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Short Communication

Microbiota Alterations in Non-Critically-Ill and Critically-Ill COVID-19 Patients

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The microbiota are related to several human diseases and influence human health [1], figure 1-4. Critical functions of microbiota are decomposition of indigestible proteins, carbohydrates, digestion and absorption of nutrients, host immunity induction, function, and instruction, including vitamin biosynthesis [2-6]. A recent study revealed that gut microbiota (GM) were stratified by occurrence of bloodstream infection (BSI) and intensive-care-unit (ICU) admission ($p < 0.05$) [7]. ICU patients and those developing BSI were specifically characterized by the over-representation of *Enterococcus* compared to the respective counterparts ($p < 0.001$), whereas *Clostridiales*, *Streptococcus*, *Blautia*, *Oscillospira*, *Lachnospiraceae*, and other *Ruminococcaceae* taxa were related to non-ICU-admitted-COVID-19 and non-BSI patients ($p < 0.001$) [7].

Interestingly, *Enterococcus* was much overrepresented in both groups of COVID-19 patients (ICU-admitted and non-ICU-admitted), particularly, closely related to ICU-admitted-COVID-19 patients ($p = 0.001$, Wilcoxon test), whereas non-ICU-admitted-COVID-19 patients demonstrated enriched *Ruminococcus* ($p = 0.0003$), as well as *Coprococcus*, *Dorea*, and *Oscillospira* ($p < 0.01$) [7]. *Enterobacteriaceae* genera, especially *Klebsiella* were mainly discriminated in critically non-COVID-19 patients ($p < 0.03$) [7]. They also found that there was a significant increase in the *Enterococcus* spp.-incidence rate was identified between 2017 and

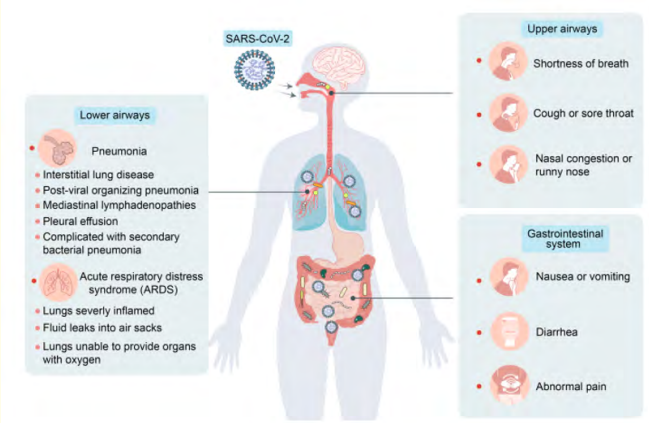

Figure 1: Demonstrating COVID-19-associated respiratory and gastrointestinal symptoms. Various respiratory and gastrointestinal manifestations occur in patients with COVID-19 including nasal congestion or runny nose, shortness of breath, cough or sore throat, pneumonia, acute respiratory distress syndrome (ARDS), nausea or vomiting, diarrhea, and abdominal pain.

(Source: Wang B, Zhang L, Wang Y, Dai T, Qin Z, Zhou F, *et al*. Alterations in microbiota of patients with COVID-19: potential mechanisms and therapeutic interventions. Signal Transduction and Targeted Therapy 2022; 7: 143. DOI: https://doi.org/10.1038/s41392-022-00986-0).

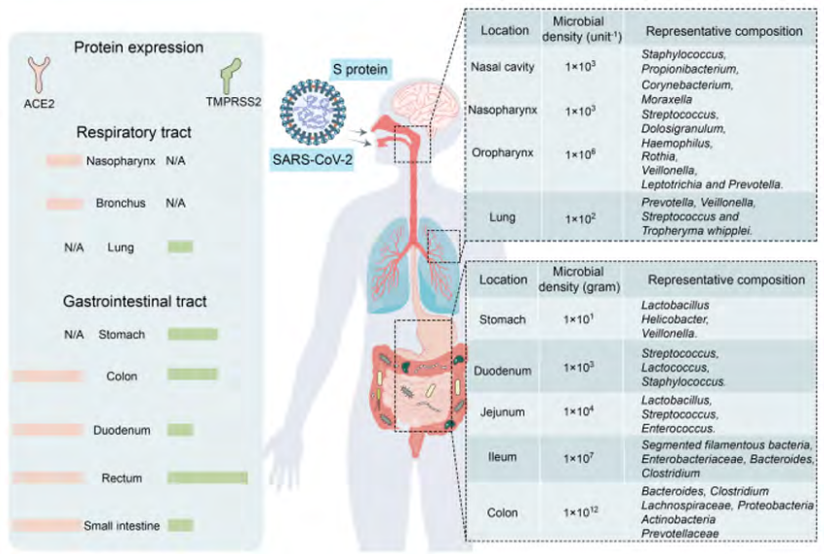

Figure 2: Demonstrating primary habitats of human microbiota: respiratory and gastrointestinal tracts as SARS-CoV-2 infection targets. SARS-CoV-2 receptors " ACE2 " and " TMPRSS2 " are expressed mainly in respiratory and gastrointestinal tracts which provide many suitable habitats for microorganisms. The right side of the figure lists representative bacterial populations in different parts of the respiratory and gastrointestinal tracts.

(Source: Wang B, Zhang L, Wang Y, Dai T, Qin Z, Zhou F, *et al*. Alterations in microbiota of patients with COVID-19: potential mechanisms and therapeutic interventions. Signal Transduction and Targeted Therapy 2022; 7: 143. DOI: https://doi.org/10.1038/s41392-022-00986-0)

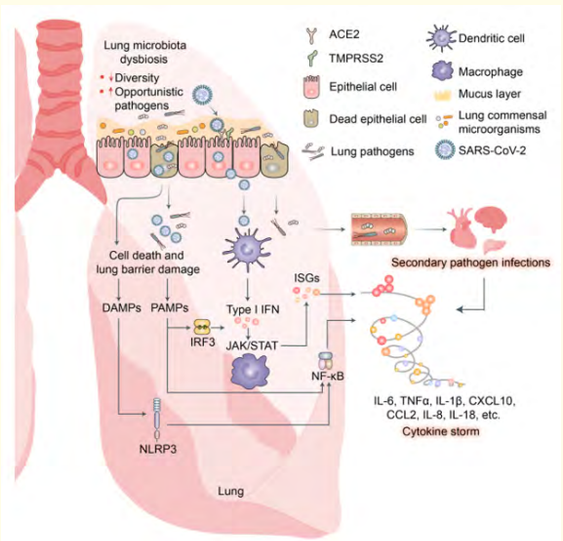

Figure 3: Demonstrating potential mechanisms of cytokine storm and secondary pathogen infections resulting from lung microbiota dysbiosis in patients with COVID-19. SARS-CoV-2 infection disrupts lung microbiota eubiosis. Increased abundance of opportunistic pathogens may intensify lung cytokine storm and cause secondary pathogen infections in patients with COVID-19. Pathogen-associated molecular patterns (PAMPs) released from invading opportunistic pathogens may be recognized by host innate lymphocytes such as macrophages and dendritic cells (DCs) via pattern recognition receptors (PRR) including Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), and NOD-like receptors (NLRs). These induce expression of proinflammatory factors via NF-κB signaling, interferons via IRF3 signaling, and numerous interferon-stimulated genes (ISGs) via JAK/STAT signaling. Excess cytokines may exacerbate COVID-19 symptoms.

(Source: Wang B, Zhang L, Wang Y, Dai T, Qin Z, Zhou F, *et al*. Alterations in microbiota of patients with COVID-19: potential mechanisms and therapeutic interventions. Signal Transduction and Targeted Therapy 2022; 7: 143. DOI: https://doi.org/10.1038/s41392-022-00986-0).

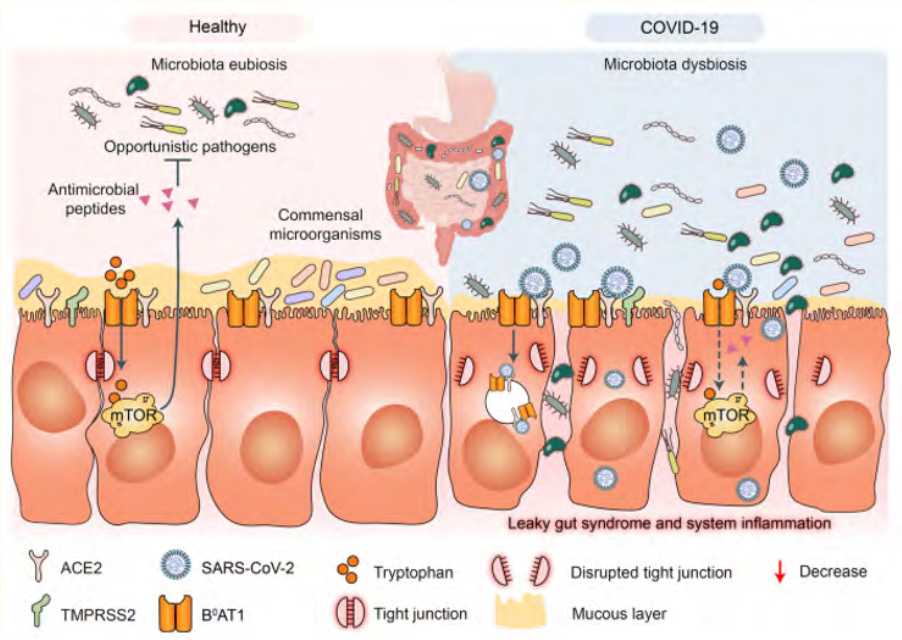

Figure 4: Demonstrating Potential mechanisms of cytokine storm and secondary pathogen infections resulting from gut microbiota dysbiosis in patients with COVID-19. Gut microbiota are also disrupted by SARS-CoV-2 infection which potentially triggers cytokine storm and secondary pathogen infections. B0AT1 mediates neutral amino acid uptake by luminal surfaces of intestinal epithelial cells. It is also a molecular ACE2 chaperone. B0AT1 substrates such as tryptophan and glutamine activate antimicrobial peptide release, promote tight junction (TJ) formation, downregulate lymphoid proinflammatory cytokines, and modulate mucosal cell autophagy via mTOR signaling. As ACE2 is a molecular B0AT1 chaperone, ACE2-associated B0AT1 may be internalized during SARS-CoV-2 infection, decrease B0AT1 on cell membranes, promote gut opportunistic pathogen invasion, facilitate cytokine storms, and exacerbate COVID-19.

(Source: Wang B, Zhang L, Wang Y, Dai T, Qin Z, Zhou F, *et al*. Alterations in microbiota of patients with COVID-19: potential mechanisms and therapeutic interventions. Signal Transduction and Targeted Therapy 2022; 7: 143. DOI: https://doi.org/10.1038/s41392-022-00986-0).

2020 (p = 0.01, Poisson regression) (14.8 (95 % CI : 0.74-2.96) in 2019 and 15.2 (95 % CI : 0.79-2.92) in 2018), whereas the relative risk of ICU-acquired E-BSI during the first 4 months of 2020 was 1.84/3.14-fold higher than in 2019 [7]. Another recent study on gut microbiota with COVID-19 severity demonstrated that gut bacteria have positive correlation with COVID-19 severity, such as *Erysipelotrichia*, *Coprobacillus*, *Actinomycetaceae*, *Proteobacteria*, *Bacteroidetes*, *Rikenellaceae*, *Alistipes*, etc. (p = 0.003-0.029; Correlation coefficient (Rho) = 0.81-0.92) [8].

In conclusion, a novel concept and targeted approach of the gut-microbiota modulation due to prolonged gut microbiome dysbiosis in COVID-19 patients may be a COVID-19 and its-comorbidity therapeutic.

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