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

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1. Introduction:

Microbiome structure influences the innate and adaptive immune response that could cause dysbiosis often linked to infectious diseases, rheumatoid arthritis, cancer, obesity, and cardiovascular diseases. Gut and lung microflora (Table 1) delivers immunomodulatory functions, but it'll undertake the path to get substituted by pathogens leading to a poor prognosis of COVID-19.

Mucosal cell lining enhances the relocation of SARSCoV-2 due to increased ACE-2 receptors, resulting in excessive transcription of proinflammatory cytokines via P38 MAPK and AP-1 pathway mainly through exhaustive macrophages and monocytes. Which eventually reduces the production of TLRs, NODs-NLRs, and SCFAs depleting the resident microflora to affect overall homeostasis.

Injured mucosal lining (Fig 1) enhances the systemic translocation of bacteria (pathogens and commensals), cell metabolites, cytokines, chemokines, and other toxins to other organs causing multiorgan injuries. Microbiome could help secrete adjuvant molecules viz., TLRs, PPRs, SCFAs etc., for faster recovery contributing to activating NK cells, attenuate the innate and adaptive immune response.

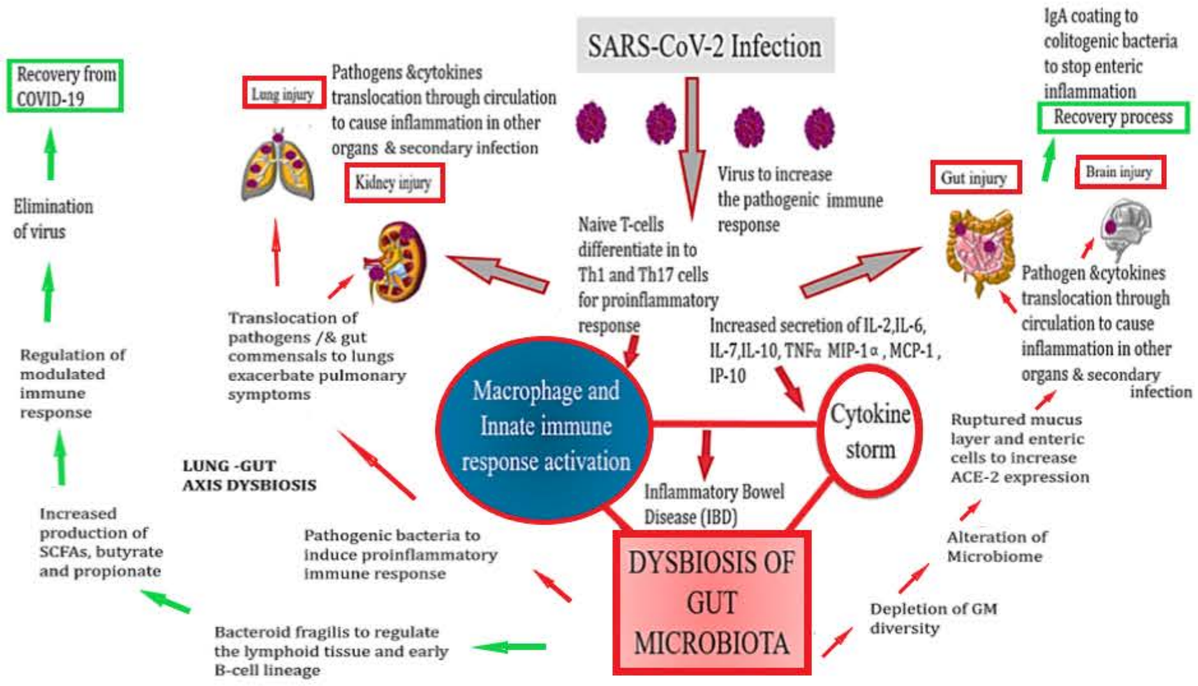

Fig 1: Representation of SARS CoV-2 infection, Cytokine Storm formation, and Microbiota activity to influence the disease severity and recovery from infection

2. Context:

Interaction among lung & gut microbiome and virome including bacteriophages and immune cells help establish the antiviral signals, ultimately implicating the health maintenance or disease progression.

Table1: Resident Microflora replaced with pathogens during COVID-19 in hospitalized patients

Etiological Observational Studies showing GIT & Lung Microbiota Substituted by Pathogens	
Reported Microflora of GIT	**Substituted Pathogens in COVID-19 Patients**
Escherichia (Protobacteria), *Lactobacillus, Bacillus, and Clostridium* (Firmicutes), *Bifidobacterium* (Actinobacteria), and *Bacteroides*	N/A **Li J et al. 2014; Ferreira C et al. 2020**
Bacteroidaceae, Lachnospiraceae, and *Ruminococcaceae* -depleted bacterial families; in 50% COVID-19 patients (with +ve viral RNA)	*Enterococcus, Staphylococcus, Serratia, and Collinsella* along with *Lactobacillus, Lactococcus, Actinomycetes* etc. **Gaibani et al. 2021**
Bacteroides dorei, Bacteroides thetaiotaomicron, Bacteroides massiliensis, and *Bacteroides ovatus,* in hospitalized patients have inverse correlation with fecal viral load	*Streptococcus spp., Rothia spp., Veillonella spp.* and *Actinomyces spp., Coprobacillus, Clostridium ramosum, Clostridium hathewayi* – in high abundance related to COVID-19 severity events **Gu et al, 2020; Zuo et al. 2020; Gaibani et al. 2021**
Parabacteroides merdae, Bacteroides stercoris, Alistipes onderdonkii, and Lachnospiraceae bacterium- lower in number	*Collinsella aerofaciens, Collinsella tanakaei, Streptococcus infantis, Morganella morganii* – signatured with high viral transcription **Zuo et al. 2021**
Bifidobacterium, Lactobacillus and *Eubacterium spp.,* are the gut anaerobes; linked with disease severity	*Corynebacterium (Actinobacteria) & Ruthenibacterium* – opportunistic pathogen noticed **Allali et al. 2021; Yamamoto et al. 2021**
N/A	*Peptostreptococcus, Fusobacterium, and Citrobacter* abundance - with high IL-18 levels forming cytokine storm with other pro-inflammatory cytokines **Tao et al. 2020**
Bacteroides, Roseburia, Faecalibacterium, Coprococcus, and *Parabacteroides* – lower abundance *Streptococcus, Clostridium, Lactobacillus,* and *Bifidobacterium* – high abundance Depleted Alpha diversity in COVID-19 than normal & influenza patients	*Rothia, Veillonella,* and *Actnomycetes* opportunistic pathogens with high C-reactive protein *Candida* and *Aspergillus*- with persisted dysbiosis ~12 days after -ve nasopharynx PCR **Yamamoto et al. 2021**
N/A	*Candida albicans* and human *alpha herpesvirus* 1- upper respiratory tract Influenza A/B or rhino or enteroviruses or respiratory syncytial virus co-infection with COVID-19 *Haemophilus parainfluenzae, Neisseria cinerea, Streptococcus mitis, Streptococcus bovis, Leptotrichia buccalis,* and *Rothia mucilaginosa* **Yammamoto et al. 2021, Zuo T, Zhan H et al. 2020**
Faecalibacterium prausnitzii – anti-inflammatory environment *Bacteroides dorei, B. massiliensis, B. ovatus* and *B. thetaiotaomicron*- downregulate ACE-2 in mice intestine	*Coprobacillus, Clostridium ramosum, Clostridium hathewayi*-related to severity *Candida albicans, Candida auris, Aspergillus flavus and Aspergillus niger* reduced the stability of intestinal microbiome **Zuo T et al. 2020; Zuo T, Zhan H et al. 2020**
BALF samples- common microflora enrichment in normal group and community acquired pneumonia patients	*Acinetobactor, Pseudomonas, Chryseobacterium, Escherichia, Streptococcus, Enterococcus, Rothia and Lactobacillus* caused dysbiosis in COVID-19 patients **Yammamoto et al, 2021**
Protobacteria, Firmicutes, and *Bacteroidetes*- most frequent phyla in transient lung ecosystem.	*Pseudomonas, Streptococcus, Prevotella, Fusobacteria, Porphyromonas,* and *Veillonella* were found **Allali et al. 2021**
	Acinetobacter, Chryseobacterium, Burkholderia, Brevundimonas, Sphingobium and Enterobacteriaceae – deceased patient's lungs *Cryptococcus, Issatchenkia, Wallemia, Cladosporium* and *Alternaria* – fungi isolated *Capnocytophaga* and *Veillonella* spp. co-infection **Yamamoto et al. 2021**
Fermicutes, Bacteroidetes, Protobacteria, Actinobacteria, and Fusobacteria -robust microbiota of nasopharynx to control SARSCoV-2	*Dolosignarulum, Moraxella, Staphylococcus, Streptococcus* – found in volunteers challenged with H3N2 **de Mai F et al., 2020**
Prevotella, Streptococcus, and *Veillonella*- in lungs of normal healthy subjects	*Acinetobacter (A. baumannii), Brevundimonas, Burkholderia, Chryseobacterium, Sphingobium* and genus from *Enterobacteriaceae. Enterobacteriaceae*- lungs of deceased patients *Cryptococcus* (reported with higher mortality), *Aspergillus, Alternaria, Dipodascus, Mortierella, Naganishia, Diutina, candida, Cladosporium, Issatchenkia,* and *Wallemia*-immunosuppressed patients **Fan J et al. 2020**

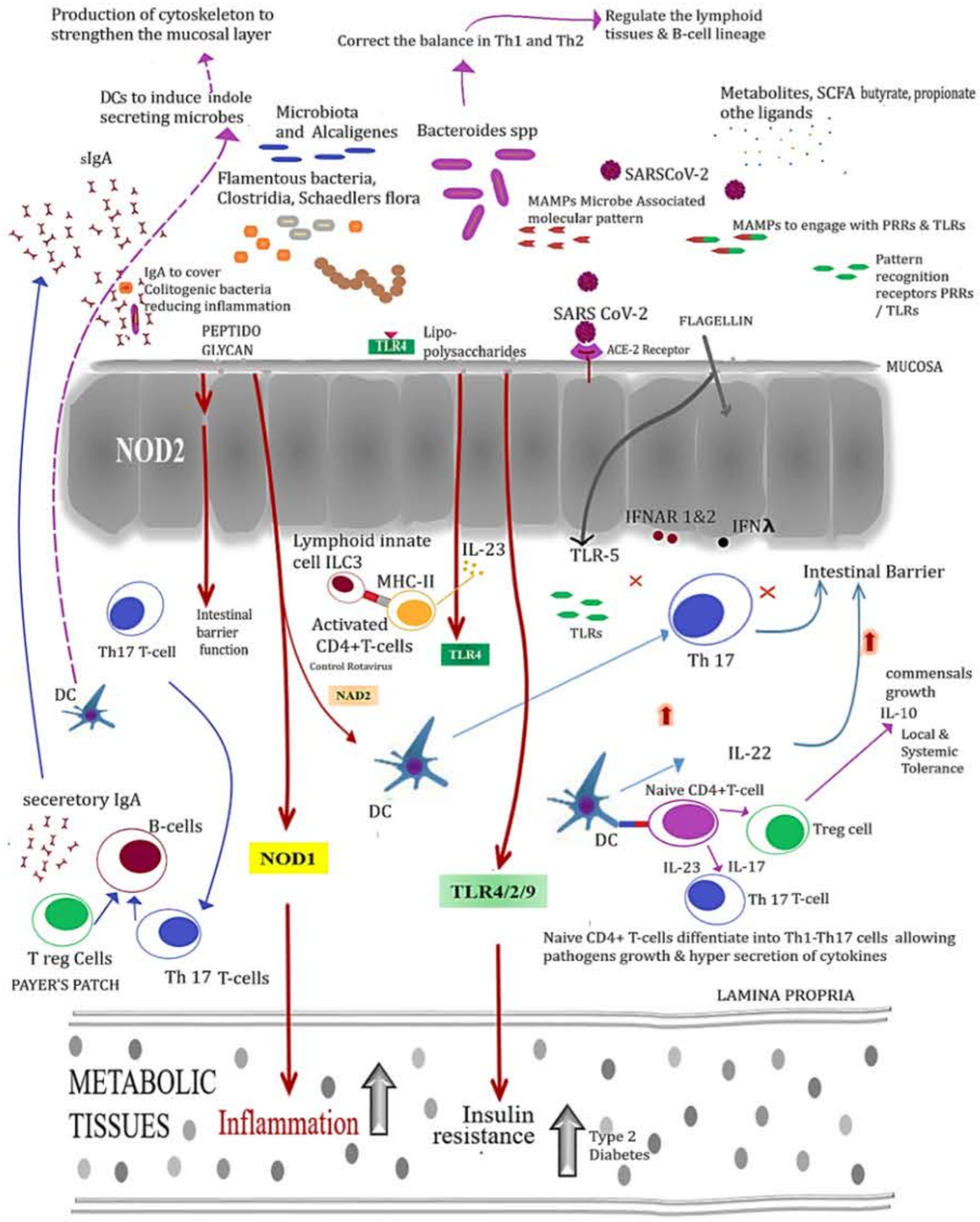

Fig 2 : Induction of immune surveillance sensing through resident microflora

3. Immune signals via resident microflora, bacteriophages and enteroviruses

Diversified immune surveillance mechanism is regulated through the lungs, gut, lamina propria, and muscular tissues. DCs minimize the effectivity of Th1 and Th2 cells, to activate Treg cells producing IL-10 to stimulate commensal's growth. Colitogenic bacteria are controlled through Treg & B-cells and IgA. Indole-producing bacteria secrete cytoskeleton to repair the mucosal lining. Viral infection is combated via ILC3 to activate CD4+ cells to produce IL-23. NOD 1&2 displays adjuvant properties of peptidoglycan. MAMPs reduce inflammation via regulating the PRRS, TLRs, and SCFAs.

Bacteriophages and enteroviruses also regulate the innate response, where TLRs and PRRs produce signals through MyD88 and TRIF. RIG and MDA-5 stimulate the IFN surveillance pathway via IFNAR 1&2 and IFNλ for the effective antiviral response. Intracellular DNAs are sensed through cGAS and STING protein adaptors to produce 2'-3'-cGAMPs to regulate the NFkB and I IFNs.

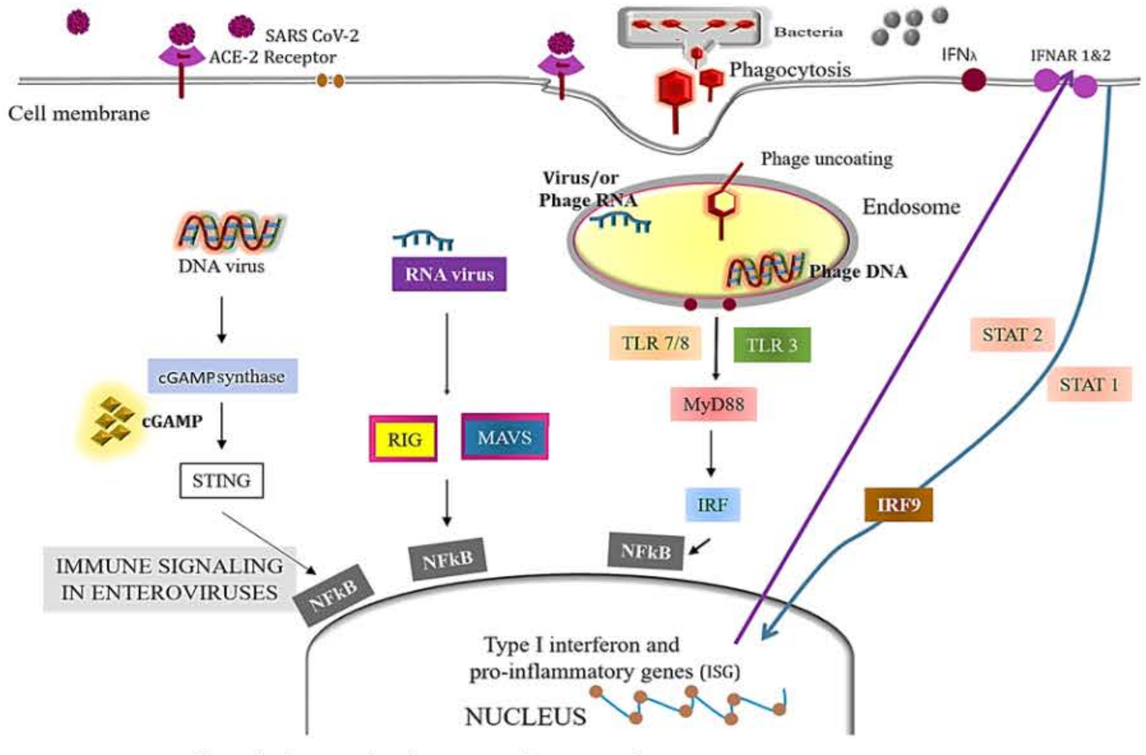

Fig 3: Immune sensing via bacteriophages and enteroviruses

4. Conclusion:

Dysbiosis-related aberrant immunogenic signals that occur in chronic conditions warrant the research to develop novel diagnostics and personalized treatments to control the impaired response without adverse effects in comorbid and immunocompromised states.