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REVIEW ARTICLE

The Immunology of Long COVID

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ABSTRACT

Purpose: This review aims to synthesize contemporary evidence elucidating the immunopathological mechanisms underlying Long COVID, with particular emphasis on chronic immune dysregulation as a central pathophysiological driver.

Materials and Methods: We conducted a comprehensive narrative review of peer-reviewed literature published between 2020 and 2025, examining human cohort studies, experimental models, and mechanistic investigations. Electronic databases were searched for studies reporting immunological parameters in Long COVID patients, including adaptive and innate immune markers, autoantibody profiles, viral persistence data, and biomarker analyses.

Results: The analysis reveals multiple interconnected pathophysiological pathways: (1) profound T-cell exhaustion characterized by elevated PD-1 and TIM-3 expression with diminished central memory CD4+ populations; (2) B-cell compartment alterations including reduced switched memory subsets and expanded plasmablast populations; (3) sustained elevations in pro-inflammatory cytokines (IL-6, IL-8, IFN-γ) and chemokines (CXCL9, CXCL10); (4) autoantibody generation targeting neural, vascular, and autonomic receptors; (5) demonstrable viral persistence in gastrointestinal and neural tissues; (6) endothelial dysfunction with fibrin-amyloid microclot formation; (7) neuroinflammatory processes involving glial activation and blood-brain barrier compromise; (8) mitochondrial bioenergetic failure; and (9) complement cascade dysregulation. These mechanisms establish self-perpetuating cycles of immune dysfunction bearing notable resemblance to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Conclusion: Long COVID can be understood as as a multifactorial post-viral syndrome driven by persistent immune dysregulation rather than direct viral cytopathic effects. The convergence of cellular exhaustion, chronic inflammation, autoimmunity, and tissue-resident viral reservoirs creates a complex pathological state requiring targeted therapeutic interventions and biomarker-guided precision medicine approaches. *(Open J Biomed Res 2025;4:13-17)*

Keywords

Long COVID, T-cell exhaustion, Immune dysregulation, Autoimmunity, Neuroinflammation, Endothelial dysfunction.

AUDIOABSTRACT

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INTRODUCTION

The COVID-19 pandemic has revealed the capacity of SARS-CoV-2 infection to induce long-lasting health consequences that extend far beyond the resolution of the acute phase. This condition, commonly referred to as Long COVID or post-acute sequelae of SARS-CoV-2 infection (PASC), encompasses a heterogeneous spectrum of clinical manifestations, including persistent fatigue, exertional dyspnea, cognitive dysfunction ("brain fog"), and autonomic disturbances that can endure for months or even years after apparent viral clearance. [1]

Accumulating evidence suggests that these prolonged symptoms are not primarily driven by ongoing viral cytopathic effects, but rather by a failure of the host immune system to return to homeostasis following acute infection. Instead, Long COVID appears to arise from a state of sustained immune dysregulation characterized by persistent inflammation, aberrant immune cell function, and maladaptive immune responses.

In this review, we synthesize current evidence on the immunopathological mechanisms underlying Long COVID, drawing on data from longitudinal cohort studies, high-dimensional immunoprofiling, and experimental models. We aim to provide an integrated framework that captures the complex interplay between adaptive and innate immune dysfunction, viral persistence, autoimmunity, and tissue-specific pathology, thereby offering mechanistic insights into this emerging and clinically significant post-viral syndrome.

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ADAPTIVE IMMUNE SYSTEM DYSFUNCTION

T-cell Abnormalities and Exhaustion

Long COVID is distinguished by profound disruptions in T-cell homeostasis that distinguish it from uncomplicated convalescence. Empirical investigations consistently demonstrate marked reductions in central memory CD4+ T-cell populations alongside expansion of terminally differentiated subsets bearing exhaustion markers including programmed cell death protein-1 (PD-1) and T-cell immunoglobulin and mucin-domain containing-3 (TIM-3).[2] Single-cell transcriptomic analyses have revealed expansion of non-classical monocyte populations coupled with exhaustion signatures in CD4+ T lymphocytes, compromising immunological surveillance and fostering chronic inflammatory states.[3]

Longitudinal immunophenotyping reveals a critical distinction between disease trajectories: whereas moderate COVID-19 cases exhibit transient exhaustion phenotypes that resolve during recovery, severe infections manifest persistent exhaustion signatures detectable months following viral clearance.[4] This prolonged dysfunction appears self-sustaining, driven by continuous exposure to inflammatory mediators, metabolic derangement, and altered T-cell receptor signaling thresholds. In particular, expansion of CD38+HLA-DR+ terminally differentiated Treg-like cells functions as an independent predictor of adverse clinical outcomes.[5] Bronchoalveolar lavage specimens from mechanically ventilated patients reveal profound local T-cell depletion coupled with enrichment of exhaustion markers, indicating that tissue microenvironments contribute substantially to immune dysfunction beyond systemic circulatory manifestations.[6]

B-cell Dysregulation and Humoral Responses

The B-cell compartment exhibits marked perturbations in Long COVID patients. Investigations have identified reduced switched memory B-cell populations alongside expanded double-negative B-cell subsets and plasmablasts, suggesting sustained autoimmune or autoinflammatory activation.[7] Although anti-receptor-binding domain (RBD) immunoglobulin G levels remain elevated for months following severe acute infection, quantitative antibody titers fail to discriminate significantly between patients with and without Long COVID when stratified by initial disease severity. This observation indicates that humoral response magnitude alone does not account for persistent symptomatology; rather, qualitative characteristics including affinity maturation, epitope specificity, and Fc-effector functions warrant further investigative attention.

INNATE IMMUNE ACTIVATION AND CHRONIC INFLAMMATION

Chronic low-grade inflammation represents a pathognomonic feature of Long COVID pathophysiology. Plasma concentrations of interleukin-6 (IL-6), IL-8 (CXCL8), IL-12, interferon-β1 (IFN-β1), interferon-λ1 (IFN-λ1), and interferon-γ (IFN-γ) remain elevated months following infection.[5] Chemokines including CXCL9 and CXCL10 consistently demonstrate sustained elevation, signifying ongoing interferon signaling and immune cell recruitment. Recent biomarker investigations consistently demonstrate that CXCL8 exhibits the lowest effective dose (0.01 μg/mL) for spike protein-induced inflammatory responses, followed by IL-6 (0.39 μg/mL) and tumor necrosis factor-α (TNF-α) (0.56 μg/mL), underscoring the exquisite sensitivity of the CXCL8 chemokine pathway in Long COVID pathogenesis.[8]

Soluble biomarkers of tissue injury including soluble urokinase plasminogen activator receptor (suPAR), vascular endothelial growth factor receptor 2 (VEGFR2), glial fibrillary acidic protein (GFAP), and neurofilament light chain (Nf-L) consistently demonstrate variable elevation patterns correlating with specific organ involvement and disease chronicity.[1]

AUTOIMMUNITY AND MOLECULAR MIMICRY

Autoimmune mechanisms contribute substantively to Long COVID pathogenesis. A discernible subset of patients develops autoantibodies targeting gangliosides, β2-adrenergic receptors, and muscarinic receptors findings, characteristic of post-infectious Guillain-Barré syndrome and postural orthostatic tachycardia syndrome (POTS).[9] These antibodies likely emerge through molecular mimicry, wherein immune responses directed against SARS-CoV-2 structural proteins cross-react with host neural tissue antigens.

Furthermore, certain Long COVID patients consistently demonstrate elevated autoantibodies against neuronal and glial antigens, including myelin oligodendrocyte glycoprotein (MOG) and N-methyl-D-aspartate (NMDA) receptors, suggesting autoimmune-mediated central nervous system inflammation.[10] Anti-interferon-α (IFN-α) autoantibodies, associated with severe acute disease, consistently demonstrate inconsistent association with Long COVID, with some cohorts identifying these in only minor percentages of patients absent clear correlation with persistent symptoms.[11]

VIRAL PERSISTENCE AND TISSUE RESERVOIRS

Viral persistence constitutes a leading hypothesis for Long COVID pathogenesis. Evidence derived from non-human primate models consistently demonstrates prolonged fecal shedding of replication-competent virus, sustained immune activation, and intestinal inflammation persisting months following initial infection.[12] Whole-body immune PET imaging reveals SARS-CoV-2 biodistribution across multiple organ systems, while autopsy studies identify viral RNA and proteins in tissues including gastrointestinal tract, brain, and lymph nodes long after respiratory clearance.

This reservoir hypothesis posits that ongoing immune stimulation from persistent viral antigens drives chronic inflammation and immune exhaustion. Empirical investigations consistently demonstrate that individuals with persistent SARS-CoV-2 infection manifest greater than 50% increased odds of reporting Long COVID at 12 weeks post-infection compared to those achieving viral clearance. [12] Torque teno virus (TTV) loads are elevated in severe Long COVID patients, potentially reflecting compromised immune control of latent viral infections, though causal relationships remain to be established.

ENDOTHELIAL DYSFUNCTION AND MICROVASCULAR INJURY

Persistent endotheliopathy characterizes Long COVID, with ongoing endothelial cell activation leading to microvascular thrombosis and impaired tissue perfusion. This endothelial dysfunction contributes to multi-organ symptomatology, particularly cardiovascular and neurological complications. [13] Circulating markers of endothelial injury correlate with symptom severity and duration, supporting a vascular component to Long COVID pathophysiology.

Recent investigations have identified heterogeneous fibrin-amyloid microclots amyloid deposits composed of fibrin(ogen) and additional plasma proteins that consistently demonstrate resistance to fibrinolysis in Long COVID patients. [14] These microclots, in conjunction with platelet hyperactivation and elevated plasminogen activator inhibitor-1 (PAI-1), establish a prothrombotic state compromising microcirculatory function. Capillary rarefaction (reduction in capillary density) has been documented in Long COVID patients, further compromising tissue oxygen delivery. [15]

NEUROINFLAMMATORY SEQUELAE AND THE GUT-BRAIN AXIS

Neurological manifestations of Long COVID including cognitive impairment, fatigue, and mood disturbances involve complex neuroimmune interactions. Principal mechanisms encompass blood-brain barrier disruption, glial activation, mitochondrial dysfunction, and cytokine-mediated oxidative stress.[16] Elevated neuroimmune biomarkers such as GFAP and Nf-L provide evidence of ongoing central nervous system injury.

Sustained activation of microglia and astrocytes plays a pivotal role in chronic neuroinflammation following SARS-CoV-2 infection. Inflammatory cytokines affect long-term potentiation and synaptic plasticity, directly contributing to cognitive dysfunction. Contemporary research highlights the gut-brain axis as a modulator of neurocognitive outcomes. Alterations in gut microbiota composition, particularly depletion of short-chain fatty acid-producing taxa such as *Faecalibacterium prausnitzii* and *Bifidobacterium spp.*, correlate with worse neurological symptoms, potentially via impaired microglial regulation and systemic inflammation.[17]

Neuroimaging studies employing positron emission tomography (PET) and magnetic resonance imaging (MRI) identify hypometabolism in frontal and parietal cortices, white matter microstructural alterations, and disturbed brain glucose metabolism, providing objective evidence of central nervous system involvement.[18] Additionally, longitudinal MRI studies have consistently demonstrated significant brain structural alterations in individuals with prior SARS-CoV-2 infection, including greater reduction in grey matter thickness and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus.[19]

METABOLIC DYSFUNCTION AND MITOCHONDRIAL IMPAIRMENT

Mitochondrial dysfunction represents a critical yet underappreciated component of Long COVID pathophysiology. Peripheral blood mononuclear cells (PBMCs) isolated from Long COVID patients consistently demonstrate significantly impaired oxidative phosphorylation, with both basal respiration and reserve capacity reduced compared to healthy controls.[20] Skeletal muscle biopsies reveal morphological and functional mitochondrial abnormalities, contributing to exercise intolerance and fatigue.

Mechanisms underlying persistent mitochondrial dysfunction include direct viral protein interaction with mitochondrial components, sustained dysregulation of mitochondrial bioenergetics, and autoimmunity targeting mitochondrial proteins.[21] This metabolic disruption establishes a vicious cycle wherein energy failure exacerbates immune dysregulation and tissue damage.

COMPLEMENT SYSTEM DYSREGULATION

The complement cascade plays a central role in Long COVID immunopathology. Persistent activation of classical, lectin, and alternative pathways has been documented months following initial infection.[22] Elevated levels of complement activation products (C4d, C3bBbP, C5a, and terminal complement complex) correlate with persistent symptoms and tissue injury. Complement activation contributes to endothelial damage through membrane attack complex (MAC) insertion, promoting release of von Willebrand factor (vWF) and thrombospondin-1 (TSP1). This drives platelet activation and microthrombus formation, creating a self-amplifying cycle of vascular injury and inflammation. [1] C1qA and COLEC12 have emerged as specific biomarkers associated with gastrointestinal, cognitive, and cardiorespiratory symptoms in Long COVID patients.[23]

DISCUSSION

The immunology of Long COVID presents a complex tapestry of interconnected pathophysiological mechanisms. The evidence reviewed herein supports a model wherein persistent immune dysregulation rather than direct viral cytopathic effects drives chronic symptoms. Several salient themes emerge from the contemporary literature.

First, T-cell exhaustion appears to constitute a central feature of Long COVID immunopathology. Unlike acute infection, wherein exhaustion may represent an adaptive response preventing immunopathology, persistent exhaustion in Long COVID reflects chronic antigenic stimulation and/or bystander activation. The observation that exhaustion signatures correlate with disease severity and persist for months suggests that therapeutic strategies aimed at restoring T-cell function such as checkpoint inhibitor blockade or metabolic reprogramming may warrant investigation, though careful consideration of potential inflammatory sequelae is necessary.[4]

Second, the viral persistence hypothesis gains increasing support from studies demonstrating SARS-CoV-2 RNA and protein in tissues months after infection. However, the relationship between viral reservoirs and symptoms is not linear; not all patients with detectable viral material develop Long COVID, and not all Long COVID patients consistently demonstrate evidence of viral persistence. This suggests that host immune factors, particularly the capacity to clear viral antigens or regulate inflammatory responses, may determine clinical outcomes. The gastrointestinal tract emerges as a particularly important site of viral persistence, with enteroendocrine cells, tuft cells, and cup cells serving as potential viral reservoirs.[12]

Third, the parallels between Long COVID and ME/CFS are striking and instructive. Both conditions share features of immune exhaustion, autonomic dysfunction, post-exertional malaise, and neuroinflammation.[6] The finding that both conditions exhibit similar cytokine profiles and immune cell dysregulation suggests common pathophysiological pathways that may transcend specific viral triggers. This convergence implies that therapeutic strategies effective in ME/CFS such as pacing, immune modulation, or metabolic interventions may benefit Long COVID patients, and vice versa.

Fourth, endothelial dysfunction and microclot formation represent potentially modifiable pathophysiological mechanisms. The presence of fibrin-amyloid microclots resistant to fibrinolysis suggests that anticoagulant or fibrinolytic strategies might benefit specific patient subgroups. However, the heterogeneity of Long COVID necessitates careful patient stratification; markers such as PAI-1, vWF, and circulating microclot burden may help identify candidates for such interventions.[15]

Fifth, the role of autoantibodies in Long COVID pathogenesis remains incompletely understood. While associations between autoantibodies against G-protein coupled receptors and symptoms such as fatigue and orthostatic intolerance have been reported, causality remains unproven. The observation that autoantibody levels decrease following therapeutic apheresis and correlate with symptom improvement suggests a potential pathogenic role, though whether these antibodies are primary drivers or epiphenomena of tissue damage requires further investigation.

Several limitations characterize the current literature. Most studies are observational, limiting causal inference. The heterogeneity of Long COVID definitions, timing of sample collection, and patient populations complicates cross-study comparisons. Additionally, the relative contribution of different pathophysiological mechanisms likely varies across patient subgroups defined by age, sex, initial disease severity, and genetic background. Future research priorities include: longitudinal studies tracking immune parameters from acute infection through recovery or progression to Long COVID, interventional trials targeting specific immune pathways (e.g., JAK-STAT inhibition, complement blockade, or metabolic enhancement), development of biomarker panels to enable precision medicine approaches and investigation of the gut-brain axis as a therapeutic target.

CONCLUSION

Long COVID represents a multifactorial and complex post-viral syndrome driven by persistent immune dysregulation involving multiple interconnected pathways. The convergence of T-cell

exhaustion, B-cell abnormalities, chronic inflammation, autoimmunity, viral persistence, endothelial dysfunction, and metabolic disruption creates a self-perpetuating pathological state. Understanding these mechanisms provides a roadmap for developing targeted therapies and biomarker-guided interventions to alleviate the burden of this condition.

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