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IMMUNE MECHANISMS UNDERLYING LONG-TERM COVID: AN UPDATE FROM THE COLLEGIUM INTERNATIONALE ALLERGOLOGICUM 2024

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Abstract
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can lead to a prolonged multisystem disorder called long COVID, which may affect up to 10% of people following coronavirus disease 2019 (COVID-19). It is currently unclear why some people do not fully recover from SARS-CoV-2 infection. In this review, we examine the immunological mechanisms that may underlie the pathophysiology of long COVID. These mechanisms include an inappropriate immune response to acute SARS-CoV-2 infection, immune cell exhaustion, metabolic reprogramming of immune cells, a persistent SARS-CoV-2 reservoir, reactivation of other viruses, inflammatory responses affecting the central nervous system, autoimmunity, microbiome dysbiosis, and dietary factors. Key messages: Unfortunately, currently available diagnostic and treatment options for long COVID are inadequate, and additional clinical trials that match experimental interventions to underlying immunological mechanisms are needed.

Keywords: Long COVID, Severe acute respiratory syndrome coronavirus 2, Inflammation, Microbiota.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection results in a wide spectrum of manifestations, from asymptomatic infection to the fatal coronavirus disease 2019 (COVID-19), which has evolved as new variants emerge in combination with immunity from vaccination and infection. Following acute infection, a significant proportion of people experience long-term symptoms that can significantly impact daily activities, quality of life, and lead to disability. Long COVID is sometimes referred to as “post-acute sequelae of COVID-19 (PASC) or post-COVID condition (PCC).” Long COVID is a multisystemic disease with symptoms including fatigue, post-exertional malaise, joint and muscle pain, and sleep disturbance. In addition, systemic manifestations such as cardiopulmonary, neurocognitive, or gastrointestinal symptoms, as well as neuropsychiatric symptoms including anxiety and depression, may occur. Long COVID remains a clinical diagnosis in which symptoms begin within 3 months of SARS-

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CoV-2 infection and require persistence of symptoms for at least 2 months in the absence of an alternative diagnosis. Although the exact pathomechanism of long-onset COVID remains unclear, some of the symptoms are related to organ damage sustained during acute COVID-19, while others may be related to the development of post-infection conditions such as fatigue. Multisystem involvement in individual patients is common, with one study reporting a median number of symptoms reported at any one time of eight . The most common symptoms reported in this cohort were fatigue, malaise after exertion, palpitations, chest pain, upset stomach/nausea, memory problems, muscle aches, and joint pain. Symptoms may only occur after initial recovery from the acute episode of COVID-19 or persist after the initial illness, and may fluctuate or recur over time . The exact number of people currently suffering from long COVID is unknown, but based on a conservative estimate of 10% of infected people (over 651 million reported cases of COVID-19 worldwide), at least 65 million people worldwide may have long COVID . However, this number may be much higher, given the many undocumented cases of COVID-19 and asymptomatic SARS-CoV-2 infections. Long COVID has been described in all age groups, and importantly, most cases occur in patients who had mild acute illness that did not require hospitalization. A recent cohort study suggests that a significant proportion of people who experience long COVID symptoms after a mild SARS-CoV2 infection recover within the first year. Why some patients recover while others experience persistent illness is unclear.

In this review, we discuss potential mechanisms underlying the pathophysiology of long COVID, in particular those related to the immune system. These mechanisms are hypothesized to include an inappropriate immune response to acute SARS-CoV-2 infection, metabolic reprogramming of immune cells, a persistent SARS-CoV-2 reservoir, the reactivation effect of other viruses such as Epstein-Barr virus (EBV), inflammatory responses affecting the central nervous system (CNS), autoimmunity (including effects on the autonomic nervous system), coagulopathy, and microbiome dysbiosis. Given the breadth of symptoms reported by patients with long COVID, it is possible that individual or a combination of multiple immune mechanisms are relevant for certain subgroups of patients.

Immune Dysfunction and Long COVID

Immune responses to SARS-CoV-2 infection during the acute and recovery phases have been shown to be associated with the risk of long COVID. Levels of circulating immune mediators and biomarkers such as cortisol, serotonin, IL-8, CCL4, IL-4, and thymic stromal lymphopoietin remain altered in long COVID patients compared to control volunteers for several months after acute infection. In addition to autoimmunity and hyperinflammation, which are discussed in more detail elsewhere, inappropriate immune responses or immune dysfunction may predispose to or be associated with long COVID. Certain peripheral blood cell (PBMC) subsets have been shown to be reduced or absent in patients, including impacted CD127lowCD8 $^{+\text{ cells}}$, CD4+ cells $^{\text{, and B cells}}$. Increased expression of the exhaustion markers programmed cell death protein 1 (PD1) and T-cell immunoglobulin and mucin domain containing-3 (TIM3) has been noted in several studies, suggesting that T-cell exhaustion may contribute to symptomatology, although studies demonstrating causal effects of loss of T-cell function remain lacking.

In a subset of patients with long COVID, it is hypothesized that insufficient immune activation during the acute phase of SARS-CoV-2 infection may contribute to disease progression. Early in the pandemic, a specific antibody signature characterized by either low IgM or low IgG3 was

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associated with an increased risk of long COVID. Moreover, altered virus-specific $CD8^+$ T cell dynamics were reported in patients with gastrointestinal symptoms. However, less is known about the innate immune response, which acts as the first line of defense to prevent viral invasion or replication. Differences in monocyte and dendritic cell subsets, including reduced PDL1 ligand (PDL1) expression on antigen-presenting cells, were observed 6 months after infection. One important innate pattern recognition receptor is mannose-binding lectin (MBL), which binds and opsonizes the S and N proteins of SARS-CoV-2, highlighting its important role in neutralizing SARS-CoV-2. Genetically determined low levels of MBL have been associated with a higher risk of SARS-CoV-2 infection. Importantly, a higher prevalence of MBL deficiency has been reported in long-term COVID patients with persistent severe fatigue and post-exertional malaise (PEM), which is similar to the symptoms experienced by patients with myalgic encephalomyelitis/chronic fatigue syndrome after EBV infection. Low MBL levels have been associated with high levels of several cytokines, including interleukin 6 (IL-6) and tumor necrosis factor alpha. MBL can directly downregulate IL-6 and tumor necrosis factor alpha production, suggesting that it is a potent regulator of the inflammatory response and may influence the severity of acute infectious diseases . Many studies have highlighted the role of IL-6 during acute COVID-19 disease . High IL-6 levels have been associated with the most severe form of the disease and the worst prognosis. Low MBL levels may potentially contribute to dysregulated IL-6 overproduction in patients with severe COVID-19, thereby contributing to an inadequate antiviral response, viral persistence, and prolonged inflammation.

Neutrophils have been shown to play an important role in defense against SARS-CoV-2 infection through the formation of neutrophil extracellular traps (NETs) and type 1 interferons (IFNs). However, excessive neutrophil infiltration and NET formation in the lungs may contribute to tissue injury and disease severity in COVID-19 . Furthermore, emerging evidence links NET persistence to pulmonary fibrosis, cardiovascular impairment, and neurological dysfunction in long-COVID . NETosis has been shown to persist at higher levels in long-COVID patients compared to recovering patients . It is unclear what may be driving the sustained activation of short-lived neutrophils in long-COVID patients, but potential mechanisms may include changes in long-lived cell effector phenotypes, bone marrow microenvironmental changes, robust senescent cells, viral resistance, or autoantibodies.

The interplay between these important key players in adaptive and innate immunity suggests that pre-existing immune dysfunction may lead to difficulties in eliminating residual viral reservoirs or infected cells. Viral persistence may then contribute to ongoing inflammation and cognitive dysfunction due to illness behavior. Thus, there is growing evidence supporting the role of immunological dysregulation in the onset and progression of long-COVID.

Immune Metabolism in Long- Covid

Viruses are obligate parasites that are completely dependent on host cells for replication. Viral infection therefore results in changes in host cell metabolism due to increased cellular metabolic demands for virus production, toxicity (e.g., oxidative damage), and increased demands from immune cells in response to infection. Immune metabolism includes all intracellular metabolic pathways that enable innate and adaptive immune cells to function at steady state and after activation. Energy-producing processes such as glycolysis and mitochondrial oxidative phosphorylation (OXPHOS) are interconnected with the tricarboxylic acid cycle, fatty acid

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oxidation, fatty acid synthesis, glutaminolysis, nucleic acid synthesis, and provide metabolic signals for cell proliferation, migration, and function. SARS-CoV-2 infects multiple cell types, primarily via angiotensin-converting enzyme 2 (ACE2), and downregulates the expression of genes encoding all five OXPHOS complexes, as demonstrated in nasopharyngeal samples from infected versus uninfected individuals and in human airway epithelium . Autopsy tissues from COVID-19 patients showed similar reductions in OXPHOS-encoding gene expression in the heart, kidney, and liver . Many other mitochondrial processes were downregulated in several tissues, with the most striking reduction in the heart. In contrast, glycolysis and regulators of glycolysis, such as hypoxia-inducible factor 1-alpha and mammalian target of rapamycin, were upregulated . Downregulation of OXPHOS and upregulation of glycolysis and hypoxia-inducible factor 1 have also been demonstrated in other SARS-CoV-2-infected human cells and tissues and in COVID-19 patients. SARS-CoV-2 infection of human lung epithelium resulted in the release of alarmins such as IL-33 and activation of retinoic acid-inducible gene I (RIG-I), inflammasome activation with IL-18 release, accompanied by inhibition of antiviral proteins such as CCL4 . In other cells, inflammasome priming and activation and IL-33 secretion are at least partly dependent on glycolysis, whereas type I and III IFN responses are dependent on OXPHOS , although the interconnectedness of these pathways complicates these findings . Upregulation of glycolysis and decreased OXPHOS in $CD4^+$ T cells from SARS-CoV-2-induced acute respiratory distress syndrome patients resulted in their exhaustion and decreased IFN-gamma release, which could be partially remedied by beta-hydroxybutyrate, a product of ketogenesis . Long-term infection and the presence of SARS-CoV-2 in multiple tissues and organs, including the heart and brain, even months after primary infection may result in decreased metabolic fitness and function of many cell types, including cardiomyocytes .

Cellular and organ metabolic abnormalities may also be reflected in circulating levels of metabolites with potent immunomodifying effects. Profound dysregulation of serum and tissue metabolism has been repeatedly demonstrated during acute COVID-19. Severe and fatal COVID-19 disease was characterized by altered serum levels of metabolites related to tryptophan metabolism, polyamine metabolism, histidine metabolism, lipid metabolism, bile acid metabolism, FAO compounds, and antioxidant responses such as plasmalogens. Some of these metabolites remain dysregulated in long-COVID patients. Glutamine, glucose, kynurenine, and choline levels were shown to be higher in the plasma of long-COVID patients compared to healthy individuals . Additionally, circulating levels of nitrite (a metabolite of endothelial nitric oxide), sarcosine, taurine, and several lysophospholipid species were shown to be decreased compared to either healthy controls or participants who had recovered from COVID-19. Similar differences in amino acid metabolism, particularly tryptophan metabolism, were observed in another study of long-COVID patients. High kynurenine and IDO2 expression coupled with low tryptophan levels were also demonstrated in PBMCs and in the brains of long-COVID patients. This was accompanied by decreased mitochondrial function, amino acid levels, and tricarboxylic acid cycle compounds in PBMCs. A recent study found that decreased serotonin levels in long-COVID patients were due to decreased tryptophan absorption, increased platelet activation, and increased serotonin turnover, all of which lead to decreased circulating serotonin levels.

Viral persistence and viral reactivation in long-term COVID

One potential contributor to the ongoing immune dysfunction in long-COVID patients may be related to a persistent reservoir of SARS-CoV-2 in the host organs. This concept is plausible given

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that other respiratory RNA viruses can persist for long periods. For example, latent persistence of respiratory syncytial virus (RSV) has been observed in mice and guinea pigs and is associated with persistent inflammation and impaired lung function. Importantly, transient immune deficiency caused by T-cell exhaustion can lead to RSV reactivation. In humans, RSV persistence and associated decline in lung function have been observed in patients with chronic obstructive pulmonary disease , who have impaired pulmonary antiviral immunity. Influenza A virus antigens (IVA) and RNA can persist in the lungs of mice for 4 months, coupled with focal increases in IL-13 and mucus expression where IVA RNA is present, resulting in chronic asthma-like lung disease lasting at least 6 months . In one patient undergoing chemotherapy, SARS-CoV-2 persistence for 8 months with intermittent reactivation and relapses of COVID-19 was reported.

The gastrointestinal tract, with its ACE-2-expressing epithelium, may also serve as a site of entry and subsequent reservoir for SARS-CoV-2. Host cells involved in the gastrointestinal barrier function are often ACE-2 positive, allowing SARS-CoV-2 infection. SARS-CoV-2 shedding in feces typically lasts an average of 17.2 days, but can persist for months. However, SARS-CoV-2 often clears over a longer period, while long-term COVID symptoms may persist. Biopsy studies in patients with pre-existing gastrointestinal diseases, including inflammatory bowel disease, irritable bowel syndrome, or gastroesophageal reflux disease, have detected SARS-CoV-2 RNA or antigen in gastrointestinal mucosal tissues in 50–70% of patients, suggesting the presence of a viral reservoir. Long-term COVID symptoms were present in 65% of patients with viral RNA/antigen persistence, but not in those without it. These results support the hypothesis that the gut may be an important SARS-CoV-2 reservoir that may facilitate SARS-CoV-2 infection of multiple organ systems and/or viral persistence. However, it remains to be seen whether a persistent viral reservoir is required for long-term COVID. Clinical trials targeting antiviral mechanisms during acute COVID-19 with metformin or nirmatrelvir have shown a reduction in the incidence of long COVID, suggesting that effective viral clearance is important for long-term outcomes.

Another possible mechanism contributing to long-COVID may be the reactivation of latent viruses due to altered host immune response during and after acute SARS-CoV-2 infection. In the lungs, reactivation of herpes viruses such as herpes simplex virus 1 (HSV-1) and cytomegalovirus (CMV) frequently occurs during acute COVID-19. Their prolonged activity due to altered antiviral immunity and in the absence of antiviral treatment may contribute to prolonged lung inflammation and associated respiratory symptoms. Additionally, reactivation of human herpesvirus 6 (HHV6) and 7 (HHV7) has been observed in the skin. There is little evidence for a direct link between reactivation of latent viruses and the onset of long-COVID. However, this concept is supported by the higher detection of Epstein-Barr virus DNA in throat swab samples from long-COVID patients several months after acute COVID-19 compared to fully recovered patients.

Neuroimmunology of Long COVID

Coronaviridae are neurotropic . Early reports from Wuhan of patients with severe acute COVID-19 disease reported that up to 34% of patients had concomitant neurological complications . Neuroinflammatory processes associated with COVID-19 disease encompass a broad spectrum of conditions that acutely damage the brain. These processes may persist and may continue to involve the nervous system during long COVID. Neuroinflammatory conditions reported following SARS-CoV-2 infection include encephalopathy, ischemic brain injury, stroke, anosmia, ageusia,

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tinnitus, hearing loss, facial paralysis, autoimmune encephalitis of the brainstem, limbic system and acute disseminated form (autoimmune myelitis), new-onset epilepsy, postural orthostatic tachycardia syndrome (POTS), headache, fatigue, memory loss, anxiety, depression, psychiatric illness and sleep disorders.

Regarding the neuroimmune aspects of long COVID, it is important to recognize that symptoms can occur both after acquired viral infection and sometimes after vaccination. However, this has not been included in the current WHO definition of long COVID.

There is a widespread cellular distribution of ACE2 in the nervous system, and direct neuronal invasion has been demonstrated. Mechanistically, SARS-CoV-2 can be actively transported along neurons via the dynein-kinesin mechanism and transported in a retrograde manner via transsynaptic transmission. Anosmia was a common feature of acute SARS-CoV-2 infection in the early waves of the pandemic, possibly due to the variants prevalent at the time. Anosmia has been associated with loss of olfactory-related brain tissue, and direct invasion of the brain by SARS-CoV-2 has been proposed as one mechanism leading to neuronal injury. SARS-CoV-2 has been shown to replicate in the brain, with viral mRNA potentially persisting for months. SARS-CoV-2 can also enter the CNS via the enteric nervous system or choroid plexus.

In addition to direct infection, endothelial inflammation can cause brain damage, which can be caused by microthrombosis and endotheliitis. Endothelial inflammation and blood-brain barrier breakdown may be the entry point of the virus into the CNS and may also be associated with necrotizing encephalopathy. It has been suggested that a significant portion of brain damage occurs due to the inflammatory cytokine storm. Cytokines have been found to be elevated in the CNS during acute COVID-19 disease, which may cause long-term damage . Indeed, the severity of acute COVID-19 disease appears to correlate with the risk of neurological complications in long COVID . In an animal model of pulmonary-limited SARS-CoV-2 infection, mild respiratory infection resulted in decreased hippocampal neurogenesis, oligodendrocytes, and myelin loss, suggesting that the immune response or elevated cytokine levels may be sufficient to cause brain injury.

Several studies have described an increase in autoantibodies after SARS-CoV-2 infection, as summarized by Choutka et al. . Serum autoantibody levels have been associated with neurological outcomes in COVID-19-related conditions. Autoantibodies can be inflammatory and lead to neuroinflammation; however, they can also lead to molecular mimicry or even neutralize chemokine responses . Some of these antibodies may be associated with brainstem injury and may contribute to POTS in long COVID . Autoantibodies recognizing G protein-coupled receptors are one mechanism thought to be important in POTS, and beta-adrenergic receptor-specific antibodies have been reported in patients with long COVID. A causal role of autoantibodies in long COVID is potentially supported by the efficacy of intravenous immunoglobulin in COVID-19-related neuroinflammatory conditions .

Neuroinflammation in long-COVID may occur through direct neuronal invasion, neurovascular events, cytokine storm-related injury, and autoimmune mechanisms. However, it is possible that multiple mechanisms may be involved, and a multiple-hit mechanism has been described that involves brain priming and neuroinflammatory injury arising from environmental stressors.

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Microbiota and Long COVID

Human mucosal surfaces and body cavities harbor diverse communities of commensal microbes that play important roles in regulating host metabolic responses, epithelial barrier function, immune formation, and immune regulation. Microbial-derived factors such as short-chain fatty acids (SCFA), indoles, and polyamines protect against aberrant inflammatory processes or hypersensitivity reactions, but also promote effector immune responses that effectively eliminate pathogens such as SARS-CoV-2. While individual microbes, microbial components, and individual metabolites are certainly important, the overall functional capacity of the community and the metabolic outputs of the community that underlie interactions with the host immune system are perhaps more relevant in understanding disease risk. A low-risk microbiome configuration may generate sufficient levels of several regulatory metabolites that are associated with protection against aberrant inflammatory responses. In contrast, a high-risk microbiome configuration may consistently generate multiple pro-inflammatory metabolites that may contribute to a higher risk of inappropriate immune reactivity. Several studies have identified taxonomic and functional microbiome differences that are associated with disease severity during acute COVID-19 . Decreases in well-characterized immune-protective microbes (e.g., those producing SCFAs) and increases in opportunistic pathogens (e.g., from the Enterobacteriaceae family) have often been described.

Persistent changes in gut bacteria and fungi, as well as their metabolism, have also been described over long periods of time following SARS-CoV-2 infection, in both long-COVID and non-long-COVID patients. These studies summarized Broadly similar gut microbiota findings to those associated with acute COVID-19 severity have been described in long-COVID patients, such as reduced levels of SCFA-producing microorganisms, altered tryptophan metabolism, reduced abundance *of Faecalibacterium prausnitzii* and *Blautia obeum* , and increased abundance *of Ruminococcus gnavus* and *Bacteroides vulgatus* . Interestingly, one study found that *R. gnavus* was positively correlated with serum IL-6 levels, whereas *F. prausnitzii* and *B. obeum* were negatively correlated with IL-6 and C-reactive protein levels in long-COVID patients. Microbiome profiling may help in early identification of those most at risk for long COVID, while targeting the microbiome with appropriate probiotics and/or prebiotics may allow the immune system to recover more quickly. However, studies of microbiota-targeted interventions in long COVID have not yet been published in the literature.

Conclusion

While some progress has been made in characterizing the immunological factors associated with long COVID, we are still far from consistent mechanisms linking SARS-CoV-2 infection to the diverse array of persistent and new symptoms that have been described in long COVID . Furthermore, relatively little detailed analysis has been conducted of the mechanisms of long COVID resulting from infection with individual SARS-CoV-2 variants of concern or vaccination. The risk of long COVID symptoms appears to increase with each subsequent infection , suggesting that we have yet to see the full impact of this virus. Even with vaccination and thus milder manifestations of acute infection in recent waves of variants, the cumulative burden of long COVID continues to increase. Efforts to diagnose, prevent, and treat acute infection must be coupled with the same emphasis on recognizing and managing the multiple organs affected by this virus, including the immune system. To better understand the potential contribution of viral

persistence and reactivation to the development of distinct long-COVID symptoms, studies that evaluate the genomes and antigens of a broad range of viruses (virome studies) in affected organs and systemically, as well as associated immune responses, are needed. As additional evidence is uncovered regarding the immune mechanisms underlying long-COVID, it will also likely lead to significant advances in understanding and treating other chronic post-infectious disorders. Unfortunately, currently available diagnostic and therapeutic options for long-COVID are limited, and more clinical trials that match experimental interventions to underlying biological mechanisms, such as those targeting viral persistence, neuroinflammation, endothelial inflammation, immune metabolism, the microbiome, and autoimmunity, are needed.

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