

# Long Covid: Latest Research

## Piecing Together the Biological Clues

### Possible Root Triggers

#### Viral Persistence

**Spike protein** was found in at least 2/3 of LC patients' megakaryocytes (MKs), suggesting bone marrow and MKs may form **viral reservoirs** capable of producing **infectious platelets**. [1]

**T cell activation** identified in multiple regions of LC patients, including the brainstem and gut wall. SC2 single-stranded spike RNA was found, whilst **double-stranded spike RNA** was detected in 3 of 5 gut tissue samples, suggesting **ongoing viral replication**. [3]

**SARS-CoV-2 protein (Pp1ab)** identified within **extracellular vesicles** in all LC patients, while absent in controls. [4]

**SC2 spike protein** accumulation found in the body for years after initial infection, especially in the **skull marrow and meninges**. [5]

Reservoirs of **replicating virus** and/or RNA fragments may **persist** in **multiple body sites**. These reservoirs could be providing **continuous antigenic exposure** to exhausted CD4+ and CD8+ T cells. [2]

#### Predisposing & Contributing Factors

**SARS-CoV-2** may exacerbate **immune dysfunction** attributed to **pre-existing infections**, or trigger the **reactivation of latent infections**. Viral, bacterial, fungal or parasitic co-infections may be crucial to the development of LC. [6]

Acute-phase **gut microbiome** composition **predicts development of Long COVID**. The bacteria that predicted LC development may be associated with **mucosal barrier degradation** and the production of **pro-inflammatory metabolites**. [8]

A large genome-wide analysis **identified eight loci** (genome regions) that are significantly associated with ME/CFS, hinting at a biological cause. These regions are associated with the immune system, nervous system, and energy metabolism. [7]

- **RABGAP1L** (viral defence)
- **BTN2A2** (T cell regulation)
- **FBXL4** (mitochondrial health)
- **SUDS3** (regulates microglial activation)
- **OLFM4** (neutrophil regulation)
- **CCPG1** (stressed ER cleaner)
- **CA10** (trans-synaptic interactions)
- **ARFGF2/CSE1L** (TNF- $\alpha$  management)

### Core Engine of Dysfunction

#### Microvasculature and Clotting

Skeletal muscle capillaries show basement-membrane **thickening and collagen IV deposits**, decreasing lumen space. These changes may lead to **reduced perfusion**, reduced oxygen uptake and increased waste buildup. [9]

**Haptoglobin drops post-exertion** in ME/CFS, suggesting a struggle to clear free hemoglobin. Hp2-1 phenotype associated with worse PEM and cognitive deficits. [11]

**Spike685 amyloid fibrils** can trigger dense clot networks that incorporate fibrin, resulting in **microclots** that are resistant to **fibrinolysis** in LC. [12]

**SC2 Spike protein** binds to fibrin, forming blood clots that cause systemic **thromboinflammation and microvascular damage**, whilst also **impairing NK cells**. [13]

SARS-CoV-2 triggers **endothelial dysfunction, impaired neurovascular coupling, and blood-brain barrier disruption**, resulting in compromised cerebral perfusion. Furthermore, infection-induced mitochondrial dysfunction enhances **oxidative stress and inflammation in cerebral endothelial cells**. [14]

**Endothelial necroptosis** in Covid-19 patients was not linked to clotting, but to microvascular red blood cell **haemolysis** (rupture), associated with **ischaemia-reperfusion injury**. [15]

**Microvascular density loss and hemodynamic reductions** disrupt the blood supply to peripheral tissues, causing **hypoxia and undernutrition**. [16]

#### Immune Dysfunction and Exhaustion

**PD-1 and TIM-3** (immune exhaustion markers) were elevated in SARS-CoV-2 nonspike-specific CD8+ T cells in LC patients. Results were suggestive of ongoing viral antigen exposure. [17]

Specific **CD8+ and innate T cells** show pronounced dysregulation and **exhaustion markers** in ME/CFS, suggestive of constant stimulation. Exhaustion markers were **upregulated following exercise**. [19]

LC patients had significantly **reduced transitional (CD27-CD38+++)** B cells. [20]

Evidence of a **dysregulated complement system** (innate immune branch) in LC. [21]

**TAF1 and MARCHF7** genes were **upregulated** in LC, interfering with autoubiquitination, which may impair immune clearance of viruses. The **JAK-STAT pathway** and certain small nucleolar RNAs (possibly involved in RNA viral replication) were also upregulated. [22]

LC was associated with a **bias towards Th2/Th17 profiles** and increased cytotoxic T lymphocytes, suggesting **immune dysregulation and autoimmunity**. [24]

LC patients had high IgG titers for SC2 Envelope and Nucleocapsid proteins but a **low IgG response to the Spike protein**. Persistent high levels of  $\alpha$ TFH and MAIT T-cells were identified, and autoantibodies were also detected. Lasting immune activation and dysregulation implied chronic antigen persistence, possibly in the mucosa. [18]

**TRPM3 ion channel function is impaired** in the NK cells of both LC and ME/CFS patients. Dyregulated TRPM3 affects intracellular Ca<sup>2+</sup>, which may **impair cytotoxic function and cytokine production**. [23]

### Perpetuating Mechanisms and Symptom Drivers

#### Post-Exertional Malaise

**Heightened innate immunity** may trigger inflammation, fatigue and PEM:
 

- **Exaggerated immune responses** found in ME/CFS. These may be caused by altered microbial metabolite levels linked to gut dysbiosis and permeability.
- Evidence of **extracellular matrix disruption, reduced cell-cell adhesion, redox imbalance and lipid abnormalities**.
- Inflammation associated with **complement activation and altered calcium signalling worsened after exercise** in patients.
- Exercise resulted in **tryptophan being increasingly converted to KYN** instead of being used for serotonin production.
- After exercise, citrate levels were reduced, implying **TCA cycle impairment**, while oxidation of fatty acids became inadequate.

 [25]

Upon exertion, **activation of the sodium pump may be diminished**. When intracellular sodium reaches a certain level, the sodium-calcium exchanger changes its transport mode, causing **calcium overload**, leading to **mitochondrial and muscular damage**. This increases ROS production and further impairs the sodium pump, resulting in a vicious cycle. [26]

**mTOR activation may impair ATG13-dependent autophagy**, cause M1 macrophage infiltration, upregulate IL-6 and RANTES by STAT3 activation, and intensify demyelination in nerves serving muscle fibers. mTOR and ATG13 may be involved in PEM. [27]

#### Gut Dysbiosis and Permeability

LC fatigue patients had **disrupted gut barriers** and subsequent low-grade inflammation, evidenced by a higher LBP/sCD14 ratio, lower IL-33 levels, and higher IL-6. [28]

**Skewed microbiome-metabolome-immune crosstalk** identified. Altered microbial metabolism (impacting SCFAs, bile, BCAAs, plasma lipids, benzoate, and tryptophan) was linked to heightened inflammatory response of MAIT and Gamma-Delta T-cells. [29]

#### Neuro-Immune-Endocrine

Chronic dysfunction of the **Vagus Nerve-HPA-Mitochondrial axis** may impair anti-inflammatory mechanisms and perpetuate LC symptoms. [36]

**Brain fog tracks with systemic increase in AMPA glutamate receptors** across the brains of Long COVID patients. [37]

Profound biological disruptions identified after SC2 infection, some of which may endure and contribute to LC:
 

- **Tryptophan levels were dramatically reduced**, pro-inflammatory lipid mediators were elevated, and methylation changes were found in metabolism-related genes.
- **High levels of inflammatory lipids** like arachidonic acid were found, as well as persistent activation of peripheral immune cells and elevated systemic oxidative stress.
- In LC patients, **IL-1 $\beta$  (pro-inflammatory cytokine) levels were raised**, which may explain the shift to immature monocytes.
- **T-cells (particularly CD8 cells) showed markers of exhaustion, poor function, and senescence** in LC patients.

 [38]

A dramatic **reduction of CRH-producing neurons** in hypothalamus, pituitary shutdown, and low cortisol levels found in severe ME/CFS. **HLA-DR15 and ACTH molecular mimicry** could contribute to **autoimmunity** against the adenohipophysis. [39]

**High levels of the neurochemicals glutamate and N-acetyl-aspartate** found in LC and ME/CFS. [41]

**SC2 spike proteins activate mast cells** via Src kinase, activating the PI3K/AKT pathway. This results in an accumulation of intracellular calcium ions and mast cell degranulation. [42]

**Vascular dysfunction, neuroinflammation, and gut-brain axis disruption** may create a self-sustaining feedback loop that maintains neurological symptoms. [43]

**Glymphatic system (brain waste removal) dysfunction** may play a key role in ME/CFS. Reduced cerebral blood flow, immune and endothelial dysfunction, and hypoxia may contribute to this, causing **brain fog**. [44]

#### Mitochondria and Oxidative Stress

**Genetic depletion of ATG13 (early autophagy protein) impairs mitochondrial energy production** and raises macrophage ROS, causing M1 polarization. [30]

In LC, **ATP synthase runs in both directions**, consuming ATP to maintain mitochondrial membrane potential instead of exclusive use for ATP (energy) production. [31]

Widespread **cardiomyocyte mitochondrial damage and myofilament degradation** found in Long Covid patients. [32]

Elevated **oxidative stress in lymphocytes** due to sex-specific abnormalities in reactive oxygen species (ROS) clearance pathways. Found in both LC and ME/CFS. [33]

SARS-CoV-2 **reduces expression of mitochondrial genes** involved in energy production to facilitate replication. [34]

**Reduced aerobic capacity** at peak exercise was found in both ME/CFS and LC, which may be driven by **impaired systemic O<sub>2</sub> extraction and preload insufficiency**. [35]

Key:

Abbreviations: LC: Long Covid | SC2: SARS-CoV-2 | PEM: Post-Exertional Malaise | Study Focus: LC: Long Covid MC: ME/CFS C: Combination of Long Covid and ME/CFS AC: Acute Covid

References: [1] Bomsel (2025) PolyBio Research Foundation 2025 Fall Symposium [Online], [2] Prakash et al. (2025), [3] Peluso et al. (2024), Abbasi et al. (2025), [4] Abbasi et al. (2025), [5] Rong et al. (2024), [6] Henrich et al. (2025), [7] Boutin et al. (2025) medRxiv, [8] Comba et al. (2024) [Preprint], [9] Slaghekke et al. (2025), [10] Yao et al. (2025) [Preprint], [11] Moezzi et al. (2025), [12] Westman et al. (2025), [13] Ryu et al. (2024), [14] Fekete et al. (2025), [15] Wu et al. (2025), [16] Koutsiaris (2024), [17] Gao et al. (2025), [18] Kwissa et al. (2025) [Preprint], [19] lu et al. (2024), [20] Korobova et al. (2025), [21] Bayarri-Olmos et al. (2025), [22] Fineschi et al. (2025), [23] Sasso et al. (2024), [24] Korobova et al. (2025), [25] Che et al. (2025), [26] Scheibenbogen & Wirth (2025), [27] Drosen et al. (2024), [28] Rohrhofer et al. (2025), [29] Xiong et al. (2025), [30] Toriola et al. (2025) [Preprint], [31] Macnaughtan et al. (2025), [32] Che et al. (2025), [33] Shankar et al. (2025), [34] Guarnieri et al. (2023), [35] Squires et al. (2025), [36] Camici et al. (2024), [37] Fujimoto et al. (2025), [38] Lage et al. (2025) [preprint], [39] Health Rising (2025) ME/CFS Autopsy Study Finds a Wrecked HPA Axis [Online], [40] Ruiz-Pablos et al. (2024), [41] Thapaliya et al. (2024), [42] Zhang et al. (2025), [43] Talkington et al. (2025), [44] Nemat-Gorgani et al. (2025)

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