The Root-cause Approach to PASC/Long COVID

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Disclosure

- Functional Naturopathic Medicine at DocereVita
- Medical Educator and Content Curator Calroy Health Sciences
- Science Advisory Board Member and Medical Education at NutriDyn, NutriDyn EU, Ananda Professionals, & KBMO Diagnostics
- Advisory Board and Faculty Functional Medicine Coaching Academy
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https://www.ovationlab.com/pvrpresources

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ANDHEALTH

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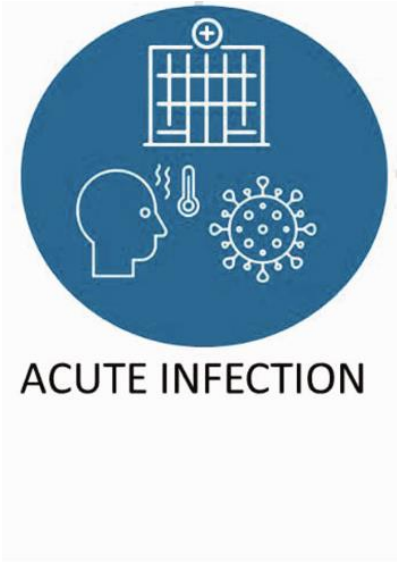
Current Landscape

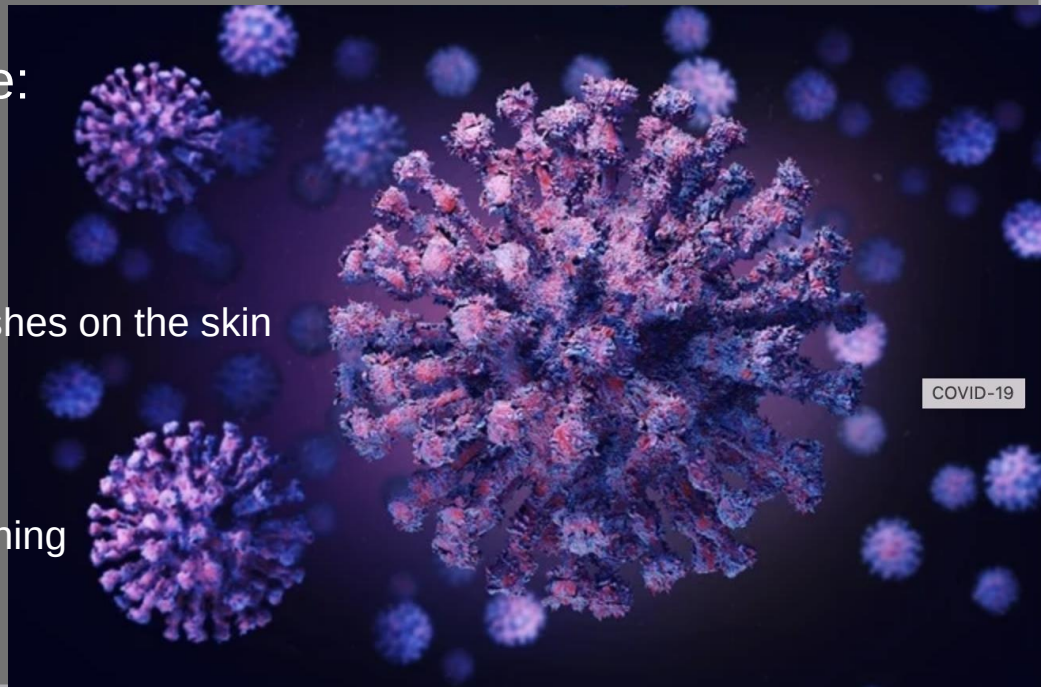
- Confusing terminology: PASC, long COVID, long haul
- 200+ symptoms: delayed, remitting, relapsing
- Long lag times before diagnosis
- No proven treatments, no standards of care = no guidelines and no trained workforce

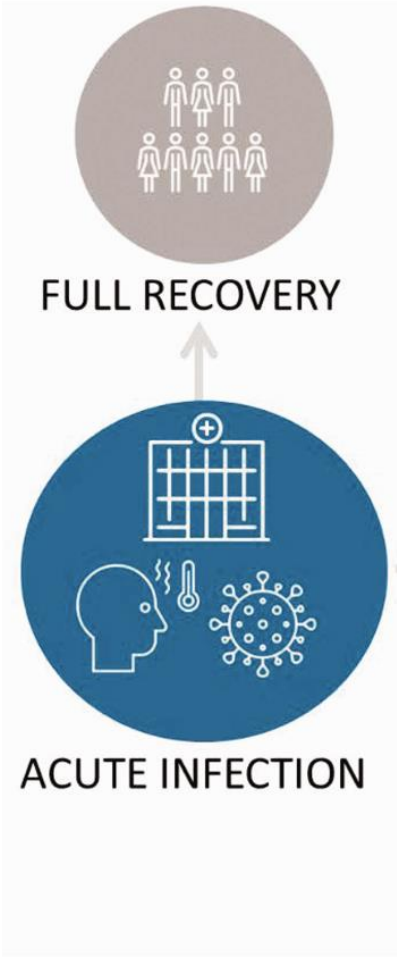


Aiyegbusi OL, Hughes SE, Turner G, et al. Symptoms, complications and management of long COVID: a review. *Journal of the Royal Society of Medicine*. 2021;114(9):428-442. doi:10.1177/01410768211032850

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

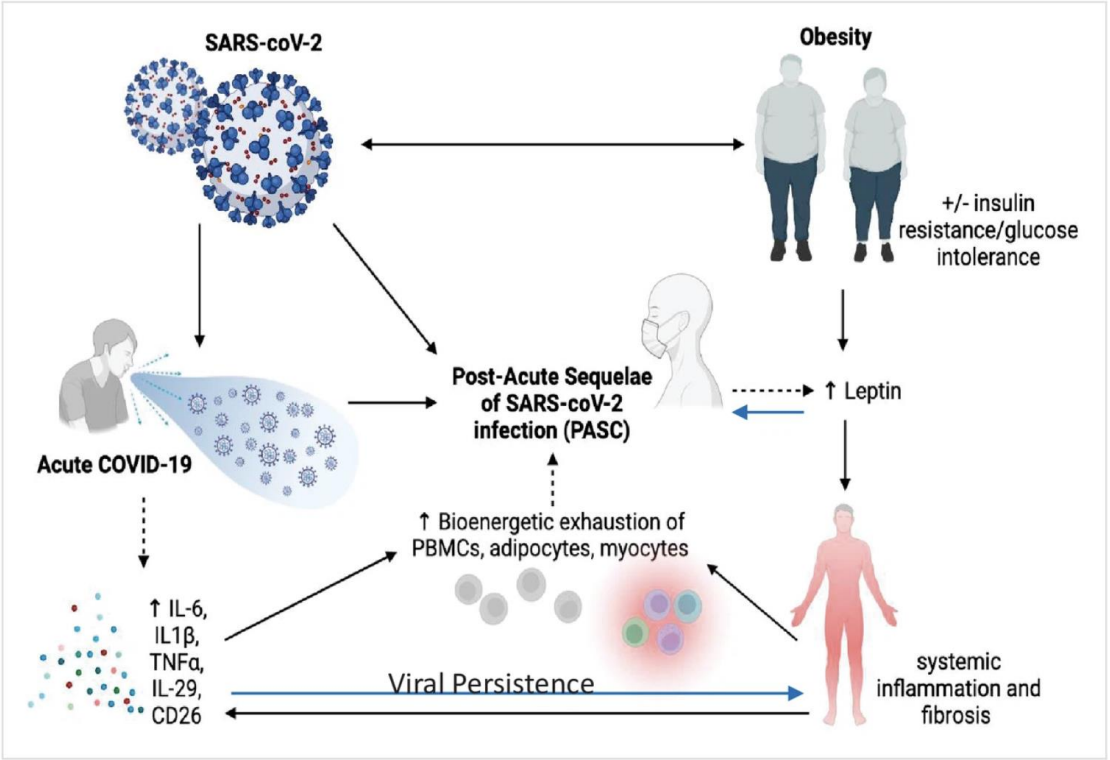
- According to WHO, the 3 main symptoms of COVID-19 are:
  - Fever - a high temperature >37.8^{O}C/100^{O}F
  - Tiredness
  - Dry cough
- Less common symptoms include:
  - Headache
  - Diarrhea
  - Loss of taste or smell
  - Sore throat
  - Discoloration of toes or fingers, or rashes on the skin
  - Aches and pains
  - Conjunctivitis
- Serious symptoms are:
  - Shortness of breath or difficulty breathing
  - Chest pain or pressure
  - Loss of movement or speech

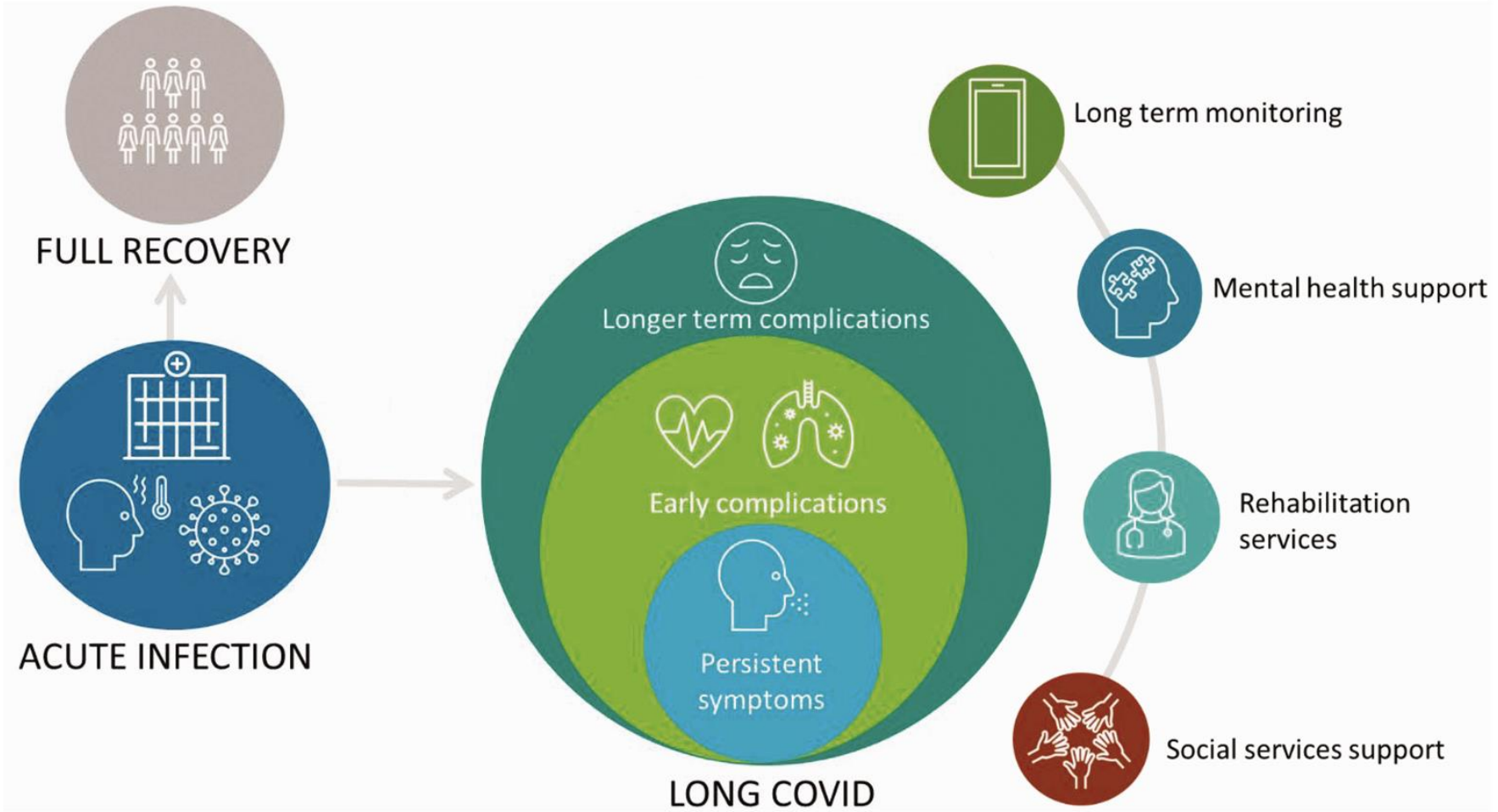




Aiyegbusi OL, Hughes SE, Turner G, et al. Symptoms, complications and management of long COVID: a review. *Journal of the Royal Society of Medicine*. 2021;114(9):428-442. doi:10.1177/01410768211032850

Metabolic Issues Impacting Acute COVID Infection & PASC





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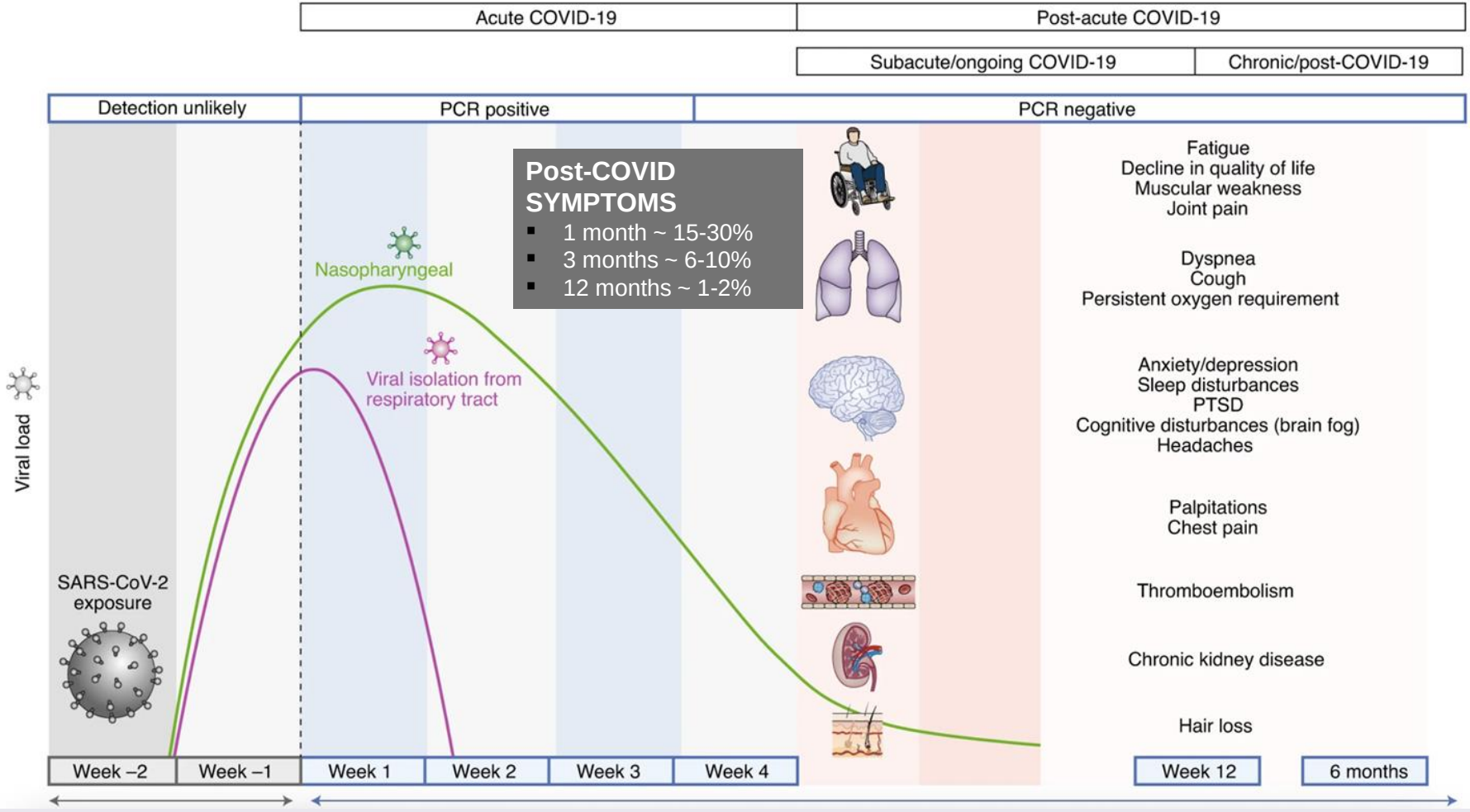
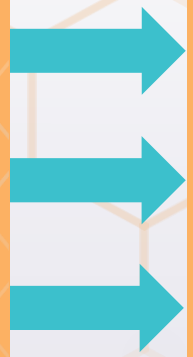


Immune Foundations | Acute COVID Infection Care | Post-acute Sequalae COVID (PASC) | Long-haul COVID

LONG COVID PREVALENCE [1]

- Greater than 80% of Americans have had acute COVID
- Most Long COVID cases occur in people with mild acute illness
- 1/3 of people with Long COVID have **no identified pre-existing conditions**
- Reinfection contributes additional risk of Long COVID

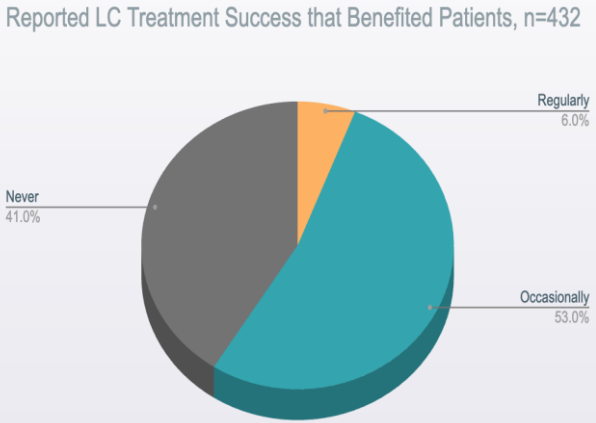
- 15-30% people have persistent symptoms @ 1 month
- 6-10% people have persistent symptoms @ 3 months
- 1-2% people have persistent symptoms @ 12 months



Long COVID Incidence Estimate

- ~ 30 million people with Post-COVID @ 1 month
- ~ 10 million people with Post-COVID @ 3 months
- ~ 2 -4 million people with Post-COVID @ 12 months

Medscape Physician Survey (2023) Key Findings



Long COVID does not appear to be self-resolving,

in the sense of spontaneous recovery or recovery in the absence of a cure or a treatment that has been validated. It further raises the importance of finding treatment because this is not going to go away.

Ziyad Al-Aly

Clinical Epidemiologist

Washington University, St Louis

STAT Health Tech, 9/20/2023 https://www.statnews.com/2023/09/20/do-long-covid-odds-increase-with-second-infection/?utm_campaign=breaking_news&utm_medium=email&_hsmi=275130536&_hsenc=p2ANqtz-_Fz5sQzp45OzS1UyaREko82SfD8HXId2tVTahbKLPYeT_IzbsU0EZCjEYEIU-qBJptPUPhyCM_6OqMIbAfcKQeCUgpWQ&utm_content=275130536&utm_source=hs_email

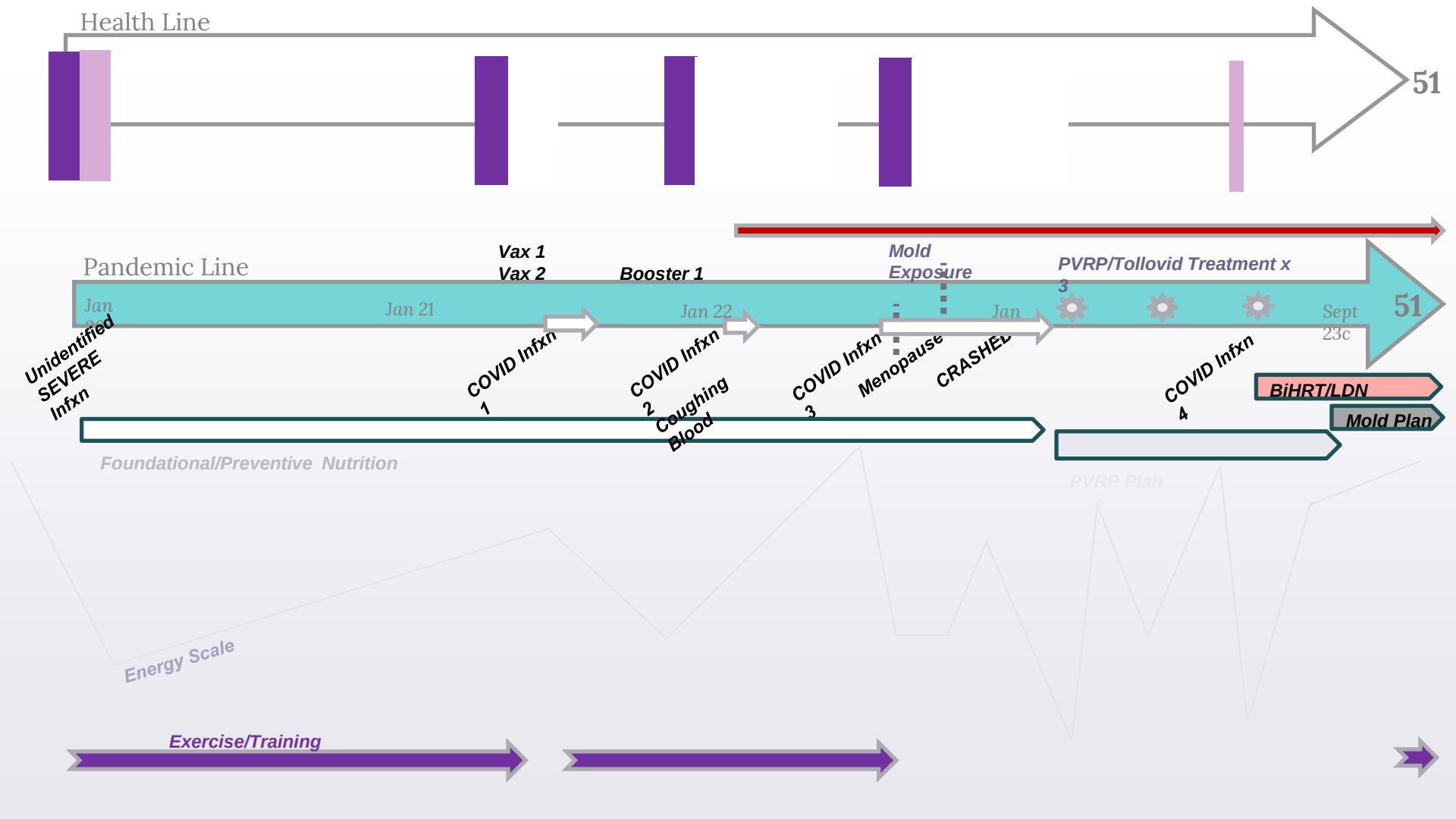
Patient Case KH

Dr. Kara Parker, MD
Faculty, Department of Family Medicine
Director of Group Medical Visits
Hennepin Healthcare Whittier Clinic

YOUR 2020 PANDEMIC STORY

- Epigenetics/Genetics/Genomics
- Family History & Tribal Lore/Ancestral Work
- Childhood Growth & Development
- Adverse Childhood Experiences
- Socio-economic Factors
- Nourishment/Foundational Nutrition
- Microbiome
- Allergies/Sensitivities
- Inflammation
- Infection
- Auto-immun-ing
- Toxicity/BioToxins/Mold
- Metabolic Imbalances
- Stress/Trauma

TRIGGERS?
Reactivation?
Intensifications?
Exacerbations?


Health Line
51
Pandemic Line
Vax 1
Vax 2
Booster 1
Mold Exposure
PVRP/Tollovid Treatment x 3
Jan
Jan 21
Jan 22
Jan
Sept 23c
51
Unidentified SEVERE Infxn
COVID Infxn 1
COVID Infxn 2
COVID Infxn 3
Menopause
CRASHED
COVID Infxn 4
Coughing Blood
BiHRT/LDN
Mold Plan
Foundational/Preventive Nutrition
PVRP Plan
Energy Scale
Exercise/Training

LONG COVID IN THE POST-PANDEMIC ERA

ASSESSING PROGRESSION AND PERSONALIZING TREATMENT USING A ROOT-CAUSE APPROACH

ACE2-Driven Tissue Damage AND/OR Inflammation/ Immune Dysregulation

ACE2 TISSUE DAMAGE

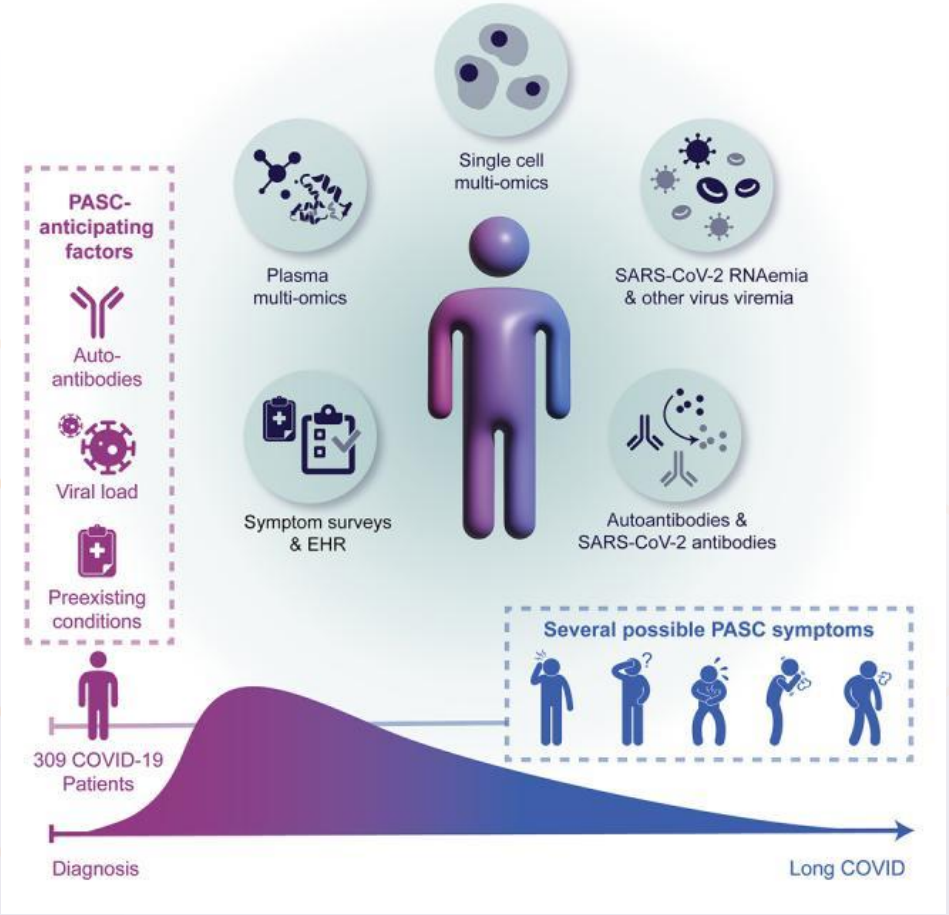
- Tissue Damage
  - Cardiac
  - Pulmonary
  - Endothelitis
  - Brain/Neural tissue
  - GI Tract
- Secondary dysfunction
  - Clotting/ Coagulation
  - Vagus nerve/ Brainstem
  - Cognitive & Mood Disorders

IMMUNE DYSREGULATION

- Infection
  - Persistent SARS-CoV-2 virus/ fragments
  - EBV Reactivation
  - Reactivation of Neurotrophic Pathogens
- Chronic Inflammation
  - T-cell Dysregulation
  - MicroGlial Activation
  - Mast Cell Activation
  - Gut/ Microbiome Dysbiosis
  - Mitochondrial Dysfunction

Multiple early factors anticipate post-acute COVID-19 sequelae

Su, Y, Yuan, D, et. al. (2022). Multiple early factors anticipate post-acute COVID-19 sequelae. Cell, 185(5). https://doi.org/10.1016/j.cell.2022.01.014



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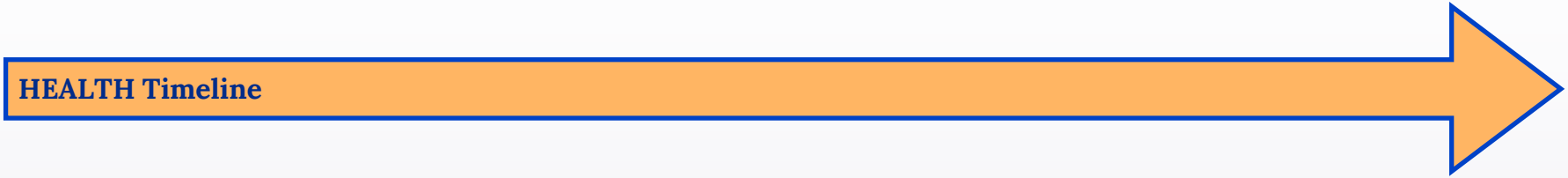

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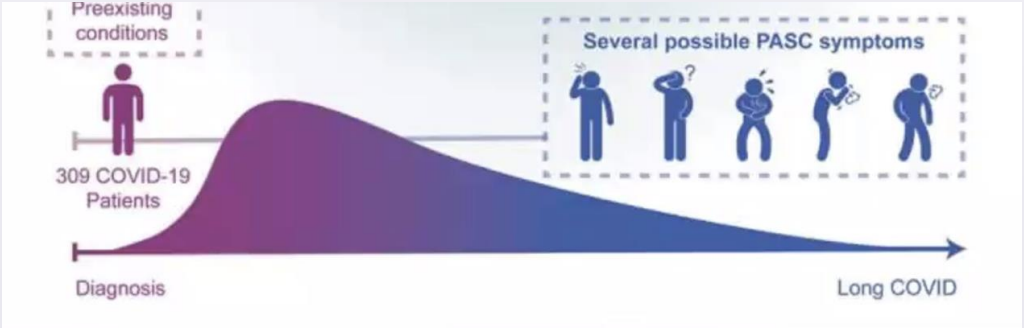
- Toxicity/BioToxins/Mold
- Metabolic Imbalances
- Stress/Trauma

TRIGGERS?
Reactivation?
Intensifications?
Exacerbations?

Antecedents for Long-haul COVID/PASC

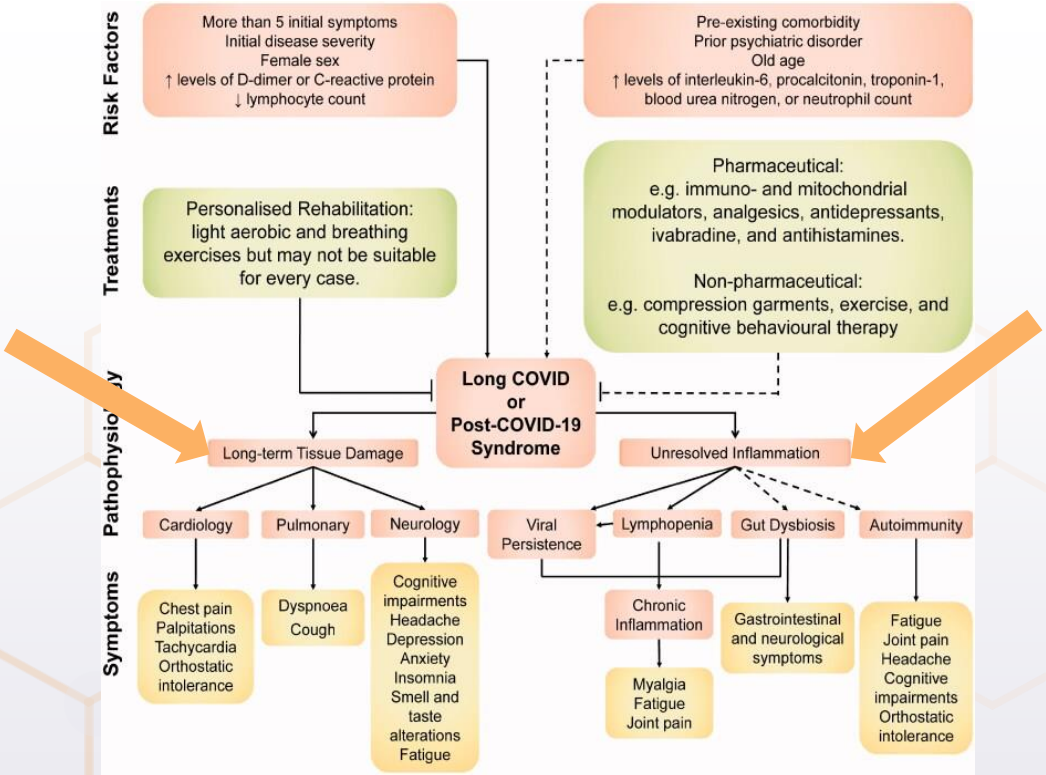
- ***Epigenetics/Genetics/Genomics***
- Family History & Tribal Lore/Ancestral Work
- Childhood Growth & Development
- Adverse Childhood Experiences
- Socio-economic Factors
- Nourishment/Foundational Nutrition
- ***Microbiome***
- Medical History Containing
  - ***Allergies/Sensitivities***
  - Inflammation
  - Auto-immun-ing
  - ***Toxicity***
  - ***BioToxins/Mold***
  - Metabolic Imbalances
  - Stress/Trauma

- Infection
  - ***Tick-borne Disease/Lyme Dz***
  - **EBV**
  - **CMV**
  - Bartonella/Babesia
  - Mycoplasma
  - Parovirus
  - HPV/HSV/HH6/HH7
  - Strep
  - SIBO
  - Parasites

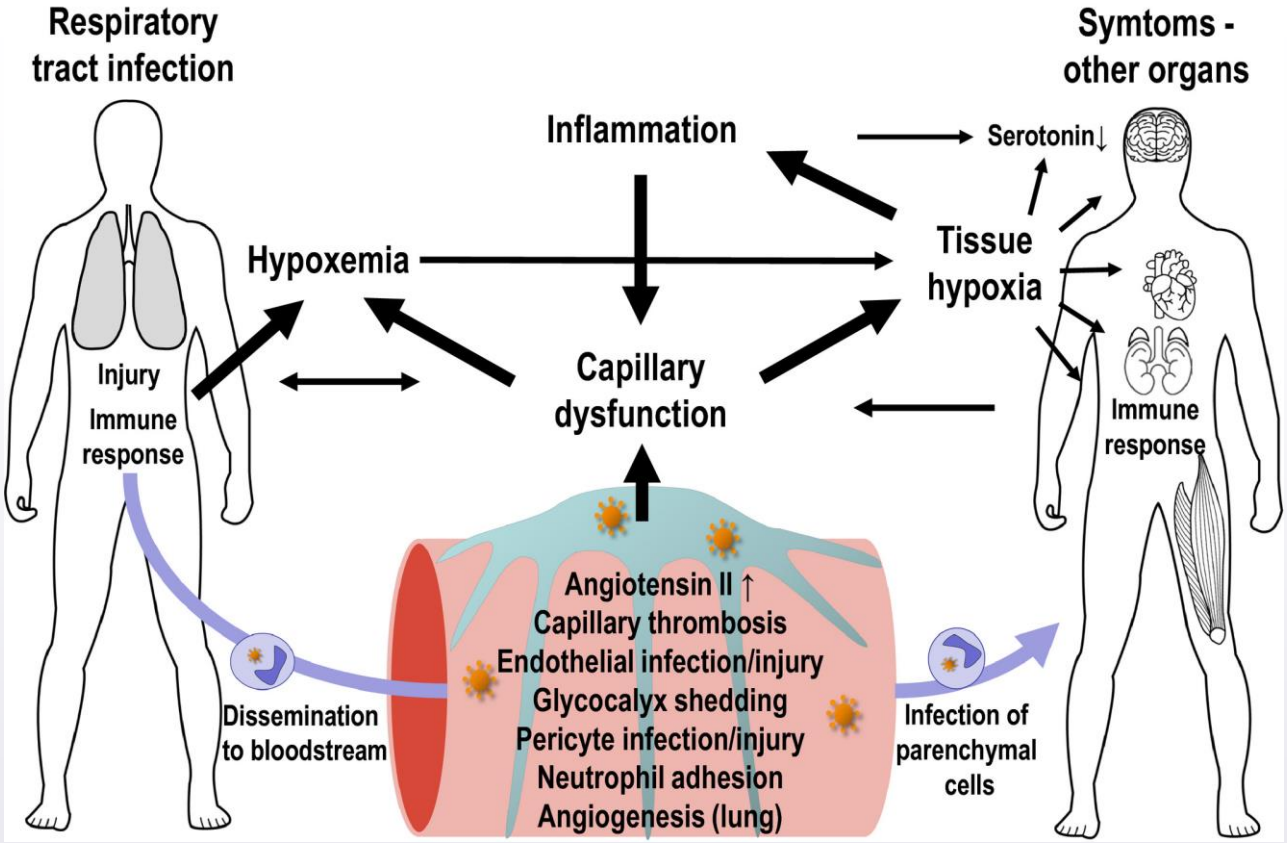


Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments

Yong, SS (2021). Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infectious Diseases, 53(10), 737–754. https://doi.org/10.1080/23744235.2021.1924397



An overview of the symptoms, putative pathophysiology, associated risk factors, and potential treatments involved in long COVID. Note: Dashed lines represent areas where evidence is relatively lacking compared to non-dashed lines. (Color online only).



SARS CoV-2 related microvascular damage and symptoms during and after COVID-19: Consequences of capillary transit-time changes, tissue hypoxia and inflammation

Physiological Reports, Volume: 9, Issue: 3, First published: 01 February 2021, DOI: (10.14814/phy2.14726)

Distinguishing features of Long COVID identified through immune profiling

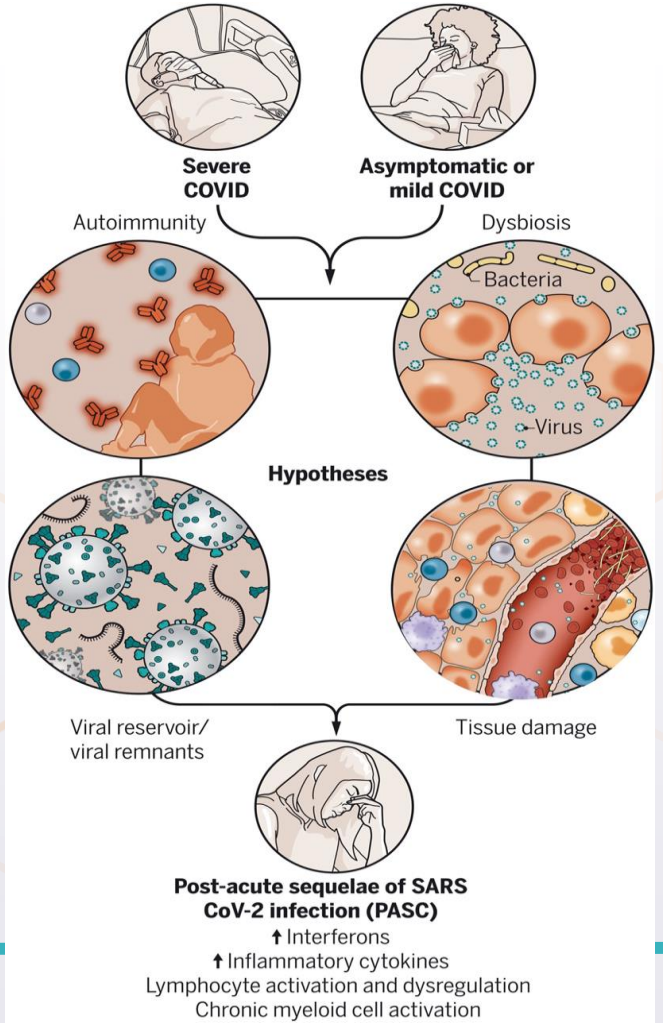
Klein, JB, Wood, JR, Iwasaki, A, et al. (2022). Distinguishing features of Long COVID identified through immune profiling. medRxiv (Cold Spring Harbor Laboratory). https://doi.org/10.1101/2022.08.09.22278592

A fraction of COVID-19 patients with either severe or mild COVID-19 develop a variety of new, recurring, or ongoing symptoms and clinical findings 4 or more weeks after infection.

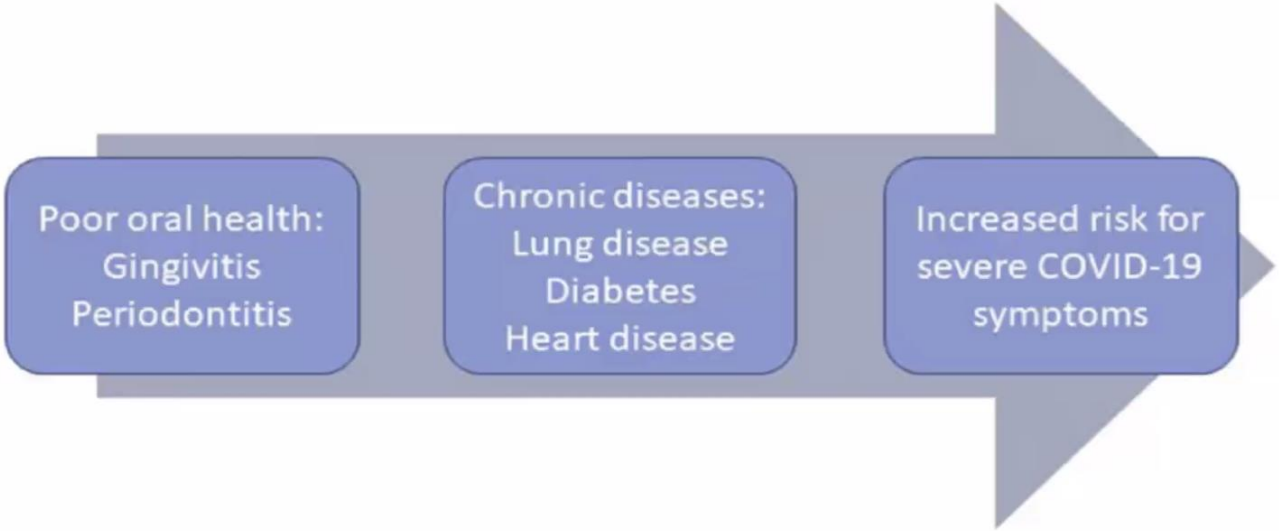
Analyses of immune responses in people with PASC reveal key inflammatory cytokines and cellular activation phenotypes that are significantly elevated over nonPASC convalescent controls.

Further studies are needed to identify the drivers of PASC pathophysiology.

Illustration: V. Altounian/Science

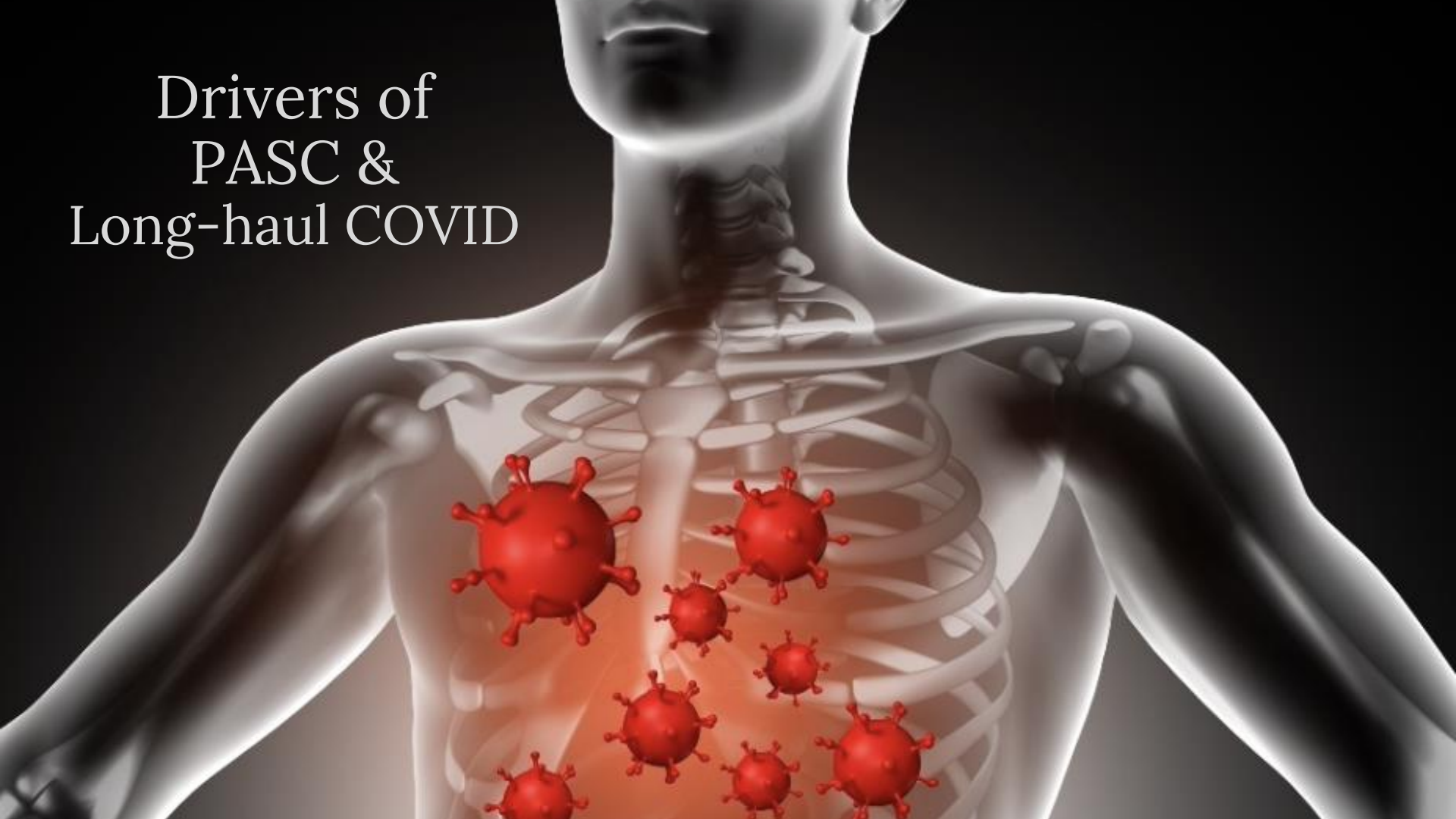


Potential links between oral health and severity of COVID-19 complications



Botros N, Iyer P, Ojcius DM. Is there an association between oral health and severity of COVID-19 complications?. *Biomed J*. 2020; S2319-4170(20)30081-0. doi:10.1016/j.bj.2020.05.016

Drivers of PASC & Long-haul COVID



Long COVID: major findings, mechanisms and recommendations

Davis, HE, McCorkell, L, Vogel, JM et al. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol 21, 133–146 (2023). https://doi.org/10.1038/s41579-022-00846-2

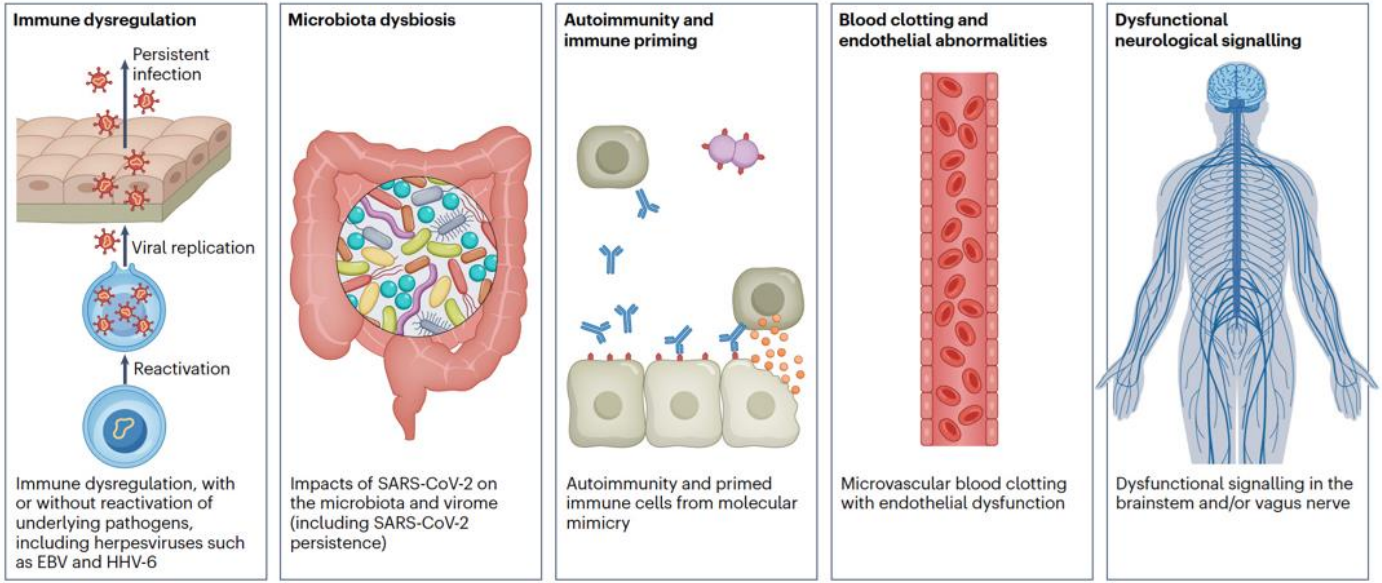
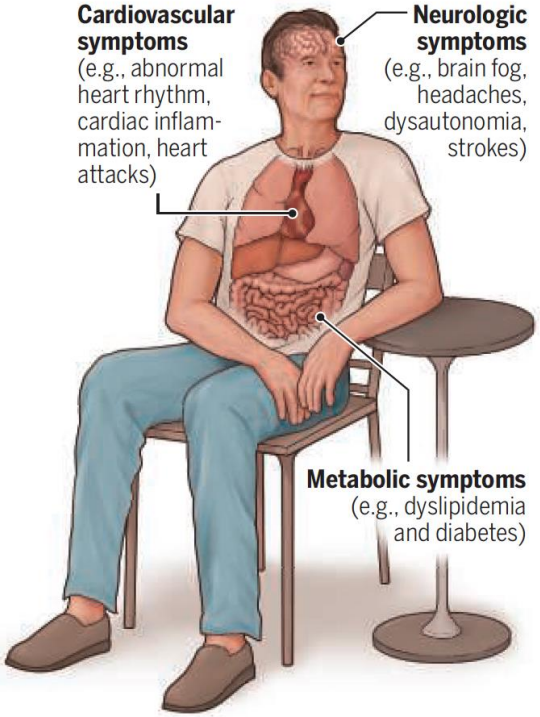
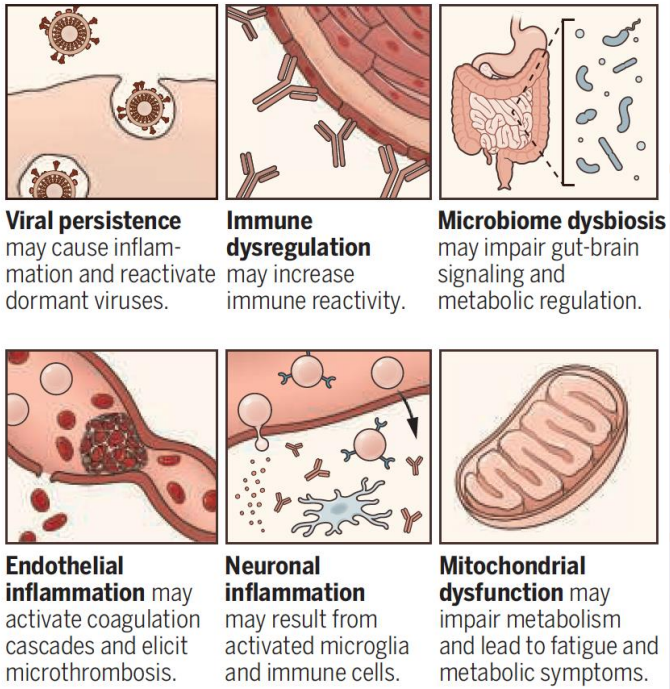


Fig. 3 | Hypothesized mechanisms of long COVID pathogenesis. There are several hypothesized mechanisms for long COVID pathogenesis, including immune dysregulation, microbiota disruption, autoimmunity, clotting and endothelial abnormality, and dysfunctional neurological signalling. EBV, Epstein–Barr virus; HHV-6, human herpesvirus 6; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Many forms of Long Covid

Long Covid is a multisystemic disease with sequelae that affect almost all organ systems. Various putative mechanisms that underlie these sequelae are not mutually exclusive and may explain the myriad health effects seen in Long Covid. Therapeutics that target these pathways, such as antivirals, anti-inflammatory agents, microbiome restoration, and anticoagulant drugs, may ameliorate symptoms.

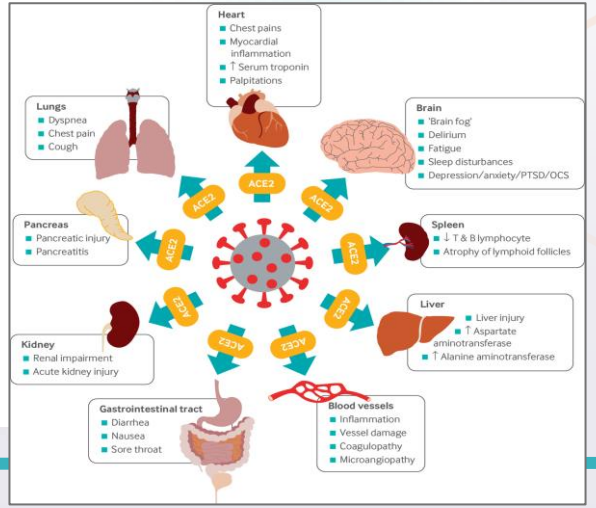


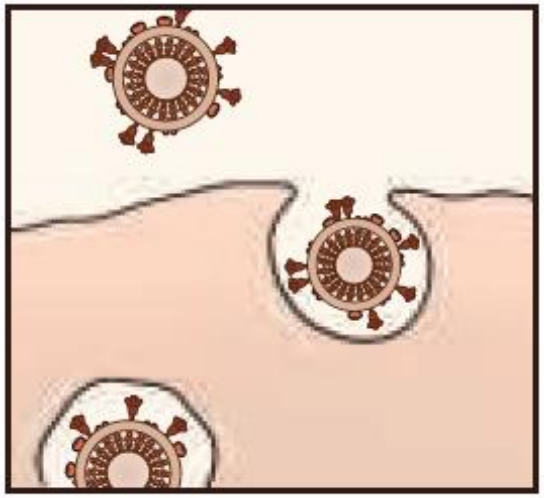


Al-Aly Z, Topol E. Solving the puzzle of Long Covid. Science. 2024 Feb 23 Vol. 383;6685:830-832. doi: 10.1126/science.adl0867.

Viral Persistence

ACE-2 Mediated Tissue Damage



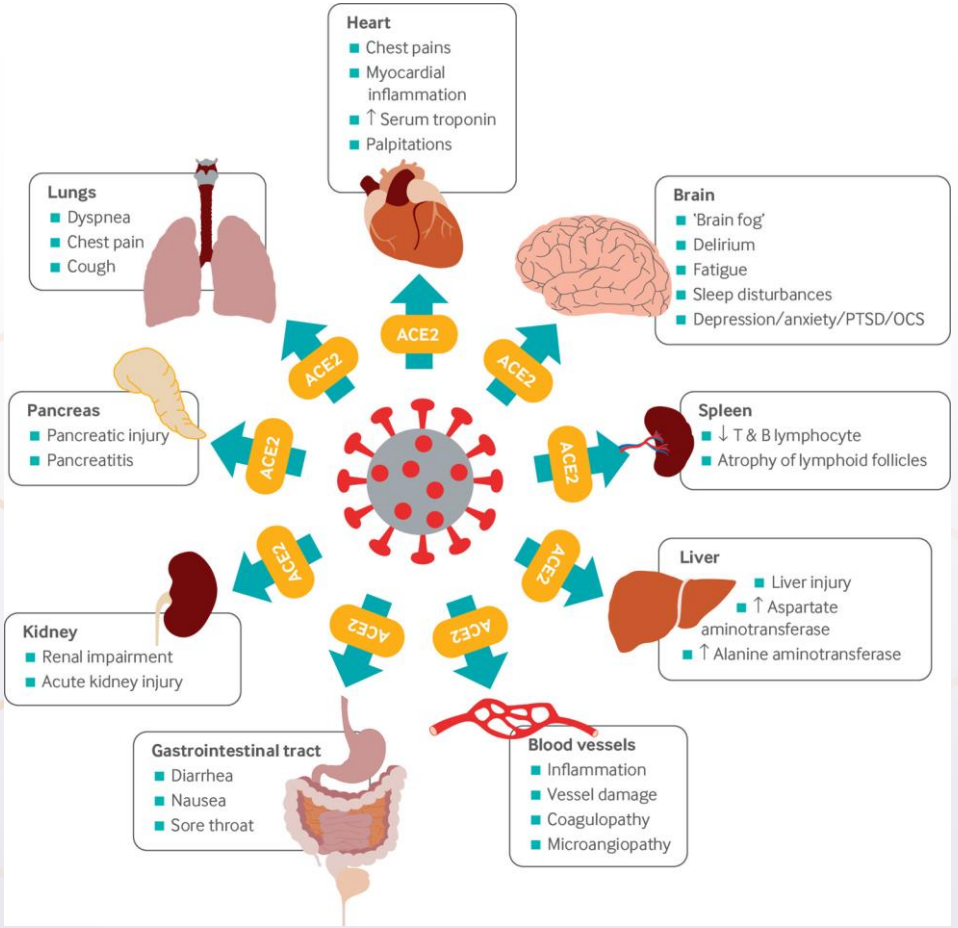


Viral persistence may cause inflammation and reactivate dormant viruses.

Al-Aly Z, Topol E. Solving the puzzle of Long Covid. Science. 2024 Feb 23
Vol. 383;6685:830-832. doi: 10.1126/science.adl0867.

Long Covid: mechanisms, risk factors, and management

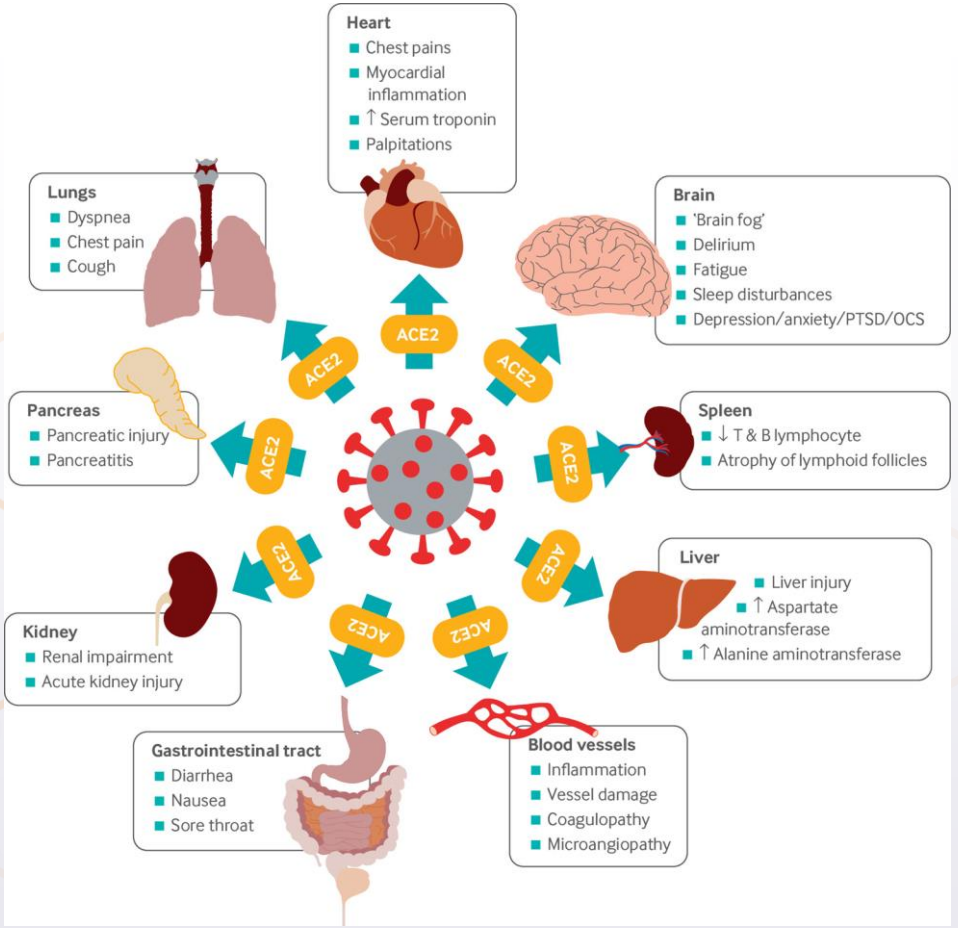
Crook, H, Raza, S, Nowell, J, Young, MK, Edison, P (2021). Long covid—mechanisms, risk factors, and management. BMJ, n1648. https://doi.org/10.1136/bmj.n1648

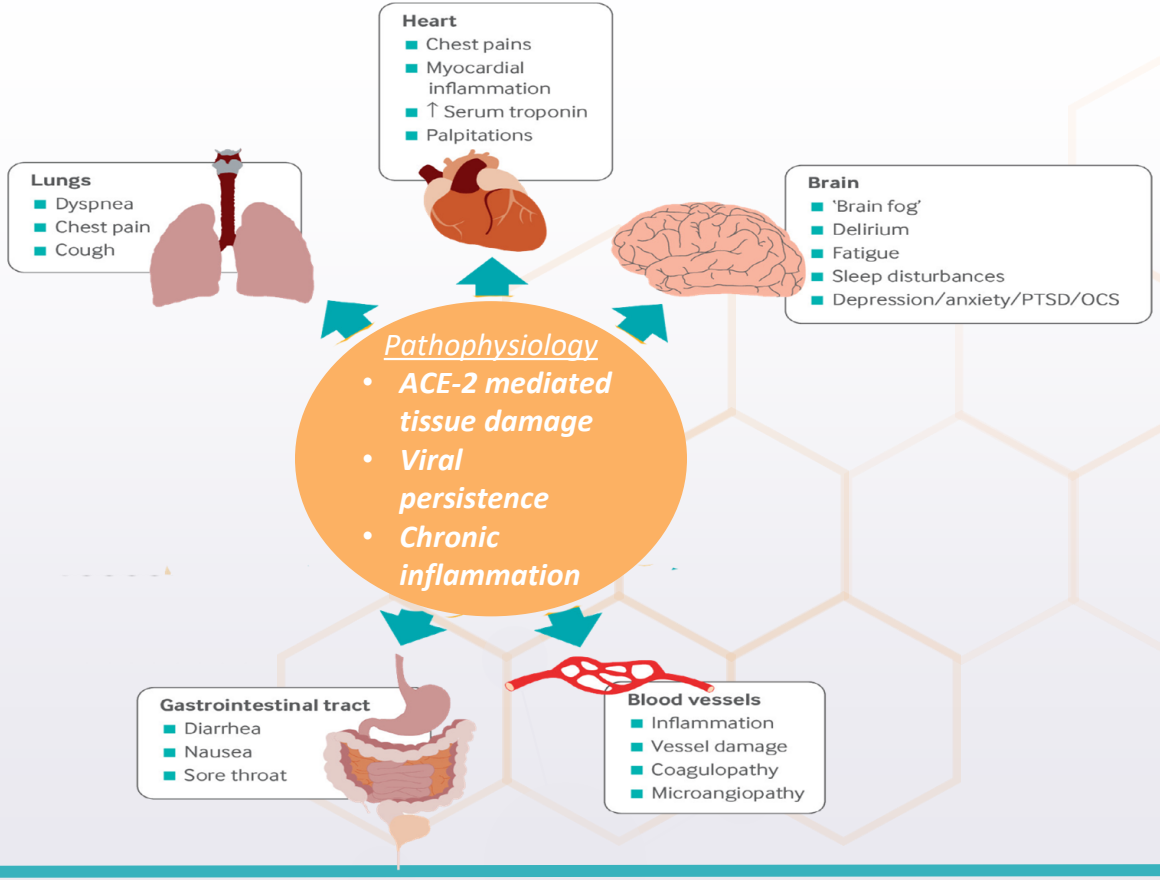


Multi-organ complications of covid-19 and long covid.

The SARS-CoV-2 virus gains entry into the cells of multiple organs via the ACE2 receptor.

Once these cells have been invaded, the virus can cause a multitude of damage ultimately leading to numerous persistent symptoms.

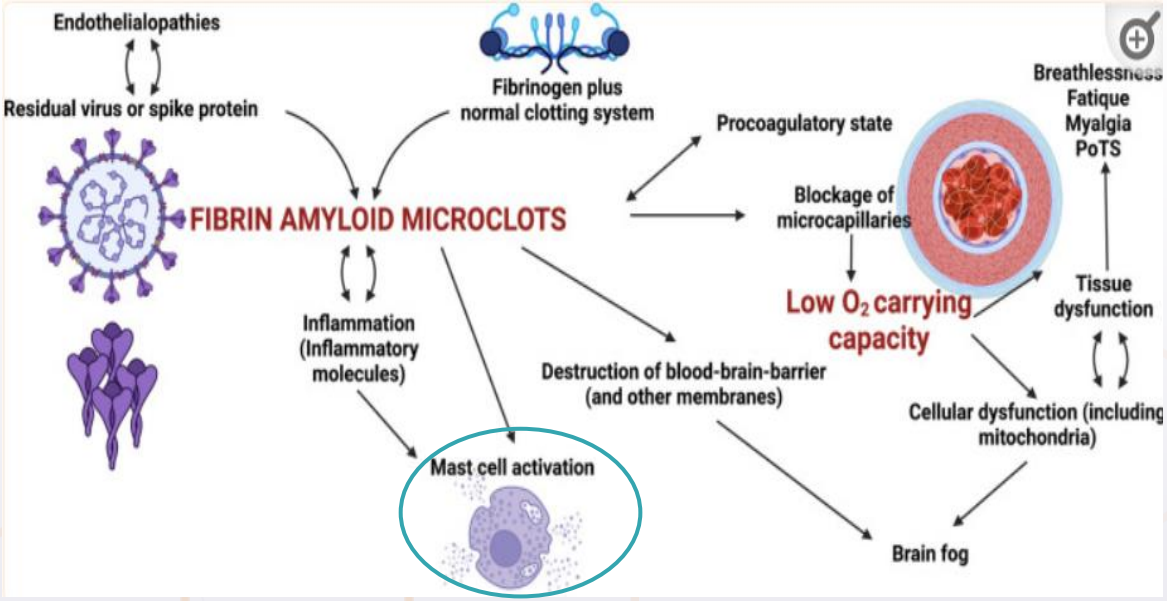



Heart
Chest pains
Myocardial inflammation
↑ Serum troponin
Palpitations
Lungs
Dyspnea
Chest pain
Cough
Brain
'Brain fog'
Delirium
Fatigue
Sleep disturbances
Depression/anxiety/PTSD/OCS
Pathophysiology
ACE-2 mediated tissue damage
Viral persistence
Chronic inflammation
Gastrointestinal tract
Diarrhea
Nausea
Sore throat
Blood vessels
Inflammation
Vessel damage
Coagulopathy
Microangiopathy

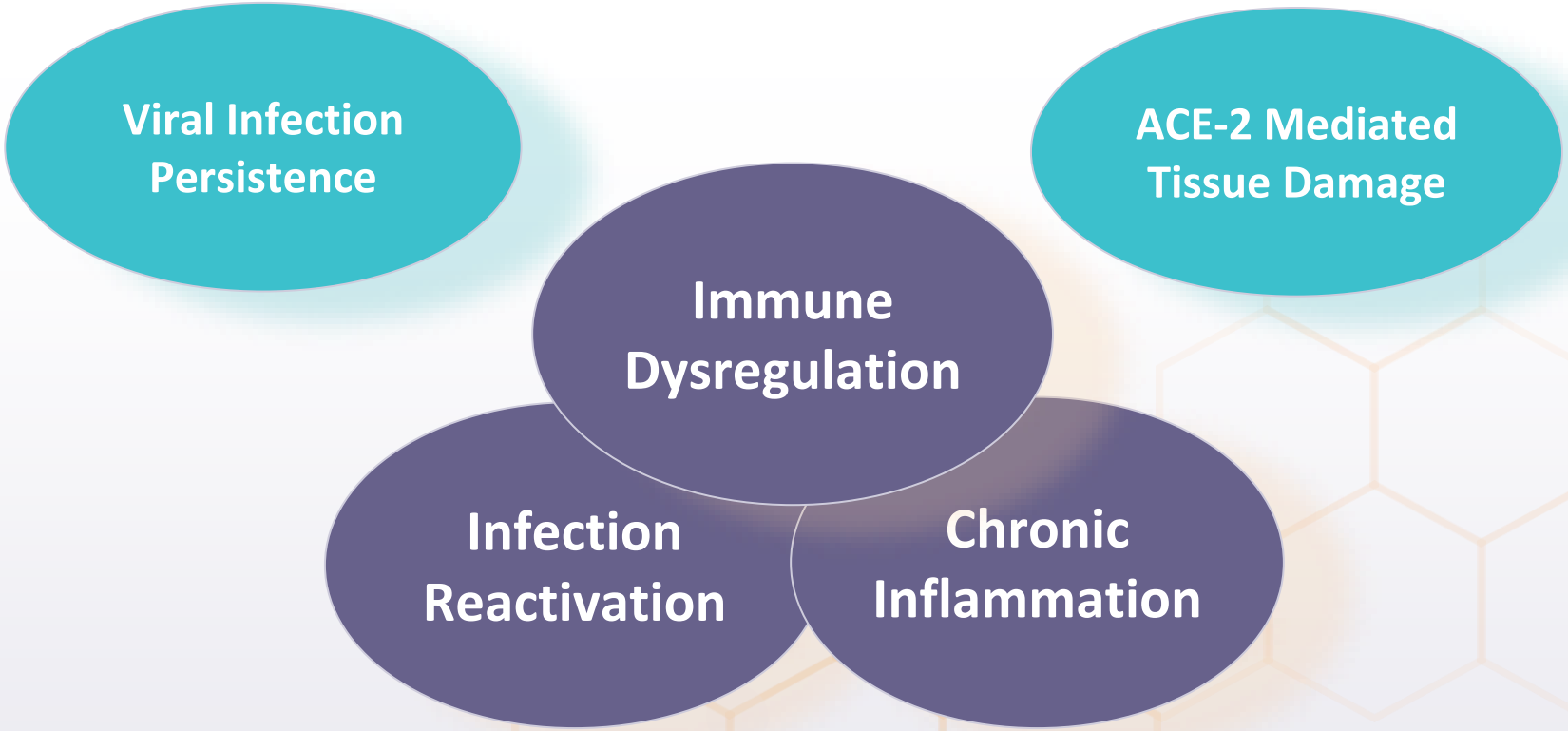
Long-lasting effects

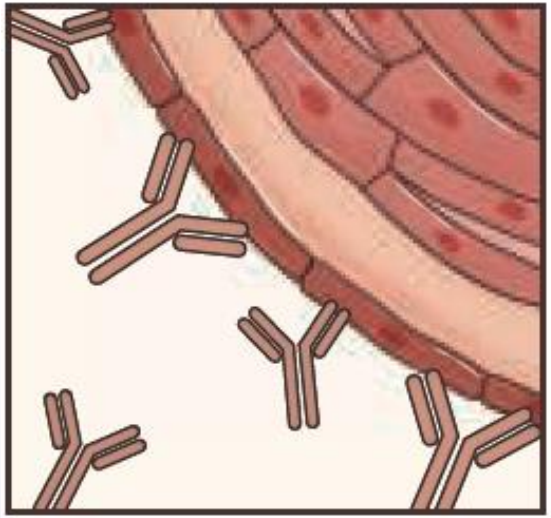
These microclots are:

- Pro-inflammatory
- Entrap molecules, including those that would break them down
- Can block capillaries, resulting in hypoxia
- May be triggered by persistent viral load and/or spike protein remnants



Kell, DB, Laubscher, GJ, & Pretorius, E. (2022). A central role for amyloid fibrin microclots in long COVID/PASC: origins and therapeutic implications. Biochemical Journal, 479(4), 537–559. https://doi.org/10.1042/bcj20220016


Viral Infection Persistence
ACE-2 Mediated Tissue Damage
Immune Dysregulation
Infection Reactivation
Chronic Inflammation



Immune dysregulation may increase immune reactivity.

Al-Aly Z, Topol E. Solving the puzzle of Long Covid. Science. 2024 Feb 23
Vol. 383;6685:830-832. doi: 10.1126/science.adl0867.

Chronic Inflammation

Scuttelaria baicalensis "Chinese Skullcap"

Herbal anti-inflammatory combination product with Curcumin, Boswellia, Cat's Claw, Bromelain, Devil's Claw

Anti-inflammatory actions:

- Decreases activation of the NLRP3 Inflammasome.
- Crosses the blood brain barrier to address brain inflammation
- Prevents organ injury by modulation of host innate immune response

Omega-3 Fatty Acids

EPA + DHA combination @ 2gm/ day

Omega-3 Fatty Acids

- Promotes anti-inflammatory prostaglandin pathways

Vitamin D3 + K2

Vitamin D3 dosing based on serum levels

Vitamin D

- Plays an important role in the modulation of the inflammation system by regulating the production of inflammatory cytokines

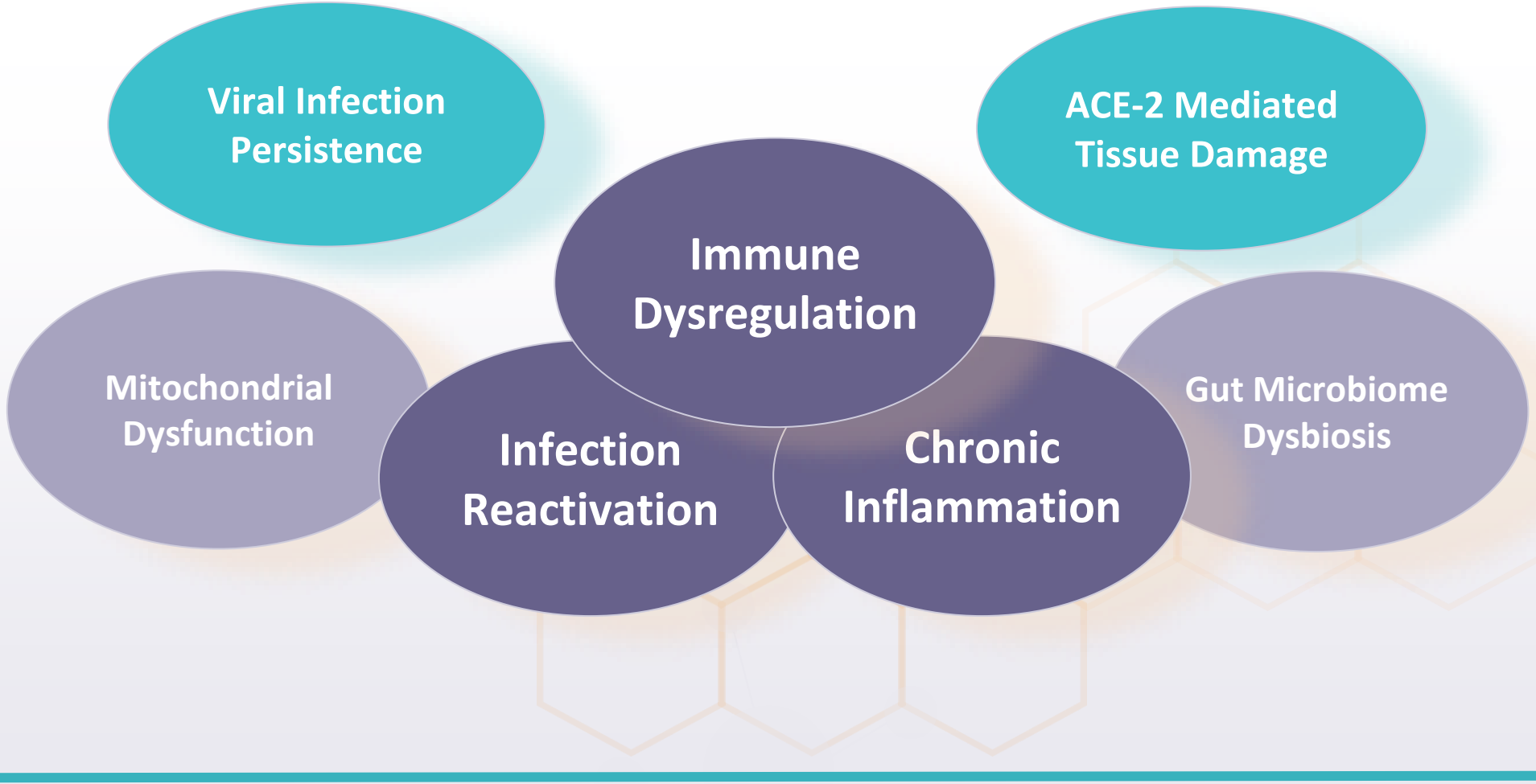
Quercetin

Anti-Oxidants

Quercetin:

- Immunomodulatory and may improve T-Reg function
- Demonstrated anti-viral activity against both RNA and DNA viruses

Shi S et al. Oral Chinese Herbal Medicine on Immune Responses During Coronavirus Disease 2019: A Systematic Review and Meta-Analysis. Front Med (Lausanne). 2022 Jan 21;8:685734. doi: 10.3389/fmed.2021.685734.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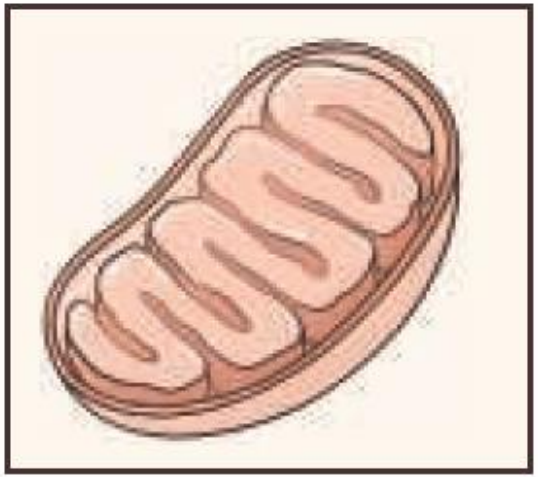
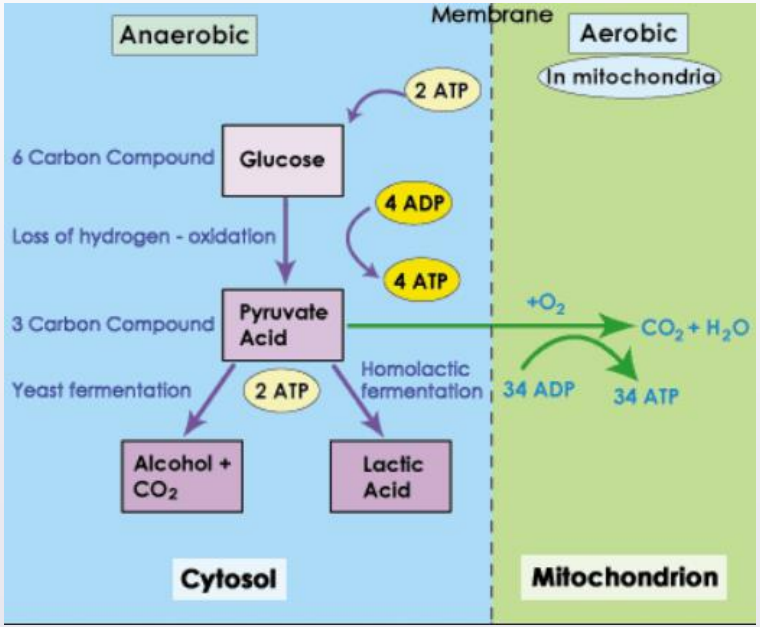
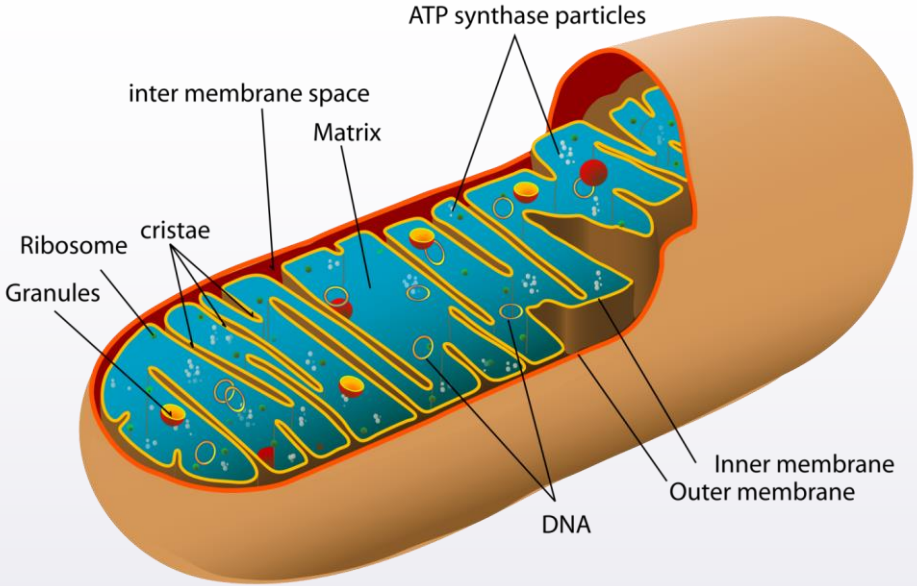


Mitochondrial dysfunction may impair metabolism and lead to fatigue and metabolic symptoms.

Al-Aly Z, Topol E. Solving the puzzle of Long Covid. Science. 2024 Feb 23 Vol. 383;6685:830-832. doi: 10.1126/science.adl0867.

Cellular Energy and Mitochondrial Function





SUPPORTING MITOCHONDRIA L FUNCTION

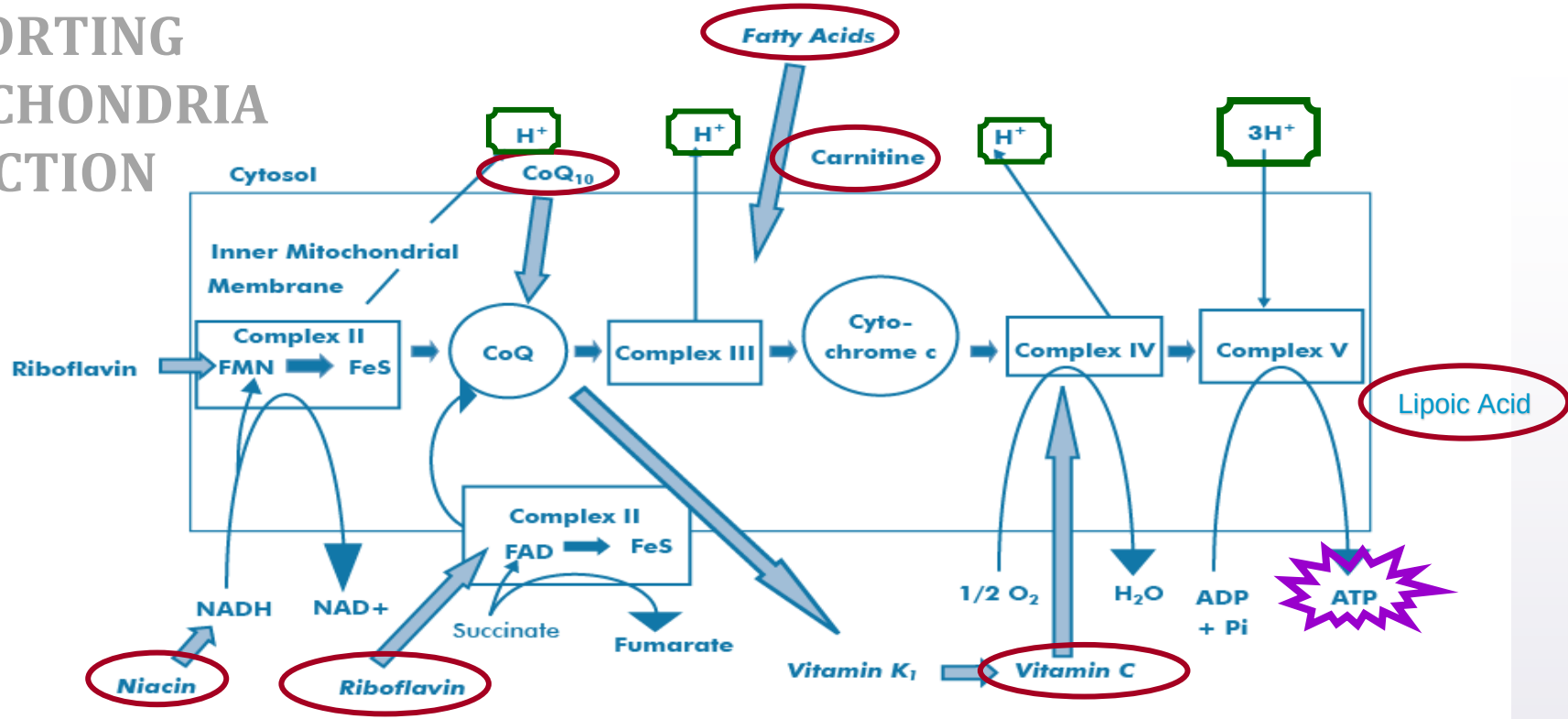
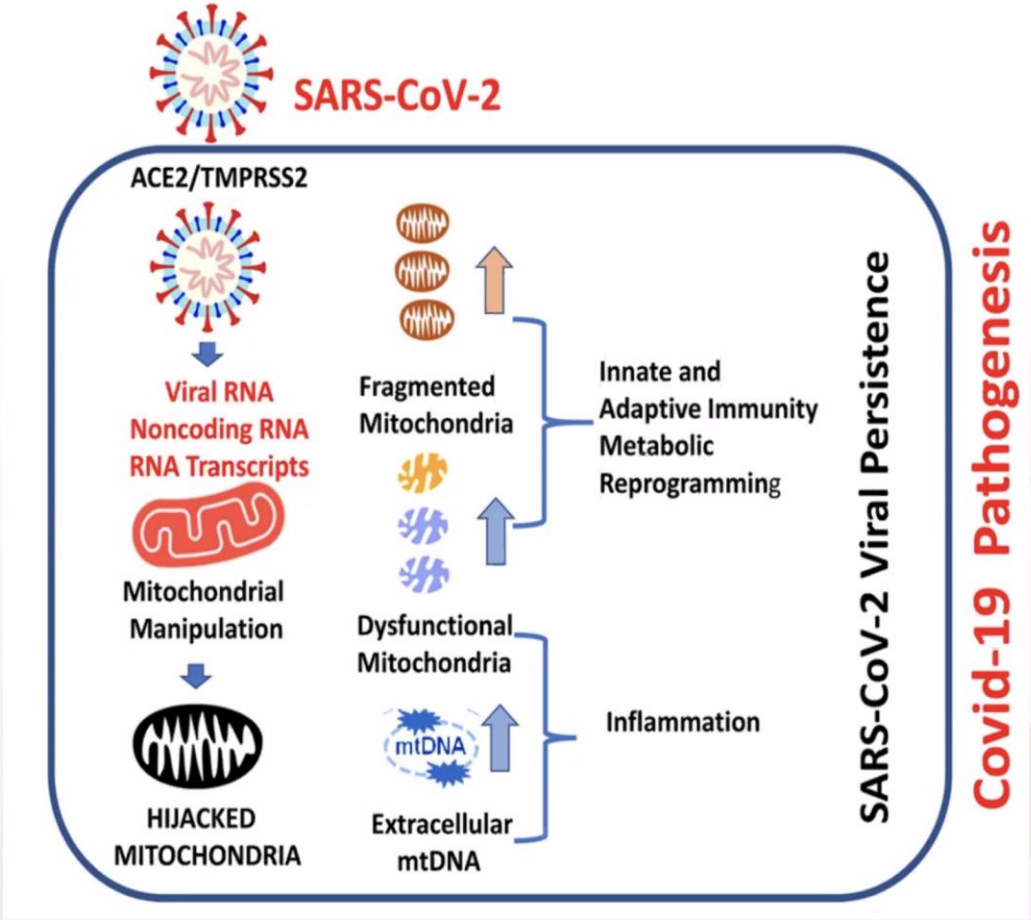


FIG. *Mitochondrial Respiratory Chain. Protons (H^+) are pumped from the mitochondrial matrix to the intermembrane space through complexes I,III, and IV. Complex V utilizes the proton gradient as a source of energy to produce ATP. Coenzyme Q_{10} transfers electrons from complexes I and II to complex III. Riboflavin is a precursor of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). The amide form of niacin, (nicotinamide) is a precursor for nicotinamide adenine dinucleotide (NAD). Vitamin K_3 in combination with vitamin C serce as electron acceptors to bypass a deficiency in complex III. Carnitine function to transfer long chain fatty acids across the mitochondrial membrane.*



- **Viral binding to mitochondrial ETC →**
  - **Dysfunction & Fatigue**
  - **Chronic Inflammation**
  - **Immune Dysregulation**

Singh, KK, Chaubey, G, Chen, JY, & Suravajhala, P. (2020). Decoding SARS-CoV-2 hijacking of host mitochondria in COVID-19 pathogenesis. American Journal of Physiology-cell Physiology, 319(2), C258–C267. https://doi.org/10.1152/ajpcell.00224.2020

Mitochondrial Dysfunction

B-Vitamin & Mineral Complex

Vitamin and Mineral Co-factors for Kreb's Cycle and Electron Transport Chain (ETC)

Anti-Oxidant Support

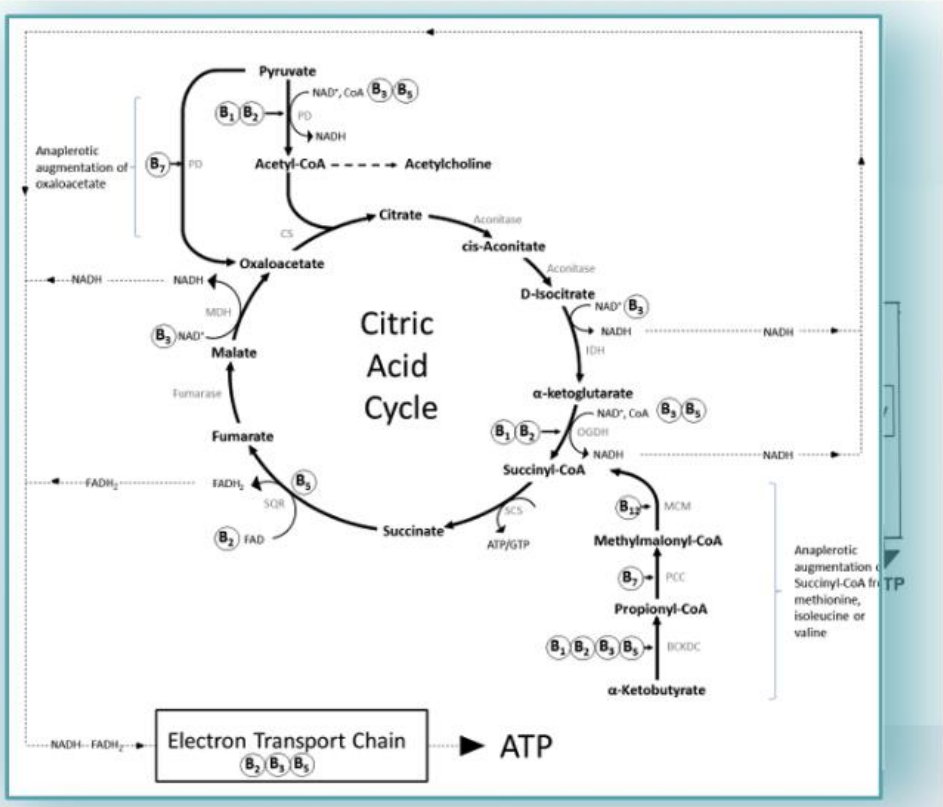
Plant-based + ALA + Tocopherols

Co-Q10

Co-Factor in Electron Transport Chain

Magnesium [chelate]

Essential nutrient for mitochondrial function



Singh, KK et al.. Decoding SARS-CoV-2 hijacking of host mitochondria in COVID-19 pathogenesis. American Journal of Physiology-cell Physiology. 2020. 319(2), C258–C267. https://doi.org/10.1152/ajpcell.00224.2020

Kennedy DO. B Vitamins and the Brain: Mechanisms, Dose and Efficacy--A Review. Nutrients. 2016;8(2):68. doi: 10.3390/nu8020068. PMID: 26828517.

Mitochondrial Dysfunction

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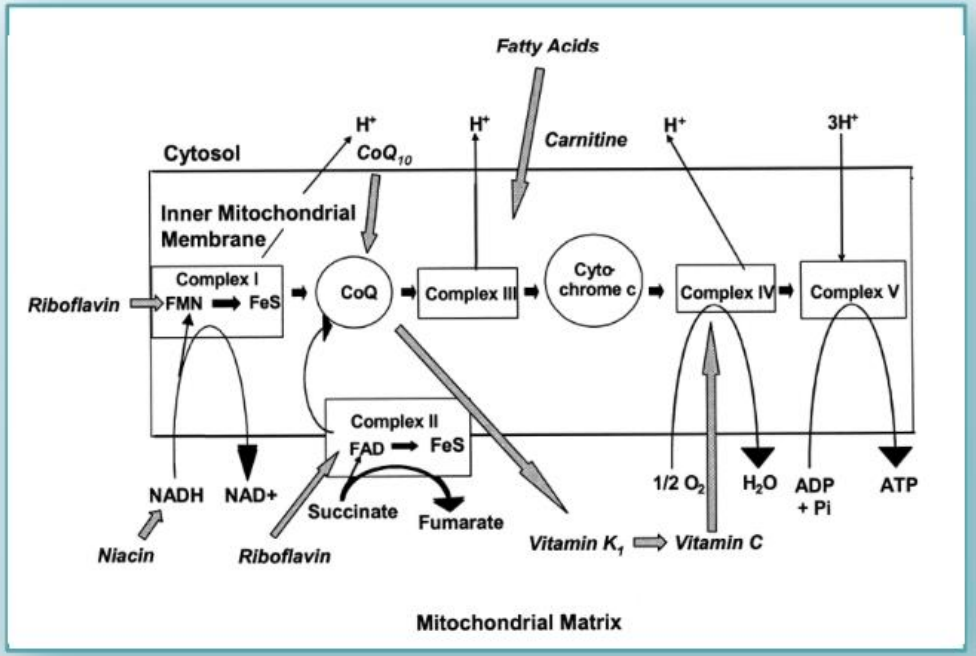
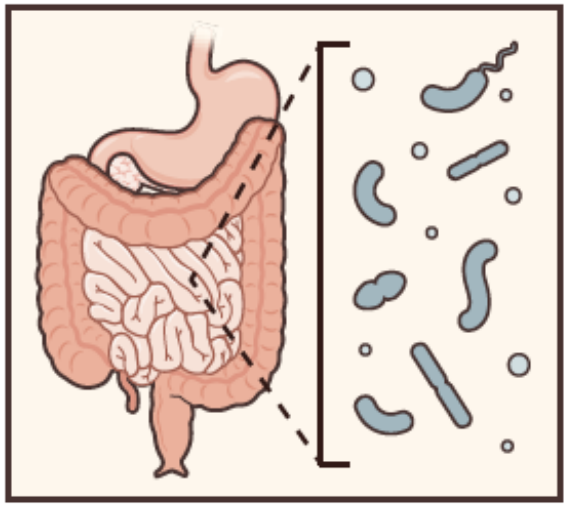


Singh, KK et al.. Decoding SARS-CoV-2 hijacking of host mitochondria in COVID-19 pathogenesis. American Journal of Physiology-cell Physiology. 2020. 319(2), C258–C267. https://doi.org/10.1152/ajpcell.00224.2020

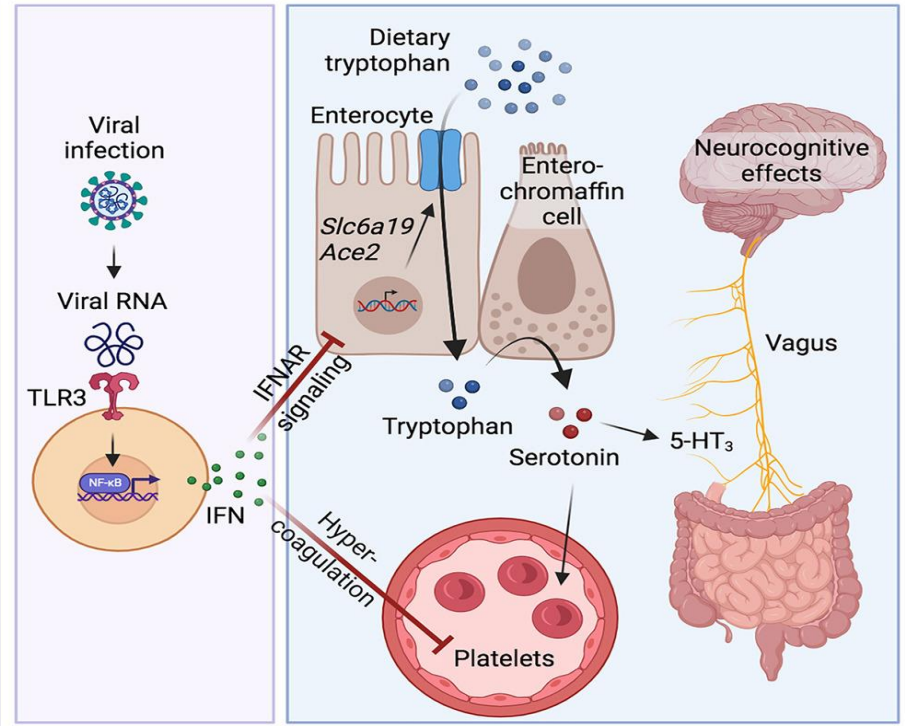
Kennedy DO. B Vitamins and the Brain: Mechanisms, Dose and Efficacy--A Review. Nutrients. 2016;8(2):68. doi: 10.3390/nu8020068. PMID: 26828517.



Microbiome dysbiosis may impair gut-brain signaling and metabolic regulation.

Al-Aly Z, Topol E. Solving the puzzle of Long Covid. Science. 2024 Feb 23
Vol. 383;6685:830-832. doi: 10.1126/science.adl0867.

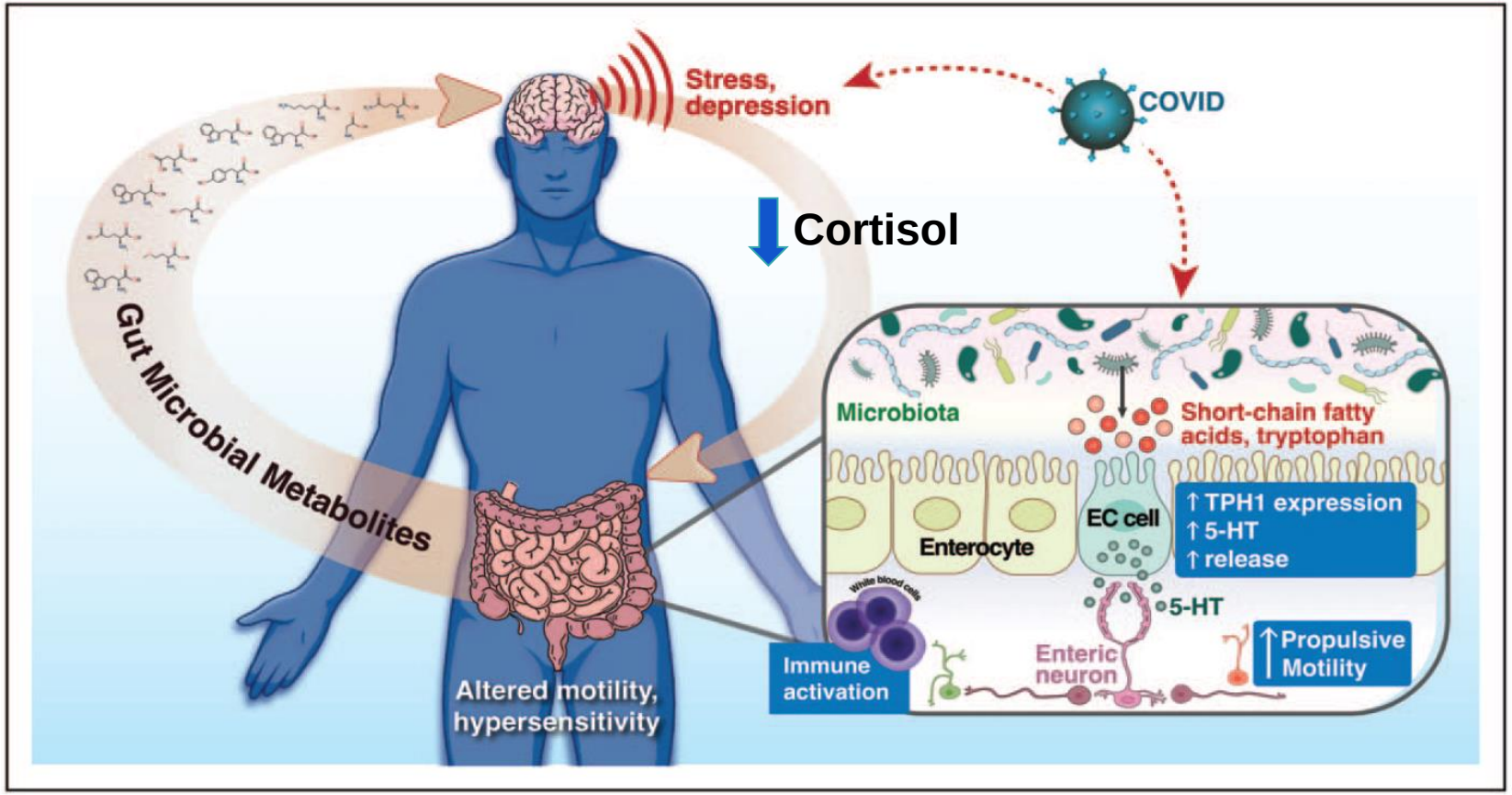
Serotonin reduction in post-acute sequelae of viral infection



Highlights

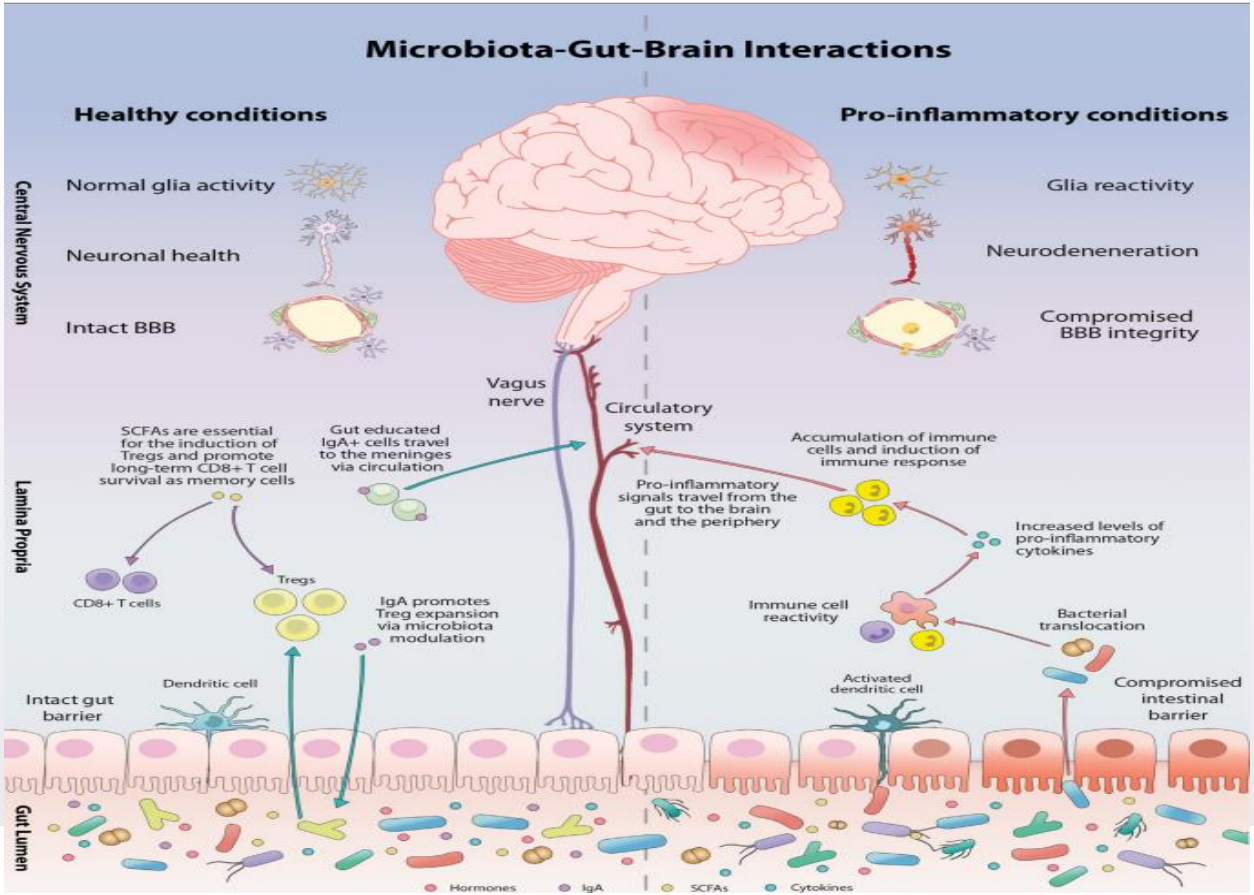
- Long COVID is associated with reduced circulating serotonin levels
- Serotonin depletion is driven by viral RNA-induced type I interferons (IFNs)
- IFNs reduce serotonin through diminished tryptophan uptake and hypercoagulability
- Peripheral serotonin deficiency impairs cognition via reduced vagal signaling

Wong, AC, et al (2023). Serotonin reduction in post-acute sequelae of viral infection. Cell. https://doi.org/10.1016/j.cell.2023.09.013



Freedberg, DE, & Chang, L. (2022). Gastrointestinal symptoms in COVID-19: the long and the short of it. Current Opinion in Gastroenterology, 38(6), 555–561. https://doi.org/10.1097/mog.0000000000000876

Microbiota-immune-brain interactions: A lifespan perspective



Current Opinion in Neurobiology 2023, **78**:102652

Gut/ Microbiome Dysbiosis

PROBIOTIC
Spore-Based Organism (SBO)
Modifying the community 'milieu'

PREBIOTIC
Spore-Based Organism (SBO)
Promoting growth of the person's beneficial commensal microbiome

Spore-Based Probiotic

- Probiotic blend of 5 Bacillus spores that have been shown to maintain healthy gut barrier and immune function
- Aims to RECONDITION the gut instead of reseeding with probiotic strains that cannot survive digestion or colonize the gut.

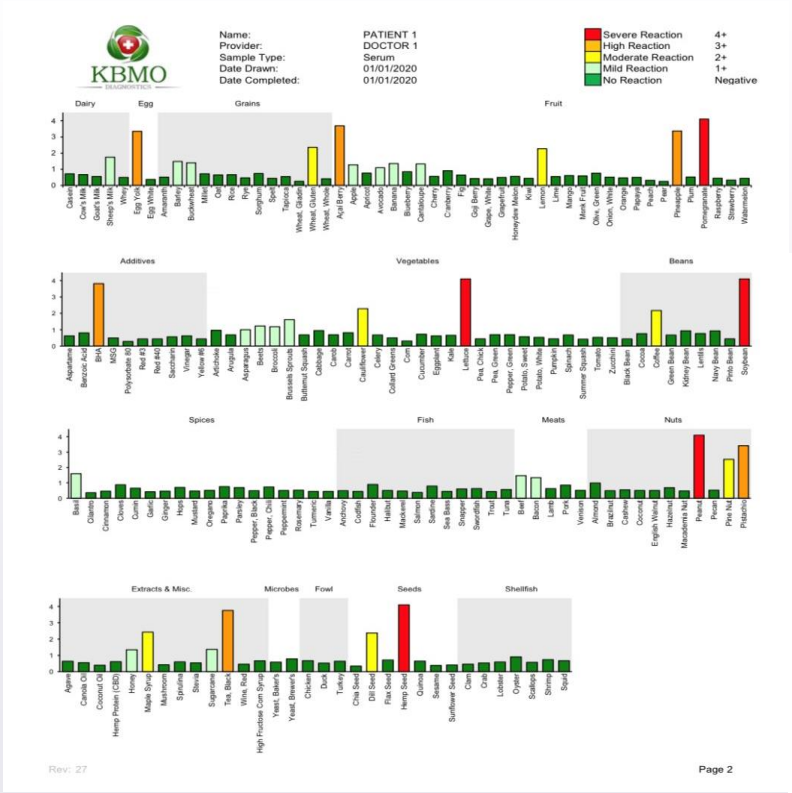
PreBiotic

- Contains non-digestible oligosaccharides that can increase microbial diversity and selectively feed beneficial bacteria like Akkermansia muciniphila, Faecalibacterium prausnitzii, and Bifidobacteria

Zhang D et al. Gut microbiota dysbiosis correlates with Long COVID-19 at one-year after discharge. J Korean Med Sci. 2023 Apr 17;38(15):e120. doi: 10.3346/jkms.2023.38.e120. PMID: 37069814

Zhang L et al. Gut microbiota-derived synbiotic formula (SIM01) as a novel adjuvant therapy for COVID-19: An open-label pilot study. J Gastroenterol Hepatol. 2022 May;37(5):823-831. doi: 10.1111/jgh.15796.PMID: 35170078

Gut Barrier Panel includes Candida, Zonulin and Occludin



KBMO

Name: PATIENT 1
Provider: DOCTOR 1
Sample Type: Serum

Gut Barrier Panel

KBMO has created a unique Gut Barrier Panel which in recognition that leaky gut occurs across a spectrum we have included the following gatekeeper markers: Candida, Zonulin and Occludin. For each marker, we measure IgG 1-4 /C3d in addition to IgA 1 and 2.

Gut Barrier Panel		
	IgG1-4+C3d	IgA1-2
Candida	Negative	Negative
Zonulin	Positive	Positive
Occludin	Positive	Positive

Candida:
we measure and use any candida overgrowth in the stomach/dysbiosis as a precursor to leaky gut occurrence

Zonulin:
Is a marker of intestinal permeability, otherwise known as leaky gut. If a patient has elevated Zonulin levels, the normal regulation of the tight junctions is compromised. This Zonulin marker is unique to KBMO please follow the link for more information:
http://kbmodiagnostics.com/zonulin-test/

Occludin:
is a marker of tight junction stabilization and optimal barrier function. Elevated occludin indicates that the tight junctions are breaking down.

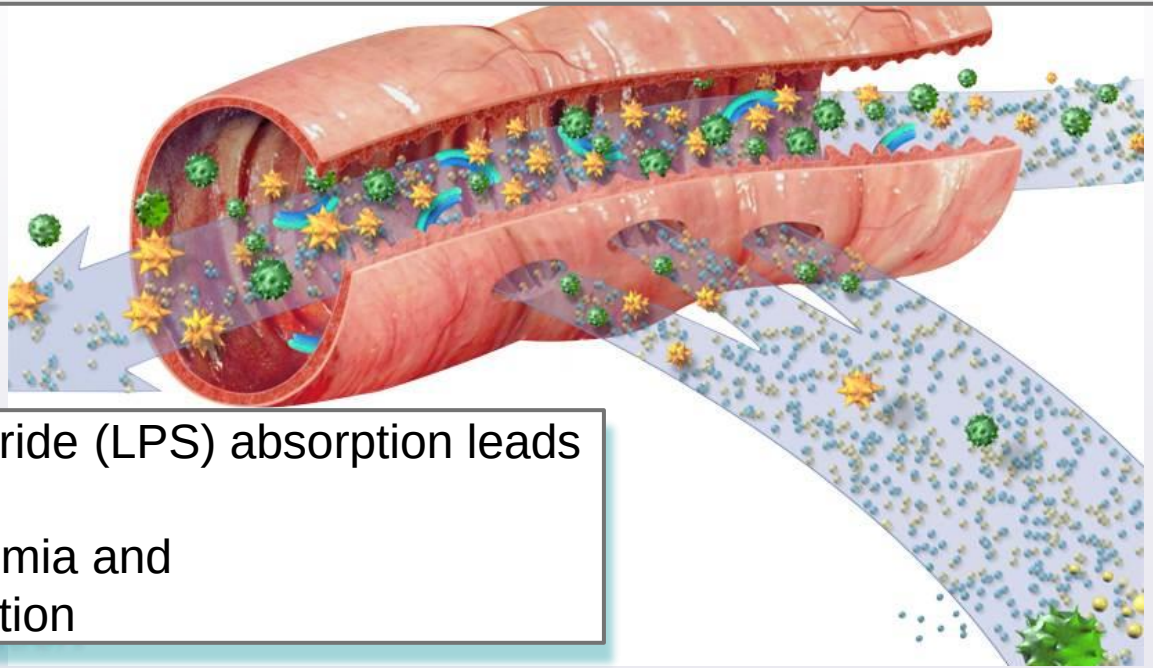
GB Panel Interpretation:
If any of the 6 markers are positive, we recommend to consult your provider with regards a gut healing protocol.

FIT: Gut Barrier Panel (GBPanel)

Gut Barrier Panel		
	IgG1-4-C3d	IgA1-2
Candida	Positive	Positive
Zonulin	Negative	Positive
Occludin	Negative	Negative
LPS	Positive	Negative

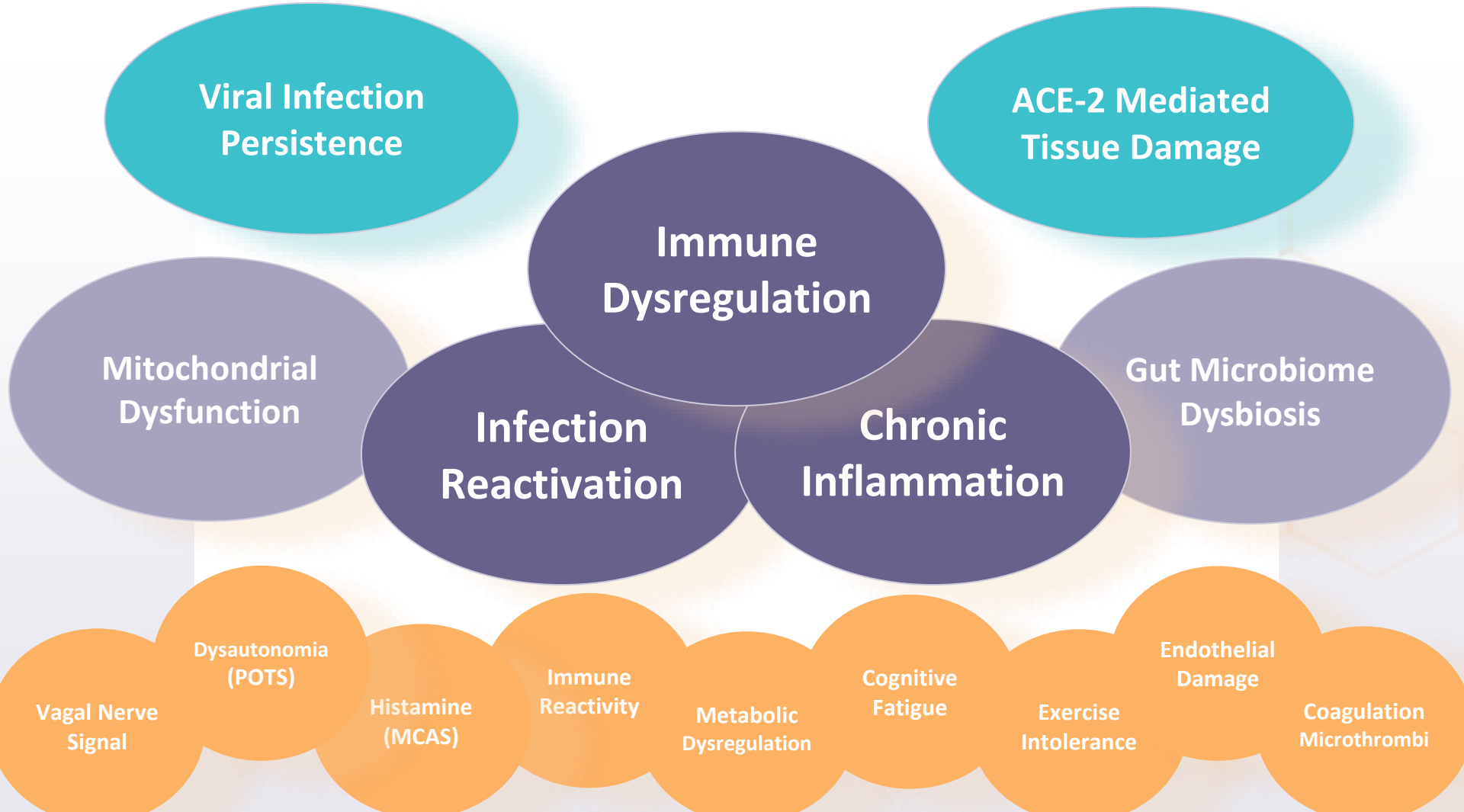
FIT 132 + FIT 176 INCLUDE THE GB Panel

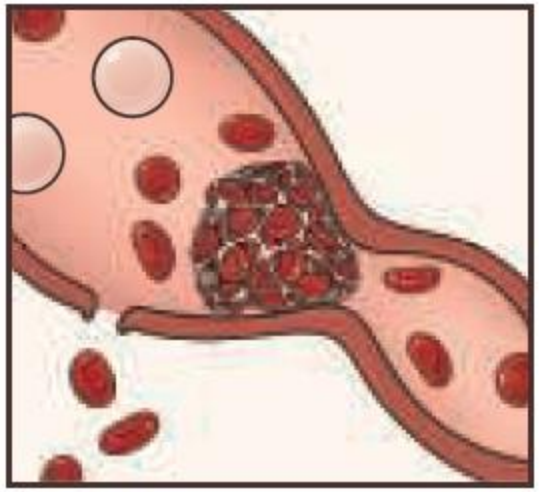
1. LPS is a potent endotoxin and a major inducer of the inflammatory response.
2. LPS is a main component of the cell wall of the gram-negative bacteria that colonize the intestines.
3. Trillions of bacteria occupy the GI tract, providing a huge reservoir of LPS endotoxin.
4. Normally only a very small amount of LPS is absorbed, but a high fat diet can lead to increased LPS absorption and endotoxemia.
5. LPS can even be incorporated into chylomicrons and absorbed into the blood as part of normal fat absorption.



Increased lipoplysaccharide (LPS) absorption leads to:

- increased endotoxemia and
- increased inflammation


Viral Infection Persistence
ACE-2 Mediated Tissue Damage
Immune Dysregulation
Mitochondrial Dysfunction
Infection Reactivation
Chronic Inflammation
Gut Microbiome Dysbiosis
Vagal Nerve Signal
Dysautonomia (POTS)
Histamine (MCAS)
Immune Reactivity
Metabolic Dysregulation
Cognitive Fatigue
Exercise Intolerance
Endothelial Damage
Coagulation Microthrombi

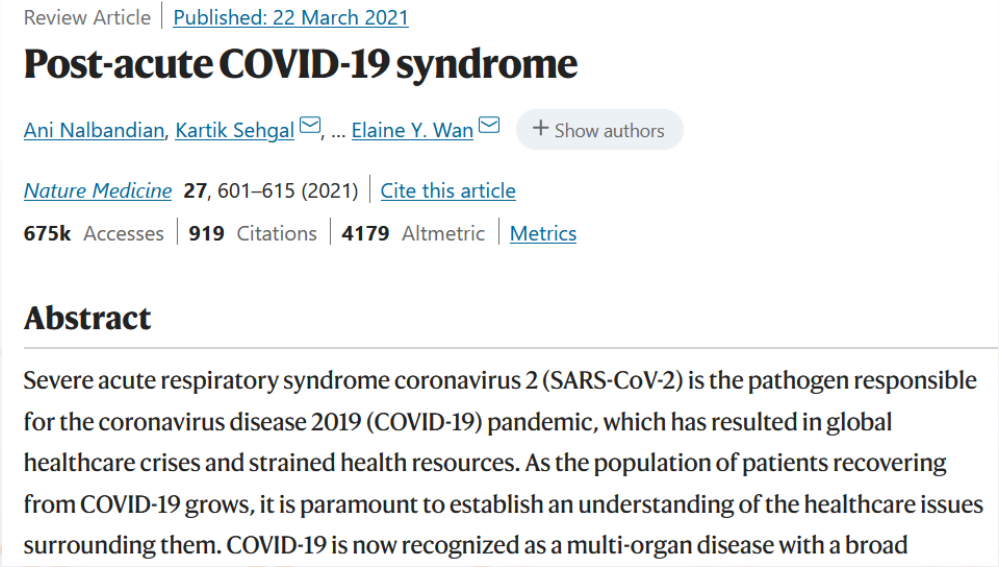


Endothelial inflammation may activate coagulation cascades and elicit microthrombosis.

Al-Aly Z, Topol E. Solving the puzzle of Long Covid. Science. 2024 Feb 23
Vol. 383;6685:830-832. doi: 10.1126/science.adl0867.

Long-lasting effects

- “Pulmonary vascular microthrombosis and macrothrombosis have been observed in 20–30% of patients with COVID-19 (refs. [63,64,65,66,67]), which is higher than in other critically ill patient populations (1–10%)[68,69].”
- “In addition, the severity of endothelial injury and widespread thrombosis with microangiopathy seen on lung autopsy is greater than that seen in ARDS from influenza[70,71].”



Review Article | Published: 22 March 2021

Post-acute COVID-19 syndrome

Ani Nalbandian, Kartik Sehgal, ... Elaine Y. Wan + Show authors

Nature Medicine **27**, 601–615 (2021) | Cite this article

675k Accesses | **919** Citations | **4179** Altmetric | Metrics

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogen responsible for the coronavirus disease 2019 (COVID-19) pandemic, which has resulted in global healthcare crises and strained health resources. As the population of patients recovering from COVID-19 grows, it is paramount to establish an understanding of the healthcare issues surrounding them. COVID-19 is now recognized as a multi-organ disease with a broad

Nalbandian, A, Sehgal, K, Gupta, A, . . . Wan, E. (2021). Post-acute COVID-19 syndrome. Nature Medicine, 27(4), 601–615. https://doi.org/10.1038/s41591-021-01283-z

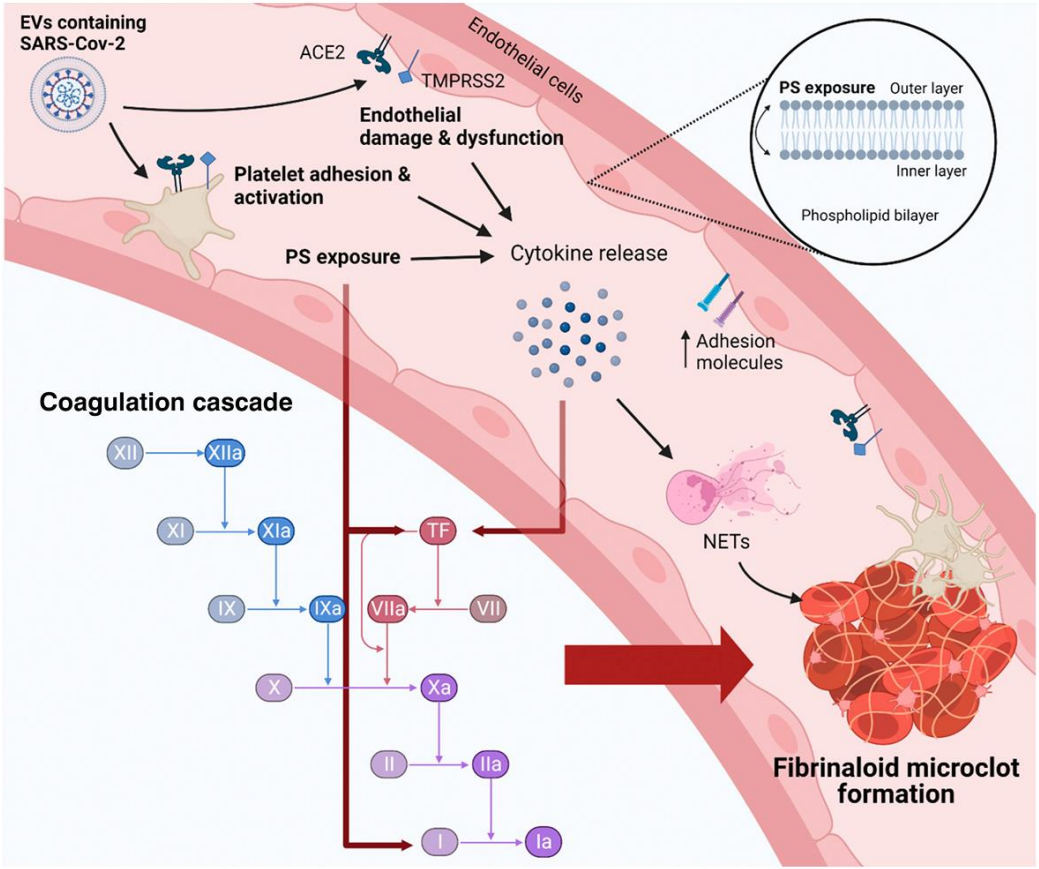
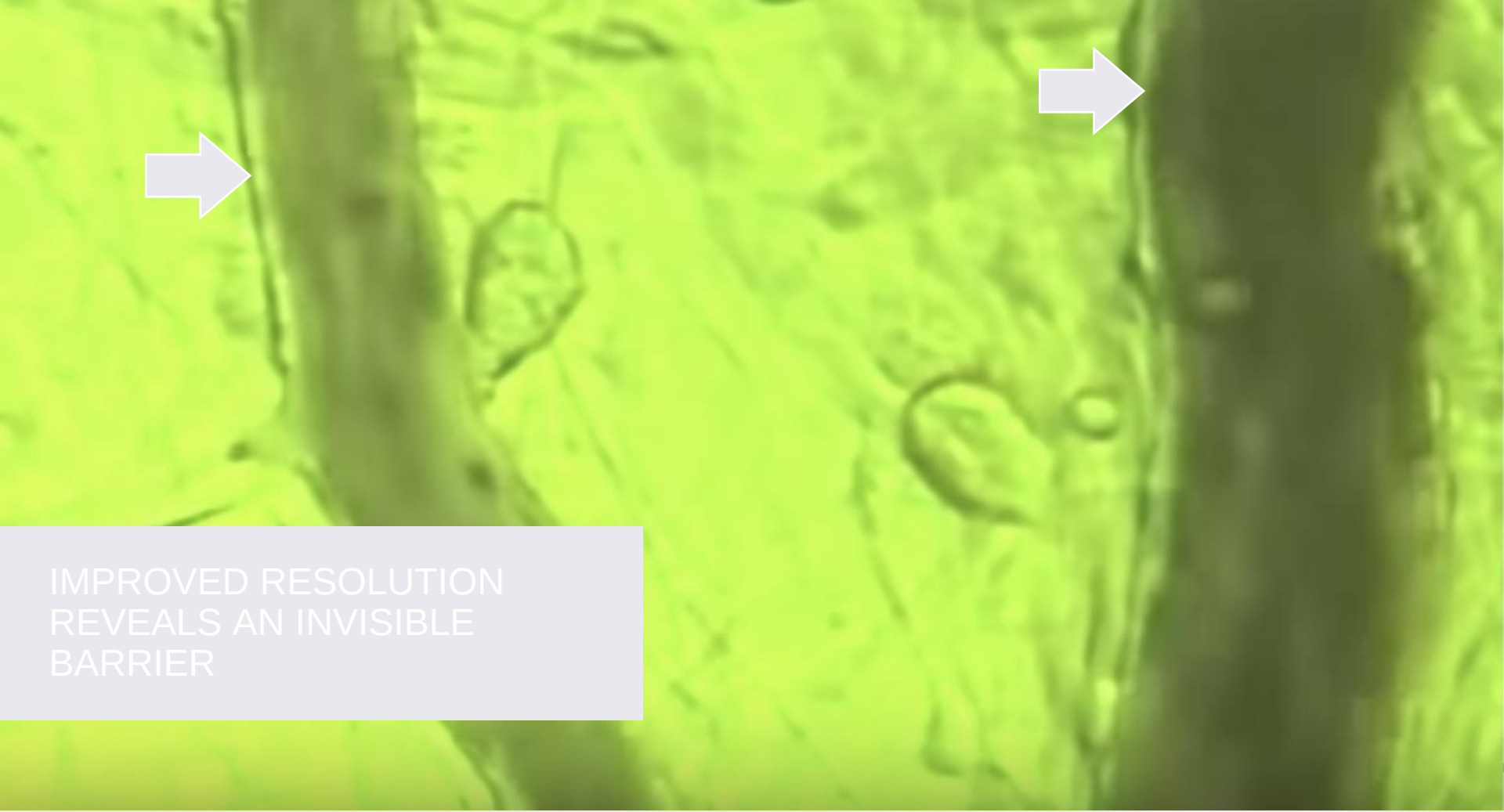


Figure 7. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may bind to e… telets via the angiotensin converting enzyme 2 (ACE2)/transmembrane protease serine 2 (TMPRSS2) receptors to promote e… and platelet hyperactivation, thereby promoting the activation of the coagulation cascade and formation of fibrinaloid microclots. In Long …OVID, SARS-CoV-2 may hide in extracellular vesicles

Messages

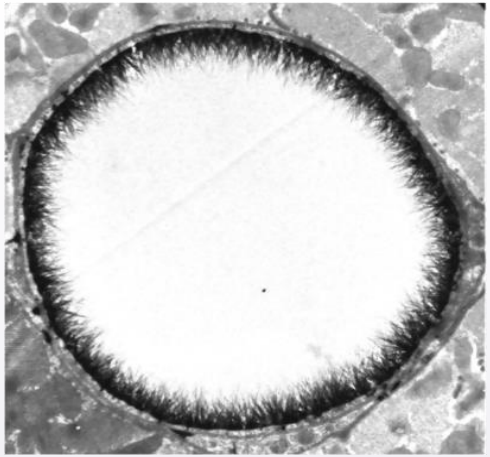
These mechanisms culminate in the long term persistence of the disorder characterized by a thrombotic endothelilitis, endothelial inflammation, hyperactivated platelets, and fibrinaloid microclots. –representing a unifying pathway for the various symptoms of LongCOVID.

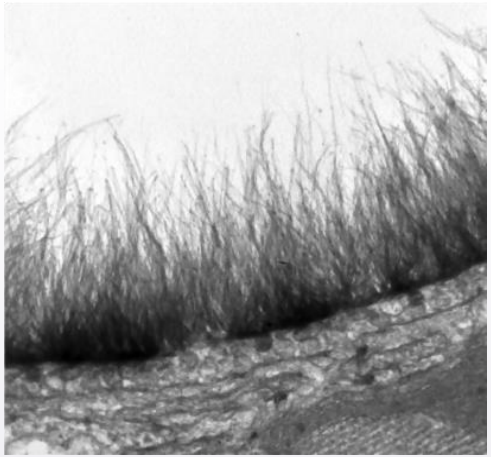
Turner, S, Khan, MA, Putrino, D, Woodcock, A, Kell, DB, & Pretorius, E. (2023). Long COVID: pathophysiological factors and abnormalities of coagulation. Trends in Endocrinology and Metabolism, 34(6), 321–344. https://doi.org/10.1016/j.tem.2023.03.002

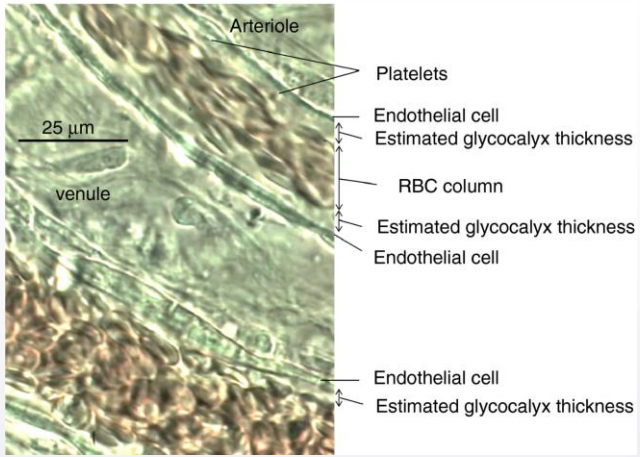


IMPROVED RESOLUTION REVEALS AN INVISIBLE BARRIER

The Endothelial Glycocalyx (EGX): Sentinel and Protector





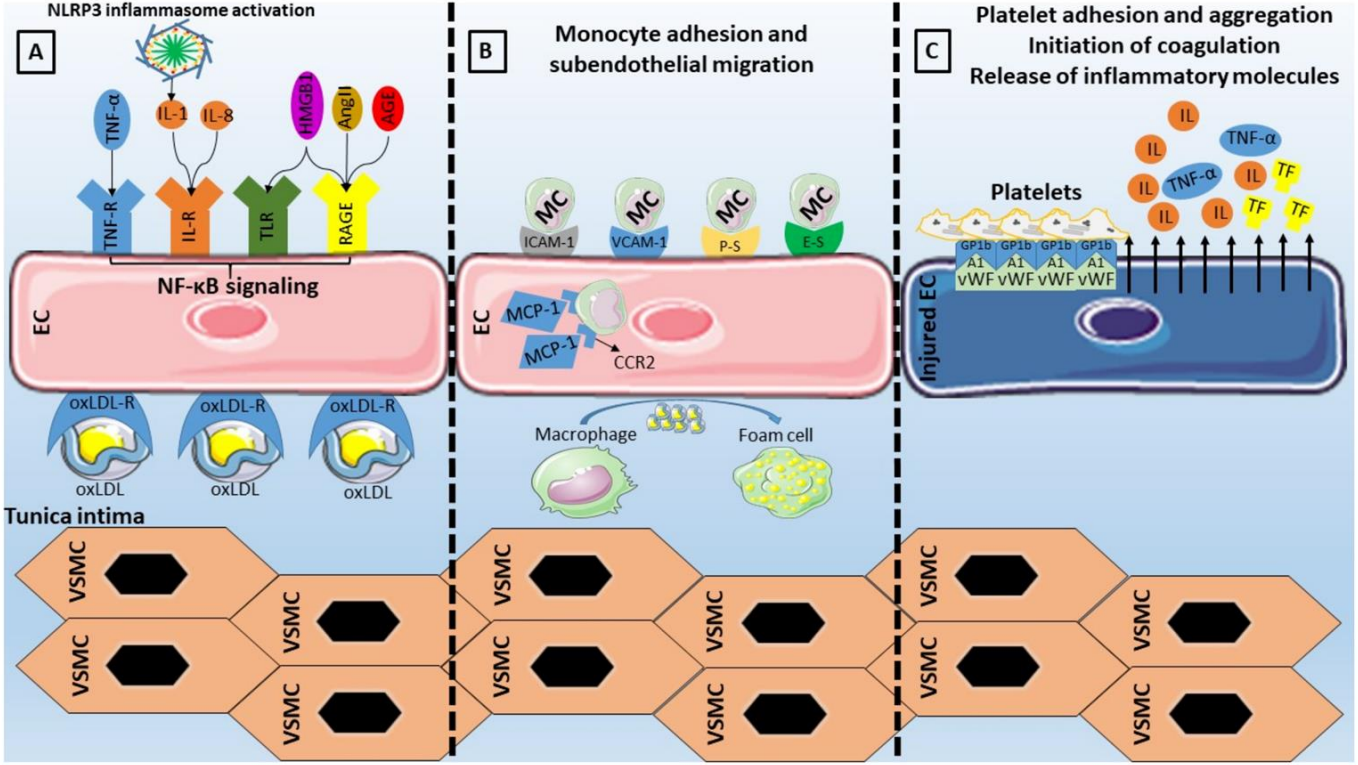


Where Endothelial Dysfunction Starts

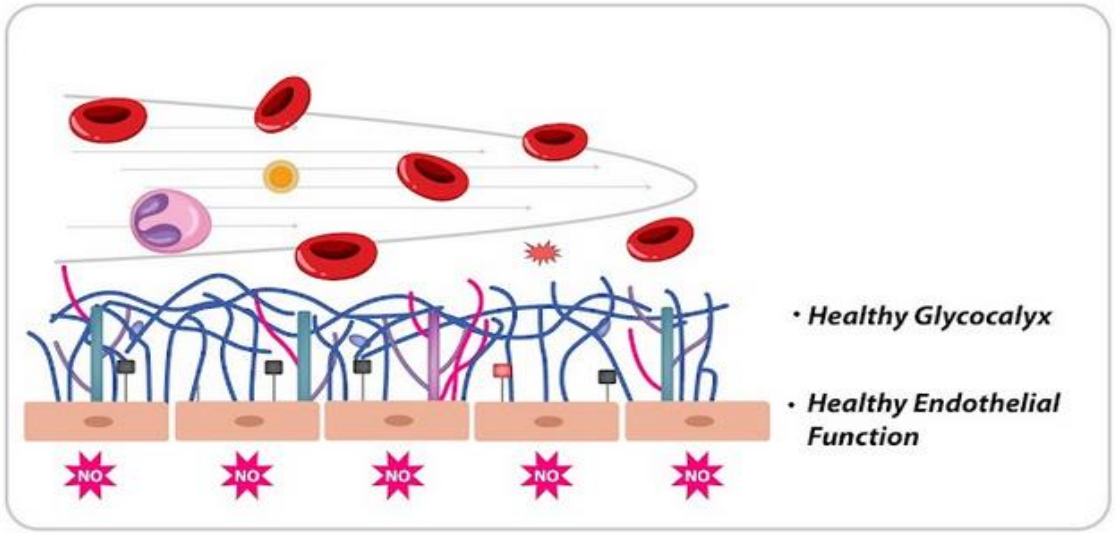
A microscopically thin gel-like layer of glycoproteins, proteoglycans, and GAGs (glycosaminoglycans) coating the luminal side of the vascular endothelium

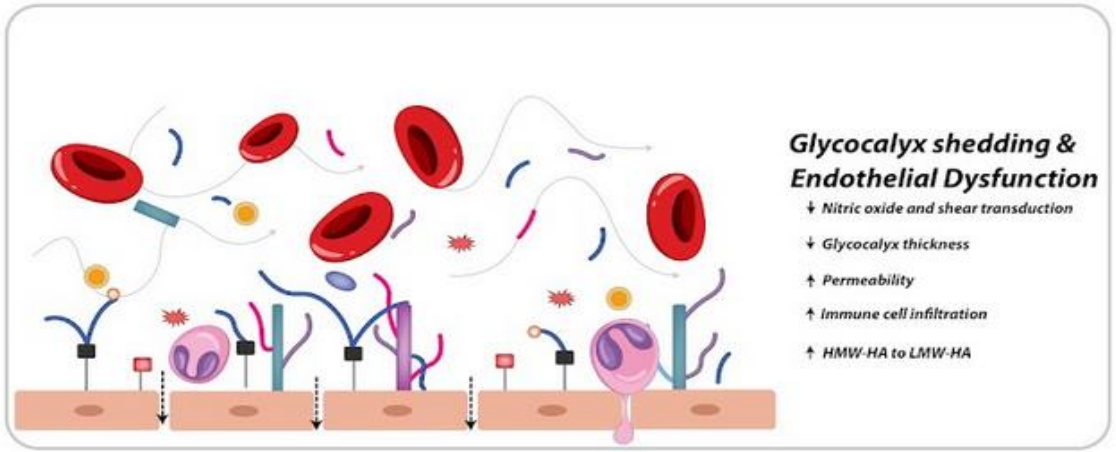
EGX damage **precedes** endothelial damage

Inflammation damages the vasculature



Theofilis P, Sagris M, Oikonomou E, et al. Inflammatory Mechanisms Contributing to Endothelial Dysfunction. *Biomedicines*. 2021;9(7):781. doi:10.3390/biomedicines9070781



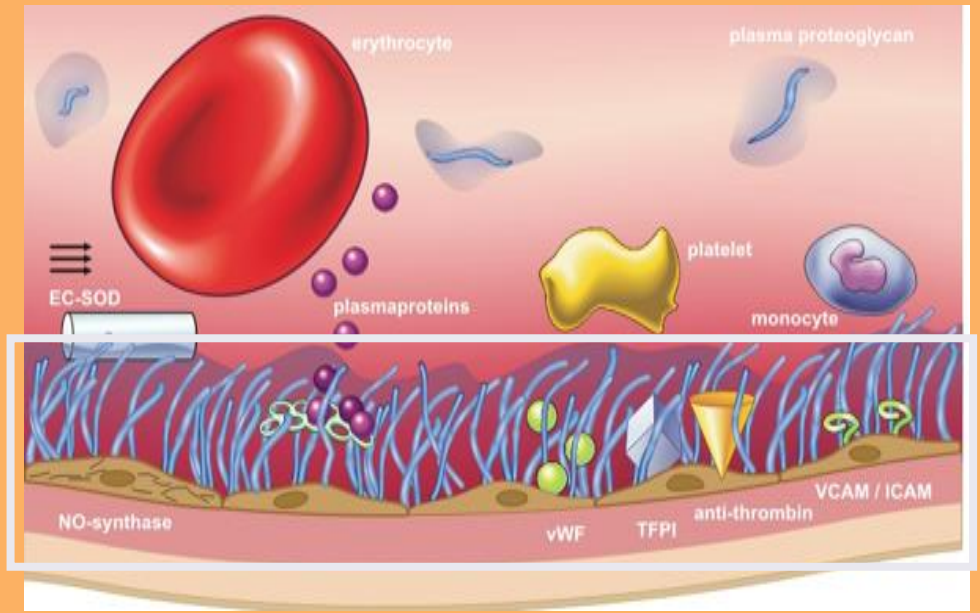


What does it do?

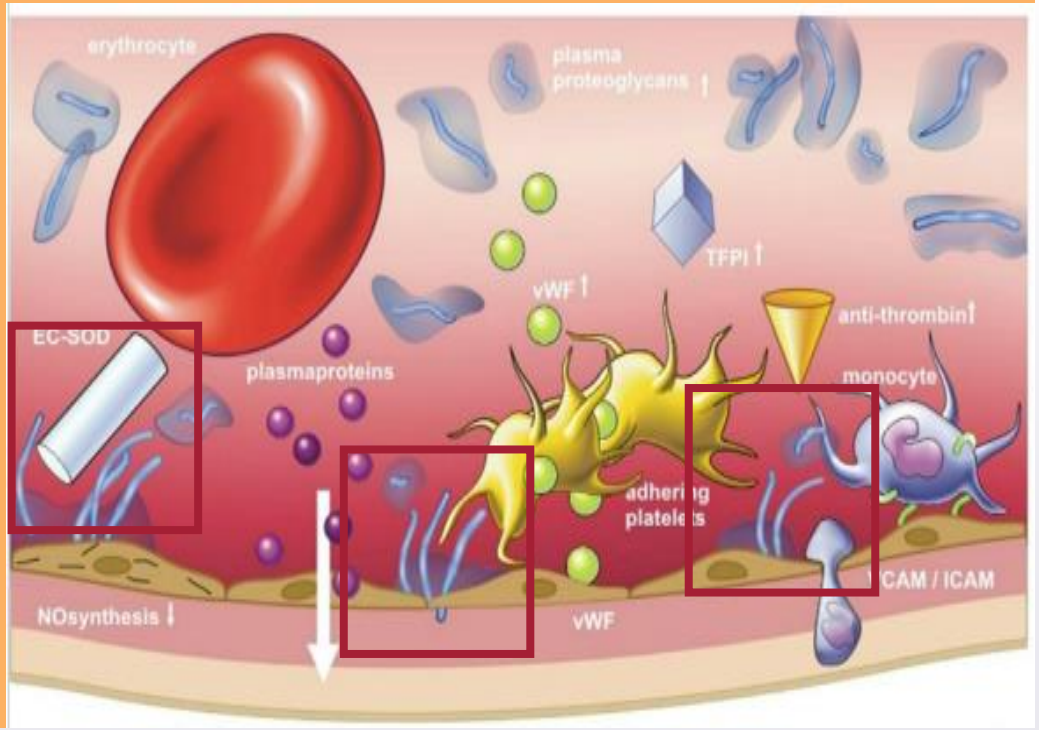
- Intelligent gatekeeper – the vascular system's "bouncer"
- Storage and docking for antioxidants
- Protective barrier to keep blood flowing smoothly
- Responds to increased blood flow by triggering nitric oxide release
- Maintains vascular homeostasis
- Regulates vascular permeability and fluid balance

Endothelial Glycocalyx

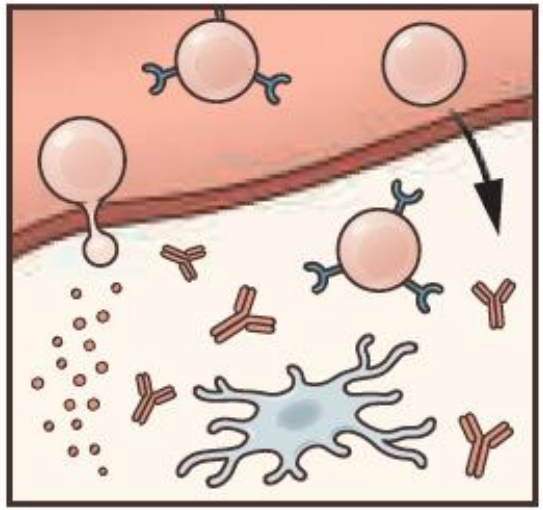
- Regulates permeability as a selective sieving barrier
- Helps regulate surface inflammatory response
- Arterial anti-adhesive
- Harbors coagulation regulatory factors
- Houses extracellular SOD – potent anti-inflammatory antioxidant enzyme
- Triggers production of nitric oxide (NO) through classical, enzymatic eNOS pathways



Compromised Glycocalyx



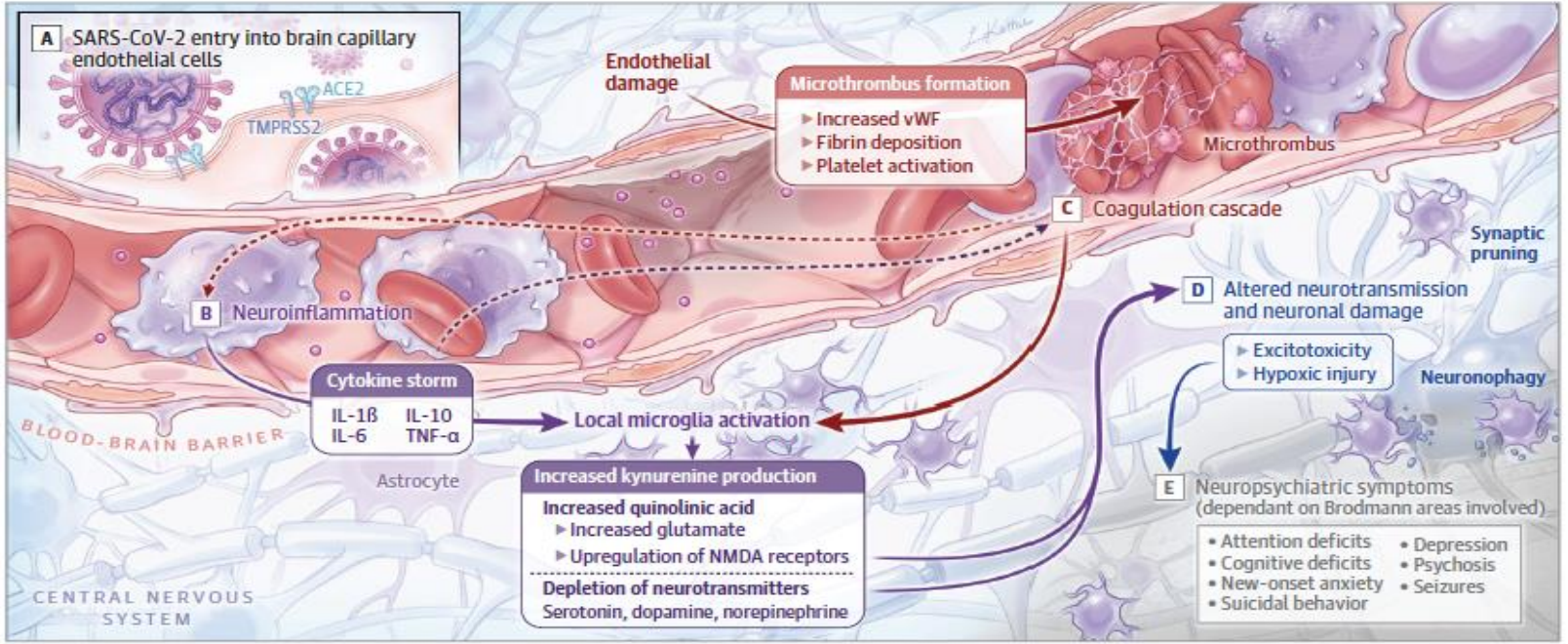
- Reduced NO availability
- Increased oxidative stress
- Increased leakage of macromolecules
- Increased platelet adherence
- Increased thrombin generation
- Increased leukocyte adhesion & diapedesis



Neuronal inflammation may result from activated microglia and immune cells.

Al-Aly Z, Topol E. Solving the puzzle of Long Covid. Science. 2024 Feb 23
Vol. 383;6685:830-832. doi: 10.1126/science.adl0867.

Figure. Brain Vascular Injury, Neurotransmitter System Dysfunction, Thrombotic Events, Neuronal Damage, and Neuropsychiatric Symptoms



A, SARS-CoV-2 invades endothelial cells via transmembrane angiotensin-converting enzyme 2 (ACE2) receptor, enabled by transmembrane protease, serine 2 (TMPRSS2). B, Cytokine elevation and microglia activation result in increased kynurenine, quinolinic acid, and glutamate, and neurotransmitter depletion. C, Coagulation cascade and elevation of von Willebrand factor (vWF) lead to thrombotic events. D, Altered neurotransmission, excitotoxicity by increased glutamate, and hypoxic injury contribute to neuronal dysfunction and loss. E, Neuropsychiatric symptoms differ depending on the Brodmann area involved. IL indicates interleukin; NMDA, *N*-methyl-D-aspartate; TNF, tumor necrosis factor.

Boldrini M, Canoll PD, Klein RS. How COVID-19 Affects the Brain. JAMA Psychiatry. 2021 Jun 1;78(6):682-683. doi: 10.1001/jamapsychiatry.2021.0500. PMID: 33769431; PMCID: PMC9894299.

Inflammation Example: The EGX and the Blood-Brain-Barrier (BBB)

- Selectively permeable
- Key role in coagulation
- Moderates inflammatory response

Received: 27 August 2020 | Revised: 3 November 2020 | Accepted: 22 November 2020

DOI: 10.1111/cns.13560

REVIEW ARTICLE

CNS Neuroscience & Therapeutics WILEY

Endothelial glycocalyx as an important factor in composition of blood-brain barrier

Fangfang Zhao[1] | Liyuan Zhong[1] | Yumin Luo[1,2,3]

[1]Institute of Cerebrovascular Disease Research and Department of Neurology, Xuanwu Hospital of Capital Medical University, Beijing, China

[2]Beijing Key Laboratory of Translational Medicine for Cerebrovascular Diseases, Beijing Geriatric Medical Research Center, Beijing, China

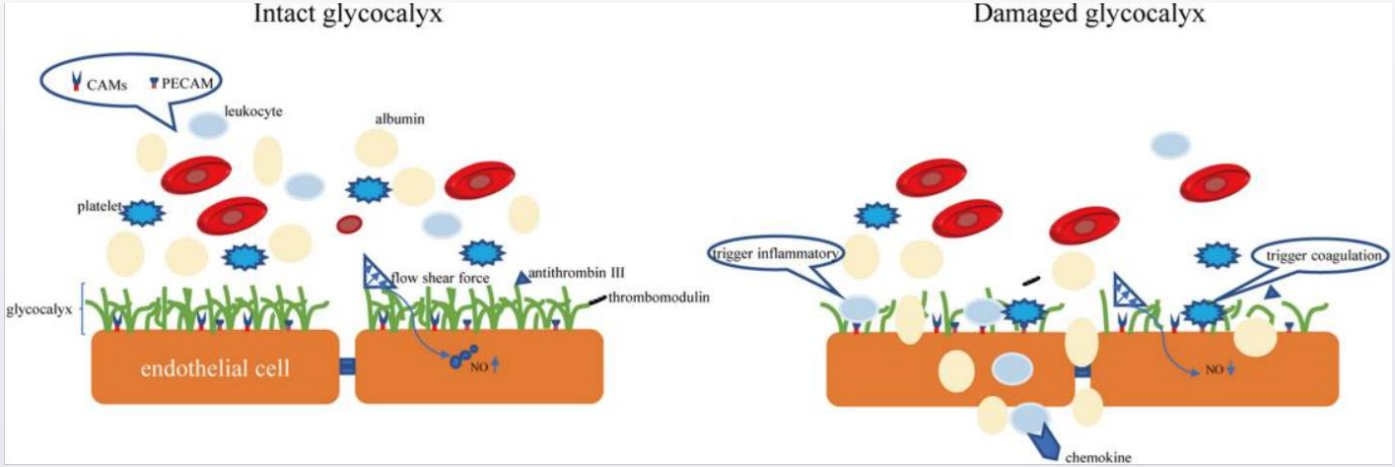
[3]Beijing Institute for Brain Disorders, Capital

Abstract

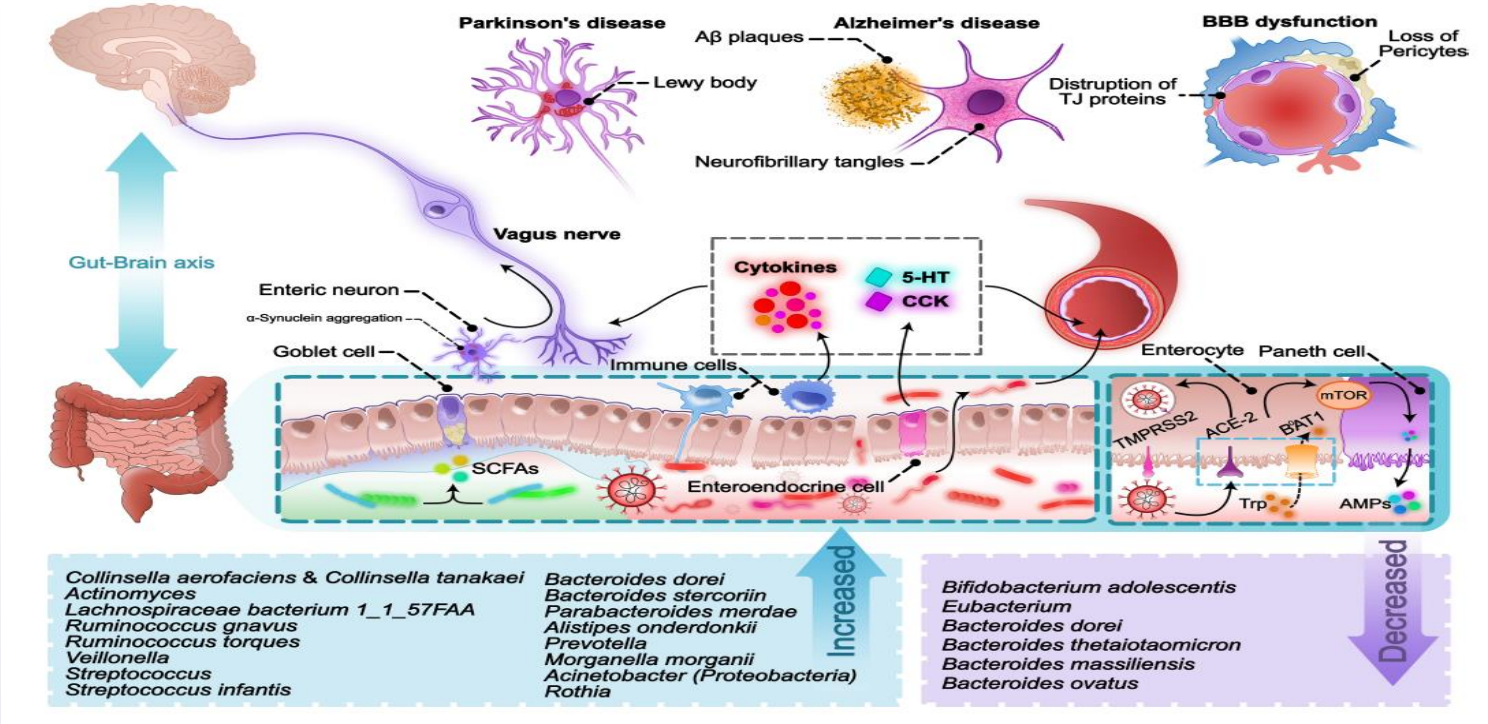
The blood-brain barrier is a dynamic and complex neurovascular unit that protects neurons from somatic circulatory factors as well as regulates the internal environmental stability of the central nervous system. Endothelial glycocalyx is a critical component of an extended neurovascular unit that influences the structure of the blood-brain barrier and plays various physiological functions, including an impor-

Example system: The EGX and the Blood-Brain-Barrier (BBB)

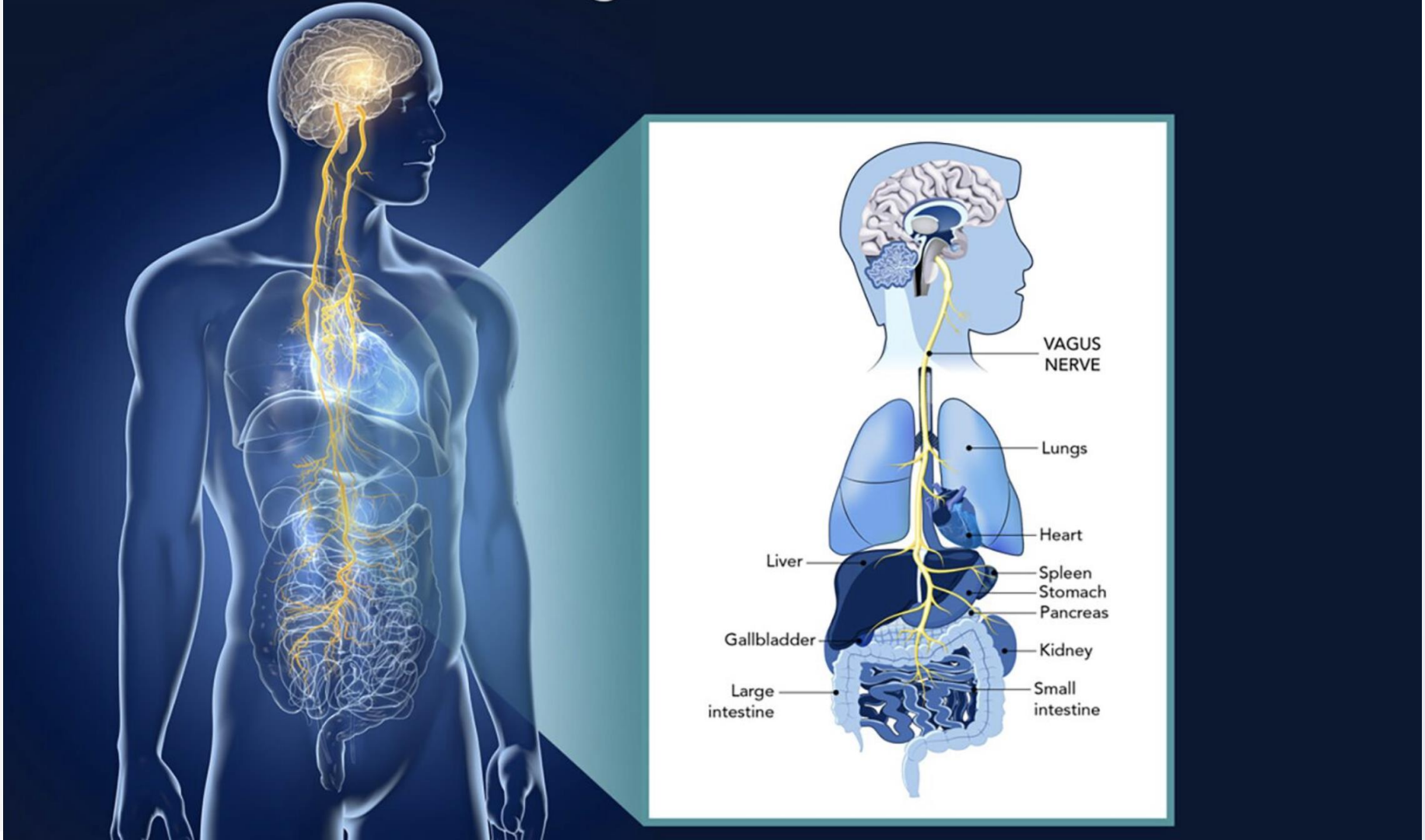
“Damage to the fragile glycocalyx can lead to increased permeability of the BBB, tissue edema, glial cell activation, up-regulation of inflammatory chemokines expression, and ultimately brain tissue damage.”



Jin J, Fang F, Gao W, et al. The Structure and Function of the Glycocalyx and Its Connection With Blood-Brain Barrier. *Front Cell Neurosci*. 2021;15:739699. doi:10.3389/fncel.2021.739699



Vakili K, et al. The contribution of gut-brain axis to development of neurological symptoms in COVID-19 recovered patients: A hypothesis and review of literature. Front Cell Infect Microbiol. 2022 Dec 22;12:983089. doi: 10.3389/fcimb.2022.983089. PMID: 36619768; PMCID: PMC9815719.


VAGUS NERVE
Lungs
Heart
Liver
Spleen
Stomach
Pancreas
Gallbladder
Kidney
Large intestine
Small intestine

The gut-brain axis (GBA) is a **bidirectional** link between the central nervous system (CNS) and the enteric nervous system (ENS) of the body. It involves direct and indirect pathways between cognitive and emotional centres in the brain with peripheral intestinal functions. In addition, the GBA involves complex crosstalk between the endocrine (hypothalamic-pituitary-adrenal axis), immune (cytokine and chemokines) and the autonomic nervous system (ANS).

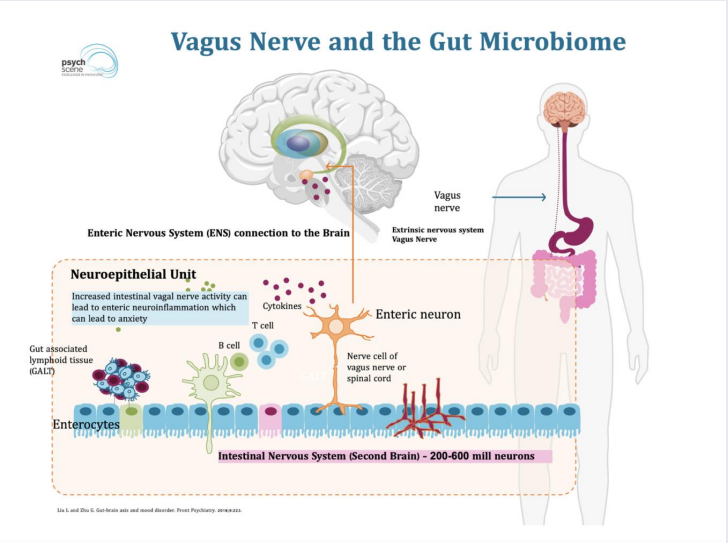
The GBA primarily combines the sympathetic and parasympathetic arms of the autonomic nervous system (ANS), which drives both afferent and efferent neural signals between the gut and the brain, respectively. The HPA axis meanwhile coordinates adaptive responses against stress, including activation of memory and emotional centres in the brain's limbic system.

The control exerted by the gut microbiota on the brain include:

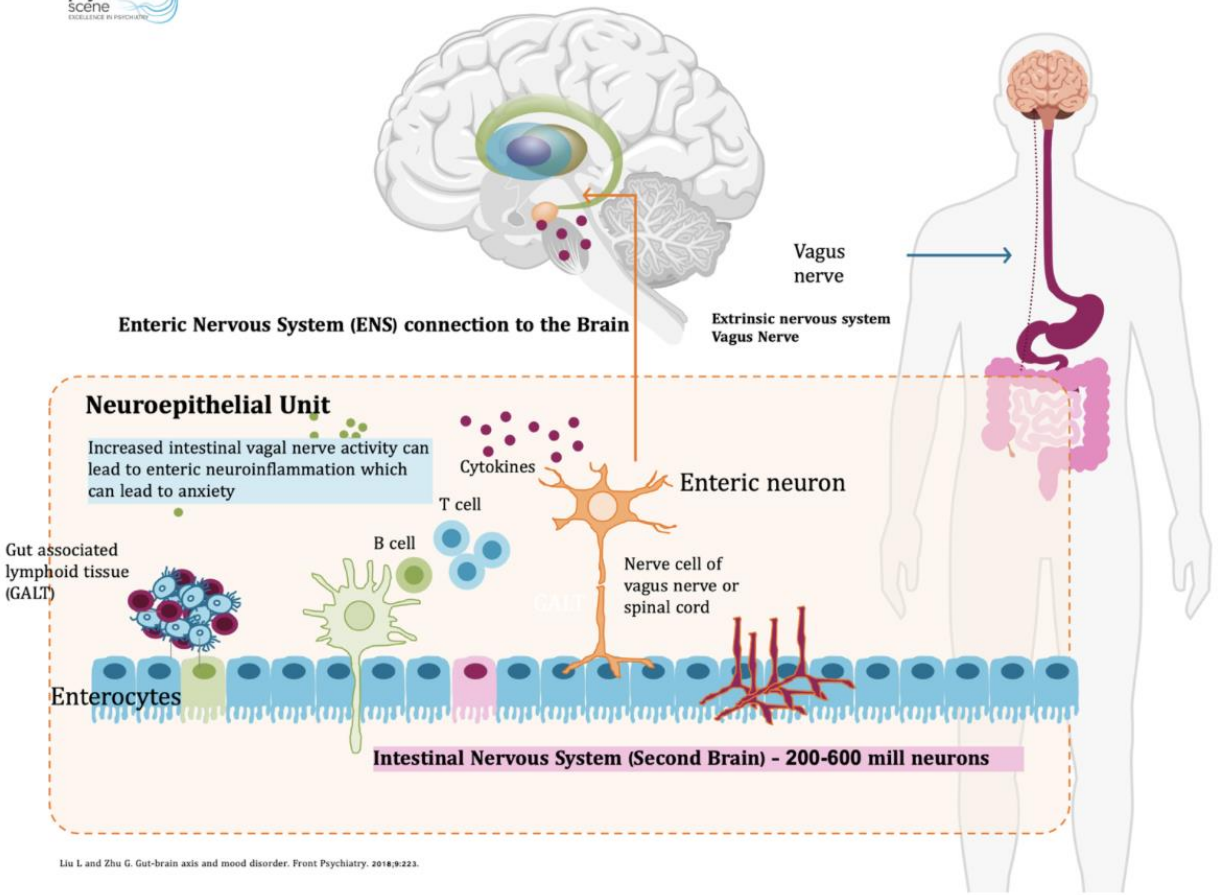
1)production, expression, and turnover of neurotransmitters such as GABA and BDNF
2)protection of tight junctions in the GI tract
3)enteric sensory function
4)bacterial metabolites which alter brain function

The brain in turn controls:

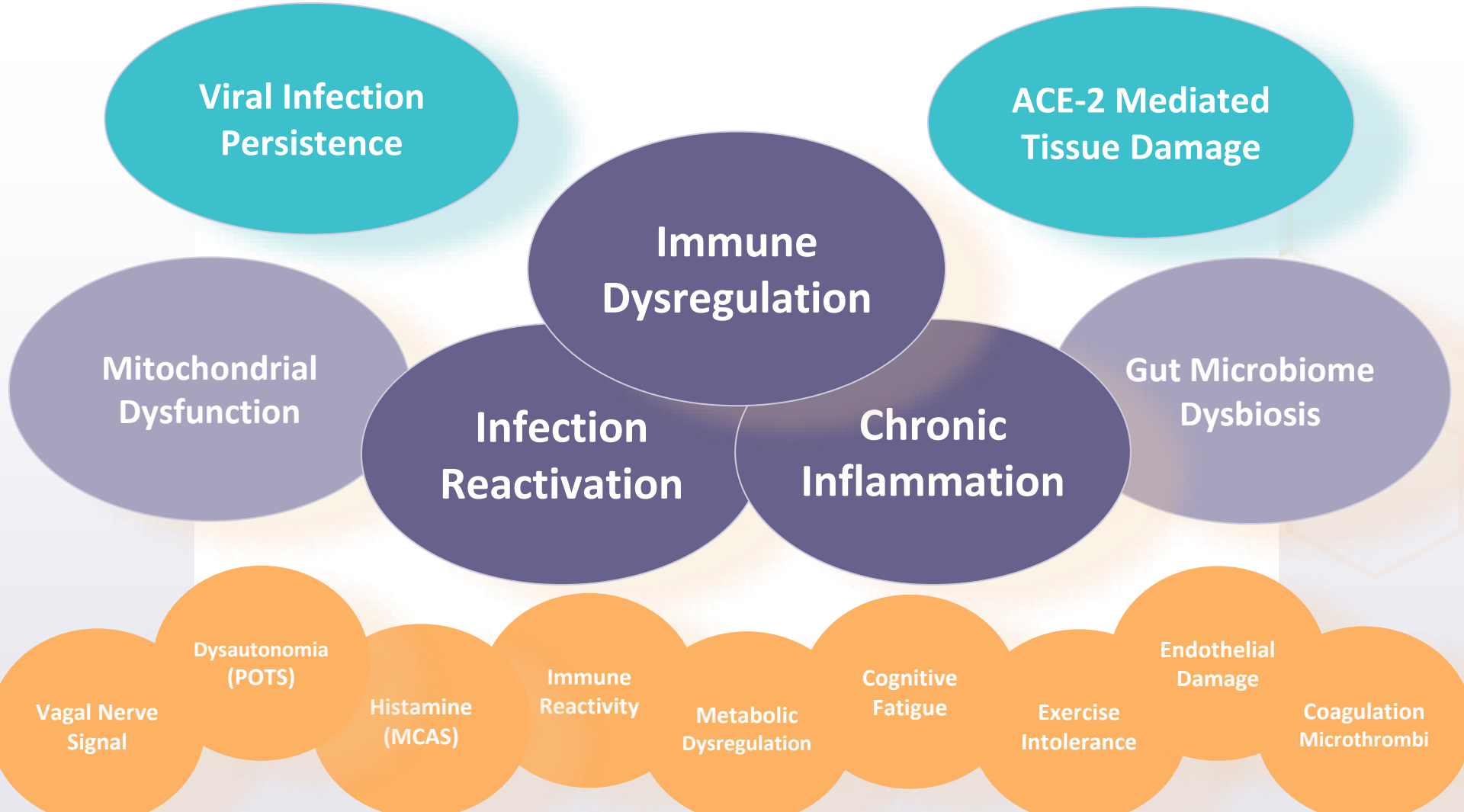
1)Mucus and biofilm production
2)GI tract motility
3)intestinal permeability
4)immune function



Vagus Nerve and the Gut Microbiome



Liu L and Zhu G. Gut-brain axis and mood disorder. Front Psychiatry. 2018;9:223.


Viral Infection Persistence
ACE-2 Mediated Tissue Damage
Immune Dysregulation
Mitochondrial Dysfunction
Infection Reactivation
Chronic Inflammation
Gut Microbiome Dysbiosis
Vagal Nerve Signal
Dysautonomia (POTS)
Histamine (MCAS)
Immune Reactivity
Metabolic Dysregulation
Cognitive Fatigue
Exercise Intolerance
Endothelial Damage
Coagulation Microthrombi

PROGRAM AND PROTOCOL OVERVIEW

KEY LIFESTYLE INTERVENTIONS OVERVIEW

- Food, Nutrition + Supplements
- Restorative Sleep
- Movement & Exercise
- Stress Modification
- Social Connection

RESOURCES

www.ovationlab.com/Resources

ovationlab.com/resources

ovationlab.com/resources

POST VIRAL RECOVERY PROGRAM

Resources for Providers and Patients

Presented by OVATIONLAB | Research and Program Development Sponsor ANDHEALTH

UPCOMING EVENTS

Wednesday, September 27th
7 pm ET/4 pm PT

WORKSHOP REPLAYS

PRACTITIONER RESOURCES AND TOOLS

FULLSCRIPT RESOURCES

- Protocol Application with Fullscript
- If you do not have an active Fullscript account, please use this link to create your no-cost account.
- If you would like to prescribe the **specialty products only**, please use this link.
- If you would like to prescribe the **full protocol** or make modifications to it, please use this link.
- Dispensary & individual patient discounts

NUTRITIONAL SUPPLEMENT SELECTIONS

- Supplement Selection
- Fullscript Patient Protocol

SAMPLE SURVEY INSTRUMENTS

- LongCOVID Patient Intake Form
  - WHO Post COVID-19 CRF
- Timeline and Progression of Symptoms Table
- PROMIS29
- Post COVID Function Scale
  - The Post-COVID-19 Functional Status scale

PATIENT CASES - Coming

PATIENT RESOURCES AND TOOLS

WHOLE30 PROGRAM RESOURCES

- Program Rules
- Plant-Based Whole30 Prep Pack
- Grocery Guide
- Shopping List
- Meal Planning
- Plant-Based Recipes

LIFESTYLE INTERVENTION RESOURCES

- How to Improve Sleep Hygiene
- Circadian Rhythms
- Stress Management
- Physical Activity and Stress
- Exercise Tolerance Assessment for Exercise Fitness & HR Recovery Instructions (from Share Care)
- WHO Support for Rehabilitation
- The Levine Protocol For Exercising With POTS - Better By The Beat
- Instructions for POTS Exercise Program—Children's Hospital of Philadelphia the Structure of the Training Calendars
- Coronavirus Recovery: Breathing Exercises | Johns Hopkins Medicine
- Bouncing Back From COVID-19
- 5 At-Home Exercises for COVID-19 Recovery | Patient Care

New Patient Experience

DocereVita's Post-pandemic Recovery Program

Coach Prep*

Coach Follow Ups

2 4 6 8 12 16

Initial Visit
- *Qualify Patient*
- *Questionnaires*
- *Order Labs*
- *Order NatRx*

Fnxal Labs
- *KBMO/GBP*
- *Vit D*
- *Omega Quant*
- *3x4 Genetics*
- *Tickborne Disease*
- *Viral Panel*
- *Mycotoxins*

2 Week Visit
- *Coach Check-in*
- *Check on Labs*
- *Discuss Lifestyle*
- *Set Goals*
- *Adjust Diet*
- *Review Schedule*
- *Start Low*

4 Week Visit
- *Review Labs*
- *Start FULL Doses for 20-30 days*
- *"Day 0" PVRP*

8 Week Visit
- *30-day Qnr*
- *Reduce Doses*

12 Week Visit
- *60-day Qnr*
- *Adjust Doses*
- *Triage Next Steps*

As Needed Visits
- *Coaching*
- *90-day Qnr*
- *Personalize Plan*
- *Retest Labs*

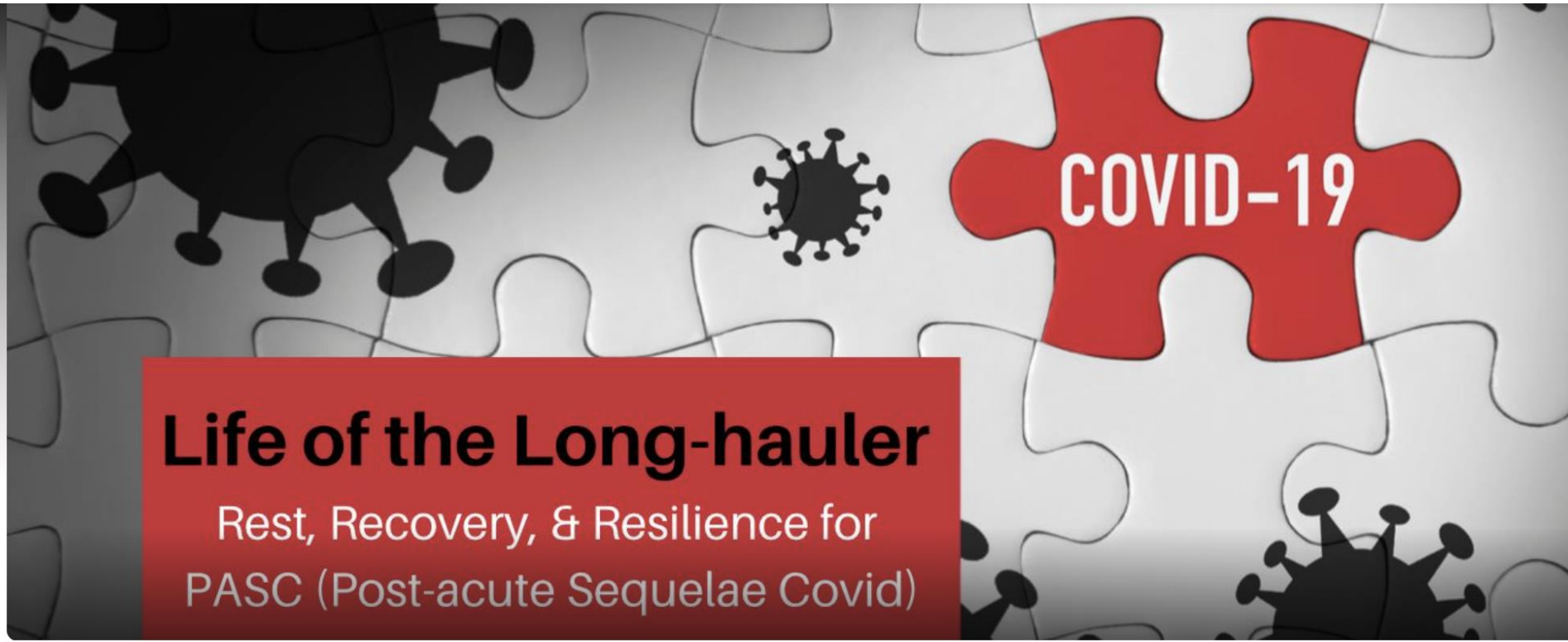
Fnxal Labs
- *KBMO/GBP*
- *Vit D*
- *Omega Quant*
- *3x4 Genetics*
- *Tickborne Disease*
- *Viral Panel*
- *Mycotoxins*

Invited to Group

Immune Resilience Group for CIRS ~ PASC ~ Long-COVID ~ TBDz ~ Mycotoxin Patients

New Patient
Welcome
Orientation
SYT L1

Access to PASC/Post-viral Recovery Program & Educational Resources in Patient Portal (self-guided)



Life of the Long-hauler ~ Rest, Recovery, and Resilience for PASC

	Preventive Nutrition	Active Infection (SARS-CoV-2)	Post-acute Sequalae COVID	Long-haul COVID Syndrome
Microbiome Support	❑ Fruits & Greens/Immune ❑ GI Integrity ❑ UltraBiotic Complete	❑ Fruits & Greens/Immune ❑ GI Integrity ❑ U/B Daily Multi-Strain	❑ GI Integrity ❑ UltraBiotics Probiotic Pro ❑ SporeProbiotic ❑ UltraBiotic Defense	❑ GI Integrity ❑ UltraBiotics Probiotic Pro ❑ SporeProbiotic ❑ UltraBiotic Defense
EFAs	❑ EPA/DHA 720 - 1000 ❑ Omega Pure Complete ❑ PRM Resolve	❑ EPA/DHA 720 - 1000 ❑ Omega Pure Complete ❑ PRM Resolve	❑ EPA/DHA 720 - 1000 ❑ Omega Pure Complete ❑ PRM Resolve	❑ EPA/DHA 720 - 1000 ❑ Omega Pure Complete ❑ PRM Resolve
Targeted Nutrients & Advanced Formulations	**Foundational Nutrition** ❑ MVM/Mito Recharge ❑ Nutri-ChelX/Glutathione ❑ Immune Support ❑ Vit D3 5000 w/K2 ❑ Mag Calm Pro ❑ Zinc Pro	**Immune/Infection** ❑ Vitamin A ❑ Vitamin C ❑ Vit D3 5000 w/K2 ❑ Glutathione ❑ Immune Resilience ❑ Zinc Pro ❑ Mag Calm Pro **Inflammation/Allergies** ❑ Inflam-eze Plus ❑ Aller Pro/Quercitin **Additional NatRxs** ❑ Tollovid ❑ Arterosil	**Oxidative Stress/Energy** ❑ Mito Recharge ❑ CoQ10 ❑ Glutathione **Immune Resilience** ❑ Immune Support ❑ Vit D3 5000 w/K2 ❑ Mag Calm Pro ❑ Zinc Pro ❑ GI Defend **Inflammation/Allergies** ❑ Dynamic Inflam-eze ❑ Inflam-eze Plus ❑ Aller Pro/Quercitin **Additional NatRxs** ❑ Tollovid (90-day) ❑ Arterosil	**Microbiome** ❑ GI Defend ❑ NutriCidin ❑ Spectrum AR **BioToxins/Mycotoxins** ❑ Lipo-flow ❑ Detox Support ❑ Glutathione ❑ Sulforaphane Complex ❑ Binder Pro **Metabolic Balance** ❑ Gluco IR ❑ Berberine Pro ❑ CardioFlow **Neuro-cognitive** ❑ Brain Support ❑ Brain Restore ❑ Neuro Balance

DOCTOR KRISTI

THANK YOU

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