Impact of the Gut's Microbiome on COVID

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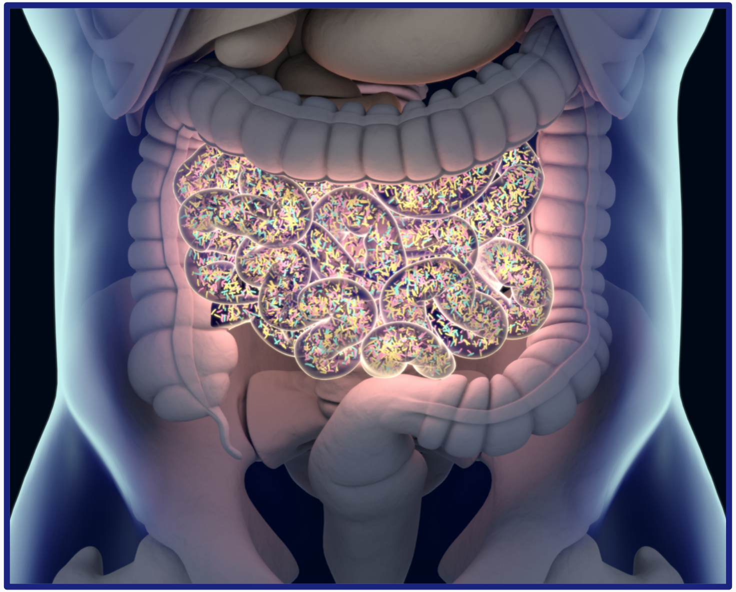
The Gut Microbiome

- “Good” & “Bad” bacteria” reside in the gut
    - ~100 trillion microorganisms make up the gut microbiota
    - Bacteria, viruses, archaea, protozoa, and fungi
- Aside from skin, the gut is the largest organ exposed to the outside world (constant exposure to toxins, bacteria, viruses, etc.)
- Diverse microbiota is essential for proper development, immunity, & metabolic health
- Microbiome moves in and out of balance quickly (affected by epigenetics)
    - Dysbiosis: imbalance of the gut microbiota
- All disease begins in the gut & results as a dysfunction of gut health!



Immune System and the Gut

- Development of innate and adaptive immune systems are closely linked to your gut composition
    - Gut balance helps regulate immune response → lack of microbial diversity and impaired metabolic function leads to poor immune response
- A study, ***Role of the Microbiome in Human Development***, found that animals that lack a gut microbiota have poor development of immune cells, weakening their immune system
    - Immune cells require a healthy gut microbiota for their production and function
- About half of our antibodies are made in the gut lining

The Gut is the Guardian to Our Health & Gateway to Disease: Gut-Immune Connection

- The gut is the motherboard to our immune system
    - 70-80% of immune cells in our body are found in the gut and depend on a healthy gut flora to function
    - “Good” bacteria produce beneficial compounds that optimize immune system functioning
    - A broken gut microbiome leads to poor immune resilience

COVID-19 & The Gut

- Impressive connection between gut health and severity of COVID-19
- Poor gut health adversely affects COVID-19 prognosis
- Prevalent GI symptoms once infected with COVID-19 demonstrate the importance of the gut for this virus

1. **Leaky gut and dysbiosis give the virus access to circulation, the digestive tract, and internal organs**
   a. Because these organs have high ACE2 receptors, they are likely to engulf the virus
   b. A healthier gut microbiome may lead to decreased expression of the ACE2 receptors
2. **The virus gains entry through the ACE2 receptors, which have a large reservoir in the small intestine**
   a. Poor gut health correlates with increased expression of ACE2 receptors

Kim, H. S. (2021). Do an altered gut microbiota and an associated leaky gut affect COVID-19 severity? *Mbio, 12*(1).

The Gut Composition at a Species Level

- Overall lower species richness of the gut microbiome both during and after COVID-19 infection
- The diversity of the actinobacteria phylum in the gut microbiota is decreased during COVID-19 infection
  - Composed of mostly gram-positive bacteria, including Bifidobacterium
- Bifidobacterium & Lactobacillus bacterium levels are decreased during a COVID-19 infection
  - ***Bifidobacterium*** (Actinobacteria)→ Immune-modulating effects that can help reduce cytokine storm, very important in our innate immune response
  - ***Lactobacillus bacterium (***Firmicutes) → play a large role in the digestive tract and female genital system, assists in immune response
- Faecalibacterium is also decreased during COVID-19 infection
  - Depleted levels are correlated with severity of infection
- Bacteroides and Enterobacteriaceae increased during COVID-19 infection

Reinold, J., Farahpour, F., Fehring, C., Dolff, S., Konik, M., Korth, J., van Baal, L., Hoffmann, D., Buer, J., Witzke, O., Westendorf, A. M., & Kehrmann, J. (2021). A Pro-Inflammatory Gut Microbiome Characterizes SARS-CoV-2 Infected Patients and a Reduction in the Connectivity of an Anti-Inflammatory Bacterial Network Associates With Severe COVID-19. *Frontiers in cellular and infection microbiology*, *11*, 747816.

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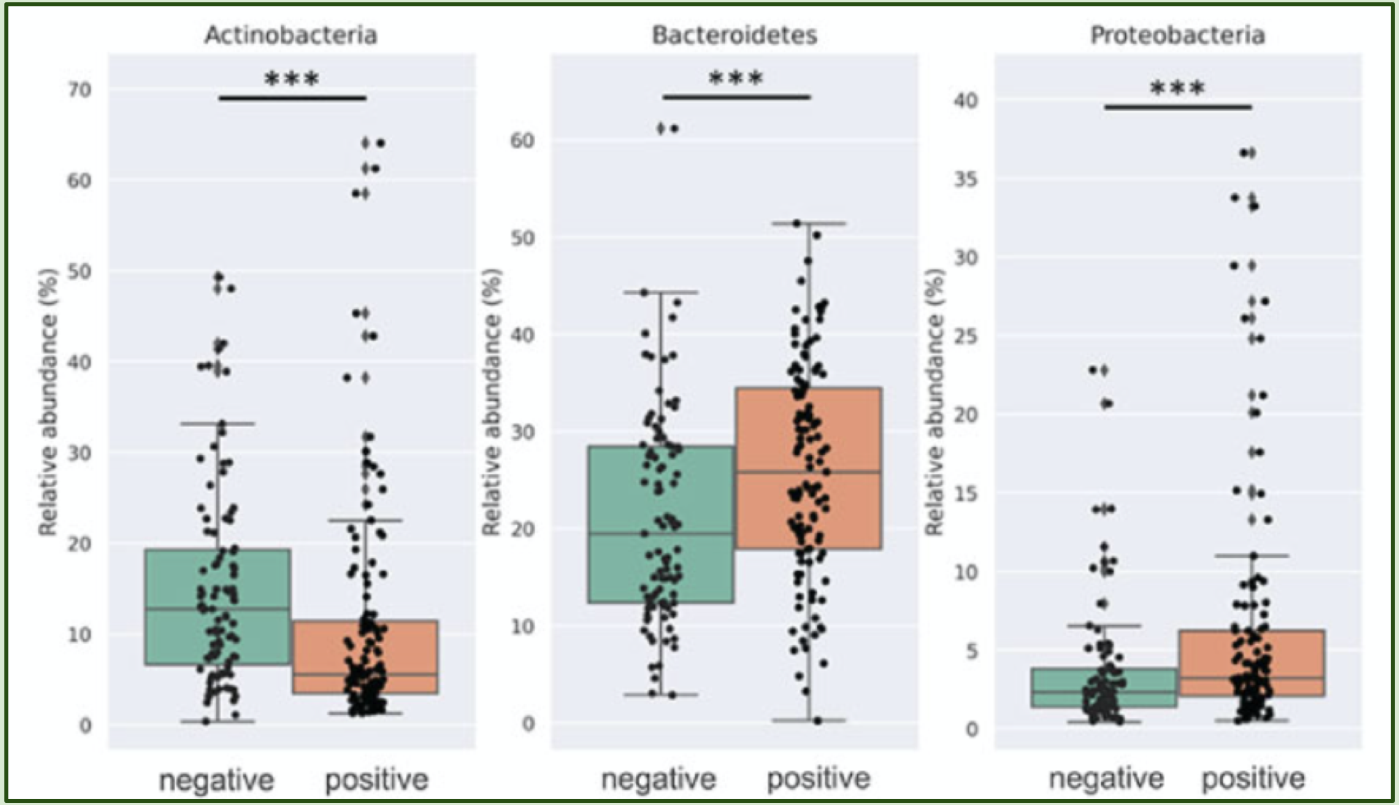
The Gut Composition at a Species Level



- ➔ Lowered levels of actinobacteria in positive patients
- ➔ Higher levels of bacteroidetes in positive patients
- ➔ Higher levels of proteobacteria in positive patients

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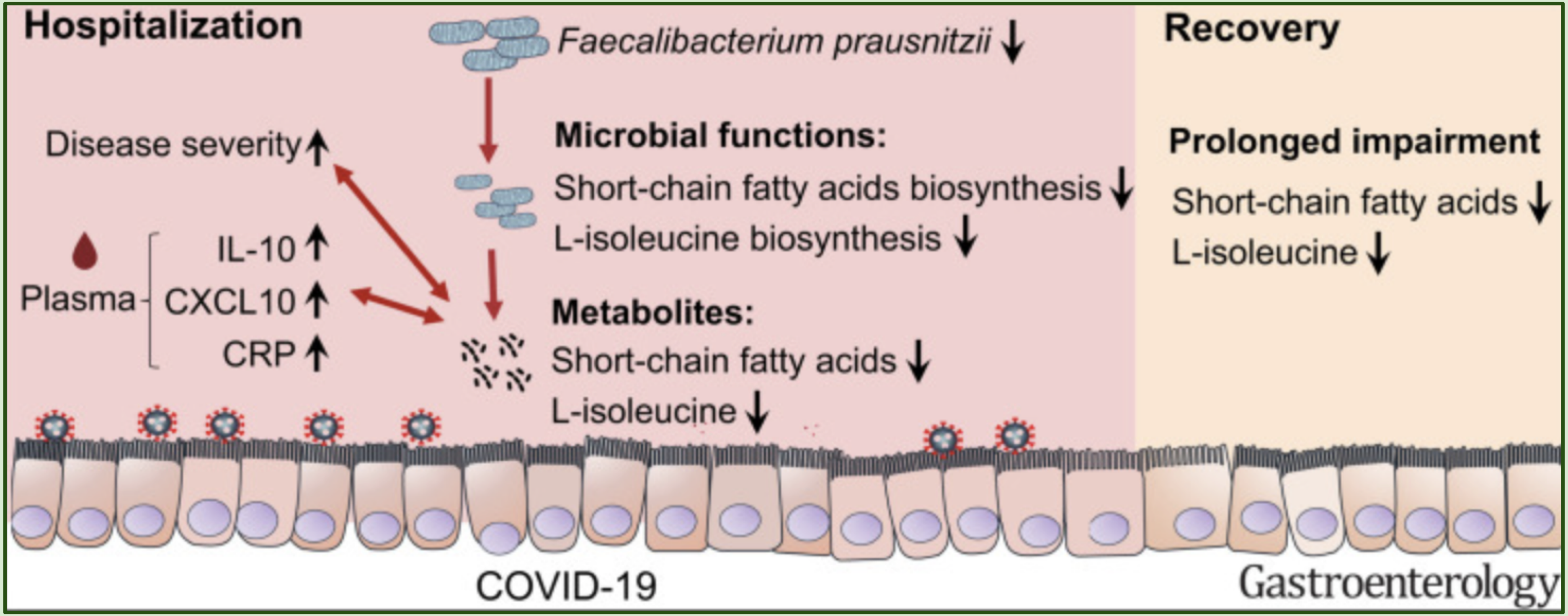
Short Chain Fatty Acids & COVID-19

- Short Chain Fatty Acids (SCFAs) are important in regulating immune responses to viruses and maintaining a strong intestinal barrier
- Groups of gut bacteria that are involved in the metabolism of SCFAs are severely decreased in patients with dysbiosis and leaky gut
- SCFAs have been hypothesized to down regulate the ACE2 receptors in the gut, an important part of the pathophysiology of COVID-19
    - A decrease in SCFAs, and the diversity of the gut microbiome correlates with a poorer prognosis

Zhang, F., Wan, Y., Zuo, T., Yeoh, Y. K., Liu, Q., Zhang, L., Zhan, H., Lu, W., Xu, W., Lui, G., Li, A., Cheung, C. P., Wong, C. K., Chan, P., Chan, F., & Ng, S. C. (2022). Prolonged Impairment of Short-Chain Fatty Acid and L-Isoleucine Biosynthesis in Gut Microbiome in Patients With COVID-19. *Gastroenterology*, *162*(2), 548–561.

Tetsuji Takabayashi, Kanako Yoshida, Yoshimasa Imoto, Robert P. Schleimer, Shigeharu Fujieda. Regulation of the Expression of SARS-CoV-2 Receptor Angiotensin-Converting Enzyme 2 in Nasal Mucosa. *American Journal of Rhinology & Allergy*, 2021.

Faecalibacterium and Short Chain Fatty Acids Depletion in COVID-19



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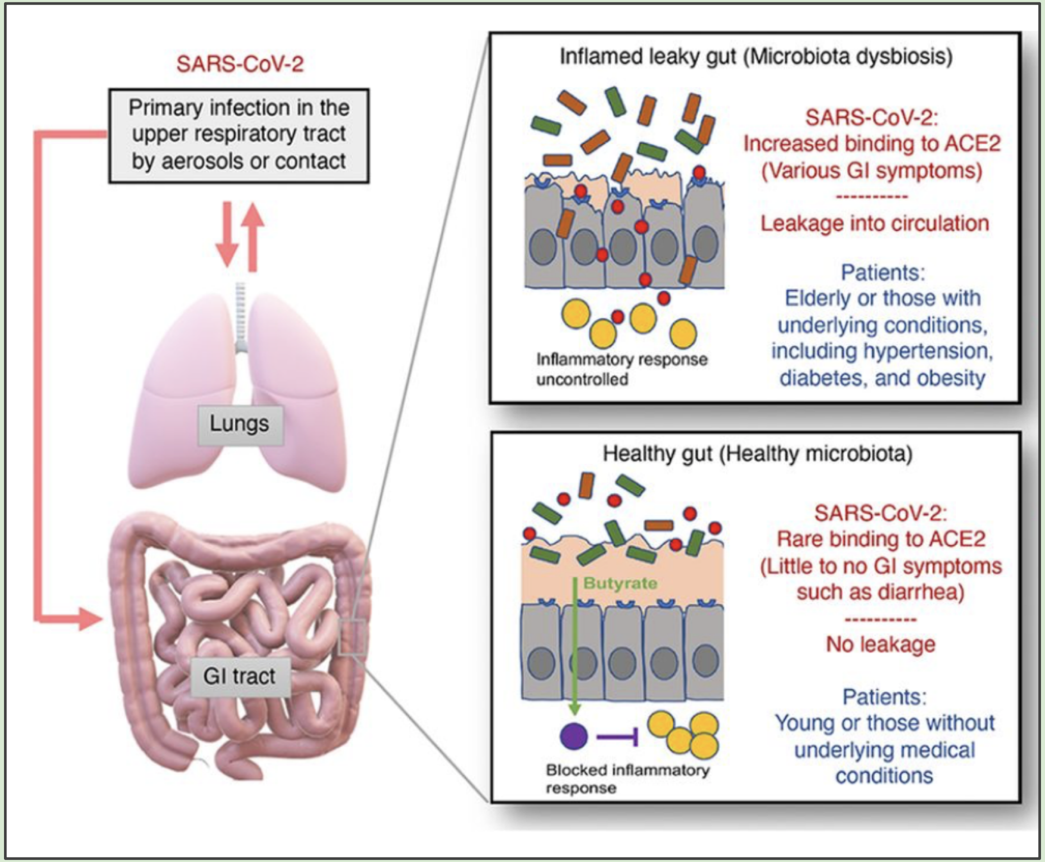
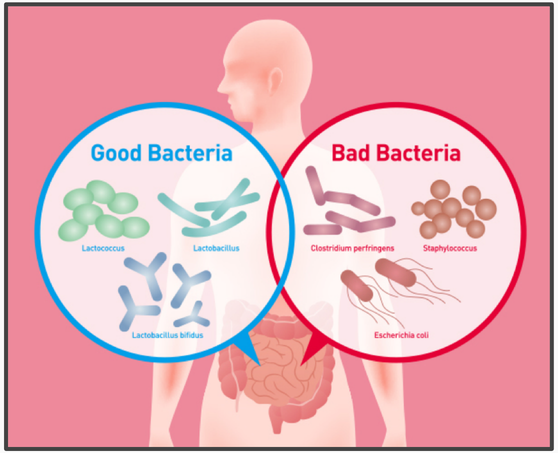
Spike Protein and ACE2 Receptors



Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome, Gut (2022).

- Found 26 species of bacteria reduced and 14 increased bacteria species
  - **Decrease in:** ("good" bacteria)
    - *Bifidobacterium pseudocatenulatum*, *F. prausnitzii*, *R. inulinivorans*, and *Roseburia hominis*
      - Related to immunity
    - *Faecalibacterium prausnitzii*
  - **Increase in:** ("bad" bacteria)
    - *Ruminococcus gnavus and Bacteroides vulgatus*
    - *Blautia obeum*
    - *Streptococcus anginosus*, *Streptococcus vestibularis*, *Streptococcus gordonii* and *Clostridium disporicum*
      - Thought to be related to respiratory symptoms in long hauler COVID



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