PERQUE INTEGRATIVE HEALTH ACADEMY

COVID-19 AND ITS IMPACT ON THE GUT MICROBIOME

Health Implications, Diagnostic, and Treatment Strategies

1

ROBIN ROSE, DO

Terrain Health

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WHAT IS 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 from a dysfunction of gut health!

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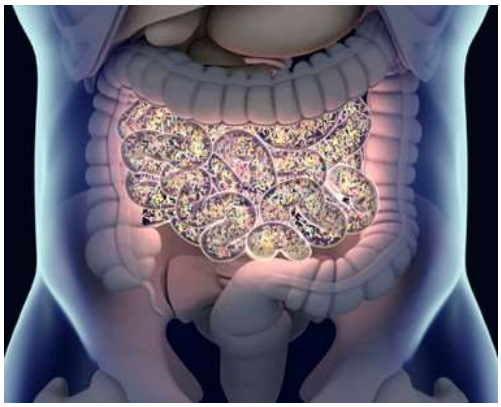
3

THE IMPORTANCE OF THE GUT CONNECTION

The role that the gut plays in health:

- Immune response
- Brain health (gut-brain connection)
- Digestive health
- Vitamin and nutrient synthesis
- Sleep, mood, & emotions
- Skin health
- Hormone health
- Stress, anxiety, & depression
- Energy levels
- Inflammation
- Other chronic disorders (neurodegenerative diseases, etc.)



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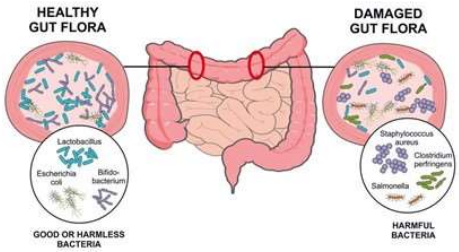
4

THE IMPORTANCE OF THE GUT CONNECTION

- The microbiota is comprised of "good" and "bad" bacteria that regulate the gut microenvironment as well as other systems in the body (*i.e.*, neurovascular, cardiovascular, immune, etc.)
- "Good" bacteria play a large role in combating disease and oxidative stress
  - Bacteria produce short chain fatty acids, synthesize vitamins and other compounds that support immune and metabolic health
- A balance of these bacteria is key to optimal health



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5

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.

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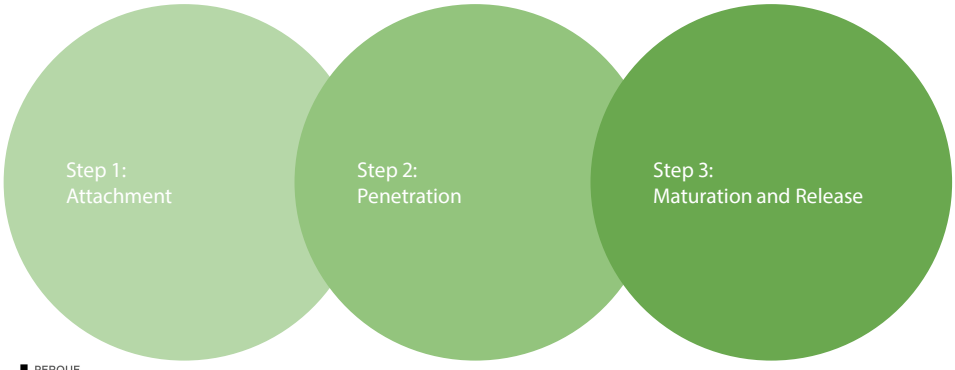
6

COVID-19 & THE GUT: PATHOPHYSIOLOGY

Steps of Infection…



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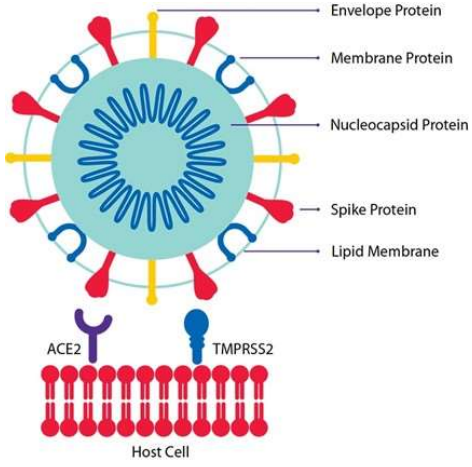
7

STEP 1: ATTACHMENT

- Virus binds to host receptors
- ACE2: receptor for COVID-19 virus
  - Promotes infection and replication of the virus by allowing the virus to enter the host cell and replicate



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8

ACE2 RECEPTORS & SPIKE PROTEIN

- Large amount of ACE2 receptors found in the small intestine and lungs
- ACE2 is highly expressed in gut:
  - Found in the epithelial cells that line the gut
  - Once ACE2 allows the virus to enter the cells, viral replication occurs and cell is destroyed → destroying tissues around organs
- Higher microbial diversity leads to significantly lower levels of ACE2 receptors
  - Healthy gut = less likely for virus to bind ACE2 receptors

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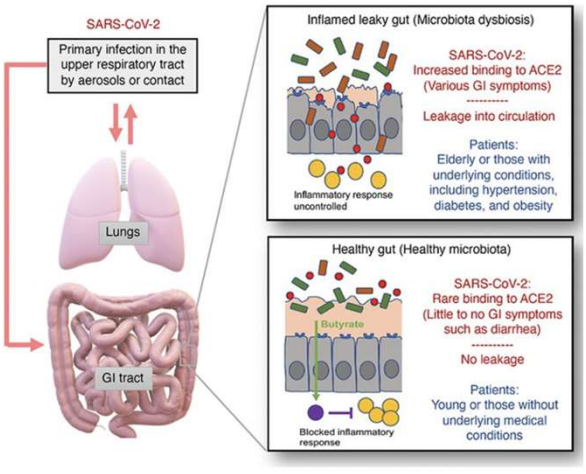
ACE2 RECEPTORS & SPIKE PROTEIN



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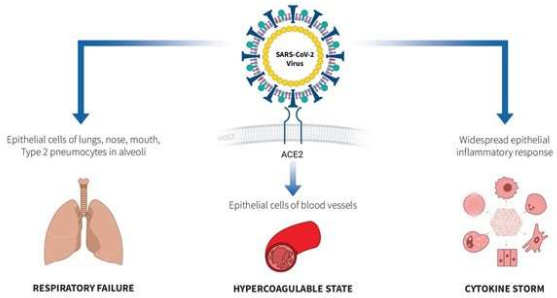
STEP 2: PENETRATION

- Virus enters cells through endocytosis or penetration of the cell membrane
- Once inside the cell, RNA virus enters the nucleus, where it begins replication



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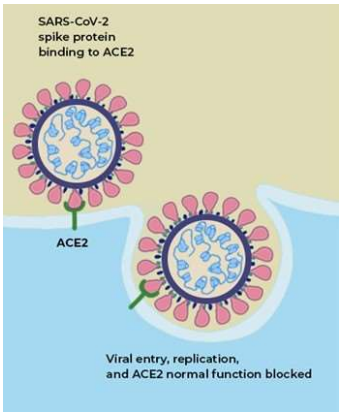
11

STEP 3: MATURATION AND RELEASE

- Viral RNA is used to synthesize viral proteins
  - Spike protein (S1 Spike)
    - Major viral protein produced once infected with the viral RNA
    - Plays a key role in allowing the virus to enter host cells & initiating infection
    - Without this protein, the virus would not be able to enter host cells
- Virus is released into host cells, initiating infection



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12

THE CONNECTION BETWEEN COVID-19 AND THE GUT

13

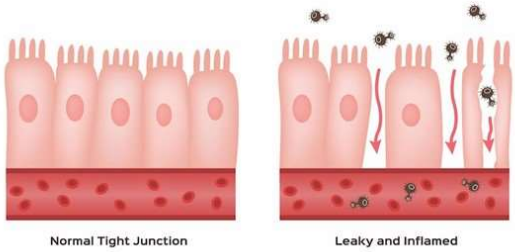
THE CONNECTION BETWEEN COVID-19 AND THE GUT: OVERVIEW

- There is a strong connection between gut health and COVID-19 severity, specifically relating to certain gut microbiota populations
  - Severity of COVID is often marked by the health of the gut microbiota
  - COVID patients are depleted of the "good bacteria" in the gut and have a higher burden of pathogens
- Poor gut health adversely effects COVID prognosis

14

TWO IMPORTANT GUT-RELATED PROCESSES WITH COVID-19

1. Intestinal permeability (IP) or "Leaky gut" and dysbiosis give the virus access to circulation, the digestive tract, and internal organs
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



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15

PATHOPHYSIOLOGY

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16

GUT BACTERIA LINKED TO IMMUNE RESPONSE TO COVID-19

- Several studies have shown the following in relation to the gut during COVID infection:
  - Positive COVID-19 patients are shown to have a lower diversity of their gut microbiota
  - Decreased levels of ***Actinobacteria*** in COVID positive patients
  - Increased levels of ***Proteobacteria*** and ***Bacteroidetes*** in positive patients
- This contributes to a pro-inflammatory gut microbiome in the presence of COVID

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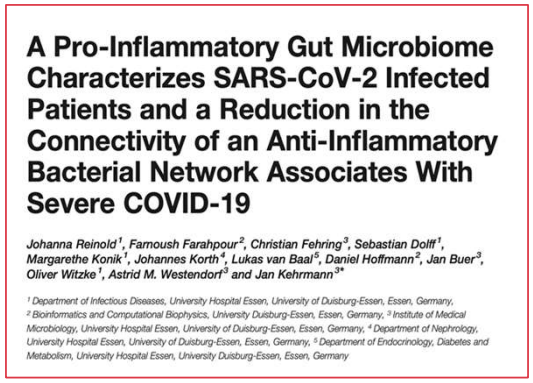
Reinold, J., Farahpour, F., Fehring, C., Dolff, S., Konik, M., Korth, J., van Baal, L., Hoffmann, D., Buer, J., Witzke, O., Westendorf, A. M., & Kehrmann, J. (2021). A Pro-Inflammatory Gut Microbiome Characterizes SARS-CoV-2 Infected Patients and a Reduction in the Connectivity of an Anti-Inflammatory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

17

FINDINGS:

- 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
- *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



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

Johanna Reinold[1], Farnoush Farahpour[2], Christian Fehring[3], Sebastian Dolff[1], Margarethe Konik[1], Johannes Korth[4], Lukas van Baal[5], Daniel Hoffmann[2], Jan Buer[3], Oliver Witzke[1], Astrid M. Westendorf[3] and Jan Kehrmann[3]

[1] Department of Infectious Diseases, University Hospital Essen, University of Duisburg-Essen, Essen, Germany, [2] Bioinformatics and Computational Biophysics, University Duisburg-Essen, Essen, Germany, [3] Institute of Medical Microbiology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany, [4] Department of Nephrology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany, [5] Department of Endocrinology, Diabetes and Metabolism, University Hospital Essen, University Duisburg-Essen, Essen, Germany

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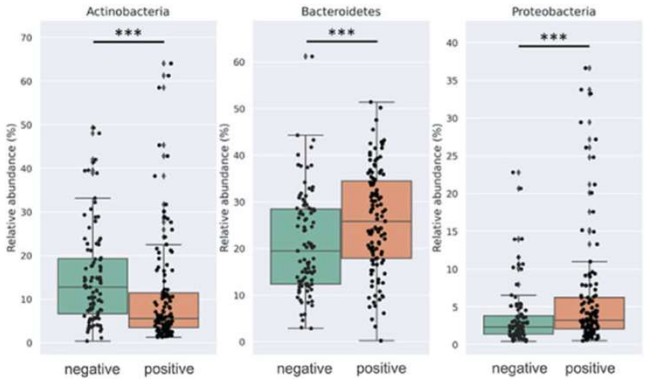
18

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

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.

19

ANOTHER STUDY INDICATING THE ROLE OF THE GUT MICROBIOME ON COVID-19 INFECTION AND SEVERITY…

Lost microbes of COVID-19: *Bifidobacterium, Faecalibacterium* depletion and decreased microbiome diversity associated with SARS-CoV-2 infection severity

Sabine Hazan,[1] Neil Stollman,[2] Huseyin S Bozkurt,[3] Sonya Dave ,[4,5] Andreas J Papoutsis,[1] Jordan Daniels,[1] Brad D Barrows,[1] Eamonn MM Quigley ,[6] Thomas J Borody[7]

A study done by Dr. Hazan and colleagues (2022) to determine the association between SARS-CoV-2 and gut microbiome composition

Looked at PCR-positive patients with mild, moderate, to severe symptoms — compared to negative control patients

20

HAZAN *ET AL.* — FINDINGS

- Patients with severe symptoms had a lower gut microbiome diversity overall
  - All positive patients had:
    - ↓ **Bifidobacterium, Faecalibacterium, and Rosburium**
    - ↑ Bacteroides
    - They also found a correlation between levels of these bacteria and disease severity
- Hypothesize that gut-immune connection provides immune system resilience depending on diversity and composition of the gut microbiome before, during, and after infection
  - Dysbiosis and depletion of *Bifidobacterium* and *Faecalibacterium* increases risk of severe infection

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Hazan, S., Stollman, N., Bozkurt, H. S., Dave, S., Papoutsis, A. J., Daniels, J., Barrows, B. D., Quigley, E. M., & Borody, T. J. (2022). Lost microbes of COVID-19: *Bifidobacterium*, *Faecalibacterium* depletion and decreased microbiome diversity associated with SARS-CoV-2 infection severity. *BMJ open gastroenterology*, *9*(1), e000871.

21

THE CONNECTION BETWEEN COVID-19 AND THE GUT: POSSIBLE PATHOPHYSIOLOGY

- High plasma levels of zonulin indicate IP & have been seen in COVID patients
- Dysbiosis and depletion of certain gut microbiota has been linked to poor COVID-19 outcomes (ex. *Bifidobacterium* depletion)
- Increased IP is associated with an increase in spike protein in circulation

So, high levels of intestinal permeability (leaky gut, dysbiosis, etc) indicate poor COVID outcomes **AND** COVID can contribute to increased intestinal permeability

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22

ZONULIN

- High zonulin levels are correlated with increased levels of IP
- Higher IP is seen in COVID-19 patients, creating higher levels of toxins that enter the bloodstream
- Higher levels of zonulin are found in patients with mild to severe COVID-19, compared to healthy and negative controls
- Zonulin levels have been especially high in hospitalized patients, compared to controls
- "Severe COVID-19 is associated with high levels of markers of tight junction permeability and microbial translocation" (Giron *et al.*, 2021)

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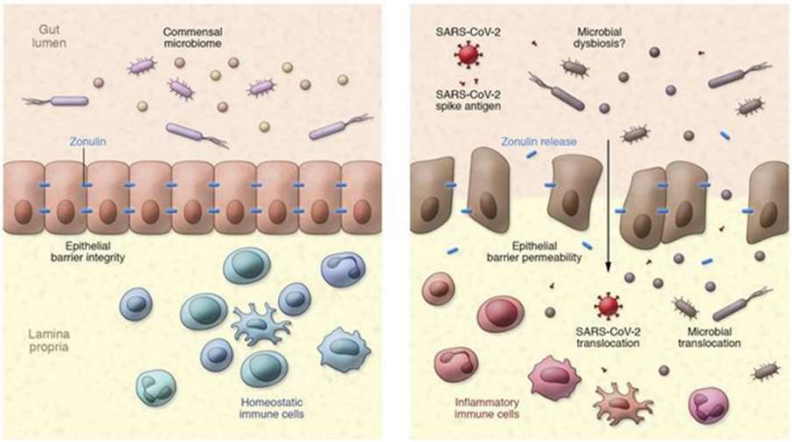
Giron, L. B., Dweep, H., Yin, X., Wang, H., Damra, M., Goldman, A. R., Gorman, N., Palmer, C. S., Tang, H. Y., Shaikh, M. W., Forsyth, C. B., Balk, R. A., Zilberstein, N. F., Liu, Q., Kossenkov, A., Keshavarzian, A., Landay, A., & Abdel-Mohsen, M. (2021). Plasma Markers of Disrupted Gut Permeability in Severe COVID-19 Patients. Frontiers in immunology, 12, 686240.

23

ZONULIN CONT.



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Hensley-McBain, T., & Manuzak, J. A. (2021). Zonulin as a biomarker and potential therapeutic target in multisystem inflammatory syndrome in children. *The Journal of clinical investigation*, *131*(14), e151467.

24

HOW DOES COVID-19 INCREASE INTESTINAL PERMEABILITY?

- Depletion of Glutamine!
  - Glutamine is:
    - Abundant amino acid in the body
    - Essential in immune system
      - Functions in lymphocyte proliferation, cytokine production, macrophage activity, neutrophil bacteria killing
    - Essential for metabolic function
    - Recommended for immunosuppressed individuals
    - Regulates intestinal permeability
    - Key to immune system!

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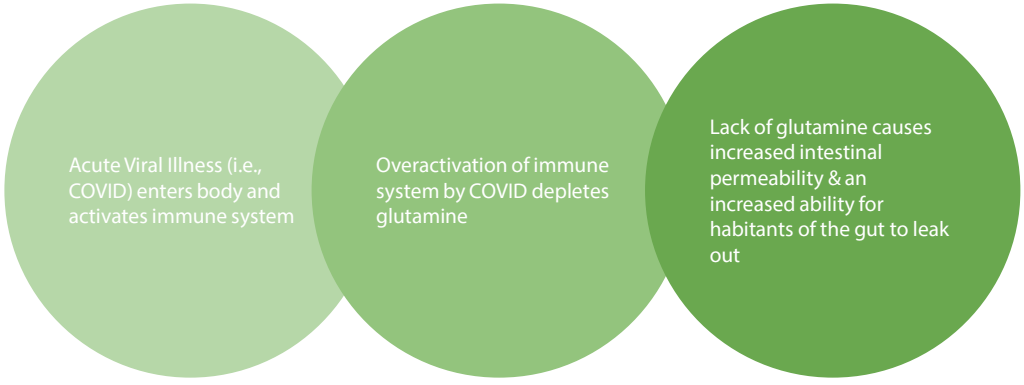
25

GLUTAMINE DEPLETION



*Note that one's individual gut composition correlates with IP and what is able to gain access to circulation

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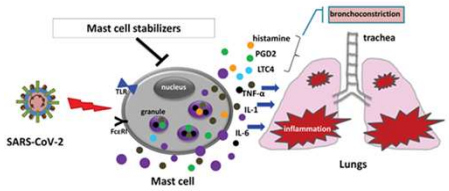
26

MAST CELLS & COVID-19

- Mast cells → granulocytes (release histamine, heparin, cytokines, etc.) found in connective tissue
  - If dysregulated, responsible for allergic reactions and inflammation
- Mast cells are activated in COVID-19 infection
- Mast cell activation syndrome is prominent in COVID-19 and Long Covid patients



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Afrin, L. B., Weinstock, L. B., & Molderings, G. J. (2020). Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*, *100*, 327–332.

27

MAST CELLS & COVID-19

- MCAS (Mast Cell Activation Syndrome) – chronic multi-organ inflammatory syndrome
  - Hyper-inflammation throughout the whole body due to mast cell activation (cytokine storms)
- There are many overlaps with inflammation that are seen with COVID and MCAS
- Mast cell stabilizers can be used in COVID-19 patients to decrease inflammation and long Covid symptoms

PERQUE INTEGRATIVE HEALTH ACADEMY

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28

MCAS STUDY

Perspective

Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome

Lawrence B. Afrin[a,*], Leonard B. Weinstock[b], Gerhard J. Molderings[c]

[a] Department of Mast Cell Studies, AIM Center for Personalized Medicine, Purchase, New York, USA
[b] Department of Medicine, Washington University, St. Louis, Missouri, USA
[c] Institute of Human Genetics, University Hospital of Bonn, Bonn, Germany

"Drugs with activity against MCs or their mediators have preliminarily been observed to be helpful in Covid-19 patients. None of the authors' treated MCAS patients with Covid-19 suffered severe infection, let alone mortality."

- They concluded that high inflammation seen in Covid and post-Covid patients may be attributed to dysfunction of mast cells, relating to MCAS
- Treating dysfunctional mast cells serves as an effective way to combat inflammation in Covid patients

29

MCAS STUDY (CONT.)

Perspective

Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome

Lawrence B. Afrin[a,*], Leonard B. Weinstock[b], Gerhard J. Molderings[c]

[a] Department of Mast Cell Studies, AIM Center for Personalized Medicine, Purchase, New York, USA
[b] Department of Medicine, Washington University, St. Louis, Missouri, USA
[c] Institute of Human Genetics, University Hospital of Bonn, Bonn, Germany

"Drugs with activity against MCs or their mediators have preliminarily been observed to be helpful in Covid-19 patients. None of the authors' treated MCAS patients with Covid-19 suffered severe infection, let alone mortality."

- Drugs that mediate inflammation: aspirin, famotidine
- Additional drugs undergoing clinical trials to treat MCAS and Covid: cromolyn, flavonoids, leukotriene inhibitors, JAK inhibitors, dexamethasone, LDN, quercetin, and ascorbic acid
- Treated patients with these drugs that demonstrated mass-inflammation during COVID-19 similar to MCAS symptoms

30

MAST CELL DEGRANULATION STUDY

ARTICLE OPEN

SARS-CoV-2-triggered mast cell rapid degranulation induces alveolar epithelial inflammation and lung injury

Meng-Li Wu[1], Feng-Liang Liu[2], Jing Sun[3], Xin Li[4], Xiao-Yan He[2,5], Hong-Yi Zheng[2], Yan-Heng Zhou[4], Qihong Yan[4], Ling Chen[4], Guo-Ying Yu[1], Junbiao Chang[1], Xia Jin[6], Jincun Zhao[3], Xin-Wen Chen[4,5]✉, Yong-Tang Zheng[2,5]✉ and Jian-Hua Wang[4,7]✉

- Wu *et al.* also confirmed that mast cell degranulation is induced by COVID-19 (in as short as 5 min)
- Their methods included using the **Spike-RBD protein** and the **ACE2** receptor in mice which yielded this mast cell degranulation in mice models
- Thus, the binding of Spike to ACE2 can induce this mast cell degranulation and inflammatory response
- So, mast cells stabilizers becomes a possible treatment for inflammation in affected cells and bodily systems

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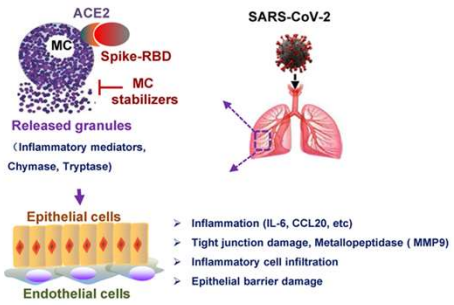
31

PATHOPHYSIOLOGY OF MAST CELLS IN COVID-19: ACE2 AND SPIKE PROTEIN

1. Spike protein binds to ACE2 receptor on mast cell
2. Mast cell is activated
3. Mast cell degranulation occurs
4. Can lead to tissue damage and inflammation through recruitment of other immune cells

*Note: the Spike protein remains in the body after both infection and vaccination



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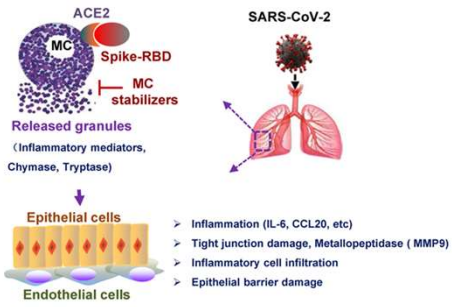
Wu, ML., Liu, FL., Sun, J. *et al.* SARS-CoV-2-triggered mast cell rapid degranulation induces alveolar epithelial inflammation and lung injury. *Sig Transduct Target Ther* 6, 428 (2021). https://doi.org/10.1038/s41392-021-00849-0

32

PATHOPHYSIOLOGY OF MAST CELLS IN COVID-19: ACE2 AND SPIKE PROTEIN

- The Spike protein is more likely to circulate in the bloodstream if you have leaky gut or dysbiosis, which can be caused by a lack of actinobacteria in the gut
- The more permeable your gut, the more Spike protein is in the circulation with the possibility of encountering mast cells at the ACE2 receptor
- Therefore, the more permeable the gut, the more likely you will have inflammation (MCAS)



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33

TOLL-LIKE RECEPTORS & COVID-19: ANOTHER POSSIBLE SOURCE OF INFLAMMATION IN COVID-19

- Spike protein induces cytokines and chemokines "IL-6, IL-1β, TNFα, CXCL1, CXCL2, and CCL2" causing inflammation, but how?
- Findings: NF-κB pathway was activated by the Spike protein in the presence of TLR2 receptor, releasing pro-inflammatory cytokines
  - A possible explanation for the cytokine storm in COVID-19

SARS-CoV-2 spike protein induces inflammation via TLR2-dependent activation of the NF-κB pathway

Shahanshah Khan[1], Mahnoush S Shafiei[1], Christopher Longoria[2], John W Schoggins[3], Rashmin C Savani[2], Hasan Zaki[1]*

[1]Department of Pathology, The University of Texas Southwestern Medical Center, Dallas, United States; [2]Department of Pediatrics, The University of Texas Southwestern Medical Center, Dallas, United States; [3]Department of Microbiology, The University of Texas Southwestern Medical Center, Dallas, United States

- The Spike protein is an important PAMP that can over-activate the innate immune responses that lead to cytokine activation and inflammation
- PAMP (pathogen associated molecular patterns): recognized by TLRs and other receptors in the body

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34

KAHN *ET AL.* (CONT.)

- Innate cells do not have high ACE2 expression, so they looked for other mechanisms that may overstimulate the innate immune responses, leading to the over-inflammation in Covid
- Found that spike protein S1 subunit activates TLR proinflammatory signaling

They suggest 3 mechanisms of inflammation by the Spike protein & TLR-2

1. "Innate immune cells like macrophages and monocytes recognize S protein of SARS-CoV-2 at the cell surface through TLR2, leading to the activation of the NF-κB pathway" (pg. 11).
2. "Innate immune cells get activated by virally infected epithelial cells. Our data suggest that epithelial cells expressing S protein in the cytosol can activate macrophages when they physically interact" (pg. 11).
3. "Like myeloid cells, epithelial cells can be activated by S protein extracellularly, leading to the induction of proinflammatory cytokines and chemokines" (pg. 11).

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Khan, S., Shafiei, M. S., Longoria, C., Schoggins, J. W., Savani, R. C., & Zaki, H. (2021). SARS-CoV-2 spike protein induces inflammation via TLR2-dependent activation of the NF-κB pathway. *eLife*, *10*, e68563.
Shirato, K., & Kizaki, T. (2021). SARS-CoV-2 spike protein S1 subunit induces pro-inflammatory responses via toll-like receptor 4 signaling in murine and human macrophages. *Heliyon*, *7*(2), e06187.

35

TREATMENTS

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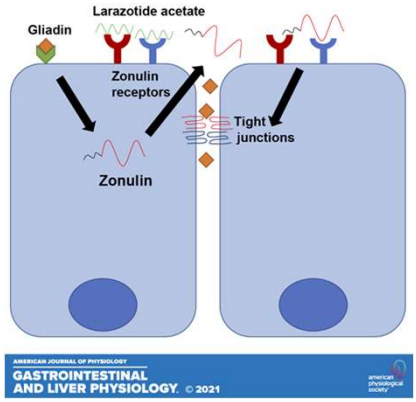
36

LARAZOTIDE

- Inhibits zonulin and works to close tight junctions, limiting intestinal permeability
- Acts as a zonulin antagonist
- In study in children diagnosed with COVID-19 MIS-C, Larazotide was given, when IVIG and steroids failed
- After administration, the spike protein was reduced in bloodstream and inflammation decreased
  - Demonstrates how important intestinal permeability is in relation to COVID/MIS-C!
- Dosing: 10 mcg/kg for 21 days



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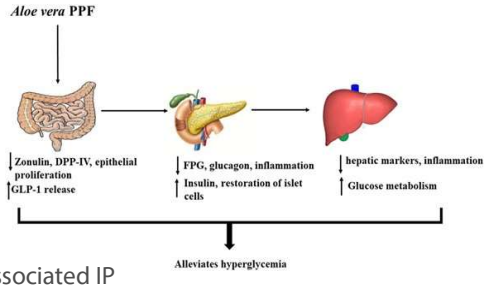
Yonker, L. M., Swank, Z., Gilboa, T., Senussi, Y., Kenyon, V., Papadakis, L., Boribong, B. P., Carroll, R. W., Walt, D. R., & Fasano, A. (2022). Zonulin Antagonist, Larazotide (AT1001), As an Adjuvant Treatment for Multisystem Inflammatory Syndrome in Children: A Case Series. *Critical care explorations*, *10*(2), e0641.
Slifer, Z. M., Krishnan, B. R., Madan, J., & Blikslager, A. T. (2021). Larazotide acetate: a pharmacological peptide approach to tight junction regulation. *American journal of physiology. Gastrointestinal and liver physiology*, *320*(6), G983–G989.

37

ALOE VERA STUDY

Role of zonulin and GLP-1/DPP-IV in alleviation of diabetes mellitus by peptide/polypeptide fraction of Aloe vera in streptozotocin- induced diabetic wistar rats

Spoorthy N Babu [1], S Govindarajan [1], M A Vijayalakshmi [1], Ayesha Noor [2]



- Aloe Vera was used to treat patients with diabetes & high associated IP
- Patients with high IP had low levels of zonulin and GLP-1
- Goal: to see if Aloe Vera plays a role in increasing zonulin and GLP-1 levels, while decreasing IP
- Observed: "An increase in GLP-1 levels with a decrease in DPP-IV and zonulin levels thereby mitigating the loss of intestinal permeability"

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38

MORINGA

- Moringa Oleifera Polysaccharide (MOP)
  - Antioxidant that protects cells from damage and reduces inflammation
- In this study, they investigated the effect of moringa on the immune cells and gut microbiota of mice
- Control and treatments groups: MOP was used in 0, 20, 40, and 60 mg/kg doses for 28 days
- Findings:
  - Increase in thymus and spleen index
  - Decrease in IL-6 and TNF-α
  - Alter gut microbiota
    - Increase Muri Bacillaceae
    - Decrease Proteobacteria, Helicobacter, Stenotrophomonas
- Overall: positive effects on gut microbiota and immune function

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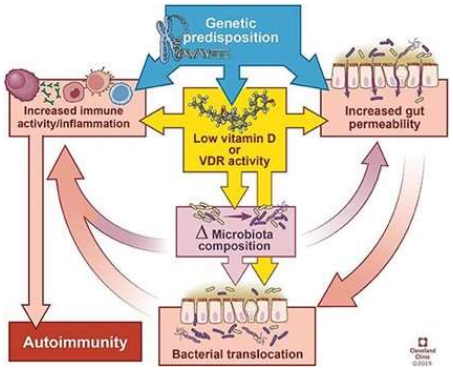
39

VITAMIN D, MAST CELLS, AND THE GUT BARRIER

- Chronic inflammation depletes Vitamin D
- If mast cells are dysregulated in COVID-19, then there are higher levels of inflammation and Vitamin D degradation
- Vitamin D supplementation increases overall gut microbiome diversity
- Vitamin D is involved in regulating inflammation through decreasing *Bacteroides* and increasing *Bifidobacterium* and *Akkermansia*
- Poor gut composition and high IP can cause higher levels of mast cell activation and vice versa



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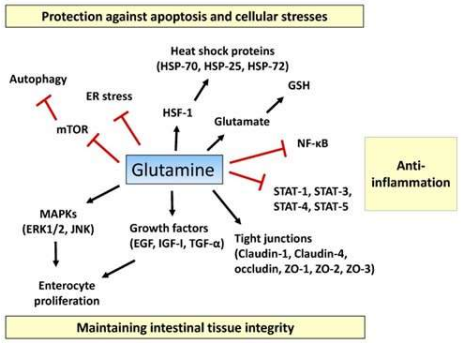
Singh, P., Rawat, A., Alwakeel, M. *et al.* The potential role of vitamin D supplementation as a gut microbiota modifier in healthy individuals. *Sci Rep* 10, 21641 (2020).
Yamamoto, E. A., & Jørgensen, T. N. (2020). Relationships Between Vitamin D, Gut Microbiome, and Systemic Autoimmunity. *Frontiers in immunology*, *10*, 3141.

40

GLUTAMINE

- Most abundant free amino acid in the body
- Maintain tight junction structure in the gut and reduce IP
- A fuel source for cells in the intestines
- "Glutamine promotes enterocyte proliferation, regulates tight junction proteins, suppresses pro-inflammatory signaling pathways, and protects cells against apoptosis and cellular stresses during normal and pathologic conditions"



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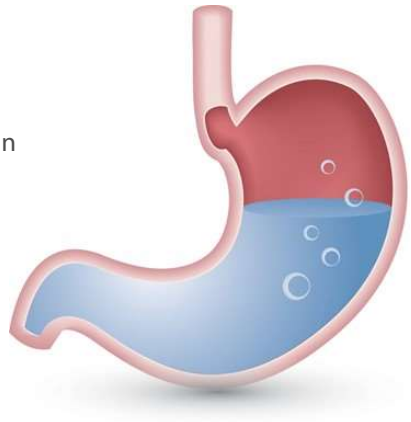
Kim, M. H., & Kim, H. (2017). The Roles of Glutamine in the Intestine and Its Implication in Intestinal Diseases. *International journal of molecular sciences*, *18*(5), 1051.

41

HYDROCHLORIC ACID

- Enzymes help further break down food and are also used by the "good" bacteria in your gut to make energy
- Enzymes are the first thing that breaks down proteins in your stomach
- If we do not break down protein in the intestine, then it can leak out into the circulation – causing immune system activation and inflammation
- Eliminates bacteria and viruses in the intestines



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42

SPORE FORMING PROBIOTICS

- Mechanism: stimulate growth of keystone and commensal organisms ("good" bacteria)
- "Probiotics may restore the composition of the gut microbiome and introduce beneficial functions to gut microbial communities, resulting in amelioration or prevention of gut inflammation and other intestinal or systemic disease phenotypes."
- Encourages good strains of bacteria
- Commensal bacteria that make up probiotics help maintain the gut lining
- Enhance innate immunity

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Hemarajata, P., & Versalovic, J. (2013). Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. *Therapeutic advances in gastroenterology*, *6*(1), 39–51.

43

VITAMIN C

- Oral vitamin C to boost immune system
- Anti-inflammatory and antioxidant properties
- Studies show that vitamin C supplementation leads to a shift in bacterial populations in the gut
  - Increase in "good" bacteria and decrease "bad" bacteria
- "Daily supplementation of high-dose vitamin C led to an increase in the relative abundances of Lachnospiraceae ($p < 0.05$), whereas decreases were observed for Bacteroidetes ($p < 0.01$), Enterococci ($p < 0.01$) and Gemmiger formicilis ($p < 0.05$)."
- Dose: 1000 mg daily for two weeks

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Otten, A. T., Bourgonje, A. R., Peters, V., Alizadeh, B. Z., Dijkstra, G., & Harmsen, H. (2021). Vitamin C Supplementation in Healthy Individuals Leads to Shifts of Bacterial Populations in the Gut-A Pilot Study. *Antioxidants (Basel, Switzerland)*, *10*(8), 1278.

44

QUERCETIN

- Zinc Ionophore
- Powerful antioxidant that helps regulate inflammatory responses in the body
- "King of flavonoids"
  - Flavonoids:
    - Naturally found in plants (secondary metabolites)
    - Typically found in fruits and vegetables
    - Have anti-oxidative, anti-inflammatory, anti-mutagenic and anti-carcinogenic properties
    - Modulate important enzymes and histamine!
- Heals leaky gut → helps with forming tight junctions in the intestines, which reduces intestinal permeability
- Ongoing research for treating COVID-19 because of its anti-viral properties!
  - Impairs binding of the Spike protein to the ACE2 receptor
- Recommended Dose: Quercetin 250 mg - 500 mg per day

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45

THANK YOU!!!

Contact Us!

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QUESTIONS?

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46

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47

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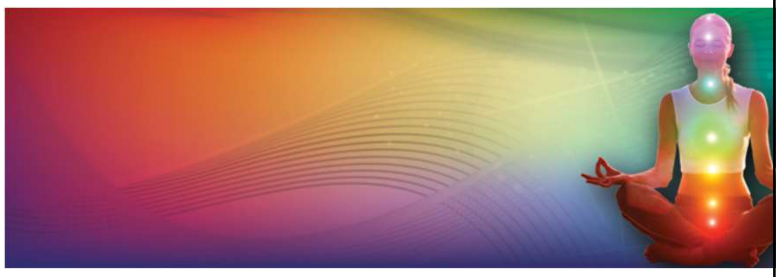

COVID-19 AND ITS IMPACT ON THE GUT MICROBIOME

Health Implications, Diagnostic, and Treatment Strategies

48