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REVIEW ARTICLE

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

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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

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

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GCSF	Granulocyte colony-stimulating factor
hsCRP	High-sensitive C-reactive protein
HDAC3	Histone deacetylase 3
IL	Interleukin
IP10	Induced protein (small inducible cytokine)
IFN-γI	Interferon γI
iNKT cells	Invariant natural killer cells
ILC3	Innate lymphoid cells
IL10R2	IFNλ receptor
IFNAR 1&2	IFN α/ β receptor
MHC-I	Major histocompatibility complex-I
MAMPs	Microbial associated molecular patterns
MNP	Mononuclear phagocyte
MyD88	Myeloid differentiation primary response 88
MDA5	Melanoma associated protein 5
MAVS	Mitochondrial antiviral signaling protein
MAP kinase	Mitogen activated protein kinase
MIP-1α	Macrophage inflammatory protein
MCP-1	Monocyte chemoattractant protein
NOD-2	Nucleotide -binding oligomerization domain-2
NFKB	Nuclear factor kappa-light chain enhancer of activated B-cells
NLRP6	NOD like receptor family pyrin domain containing 6
OAS	Oligo adenylate synthase
OLRs	OAS like receptors
PC3	Pathogen containment level 3
PRRs	Pattern recognition receptors
PI3K	Phosphoinositide 3 kinase
RANKL	Receptor activator of nuclear factor kappa-B ligand
RORγ, RAR	Related orphan receptor gamma
RIG-1	Retinoic acid inducible gene I
STAT	Signal transducer and activator of transcription
SCFAs	Short chain fatty acids
STING	Stimulator of interferon genes
Syk	Spleen tyrosin kinase
TNF-α	Tumor necrosis factor α
Th1-Th17 cells	Thymus cells
Tfh cells	Follicular helper T-cell
TRIF	TIR-domain-containing adaptor-inducing interferon-β
TBK1	Tank binding kinase
T1D	Type 1 diabetes
TLRs	Toll like receptors

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 state of interstitial pneumonia with high viral loads, and activated macrophages, monocytes producing pro-inflammatory cytokines could result into ARDS along with the complications of GI, neurological, thrombotic, thromboembolic diseases and multiorgan failure [11–13]. The disease severity in COVID-19 is reported higher in terms of morbidity and mortality [14], which principally explains the virulent nature of the virus evading the host's immune system and even becoming more transmissible by producing relevant mutations in spike (S) protein/ or receptor binding domain (RBD) [6, 11, 12, 15, 16]. A range of emergency drugs, vaccines and antibodies are being used at present to control the infection [6, 17].

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 (*Lactobacilllus, 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 in commensals such as, *Bacteroidaceae*, *Lachnospiraceae*, and *Ruminococcaceae*, substituted by *Enterococcus*, *Staphylococcus*, *Serratia*, and *Collinsella* along with *Lactobacillus*, *Lactococcus*, *Actinomycetes* 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* sps. *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 *Actnomycetes* were positively correlated with C-reactive protein, an indication of bacterial infection. Fecal mycobiota 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 planatarum* 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 SARSCoV-2 infection

Microbiota change in gastointestinal tract and respiratory tract during sarscov-2 infection		
Commensals	Pathogens	References
Escherichia (Protobacteria), *Lactobacilllus, 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 *Coprobacillus, Clostridium ramosum, Clostridium hathewayi* abundance were directly correlated with COVID-19 severity events	[20, 23, 25, 28]
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	*Fermicutes 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 + vely correlated with IL-18 levels might contribute to the SARSCoV-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 *Eubacterium* were also decreased Depletion in alpha diversity was found more in COVID-19 patients than normal healthy individuals and influenza patients	*Rothia, Veillonella,* and *Actnomycetes* revealed more in number as opportunistic pathogens among COVID-19 patients; were + vely correlated with CRP (indicator of bacterial infection) *Candida* and *Aspergillus* were the enriched fungal pathogens than the control subjects, prolonged the dysbiosis persisted for ~ 12 days after disappearance of SARSCoV-2 from nasopharynx	[3]
N/A	*Candida albicans* and human *alpha herpesvirus* 1 in upper respiratory tract were found in 46.7% COVID-19 patients Influenza A/B or rhino or enteroviruses or respiratory syncytial virus co-infection found to developed with SARS CoV-2 *Haemophilus parainfluenzae, Neisseria cinerea, Streptococcus mitis, Streptococcus bovis, Leptotrichia buccalis,* and *Rothia mucilaginosa* were detected in COVID-19 patient microflora through throat swab	[3, 25]
Faecalibacterium prausnitzii favors anti-inflammatory environment and was inversely correlated with COVID-19 severity *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	*Coprobacillus, Clostridium ramosum, Clostridium hathewayi* are positively correlated with COVID-19 severity	[25, 28, 32]
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	*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 gastointestinal 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	*Acinetobactor, Pseudomonas, Chryseobacterium, Escherichia, Streptococcus, Enterococcus, Rothia and Lactobacillus*, were responsible for developing dysbiosis in lung microbiota of COVID-19 patients	[3]
Protobacteria, 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 *Cryptococcus, Issatchenkia, Wallemia, Cladosporium* and *Alternaria* were the prevalent fungi identified	[3]
N/A	*Capnocytophaga* and *Veillonella* spp. co-infection with unknown pathogenicity; obtained from BALF samples of two COVID-19 patients	[3]
Fermicutes, Bacteroidetes, Protobacteria, Actinobacteria, and Fusobacteria remained robust in microbiota of nasopharynx, eventually stopped the SARS CoV-2 growth	*Dolosignarulum, Moraxella, Staphylococcus, Streptococcus* etc. were obtained after volunteers experienced the mild disease when challenged with H3N2	[33]
Prevotella, Streptococcus, and *Veillonella* were present in the lungs of normal healthy subjects	*Acinetobacter (A. baumannii), Brevundimonas, Burkholderia, Chryseobacterium, Sphingobium* and genus from *Enterobacteriaceae*. *Enterobacteriaceae* included some pathogenic bacteria like *Enterobacter, Escherichia coli, Klesiella*, and *Proteus* detected in the lung samples of deceased patients *Cryptococcus, Aspergillus, Alternaria, Dipodascus, Mortierella, Naganishia, Diutina, candida, Cladosporium, Issatchenkia,* and *Wallemia*. Opportunistic species such as, *Issatchenkia, Cladosporium,* and *Candida* are the lung mycobiota responsible for causing mycosis in immunosuppressed patients *Cryptococcus* related infections cause higher mortality in immunocompromised patients	[34]

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, *Protobacteria*, *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*, *Issatchenkia*, *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 *Fermicutes*, *Bacteroidetes*, *Protobacteria*, *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 SARSCoV-2 infection. Indeed, pharyngeal heterogenous microflora influence the virus adherence, changed immune response, allowing pathogens/or commensals from gut to re-translocate systemically 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

signal the Treg cells to naive T-cells through DCs, prompting the secretion of anti-inflammatory cytokine IL-10, disseminating the local/ and systemic tolerance (Figs. 1, 2).

Gut microbiome/ virome during IBD activates the DCs, through secretion of inflammasomes, allowing them to migrate through circulatory & lymphatic system, hence influencing the T-cell response in the lungs in case of influenza. Similarly, the possible alteration of gut microbiome/ virome could affect the outcome of COVID-19 disease [47, 48]. SARSCoV-2 produce type I-III IFN in human enteroids to activate the cytokine genes such as, CCR1, CCR8, IL16, IL3 and CXCL10(IP10) observed to be upregulated, but CCR2, CCR5, and IL5 were seen downregulated [28]. Type I IFN (IFNα and IFNβ) prevent the viral replication evidenced in GF mice failed to produce IFNα, IFNβ, IL-6, TNF-α, IL-12 and IL-18 against viral infections [49, 50].

Innate Immune Response and Microbiota

Lymphocytes regulate the immune surveillance & defense, and goblet cells synthesize the functional mucosal 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, IL-10, 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 cathelicidin AMPs of pancreas lack the calcium channel regulator 'Orai 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 caspases and microbiota metabolites balance their expression by NLRP6 inflammasome signals. NRLP3 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].

Absent 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 Th 17 immunity activates, when *Trichomonas musculis* 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]. Innate 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.

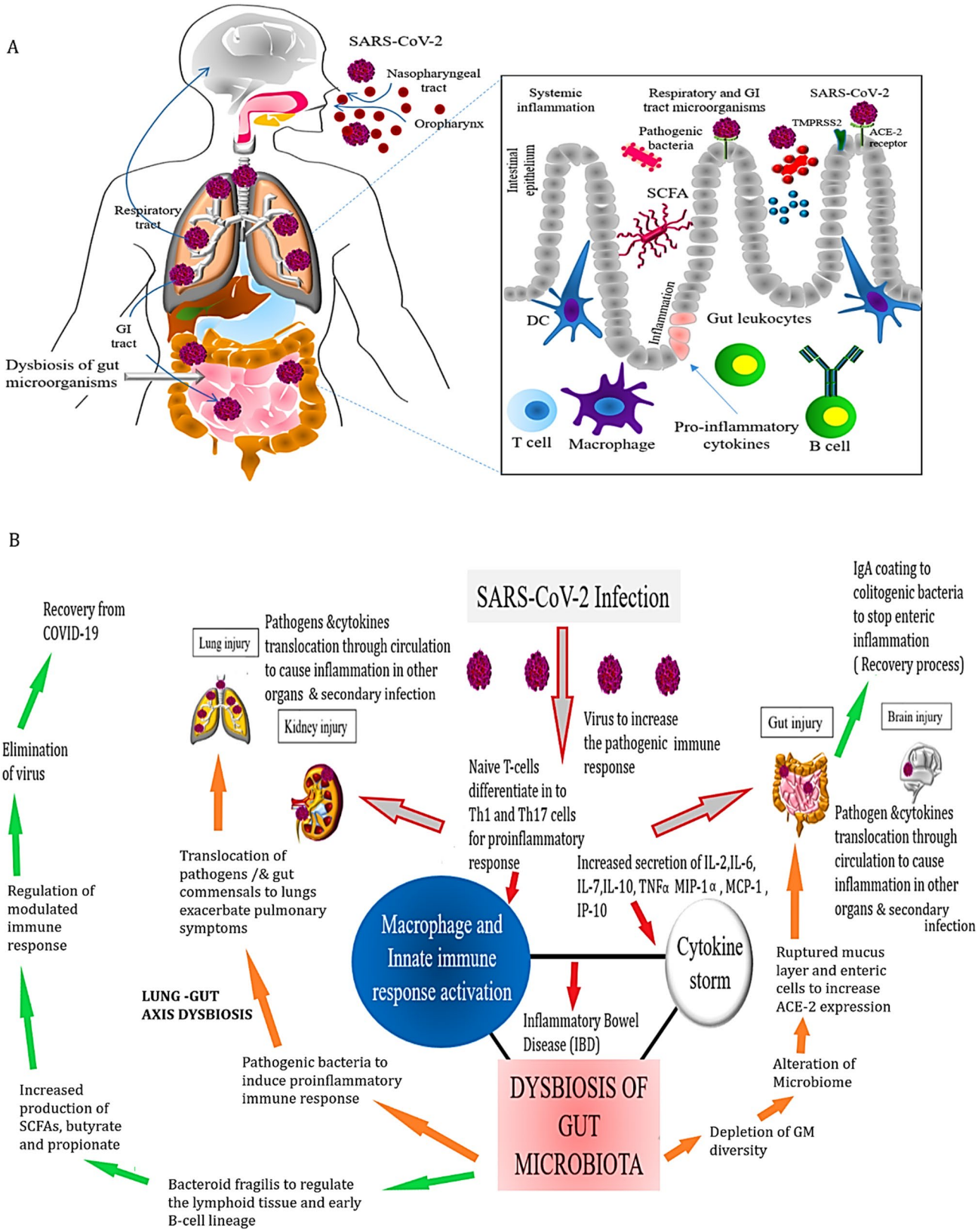


Fig. 1 **A** SARSCoV-2 infection via nasal passage infecting lungs and the virus multiplies in the alveolar cells, disrupt the immune system virus travels to the gut via mucosal lung-gut axis to create dysbiosis in the microbiota. **B** Schematic representation of gut microbiota dysbiosis and the establishment 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 NFkB; 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. Secretary 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].

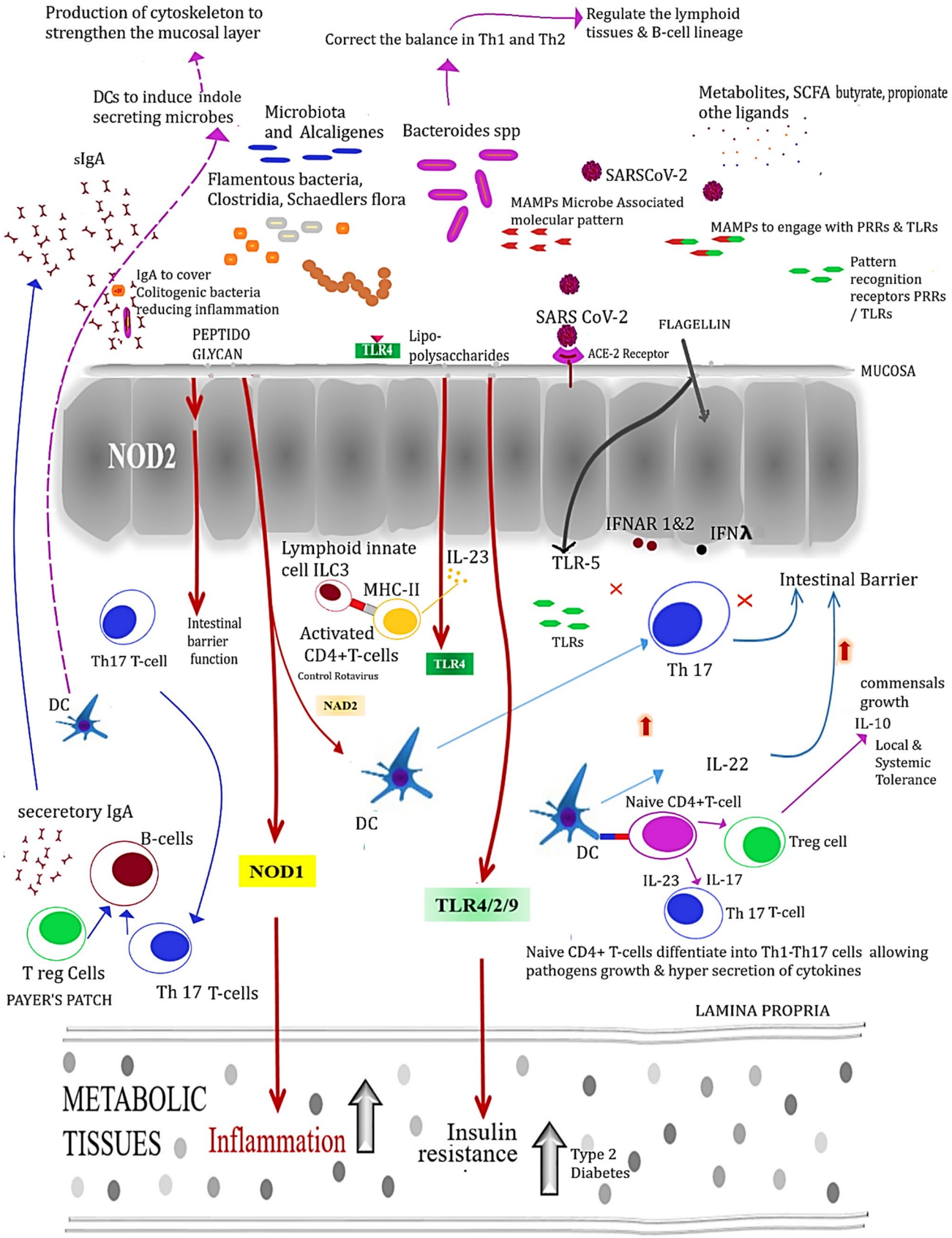
In Peyer's patches, Tfh cells lower the access to IL-2 to CD4 + T-cells, hence amplifying the Bcl-6 on Tfh cells. But Tfh cells can also boost the autoantibody formation to induce arthritis [67]. DCs are the important class of APCs, which directly send the dendrites to outside epithelium to capture the 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. NFkB 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 *Bacteroide 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 microbial community [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 *Bacteroidis* 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


Production of cytoskeleton to strengthen the mucosal layer
Correct the balance in Th1 and Th2
Regulate the lymphoid tissues & B-cell lineage
DCs to induce indole secreting microbes
Microbiota and Alcaligenes
Bacteroides spp
Metabolites, SCFA butyrate, propionate othe ligands
sIgA
Flamentous bacteria, Clostridia, Schaedlers flora
SARSCoV-2
MAMPs Microbe Associated molecular pattern
MAMPs to engage with PRRs & TLRs
Pattern recognition receptors PRRs / TLRs
IgA to cover Colitogenic bacteria reducing inflammation
SARS CoV-2
FLAGELLIN
PEPTIDO GLYCAN
TLR4
Lipo-polysaccharides
ACE-2 Receptor
MUCOSA
NOD2
IFNAR 1&2
IFNλ
Lymphoid innate cell ILC3
IL-23
TLR-5
Intestinal Barrier
MHC-II
Activated CD4+T-cells
Control Rotavirus
Intestinal barrier function
Th17 T-cell
TLR4
TLRs
Th 17
commensals growth
IL-10
Local & Systemic Tolerance
DC
NAD2
IL-22
Naive CD4+T-cell
seceretory IgA
B-cells
NOD1
DC
Treg cell
TLR4/2/9
IL-23
IL-17
Th 17 T-cell
T reg Cells
PAYER'S PATCH
Th 17 T-cells
Naive CD4+ T-cells diffentiate into Th1-Th17 cells allowing pathogens growth & hyper secretion of cytokines
LAMINA PROPRIA
METABOLIC TISSUES
Inflammation
Insulin resistance
Type 2 Diabetes

◂**Fig. 2** Regulation the immune response by diversified gut microbiota through gut to lamina propria and muscular tissues. DCs to induce the indole producing microbes to secrete cytoskeleton proteins repairing the mucosal layer. DCs to reduce the efficacy of Th1—Th17, induce naïve T-cells to stimulate Treg producing IL-10, help grow the commensals. Treg, B-cells and IgA control the pathogenic effect from colitogenic bacteria. ILC3 activated CD4 + cells inducing IL-23controlling viral infection. NOD1 and NOD2 modulate the Th1 function and help perform the adjuvant property of peptidoglycan. LPS regulate through TLR4 and TLR4/2/9 can cause insulin resistance in T2D. MAMPs to engage with PRRs and TLRs to keep the stimulate regulation on bacterial metabolites such as SCFAs, butyrate and propionate to reduce the inflammation

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 (IFNLR1)/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.

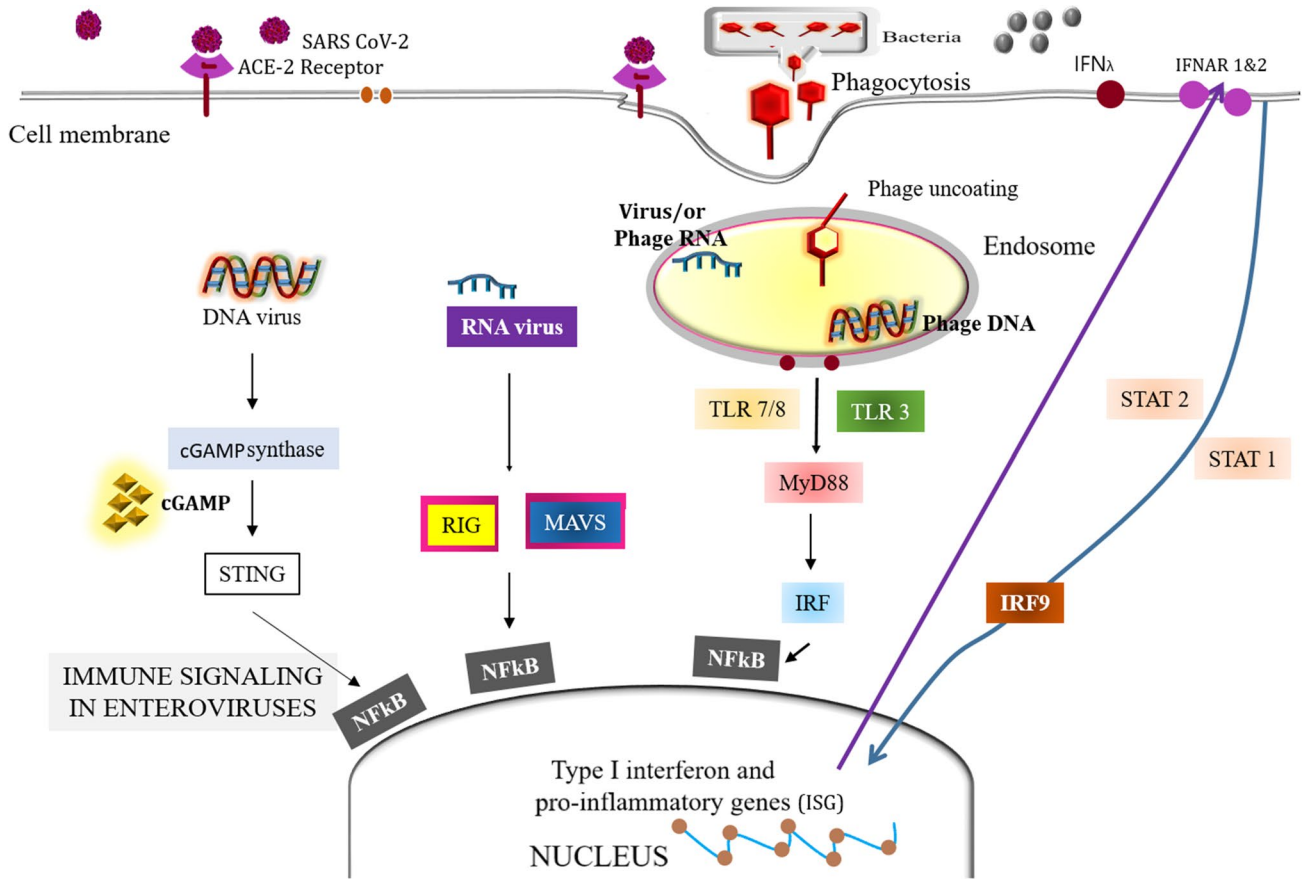


Fig. 3 Endosomal and cytosolic innate immune surveillance regulated by enteroviruses and bacteriophages. The viral DNA and RNA are signaled via TLRs or PRRs. The endosomal TLR signals are processed through MyD88 and TRIF. The cytosolic RIG-1 and MDA5 signals through MAVS to stimulate the expression of IFN I and IFN III, which attach through IFNAR 1&2 (IFN α, IFN β) and IL10R2 (IFNλ) receptors to induce antiviral response. The intracellular DNA is sensed via cGAS-STING pathway, producing 2′, 3′-cGAMP to activate STING stimulating the expression of IFNs through NFkB

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 drugs is a standard method to treat chronic hepatitis C, but always associated with toxicity, including gastrointestinal illness [83].

Virome and susceptible genes interact to aggravate the IBD, this experiment is performed by using murine norovirus, which showed that viruses are the functional members of microbiome. Autophagy Related 16-Like 1 (ATG16L1) gene is involved in cellular degenerative pathway by autophagy, and is linked with increased susceptibility to form IBD. For example, mice deficient in IL-10 and multi-drug resistance mutation 1 (MDR1), a toxin transporter colonized by *Helicobacter bilis* may accelerate the intestinal inflammation [84, 85]. Intestinal virome could also influence the autoimmune disorders, if they extend beyond the GIT. Experimental mice were given the infection with rotavirus increase the IFN I dependent activation of lymphocytes in the pancreatic lymph nodes and initiate the progression of type 1 diabetes (T1D) due the spread of the virus to mesentery and pancreatic lymph nodes [86, 87]. The virome-host interaction along with microbiome could contribute to the health maintenance, disease prognosis and regulation of the immune response, to get the beneficial or detrimental outcome for the host [84, 88–90]. Therefore, virome does play a significant role in regulating the gut balance / or causing dysbiosis, can't be ruled out.

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 SARSCoV-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 medicines to control the immune response in comorbid, immunocompromised/or immunosuppressed individuals.

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