, predation, antagonistic coevolution, *etc* shape the taxonomical and functional niches of the gut microbiome, which in turn affect host health. According to various literature reviews, it can be inferred that co-culture of *Faecalibacterium prausnitzii* and *Bifidobacterium catenulatum* improve growth, gut colonization, and most importantly butyrate production, by *Faecalibacterium prausnitzii*. *In vitro* co-culture secretions have been shown to reduce the amount of pro-inflammatory cytokines produced by HT-29 cells and RAW264.7 macrophages. Moreover, in a dextran sodium sulfate (DSS) -induced colitis mouse model feeding with both *Faecalibacterium* and *Bifidobacterium* enhanced *F. prausnitzii* gut colonization, decreased interleukin (IL)-8 levels in the colon, increased butyrate level in the cecum, and significantly increased the relative abundance of *Akkermansia* compared with healthy mice. According to Kim *et al*[6] three major phyla that are prevalent in the human gut are represented in a co-occurrence network for profuse species of microbes. Acetate, lactate and formate producing *Bifidobacterium adolescentis* and succinate, propionate producing *Bacteroides thetaiotaomicron* are prevalent in the human gut. One of

the gut dwelling bacteria *F. prausnitzii* consumed disaccharides more slowly and *R. inulinivorans* consumed glucose more slowly in culture medium without acetate. The presence or absence of acetate in the media revealed how variations in SCFA metabolism impact the amount of various SCFAs produced. Hence *Faecalibacterium* and *Roseburia* are in a positive relationship. Keystone species of the gut microbial community are the primary fiber degraders like *R. bromii*, which is considered as keystone species for degradation of resistant starch and significantly contributes to butyrate production although it itself does not produce butyrate[7]. Guild is an important concept coined by Zhao *et al*[8]. A group of species that "exploit the same subsection of environmental resources in an analogous way" is referred to as a guild. Members of a guild coexist when they adjust to a changing environment, even if they do not share taxonomic similarities. According to Zhao *et al*[8] who found that 15 positive responders to a fiber-enriched diet in patients with type 2 diabetes (T2D) were from three different phyla but acted as a guild to augment a deficiency in SCFA production in the gut environment by reacting in similar ways to the increased availability of fermentable carbohydrates. Hence the ecosystem of gut microbiome is very complex and interconnected at various levels[8] (Figure 1 and Table 1).

OVERVIEW OF HUMAN *VS* MOUSE GUT MICROBIOME

Humans and mice share 90% of the phyla and 89% of the genera, but taxonomically fewer than 3% of the microbial species are shared[9]. But when these host-specific microbiotas are looked upon from a functional perspective, there are major similarities facilitate translation of microbiota-related research between humans and mice. Conserved metabolic functions are often performed by hosts with very different taxa. Butyrate metabolism is an example. Butyrate is a SCFA that is the primary energy source of the intestinal enterocytes and plays the major role in maintaining the oxygen-free environment of the gut. Previous studies of inflammatory bowel disease and metabolic syndrome link butyrate with various immunological and metabolic pathways like induction of peripheral T-regulatory cells. Dietary fiber and amino acids like glutamate and lysine are converted to butyrate by the direct butyrate CoA-transferase pathway (BCoAT) or an indirect phosphotransferase pathway (PTB/BUK). The pathways are common to both the mouse and human microbiomes, but the phosphotransferase pathway appears to be more prominent in mice, contradicting the conventional wisdom that the direct pathway is the primary mechanism of butyrate production by the microbiota in humans[10] (Tables 2 and 3, Figure 2).

PATHOPHYSIOLOGY OF GUT MICROBIOME BY REGULATING IMMUNE SYSTEM

The gastrointestinal (GI) tract of mammals harbors a vast and intricate ecosystem of commensal microorganisms. Over millennia, this gut microbial community—known as the microbiota—has coevolved with its host and benefits the host in numerous ways, such as digestion, nutrient generation, detoxification, defense against infection, and most important, immune system modulation. To maintain immunological homeostasis, the gut microbiota shapes innate as well as adaptive immunity.

The immune system and gut flora coexist in a symbiotic manner. Gut mucosa- minimizes direct contact between microorganisms and intestinal epithelial cells is achieved through the secretion of mucus by goblet cells, antimicrobial peptides by Paneth cells, and a physical barrier provided by the intestinal epithelial cells. The mucosal innate immune system secretes cytokines, chemokines, and inflammatory mediators to control the immune response after receiving signals from the sensory system, such as metabolites of the gut microbiota.

Adaptive immune cells in the intestinal mucosal immune system include CD4+ T cells that can develop into Tregs if polarized by microbiota-derived signals, and type 1 T-helper cells (Th1), Th2, and Th17 cells that perform various tasks. Dendritic cells identify pathogenic microbes and present microbial antigens to T cells so that they may eliminate them, and regulatory Tfh cells encourage plasma cell development and secretory IgA class switching. ILCs secrete a variety of antibacterial cytokines, B cells secrete IgAs against specific microbial epitopes, and Tregs assist in controlling excessive inflammation in the host. Together, the innate and adaptive immune systems keep the gut microbiota and host in a state of equilibrium.

The interplay between intestinal bacteria and host immunity sustains gut homeostasis. In response to intestinal bacteria or their metabolites, innate immune cells either stimulate or inhibit distinct immune cell activation and differentiation. A class of receptors known as pattern recognition receptors, which includes nucleotide-binding oligomerization domain-like (NOD-like) receptors and Toll-like receptors (TLRs), is essential for innate immune responses[11]. TLRs are important, highly specific innate immune receptors that are found in the gut epithelial layer and recognize pathogen-associated molecular patterns. Various immune cells, including macrophages and dendritic cells, control T-cell proliferation and differentiation in the intestinal lamina propria by releasing cytokines in response to commensal bacteria and their byproducts. According to certain findings, Th17 growth in a healthy murine gut is promoted by CD70+ and CD11b+ T cells and dendritic cells. (DCs) that produce TGF-β, IL-6, and IL-23 in response to commensal bacteria. DCs connect the innate and adaptive immune systems, resulting in an immunological response to pathogens. They typically localize in the lamina propria and gut-associated lymphoid tissues of the colon and intestine[12]. Through the production of B cell-activating factor of the tumor necrosis factor family and proliferation-inducing ligand, DCs strongly stimulate IgA type class-switch recombination in B cells. Intestinal macrophages also play an important role in producing various cytokines like IL-10. Treg cells are activated to decrease inflammation by IL-10, which is produced by intestinal macrophages. In addition, recent research has shown that commensal bacteria function to maintain gut homeostasis by regulating the immune system. The intestine is home to a vast population of commensal bacteria, some of which—or their meta-

Table 1 Distribution of microbes in different organs

Site	Cell count	pO_2 in mmHg	pH	Presence of microbes
Oral cavity	10^9	83-113	6.2-7.5	*Streptococcus, Haemophilus, Prevotella, Veillonela, Gemella Neisseria*
Stomach	10^3-10^4	60-77	1.5-3	*Streptococcus, Prevotella, Helicobacter, Gemella*
Duodenum	10^3-10^4	5.6-8	6	*Bacteroides, Clostridium, Streptococcus*
Jejunum	10^3-10^4	10-34	5.7-7.5	
Ileum	10^8	10-34	5.7-7.5	
Colon	10^{11}	0.5-11	6.7-8.5	*Bacteroides, Prevotella Ruminococcus*

Table 2 Longitudinal distribution of gut microbes in the human gastrointestinal tract with respect to the pO_2 and pH of different regions

Gastrointestinal tract	Prevalence in human	Prevalence in mouse
Stomach	Cardiac, fundic, body, pylorus, pH-1.5 to 3.5	Fore stomach, body, pylorus, pH-3 to 4
Small intestine	6 m, pH-6.4 to 7.3	350 mm, pH-4.7 to 5.2
Colon	Ascending, transcending and descending colon, pH-6.7	Undivided, No fermentation, pH-4.4 to 5.0

Table 3 Representation of the diversity of micro- and myco-biome in both human and mice gut

Type of gut micro- and myco-biome	Humans	Mice
Microbiome	*Faecalibacterium, Mitsuokellla, Megasphera, Dialister, Asteroleplasma, Succinivibrio, Sutterella, Paraprevotella* and *Phascolarctobacterium*	*Mucispirillum*
Mycobiome	*Candida, Malassezia, Saccharomyces, Cladosporium*	*Ascomycota, Basidiomycota, Chytriodiomycota, Zygomycota*

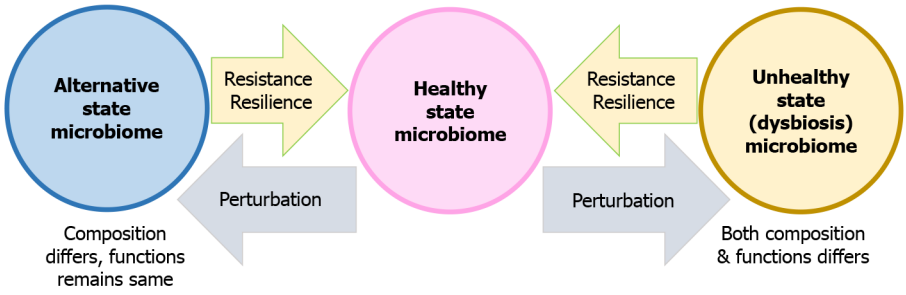

Figure 1 Healthy or equilibrium state of the gut microbiome is characterized by a high microbial diversity, which favors functional diversity and microbe-microbe and host-microbe interactions. When perturbation of this ecosystem occurs the microbe composition may shift to an alternative healthy state that differs from the initial state but maintains the same functionality.

bolites—have been shown to stimulate the T-cell immune response or improve the function of the mucosal barrier in the gut, so promoting host defense and preventing intestinal inflammation. Commensal gut bacteria create an intact intestinal epithelial layer by maintaining the tissue integrity and preserve homeostasis by TLR signaling. IgA is secreted by commensal bacteria, and it is thought that these antibodies work in tandem with natural defense mechanisms to safeguard the epithelium and enhance its barrier function. Various intestinal bacteria like segmented intestinal bacteria specifically induce Th17 immune cells to produce serum amyloid A and eventually generates reactive oxygen species in the intestinal epithelial layer. Thus, accumulation of intestinal segmented bacteria may result in the development of various inflammatory diseases. The gastrointestinal tract of animals, including mice and humans, contains a family of spore-forming commensals known as segmented filamentous bacteria (SFB), which are anaerobic and linked to Clostridia. SFB are closely bonded to the epithelial lining of the GI tract and actively engage in immune system interactions. The results of many studies show that intestinal SFB colonization stimulates Th1 and Th17 cell differentiation and the growth of Treg cells in response to pathogenic invasion. Certain beneficial bacteria, such as *Clostridium*, suppress host immunity by promoting the growth of Foxp3+ T reg cells in the intestinal lamina propria. It has also been shown that oral administration of *Clostridium* can cause resistance to intestinal inflammation[13]. Vitamins, SCFAs, and

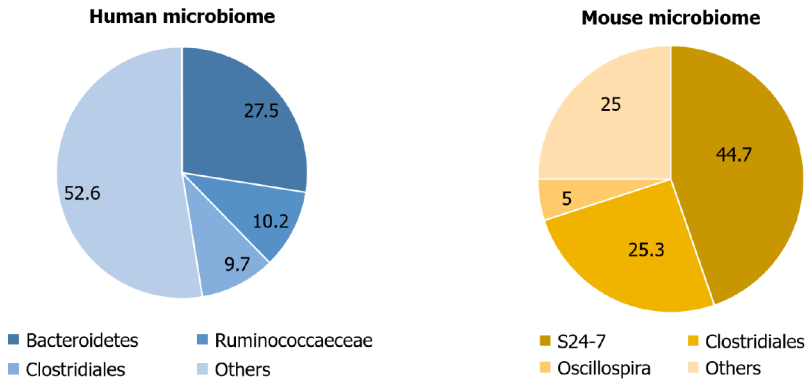

Figure 2 Similarities of the human and mouse gut microbiomes by percentage.

secondary bile acids are examples of commensal bacterial metabolites that influence the associations within the gut microbiome and alter the host's immune system. SCFAs like butyrate, acetate and propionate induce Treg cell differentiation, which suppresses the production of pro-inflammatory markers. The commensal gut bacterium *Bifidobacterium infantis* 35624 has been shown to stimulate the production of Treg cells that regulate the activation of NF-κB in Balb/c mice and NF-κB$_{lux}$ transgenic mice on infection with *Salmonella typhimurium* and injection with lipopolysaccharides (LPS). This helps to maintain host homeostasis and defends against pathogens such as *Salmonella typhimurium* by preventing improper activation of the innate immunity.

Human health depends on the balance of the gut's beneficial microbiota (commensals) and pathogens. This balance is the result of complex, finely regulated interactions between bacteria and their hosts as well as crosstalk among them. *Escherichia coli*, a significant gut resident bacterium, secretes indole, which may reduce pathogenic *E. coli* chemotaxis, motility, and adhesion to host intestinal epithelial cells. It has been confirmed that indole reduces inflammatory markers such as TNF-α-mediated NF-κB activation and pro-inflammatory IL-8 expression. It is now known that the variety and constitution of the commensal microbiota in the human gut may affect the balance between Tregs and conventional T cells, which in turn affects host gut immunity[13]. The gut microbiome can affect the immune system by various mechanisms. Microbial metabolites, NOD and TLR can act directly on gut epithelial cells, these metabolites often taken up by enterocytes pass through the basal membrane and enter the systemic circulation to modulate immune system at various levels. The development of most high-affinity antibodies, memory B cells, germinal centers, and Treg cells, a specialized subset of T cells that function to suppress immune responses and preserve homeostasis and self-tolerance, all depend on Peyer's patches, which maintain and regulate the microbial composition in the gut by promoting B cell class-switch and production of secretory IgAs that provide host protection against microbes and tolerance of the gut commensals, respectively.

Interaction of intestinal epithelial cells with immune cells and gut commensals

Employing different cytokines or presenting antigens to DCs or T cells, intestinal epithelial cells interact indirectly or directly with innate and adaptive immune cells. In healthy conditions, enterocytes produce reactive oxygen species in response to SFB or adhesion of pathogenic bacteria, which leads to Th17 cell differentiation. In addition, goblet cells produce MUC2, which organizes the mucus layer and constrains the immunogenicity of gut antigens by delivering tolerogenic signals to DCs. Intestinal epithelial cells and immune cells in the intestinal layer reacts by secreting cytokines. IL-22, IL-17 are produced by various immune cells, including T-cells, which in turn activates the secretion of anti-microbial proteins from intestinal cells. In the case of gut inflammation like inflammatory bowel disease (IBD), after neutrophil infiltration, inflammatory monocytes are attracted to the wound site to aid in healing of the mucosal barrier. The epithelial progenitor niche of the colon is stimulated by activated macrophages that are distinguished from recruited monocytes, hence promoting epithelial regeneration. It has come to light that a compromised gut microbiome is intrinsically linked to metabolic issues, cognitive dysfunction, and gastrointestinal ailments.

Microbes and vaccine immunity

Variation of immunization outcome has been attributed to differences in the composition of the gut microbiome. In 2018, Zimmerman and Curtis[14] published a systematic review of data from 26 human interventional studies that used probiotics to boost the effectiveness of 17 different vaccines. The review concluded that half of the studies had positive findings. When compared with adult trials, the use of probiotic strains of *Lactobacillus* and *Bifidobacterium* in neonates and children between 0 and 16 weeks of age was associated with higher rates of humoral immunity after administration of rotavirus, polio, influenza and diphtheria vaccines. Nonetheless, it is difficult to reach solid conclusions because of differences in study design including the bacterial strain that were used. Future research will certainly open a new avenue in the study of the impact of specific probiotics on the process of immunization and vaccination.

DIFFERENT METABOLITES SECRETED BY GUT MICROBIOME

Microbial metabolites include: (1) SCFAs like acetate, propionate, butyrate, hexanoate, isovalerate, isobutyrate, 2-methylpropionate, valerate that are produced during microbial fermentation of partially digested and nondigestible polysaccharides; (2) Bile acids cholate, hyocholate, deoxycholate, taurohyocholate, ursodeoxycholate, taurocholate, and tauro-α muricholate; (3) Gases like H_2S, H_2, CO_2, CH_4, and NO; (4) Tryptophan and indole derivatives indole-3-lactic acid, indole acetic acid, indole-3-acetamide, indole pyruvic acid, indoxyl sulfuric acid, indole, and serotonin; (5) Choline metabolites TMA, methylamine, dimethylglycine, dimethylamine; and (6) Vitamins B2, B3, B5, B6, B9, B12, and K[15]. All these metabolites have important direct or indirect involvement in maintaining the healthy physiology of the host.

SCFAs like acetate, propionate, butyrate, hexanoate, isovalerate, isobutyrate, 2-methylpropionate, valerate are produced by microbial fermentation of partially digested and nondigestible polysaccharides. SCFAs have a huge role in the host pathophysiology, and the most important is butyrate. Fuel substrates in both the GI lumen and the blood are used by colonocytes. Butyrate is often described as the major lumen-derived fuel substrate for intestinal epithelial cells. Butyrate is taken up by colonic epithelial cells by proton-coupled monocarboxylate-transporter-1 (MCT1/*SLC16A1*) and sodium-coupled mono carboxylate transporter-1 (SMCT1/*SLC5A8*) and carried to the mitochondria, where it is oxidized to produce acetyl-CoA, which is used for production of ATP in the tricarboxylic acid cycle and by oxidative phosphorylation[16].

There are various receptors on which SCFAs act on like FFAR3/GPR41, FFAR 2/GPR43, GPR109A, OLFR 78, GPR81, GPR91, HDAC1 and HDAC3[17]. They bring out considerable effects in modulation of metabolism and immunity of the host, gut hormone production, regulation of appetite, stimulate water and sodium absorption and are linked to various diseases like diabetes, obesity, radiation proctitis, ulcerative colitis, chronic renal disease, hypertension, atherosclerosis, alcoholic fatty liver disease, CD, autism spectrum disorder, sclerosis, and Parkinson's disease. Literature reviews describe mechanisms of SCFA, primarily butyrate, binding to the previously mentioned receptors, activation of histone acetyl transferase in colonocytes and macrophages, and inhibition of histone deacetylase (HDAC) to preserve the intestinal barrier and regulate inflammation. This inhibition causes the DNA to be translated and transcription factors to be produced, which stabilizes hypoxia inducible factor, improves the integrity of the intestinal barrier, and reduces the generation of inflammatory mediators hence resulting in a more tolerant environment for the bacteria to survive in the colon[18-20]. SCFAs also play a major role in metabolism by binding to GPR 43, which is also known as free fatty acid receptor 2 or FFAR2 or GPR 41, which is also known as free fatty acid receptor 3 or FFAR3 in the endocrine L cells of the intestine. The result is secretion of peptide YY (PYY) and glucagon like peptide 1 (GLP1) thereby directly controlling glucose and lipid metabolism and appetite regulation. In adipose tissue, SCFAs regulate lipid homeostasis and renal blood pressure through the OLFR 78 pathway (Figure 3).

METHODS FOR STUDYING THE MICROBIOTA

The sequencing of 16S rRNA genes has allowed the development of techniques to investigate organisms that are not suitable for culture. 16S rRNA sequencing can only be used for bacteria and archaea, 18S rRNA sequencing is suitable for fungi, and shotgun sequencing of the whole metagenome provides information about the functional and metabolic potential of the entire gut microbial community, including bacteria, archaea, fungi, and viruses (Figure 4).

CROSS TALKS OF GUT MICROBIOME

Hormonal metabolism of microbes in the gut

The precise pathway of microbiota-hormonal signaling has yet to be revealed. However, there are previous reports of microbiota producing and secreting hormones, as well as responding to host hormones and regulating their expression [19]. The estrobolome, or the "aggregation of enteric bacterial genes whose products are capable of metabolizing estrogens" was first reported by Plottel and Blaser[21]. In both humans and mice, bacterial β-glucuronidase released by the gut microbiome deconjugates phytoestrogens and conjugated estrogens secreted by bile acids. This enables the gut to reabsorb the metabolized estrogen and phytoestrogens and allow them to translocate into the bloodstream. That affecting the circulatory hormone concentrations allowing these estrogen and phytoestrogens metabolites to act on estrogen receptors at distal sites. According to human microbiome project, 60 bacterial genera that encode ß-glucuronidase and/or ß-galactosidase colonize the human intestinal tract That explains the observations of Adlercreutz *et al*[22] who they found that antibiotic treatment reduced estrogen levels. They also studied the relationships of fecal microbiome composition and richness, urine estrogen level, and *Clostridium* taxa, including non-clostridiales and three genera in family Ruminococcaceae. Dietary phytoestrogens are also important here. The main classes of phytoestrogens found in food are lignan, isoflavones, coumestans, and prenylflavonoids, and isoflavones can be metabolized into equol and O-demethylangolensin (O-DMA) by the gut estrobolome, which thereby affects the systemic level, potency, and half-life of these phytoestrogen[23] (Figure 5)

Crosstalk of gut microbial metabolites

Secretory metabolites of the microbiome participate in both innate and adaptive immune responses. Hypoxia inducible factor-1 coordinates barrier protection and activates signal transducer and activator of transcription factor 3 and

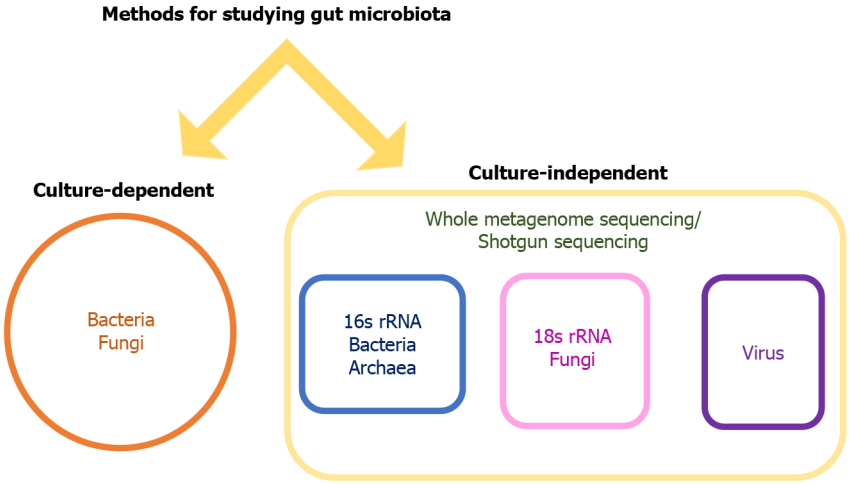

Figure 3 Methods of studying the gut microbiota.

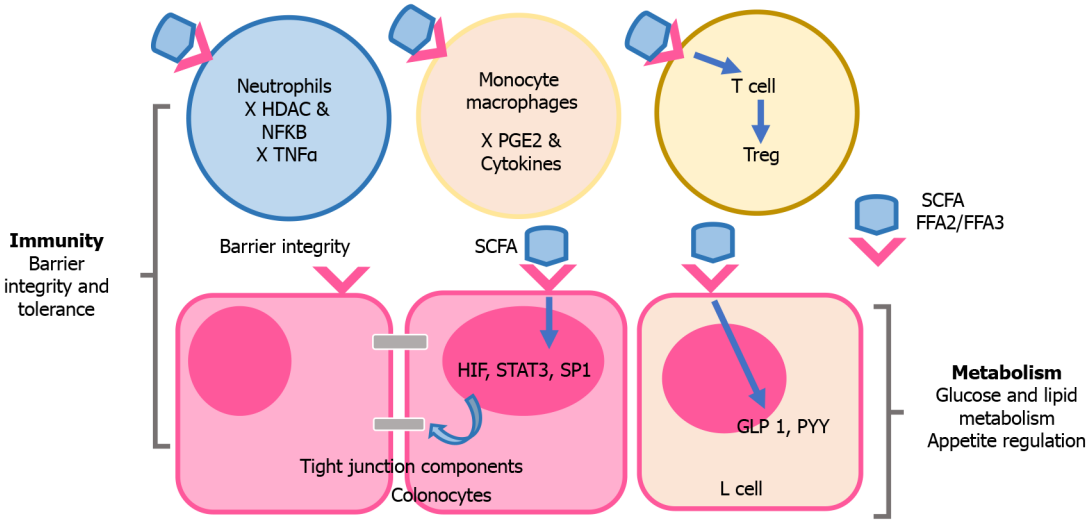

Figure 4 Short-chain fatty acids participate in maintaining intestinal/colonic mucosal integrity by upregulating the expression of tight junction proteins. They induce immune tolerance by downregulation of histone deacetylase and NFB, manipulating proinflammatory gene expression by inhibition of tumor necrosis factor, prostaglandin E2, *etc* thereby resulting in formation of more Treg cells. SCFAs promote production of glucagon like peptide 1 and pancreatic peptide YY by binding to the free fatty acid receptor 2/3 of the intestinal endocrine L cells thereby controlling the appetite of the host along with glucose and lipid metabolism. FFA2/3: Free fatty acid receptor 2/3; GLP1: Glucagon like peptide 1; PEG2: Prostaglandin E2; PYY: Pancreatic peptide YY; SCFA: Short-chain fatty acids.

specificity protein 1, which leads to activation of genes coding for tight junction components and regulation of intestinal barrier integrity. Metabolites also downregulate HDACs and NFκB, which consequently manipulate gene expression, such as inhibiting TNF-α when a pathogenic stimulus (LPS) is induced, thereby providing tolerance to the gut environment. Metabolites also activate monocytes and macrophages, which regulate the production of cytokines and prostaglandin E2. In case of adaptive immunity, metabolites activate the number of Tregs. Tregs increased in number because of free fatty acid receptor 2 (FFAR2)-mediated inhibition of the HDAC pathway, which also results in the polarization and activation of Th1, Th2 and Th17. FFAR2-mediated histone deacetylase inhibition promotes interferon gamma (IFNG) expression.

Cross talk of Gut microbiome with different organs

Gut-liver axis: The liver is anatomically connected to the gut *via* the portal venous circulation and bile duct system, hence is constantly exposed to gut microbiome products. Microbe-associated molecular patterns from the gut microbiome influence the function and maturation of hepatic innate immune or Kupffer cells[24]. Different cell types in the liver recognize bacterial LPS through TLR4, which causes an increase in pro-inflammatory chemokines and adhesion molecules. Probiotics containing glycolipid antigens can activate hepatic natural killer T cells of the liver. Primary sclerosing cholangitis (PSC) is a chronic inflammatory and cholestatic liver disease. As a result of intestinal epithelial barrier disruption caused by the enteric pathobiont *Klebsiella pneumonia*e, bacterial translocation is induced in the mouse liver, stimulating Th17 cell responses. Similarly increased *Enterococcus faecalis* abundance is seen in PSC along with

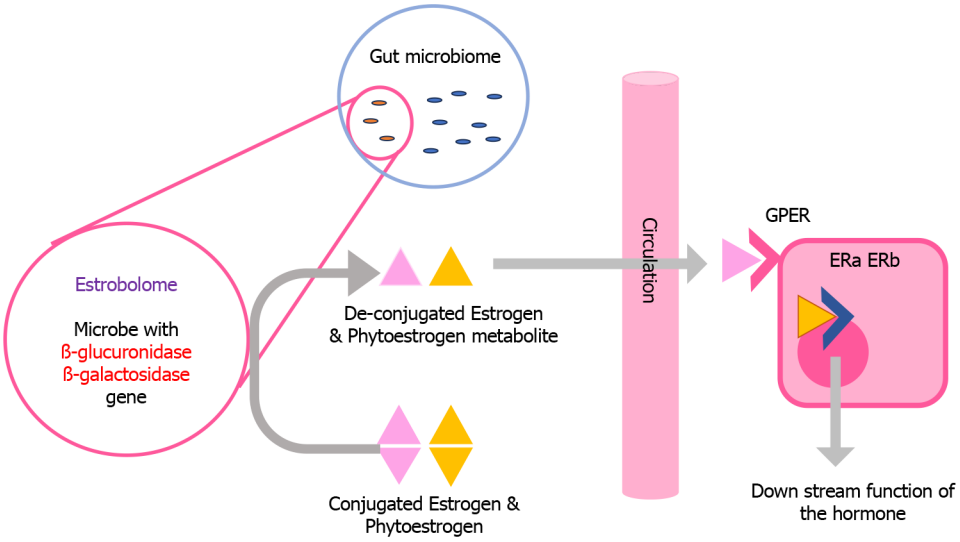

Figure 5 Estrobolome refers to the aggregation of enteric bacterial genes (ß-glucuronidase and ß-galactosidase) whose products metabolize conjugated estrogens to its free form, which can be returned to the circulation. Era: Estrogen receptor alpha; ERb: Estrogen receptor beta; GPER: G protein coupled estrogen receptor 1.

reduced healthy microbial diversity, which significantly points towards the gut liver microbial connections in progression of diseases like with nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis or cirrhosis[25-27].

Gut-brain axis: The gastrointestinal-brain connections are well known through the hunger satiation axis but recent research is focused on possible higher-order cognitive and psychological effects[28]. In adult BALB/c mice, various microbes are capable of synthesizing neurotransmitters. These microbial neurotransmitters along with other microbial metabolites affect the brain directly through the vagus nerve indirectly by modulating the immune system. Gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the mammalian central nervous system, can be produced by the gut microbiota thereby influencing homeostatic host behavior. Alterations of the central GABA pathway are responsible for the pathogenesis of anxiety and depression. *Lactobacillus rhamnosus* is a gut microbe that is capable of producing GABA and may act through the vagus nerve to ameliorate depression and anxiety like response in adult male Balb/c mice[28]. Other gut microbes like *Bifidobacterium longum, Lactobacillus reuteri* are some of the bacteria which act through the vagus nerve by increasing the secretions of neurotransmitters like brain derived neurotrophic factor and Oxytocin respectively. Oxytocin is a neuropeptide system that modulates social behavior, bonding, mating and stress in animals. It is also known to be associated with symptoms of autism spectrum disorder[29]. Tryptophan, 5-HT and 5-hydroxyindoleacetic acid were elevated in hippocampus of male germ-free (GF) mice[30]. Some of the important gut microbiota, like, *Streptococcus, Escherichia and Enterococcus spp*. produce serotonin, a neurotransmitter involved in controlling mood, social behavior, gut motility and the sleep cycle. Moreover, some gut dwelling microbiota like *Bacillus* and *Serrati* can produce and respond to dopamine[31], which is in line with a study by Wikoff *et al*[32] in which low plasma serotonin levels were seen in GF mice. Hence a proper diet that can ultimately maintain a proper gut microbiome may be an important aspect to consider while dealing with not only physical well- being but also mental and stress response. Various recent studies have focused on the cross-connected axis between the gut microbiome and other organs like the brain, liver, skin, lungs, *etc* (Figure 6).

Cross talk between gut microbiome and allergens

Primary aim of any immune response is to remove any exogenous or endogenous antigens and restore homeostasis. In certain circumstances, an inappropriate deleterious immune response is raised against harmless antigens and is referred to as an allergic response. This inflammatory response can cause deleterious outcomes resulting in diseases and host tissue injury. Food allergies, respiratory allergies like asthma, and skin allergies like atopic dermatitis are some of the most common and prevalent manifestations in humans. Other than dietary factors, the microbiota comprise the main antigen load of the gut and probably play an important role in maintaining the gut barrier that prevents pathogenic bacteria from entering the circulation and in increasing tolerance by Treg cell activation. It has been previously reported that Treg cells, CXCR1+macrophages, and dendritic cells activated by metabolic products such as SCFAs from the gut microbiome. The gut microbiome also has a positive impact on IL-22 and IL-17 expression by innate lymphoid cells (ILCs) and T cells. In murine studies, *Bacteroides fragilis*, a bacteroidetes species that produces polysaccharide A, increases the suppressive ability of Treg cells by increasing IL-10 production from foxp3+ T cells by mediating tolerance[12]. Similarly, among Firmicutes, an abundance of *Clostridia* has been negatively associated with food allergy in children. It promotes accumulation of Treg cells and increases production of IL-22 and IL-17 by intestinal epithelial cells and T cells thereby promoting tolerance. Various epidemiological and microbiological studies have found critical roles of the gastrointestinal microbiome in respiratory allergies. *Clostridium* and SFB support TH 17 and IgA antibody responses[13]. Mice treated with *B. longum* (IM55) and *L. plantarum* (IM76) reduced the level of serum IgE and decreased two of the most important

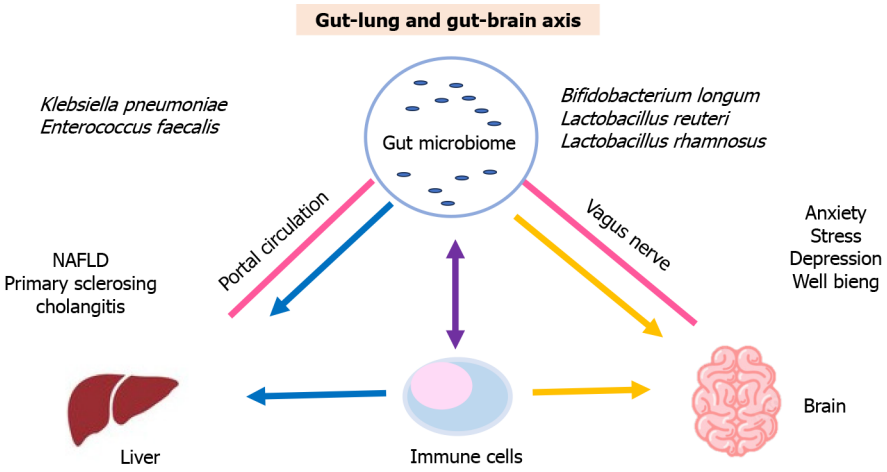

Figure 6 The gut is directly connected to the liver by the portal system and directly connected to the brain by the vagus nerve. Microbial metabolites can directly influence this organ through these connections and indirectly influence these organs by regulating the immune system. NAFLD: Non-alcoholic fatty liver disease.

interleukins associated with allergic disorders, IL-4 and IL-5 in ovalbumin-induced allergy models[13].

RELATIONSHIP BETWEEN GUT MICROBIOME AND DIFFERENT INFLAMMATORY DISEASES

Gut microbiome and metabolic syndrome

Dysbiosis of gut microbiota hampers the normal physiological functioning of the host. Various pathological conditions, such as metabolic diseases like diabetes and obesity, inflammatory disorders like inflammatory bowel syndrome, ulcerative colitis, and CD, and even psychological disorders like anxiety, depression, and attention deficit hyperactivity disorder have shown links to gut microbial dysbiosis in their manifestations[33,34]. Metabolic disease refers to diseases that affect the body's processing and distribution of macronutrients like carbohydrates, protein, and fats, hence disrupting normal metabolism and the process of converting food to energy on a cellular level. Chronic low-grade inflammation is thought to be a defining feature of metabolic diseases, such as NAFLD, diabetes mellitus, obesity, and atherosclerosis. The pathophysiology of metabolic illness is significantly influenced by the interaction between immune cells and parenchymal cells in highly metabolically active organs including the liver and adipose tissue[35-37]. It was also found that the ratio of Firmicutes to Bacteroidetes is affected in metabolic diseases. In addition, there is an increase in Proteobacteria that elevates the levels of branched chain amino acids in the bloodstream. As *Bacteroides thetaiotaomicron* is the microorganism that transforms glutamate into glutamine, it was also discovered that in obesity, microbiota was linked to elevated serum glutamate levels.

In a study by Li *et al*[38], significant decreases in *Bifidobacterium* and *Akkermansia* and a significant increase in *Dorea* led to T2D. *Dorea* has been previously reported to be negatively associated with the abundance of butyrate-producing bacteria. Other operational taxonomic units (OTUs) belonging to members of the families Lachnospiraceae, Dorea, Clostridiales, and Clostridiaceae as well as the genera *Bifidobacterium*, *Parabacteroides*, *Oscillospira*, and *Bacteroides* were associated with T2D samples other OTUs from these families were associated with healthy samples. Some recent studies have that increases in the abundance of *A. muciniphila* and *F. prausnitzii*, which regulate metabolism and seem to have benefits associated with preventing the development of obesity, T2D, and atherosclerosis, have also observed in pre-diabetes, and decreased abundance of *A. muciniphila* and *F. prausnitzii* in T2D. Treatment with *A. muciniphila* decreases both body weight and accumulation of fat mass by 40% to 50% in high fat diet induced mice model. Furthermore, it tended to ameliorate insulin resistance and glucose intolerance independent of growth media and food consumption[39]. Surprisingly, they found that pasteurizing *A. muciniphila* improved its ability to lessen the formation of fat mass, insulin resistance, and dyslipidemia in mice. A literature review reported that Amuc_1100, a protein isolated from the outer membrane *A. muciniphila* interacted with TLR-2, remained stable at pasteurization temperatures, enhanced the gut barrier, and partially recapitulated the positive effects of the bacterium. This finding highlights the critical fact that live bacteria can also modulate the host immune system. An interesting study conducted by Yang *et al*[40] in 2019 in a mouse diabetes model found that homozygous db/db diabetic mice with a spontaneous mutation of the leptin receptor (*Lepr*^{db}), had five-fold higher blood LPS levels than their littermates, which indicated increased intestinal permeability in the db/db mice compared the littermates. The colons of the db/db mice had significantly decreased levels of ZO-1 mRNA and protein. The abundance of seven genera (*Allobaculum, Faecalibacterium, Ruminococcus, Prevotella, Bifidobacterium, Oscillospira,* and *Mucispirillum*) was decreased ($P < 0.05$). Conversely, the abundance of five taxa: *Arthromitus, Anaerofustis, Streptococcus, Candidatus* and *Helicobacter* increased ($P < 0.05$) in the gut microbiota of db/db mice. The study also found that diabetes significantly reduced the abundance of *Faecalibacterium prausnitzii* in the gastrointestinal tract, caused compositional dysbiosis of the gut microbiota, and compromised the integrity of the gut barrier. Microbial anti-inflammatory molecules (MAMs) derived from *Faecalibacterium prausnitzii* repair the gut barrier in diabetics, possibly by

controlling the tight junction pathway. *Faecalibacterium prausnitzii, Akkermansia muciniphila, Bifidobacterium catenulatum,* and *Bacteroides thetaiotaomicron* are some of the important gut microbial species that are associated with the healthy individuals, and decreased abundance of these species results in metabolic changes causing pathological conditions like diabetes and obesity. *Dysosmobacter welbionis* has beneficial properties comparable to those of *A. muciniphila*. When diet-induced obese and diabetic mice were supplemented with live *D. welbionis J115T* (1.0 × 109 daily), as opposed to the same pasteurized strains, inflammation, hypertrophy of white adipose tissue, and accumulation of fat body were reduced. Giving the mice *D. welbionis J115T* protected them from inflammation of adipose tissue that was correlated with an increase in the number of mitochondria number[41]. Daily administration of *Christensenella minuta* (2×10^9 bacterial cells) decreased hepatic triglycerides and free fatty acid accumulation, prevented adipogenesis, and preserved the integrity of the gut epithelium in diet-induced obese mice. It also prevented weight gain and decreased glycemia and plasma leptin levels.

Multi-Species probiotic strain mixture improves intestinal Barrier function in LPS stimulated Caco-2 cells *via* controlling inflammation and tight junctions thereby enhancing transepithelial electrical resistance[42]. Satiation plays an important role in metabolic disorders. Two hormones, glucagon like peptide 1 (GLP1) and pancreatic peptide YY secreted by enteroendocrine L cells, along with ghrelin, insulin and leptin from the stomach, pancreas and adipose tissue, respectively act to control the appetite *via* several neurohormonal pathways. In a study by Lam *et al*[37], vancomycin treatment decreased circulating leptin level in rats. In studies conducted in male rats, *Bifidobacterium*, *Lactobacillus, Mucispirillium, Lactococcus* and an uncultured member of family *Lachnospiraceae* were found to be positively correlated with circulating leptin concentrations and *Clostridium, Bacteroides, Prevotella*, and *Allobaculum* were negatively correlated [43,44]. *Bacteroides* and *Prevotella* spp. were reported to be positively correlated, and *Bifidobacterium, Lactobacillus,* and *B. coccoides–E. rectale* were negatively correlated[45]. A similar study found that *Clostridium spp. and B. intestinalis* were positively correlated with insulin levels[46]. Bacterial transfer from lean donors to metabolic syndrome patients resulted in an increase of butyrate-producing microbes[47]. Germ-free mice have low GLP-1 levels, and treatment with probiotics like *B. breve, B. longum, B. infantis, L. acidophilus, L. plantarum, L. paracasei, L. bulgaricus,* and *Streptococcus thermophilus* increase GLP1 levels (Figure 7).

Gut microbiome and inflammatory bowel disease

An imbalance of the microbial equilibrium allows pathogens to colonize and invade the gut, increasing the likelihood of a host immunological reaction and encouraging the onset of IBD. It is important to emphasize that the pathogenesis of IBD involves fluctuations of gut microbiota composition that are greater than those seen in healthy individuals[48]. Compared to healthy individuals, various bacteria such as *Bifidobacterium longum*, *Eubacterium rectate, Faecalibacterium prausnitzii,* and *Roseburia intestinalis* are reduced in ulcerative colitis and CD and harmful bacteria including, *Ruminococcus* spp. and *Bacteroides fragilis* are increased. Pathogenic bacteria such as Prevotellaceae and *Helicobacter* participate in dextran sodium sulfate-induced (DSS) enteritis in BALB/c mice. Researchers have found that *Peptostreptococcus* commensal bacteria can produce indole propionic acid that influences goblet cells to secrete mucin, which is highly reduced in DSS-induced murine groups. Tryptophan is converted to serotonin by *Bacteroides*. Serotonin is the precursor of melatonin and can have a variety of effects by attaching to various serotonin receptors, particularly in the control of intestinal inflammation. In mice with induced IBD, bacterial tryptophan metabolism decreases, leading to disruption of the intestinal microenvironment and the onset of enteritis. When the genomic abundance of *Clostridium hathewayi, C. bolteae*, and *R. gnavus* in *in-vivo* mouse models were compared, it was discovered that the transcriptional activity of *C. bolteae* and *R. gnavus* was significantly increased in mice with IBD, suggesting that they may be important regulators of IBD. In mice with colitis induced by dinitrobenzene sulfonic acid, commensal bacteria such as *F. prausnitzii* provided protection[49]. Furthermore, studies have demonstrated that MAM, a protein unique to *F. prausnitzii*, suppressed the NFB pathway in gut-based tissue and resisted inflammation. A lower abundance of this specific bacterium resulted in the risk of occurrence of IBD. Mice with induced IBD had markedly reduced numbers of SCFA-producing bacteria in their feces, which in turn caused a decrease in intestinal SCFAs and an increase in intestinal inflammation[50,51].

POSSIBLE THERAPEUTIC APPROACHES TO RECREATE EUBIOTIC GUT STATE FROM DYSBIOSIS

Over the last 10 years, a significant amount of research has been conducted on microbiome-immune interactions, which has improved our understanding of their molecular underpinnings and highlighted their significance in relation to a range of disorders in humans. These discoveries are already accelerating the creation of microbe-mediated disease treatment. Hence modulation of gut microbes is an important avenue not only for amelioration of various diseases but also for the well-being of the host. Diet is the most important component that can directly affect the gut microbial composition. A varied and stable population of gut microbiota can be fostered by eating a diet high in a variety of fibers with various physicochemical characteristics, such as chain length, molecular weight, solubility, viscosity, water-holding capacity, binding skills, fermentability, and monosaccharide composition. Fibrous foods also include bioactive compounds like polyphenols that encourage the diversity of bacteria in the gut. For a fiber to be categorized as prebiotic, it must be selectively utilized by host microbes, resulting in a positive impact on health. The fructo-oligosaccharides (FOS) in prebiotic fibers, galacto-oligosaccharides, and inulin are the most widely investigated. Plant extracts rich in polyphenols may also act as prebiotics under certain conditions. Administration of FOS two times daily in inflammatory bowel syndrome (IBS) patients resulted in improved clinical features along with an increased abundance of *Bifidobacteria*. Inulin (oligofructose enriched) dissolved in boiled water (1 × daily), when administered to obese children 7-12 years of age resulted in a significant decrease in body mass index (BMI) and increase in the abundance of *Actinobacteria* and

	Microbes associated with disease	Microbes associated with health
Diabetes	*Prevotella copri* *Bacteroides vulgatus* *Dorea, Allobaculum* *Clostridiales, Clostridiaceae* *Streptococcus, Candidatus,* *Arthromitus, Anaerofustis* *Helicobacter, Clostridium,* *Bacteroides*	*Faecalibacterium prausnitzii,* *Akkermansia muciniphila,* *Bifidobacterium catenulatum* *Bacteroides thetaiotaomicron* *Dehalobacterium, Oscillospira,* *Ruminococcus, Lactococcus* *Christensenella minuta* *Lactobacillus, Mucispirillium,* *Dysosmobacter welbionis* *B. breve, B. longum, B. infantis,* *L. acidophilus, L. plantarum,* *L. paracasei, L. bulgaricus* *Streptococcus thermophilus*
IBD (inflammatory bowel disease)	*Ruminococcus strains* *Bacteroides fragilis* *Prevotellaceae* *Helicobacter* *Clostridium hathewayi* *C. Bolteae* *R. gnavus*	*Eubacterium rectate,* *Faecalibacterium prausnitzii* *Roseburia intestinalis* *Peptostreptococcus* *Bacteroides* *B. vulgatus,* *Alistipes putredinis*

Figure 7 Balance of the abundance of positive and negative microbiome taxa governs manifestation of diseases like diabetes and inflammatory bowel disease.

Bifidobacterium. In addition to prebiotics, probiotics also play an important role in restoring gut health. The World Health Organization defines probiotics "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host". *Bifidobacterium* (*adolescentis, animalis, bifidum, breve* and *longum*), *Lactobacillus* (*acidophilus, casei, fermentum, gasseri, johnsonii, paracasei, plantarum, rhamnosus* and *salivarius), Streptococcus,* and *Saccharomyces* are some of the most commonly used probiotics. Probiotics compete with pathogens and colonize the host digestive system, helps in the fermentation of food, and supply the host with useful byproducts. In some cases, they complement host deficiency of gene materials by products of their own genes. Postbiotics are byproducts that the host produces when it breaks down probiotics and prebiotics, like vitamins, amino acids, and antimicrobial peptides that aid in inhibiting the growth of pathogenic bacteria. Postbiotics may have protective modulations against pathogens often by competing for adhesion sites. They can also affect epithelial barrier function and modulate immune function (Figure 8).

Recent research focused on fecal microbial transplantation as a therapeutic approach to treat diabetes-based gut microbial dysbiosis. Various studies conducted in both mice and humans showed that fecal microbiota, when transplanted from healthy to unhealthy gut microbiota, ameliorated disease symptoms and prevented progression of the disease while disease symptoms were manifested when the diseased microbiota was implanted in a healthy host. A study of adoptive fecal microbiome transplantation by Markle *et al*[52] showed how microbes regulated the sex hormone testosterone and the immune system and interacted to bring about the pathophysiology of type 1 diabetes (T1D) in nonobese diabetic (NOD) mice. NOD specific pathogen free (SPF) mice have a > 2:1 female-to-male sex skew and spontaneous, immune-mediated pancreatic beta-cell death that lead to (T1D), which has a complicated genetic and environmental etiology. However, for the same strain in germ-free conditions (GF NOD), the incidence of T1D was equal in males and females. Comparing GF females to SPF females, the levels of testosterone were higher ($P < 0.05$) in the former case, and lower ($P < 0.05$) in the latter, suggesting that testosterone synthesis was regulated by commensal colonization (SFB, *E. coli*, and Shigella-like bacteria).

Serum concentrations of long-chain fatty acids derived from sphingolipids and glycerophospholipids decreased following transfer of male, but not female, microbiota, indicating that the metabolic outcome in the recipient was related only to the sex of the microbiome donor. They also investigated whether intestinal epithelial cells, which are constantly shed into the gut lumen, were present in the gavage inoculum and had an impact. After obtaining pure splenic T cells from either unaltered NOD females, M→F gavage receivers, or M→F gavage recipients that were administered flutamide to counteract Androgen signaling, the cells were injected intravenously into NOD-severe combined immunodeficiency disease (SCID) recipients.

As mice with SCID lack T cells of their own, the only T cell they had were from the donor mice. Female mice who received T cells from males (M→F gavage recipients) were protected against the disease ($P < 0.002$ compared with the two other groups). Hence the interconnected and intertwined complex networks of various gut microbes with other host systems are certainly an important area to investigate in future.

DRAWBACKS AND LOOSE ENDS IN MICROBIOME-IMMUNITY RESEARH

The gut microbiome is an immensely complex network of organisms that is influenced by various external factors, making gut microbiome research quite challenging. The majority of gut microbiome studies use 16s-RNA sequencing to identify bacteria to the genus and not the species level. Most studies are focused on gut bacterial diversity, hence the roles

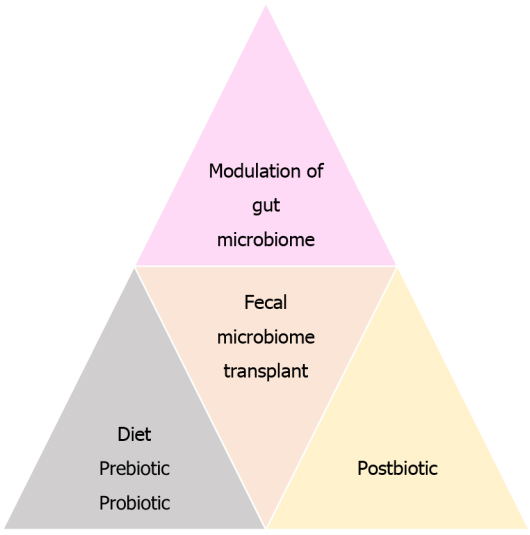

Figure 8 Modulation of the microbiome by diet, prebiotics, probiotics, postbiotics, and fecal transplantation as therapeutic interventions against dysbiosis-associated disease.

of viruses, fungi and parasites are often overlooked. A direct relationship between the gut microbiome and immune parameters before the onset of a disease or in acute or chronic disease is yet to be discovered. A critical problem often faced in microbiome studies is whether the results obtained in laboratory mice are at all transferable to human disease. This problem can be easily overcome by investigating functional aspects of the gut microbiome, that is, microbial metabolites, which vary the least among species. The abundance of gut microbiome species is more variable than its functional properties. Finally, the intrinsic inter-individual variability and related complexity present both a significant potential and a big experimental problem.

Hence exploration of networks of microbial metabolites will become an important area of study because identifying only the microbial species may not provide us with a comprehensive overview of the anomalies occurring in the gut. Positive modulation of beneficial gut microbiome by incorporation of prebiotics and probiotics along with dietary modifications may serve as a therapeutic and prophylactic methods in a number of inflammatory diseases such as IBD and metabolic diseases like diabetes and obesity.

CONCLUSION

Gut microbe and immunity: Perspective on their inter-relationship

Gut microbial ecosystem is a complex ecological system with intricate networks of bacteria, fungi, viruses and interactions with host cells that affect homeostasis. These microbes have long coevolved with their host species. They have colonized their specific hosts by interacting with the host immunity, thereby making the gut microbiome an important area to consider. Interactions between the gut microbiome and the immune system occur at multiple levels and ultimately maintain normal homeostasis in the host. The Gut microbiome differs largely not only at species level but also at individual level. The resilience and resistance of the gut microbiome maintain the ecological diversity and function of the microbial ecology within the host. In response to external pressure from the environment, the healthy state of the microbiota shifts to an alternate state where although the diversity and abundance of the microbiome are different, the functional integrity remains unchanged. But change in microbial profile past a tipping point may result in dysbiosis. Dysbiosis in the gut microbiome can be linked to various diseases, especially inflammatory and metabolic disorders. Numerous studies have linked specific diseases to dysregulation in gut microbial species and their functional metabolites. Hence, gut microbial studies have become increasingly important areas of research for the future. Mouse models are commonly used to study human diseases, although their gut microbiome profile differs from that of humans. Nonetheless, the functional orientation of their gut microbial networks is quite similar, as many microbes share a common repertoire of genes that serve the same collective function. Therefore, modulation of gut microbial metabolites with the help of various therapeutic approaches will be an important area to investigate as treatment of chronic disorders like diabetes, obesity and inflammatory bowel syndrome. In time, gut commensals may be recognized as gut mutuals for the benefits they provide to their immediate host. Hence focusing on functional aspects of gut microbiome apart from the compositional aspects is essential as majority of the experiments occur in laboratory mice but the long-term focus is human health benefits.

The taxonomic similarity of phyla and genera shared by humans and mice is 90% and 89%, respectively. Functional parallels between these host-specific microbiotas make it easier to translate microbiota-related studies from mice to humans. Butyrate metabolism is one example of how conserved metabolic processes are frequently carried out by extremely diverse species among hosts. Butyrate, a short-chain fatty acid, is the primary energy source for intestinal enterocytes and a key factor in preserving the oxygen-free environment of the gut. Butyrate is linked to a number of

immunological and metabolic pathways, including the stimulation of peripheral Tregs, according to previous studies of the metabolic syndrome and IBD. Fewer than 3% of microbial species are taxonomically shared by humans and mice, so there is a high probability of a lack of relevance between preclinical and clinical research. Mere phenotypic identification of the species present in preclinical mouse models may not mimic human conditions. However, there are significant functional parallels between these host-specific microbiotas that make it easier to translate microbiota-related studies from mice to humans like the butyrate metabolism, which is carried out in extremely diverse host species. Therefore, functional microbial network studies become extremely important for translating data to human from preclinical studies.

The ecological landscape of the gut microbiome is versatile and is established in the uterus. Dynamic changes in the gut microbiome occur in the early stages of life and is affected by the mother's vaginal, skin, and milk microbiome. The intestinal microbiota plays an important role in child growth by participating in the metabolism of human milk oligosaccharides[53]. States of healthy and restricted systemic growth in childhood may be regulated by the mutual interaction of the gut microbiota, growth hormone/insulin-like growth factor 1 GH/IGF1 somatotropic axis, and nutritional status[54]. Moreover, hormones important for controlling host metabolism and appetite are influenced by the composition of the gut microbiota. Studies have shown that vancomycin-treated rats had decreased leptin levels[55]. *Bactroides* and *Pervotella* were positively correlated and *Bifidobacterium* and *Lactobacillus* were negatively correlated with leptin and ghrelin levels in male rats. The transition from breast milk to solid food marks the first big change in gut microbial composition followed by puberty and adolescence with shifts of the microbiota toward sex-specific dimorphism. Dramatic remodeling of gut microbiota is also observed in pregnancy. Comparison of trimester 1 (T1) and trimester 3 (T3) pregnancies shows an increase in Proteobacteria and Actinobacteria and a decrease in alpha diversity over the course of pregnancy. Transfer of human fecal microbiota from T3 pregnancies to GF mice resulted in increase in adiposity and blood glucose level mimicking the metabolic changes that occur during later stages of pregnancy. Contrary to obesity and diabetes, which cause Bacteroidetes to become less abundant, the relative abundance of Firmicutes and Bacteroidetes remains mostly unchanged during pregnancy. Instead, low taxonomic richness and reduced homogeneity led to an increase in Proteobacteria, which has been associated with increased efficiency of energy production during pregnancy[56]. As adulthood approaches, changes in immunology, mucosal function, food, metabolism, illness and other variables may account for ongoing variation in the growth of the gut microbiome. Similar to pregnancy, changes of the gut microbiota occur during menopause. A study by Peters *et al*[57] included 2300 participants, among whom 295 were pre-menopausal, 1027 were post-menopausal, and 978 were male controls who were matched to pre- and post-menopausal women by age, BMI, and Hispanic/Latino background. The control patient groups had reduced alpha and beta diversity. The composition of the post-menopausal microbiome was more like that of adult men than that of premenopausal. Menopause was linked to decreases of *Escherichiacoli-Shigella spp., Oscillibacter sp. KLE1745, Akkermansia muciniphila, Clostridium lactatifermentans, Parabacteroides johnsonii, and Veillonella seminalis*, and increase in *Bacteroides sp. Ga6A1, Prevotellamarshii,* and *Sutterella wadsworthensis*. Diversity of the gut microbiome peaked at around the fourth decade of life, and the composition shifted with age to become adapt to each individual. The microbiota of younger adults differed from that of extremely long-lived people (*i.e.* nonagenarians and centenarians). Some gut microbiome traits, including high uniqueness and lower dominance of Bacteroides have been linked to healthy ageing and longevity[58]. The modifiable nature of the gut microbial composition helps to better understand its role at every stage of life, which will be critical in the identification of novel opportunities for well-being and health.

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Country of origin: India

ORCID number: Akashlina Marik 0000-0002-3630-9435; Ena Ray Banerjee 0000-0002-6180-4825.

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