Association of Gut Microbiota with Inflammatory Bowel Disease and COVID-19 Severity: A Possible Outcome of the Altered Immune Response

Anju Kaushal1 · Rashed Noor2

Received: 6 November 2021 / Accepted: 12 April 2022 / Published online: 5 May 2022
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

Abstract
Inflammatory bowel disease could be induced by SARS-CoV-2, involved in alteration of gut microbiota during the respiratory viral infection. Presence of viral RNA in fecal samples for longer period, even after the clearance of the virus from respiratory tract, is suggestive of dysbiosis leading to the poor prognosis of COVID-19 in hospitalized patients. Gut microbiome (GM) plays a significant role to stimulate the modulated antiviral immune response against invading pathogens regulating the physiological homeostasis. GM profile of COVID-19 patients has revealed the drastic depletion of dominant families of commensals in the gut such as, Bacteroidaceae, Lachnospiraceae and Ruminococcaceae to be replaced with Enterococcus, Staphylococcus, Streptococcus, Serratia etc. Immune dysfunction of Th1–Th17 cells along gut-lung axis impairs the mucosal lining translocating the microorganisms including commensals and metabolites to other body organs like lungs, brain, kidney through circulation. These events may cause hyper inflammations associated with excessive secretion of cytokines and chemokines to form the cytokine storm causing ARDS. Gut virome could interact with microbiome and immune cells, help establishing the antiviral immune signaling, important for health maintenance/ or in disease progression. Essentially, these immunological strategies are needed to use in future prospective therapeutics to control the severity events.

Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| AP1          | Activator protein transcription factor |
| ATP-gated P2RX7 receptor | Purinergic P2X receptor ligand-gated ion channel 7; in response to extracellular ATP |
| APCs         | Antigen presenting cells |
| ATG16L1 Gene | Autophagy related 16 like 1 |
| ARDS         | Acute respiratory distress syndrome |
| BP-38-CAP    | Carboxypeptidase derived BP-38-CAP protein |

| CCR          | Chemokine receptor (transmembrane- g protein coupled receptor) |
| CXCL         | Chemokine (C-X-C motif) ligand |
| CX3CR1 +     | Chemokine CX3C motifs receptor 1 |
| Calu3 2B4 cells | CelloSaurus cell line |
| 2′ 3′–cGAMP | Cyclic GAS dimerises to form cyclic GMP-AMP |
| CDN          | Cyclic dinucleotide |
| CTT          | C-terminal tail |
| cGAS-STING pathway | Cyclic GMP-AMP synthase-stimulator of interferon genes |
| CERB         | Cyclic response element binding protein |
| DEX          | Dexamethasone |
| Ffar2        | Free fatty acid receptor |
| GPxs         | Glutathione peroxidase |
| GSK 3 β      | Glycogen synthase kinase 3β |
| GATA 4       | GATA binding protein 4 |
| GALT         | Gut associated lymphoid tissues |
| GAS          | GMP-AMP synthase |

* Anju Kaushal
  anju kaushal186@hotmail.com; anju kaushal186@gmail.com

* Rashed Noor
  rashednoor@iub.edu.bd

1 Auckland, New Zealand
2 Independent University, Bangladesh (IUB), Dhaka, Bangladesh
Introduction

Human physiological homeostasis and onset of disease largely depends on the interactions among the resident microbiome of different habitats, such as skin surface, oral cavity, respiratory tract, gastrointestinal system, genital area, and host’s protective immunity [1, 2]. The gut dysbiosis could also be linked with various diseases like, rheumatoid arthritis, cancer, obesity, diabetes, cardiovascular diseases and infectious diseases [1].

The gut microbiome has the capacity to influence innate and adaptive immune arms and mediate the interactions among immune cells by secreting secondary metabolites to balance the inflammatory response against the pathogens. Induction of type I IFNs create the antiviral state; however, any change occurs in microbiota could result in debilitating hyperinflammation instigating the opportunistic pathogens to propagate [1, 3, 4]. Gut microflora like Faecalibacterium prausnitzii, Eubacterium rectale and bifidobacteria (probiotics in stomach and intestine) harbor the immunomodulatory properties, noted to be depleted in hospitalized patients even after the disease resolution than healthy individuals [5].

Recent studies in metagenomics have also revealed the phenomenal association of virome, microbiome and immune cells. Virome/microbiome linkage may regulate the immune cells like T-cells, B-cells, NK-cells, monocytes and macrophages [4, 6, 7]. Bacterial population can be evolved by the acquisition of genes transferred by phage in the intestine. Phage/virus-host dynamics can influence the homogeneity /or may be responsible for causing dysbiosis [8]. The secondary infections with COVID-19, could increase the expression of ACE-2 receptors in gut and colon; especially in elderly patients with higher chances of getting dysbiosis leading to cause IBD; suggesting the potential entry of virus through altered microbiome [2, 6]. A single cell transcriptomic study revealed that ACE-2 receptors are highly expressed in the oesophageal epithelium, and enterocytes of intestines helping in effective dissemination [9].

Excessive secretion of pro-inflammatory cytokines, change in O2 level, reduction in the antimicrobial peptides, TLRs, NOD/NLRs, and SCFAs production eventually disrupt the function of microbiome. Increasing the translocation
of microbes including pathogens can cause systemic infection and organ dysfunction. The interconnection of lung-gut axis is particularly important in context with COVID-19 disease severity [2, 10].

Many studies on dysbiosis due to COVID-19, have been hampered because of the ongoing pandemic. Most of the efforts have been made for the urgent development of therapeutics, vaccines, convalescent and monoclonal sera. However, based on some important findings, we highlighted the possible implications of microbes, viruses, secretary molecules and gut on the immune response in context with IBD and COVID-19 severity.

The common symptoms of SARSCoV-2 infection are fever, cough, fatigue, headache, diarrhoeas etc., where abdominal pain is referred to the GI symptoms. A developed effort has been made for the urgent development of therapeutics, vaccines, convalescent and monoclonal sera. However, based on some important findings, we highlighted the possible implications of microbes, viruses, secretary molecules and gut on the immune response in context with IBD and COVID-19 severity.

The common symptoms of SARSCoV-2 infection are fever, cough, fatigue, headache, diarrhoeas etc., where abdominal pain is referred to the GI symptoms. A developed effort has been made for the urgent development of therapeutics, vaccines, convalescent and monoclonal sera. However, based on some important findings, we highlighted the possible implications of microbes, viruses, secretary molecules and gut on the immune response in context with IBD and COVID-19 severity.

The common symptoms of SARSCoV-2 infection are fever, cough, fatigue, headache, diarrhoeas etc., where abdominal pain is referred to the GI symptoms. A developed effort has been made for the urgent development of therapeutics, vaccines, convalescent and monoclonal sera. However, based on some important findings, we highlighted the possible implications of microbes, viruses, secretary molecules and gut on the immune response in context with IBD and COVID-19 severity.

The common symptoms of SARSCoV-2 infection are fever, cough, fatigue, headache, diarrhoeas etc., where abdominal pain is referred to the GI symptoms. A developed effort has been made for the urgent development of therapeutics, vaccines, convalescent and monoclonal sera. However, based on some important findings, we highlighted the possible implications of microbes, viruses, secretary molecules and gut on the immune response in context with IBD and COVID-19 severity.

Gut Dysbiosis: Commensals Replacing the Pathogens in COVID-19

During the past decades, the microbiome research has been given more attention, especially in regard to its relevance in maintaining the physiological balance. Human GIT contains up to 2000 bacterial species, and classified in 12 different phyla such as Protobacteria (Escherichia), Firmicutes (Lactobacillus, Bacillus, and Clostridium), Actinobacteria (Bifidobacterium), and Bacteroides (Bacteroides) [18, 19]. In addition, the gut microbiome constitutes appx. 3 million genes are 150 times more than the human genome [10].

The relevance of GM realized, when the 50% hospitalized COVID-19 patients in Italy were detected with viral RNA in their stool and the GM profile signatured with depletion of commensals such as, Bacteroidaceae, Lachnospiraceae, and Ruminococcaceae, substituted by Enterococcus, Staphylococcus, Serratia, and Collinsella along with Lactobacillus, Lactococcus, Actinomyces etc. ICU patients were also reported to develop enterococcal septicemia [20].

The ruptured mucosa of intestine shifts gut microbes and other molecules e.g., endotoxins, cell components, metabolites etc., along the gut-lung axis, instigating the immune dysfunction and secondary bacterial and fungal infections causing systemic hyperinflammation in hospitalized patients [6, 20–22]. SARSCoV-2 infection in enterocytes persists longer, even after the clearance of virus from respiratory tract manifesting the clinical severity with GI disorders [23–27]. Gut dysbiosis took place at the time of hospitalization presented with IBD in some patients. A significant increase in the opportunistic pathogens like Streptococcus spp., Rothia spp., Veillonella spp. and Actinomyces spp.; were also reported in COVID-19 patients [23, 26].

Over the course of hospitalization, the depletion of Bacteroides dorei, Bacteroides thetaiotaomicron, Bacteroides massiliensis, and Bacteroides ovatus, were found to be replaced with Coprobacillus, Clostridium ramosum, Clostridium hathewayi; establishing a direct correlation with fecal viral loads & occurring COVID-19 severity events [20, 23, 25, 28]. Moreover, the higher transcriptional activities from 3′-5′ ends of SARSCoV-2 were correlated with the presence of Collinsella, Streptococcus and Morganella spp. Parabacteroides, Bacteroides, Alistipes and Lachnospiraceae, the SCFAs producing bacteria, were found depleted [26, 29]. The fecal samples with higher infectivity are related to the active functional metabolic pathways of nucleotide, amino-acid biosynthesis and glycolysis. Essentially, the building blocks and macromolecules formation is significant for bacterial multiplications. However, the exact relationship among them is yet to be revealed. The 15 taxa out of 23 taxa of fecal microbiome, were related to the phylum of Firmicutes-Coprobacillus spp., Clostridium ramosum, and C. hathewayi [3, 23, 25, 28]. The production of pro-inflammatory cytokine IL-18 was correlated with relative abundance of Peptostreptococcus, Fusobacterium, and Citrobacter, which alter the gut microbiota stimulating the intestinal cytokine formation and subsequently form the ‘cytokine storm’ [30]. Some studies authenticate the commensals substituting the pathogens in COVID-19 with in GI and respiratory tract, are presented in Table 1.

Rothia, Veillonella, and Actinomyces were positively correlated with C-reactive protein, an indication of bacterial infection. Fecal myobiota enriched with Candida and Aspergillus prolonged the dysbiosis persisted ~ 12 days (Table 1, [3]. In addition, Faecalibacterium prausnitzii, Bacteroides dorei, B. massiliensis, B. ovatus and B. thetaiotaomicron, were inversely correlated to the viral load & downregulating the ACE-2 expression in the intestine of mice [25, 28, 32]. The antiviral effects of Lactobacillus plantarum has been studied, in animal model, to control the SARSCoV-2 infection. Previously, L. plantarum experimented on porcine enterocytes cells (IPEC-J2) to control the porcine epidemic diarrhea virus and gastroenteritis virus [31, 35]. Lactobacillus rhamnosus GG is also reported to regulate the intestinal permeability, spleen-colon homeostasis, inflammatory...
### Table 1  Etiological observational studies on the alteration of microbiota through commensals being substituted by pathogens under different conditions during SARS-CoV-2 infection

| Commensals                                                                 | Pathogens                                                                 | References |
|----------------------------------------------------------------------------|---------------------------------------------------------------------------|------------|
| *Escherichia* (Protobacteria), *Lactobacillus*, *Bacillus*, and *Clostridium* (Firmicutes), *Bifidobacterium* (Actinobacteria), and *Bacteroides* are present in normal GIT | N/A                                                                      | [18, 19]   |
| *Bacteroidaceae*, *Lachnospiraceae*, and *Ruminococcaceae* were depleted bacterial families; reported in 50% COVID-19 patients (with +ve viral RNA) | Enterococcus, *Staphylococcus*, *Serratia*, and *Collinsella* along with *Lactobacillus*, *Lactococcus*, *Actinomycetes* etc. were the substituted pathogens | [20]       |
| *Bacteroides dorei*, *Bacteroides thetaiotaomicron*, *Bacteroides massiliensis*, and *Bacteroides ovatus*, over the course of hospitalization; inversely correlated with viral loads in the fecal samples | *Streptococcus* spp., *Rothia* spp., *Veillonella* spp. and *Actinomyces* spp; were reported to increase significantly | [20, 23, 25, 28] |
| *Bifidobacterium* are present in normal GIT *Bacteroides* (Actinobacteria), and *Ruminococcaceae* were depleted bacterial and *Bacteroidaceae*, *Lachnospiraceae*, *Enterococcus*, *Staphylococcus*, *Serratia*, and *Collinsella* etc. were the substituted pathogens | *Coprobacillus*, *Clostridium ramosum*, *Clostridium hathewayi* abundance were directly correlated with COVID-19 severity events |           |
| *Parabacteroides merdae*, *Bacteroides stercoris*, *Alistipes onderdonkii*, and *Lachnospiraceae bacterium*; the SCFA producing bacteria were reported less in number | *Collinsella aerofaciens*, *Collinsella tanakaei*, *Streptococcus infantis*, *Morganella morganii* etc.; were associated with high virus transcriptional signature | [26]       |
| *Bifidobacterium*, *Lactobacillus* and *Eubacterium* spp., are the gut anaerobes; linked with disease severity with concomitant increase in the opportunistic pathogens | *Corynebacterium* (Actinobacteria) & *Ruthenibacterium* were noticeable opportunistic pathogens especially in the hospitalized patients | [3, 31]    |
| *Firmicutes*-*Coprobacillus* spp., *Clostridium ramosum*, and *C. hathewayi* are the bacterial taxa involved with fecal microbiome | *Firmicutes* spp. appeared to be diversely affected in the COVID-19 patients | [3, 23, 25, 28] |
| *Parabacteroides*, *Bacteroides*, and *Lachnospiraceae* families of gut microbiota are known to produce SCFAs, butyric acid help modulate the immune response and maintain the mucosal integrity against endotoxin infiltration | N/A                                                                      | [3, 20, 23, 31] |
| N/A                                                                        | *Peptostreptococcus*, *Fusobacterium*, and *Citrobacter* abundance + ve correlated with IL-18 levels might contribute to the SARS-CoV-2 induced production of inflammatory cytokines, have the potential to develop cytokine storm | [30]       |
| *Bacteroides*, *Roseburia*, *Faecalibacterium*, *Coprococcus*, and *Parabacteroides* were found to be in lower abundance, but *Streptococcus*, *Clostridium*, *Lactobacillus*, and *Bifidobacterium* served in increasing number in COVID-19 patients than the control group | *Rothia*, *Veillonella*, and *Actinomyces* revealed more in number as opportunistic pathogens among COVID-19 patients; were + ve correlated with CRP (indicator of bacterial infection) | [3]         |
| *Eubacterium* were also decreased Depletion in alpha diversity was found more in COVID-19 patients than normal healthy individuals and influenza patients | *Candida* and *Aspergillus* were the enriched fungal pathogens than the control subjects, prolonged the dysbiosis persisted for ~12 days after disappearance of SARS-CoV-2 from nasopharynx |           |
| N/A                                                                        | *Candida albicans* and human alpha herpesvirus 1 in upper respiratory tract were found in 46.7% COVID-19 patients | [3, 25]    |
| *Faecalibacterium prausnitzii* favors anti-inflammatory environment and was inversely correlated with COVID-19 severity | Influenza A/B or rhino or enteroviruses or respiratory syncytial virus co-infection found to developed with SARS CoV-2 |           |
| *Bacteroides dorei*, *B. massiliensis*, *B. ovatus* and *B. thetaiotaomicron*, were inversely correlated with viral loads detected in the fecal samples of patients during hospitalization; and have shown to downregulate the ACE-2 expression in the mouse intestine | *Haemophilus parainfluenzae*, *Neisseria cinerea*, *Streptococcus mitis*, *Streptococcus bovis*, *Leptotrichia buccalis*, and *Rothia mucilaginosa* were detected in COVID-19 patient microflora through throat swab |           |
| *A. flavus* and *A. niger* were detected in the fecal mycobiome after recovery from the respiratory symptoms provided the indication of unstable intestinal microbiome in some patients | *Coprobacillus*, *Clostridium ramosum*, *Clostridium hathewayi* are positively correlated with COVID-19 severity | [25, 28, 32] |
|                                                                              | *Candida albicans*, *Candida auris*, *Aspergillus flavus* and *Aspergillus niger* were detected as opportunistic fungi during hospitalization by shotgun metagenomic profiling | [25]       |
Table 1 (continued)

Microbiota change in gastrointestinal tract and respiratory tract during sarscov-2 infection

| Commensals                                                                 | Pathogens                                                                 | References |
|----------------------------------------------------------------------------|---------------------------------------------------------------------------|------------|
| BALF samples demonstrated the enrichment of commensal microflora in control group and patients with community acquired pneumonia (CAP) than COVID-19 patients | Acinetobacter, Pseudomonas, Chryseobacterium, Escherichia, Streptococcus, Enterococcus, Rothia and Lactobacillus, were responsible for developing dysbiosis in lung microbiota of COVID-19 patients | [3]        |
| **Proteobacteria, Firmicutes, and Bacteroidetes** are the most frequent phyla noticed through transient lung ecosystem | Pseudomonas, Streptococcus, Prevotella, Fusobacteria, Porphyromonas, and Veillonella have been mainly studied | [31]       |
| N/A                                                                        | Acinetobacter, Chryseobacterium, Burkholderia, Brevundimonas, Sphingobium and Enterobacteriaceae are the common bacteria isolated from the lungs of deceased patients | [3]        |
| N/A                                                                        | Cryptococcus, Issatchenka, Wallemia, Cladosporium and Alternaria were the prevalent fungi identified | [3]        |
| **Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, and Fusobacteria** remained robust in microbiota of nasopharynx, eventually stopped the SARS CoV-2 growth | Capnocytophaga and Veillonella spp. co-infection with unknown pathogenicity; obtained from BALF samples of two COVID-19 patients | [3]        |
| Prevotella, Streptococcus, and Veillonella were present in the lungs of normal healthy subjects | Dolosignarulum, Moraxella, Staphylococcus, Streptococcus etc. were obtained after volunteers experienced the mild disease when challenged with H3N2 | [33]       |
| DataTable 3: Acinetobacter (A. baumannii), Brevundimonas, Burkholderia, Chryseobacterium, Sphingobium and genus from Enterobacteriaceae. Enterobacteriaceae included some pathogenic bacteria like Enterobacter, Escherichia coli, Klebsiella, and Proteus detected in the lung samples of deceased patients | Cryptococcus, Aspergillus, Alternaria, Diplodocus, Mortierella, Naganishia, Diutina, candida, Cladosporium, Issatchenka, and Wallemia. Opportunistic species such as, Issatchenka, Cladosporium, and Candida are the lung mycobiotics responsible for causing mycosis in immunocompromised patients | [34]       |
| N/A                                                                        | Cryptococcus related infections cause higher mortality in immunocompromised patients | [3]        |

**GIT** human gastrointestinal tract, **SCFA** short chain fatty acid, **CRP** C-reactive protein, **BALF** bronchoalveolar lavage fluid, **CAP** community acquired pneumonia, **N/A** not applicable
response modulation to increase the regulatory T (Treg) cells with concomitant decrease in the pro-inflammatory cytokines production and apoptosis along the lung-gut region against *Pseudomonas aerogenosa* pneumonia. Many other non-communicable disorders such as, obesity, diabetes, hypertension, and heart diseases are known to be linked with dysbiosis, increasing the COVID-19 complications [31].

**Upper and Lower Respiratory Tract Microbiome**

Lung microbiome is dynamically transient ecosystem; its microflora basically builds from inhaling air, oral sphere, and micro-aspiration. Most frequent phyla are observed as, *Proteobacteria, Firmicutes, and Bacteroidetes*. However, the genus *Pseudomonas, Streptococcus, Prevotella, Fusobacteria, Porphyromonas*, and *Veillonella* have been mainly studied [31] (Table 1). A study based on 16S rRNA sequence of lung tissues of deceased patients reported that *Acinetobacter* was the most common bacterial genus followed by *Chryseobacterium, Burkholderia, Brevundimonas, Sphingobium* and *Enterobacteriaceae*. *Cryptococcus, Issatchenka, Wallemia, Cladosporium* and *Alternaria* are the prevalent fungi identified. Another case study reported the co-infection of *Capnocytophaga* and *Veillonella* spp. with unknown pathogenicity were obtained from two COVID-19 patients [3, 34].

de Mai et al. [33], noticed the resilience in the bacterial community of nasopharynx belong to the phyla *Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria*, and *Fusobacteria*. Global functional profiling has shown that 44 coded enzymes characterized in COVID-19, community acquired pneumonia (CAP) patients and healthy controls [36]. Metaproteome study has revealed the EC features in the COVID-19 respiratory samples with increasing activity of diaminopimelate decarboxylase. But glycan biosynthesis, lipid and sphingolipid metabolisms were limited. Less alpha-gal contents supported the negative correlation between anti-gal antibody titres and COVID-19 severity. In addition, bacteria associated with lesser content of host glycosaminoglycan heparan sulfate modification were linked to COVID-19 susceptibility [36]. This specific area that needed to be explored in regard to enzymes/proteins regulating microbial functions is yet to be discovered.

**Gut-Lung Axis Dysbiosis to Facilitate Chronic Disorders**

The microbe-mediated cross talk along the gut-lung axis has been evidenced by intestinal barrier disruption, spread of microbes, endotoxins and other metabolites could increase the severity events of COVID-19. Most of the immune cells and microbiota in the intestine play an important role in regulating the immune response. Altered gut microbiota can enhance the etiologies of metabolic, neurodegenerative, non-communicable disorders and infectious diseases. It’s role in affecting the metabolic system is yet to be elucidated [3, 36–39]. COVID-19 severity enhanced by altered microbiota led to the secondary pulmonary infections by establishing the regular fecal–oral route to regularize them [21].

*Bifidobacterium, Akkermansia* and *Faecalbacterium* in human neonatal microbiome are linked with high risk of childhood atopy and asthma [40]. Respiratory influenza infection caused the intestinal injury and subsequent change in gut microbiome composition with increased number of microbes from *Enterobacteriaceae* with concomitant decrease in *Lactobacillus and Lactococcus* [41]. Hence, IBD is associated with pulmonary diseases [42].

Inflammatory response in type 2 diabetes, obesity, hypertension, coronary heart disease and age-related disorders, are involved with comorbidities [25, 28]. Excessive pro-inflammatory cytokine secretion forms the ‘cytokine storm’, consequently led to the poor prognosis of COVID-19 [43]. Dysbiosis occurred through damaged epithelial layer induce ACE-2 receptors, therefore increase the virus replication. Hospitalized patients (46.7%) have virus remained dormant in the gut to help establish the fecal–oral route as well. *Candida albicans, Candida auris, Aspergillus flavus* and *Aspergillus niger* were noticeable fungi during all time point of hospitalization, while after fully recovery *A. flavus* and *A. niger* were detected in the fecal mycobiome [25, 28].

The older patients exhibited the decreased microbial diversity and heterogenous microbiota suggested age dependent dysbiosis and susceptibility to SARS-CoV-2 infection. Indeed, pharyngeal heterogenous microflora influence the virus adherence, changed immune response, allowing pathogens/commensals from gut to re-translocate systematically and to the other organs to exacerbate the respiratory illness [33, 34, 44, 45]. Hence, it is speculated that commensals and pathogenic microbes aggravate the COVID-19 under different conditions, depicted in Table 1.

**Immune Response Augmentation by Host Microbiome/and Virome**

The most crucial character associated with COVID-19 is the different clinical outcomes; could be affected by genetics, life style and environment. Interaction of SARS-CoV-2 with gut could trigger the deleterious biological pathways inducing pro-inflammatory cytokines, as it enters the T-cells [11, 12, 18]. Pathogenic and protective effects are elicited due to MAMPs engaging with PRRs to regularize the innate and adaptive host immune response, along with subsequent pro- or anti-inflammatory response [46]. Commensal microbes...
Association of Gut Microbiota with Inflammatory Bowel Disease and COVID-19 Severity: A Possible…

Innate Immune Response and Microbiota

Lymphocytes regulate the immune surveillance & defense, and goblet cells synthesize the functional mucusal layer in gut. Naïve T-cells differentiated into Th1 and Th17 to raise pro-inflammatory response by pathogens. Epithelial injuries occur by systemic endotoxemia translocating the bacterial components; causing the immune imbalance and systemic inflammation to establish ‘hypercytokinemia’ and dysbiosis. Lymphocytopenia and exhausted T-cells increase the secretion of IL-2, IL-6, IL-7, TNFα, GCSF, MIP-1, MCP-1 and 10 kD IFN-IP10, in severe infection [46]. The plausible role of microflora in dictating dysbiosis, inflammation and susceptibility to SARS CoV-2 infection is outlined in Figs. 1 and 2.

GF mice have the reduced Lymphocytes (Aβ and γδ) and no immunomodulator cells VIZ. IL-17 + CD4 + T-cells; Th T-17 in lamina propria; which could induce T-cells (Th 1, Th2) production, if they are colonized with filamentous bacteria. Bacteroides fragilis polysaccharide regulates the T and B-cell lineage, involving the induction of all antibodies. The activation of the innate immune receptors like, TLR5/ or NOD are mediated by the counter selection of the flagellin [51, 52] (Fig. 2). The hyperglycosylated mucin-2 layer (MUC2) regulates the immune system and help translocate the enteric DCs towards anti-inflammatory state.

IgA antibodies and antimicrobial peptides (AMPs) to present the mucosal barrier function (Fig. 2). Enteric DCs play a significant role by presenting the enteric bacterial antigens to the enteric cells [53]. AMPs interact with microbiota many times and contribute to maintain homeostasis by pancreas acini. Reduction in cathericidin AMPs of pancreas lack the calcium channel regulator ‘Oral 1’; which eventually cause the spread of microbes and subsequent inflammation via activated T-cells [52].

Commensals produce PRRs and TLRs to induce the protective immunity and TLR-5 shaping the microbiota constitution. Polysaccharides producing Bacteroides fragilis promotes for symbiont formation and educate the host immune system. TLR1/TLR2 and Dectin-1 signal the downstream activation of PI3K pathway, which inactivate the 3β (GSK 3β) inducing the cAMP response element binding (CREB) protein dependent expression of the inflammatory genes. Dectin -1 regulate the Treg differentiation and PRR through NOD like receptors serve as the innate sensor to maintain the intestinal homeostasis [54].

Modulated innate response generated through MyD88 via IL-1 and IL-18; controls the activation of epithelial cells by AMPs against gram + ve bacteria, thus, balancing the adaptive response. It also regulates the Th17 by activation of T-cells and IgA stimulation [55]. NLRs inflammasomes stimulate pyroptosis through activated IL-1β and IL-18 caspas and microbiota metabolites balance their expression by NLRP6 inflammasome signals. NLRP3 inflammasome in ulcerative colitis engages with IgG and activates the FcγR macrophages to induce IL-1β. Proteus spp. at the time of intestinal injury activate the monocytes to induce NLRP3 IL-1, increasing the inflammation. Peptidoglycan substances through innate system and PRRs are crucial for activating the immune cell health [56].

Absence in melanoma 2 (AIM2) generates signals through IL-18, IL-22 and STAT3 pathways to control homeostasis. Synergistic effects NOD2 help control the colitis via signals of IL-18, IL-22 and STAT3 pathway and mammalian peptidoglycan recognition proteins (PGRPs) to control the colitis by balancing cytotoxic IFNγ produced by NK cells [57, 58]. NOD-LLR family of proteins recognizes the intracellular flagellin protein and also activates the inflammasome, which stimulate capcase-1 and promotes IL-1β in TLR-5 independently in Salmonella infected macrophages. PRRs regulation of host-microbiome symbiosis needs more studies on inducible gene RIG-like receptors and OLRs [52, 59]. DC driven Th1 and Th17 immunity activates, when Trichomonas musculus protects against the enteric bacterial infection in mice via activation of inflammasomes [60]. Microbiota driven polysaccharides induce anti-inflammatory response in intestinal macrophages in mice. Butyrate can drive monocytes to macrophages differentiation through HDAC3 inhibition through amplifying antimicrobial mechanisms. Trimethylamine N-oxide can drive murine macrophage polarization in an NLRP3 inflammasome dependent manner [61, 62]. Intrae Lymphoid cells (ILCs) help repair the mucosal layer to combat enteric infection and help proliferate Ffar2. In mice model, ILCs with Helicobacter negatively regulate the RORγt. ILCs are important for host immunity and inflammation. Type 3ILC mediates the immune surveillance in microbiota through transcriptional factor ID2 -dependent regulation of IL-22.
Fig. 1  A SARS-CoV-2 infection via nasal passage infecting lungs and the virus multiplies in the alveolar cells, disrupt the immune system with the virus travels to the gut via mucosal lung-gut axis to create dysbiosis in the microbiota. B Schematic representation of gut microbiota dysbiosis and the establishment of flow of microflora through lung-gut axis to exacerbate the infection.
Adaptive Immune Response and Microbiota

CD4+ and CD8+ T-cells production is negatively correlated with IL-6, IL-10 and TNF-α induction. However, T-cells function eventually gets fully restored after recovery reducing the cytokine and chemokine production. Gut microbiota is the key regulator of CD8+ cell function, by producing SCFAs, butyrate and propionate directly to modulate the CD8+ and Tc17 cells. IFNγ and granzyme B expression promote Tc17 cell towards cytotoxic function in COVID-19 infection [2]. Notably, antiviral immunity involves the TLR4 against the lipopolysaccharides (LPS) from the gram-negative microflora signaling the pathway through NFκB; and the enteric viruses to protect against the intestinal damage and pathogenic bacteria [48].

B-cells maintain the homeostasis by secreting IgA antibodies, to upregulate the immune function, shaping the microbiota composition. Secretory sIgA antibodies make coat around the colitogenic bacteria inhibiting the perturbation of enteric inflammation. Repression in transcription factor GATA 4 metabolites results in increasing the absorption and metabolic alterations. Mesenchymal cells secrete a cytokine RANKL which help cells to adopt IgA production and gut microbiota diversification. Absence of commensals in mice models, repress the CD4+ cell differentiation. Th17 cells induced by Citrobacter spp. are mostly studied, which is the source of potent cytokines inducing the differentiation of Th17 largely in intestine and skin. CD8+ cytotoxic T-cells (Tc) are also regulated by microbiome, and largely associated with removal of pathogens and cancer cells [63, 64].

The bile converted into secondary bile in colon by microbiota helps regulate the gut RORγ+ regulatory T-cell homeostasis. Tfh cells are crucial to help B-cell and also contribute to the germinal cell formation, memory B-cells, affinity maturation and building response in high affinity antibody formation. However, lack of Tfh cells repress the programmed cell death (PD-1) and the ATP-gated P2RX7 receptor can alter the gut microbiota. Tfh cells association with microbiota is reciprocal, as in GF mice lack of Tfh cells can be restored by producing TLR2 receptor agonist by microbiota to activate MyD88 signaling [65, 66].

In Peyer’s patches, Tfh cells lower the access to IL-2 to CD4+ T-cells, hence amplifying the Bcl-6 on Tfh cells. But Tfh cells can also boost the autoantibody formation to induce arthritis [67]. DCs are the important class of APCs, which directly send the dendrites to outside epithelium to capture the pathogens. Spleen tyrosin kinase (Syk) signaling pathway is critical for adaptive immune signaling to induce of IL-17 and IL-22 in CD4+ T-cells. NFκB is also a crucial kinase for DC functions, to alter the secretion of IgA with changed microbiota rendering the mice vulnerable to enteric pathogens [68, 69]. GF mice showing less mature phenotype iNKT with exposure to Bacteroides fragilis were able to regain the activity of iNKT cells and protected the animals from oxazolone-induced colitis [70].

Immune Response Executed by Virome

The human gut virome, an emerging concept, is composed of prokaryotic viruses or bacteriophages and eukaryotic viruses to share the required genomic information with microflora and host cells, which may influence the composition and function of gut microbiota [71]. Constant sharing of genes between bacteriophages and bacteria may help sustain the important functions like, oxidative stress & antibiotic use tolerance. Nayfach et al. [8], reported that > 75% genome composed of DNA phages to infect Bacteroides and Clostridia classes and suggested a new gut database could help explore the functionality of gut virome and other associated retro elements for diversifying the phage community and bacterial hosts. It is possible to transplant the fecal microbiome (FMT) consists of bacteriophages because patients with C. difficile infection have altered bacteriophage abundance than the normal controls. A successful transplantation appears to be associated with implantation of Caudovirales spp. [72]. In opposite, the eukaryotic viruses such as, norwalk, rotaviruses, enteroviruses and now SARS CoV-2 can cause IBD. [18, 73]. Evidences have shown that virome related immune response is different from individual to individual, contributing to the gut physiology and homeostasis [74, 75].

Enteric cells are the barriers for virus invasion; DCs, macrophages, and lymphoid tissues (GALT/ or Peyer’s patches encounter the viruses. Viral nucleic acids are sensed by the PRRs such as TLRs; and these endosomal receptors signal through MyD88 and TRIF. The cytosolic RIG-1 and MDA5 signal through MAVS to stimulate the expression of IFN I and IFN III (Fig. 3) [76, 77]. Both RIG and MDA5 are essential to produce optimal antiviral immune response against rotavirus and dsRNA that infects small intestine. GI causing viruses e.g., norovirus, the ssRNA sensing occurs through TLR3, TLR7 and MDA5. Cytosolic NLRs also have a role in restricting the viruses [78]. NLRP6, a cofactor, signals through MAVS, deficient mice provide the dysregulated response to IFN I and IFN III, and become susceptible to encephalomyocarditis virus and murine norovirus [55]. Rotavirus sensed by NLRP9b is essential for inflammasome mediated apoptosis/or pyroptosis. Notably, rotavirus signaling associated with this pathway to induce IFN has already explained that the other PRRs are not enough to control the viral infection [29].

IFN I (IFNα and IFNβ) attach through the IFN α /β receptors (IFNAR 1 and 2 complexes), while IFN III (IFN λ) binds to interferon receptor IFNR1 or IL10R2 complex to induce an antiviral gene expression. It is presumed that
the antiviral response happened in gut cells, would most likely be similar to the cells present on other sites, which involved with IFN stimulated genes (ISGs) to reduce the viral replication and induce this recalcitrant state in the other neighboring cells too. The IFN-α and β receptor subunit 1 (IFNAR1) is broadly expressed in all cell types and helps stop the systemic spread to eliminate the murine norovirus, rotavirus and reovirus [79]. IFN I-receptor 1 (IFNL1)/IL10R2 along with IL-22 production by innate lymphoid ILC3 cells effectively control the rotavirus infection. IFN-λ also regulates the viral replication. IFNs also promote the adaptive immune response including CD8 + T-cell responses in controlling the murine norovirus. However, the rotavirus vaccination correlates with IgA antibodies production [80, 81].

In mammals, the cGAS & STING pathway is critical in sensing the intracellular DNA; to produce the immune signals against DNA viruses. The cGAS binds to the cytosolic DNA, and 2′, 3′-cGAMP to produce CDN, a second messenger to activate STING. The activated STING uses its C-terminal tail (CTT) to appoint serine/threonine kinase (TBK1), which phosphorylates and activates the transcription factor IRF3 to induce the expression of IFNs. IFNs go through the JAK-STAT pathways to stimulate the transcription of many antiviral genes (ISGs). STING has the capability to induce other pathways, to activate NFkB, MAP kinase, STAT6, autophagy, senescence and apoptosis [82]. The detailed process on these immune signaling is yet to be understood.
Traditionally, viruses are known to induce the localized infection, but influenza A virus can produce the local response could induce hepatitis and intestinal damage without local infections. It is important to find out the novel ways to harness the great potential of viruses for therapeutics. Treatment of mice with antiviral cocktails escalate the dextran sulfate sodium (DSS) induced colitis, but when treatment is replaced with inactivated rotavirus or agonized/ attenuated TLR3 and TLR7, the disease is reduced dramatically. The TLRs provide the protective effect to be associated with IFN I expressed by DCs. However, TLRs are also linked to the disease severity of IBD in patients. IFN I in combination with antiviral therapeutics. Treatment of mice with antiviral cocktails could provide clues for new diagnostics biomarkers related to dysbiosis, modulation of microbiota to design new therapies to help control the hyperinflammatory response safely and effectively. Development of personalized medicines to control the immune response in comorbid, immunocompromised/or immunosuppressed individuals.

Acknowledgements Authors have extended their gratitude to all the researchers and scientists who added their incredible efforts, during the pandemic, to carry out the research work on the microbiota dysbiosis and its association with risks involved with COVID-19 disease.

Author Contributions Conceptualization: RN, AK; formal analysis: AK, RN; investigation: AK, RN; resources: AK, RN; writing-original draft preparation: RN; editing: AK, RN; visualization: AK, RN; supervision: AK.

Funding There was no fund/grant for writing this review article.

Data Availability Not applicable.

Declarations

Conflict of interest Authors have declared that they have no conflict of interest.

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Authors have read and approved the final manuscript for publication.

References

1. Noor R, Naz A, Maniha SM, Tabassum N et al (2021) Microorganisms and cardiovascular diseases: importance of gut bacteria. Front Biosci-Landmark 26(5):22–28. https://doi.org/10.52586/4921
2. Segal JP, Mak JWY, Mullish BH et al (2020) The gut microbiome: an under-recognised contributor to the COVID-19 pandemic? Therap Adv Gastroenterol 13:1756284820974914. https://doi.org/10.1177/1756284820974914
3. Yamamoto S, Saito M, Tamura A, Prawisuda D, Mizutani T, Yot-suyanagi H (2021) The human microbiome and COVID-19: a systematic review. PLoS ONE 16(6):e0253293. https://doi.org/10.1371/journal.pone.0253293
4. Zheng T, Li J, Ni Y, Kang K et al (2019) Mining, analyzing, and integrating viral signals from metagenomic data. Microbiome 7(1):42. https://doi.org/10.1186/s40168-019-0567-y
5. Yeoh YK, Zuo T, Liu GC, Zhang F, Liu Q, Li AY et al (2021) Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. Gut 70(4):698–706. https://doi.org/10.1136/gutjnl-2020-323020
6. Noor R (2021) Human gut microorganisms in the protection against COVID-19. GENOMEDEN 5–6. http://genomeden.com/wp-content/uploads/2021/06/GENOMEDEN-June-issue-2021-pdf-compressed-1.pdf
7. Vu DL, Kaiser L (2017) The concept of commensal viruses almost 20 years later: redefining borders in clinical virology. Clin Microbiol Infect 23(10):688–690. https://doi.org/10.1111/j.1469-0691.2017.03.005
8. Nayfach S, Páez-Espino D, Lee C et al (2021) Metagenomic compendium of 189, 680 DNA viruses from human gut microbiome. Nat Microbiol 6:960–970

Conclusions

Gut microbiota including viruses and bacteriophages are important to carry out the systematic balance in gut, circulatory and respiratory systems; certainly warrants the further studies on the interactions with SARS-CoV-2. It could provide clues for new diagnostics biomarkers related to dysbiosis, modulation of microbiota to design new treatments to help control the hyperinflammatory response safely and effectively. Development of personalized

Springer
1. Kaushal A (2020) Mutation and variants of SARS-CoV-2 across the globe-A comprehensive review. Acta Sci Microbiol 4(5):93–113
2. Kaushal A (2020) Immune response and pathogenesis of COVID-19 and the strategies for developing targeted drugs. Acta Sci Microbiol 3(3):92–102
3. Noor R, Maniha SM (2020) A brief outline of respiratory viral diseases. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7148745/
4. WHO (World Health Organization) Coronavirus diseases (COVID-19) Dashboard. Updated on 5:30pm CEST, 3 August 2021. https://covid19.who.int/ Accessed 25 Aug 2021.
5. Gómez CE, Perdigueró B, Esteban M (2021) Emerging SARS-CoV-2 variants and impact in global vaccination programs against SARS-CoV-2/COVID-19. Vaccines (Basel) 9(3):243. https://doi.org/10.3390/vaccines9030243
6. Hoffmann M, Arora P, Groß R, Seidel A et al (2021) SARS-CoV-2: Infection of bat and human intestinal organoids by SARS-Cov-2 faecal viral activity in association with dominant pathobiontic bacteria in the nasopharyngeal microbiota. Cell 184(9):2384–2393.e12. https://doi.org/10.1016/j.cell.2021.03.036
7. Fan J, Li X, Gao Y, Zhou J et al (2021) The lung tissue microbiota features of 20 deceased patients with COVID-19. J Infect 81:e64–e67. https://doi.org/10.1016/j.jinf.2020.06.047
8. de Maio F, Postaroro B, Ponziani FR et al (2020) Nasopharyngeal microbiota profiling of SARS-CoV-2 infected patients. Biol Proc cardiomed 22:18. https://doi.org/10.1186/s12575-020-00131-7
9. Zuo T, Zhan H, Zhang F, Liu Q, Tso EYK, Lui GCY et al (2020) Alterations in fecal fungal microbiome of patients with COVID-19 during time of hospitalization until discharge. Gastroenterology 159(1302–10):e5. https://doi.org/10.1053/j.gastro.2020.06.048
10. Zhu S, Ding S, Wang P, Wei Z et al (2017) Nlrp9b inflammasome restricts rotavirus infection in intestinal epithelial cells. Nature 546:667–670
11. Tao W, Zhang G, Wang X, Guo M, Zeng W, Xu Z et al (2020) Analysis of the intestinal microbiota in COVID-19 patients and its correlation with the inflammatory factor IL-18. Med Microbiol 5:100023. https://doi.org/10.1016/j.medmicro.2020.100023
12. Allalì I, Bakri Y, Amzazi S, Ghazal H (2021) Gut-lung axis in COVID-19. Interdiscip Perspect Infect Dis 2021:6655380. https://doi.org/10.1155/2021/6655380
13. Geva-Zatorsky N, Sefik E, Kua L, Pasman L et al (2017) Mining the human gut microbiota for immunomodulatory organisms. Cell 168(298–43):e11. https://doi.org/10.1016/j.cell.2017.01.022
14. Dumas A, Bernard L, Poquet Y et al (2018) The role of lung microbiota associates with childhood multisensitized atopy and T cell differentiation. Nat Med 22(10):1187–1191
15. Wang J, Li F, Wei H et al (2014) Respiratory influenza virus infection induces intestinal immune injury via microbiota-mediated Th17 cell-dependent inflammation. J Exp Med 211(12):2397–2410
16. Lee HK, Gordon A, Shedden K, Kuan G et al (2019) The respiratory microbiome and susceptibility to influenza virus infection. PLoS ONE 14:e0207898. https://doi.org/10.1371/journal.pone.0207898
17. Xiong Y, Liu Y, Cao L, Wang D, Guo M, Jiang A et al (2020) Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. Emerg Microbes Infect 9:761–770. https://doi.org/10.1080/2222751.2020.1747363
18. Budding A, Sieswerda E, Wintermans B, Bos M (2021) An age dependent pharyngeal microbiota signature associated with SARS-CoV-2 infection. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3582780. Accessed 15 Jan 15 2021
19. Qin T, Geng T, Zhou H, Han Y, Ren H, Qiu Z et al (2020) Super-dominant pathobionic bacteria in the nasopharyngeal microbiota as causative agents of secondary bacterial infection in influenza patients. Emerg Microbes Infect 9:605–615. https://doi.org/10.1080/22227517.2020.1737578
46. Barko PC, McMichael MA, Swanson KS, Williams DA (2018) The gastrointestinal microbiome: a review. J Vet Intern Med 32:9–25
47. Zhao EA, Eaten L et al (2020) Gut microbiota modulate CD4+ T-cell response to influence colitis associated tumorigenesis. Cell Rep 31:107471
48. Weaver LK, Minichino D, Biswas C et al (2019) Microbiota dependent signals are required to sustain TLR mediated immune responses. JCI Insight 4:e124370
49. Bradley KC, Finsterbusch K, Schnepf D, Crotta S, Llorian M, Davidson S et al (2019) Microbiota-driven tonic interferon signals in lung stromal cells protect from influenza virus infection. Cell Rep 28:245–256.e4. https://doi.org/10.1016/j.celrep.2019.05.105
50. Nefkens J, Lambrecht BN (2013) The role of lung dendritic cell subsets in immunity to respiratory viruses. Immunol Rev 255:57–67. https://doi.org/10.1111/jirm.12100
51. Ivanov II et al (2009) Induction of intestinal Th17 cells by segmented filamentous bacteria. Cell 139:485–498
52. Zheng D, Liwinski T, Elinav E (2020) Interaction between microbiota and immunity in health and disease. Cell Res 30:492–506
53. Bansal T, Alaniz RC, Wood TK, Jayaraman A (2010) The bacterial signal indole increases epithelial-cell tight-junction resistance and attenuates indicators of inflammation. Proc Natl Acad Sci USA 107:228–233
54. Erteurk-Hasdemir D et al (2019) Symbionts exploit complex signaling to educate the immune system. Proc Natl Acad Sci USA. https://doi.org/10.1073/pnas.1915978116
55. Wang P, Zhu S, Yang L et al (2015) Nramp6 regulates intestinal antiviral innate immunity. Science 350:826–830
56. Wolf AJ, Underhill DM (2018) Peptidoglycan recognition by the innate immune system. Nat Rev Immunol 18:243–254
57. Ratsimandresy RA, Lindromohan H, Dorleutner A, Stehlik C (2017) The AIM2 inflammasome is a central regulator of intestinal homeostasis through the IL-18/IL-22/STAT3 pathway. Cell Mol Immunol 14:127–142
58. Saha S et al (2010) Peptidoglycan recognition proteins protect mice from experimental colitis by promoting normal gut flora and preventing induction of interferon-gamma. Cell Host Microbe 8:147–162
59. Franchi L et al (2006) Cytosolic flagellin requires Ipaf for activation of caspase-1 and interleukin Ibetta in salmonella-infected macrophages. Nat Immunol 7:576–582
60. Chudnovskiy A et al (2016) Host-prototozoan interactions protect macrophages from mucosal infections through activation of the inflammasome. Cell 167:444–456
61. Schultess J et al (2019) The short chain fatty acid butyrate imprints an antimicrobial program in macrophages. Immunity 50:432–445
62. Wu K et al (2020) Gut microbial metabolite trimethylamine N-oxide aggravates GVHD by inducing M1 macrophage polarization in mice. Blood. https://doi.org/10.1182/blood.2019003990
63. Bachem A et al (2019) Microbiota-derived short-chain fatty acids promote the memory potential of antigen-activated CD8(+) T cells. Immunity 51:285–297
64. Song X et al (2020) Microbial bile acid metabolites modulate gut RORgamma (+) regulatory T cell homeostasis. Nature 577(410–415):220
65. Kubnak JL et al (2015) MyD88 signalling in T cells directs IgA-mediated control of the microbiota to promote health. Cell Host Microbe 17:153–163
66. Proietti M et al (2014) ATP-gated ionotropic P2X7 receptor controls follicular T helper cell numbers in Peyer’s patches to promote host-microbiota mutualism. Immunity 41:789–801
67. Teng F et al (2016) Gut microbiota drive autoimmune arthritis by promoting differentiation and migration of Peyer’s patch T follicular helper cells. Immunity 44:875–888
68. Jie Z et al (2018) NIK signaling axis regulates dendritic cell function in intestinal immunity and homeostasis. Nat Immunol 19:1224–1235
69. Martínez-López M et al (2019) Microbiota sensing by Mincle-Syk axis in dendritic cells regulates interleukin-17 and -22 production and promotes intestinal barrier integrity. Immunity 50:446–461
70. An D et al (2014) Sphingolipids from a symbiotic microbe regulate homeostasis of host intestinal natural killer T cells. Cell 156:123–133
71. Scarpellini E, Ianro G, Attiti F et al (2015) The human gut microbiota and virome: potential therapeutic implications. Dig Liver Dis 47:1007–1012
72. Zuo T, Wong SH, Lam K, Lui R et al (2017) Bacteriophage transfer during faecal microbiota transplantation in Clostridium difficile infection is associated with treatment outcome. Gut 67:634–643
73. Garmaeva S, Sinha T, Kurilshikov A, Fu J, Wijmenga C (2019) Studying the gut virome in the metagenomic era: challenges and perspectives. BMC Biol 17:84
74. Carding SR, Davis N, Hoyles L (2017) Review article: the human intestinal virome in health and disease. Aliment Pharmacol Ther 46:800–815
75. Kim MS, Park EJ, Roh SW, Bae JW (2011) Diversity and abundance of single-stranded DNA viruses in human feces. Appl Environ Microbiol 77:8062–8070
76. Broquet AH, Hirata Y, McAllister CS, Kagnoff MF (2011) RIG-I/MDA5/MAVS are required to signal a protective IFN response in rotavirus-infected intestinal epithelium. J Immunol 186:1618–1626
77. Metzger RN, Krug AB, Eisenacher K (2018) Enteric virome sensing-its role in intestinal homeostasis and immunity. Viruses 10:146
78. Abt MC, Buffie CG, Susac S, Becattini S et al (2016) TLR-7 activation enhances IL-22-mediated colonization resistance against vancomycin-resistant enterococcus. Sci Transl Med 8:327ra325
79. Ingle H, Peterson ST, Baldridge MT (2018) Distinct effects of type I and III interferons on enteric viruses. Viruses 10:46
80. Hernandez PP, Mahlakoiv T, Yang I et al (2015) Interferon-lambda and interleukin 22 act synergistically for the induction of interferon-stimulated genes and control of rotavirus infection. Nat Immunol 16:698–704
81. Neil JA, Cadwell K (2018) The intestinal virome and immunity virome and immune response. J Immunol 201(6):1615–1624. https://doi.org/10.4049/jimmunol.1800631
82. Shally RM, Peter AD, Beth MH et al (2021) The STING ligand 2’ 3’-cGAMP induces an NF-kB- dependent anti-bacterial innate immune response in the starlet sea anemone Nematostella vectensis. BioRxiv. https://doi.org/10.1101/2021.05.13.443009
83. Yang JY, Kim MS, Kim E, Cheon JH, Lee YS, Kim Y, Lee SH, Seo SU, Shin SH, Choi SS, Kim B, Chang SY, Ko HJ, Bae JW, Kweon MN (2016) Enteric viruses ameliorate gut inflammation via toll-like receptor 3 and toll-like receptor 7-mediated interferon-beta production. Immunity 44(889–900):1
84. Basic M, Keubler LM, Buettner M, Achard M et al (2014) Norovirus triggered microbiota-driven mucosal inflammation in interleukin 10-deficient mice. Inflamm Bowel Dis 20:431–443
85. Hutenhower C, Kostic AD, Xavier RJ (2014) Inflammatory bowel disease as a model for translating the microbiome. Immunity 40:843–854
86. Graham KL, Sanders N, Tan Y, Allison J et al (2008) Rotavirus infection accelerates type 1 diabetes in mice with established insulitis. J Virol 82(13):6139–6149
87. Pane JA, Webster NL, Graham KL et al (2013) Rotavirus acceleration of murine type 1 diabetes is associated with a T helper...
1-dependent specific serum antibody response and virus effects in regional lymph nodes. Diabetologia 56:573–582

88. Dickson RP, Erb-Downward JR, Freeman CM et al (2015) Spatial variation in the healthy human lung microbiome and the adapted island model of lung biogeography. Ann Am Thorac Soc 12(8):21–30. https://doi.org/10.1513/AnnalsATS.201501-029OC

89. Doi Y, Murray GL, Peleg AY (2015) Acinetobacter baumannii: evolution of antimicrobial resistance-treatment options. Semin Respir Crit Care Med 36:85–98. https://doi.org/10.1055/s-0034-1398388

90. Man WH, de Steenhuijsen Piters WAA, Bogaert D (2017) The microbiota of the respiratory tract: gatekeeper to respiratory health. Nat Rev Microbiol 15:259–270. https://doi.org/10.1038/nrmicro.2017.14

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.