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CHRONIC INFLAMMATION AND LONG COVID: ONGOING STUDIES INTO THE PROINFLAMMATORY AND IMMUNE EXHAUSTION PATHWAYS ACTIVATED DURING LONG-TERM POST VIRAL CONDITIONS

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ABSTRACT

Long-term COVID, or post-acute sequelae of SARS-CoV-2 infection (PASC) as a chronic multisystem disorder with neuroinflammation, endothelial dysfunction, metabolic dysfunction, and sustained immunological dysregulation after initial infection is becoming more recognized. More and more evidence is beginning to indicate that the continued activation of the pro-inflammatory and immunological exhaustion mechanisms and the inability to resolve inflammation play a significant role in disease persistence. This review is a summary of mechanistic research of cytokine dysregulation, NF-KB and JAK-STAT activation, inflammasome signalling, T-cell fatigue, myeloid cell reprogramming, viral persistence, autoimmunity, mitochondrial dysfunction, and microvascular damage in Long COVID. Findings are put in perspective by providing comparative data of various post-viral illnesses. The existing immunomodulatory clinical trials and biomarker opportunities are assessed on a global basis. The evidence all points towards a multifactorial mechanism involving the combination of the ongoing antigenic stimulation, maladaptive immune resolution and endothelial-metabolic dysfunction to sustain chronic inflammation. The dual relationship between these pathways determines the need to comprehend them to make a difference in post-viral disease therapy stratification and precision medicine.

Introduction

SARS-CoV-2 infection has shifted the global burden associated with acute pandemic disaster to the impact of the long-term issue of public health manifested by the persistent and even debilitating consequences in a significant fraction of survivors. Whereas preventing the acute infection and decreasing the death were not the primary tasks of the initial public health campaigns, growing clinical and epidemiological data suggest the implications of being infected go much further than the initial viral phase (Nalbandian et al., 2021). Since the cases of individuals that have had acute COVID-19 recovery continue to soar all over the world as well as the number of patients that have been having prolonged symptoms, scientific focus has shifted towards the long-term biology and clinical consequences of the illness.

According to epidemiological research, 10-30 percent of SARS-CoV-2 infections lead to persistent symptoms that persist beyond three months of the acute stage of illness. Sudre et al. (2021) note that the disease is the Long COVID, or Post-Acute Sequelae of SARS-CoV-2 infection

(PASC). Notably, these chronic symptoms may also be found in patients who develop mild or even asymptomatic infection. The systemic nature of SARS-CoV-2 infection leads to the occurrence of a wide range of symptoms and because of its multisystemic nature. The most common symptoms are chronic fatigue, the cognitive impairment often called the brain fog, dyspnoea, chest pain, palpitations, autonomic dysfunction, sleep problems, anosmia, and a series of neuropsychiatric symptoms, including anxiety and depression (World Health Organization, 2023). The variety of clinical manifestations indicate that Long COVID is more of a syndrome than a disease, and is a combination of various overlapping pathophysiological processes.

There has been an ongoing development of immunology and systems biology, which is starting to shed light on the possible pathophysiology of this illness. The reports of longitudinal studies of immunological profiles indicate convergent results that indicate that long-term COVID patients still have dysregulated innate immune responses, distorted T-cell morphologies, and increased levels of pro-inflammatory cytokines after the acute infection is over (Peluso et al., 2021; Phetsouphanh et al., 2022). Specifically, defects in monocyte activation, interferon signaling pathways, and persistence of inflammatory mediators (TNF- 1 and interleukin- 6 (IL-6)) have been described. These results indicate that the situation of the Long COVID can be viewed as a state of persistent immune imbalance and not just the effects of acute tissue damage.

Besides chronic inflammation, a number of other biochemical processes have been suggested to be involved in the continuation of sickness. These are endothelial dysfunction, microvascular damage, autoimmune caused by molecular mimicry, an antigen in tissue reservoirs, and the autonomic nervous system disturbance (Proal & VanElzakker, 2021; Su et al., 2022). The presence of the autoimmune processes persisting after viral elimination, as evidenced by the observation of the presence of autoantibodies in the circulation of certain patients against tissue antigens and immune regulators, can be explained by the hypothesis that the SARS-CoV-2 infection can trigger autoimmune mechanisms. Moreover, it has been shown that metabolic pathways and mitochondrial activity are altered, and this can be one of the reasons why long-term COVID patients experience fatigue and other symptoms of impaired energy metabolism.

An early pro-inflammatory stage to eliminate the virus is followed by a highly regulated resolution phase that restores equilibrium in the normal process of immune response to viral infection. Regulatory cytokines, immunological checkpoint pathways, and specialized pro-resolving lipid mediators play an active role in coordinating this resolution process that facilitates tissue healing and reduces excessive inflammation (Serhan, 2014). These resolution mechanisms restore physiological balance during a successful viral infection recovery, and this lowers immune activity.

Nevertheless, recent findings indicate that the resolution processes can be poor or ineffective in people with Long COVID. The immune response seems not to pass completely to a restorative stage, but is in a condition of chronic low-grade activation. The impaired resolution of immune responses can be caused by persistent inflammatory cues, insufficient synthesis of pro-resolving cue, and dysfunctional regulatory T-cell responses (Phetsouphanh et al., 2022). This immune imbalance can lead to neurological manifestations, tissue chronic stress, and general metabolic dysfunction.

Thus, molecular and cellular factors underlying this immune resolution defect need to be studied to explain the etiology of Long COVID. The identification of particular immunological pathways related to chronic inflammation could inform the creation of particular therapy methods aimed at restoring immune homeostasis along with improved diagnostic markers. The studies will require the combination of ideas in immunology, virology, and systems medicine to deal with the health outcomes of SARS-CoV-2 infection in the long run and decrease the increase in the global burden of Long COVID.

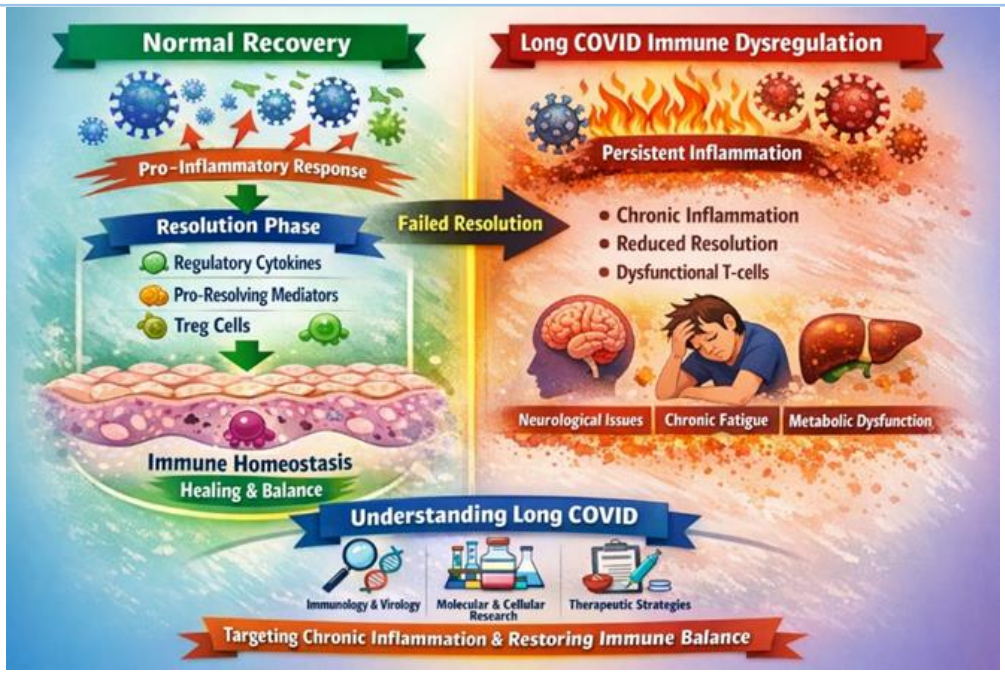

Fig.1: Symptoms of long COVID

Chronic inflammation in Long COVID Molecular Architecture

A long-term Cytokine Signaling

Repeated engagement of inflammatory cytokine networks is one of the most frequently reported immunological atypicalities in persons with Long COVID. A large number of longitudinal studies have demonstrated that pro-inflammatory cytokines are still high months following acute SARS-CoV-2 infection has eradicated showing evidence that immunological homeostasis has not been entirely restored in some cohort of individuals. Humans have also been reported to have raised levels of cytokines including interleukin-6 (IL-6), tumour necrosis factor-alpha, (TNF- 6), chemokine ligand 10 (CXCL10), and interferon-B (IFN-B) as many as eight months following the initial infection indicating the presence of a persistent chronic inflammatory milieu (Phetsouphanh et al., 2022). These results suggest that long-term immunological activation in addition to organ damage secondary to the acute infection could be part of Long COVID.

Proteomic and multi-omics research will provide additional information on the dynamics of longitudinal changes in immunological dysregulations in Long COVID. The demonstration of large-scale longitudinal assessments is that some immunological markers, which are available in the initial stages of infection, can indicate the emergence of chronic symptoms in the future. As an example, specific patterns of inflammatory proteins and interferon-based signaling that can be observed soon after infection were linked to a higher probability of developing post-acute sequelae (Su et al., 2022). These findings are indicative of the possibility of the initial immune response to SARS-CoV-2 to trigger sustained immune pathways that precondition the emergence of chronic inflammation and the persistence of symptoms in certain individuals.

The IL-6 is one of the cytokines that have gained special attention with regards to the pathophysiology of Long COVID because of its fundamental role in the regulation of systemic inflammatory processes. The pleiotropic cytokine IL-6 affects the physiological systems involved in the formation of immune cells, metabolic regulation, and the acute-phase response. The IL-6 induces the expression of inflammatory and immunological control related genes via the activation of the Janus kinase signal transducer activator of transcription (JAK3) signaling pathway (Tanaka et al., 2014). The long-term effects of IL-6 signaling may include endothelial activation,

greater production of hepatic acute-phase proteins including C- reactive protein and polarisation of T helper cells to become Th17-like. The effects of these immunological alterations might enhance the processes of inflammatory cascases, potentially enhancing tissue damage.

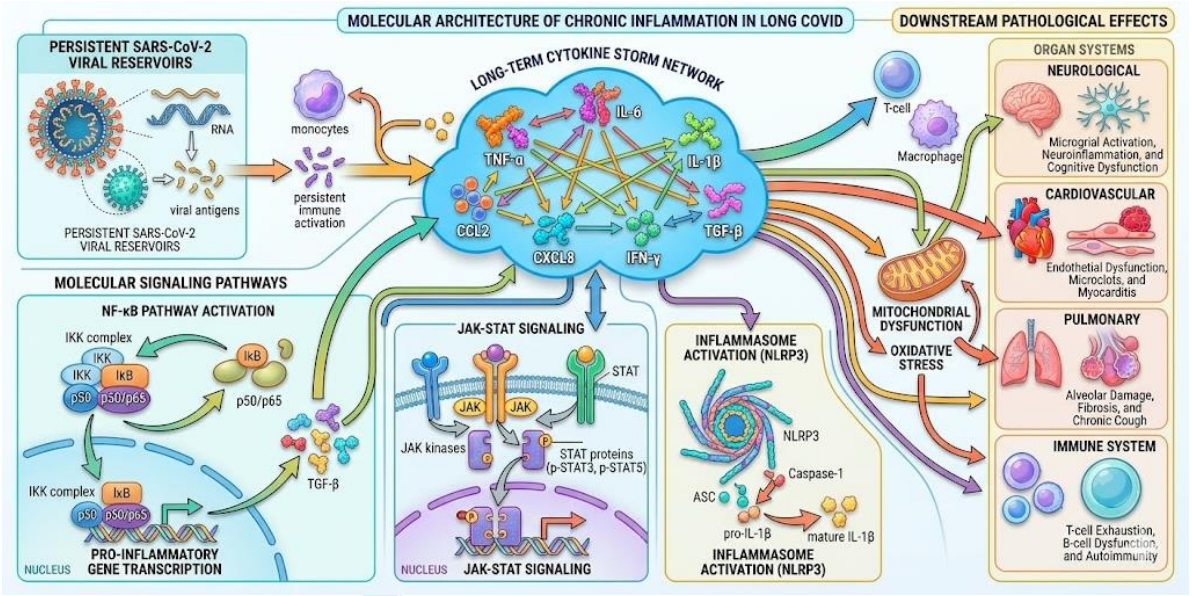

Fig. 2: Chronic inflammation in long covid

The long-term effects of IL-6 exposure may also affect the neurological and metabolic processes associated with the chronic effect of COVID. Increased levels of IL-6 have been linked to changes in energy balance, insulin signaling and mitochondrial metabolism, which may be linked to the amount of excessive fatigue experienced by many patients. Neuroinflammatory mechanisms in the central nervous system could also be mediated by IL-6 which stimulates the activation of the microglial. Clinical research has discovered that patients with Long COVID are associated with high levels of IL-6 and harshness of signs, including fatigue, neuropsychiatric issues, and cognitive dysfunction (Peluso et al., 2021). The results suggest the fact that the neurological and systemic symptoms of the illness are directly induced by the unremitting cytokine signaling.

Type I interferons play a major role in the prolonged inflammatory response, which is seen in Long COVID. Interferons protecting against acute viral infection are strengthening antiviral defenses, promoting viral clearance, and initiating viral clearance through the activation of innate immune pathways. Nevertheless, deregulated or protracted interferon signaling can be harmful. According to Herry and Kurachi (2015), chronic immunological activation, hindering the process of tissue repair, and destroying immune cells may be encouraged by prolonged interferon activity. Longitudinal immunological test data indicate that a small percentage of patients with Long COVID retain interferon traces months after infection, which means that even without active viral replication, people are still stimulated in their innate immune (Phetsouphanh et al., 2022).

The interferon signaling, which persists, can also cause immunological dysregulation in a number of downstream mechanisms. Prolonged exposure to interferon can induce the production of inflammatory chemokines such as CXCL10 that attracts immune cells to the tissues and extends inflammation in the area. These changes can be used to explain why despite their seeming recovery following the initial infection, some people still display chronic immune activation.

Dysregulation of JAK STAT Pathway

One such important intracellular signaling pathway is the Janus kinase signal transducer and activator of transcription (JAKSTAT), which regulates the action of a number of cytokines that

lead to the development of Long COVID. This system, according to O'Shea et al. (2015), converts extracellular cytokines into transcriptional responses of immune and non-immune cells, and therefore, regulates inflammation, immune cell development, and anti-viral response. Gene expression programs that regulate immune responses are activated by cytokines (IL-6), interferon (IFN-α), interferon (IFN-V), and other interleukins through JAK-STAT signaling cascade. The pathway is activated by the recruitment and activation of Janus kinase enzymes when cell-surface receptors to cytokines bind the enzymes. These kinases create signal transducer and activator of transcription (STAT) protein docking sites by phosphorylation of receptors associate tyrosine residues. After recruitment, the phosphorylation enables the dimerisation of the STAT proteins after which they enter the nucleus and regulate the transcription of genes associated with immunological activation, cell division, and inflammatory responses (O'Shea et al., 2015).

Recent transcriptome and proteomic research have shown that JAK-STAT signaling is on-going in patients with Long COVID. The post-COVID cohort gene expression studies have also shown a long-lasting upregulation of genes under the regulation of STAT1- and STAT3-even after initial infection is cured, which suggests that the persistence of cytokine-mediated signaling (Su et al., 2022). This sustained transcriptional activation may result in immunological dysregulation and chronic inflammation and indicate that immune cells are still being activated.

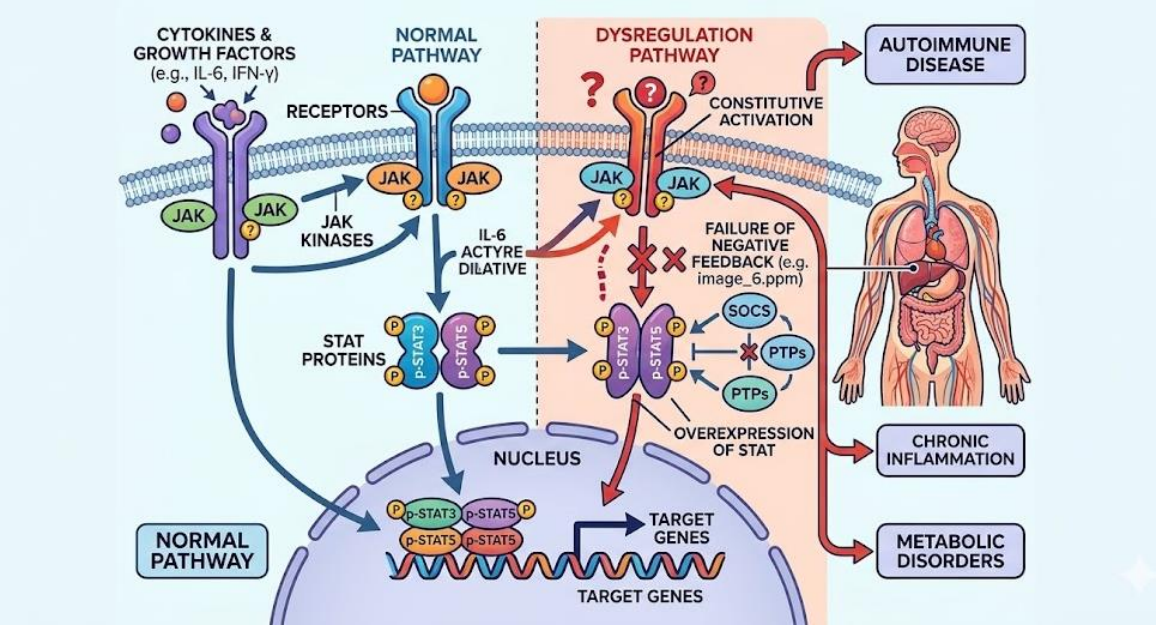

Fig. 3: Dysregulation of JAK-STAT pathway

Long-term activation of STAT3 is of particular interest to its pathophysiology of long-term inflammatory conditions. The signaling of STAT3 has been shown to influence numerous immune regulatory processes, such as, T helper cell differentiation, encouragement of pro-inflammatory responses, and suppression of regulatory T-cell activity (Hillmer et al., 2016). This persistent stimulation of STAT3 may disturb the immunological homeostasis and prefer the inflammatory signaling pathways related to autoimmune and chronic inflammatory disease. These changes may lead to immunological dysregulation that is observed in Long Covid and includes the formation of autoantibodies and persistent inflammatory symptoms.

Prolonged JAK-STAT signaling may also interfere with the interaction of the immune and non-immune systems. As an illustration, endothelial cells can respond to the activation of STAT3 to enhance leukocyte recruiting, amplify the synthesis of adhesion molecules, and curtail vascular inflammation. These alterations might be contributory to the microvascular dysfunction and

endothelial activation commonly seen in the case of the persistent post-COVID symptoms. Moreover, the JAKSTAT signaling has an impact on immune cell metabolic pathways, which connect long-term inflammation to a change in the cellular energy metabolism and dysfunctioning of the mitochondria.

The JAK statist pathway has become the target of possible therapeutic intervention in Long COVID because of its essential role in the coordination of cytokine signaling networks. JAK kinase pharmacological inhibitors have proven to be clinically effective in diverse inflammatory and autoimmune disorders since they inhibit a number of cytokine pathways. Modifying signaling in response to cytokines such as IL-6, interferons, among others, JAK inhibitors have the potential to suppress a chronic inflammatory response and recover immunological homeostasis in affected individuals. Although the studies are still underway, the therapeutic assessment of JAK inhibitors shows the value of consistent activations of JAK-STAT pathways as an essential characteristic that contributes to the pathogenesis of Long COVID (O'Shea et al., 2015).

NF- kB and Inflammasome Activation

NF- 0 B signaling is an important aspect of chronic inflammation. Viral RNA triggers the activation of toll-like receptors during acute SARS-CoV-2 infection leading to the production of cytokines by NF- B (Merad & Martin, 2020). Research indicates that some of the long-term COVID patients have elevated NF- kB target genes long after infection (Su et al., 2022).

Both acute and chronic COVID-related inflammation has also been linked to NLRP3 inflammasome activation (Rodrigues et al., 2021). The IL-18 and IL-1β that are produced with the help of NLRP3 inflammasome enhance the progression of inflammatory pathways. The sustained inflammasome activation can be due to the malfunctioning and the presence of damage-associated molecular patterns of the mitochondrial malfunction (Saleh et al., 2020).

The continued stimulation of NF-κB and inflammasomes gives rise to a feed-forward loop of inflammatory response which does not allow the restoration of balance. Long-term activation of these pathways is linked to neurodegenerative and autoimmune diseases, which implies that there are more pathogenic similarities (Liu et al., 2017).

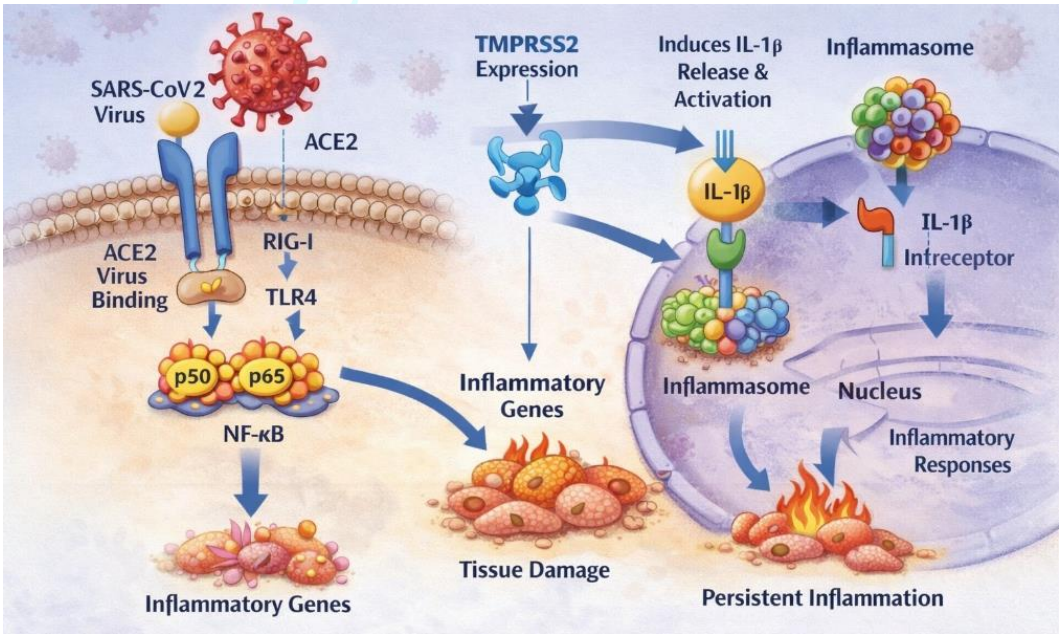

Fig. 4: NF-Kb and inflammasome activation in long Covid

Dysregulation and Exhaustion of the Adaptive Immune Response

T-Cell Exhaustion Epigenetically Programmed

The loss of T-cells is being considered as an effect of long-term antigen exposure by long-term COVID immuno phenotyping studies (Phetsouphanh et al., 2022). T cells that are affected by exhaustion are characterized by the continuous presence of inhibitory receptors, such as programmed cell death protein 1 (PD-1), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), and lymphocyte activation gene-3 (LAG-3), as well as, the reduction of cytokine production and cytotoxic ability (Wherry & Kurachi, 2015). High PD-1 levels on CD8+ T cells in Long COVID cohort is found months after the initial infection, in patients with mild acute sickness (Peluso et al., 2021).

Along with the expression of surface receptors, exhaustion is accompanied by long-term epigenetic remodeling that confines T cells to defective transcriptional states (Pauken et al., 2016). Chronic exposure to type I interferons and IL-6 strengthens transcription factors including TOX and NR4A that promote the inaccessibility of effector genes and maintenance of receptor inhibitors (Wherry and Kurachi, 2015). Long-term interferon changes in patients with Long COVID indicate that this reprogramming can persist even after viral elimination (Su et al., 2022). This is problematic since such epigenetic changes are so stable that immune malfunction can persist even in case of decreased antigenic stimulation. Paradoxically, a lowered cytotoxic effect is possible to be combined with the systemic inflammation. Exhausted T cells no longer have antiviral activity, and innate immunity mechanisms are still active and can maintain inflammatory signaling (Merad & Martin, 2020). The separation of the innate and adaptive impairment can cause a chronic symptomatology.

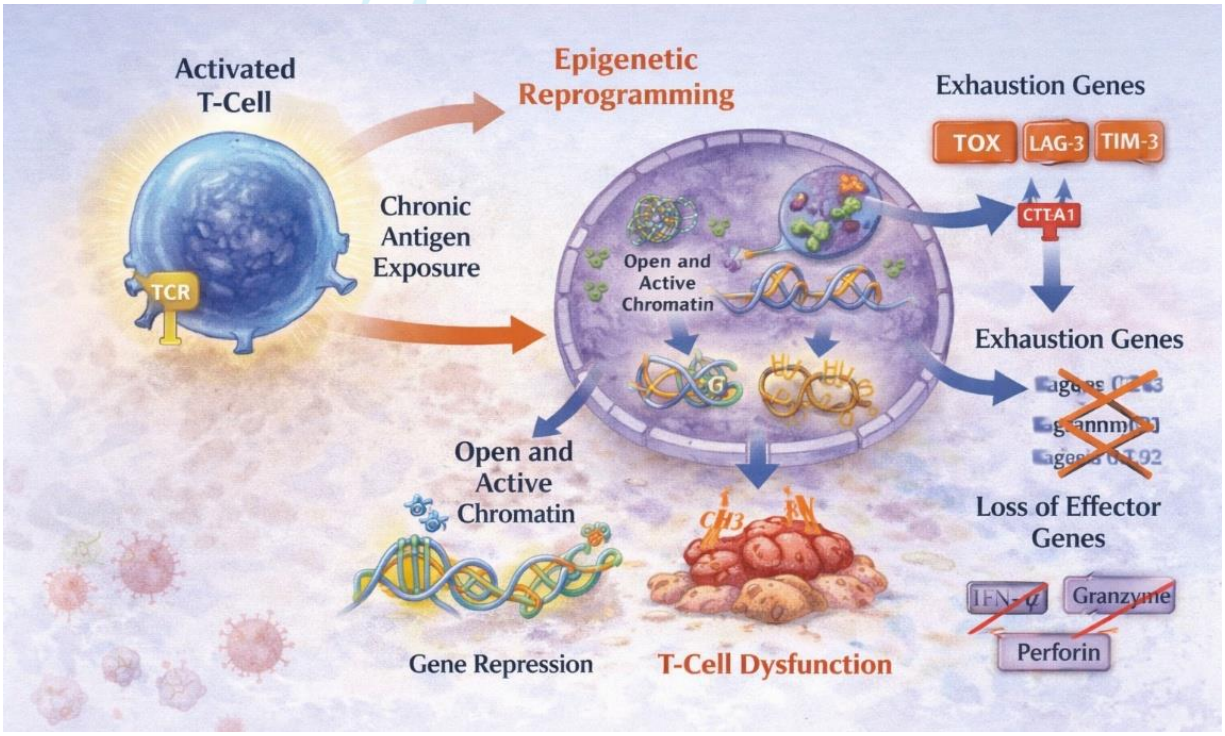

Fig. 5: T-cell exhaustion epigenetically programmed

B-cell Dysregulation and Germinal center Disruption

B-cell abnormalities have been reported following the SARS-CoV-2 infection, too. The reduction of germinal center development and additional activation of extrafollicular B-cells is linked to acute COVID-19 and can dysregulate the immunological response in the long term

(Woodruff et al., 2020). The disruption of the germinal center increases the probability of the survival of autoreactive clones through tolerance checkpoints and affinity development (Kaneko et al., 2020). Long COVID months following infection have been reported to have persistent plasma blast populations, as well as B-cell morphology changes (Su et al., 2022). Tanaka et al. (2014) assert that further impairment of immunological tolerance can be caused by promoting the growth of plasma blasts and suppressing the action of regulatory B-cells through prolonged IL-6 signaling. This maladaptation gives a mechanistic relationship between the production of autoantibodies and unremitting inflammation. Persistent symptoms that remain after treatment have been identified in a sub-group of patients to be associated with autoantibodies targeted at G-protein-coupled receptors and interferon pathways (Wallukat et al., 2021; Bastard et al., 2020). Despite the absence of it all the time, our results determine the hypothesis that B-cell dysregulation is a contributing factor to the heterogeneity of illnesses.

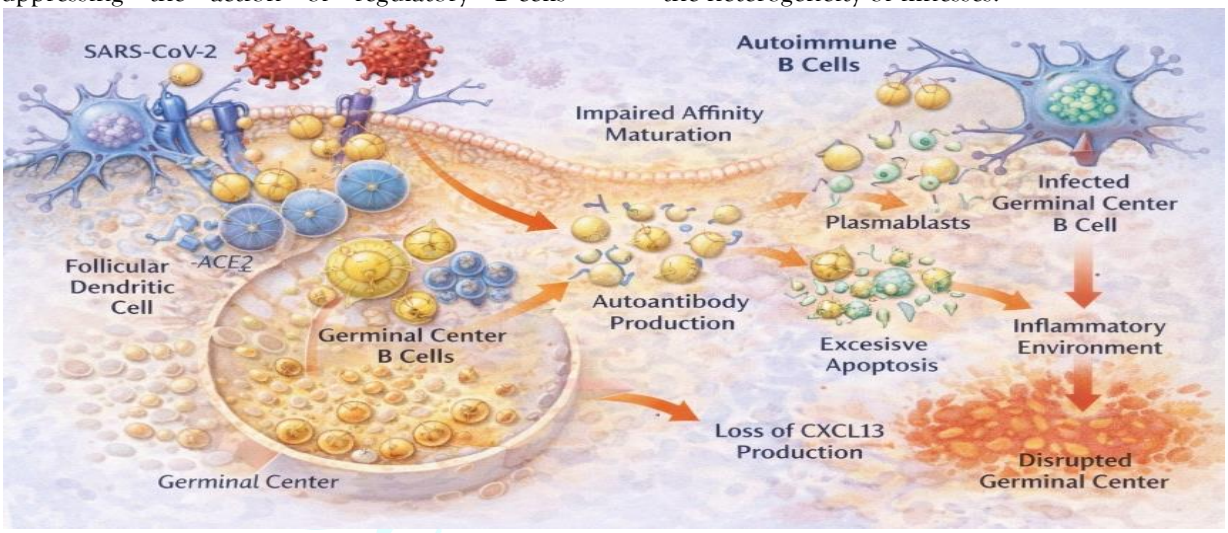

Fig.6: B-cell dysregulation and germinal center disruption

Endothelial Pathobiology and Microvascular Injury

Endothelial malfunction is a chronic consequence of Long COVID, which is gaining more and more popularity. The acute sickness of SARS-CoV-2 leads to endothelialitis when the endothelium cells are directly infected through ACE2 receptors (Varga et al., 2020). Examples of endothelial activation markers that some patients remain high months after becoming infected are von Willebrand factor and soluble ICAM-1 (Fogarty et al., 2021).

Microvascular injury may also be aggravated by immune-mediated processes. Repeated exposure to cytokines over time boosts leucocyte recruitment and synthesis of endothelial adhesion molecules that perpetuate local inflammation (Merad & Martin, 2020). Pretorius et al. (2021) found fibrin amyloid microclots that are resistant to fibrinolysis in patients with Long COVID, which indicates that the immune activation and coagulation problems are correlated. Microvascular dysfunction can aggravate fatigue and cognitive impairment due to the reduced levels of tissue oxygenation and mitochondrial stress (Saleh et al., 2020). Vascular illness plus immunological malfunction is probably the main cause of the chronic multisystem symptoms.

Metabolic Rewiring and Mitochondrial Signaling.

Close interconnection exists between cellular metabolism and immune activation. Netea et al. (2020) state that stimulated immune cells reprogram their metabolic processes to turn towards aerobic glycolysis and accelerate the synthesis of cytokines. This glycolytic condition might be maintained by continuous inflammatory signals in Long COVID which hinders the restoration of efficient oxidative phosphorylation.

The indicators of mitochondrial dysfunction are reduced respiratory chain activity and elevated reactive oxygen species production, which have been linked to chronic post-COVID fatigue (Su et al., 2022). Reactive oxygen species enhance the inflammatory circuits by activating redox- sensitive transcription factors like NF- 0 -B (Saleh et al., 2020). This shows the two-way interaction between metabolic impairment and chronic inflammation.

The toll-like receptor and NLRP3 inflammasome are triggered by parts of mitochondrial DNA and other molecular patterns that are related to mitochondrial damage (Rodrigues et al., 2021). Thus, inflammation can be caused and also sustained by mitochondrial failure.

Table 1: Key Immune Pathways Implicated in Long COVID Pathogenesis

Pathway	Principal Mediators	Mechanistic Consequence	Representative Studies
IL-6 / JAK–STAT3	IL-6, STAT3	Chronic systemic inflammation, Th17 polarization	Tanaka et al., 2014; Peluso et al., 2021
Type I Interferon	IFN-β, STAT1	Sustained innate activation, T-cell exhaustion	Phetsouphanh et al., 2022
NF-κB Signaling	TNF-α, IL-1β	Amplified cytokine transcription	Liu et al., 2017
NLRP3 Inflammasome	IL-1β, IL-18	Persistent inflammatory loop	Rodrigues et al., 2021
T-Cell Exhaustion	PD-1, TIM-3	Reduced cytotoxicity	Wherry & Kurachi, 2015
Endothelial Activation	ICAM-1, vWF	Microvascular dysfunction	Fogarty et al., 2021
Mitochondrial Dysfunction	ROS, mtDNA	Energy deficit, oxidative stress	Saleh et al., 2020

Viral Persistence: Evidence in the Emerging 2023-2026

The recent research on autopsy and biopsy studies has given supplementary evidence of viral antigen retention in various tissues months after the acute infection (Chertow et al., 2021). Viral RNA fragments have been detected in the intestinal biopsies of recovered patients, indicating the possible reservoir in the mucosal tissues (Gaebler et al., 2021). Persistent antigen has the capability to maintain low level of immune activation in the absence of productive replication.

Animal models also have further indications that viral proteins can be retained in tissue macrophages and that they may induce the expression of chronic cytokines.

(Proal & VanElzakker, 2021). It is also under investigation as to whether persistent antigen is an effect of an infective virus in persistence or of the leftover fragments that are noninfectious. However, nonreplicating viral components are capable of maintaining innate immune monitoring, as well as inflammatory signaling.

Table 2: Clinical infestations and Proposed Mechanistic Correlates in Long COVID

Clinical Feature	Proposed Mechanistic Basis	Supporting Evidence
Fatigue	Mitochondrial dysfunction, IL-6 elevation	Missailidis et al., 2020; Peluso et al., 2021
Cognitive impairment	Neuroinflammation, microvascular injury	Douaud et al., 2022
Dyspnea	Endothelial dysfunction, microclots	Pretorius et al., 2021
Autonomic instability	Immune-mediated receptor autoantibodies	Wallukat et al., 2021
Exercise intolerance	Impaired oxidative phosphorylation	Tomas et al., 2017

Neuroinflammation and Central Nervous System Immune Activation

Neurological and cognitive symptoms have remained one of the most disabling signs of Long COVID affecting the memory, attention, executive functioning, sleep, and mood management (Nalbandian et al., 2021). A biological explanation of the connection between systemic immune dysregulation and dysfunction in the central nervous system is given by neuroinflammation. Varathararaj et al. (2020) indicate that the peripheral cytokines (TNF- 2 and IL- 6) may disrupt the blood-brain barrier and permit the activated leukocytes and immune mediators to enter the central nervous system. Long COVID patients have a functional correlation between the peripheral and central immunity, reflected in the fact that an increase in systemic inflammatory biomarkers correlates with the severity of cognitive symptoms (Peluso et al., 2021).

Acute COVID-19 post-mortem studies have shown that in the places where there is no direct viral neuroinvasion, microglial activation and Astro cytosis are widespread (Matschke et al., 2020). Stimulation of microglia leads to the generation of reactive oxygen species, IL-1B, and IL-6 that could inhibit neuronal signaling and synaptic plasticity (Heneka et al., 2020). The neuroimmune persistence was also suggested by the neuroimaging results, indicating structural and metabolic changes in limbic and cortical areas months after infection (Douaud et al., 2022). These results indicate that negative cognitive outcomes over a long period post-COVID can be due to persistent neuroinflammatory reaction as opposed to irreversible loss of neurons.

The dysfunction of the mitochondria causes even more susceptibility to the central nervous system. The effect of oxidative stress can be inflammatory cytokines that interfere with mitochondrial respiration because oxidative phosphorylation is vital to neurons (Saleh et al., 2020). NF-KB is activated by reactive oxygen species, which causes a feed-forward inflammatory loop in brain tissue (Liu et al., 2017). Systemic inflammation, endothelial dysfunction and mitochondrial stress form a physiologic response to explain long term cognitive and neuropsychiatric issues.

Disruption of the Gut Immunes and the Microbiome

A major role in the pathogenesis of long covid-19 is played by the digestive system. Months after the respiratory clearance, intestinal tissue has been found to be infected by viral RNA, and ACE2 receptors allow SARS-CoV-2 to infect enterocytes (Lamers et al., 2020; Gaebler et al., 2021). The integrity of the intestinal barrier may be damaged by prolonged activation of the mucosal immune system leading to microbial translocation and systemic inflammation (Proal & VanElzakker, 2021).

It has also been reported that acute COVID-19 has a changed composition of the gut microbiome, including both decreased diversity and the elimination of commensal species linked to immunological control (Su et al., 2022). The dysbiosis can augment systemic NF- kB signaling, which stimulates long-term activation of the toll-like receptor pathways with the exposure to LPS (Liu et al., 2017). Therefore, persistent inflammatory activation could be a reason of the gut-immune axis. As recent studies have indicated, the composition of the microbiome is related to inflammatory biomarkers profiles in Long COVID cohorts (Venzon et al., 2022). Restoring microbial homeostasis is a feasible treatment option even on how to study the causal relationships. More mechanistic research is needed in order to understand the correlation between viral persistence, mucosal immunity, and systemic inflammation.

Comparative Study to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.

Long COVID and Myalgic encephalomyelitis/chronic fatigue disease (ME/CFS) symptoms have generated fresh interest in the associated immunopathological mechanisms (Komaroff and Bateman, 2021). Autonomic instability, post-exertional malaise,

and cognitive impairment are ME/CFS symptoms, which are commonly observed in long Covid (Montoya et al., 2017). Some of the immunological issues associated with ME/CFS are low cytotoxicity of natural killer cells, altered cytokine response, and mitochondrial dysfunction (Tomas et al., 2017).

Table 3: Neuroimmune and Gut–Immune Mechanisms in Long COVID

System	Pathophysiological Mechanism	Key Molecular Mediators	Representative Evidence
Central nervous system	Microglial activation	IL-1β, IL-6, ROS	Matschke et al., 2020
Blood–brain barrier	Increased permeability	TNF-α, IL-6	Varatharaj et al., 2020
Mitochondrial dysfunction	Oxidative stress	ROS, mtDNA	Saleh et al., 2020
Gut mucosal persistence	Viral RNA retention	SARS-CoV-2 antigen	Gaebler et al., 2021
Microbiome dysbiosis	Toll-like receptor activation	LPS, NF-κB	Venzon et al., 2022

Recent research has associated the two diseases with immune-metabolic dysregulation and chronic low-grade inflammation (Missailidis et al., 2020). Nevertheless, in Long COVID, the temporal definition of early infection can be used, and changes in immunology between acute infection and chronic disease can be traced. Therefore, the comparison analysis can help understand whether immune depletion, metabolic pathways are common features of post-viral diseases.

In both cases, interferon dysregulation has been noted, and an increase in IL-6, although it varies depending on the cohort (Montoya et al., 2017). These similarities tend to give credence to the fact that immunological resolution after being infected by a virus is the cause of the persistent tiredness disorders.

Biomarker Stratification and Clinical Endotypes

Long Covid is unlikely to be a single pathogenic disease. Multi-omics studies have provided insights into a number of inflammatory endotypes, each with a different cytokine composition, immunological exhaustion indicators, and metabolic signature (Su et al., 2022). To work with classifying patients and customizing the treatment plan, good biomarkers should be located. Some of the candidate biomarkers are circulating microclots, soluble endothelium adhesion molecules, interferon gene signatures, and T-cell exhaustion markers (PD-1 expression) (Peluso et al., 2021; Pretorius et al., 2021). Transcriptome and proteomic data could be useful in predicting disease trajectory with the help of integrating the data.

Table 4: Candidate Biomarkers under Investigation in Long COVID

Biomarker Category	Specific Marker	Proposed Clinical Utility	Supporting Study
Pro-inflammatory cytokine	IL-6	Indicator of systemic inflammation	Peluso et al., 2021
Interferon signature	IFN-β, STAT1 expression	Marker of innate activation	Phetsouphanh et al., 2022
Endothelial marker	Soluble ICAM-1	Vascular dysfunction	Fogarty et al., 2021
Coagulation abnormality	Fibrin microclots	Microvascular pathology	Pretorius et al., 2021
T-cell exhaustion	PD-1 expression	Adaptive immune dysfunction	Wherry & Kurachi, 2015

Ongoing Clinical Trials and Therapeutic Targeting

The field of clinical research of therapeutic approaches to Long COVID has grown almost

incredibly quickly, as the healthcare community tries to deal with the immunological and vascular processes behind the disease. Following accumulating information, a number of clinical trials have been designed with immunomodulatory therapies aiming at teichoic acid deregulated cytokine signaling and prolonged immunological activation as significant elements of the disease. Two of the most popular treatments are Janus kinase (JAK) and interleukin-6 (IL-6) signaling blockers. The longitudinal follow-ups of SARS-CoV-2 infection patients with post-acute sequelae have reported continuous increases of pro-inflammatory cytokines, including IL-6, which indicates that chronic cytokine actions can be linked to persistent symptomatology (Phetsouphanh et al., 2022). Therefore, the possibility of the IL-6 receptor antagonists that had previously been utilized to treat inflammatory and autoimmune diseases is being investigated to decrease systemic inflammation and return immunological balance. Similarly, JAK inhibitors are under investigation since they disrupt intracellular cytokine signaling mediated by the JAK–STAT pathway and required to activate immune cells and induce the expression of inflammatory genes (O'Shea et al., 2015). Suggestions on early-phase clinical trials indicate that preventing functional recovery, decreasing the symptom load, and long-term immunological dys-regulation could be enhanced through targeted inhibition of these pathways.

Along with immunomodulatory therapy, antiviral therapies are under study following the hypothesis that low-level viral reservoirs or persistent viral antigens could be involved in the persistent immunological activation of some individuals. Some of the studies revealed that SARS-CoV-2 RNA or proteins can be found in the gastrointestinal tract, lymphoid organs, or central nervous system long after the acute infection has resolved (Proal & VanElzakker, 2021). Provided that viral components are left in these reservoirs, they can constantly activate the immune system and extend the inflammatory responses. Clinical trials are underway to determine whether or not antiviral drugs used in the course of the post-acute phase can clear up the remaining virus particles and suppress immunological responses.

The other critical treatment plan is on the vascular and coagulation complications commonly witnessed in Long COVID. It is proven that microvascular damage and chronic endothelial dysfunction could play a significant role in the development of symptoms, especially fatigue, cognitive impairment, and exercise intolerance. Long COVID has been observed to cause platelet hyper activation and irregular fibrin amyloid micro clots, thus potentially reducing the oxygen supply to tissues and microcirculatory blood flow (Pretorius et al., 2021). To treat these abnormalities, anticoagulant and anti-platelet interventions that are intended to ameliorate the microvascular perfusion and thrombotic risk are undergoing clinical trials.

The issue of neuroinflammation has also been a topic of research due to neurological issues like chronic weariness, cognitive impairment, and sensory abnormalities. Low-dose naltrexone is one of the medicines that are being studied more and more, and it is often used in more significant doses to manage opiate misuse. However, in low doses, naltrexone seems to modify the activation of microglia and lower neuroinflammatory signals in the central nervous system (Younger et al., 2014). As microglial activation has been linked with a number of chronic inflammatory neurological diseases, scholars are considering the possible role of low-dose naltrexone in reducing cognitive and neurological symptoms of Long COVID.

Although these treatments have potential benefits, the heterogeneity of Long COVID implies that there will be few universal therapeutic approaches that can be effective at least in all patients. It is now evident that persons can possess different immunological phenotypes, such as metabolic inefficient, autoimmune, immune exhaustion, or hyper activation of the inflammatory response. Precision medicine approaches are thus becoming a suggested approach of treatment. Clinicians can possibly group patients based on physiological categories by identifying distinct signatures of biomarkers, e.g. cytokine profiles, immune cell morphology, or indicators of metabolic activity. Such categorization can decrease unnecessary

immunosuppression or other adverse effects and enhance the treatment outcomes by allowing the selection of medications to be customized.

Combined Immune Metabolic Endothelial Long COVID Pathways

There is an increasing consensus that this is due to the fact that the pathophysiology of Long COVID is not caused by one factor. A complex interaction between persistence of immunological activation, metabolic derangements, and endothelial dysfunction and microvascular damages maintains the occurrence of chronic symptoms. When these systems feedback on each other in a variety of ways, a self-sustaining cycle of tissue stress and inflammation is generated.

It is believed that a key aspect of this network on the molecular level is maintained inflammatory signaling. Two such intracellular signaling pathways would be nuclear factor- kB (NF- κB) and Janus kinase- signal transducer and activator of transcription (JAK- STAT) which can be activated by increased concentration of cytokines like IL-6 and type I interferons. The stimulation of such pathways facilitates the expression of a large number of pro-inflammatory genes and adhesion molecules in endothelial cells (Merad & Martin, 2020). The amplified expression of endothelial adhesion molecules facilitates the migration of leukocytes to vascular tissues, which aggravates inflammation and damage of the endothelia. Additionally, these proinflammatory cues might stimulate platelet activation and micro clot development, which might slow down microvascular flow and exacerbate organ-specific symptoms such as dyspnea or cognitive impairment (Su et al., 2022).

The main constituent of this sick network is metabolic dysfunction. The chronic inflammation has the potential to interfere with the mitochondrial activity of immune cells and other tissues, affecting the production of energy in cells. The mitochondrial failure can result in the upsurge of the reactive oxygen species (ROS) production that could cause damages to the cell structures and boost the inflammatory signals. Overproduction of ROS may activate intracellular inflammasome, which are multi-protein monoliths that release pro-inflammatory cytokines such as interleukin-1b, therefore, worsening systemic inflammation (Saleh et al., 2020; Rodrigues et al., 2021). This immune activation and metabolic stress interaction can explain the high levels of fatigue and intolerance to exercise commonly reported in people with Long COVID. Nevertheless, it turns out that maladaptive adaptive immune responses are barriers to the elimination of inflammation. T-cell fatigue is a disease that develops as a result of a prolonged exposure to antigens or other inflammatory signals, resulting in the gradual loss of T cell ability to eliminate infections and control immune responses. Due to reduced production of cytokines and lower proliferation ability of tired T cells, their ability to maintain immunological homeostasis is limited (Wherry & Kurachi, 2015). Long-term COVID has also been linked to dysregulation of B-cell populations, in particular, the production of autoantibodies that attack host organs. Many studies have found that receptors to which functional autoantibodies target include vascular and autonomic regulation, which would indicate a potential autoimmune factor to symptoms such as orthostatic intolerance and cardiovascular abnormalities (Wallukat et al., 2021).

These interrelated systems provide an example of feed-forward inflammatory loops. Damage to endothelium, immunological dysregulation, sustained viral antigens and metabolic stress all support each other via overlapping signaling pathways. As an example, endothelial damage leads to increased release of inflammatory cytokines, which further increases immune activation and damage vascular tissues. Similarly, mitochondrial dysfunction augments oxidative stress, which is able to extend cell injury and set up other inflammatory caspades. These self-reinforcing loops could explain the persistence of the symptoms following the initial viral infection which has already swept away.

The studies on systems biology have more and more indicated that one pathogenic pathway is not sufficient to characterize long-term COVID. The sickness, instead, seems to be the result of the interplay of overlapping immunological,

metabolic, and vascular abnormalities that interact dynamically in a number of organ systems. As such, to comprehend the etiology of sickness and develop a successful treatment plan, the methodology needs to integrate vascular biomarkers, metabolic analysis, and immunological profiling (Su et al., 2022). Research on these complex networks will be essential in order to come up with specific treatments that have the potential to break the pathogenic feedback loops that drive Long COVID.

Table 5 Key Interconnected Pathways in Long COVID Pathogenesis

Pathway Node	Molecular Drivers	Clinical Correlate	Potential Intervention
Cytokine Signaling	IL-6, STAT3, IFN-β	Fatigue, Brain Fog	JAK inhibitors (Baricitinib), mAbs (Tocilizumab)
Innate Immunity	NF-κB, NLRP3, IL-1β	Myalgia, Dyspnea	Colchicine, NLRP3 inhibitors
Adaptive Immunity	PD-1+, TOX+, Autoantibodies	Impaired Viral Clearance	IL-7 therapy, Checkpoint modulators
Vascular Health	ICAM-1, vWF, Microclots	Cognitive Dysfunction	Anticoagulants, Antiplatelet therapy
Metabolic State	ROS, mtDNA, Low ATP	Exercise Intolerance (PEM)	CoQ10, Mitochondrial antioxidants
Barrier Integrity	LPS, Gut Dysbiosis	Systemic Inflammation	Probiotics, Dietary modification

Knowledge Lapses and Open-ended questions

Even with the major improvements, there are a number of unanswered questions with regard to long-term COVID research. It remains unclear what is the particular role of viral persistence vs immune maladaptation, and tissue reservoirs of SARS-CoV-2 antigens are a debated issue (Chertow et al., 2021). More mechanistic understanding is needed to gain a better understanding of the relationship between immunological exhaustion and metabolic dysregulation. Multi-omics and neuroimaging with longitudinal studies that include clinical phenotyping are required to distinguish the various endotypes. Moreover, the variety of symptom courses highlights the importance of validated biomarkers that can be used to stratify patients to get specific therapy (Su et al., 2022). It can be possible to determine whether there are common immune-metabolic-endothelial pathways peculiar to SARS-CoV-2 infection or not through a comparison of research with ME/CFS and other post-viral illnesses (Komaroff and Bateman, 2021; Montoya et al., 2017).

Future Directions

The field of systems-level biology should be included into the future studies to recreate the route connections and find therapeutic targets. Interactions Convergent pathways can be observed by combining proteomic and metabolomics profiling with high-dimensional single-cell studies of immunological populations. Biomarker-based stratification of clinical trials should include the use of immunomodulatory, antiviral, or metabolic therapies. Besides, the study of microbiome restoration and mitochondrial support medicines could provide new complementary methods of approach. Cognitive tests, functional tests, and biomarker panels, among other types of standardized outcome measures, should be developed so that they can be compared across studies. Large-scale longitudinal analyses required to solve clinical phenotypic heterogeneity will be made possible by international consortiums and data-sharing platforms.

Conclusion:

Long COVID has endothelial dysfunction, metabolic and mitochondrial dysfunction, chronic inflammation, and chronic

immunological dysregulation. Besides adaptive immune exhaustion and B-cell dysregulation, dysregulated pro-inflammatory signaling of IL-6, type I interferons, NF-KB, and inflammasomes establishes a positive feedback pathogenesis. Examples of multisystem symptoms due to the interaction of these pathways with dysfunction in endothelium and microvascular impairment include dysautonomia, fatigue, and cognitive impairment. The multi-omics analysis and biomarker profiling would require the use of mechanistic studies to stratify patients and direct precision medicine therapies. Although we are yet to comprehend viral persistence, immune-metabolic interactions, and tailored response to treatment, the available information would form a strong molecular backbone to guide future studies and clinical practice.

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