Digestion

Review

Digestion
DOI: 10.1159/000525925

Received: June 10, 2022
Accepted: July 1, 2022
Published online: July 28, 2022

# Alteration of the Gut Microbiome in Inflammatory Bowel Disease

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**Keywords**
Short-chain fatty acids · Butyrate · Mycobiome · Virome

**Abstract**
***Background:*** Alteration of the gut microbial structure and function (dysbiosis) is associated with the pathogenesis of various disorders including inflammatory bowel disease (IBD). ***Summary:*** Under normal conditions, β-oxidation of butyrate consumes oxygen in colonocytes and maintains the anaerobic environment in the lumen. Depletion of butyrate-producing bacteria results in anaerobic glycolysis in colonocytes and increases oxygen diffusion into the lumen, leading to a luminal facultative anaerobe expansion. Dysbiosis in IBD is characterized by the reduced abundance of the phylum Firmicutes (e.g., *Faecalibacterium*, *Roseburia*, and *Ruminococcus*) and an increase of the phylum Proteobacteria (e.g., *Enterobacteriaceae*). The overall structure of the gut mycobiome differs markedly in IBD patients, particularly Crohn's disease (CD), compared with healthy individuals. An increase in the genus *Candida* is a major contributory factor in the alteration of the mycobiome in Japanese CD patients, but an increase in the genus *Saccharomyces* is characteristic in Western patients. The gut virome, which is mainly composed of bacteriophages (phages), influences gut homeostasis and pathogenic conditions via an interaction with the gut bacterial community. Alterations in the gut virome have been suggested in patients with IBD. This may alter either the immunogenicity of bacteria, thus affecting the bacteria-host interactions, or the bacterial functions such as antibiotic resistance and toxin synthesis. ***Key Message:*** Advances in DNA sequencing technology and bioinformatics have revolutionized our understanding of the microbiome in the gut.



## Introduction

Inflammatory bowel diseases (IBDs), comprising Crohn's disease (CD) and ulcerative colitis (UC), are complex chronic inflammatory disorders of the gastrointestinal (GI) tract with unknown etiology. The number of patients with IBD is continuously growing in Western countries, and this trend has shifted to newly industrialized countries in Asia and South America in recent decades [1, 2]. This phenomenon is associated with the westernization of diets and environments, which modulate the gut microbiome and increase the risk of IBD onset in genetically susceptible hosts [1, 2].

The lower part of the GI tract has an enormous and complex ecosystem comprising microorganisms such as bacteria, fungi, viruses, and other organisms [3–5]. Crosstalk between the gut microbiome and the gut immune system is important for maintaining homeostasis of the

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GI tract, and an alteration of the diversity and composition of the gut bacteriome (dysbiosis) plays a crucial role in the pathogenesis of IBD [6–8]. Recent studies have reported marked changes in the gut mycobiome and virome in patients with IBD. This mini-review summarizes the recent findings of the gut bacteriome, mycobiome, and virome in IBD [8–11].

## Gut Bacteriome

Bacteria make up the majority of the gut microbiome with 100 trillion cells of more than 1,000 species, and this community comprises 100-fold more genes than the human genome [12]. Over 99% of the gut bacteriome is composed of species within 4 phyla: Firmicutes (60%~), Bacteroidetes (20%~), Proteobacteria, and Actinobacteria [12]. The bacterial load is lowest in the upper GI tract (stomach 0–$10^2$ cells/g luminal contents, duodenum $10^2$, proximal ileum $10^3$) and gradually increases by $10^7$–$10^8$ in the terminal ileum and $10^{12}$ in the colon [12]. This microbial profile can be modulated by factors such as genetics, birth route, diet, hygiene, psychological distress, environment and lifestyle, infection, and medications, especially antibiotics [13].

## Short-Chain Fatty Acids

The metabolites of the gut microbiome strongly influence favorable relationships and beneficial interactions within the gut microorganisms themselves and with the host. One such group of critical metabolites is the short-chain fatty acids (SCFAs): propionate, butyrate, and acetates. In the colon, SCFAs are produced through fermentation of undigested carbohydrates by obligate anaerobes (mainly *Firmicutes* and *Bacteroidetes*) that collaborate with bacteria specialized in oligosaccharide fermentation (e.g., *Bifidobacterium*) [14–16]. SCFAs, particularly butyrate, are a primary energy source for colonic epithelial cells (ECs), and it is estimated that they provide 10% of the total dietary energy supply in humans [17]. Butyrate and propionate can regulate intestinal physiology and immune function, while acetate acts as a substrate for lipogenesis and gluconeogenesis [18].

SCFA levels are associated with fermentation and are mainly determined by microbial composition. The majority of fermentation occurs in the proximal colon, but the gut microbiota uses other substrates (e.g., protein or amino acids) in the distal colon due to the depletion of carbohydrates. The colonic pH is therefore lower in the proximal colon where fermentation is highest (pH 5.5–6.5) compared to the pH in the distal colon (pH 6.5–7.0) [19]. Fermentation of amino acids leads to the generation of a range of potentially harmful compounds like ammonia, phenols, p-cresol, certain amines, and hydrogen sulfide. Some of these compounds may be involved in diseases of the digestive system such as colon cancer or IBD. In contrast, high luminal SCFAs inhibit the growth of gram-negative Enterobacteriaceae including the familiar pathogens *Salmonella* spp. And *Escherichia coli* [19, 20] contribute to the maintenance of a favorable environment in the colon.

The dominance of obligate anaerobes such as the phyla Firmicutes and Bacteroidetes in the colon is closely associated with the strict anaerobic environment. Colonic ECs (colonocytes) are the main cellular source of oxygen in the colon [21, 22], and oxygen diffusing from colonocytes into the lumen is strictly limited. Surface colonocytes contain less than 1% oxygen, but host tissues contain between 3% and 10% oxygen. The intracellular hypoxic condition of colonocytes is mediated by oxygen consumption within themselves through mitochondrial β-oxidation of bacteria-derived butyrate to carbon dioxide which represents their main pathway for producing energy [21] (Fig. 1). Depletion of butyrate-producing bacteria reduces luminal butyrate levels, resulting in a metabolic reorientation of surface colonocytes toward anaerobic glycolysis and an increase of oxygen diffusion into the lumen, thereby driving a luminal aerobe and/or facultative anaerobe expansion by aerobic respiration.

## Bacterial Tryptophan Metabolism

Tryptophan plays crucial roles in the balance between intestinal immune tolerance and gut microbiota maintenance. Tryptophan can be converted into bioactive indole-containing metabolites (indole, indolic acid, skatole, and tryptamine) by gut bacteria [23], and indole derivatives affect the host by activating aryl hydrocarbon receptor (AhR). AhR activation promotes host immune homeostasis via two mechanisms. First, AhR stimulates interleukin (IL)-22 secretion from $CD4^+$ T cells and innate lymphoid cells in the gut. IL-22 can induce the release of antimicrobial peptides and modulates microbial composition. Second, AhR signaling mediates the development of intraepithelial lymphocytes and innate lymphoid cells and plays an anti-inflammatory role. Further, indoleacrylic acid, a specific indole derivative produced by the

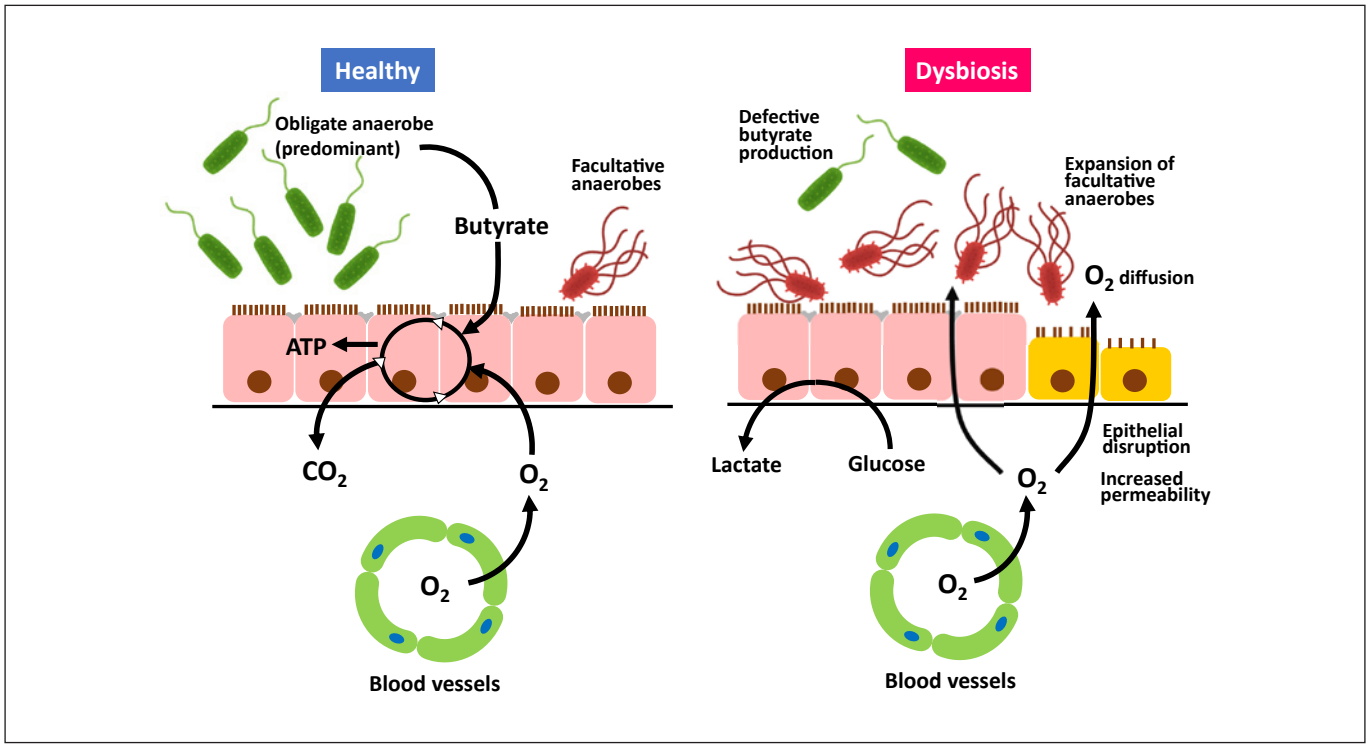


**Fig. 1.** Butyrate production by obligate bacteria is important for maintaining homeostasis in the colon. Under normal conditions, β-oxidation of obligate anaerobe-derived butyrate consumes oxygen and induces epithelial hypoxia, which maintains an anaerobic environment in the lumen of the colon. In turn, the luminal anaerobic environment maintains a predominance of obligate anaerobes within the gut bacteriome. On the other hand, gut dysbiosis induces anaerobic glycogenesis in colonocytes, which leads to increased epithelial oxygenation. This epithelial dysfunction disrupts the anaerobic environment in the lumen, thereby driving an expansion of facultative anaerobes such as Proteobacteria. This is a modified version of the original picture that appeared in *Science* [22] under permission number 5295780022586.

mucus-utilizing bacterium *Peptostreptococcus*, induces mucin gene expression and activates the nuclear factor erythroid 2 related factor 2 pathway [24]. This indicates that a tryptophan derivative produced by gut bacteria increases mucus production and decreases inflammatory cytokine secretion. In a human study, patients with IBD exhibited reduced tryptophan metabolism, presumably due to an altered bacterial gut community [25]. On the other hand, approximately 95% of the ingested tryptophan is degraded to endogenous tryptophan metabolites such as kynurenine and kynurenic acid, and these can also function as direct AhR ligands [23].

### Bile Acid Metabolism

Bile acids are metabolized by the gut bacteria, and this is a central process for maintaining homeostasis in the GI tract [26]. Liver-derived primary bile acids (PBAs), such as cholic acid and chenodeoxycholic acid (CDCA), are conjugated with glycine or taurine to increase water solubility before excretion into the biliary duct. These PBAs promote lipid digestion and absorption via their amphipathic properties in the small intestine. Conjugated PBAs are metabolized by two bacteria-mediated processes, bile acid deconjugation and 7α-dehydroxylation [26, 27]. The first step is mediated by bile salt hydrolases, which deconjugate taurine and glycine from conjugated forms and reform the unconjugated PBAs. Bile salt hydrolases are widely distributed across gram-positive and gram-negative bacteria in the gut including species belonging to the *Clostridium*, *Bifidobacterium*, *Bacteroides*, *Lactobacillus*, and *Enterococcus*. In the terminal ileum, 95% of deconjugated PBAs are reabsorbed via the apical sodium-dependent bile salt transporter, while the remaining 5% enter the colon [28]. The second step is 7α-dehydroxylation in the distal ileum and colon, by which unconjugated PBAs (cholic

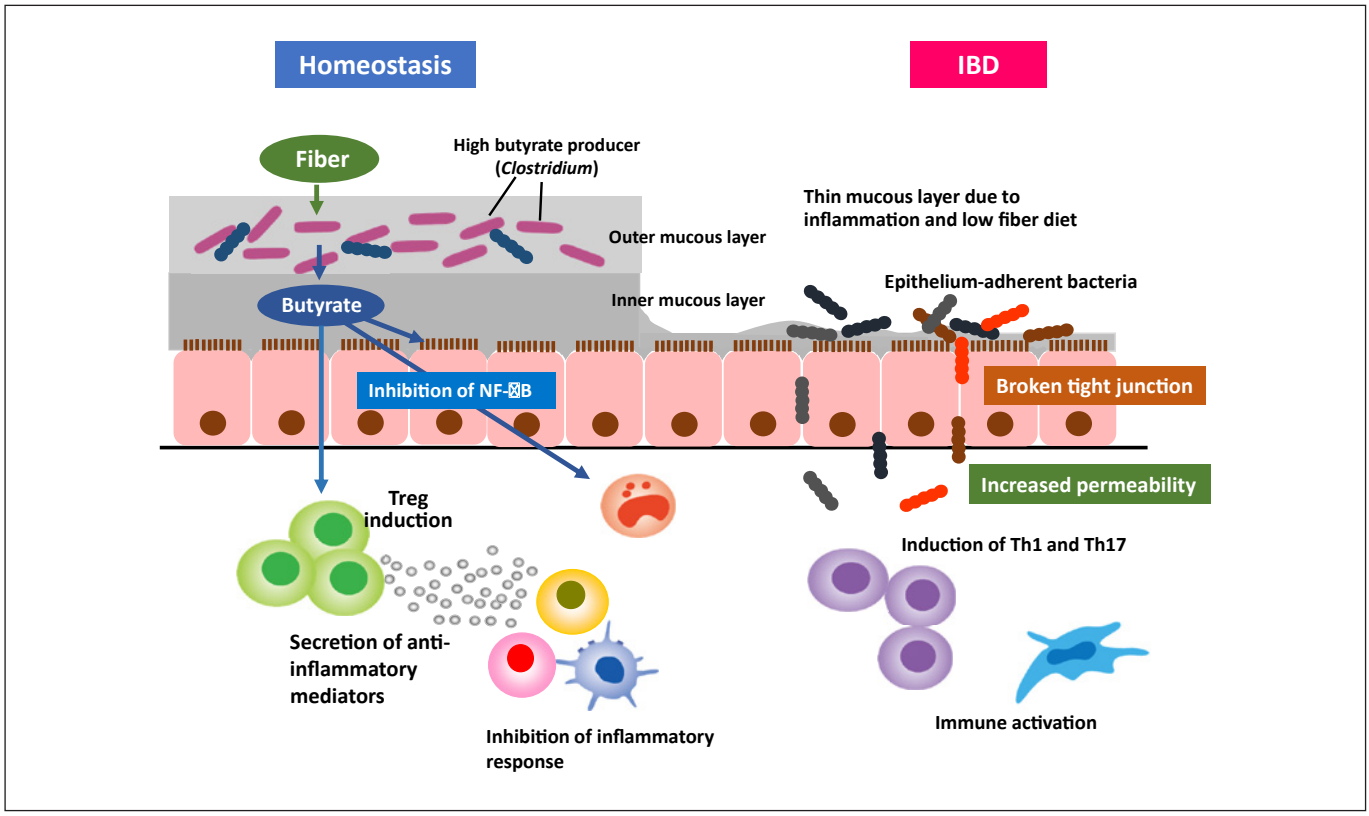


**Fig. 2.** Role of gut microbes and short-chain fatty acids (SCFAs) in mucosal immune responses. Butyrate, derived from high butyrate-producing bacteria (e.g., the order Clostridiales), induces regulatory T cells (Tregs) and inhibits NF-κB activation in various cells. The action of butyrate is mediated by the inhibition of histone deacetylase activity. On the other hand, a low-fiber diet is associated with a thinning of the mucous layer and induces easy access of bacteria to the epithelial cells. Th17 cell induction is mediated by epithelial cell-adhesive bacteria spp. This figure is a modified version of the author's picture that first appeared in *Digestion* 2016; 93:176.

acid and CDCA) are converted to secondary bile acids such as deoxycholic acid and lithocholic acid [26, 27]. At present, only a few bacteria are known to mediate this step [26]. Ursodeoxycholic acid is another secondary bile acid in humans that is produced in small quantities following epimerization of the 7α-hydroxyl group of deconjugated CDCA.

### Regulation of Immune and Inflammatory Responses

Regulatory T cells (Tregs) are a subpopulation of T cells that modulate the immune system, maintain tolerance to self-antigens, and abrogate autoimmune disease [29]. These cells generally suppress or downregulate the induction and proliferation of effector T cells. Previous studies have demonstrated that *Clostridium* is a strong inducer of Tregs through butyrate production [29–31] (Fig. 2). In germ-free mice, a reduced luminal concentration of SCFAs is accompanied by impaired development of intestinal Treg cells [31, 32]. Therefore, a decrease in the relative abundance of butyrate-producing bacteria, such as *Faecalibacterium prausnitzii*, may lead to a disruption in mucosal homeostasis [33].

The gut bacteria also play a crucial role in the induction of effector T cells in the GI tract. Th17 cells are a class of $CD4^+$ T cells characterized by the secretion of IL-17A, IL-17F, IL-21, and IL-22 [34]. Aberrant regulation of Th17 cells plays a significant role in the pathogenesis of inflammatory and autoimmune disorders [34]. The EC-adhesive character of microbes is crucial for induction of Th17 cells in the mucosa [35]. Moreover, it has been reported that a mixture of 20 bacterial strains, isolated from a patient with UC, stimulated Th17 induction and exhibited EC-adhesive characteristics [35].

### Epigenetic Modulation of Gene Expression by Butyrate

SCFAs, particularly butyrate, have strong anti-inflammatory effects via modulation of the production of inflammatory mediators in many cell types [36]. These effects are mediated by the inhibition of histone deacetylase (HDAC) activity. HDAC activity, combined with histone acetyltransferases, regulates the degree of protein acetylation. By inhibiting the HDAC activity, butyrate induces a hyperacetylation of histone and nonhistone proteins [37, 38]. Histone hyperacetylation leads to a more relaxed chromatin structure, thus facilitating transcription factor access to the promoter regions of certain genes [39]. In contrast, butyrate downregulates the activation of transcription factors including NF-κB and modulates gene expression.

### Altered Gut Bacteriome (Dysbiosis) in IBD

Dysbiosis in the gut is defined as negative alterations of the microbial community, which is associated with health and disease [12]. The global alteration of the gut microbial community, rather than the presence of specific genera, is important in the pathogenesis of IBD. Previous studies using fecal samples identified dysbiosis in IBD, which is characterized by the reduced abundance of the phylum Firmicutes (e.g., *Faecalibacterium*, *Roseburia*, and *Ruminococcus*) and an increase of the phylum Proteobacteria (e.g., *Enterobacteriaceae*) [12, 40–43]. These changes are more prominent in CD than UC [44, 45]. Similar findings have also been reported in mucus samples where the abundance of putative aggressive bacteria, such as the genus *Escherichia*, the genus *Ruminococcus* (*R. gnavus*), and *Fusobacteria* species, is significantly increased and the abundance of bacteria such as the genera *Faecalibacterium*, *Coprococcus*, and *Roseburia* is significantly decreased in CD patients compared to healthy controls [6, 7, 45, 46].

It remains unclear whether dysbiosis in IBD is the cause or consequence of inflammation. Some experimental reports suggest that dysbiosis is a cause of IBD. For example, mice develop more aggressive colitis after the transfer of feces from mice with colitis compared with control mice [7]. In contrast, some findings have suggested that dysbiosis is the response to inflammation. Mucosal defects accompanying bleeding and increased permeability induce a disruption of the anaerobic environment in the colon leading to a reduction of anti-inflammatory activity through the reduced abundance of butyrate-producing obligate anaerobes [21, 42]. As mentioned earlier (Fig. 1), depletion of butyrate-producing bacteria results in a metabolic reorientation of surface colonocytes toward anaerobic glycolysis and an increase of oxygen diffusion into the lumen and induces a luminal aerobe and/or facultative anaerobe expansion by aerobic respiration. Thus, the dysbiosis observed in IBD could be explained by a complex interaction between the decrease of butyrate-producing bacteria, increase of epithelial oxygenation, oxygen diffusion into the lumen, and expansion of facultative bacteria (Proteobacteria). A recent multi-omics study showed functional dysbiosis in the gut microbiome of IBD patients, which is characterized by molecular disruption of microbial transcription, metabolite pools (bile acids and SCFAs), and antibodies in host serum [47].

### Altered Gut Mycobiome in IBD

Fungi have been reported to be detectable in the GI tract in approximately 70% of healthy humans. They account for approximately 0.1% of the gut microbiome and have an antagonistic and/or synergistic relationship with bacteria and viruses in the gut [48]. The number of fungi sequentially increases from the ileum to the colon and reaches a maximum at the distal colon [48]. The diversity and abundance of fungi in the GI tract are much lower than those of bacteria, and their composition is considered to be diverse and unstable [49]. The mycobiome of the human GI tract mainly consists of three major phyla: Ascomycota, Basidiomycota, and Chytridiomycota. The genus *Candida* is predominant, and other fungal genera, such as *Aspergillus, Cryptococcus, Rhodotorula, Mucor*, and *Trichosporon*, are occasionally detectable [48].

There is a growing body of evidence favoring pro-inflammatory roles for the gut mycobiome in the pathophysiology of IBD [50, 51]. However, there are a few reports on the gut mycobiome in the Japanese population. The mycobiome of healthy Japanese mainly consists of the phyla *Ascomycota* and *Basidiomycota* [8]. These are comparable with those of Western populations [10], though there are considerable differences at the genus level. The genus *Saccharomyces* is dominant in both Japanese and Western populations, but other major taxa of the Japanese population, e.g., the genera *Sarocladium* and *Leucosporidium*, were not detected in Western population [10]. In contrast, major taxa reported in Western populations, e.g., the genera *Debaryomyces* and *Penicillium*, were not detected in the Japanese samples [10].

In IBD patients, and particularly in CD, the overall structure of the mycobiome differs markedly from that of healthy individuals [8, 10]. Therefore, the compositional structure of the gut mycobiome differs considerably between Japanese and Western patients with IBD. The phylum Basidiomycota was lower, and the phylum Ascomycota was higher in Japanese IBD patients, but in Western IBD patients, Basidiomycota is higher and Ascomycota was lower. An increase of the genus *Candida* is a major factor contributing to the alteration of mycobiome in Japanese CD patients, but an increase of the genus *Saccharomyces* is characteristic in Western patients.

### Altered Gut Virome in IBD

The gut virome, which is mainly composed of bacteriophages (phages), influences gut homeostasis and pathogenic conditions via an interaction with the gut bacterial community [5, 9, 52]. Viruses that infect prokaryotic cells (bacteria and/or archaea) account for 90% of all viruses, and the remaining 10% are eukaryotic viruses that infect plants and animals including humans [53]. Phages replicate and proliferate in the infected cells (bacteria) and are subsequently released via cell rupture (the lytic cycle) [53, 54]. The lytic cycle modifies the proportion of bacterial strains and is deeply involved in shaping the gut bacterial community. On the other hand, some phages insert their genetic information directly into the genome of the infected cells and transmit viral genomic information to the next generation of host cells (lysogeny) [53, 54]. In the gut, many phages exist in a lysogenic or latent state and are retained as integrated prophages within the host bacterium [5]. This process may alter either the immunogenicity of bacteria, thus affecting the bacteria-host interactions, or the bacterial functions such as antibiotic resistance and toxin synthesis [9, 53].

The human gut virome in healthy individuals is primarily diverse between individuals and temporally stable [55, 56]. In healthy individuals, the order Caudovirales or the family Microviridae phages are predominant, latently infecting their bacterial hosts and generating few viral progenies that may infect and kill other bacteria [55, 57]. In patients with IBD, alterations in the gut virome have been suggested. Pérez-Brocal et al. [58] reported an increase in the abundance of Clostridiales, Alteromonadales, and *Clostridium acetobutylicum*-infecting phages, as well as the Retroviridae family in IBD. Zuo et al. [11] recently reported Caudovirales phage expansion in clinically active UC patients, and this was accompanied by an increased abundance of the *Escherichia* and *Enterobacteria* phages [11]. Norman et al. [52] observed a selective increase in the richness of the Caudovirales phage in IBD patients, indicating that phage expansion was restricted to certain taxa. However, there are still only a limited number of reports on the gut virome of IBD patients.

### Future Directions

In association with industrialization, the number of patients with IBD is growing globally. Alteration of the gut microbiome may be one of the factors contributing to the pathogenesis of IBD. The compositional and functional changes in the luminal and mucosal bacteriome, mycobiome, and virome are reproducibly altered in IBD, and this dysbiosis promotes aggressive mucosal immune responses and injury. However, there are many issues to be clarified, in particular in the mycobiome and virome. These can be identified using available genomic, transcriptomic, and metabolomic technologies and rapidly developing computational and biostatistics tools.

### Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.


### Funding Sources

This work was supported by the Japan Agency for Medical Research and Development (AMED) under Grant No. JP-20gm1010008h9904 (A.A.), in part by a Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan under Grant No. 22K07664 (A.A.), and in part by a Health and Labour Sciences Research Grants for Research on Intractable Diseases from the Ministry of Health, Labour and Welfare of Japan under Grant No. 20FC1037 (A.A.).


### Author Contributions

Akira Andoh and Atsushi Nishida equally contributed to this work.

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