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Review

Tissue Injury and Leukocyte Changes in Post-Acute Sequelae of SARS-CoV-2: Review of 2833 Post-acute Patient Outcomes per Immune Dysregulation and Microbial Translocation in Long COVID

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Abstract: A significant number of persons with coronavirus disease 2019 (COVID-19) experience persistent, recurrent, or new symptoms several months after the acute stage of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This phenomenon, termed Post-Acute Sequelae of SARS-CoV-2 (PASC) or Long COVID, is associated with high viral titers during acute infection, a persistently hyperactivated immune system, tissue injury by NETosis-induced microthrombofibrosis (NETinjury), microbial translocation, complement deposition, fibrotic macrophages, the presence of auto-antibodies, and lymphopenic immune environments. Here, we review the current literature on the immunological imbalances that occur during PASC. Specifically, we focus on data supporting common immunopathogenesis and tissue injury mechanisms shared across this highly heterogenous disorder including NETosis, coagulopathy, and fibrosis. Mechanisms include changes in leukocyte subsets/functions, fibroblast activation, cytokine imbalances, lower cortisol, autoantibodies, co-pathogen reactivation, and residual immune activation driven by persistent viral antigens and/or microbial translocation. Taken together, we develop the premise that SARS-CoV-2 infection results in PASC as a consequence of acute and/or persistent single or multiple organ injury mediated by PASC determinants to include degree of host response (inflammation, NETinjury), residual viral antigen (persistent antigen) and exogenous factors (microbial translocation). Determinants of PASC may be amplified by co-morbidities, age, and sex.

Keywords: long COVID; PASC; long haulers; NETosis; T cell; NK cell; DC; neutrophil; macrophage

Abbreviations:

ACC: Active COVID-10
ACE2: Angiotensin-Converting Enzyme 2
ADCD: Antibody-Dependent Complement Deposition
AREG: Amphiregulin
AutoAbs: Autoantibodies
Bcl6: B-cell lymphoma 6
COVID-19: Coronavirus disease 2019
CRP: C-reactive protein
CTLA-4: Cytotoxic T-Lymphocyte-Associated Protein 4
DC: Dendritic cells
EMT: Epithelial to Mesenchymal Transition

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EndoMT: Endothelial to Mesenchymal Transition
E-protein: Envelope protein
ERS: early recovery stage
HC: Healthy Control
HGF: hepatocyte growth factor
HLA-DR: Human Leukocyte Antigen – DR isotype
IFN: Interferon
IgG: Immunoglobulin G
IgM: Immunoglobulin M
IL: Interleukin
IP-10: Interferon gamma-induced protein 10 (aka. CXCL10)
LCR: long-time follow up
LRS: late recovery stage
M protein: Membrane Protein
MAIT: Mucosal-Associated Invariant T cells
MCP-1: Monocyte chemoattractant protein-1 (aka. CCL2)
mDCs: myeloid DC
N protein: Nucleocapsid Protein
NAbs: Neutralizing Antibodies
N.D.: Not determined
NK cells: Natural Killer cells
NETs: Neutrophil extracellular traps
NETosis: The process of neutrophil deposition of NETs
NETinjury: NETosis-mediated tissue injury
OXPHOS: oxidative phosphorylation
PASC: post-acute sequelae of SARS-CoV-2 infection
PD-1: Programmed Cell Death Protein 1
pDCs: plasmacytoid DC
POS: post-onset of symptoms
PSGL1: P-selectin glycoprotein ligand-1
RBD: Receptor-Binding Domain
S protein: Spike protein
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
SCR: short-time follow up;
Tfh: Follicular T helper cells
TIGIT: T cell immunoreceptor with Ig and ITIM domains
TIM-3: T cell immunoglobulin and mucin-domain containing-3
TNF: Tumor Necrosis Factor
Treg: Regulatory T cells
VEGFA: vascular endothelial growth factor A.

1. Introduction

After recovery from acute SARS-CoV-2 infection, as indicated by a negative nucleic acid test in the absence of compromised lung function (1), one-third to one-half of the otherwise recovered individuals experience fatigue, joint pains, breathing problems, as well as gastrointestinal (GI), cardiovascular, and other symptoms, for months, indicating injury to one or more organs (2). These persistent and insidious symptoms initially were termed “long COVID” or “long-haulers” and are now referred to as Post-Acute Sequelae of SARS-CoV-2 (PASC) (3-6). The heterogeneous clinical presentations and multiple organ systems associated with PASC have made it difficult to determine the root causes underlying this complex condition (7). Multiple areas remain unexplained, including, but not limited to: i) the role of sustained hyperactivated inflammatory responses in the development or persistence of PASC, ii) the degree of viral persistence in immune-privileged sites during PASC, iii) the link between induced autoantibodies, whether in blood or the central nervous system (CNS) of persons with PASC, iv) the role of pre-existing comorbidities

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(e.g., diabetes, high blood pressure, and chronic viral infections), or demographic characteristics (e.g., age, race, sex, and weight), in favoring specific PASC symptoms, and v) the impact of alcohol or substance use disorders on PASC-induced organ injury in the GI tract, liver, or CNS (8-10). In addition to these questions, limited data are available on what causes PASC-related symptoms to develop and persist, as most studies to date have been correlative.

It is plausible that hyper-immune activation and autoimmunity are potential contributors to PASC, as persons with SARS-CoV-2 have shown evidence of such immunological abnormalities both during and after active infection (11, 12). SARS-CoV-2 proteins have been found to interact directly with immune mediators, resulting in dysregulated type-1 interferon production and increased neutrophil activation. A link also has been established between NETosis and organ injury via a microthrombi pathway (13, 14), and elevated TGF-β1 signaling and local collagen deposition have been shown to contribute to fibrosis (15, 16). The latter cascade of events, which starts with NETosis and coagulopathy, followed by fibrosis, is referred to as "NETinjury." These tissue injury mechanisms include both immune and microthrombosis events associated with acute COVID-19. In short, NETinjury presents a scenario whereby the sum, or the magnitude of any specific organ injury, depends on the dynamic interaction between contributing parts, represented by local tissue microenvironments, SARS-CoV-2 antigen, inflammation, a persistent NETosis response, and the resulting tissue injury.

Here, we review data supporting a link between PASC and persistent dysregulated circulating leukocyte subsets (i.e., neutrophil, monocytes, dendritic cells, and T cells response); cytokine secretion (i.e., IL-6, IP-10, TNF, IL-8, IL-1β, and IFNs); coagulopathy; the presence of autoantibodies in blood or the CNS; as well as other immune activation pathways linked to microbial translocation from the gut and/or the lung to the blood. We examine potential factors contributing to tissue injury to look for common features among otherwise highly variable clinical presentations of PASC (**Figure 1**). The mechanistic contributions of comorbid conditions to PASC are not addressed here, although links between PASC symptoms, such as fatigue and neurocognitive function, have been previously associated with Epstein Barr Virus (EBV) reactivation and HIV co-infection, respectively (17). We also do not address specific conditions (i.e., obesity, diabetes, and aging-associated disorders) that may be linked to COVID-19 severity and the development of PASC.

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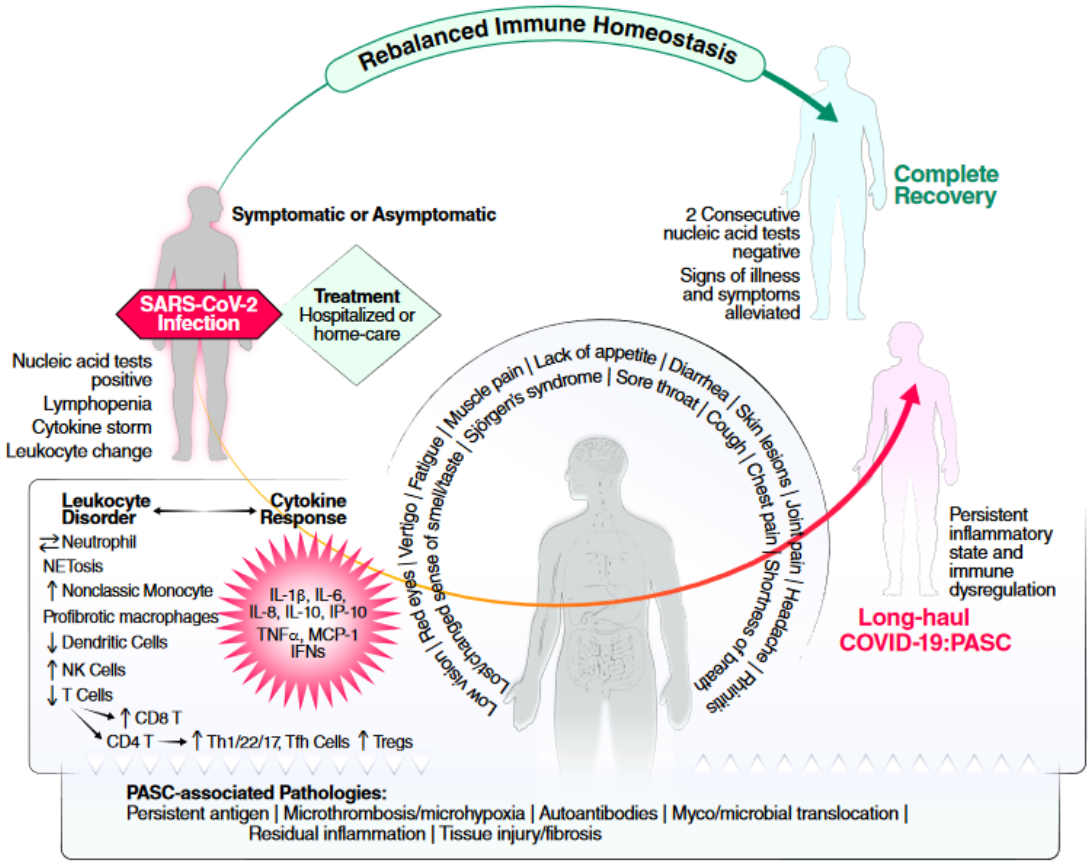

Figure 1. Major blood leukocyte, cytokine changes, PASC-associated symptoms and pathologies following SARS-CoV-2 infection. Conceptual model of the interplay between immune activation, immunopathogenesis, and clinical pathology in persons with PASC.

2. The impact of Acute SARS-CoV-2 Infection on the immune system

Innate immune responses are modulated by SARS-CoV-2 infection. Excessive proinflammatory cytokine release, together with lymphopenia, lymphocyte dysfunction, and granulocyte and monocyte abnormalities, are significant hallmarks in the pathogenesis of severe COVID-19 (11, 18). Moreover, abnormal neutrophils, in terms of both phenotype and functionality—such as neutrophil extracellular traps formation, low numbers of dendritic cells (DCs), mainly conventional DCs type 2 (cDC2) and plasmacytoid DCs (pDC), and natural killer (NK) cells—are all known to impact the severity of SARS-CoV-2 infections (11, 19-21). Additionally, monocyte and macrophage dysfunction (defined by HLA-DR and FCN1 and SPP1 expression profiles, respectively) have been found to influence COVID-19 severity (22, 23). Concerning cytokine responses, elevated levels of proinflammatory cytokines and chemokines (potentially produced by macrophages or monocytes, including IL-6, IFNγ, MCP-1, IP-10, and TNF) are associated with severe disease outcomes (11). Finally, a lack of an interferon-mediated antiviral response (e.g., IFN types I and III) at the onset of disease can increase the risk for infection (24).

Adaptive immune responses are also modulated by SARS-CoV-2 infection. Several studies report decreases in $CD4^+$ T cells, $CD8^+$ T cells, $CD4^+FoxP3^+$ regulatory T cells (Tregs), MAIT ($CD8^+$ mucosal-associated invariant T) cells, γδ T cells, and αβ T cells in persons with mild or severe COVID-19 (25-28). Conversely, increases in the ratio of $CD4^+/CD8^+$ T cells, or T_{regs} number, have also been reported in persons with COVID-19 (29, 30). In addition, T cells are documented as "functionally exhausted" (defined by up-regulated expression of PD-1, CTLA-4, TIGIT, and TIM-3 and downregulated expression

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of granzyme B, IFN-γ, IL-2, and TNF) in persons with COVID-19 (31). However, protective T cells, which respond against viral antigens, were also observed in COVID-19 infection, including T cell responses against spike (S), membrane (M), and nucleocapsid (N) proteins (32). Regarding B cell responses, COVID-19 infection has been associated with differential antibody Fc-mediated innate functions, with pronounced antibody-dependent complement deposition (ADCD) in severe cases (33).

Taken together, it is clear that SARS-CoV-2 infection intensely disrupts the host immune homeostasis during disease. This disruption, in turn, can initiate infection and tissue injury processes linked to PASC. It is unclear if these immune dysregulation events persist after recovery and contribute to PASC. However, in the following sections, we will describe evidence to date indicating the persistence of dysregulated immune functions before and during PASC.

3. Dynamics and persistence of dysregulated immune system DURING PASC

The post-COVID-19 complications can exist for varying amounts of time after infection, and persons with PASC show a diverse array of pathological states, with symptoms related to pulmonary, cardiovascular, neural, reproductive, gastrointestinal, dermatological, and cognitive health (5, 34, 35). Given the diversity of clinical presentations, our review will focus on leukocyte, cytokine, and plasma factors that are most common among individuals with PASC, as reported to date.

3.1. Persistence of dysregulated innate immune systems

3.1.1. Neutrophils

Elevated neutrophil levels, along with associated abnormalities in their characteristics and function, are common findings in cases of severe COVID-19. These abnormalities include the presence of neutrophil extracellular traps (NETs and NETosis) and associated immunothrombosis (11, 36). A small cohort study reported that NET marker (i.e., citrullinated histone H3, cell-free DNA, neutrophil elastase) plasma levels resolved in convalescent persons after 4 months post-infection, providing a possible mechanistic link between tissue injury and short-term PASC (i.e., symptoms that persist months after the initial infection) (37). Longitudinal studies linking the prevalence of systemic NETosis to long COVID have not been reported to date. NETosis-mediated tissue injury during PASC may be restricted to sites where antigens persist, as suggested by findings on persistent Spike antigenemia in post-acute periods and/or PASC (38-41). This may also explain why PASC presentations are so diverse across individuals (13, 14). It also remains to be determined whether autoantibodies can extend incidences of NETinjury as recent data show that anti-NET antibodies may impede NET clearance and, thus, potentially exacerbate NETinjury (42). Although we can speculate that organ-specific NETosis and organ injury may result from damage during infection, or as a consequence of persistent sources of immune activation after resolution, additional data or interventional studies targeting NETosis are needed to confirm whether this immune response and resulting tissue injury contribute to PASC after COVID-19 infection.

3.1.2. Monocytes and Macrophages

The role of monocytes and macrophages in the immunopathogenesis of COVID-19 continues to be central to understanding lung fibrotic tissue injury (43)—either as contributors to the overall activation via SARS-CoV2/ACE2 interactions (44), or by driving FcgR-mediated SARS-CoV2 infection (45). Sustained myeloid hyper-activation can also result from continuous TLR- and Dectin-1-mediated activation following bacterial and fungal translocation (46, 47). Myeloid cells likely play a dual role in PASC, contributing to local fibrosis-mediated tissue injury, which then leads to PASC symptoms, as well as working to sustain pro-inflammatory cytokine levels.

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Increases in absolute number and percentage of monocytes in persons with COVID-19 may persist more than 6 months after disease onset (48). The proportion of classic monocytes has been shown to decrease over time. In contrast, the percentages of both inflammatory $CD14^{+}CD16^{+}$ and non-classical monocytes ($CD14^{lo}CD16^{+}$) increase weeks to months after the initial infection (from 0.5 to 4 months). The proportion of circulating monocytes may remain dysregulated, especially in convalescent persons with low CCR2 expression and high CX3CR1 expression in intermediate and non-classical monocyte populations 1 to 3 months post-infection (49). Compared with persons with acute COVID-19 infection or those who are uninfected, recovered individuals show increases in monocytic IL-6, TNF, and CCL2. The surface expression of LFA-1, VLA-4, and CD31/PECAM on monocytes was also higher in fully recovered persons compared with uninfected control persons, although CD62L and CXCR6 expression remained significantly reduced (49). Even the expression of CD11b was elevated on monocytes at 1 to 3 months from disease onset (50). A similar observation was documented in a study comparing healthy control persons with persons experiencing acute COVID-19. That study showed that monocyte changes did not resolve until 6-months into the follow-up period (51). CCR2, CCR5, CD86, and HLA-DR expression on the surface of circulating monocytes, as well as monocyte-produced IP-10 (CXCL10), remained increased (51). A separate study at different time points (2 months and 8 months) showed that the percentage of classical $CD14^{+}CD16^{-}$ and inflammatory $CD14^{+}CD16^{+}$ monocytes were restored after 2 months post-infection, whereas restoration of non-classical monocytes ($CD14^{-}CD16^{+}$) took up to 8 months after disease onset to resolve (52, 53). It was also shown that, compared with healthy controls, the proportions of both intermediate or inflammatory monocytes ($CD14^{+}CD16^{+}$) and non-classical monocytes ($CD14^{lo}$ $CD16^{+}$) were significantly higher in persons with PASC up to 15 months post-infection (54). In contrast, the proportion of classical monocytes ($CD14^{hi}$ $CD16^{+}$) found among long haulers was not significantly altered. At the same time, activation markers (i.e., sCD14, C-reactive protein [CRP], sCD163, and soluble tissue factor) of plasma monocytes decreased over 180 days post-COVID-19 (48). Additional studies report that proinflammatory metabolite production (i.e., eicosanoids), type I IFN responses, and chemokine responses by monocyte-derived macrophages were enhanced, remaining unstable 3 to 5 months post-infection (55). Importantly, these inflammatory metabolites also returned to baseline levels 12 months post-recovery (55). Strikingly, these monocyte subsets remained essentially unchanged during severe COVID-19, compared with healthy controls, even in cases where the subsets were found to be different after the infection was resolved (54). Taken together, all reports to date on persons with PASC show a common finding; abnormal monocyte responses do not fully resolve in recovered persons, as evidenced by: i) increases in the percentage of non-classical monocytes ($CD14^{lo}$ $CD16^{+}$); ii) increases in the propensity of monocytes to produce cytokines (IL-6, TNF, and IP-10); iii) increases in monocyte migration markers (LFA-1, VLA-4, and CD31); and iv) reduced numbers of classical monocytes ($CD14^{hi}CD16^{+}$) that persist at least 3 to 6 months post-infection. Sustained myeloid activation, either by continued TLR- or Dectin1-mediated activation (see microbial translocation below), likely is vital in the onset and severity of PASC.

3.1.3. Dendritic cells (DCs)

The function of DCs in the immunopathogenesis of COVID-19 remains less investigated than monocyte/macrophage subsets. However, single-cell analysis of bronchoalveolar immune cells from persons with COVID-19 found that the number of DCs in the bronchoalveolar lavage fluids declined among severe cases (23). Specifically, several studies reported that the number and functionality of the plasmacytoid DC (pDCs) and myeloid DC (mDCs) were impaired, especially among persons with severe COVID-19 (20, 56-58). Intriguingly, Peruzzi and colleagues reported that conventional DCs type 2 (cDC2) were more likely to be vulnerable to SARS-CoV-2 infection compared with other subtypes (57). In contrast, Borcherding and colleagues observed that lung mDCs were amplified at

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later stages in diffuse alveolar damage among persons with SARS-CoV-2 (59). With regard to PASC, a recent study reported that the number of CD1c$^+$ myeloid DCs and pDCs remained at low levels for 7 months post-infection among persons in recovery when compared with levels found in uninfected control individuals (60). Several activation markers expressed on pDCs or mDCs (e.g., integrin β7, indoleamine 2,3-dioxygenase [IDO], and CCR7) also did not normalize among otherwise recovered persons, even though the expression of other cell surface markers (CD86 and CD4) returned to uninfected control levels (60). Although data are lacking on how dysregulated DC subsets or their responses impact PASC, there is evidence that functional and phenotypic abnormalities in pDC (i.e., expression of activation marker, low count) persist for more than 6 months, indicating that DC subsets are also dysregulated (like the monocyte subsets above) in PASC (60).

3.1.4. NK cells

Abnormalities in NK cell proportion, phenotype (characterized by high expression of Ki-67, HLA-DR, CD69, TIM-3, and PD-L1), and function (i.e., abnormal expression perforin and granzyme) have been reported during severe SARS-CoV-2 infections (19, 61, 62). Some NK cells (CD56$^+$CD16$^+$) tend to normalize during recovery, typically within 2 months of COVID-19 infection (52, 53, 63), whereas other NK cells (CD56$^+$) have been found to remain low after 2 weeks of recovery (64, 65). Circulating NK numbers obtained between 3-7 months from disease onset likely are more variable than profiles of myeloid subsets, which typically remain dysregulated for more extended periods in PASC (66-68). Taken together, the delayed recovery of NK cells and how that relates to PASC remains to be determined. For example, it is not clear if microbial translocation (discussed below) acts to sustain immune cell (including NK cell) activation (69, 70), contributing to cytokine secretion and NK modulation.

3.2. Persistence of dysregulated adaptive immune systems

3.2.1. T cells

Cell-mediated responses by antigen-specific T cells are vital for clearing SARS-CoV-2-infected cells. T cell frequencies typically are decreased in persons with COVID-19. Notably, the counts of total T cells, including CD4$^+$ and CD8$^+$ T cells, are reduced in persons with COVID-19 and adversely associated with survival (71). Moreover, the proportion or counts of Tregs, MAIT cells, γδ T cells, and αβ T cells are correspondingly reduced in persons with mild or severe COVID-19 (25-28). Strikingly, it has been reported that T cells are functionally exhausted (defined by upregulated expression of Fas, PD-1, CTLA-4, TIGIT, and TIM-3, and downregulated expression of granzyme B, IFN-γ, IL-2, and TNF) in persons with COVID-19 (31). Of note, an increase in CD4/CD8 cells ratio, or Tregs number, has also been observed in persons with COVID-19 (29, 30). In addition, protective T cell responses aimed at eliminating the virus have been observed in persons with COVID-19, including T cell responses against spike (S), membrane (M), and nucleocapsid (N) proteins (32). Whether the sustained activation of T cells after COVID is driven by persistent SARS-CoV-2 viral antigen (38-41) or other factors (i.e., reactivation of EBV infection) should be further determined.

After 1 to 2 months post-infection, the number of Th9, CD8$^+$ effector T cells, and CD4$^+$ effector memory T cells and the expression of activation markers (CD69, HLA-DR, OX40, and TIM-3) on both CD4$^+$ and CD8$^+$ T cell continued to increase. In contrast, the fraction of T follicular helper cells (Tfh), MAIT cells, and γδ T cells decreases (72-75). Although the cellular exhaustion marker (TIGIT, PD-L1) on CD4$^+$ T cells is high at the early stage of infection, it declines during recovery. Conversely, exhaustion markers (TIGIT, PD-L1) on CD8$^+$T cells are augmented over time (72). Notably, the ratio of peripheral blood CD4/CD8 T cells did not re-establish by that time (74). Multiple cohort studies have reported that the activated CD4$^+$ T cells, Th22, Th17, naïve T_{regs}, Tfh, effector CD8$^+$ T cells, and virus-specific T cells responses increase 3 to 6 months post-infection, whereas CD4$^+$ T cell, IFN-

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γ producing T cells, PD-1^{+}CD4^{+} T cells and Th9 are sustained or in decline (68, 76-78). An immunoproteomic analysis of peripheral blood and bronchoalveolar lavage from persons with PASC with persistent respiratory symptoms at 3 to 6 months post-COVID-19 revealed that cytotoxic T cells are higher in the airways but not in blood compared with healthy controls (79). Importantly, the altered immune profiles in these airways resolved after 1 year of recovery (79). A similar prolonged profile of dysregulated T cells responses (i.e., the lesser fraction of effector memory T cells, both CD4 and CD8 T cells, and amplified PD-1 expression on central memory T cells) can endure up to 9 months or 1-year post-infection (80, 81). Remarkably, the lymphopenic microenvironment caused by SARS-CoV-2 infection can also persist during the recovery stage (73, 74).

Taken together, imbalanced T-cell responses caused by SARS-CoV-2 are expected to resolve after infection. However, evidence of upregulation in markers of T-cell exhaustion can be observed for up to 1 year post-recovery, showing that ongoing activation of T-cell responses is a potential correlate to persistent Spike antigens during PASC (38-41). Whether T-cell responses are a primary contributor to PASC remains to be determined.

3.2.2. B cells

Antibodies with a high complement deposition capacity and autoantibodies (AutoAbs) may be a potential mechanism to explain the humoral response to tissue injury found during and after active COVID and may contribute to PASC. Antibody-dependent complement deposition (ADCD) is increased during severe COVID infection (33). If this increase persists due to sustained antigenemia (38), it could contribute to tissue injury by activating the complement pathway. This could lead to the deposition of C3b, the release of C3a and C5a, and the resulting neutrophil infiltration (NETosis and NETinjury), as discussed above (36). Little attention has been paid to the role of antibodies in mediating endothelial damage, complement activation, and tissue injury during PASC (82, 83). Indeed, a recent report linking anti-NET antibody titers with disease severity suggests that high levels of anti-NET IgG and IgM antibodies have the capacity to decrease the clearance of NETs, which can potentiate tissue injury via NETinjury (42). However, the link between PASC and ADCD, or anti-NETs titers and tissue injury, remains to be determined.

B-cell changes during PASC have also been described, including increases in activated (CD86^{hi}HLA-DR^{hi}) and double negative (IgD^{-}/CD27^{-}/CD24^{-}/CD38^{-}) subsets. In addition, such B cell change is positively associated with high anti-spike antibody responses (indicating the persistent spike antigen) and responses against non-SARS-CoV2 antigens (indicating the reactivation of latent herpesvirus infections, such as Epstein-Barr Virus (EBV))(17, 84).

Auto-antibodies (AutoAbs) of the IgM, IgG, and IgA classes, which react with various serum proteins, cell surface structures, and intracellular structures, are common in healthy individuals (85). However, in some subsets of persons with COVID-19, detectable AutoAbs are considered a pathogenic outcome of PASC, especially AutoAbs that act against ubiquitous and abundant intracellular self-antigens, such as cardiolipin, phospholipid, and receptor molecules (e.g., G protein-coupled receptors) which could result in neurological, pulmonary, and cardiovascular symptoms (10, 86, 87). Persons with COVID-19 show an augmented number of AutoAbs against natural cytokines (GM-CSF, IFN, IL-6, IL-18, IL-1β, and IL-21R), chemokines (CXCL7, CXCL1), growth factor, complement components (C1q), and cell-surface proteins (88). A recent study revealed that almost half of the persons with severe COVID-19 had at least one type of autoantibodies, such as anti-cardiolipin, anti-interferon, and anti-fibrinogen AutoAbs, circulating in their bloodstream (89). Further studies suggest that autoantibody responses are more prominent following asymptomatic infection in women, whereas men tend to show a response after mild symptomatic infections (90). Recent studies further revealed that AutoAbs detected during COVID-19 may have been present pre-infection. These AutoAbs, which could be exacer-

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bated during infection, have been found to persist for more than 1-year (i.e., anti-cardiolipin) postinfection (10, 91, 92). Further supporting the link between AutoAbs and tissue damage, anti-tissue transglutaminase and anti-cyclic citrullinated peptide AutoAbs have been detected 4-8 months post-infection (93). Of interest, although RNA-based vaccines can result in inflammatory responses that resemble SARS-CoV-2 infection (i.e., increases in antibodies and $CD14^{+}CD16^{+}$ frequencies), vaccination has a lower risk of developing autoimmune antibodies compared with a history of active infection in persons with inflammatory arthritis. The latter suggests that local muscle antigen expression following vaccination is not enough to mediate an AutoAbs response (94, 95). Whether increases in AutoAbs in PASC are due to the stimulation of pre-existing autoreactive AutoAbs, or whether their emergence is due to specific effects by SARS-CoV-2 antigens, is an ongoing area of investigation (10).

3.3. Persistent microbial translocation before and during PASC

Microbial (both bacterial and fungal) translocation (MT) refers to the passage of the commensal microbiota and/or microbiota byproducts from their primary site (predominately gut and lung) into the systemic circulation, thereby contributing to secondary infections or inflammation (96, 97). It is well established that intestinal microorganisms, microbial fragments (e.g., LPS or microbial DNA), and metabolites (e.g., short-chain fatty acids or fatty acid-binding protein) can cross the intestinal mucosal barrier and travel to the lung, where they impact the lung immune response (98). Simultaneously, ACE2 (angiotensin-converting enzyme 2; primary receptor for SARS-CoV-2) is highly expressed in the respiratory tract and the intestines. In fact, ACE2 is mainly found in human nasal epithelial cells and the colon (99), suggesting that large mucosal surfaces could be compromised by SARS-CoV-2 viremia and consequently resulted in long-term tissue injury and PASC. Indeed, gut-related symptoms and fecal shedding are early signs of acute SARS-CoV-2 infection (100, 101). In addition, SARS-CoV-2 antigen has been documented in the gut 4 months post-infection (40, 41). A recent multi-omics systems biology study reported that persons with severe COVID-19 showed high levels of plasma zonulin (a marker of tight junction permeability) and translocation of both bacterial and fungal products (i.e., LPS-binding protein [LBP] and β-glucan) into the blood (46). This change was strongly associated with increased MT-mediated inflammation markers (i.e., soluble CD14, myeloperoxidase), immune activation markers, and decreased markers of intestinal function (46). Several other studies substantiated a similar association between severe COVID-19 and microbial translocation to the blood (21, 102, 103). Recently, a direct association was found between elevated fungal translocation and PASC, highlighting sustained Dectin-1 interactions with myeloid cells and metabolic mediators as a potential contributor to immune activation and myeloid modulation during PASC (47).

As viral infections (e.g., human immunodeficiency virus type 1 (HIV-1) infection, hepatitis B virus, and hepatitis C), intestinal inflammatory conditions, aging, and substance use disorders can all impact pre-existing levels of microbial translocation (104-108), it is likely these factors also may impact the degree by which SARS-CoV-2 infection can alter gut barriers and sustained activation. When compared to persons without HIV, people living with HIV who have recovered from COVID-19 disease have a higher rate to develop PASC (odds ratio 4.01, p= 0.008)(109). Thus, just as gut microbiota alterations are linked to COVID-19 disease severity, the persistence of such alterations can also affect the gut microbiome ecology, potentially contributing to PASC (110, 111).

The study of long-term effects of SARS-CoV-2 infection on gut microbiota showed that persons with PASC exhibited gut microbiome compositions significantly different from uninfected controls 6 months after virus clearance (112). Persons without PASC had restored gut microbiota profiles equivalent to non-COVID-19 controls (112). The authors reported that persons with PASC had higher numbers of bacterial clusters of *Ruminococcus gnavus* and *Bacteroides vulgatus* and lower numbers of *Faecalibacterium prausnitzii*, *Collin-*

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sella aerofaciens, and *Blautia obeum* (112). Surprisingly, changes in the gut microbiota composition among persons with PASC enabled several opportunistic pathogen populations (e.g., *Clostridium innocuum* and *Actinomyces naeslundii*) to gain a foothold and weakened the anti-inflammatory bacterial population (e.g., butyrate-producing bacteria) associated with adverse secondary outcomes (i.e., fatigue, hair loss) (112). Of note, a separate study showed that alterations in gut microbiota composition did not return to normal after 6-months of recovery (113). Changes in the microbiota also may span beyond the gut. A recent study of persons with PASC reported alterations in oral microbiome (characterized by significant abundances of *Prevotella* and *Veillonella* species, when compared with persons with symptomatic COVID-19 (114). Interestingly, the oral microbiome composition found in persons with PASC was comparable to that in persons with chronic fatigue syndrome (114). Moreover, a metabolic pathways enrichment study also revealed that proinflammatory molecule synthesis (e.g., chorismite, colanic acid, nicotinamide adenine dinucleotide biosynthesis, O-antigen building block biosynthesis, phospholipid biosynthesis, deoxythymidine diphosphate-L-rhamnose, pyrimidine, and purine deoxyribonucleotides) was higher in individuals with PASC compared with those without. In contrast, anti-inflammatory molecule biosynthesis (such as polyisoprenoid biosynthesis, branched amino acids, tetrapyrrole, and farnesol) was lower (114).

Although relatively unexplored, fungal translocation is another area linked to PASC (47). Persons with PASC showed an increase in tight junction permeability (characterized by high serum concentration of zonulin) and plasma β-glucan, compared with individuals who did not have PASC or with SARS-CoV-2 negative controls (47). As expected, the increased levels of β-glucan were associated with high levels of inflammatory indicators (i.e., TNF, IL-6, and IP-10) in persons with PASC. In addition to causing persistent high levels of proinflammatory cytokines, microbial translocation during PASC may also contribute to organ injury and neurotoxicity by triggering metabolic dysregulations through the activation of N-Methyl-D-aspartate receptors (47, 115).

Taken together, long-term alterations in gut microbiota composition in persons with COVID-19, along with persistent MT-mediated immune activation, may contribute to both acute and chronic changes during an infection—changes that may persist/exacerbate the incidence and severity of PASC (**Figure 2**). It remains to be determined if targeting myeloid cell TLR- or Dectin-1-mediated proinflammatory responses, resulting from increased levels and compromised intestinal barriers, could impact PASC severity and/or recovery (33, 116, 117).

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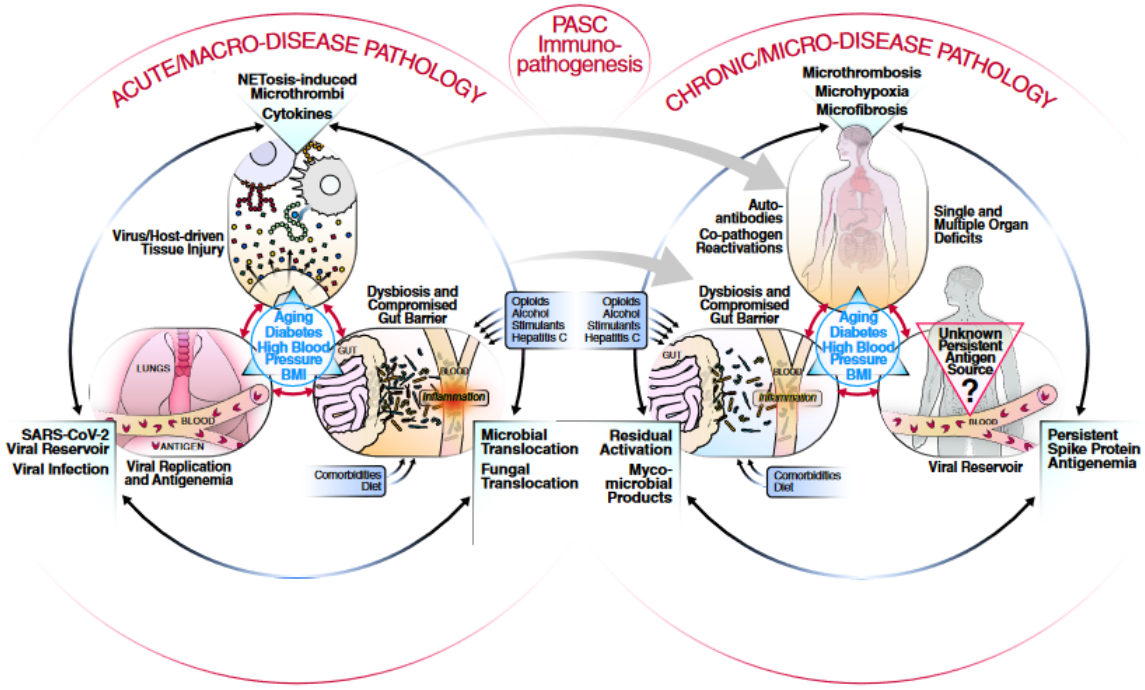

Figure 2. PASC immunopathogenesis model showing interactions between acute and chronic factors in sustaining immune activation and tissue injury. Conceptual model of observations associated with PASC after resolution of SARS-CoV-2 infection. The persistent immune activation in PASC, summarized in 1, is further illustrated here to show how acute tissue injury (driven by host responses against viral antigen and microbial translocation) occurs in active infection (left circle) and in organ dysfunction. Even mild disruptions, if chronically sustained (right circle), may result in tissue injury and PASC. The additive effects of co-morbidities in both acute and chronic mechanisms are also shown.

3.4. The undefined role of the leukocyte-fibroblast axis in tissue remodeling

Fibroblasts are located in the interstitium of all tissues and play a central role in tissue injury through various mechanisms, including activating TLR receptor expression, promoting inflammation, and contributing to the development of extracellular matrix (collagen). This leads to tissue re-modeling or fibrosis from immune activation and sustained levels of TGF-1 (118). Little is known about fibroblast activation during PASC, apart from its potential contribution to IL-33 production (pro-fibrotic cytokine). Its role in endothelial or epithelial cell transitions to mesenchymal cells is crucial to developing tissue fibrosis, vascular remodeling, and mucosal (lung/gut) compromised mucosal barriers, respectively (119-123).

Local and sustained activation of mucosal barriers likely causes epithelial cells in the gut to transition with fibroblasts through epithelial-to-mesenchymal transition (EMT). This transition results in higher production of fibrin and disruption of basal membranes (124). Similar changes occur at the vascular-bed level, where endothelial cells change to fibroblasts (endoMT). This results in a chronic activation of cardiac and renal endothelial cells, causing a shift to fibroblasts (125). Although persistent leukocyte activation (PMN or myeloid) and microthrombosis have the potential to result in tissue injury or compromise function via fibroblast-mediated tissue remodeling, this remains to be explored (119-123). It is clear, however, that SARS-CoV-2 infection has been linked to increases in profibrotic macrophages, which may reflect an attempt by the host to contain inflammation that ultimately results in tissue injury (43).

3.5. Persistence of dysregulated cytokines or soluble immune mediators

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Cytokine storm is a common feature of COVID-19 severity and is associated with respiratory malfunction, acute respiratory distress syndrome (ARDS), and undesirable clinical outcomes (11, 126). It was reported that cytokine levels (i.e., IL-2, IL-4, IL-6, IL-10, TNF, IFN-γ, and IL-17) remained elevated in persons at 2 weeks after recovery from acute COVID-19 symptoms (n=33) when compared with healthy donors (n=28) (64). A summary of data supporting high cytokine levels (especially IL-1β, IL-6 and TNF) (127) in PASC is shown in **Table 1**. Several reports have documented dysregulated cytokine levels. For example, a study of persons with COVID-19 at 6 months of recovery exhibited higher plasma levels of IL-17A, stem cell factor, IL-12p70, IL-1β, MIP-1β (macrophage inflammatory protein-1 beta), brain-derived neurotrophic factor, and vascular endothelial growth factor, compared with healthy controls (128). Because cytokine elevations and PASC can occur following sustained inflammatory states, anti-cytokine-based interventions during early PASC, which target persistent inflammation, may offer a therapeutic approach against long-term PASC symptoms. This is supported by a negative correlation between inflammatory markers (hsCRP, IL-6, TNF) and SARS-CoV-2 antibody levels, occurring early in PASC with peak VO_2 more than 1 year later (129). For example, IL-6 targeted therapy (e.g., tocilizumab and sarilumab) (130) likely improves outcomes in COVID-19 survivors by limiting events associated with sustained high levels of IL-6, such as fibrosis, edema, thrombocytosis, and anemia (131). Likewise, targeting proinflammatory cytokine such as IL-1β, IL-17, TNF, MCP-1, and IP-10, which are present in elevated levels for a short period (~ 2-3 months) after recovery, could help determine whether these cytokines cause other chronic inflammatory diseases such as encephalitis, dermatitis, and myocarditis (132-134). Finally, IFNs (type I and III) may be therapeutic targets, as they remain at high levels in post-acute periods nearly 8 months after recovery (2.44 to 7.92-fold compare to healthy control) (135, 136) and may have autoimmune consequences for survivors (137).

Table 1. Immunological studies of COVID-19 survivor.

No. of persons	Study time follow-up	Samples	Key findings: follow-up of post-recovered individuals	Reference
• HC: 44 • ACI[a]: N.D. • Post-Recovery[g]: 44 o PASC: N.D. o Non-PASC: N.D.	1 month (approx.)	PBMC	• Activated CD8 T cells increased than HC • Total counts of B, T, and NK cells and their subsets did not differ significantly compared to HCs	(159)
• HC: 16 • ACI: 19 • Post-Recovery: 19 o PASC: N.D. Non-PASC: N.D.	1 month (approx.)	Serum and PBMC	• The levels of cytokines (IL17A, IFNα, IFNγ, IL1β, TNF, IL-4, IL-8) were higher than in HCs • The concentration of TNF, IL-4, IL-8, and IFNγ were higher and IL-6, GCSF, IL-7, IL-10, and IP-10 were lower than ACIs • Almost 25% of post-recovered persons with COVID-19 exhibited AutoAbs in serum (anti-cardiolipin,	(160)

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			anti-rheumatoid factor, anti-IFNα, anti-thyroid peroxidase)	
• HC: 10 • ACI: 37 • Post-Recovery: 50 o PASC: N.D. o Non-PASC: N.D.	1.5 months (approx.)	PBMC	• Decreased NKT and Vδ2 T cells than HC • Increased neutrophils, non-classical monocytes, and hyperactivated CD8 T cells than ACI • Elevated proinflammatory cytokines (HGF, VEGFA, and TNF) than HC	(161)
• HC: 10 • ACI: 11 • Post-Recovery: 74 o PASC: N.D. o Non-PASC: N.D.	2 months	PBMC and serum	• Sustained/reduced levels of granulocytes, CD4 T cells, CD8 T cells, regulatory T cells, and B cells than HC • Sustained/higher levels of Th2, Th9, Th17, NKT cells than HC	(53)
• HC: 27 • ACI: 2 • Post-Recovery: 49 o PASC: N.D. o Non-PASC: N.D.	> 3 months	PBMC	• Significantly decreased invariant NKT and NKT-like cells than HC • Increased Tregs number than HC • Increased expression of TIM-3, Ki-67 on CD4 T cells and CD8 T cells than HC • Significantly decreased T cell and NKT-like cell cytotoxic potential than HC • No significant differences in absolute numbers and frequencies of total T cells, $CD8^+$ T cells, B cells, NK cells, and monocytes than HC	(162)
• HC: 98 • ACI: N.D. • Post-Recovery: 109 o PASC: N.D. o Non-PASC: N.D.	2.5 months	PBMC	• Tregs significantly reduced • Lower neutrophil count • Higher expression of HLA-DR and CD38 on $CD3^+$ T cells.	(163)
• HC^b: 11 • ACI: N.D. • Post-Recovery: 22 o PASC: N.D. o Non-PASC: N.D.	SCR: 1-3 months LCR: 6-9 months	Serum and PBMC	• Among SCR: o High level of CRP, TNF, and IL-6 o Higher expression of monocytic activation	(50)

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			marker and leukocyte migratory marker o Expansion of Tregs, central memory CD4 T cells ($CD45RA^{-}CCR7^{+}$), terminally differentiated CD8 T cells ($CD45RA^{+}CCR7^{-}CD57^{+}CD28^{-}$) o Decreased in NK cells count • Among LCR: o Sustained/high CRP o Most of the SCR abnormalities resolved o Lower ratio of myeloid to lymphoid cells	
• HC: 5 • ACI: N.D. • Post-Recovery: 10 o PASC: N.D. o Non-PASC: N.D.	3 months	PBMC	• High $TBET^{hi}$ $CD16^{+}$ and $IRF1^{hi}$ $CD14^{+}$ monocytes • Increased effector and memory CD8 T cells • Enhanced chromatin accessibility of inflammatory cytokine genes (IL-1β, IL-6, IL-8, CCL2, CCL3, and CCL7).	(164)
• HC^{c}: 8 • ACI: N.D. • Post-Recovery^{c}: 5 o PASC: N.D. o Non-PASC: N.D.	3 months	PBMC and Umbilical cord blood	• Increased Plasma B cells, Tc2, Tfh17, memory B cells, virus-specific T cells. • Decreased naïve B cells, IL-1ra, MCP-1 • Increased $CD68^{+}$ macrophage infiltration in placenta	(165)
• HC: 5 • ACI: 3 • Post-Recovery: 3 o PASC: N.D. o Non-PASC: N.D.	3 months	PBMC	• Did not restore B cells and CD4 T cell counts • Increased CD8 T cells count • CD4 and CD8 T cells expressing T-bet and Granzyme B remained increased	(166)
• HC: N.D. • ACI: 19 • Post-Recovery: 43 o PASC: N.D. o Non-PASC: N.D.	3 months	Serum	• Increased TNF and IL-6 in persons after recovery of COVID-19 • Increased expression of leukocyte migration markers (i.e., CXCR6, CD31/PECAM, VLA-4, and LFA-1) on monocytes	(49)

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• HC: 50 • ACI: N.D. • Post-Recovery: o PASC: 111 o Non-PASC: 56	3 months	Plasma	• Increased fungal translocation marker i.e., β-glucan, and zonulin. • Increased TNF, IL-6, and IP-10 • Activated Dectin-1/Syk/NF-κB signaling • Activated tryptophan catabolism pathway	(47)
• HC: 45 • ACI: N.D. • Post-Recovery: 207 o PASC: N.D. o Non-PASC: N.D.	3 months	Plasma and PBMC	• Sustained/high levels of IL-6, TNF, IL-10, and IL-1β • Reduced mDCs, non-classical and intermediate monocytes, NK cells, MAIT cells, CD4 T cells, γδT cell, CD8 T cells, naive and memory B cells • Prominent late OXPHOS signature • Recovery of cellular immune abnormalities varied with disease severity	(75)
• HC: 30 • ACI: 106 • Post-Recovery: 55 o PASC: N.D. o Non-PASC: N.D.	4 months	Plasma	• NET marker[d] in in persons after recovery of COVID-19 resolved to basal level, similar to HCs	(37)
• HC: 40 • ACI: N.D. • Post-Recovery: 111 o SCR: 40 o LCR: 71 o PASC: N.D. o Non-PASC: N.D.	SCR: 2 months (approx.) LCR: 3.5 months (approx..)	PBMC	• Among SCR: o Sustained/high levels of intermediate monocytes, effector CD8, activated CD4 and CD8 T cells o Sustained/low levels of naïve $CD4^+$ and $CD8^+$ T cells. • Among LCR: o Sustained/high CD8 T cells o Resolved abnormalities in intermediate monocytes, effector CD8, activated CD4, and naïve CD4 and CD8 T cells. o Persons >60 years: ▪ Reduced naïve CD4 and CD8 T cells ▪ Sustained/high CD4 T cells	(76)

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• HC: 52 • ACI: N.D. • Post-Recovery: 115 o SCR: 58 o LCR: 57 o PASC: N.D. o Non-PASC: N.D.	SCR: 1-2 months (approx.) LCR: 5-6 months (approx.)	PBMC	• Among SCR: o High effector CD8 T cells and effector memory CD8 T cells o Low naïve T cells, central memory T cells • Among LCR: o Low Th1, Tfh, PD-1$^+$ CD4 T cells, IFN-γ producing T cells o High Tc17 and IL-2-secreting T cells o Sustained virus-specific T cell responses for 6 months	(78)
• HC: 36 • ACI: N.D. • Post-Recovery: 68 o PASC: N.D. o Non-PASC: N.D.	5 months	PBMC	• Persistent upregulation/expression of CCL2, CCL8, and CCL7 on monocyte-derived macrophages • Increased amounts of inflammatory metabolites (i.e., 5-lipoxygenase-derived leukotrienes)	(55)
• HC: 82 • ACI: 92 • Post-Recovery: 204 o PASC: N.D. o Non-PASC: N.D.	5 months (approx.)	Serum and PBMC	• Decreased virus-specific humoral immune response • Significantly increased absolute number of CD3$^+$ T cells, γδ T cells, NK cells • Decreased and heterogenous T cells	(167)
• HC: 30 • ACI: 46 • Post-Recovery: 260 o PASC: N.D. o Non-PASC: N.D.	~ 6 months	Serum and Plasma	• Sustained/high levels of absolute number of total monocytes, frequencies of intermediate and non-classical monocytes after 3 months. • Decreased frequencies and number of classical monocytes after 5 months • Decreased plasma sCD14, CRP, sCD163 and soluble Tissue Factor after 6 months	(48)
• HC: 45 • ACI: 131 • Post-Recovery: 52 o PASC: N.D.	6 months	PBMC	• Decreased intermediate monocytes compared with ACCs; but sustained/high levels compared with HC	(51)

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o Non-PASC: N.D.			• Decreased expression of CD16, CD33, and CD11b on monocytes compared with ACCs • Increased expression of CCR2, CCR5, CD86 and HLA-DR on monocytes in upregulated compared with ACCs • Decreased levels of CXCL10 • Increased genes expression of BCL6, AREG and IL-10	
• HC: N.D. • ACI: N.D. • Post-Recovery: 50 o PASC: N.D. o Non-PASC: N.D.	6 months	PBMC	• Sustained/high numbers of $CD3^+$ cells, CD4 T cells, CD8 T cells, B cells, and NK cells	(67)
• HC: 14 • ACI: N.D. • Post-Recovery: 69 o PASC: N.D. o Non-PASC: N.D.	6 months	PBMC	• Stable anti-S protein and anti-RBD IgG responses • Sustained/high NK cells, granulocytes, LD neutrophils, and tissue-homing $CXCR3^+$ monocytes • No significant difference in total Treg count • Sustained transcriptional dysregulation, including multiple platelets, cell cycle, and immune-related blood transcriptional modules	(68)
• HC: N.D. • ACI: N.D. • Post-Recovery: 100 o PASC: N.D. Non-PASC: N.D.	6 months	PBMC	• Sustained cellular immune response after 6 months • Significantly increased $IL\text{-}2^+$ CD4 subset • Ratio of CD4 T cells to CD8 effector cells was 2:1 • Decreased IL-10, IL-4, and TNF expression on virus-specific T cells • Increased IL-2 expression on virus-specific T cells • Decreased relative proportion of Th1 ($IFN\gamma^+$ $CD4^+$) cells	(168)

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			• Sustained/high virus-specific T cell responses against N and M proteins after 6 months	
• HC: 38 • ACI: 58 • Post-Recovery: 83 o PASC: N.D. o Non-PASC: N.D.	6 months	PBMC	• Increased CD8 T cell proportions • Increased production of type 1 cytokines (IFNγ, TNF), and IL-17 from T cells • Restored B cells changes after 6 months	(169)
• HC: 27 • ACI: 33 • Post-Recovery: 38 o PASC: N.D. o Non-PASC: N.D.	7 months	PBMC	• Sustained/low number of $CD1c^+$ myeloid DCs and pDCs Sustained abnormal DC activation markers expressions on pDCs or mDCs (e.g., integrin β7, indoleamine 2,3-dioxygenase, and CCR7)	(60)
• HC: 119 • ACI: n • Post-Recovery: 88 o PASC: N.D. o Non-PASC: N.D.	8 months	Serum and PBMC	• Stable RBD- and S-specific IgG levels after 6 months • Sustained/stable memory B and T cell responses at least 6–8 months after infection • Sustained/stable NAbs up to 91–180 days post-infection, but significant decreases at 181–240 days • Virus-specific IL-2 and/or IFNγ–producing cells are maintained for 6-8 months.	(170)
• HC: 10 • ACI: N.D. • Post-Recovery: 47 o SCR: N.D. o LCR: N.D. o PASC: N.D. o Non-PASC: N.D.	SCR: 2 months LCR: 8 months	Plasma	• Among SCR: o Restored intermediate monocytes and NK cells to healthy basal levels o Sustained COVID-19's skewed Th1 and Th2 cell response • Among LCR: o Resolved non-classical monocytes and $CD11b^-$ granulocytes to healthy basal levels o Deceased levels of total B cells	(52)

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			○ Sustained/low levels of $CD8^+$ Tregs and changes in the NKT cell	
• HC: 71 • ACI: N.D. • Post-Recovery: 62 ○ PASC: 31 ○ Non-PASC: 31	3 months, 8 months	Serum and PBMC	• Sustained/increased innate immune cells (e.g., $CD38^+HLA\text{-}DR^+$ myeloid cells, $CD14^+CD16^+$ monocytes, $CD86^+$ $CD38^+$ pDC) after 8 months. • Reduced naive T and B cells • Sustained/high levels of IFNβ, IFNλ1, IFNγ, CXCL9, IP-10, IL-8, and sTIM-3 after 8 months.	(135)
• HC: 20 • ACI: N.D. • Post-Recovery: 41 ○ SCR: N.D. ○ LCR: N.D. ○ PASC: N.D. ○ Non-PASC: N.D.	SCR: 1.3 months LCR: 8 months	Serum and PBMC	• Among SCR: ○ The relative proportions of circulating CD4 T cells, central memory CD4 and CD8 T cells decreased ○ The relative proportions of circulating CD8 T cells increased ○ Expression of PD-1 decreased on both CD4 and CD8 T cells • Among LCR: ○ The relative proportions of circulating CD4 T cells and CD8 T cells normalized ○ The relative proportions of SARS-CoV-2 antigen specific CD4 T cells and central memory CD4 and CD8 T cells decreased ○ Expression of PD-1 decreased on both CD4 and CD8 T cells	(74)
• HC: 38 • ACI: 72 • Post-Recovery: 147 ○ PASC: N.D. ○ Non-PASC: N.D.	2-9 months	Serum	• Sustained/high expression of CXCR6 and PSGL1 on monocytes Sustained/low expression of Cyclo-oxygenase 2 on monocytes	(171)

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• HC: N.D. • ACI[e]: 70 • Post-Recovery: o SCR: 65 ▪ PASC: 35 ▪ Non-PASC: 30 o LCR: 70	SCR: 4 months LCR: 8.9 months	PMBC, plasma, serum, and saliva	• Among SCR: o Low CD8 T cell responses o High IP-10 o Low frequency of degranulating virus-specific CD8 T cells in individuals with PASC • Among LCR: o Stable virus-specific T cells response o High N-protein specific non-naive (memory) CD4 and CD8 T cell responses	(80)
• HC[f]: 100 and (8) • ACI[f]: 33 (12) • Post-Recovery: 33 o PASC[f]: 33 (12) o Non-PASC: N.D.	7-11 months	Serum and PBMC	• Sustained/high levels of IFNα, TNF, G-CSF, IL-17A, IL-6, IL-1β, and IL-13, • Decreased IP-10 • Sustained/high levels of Th9, CD8 effector T cells, naive B cells, and CD4 effector memory T cells • Higher frequency of β2GP1 (anti-β2 glycoprotein-1) IgM autoantibodies Increased levels of IgG anti-SARS-CoV-2 S1 antibodies	(73)
• HC: 30 • ACI: 72 • Post-Recovery: 171 o PASC: N.D. o Non-PASC: N.D.	4-6 months 7-8 months 9-11 months	Serum and PBMC	• Positive NP-, RBD-, S1-, and NP-S1-specific IgA, IgM, and IgG antibodies in most persons 4-11 months after the onset of illness • Sustained lymphopenic condition for 4~6 months; after 7~8 months, returned to control levels • Decreased IL-4 levels within 7~8 months • Decreased number of $CD3^+$ T cells, CD8 T cells, B cells, and NK cells after 9~11 months • Almost 71.4% of persons with PASC maintained NAbs after 9~11 months. • Increased IL-4 levels within 9~11 months	(66)

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			• Sustained/high levels of IL-8, IL-5, IL-6, and IL-1β levels persisted at 11 months	
• HC: 29 • ACI: 38 • Post-Recovery: 38 o PASC: 38 ▪ SCR: 38 ▪ LCR:3 o Non-PASC: N.D.	SCR: 3-6 months LCR: 12 months	Blood and Bronchoalveolar Lavage	• In airways: o Increased macrophages, T cells, and B cells o Decreased monocytes and neutrophils o Enriched immunoproteomic profiles (i.e., enrichment of 22 proteins) o Increased cytotoxic CD8 T cell frequencies o Higher CXCL10 and CXCL11 • In blood: o Low numbers of NK and NKT cells o No significant changes in immunoproteomic profile	(79)
• HC: 29 • ACI: 51 • Post-Recovery: 64 o PASC: 64 o Non-PASC: N.D.	15 months	PBMC	• Significantly high levels of intermediate and non-classical monocytes • Contained SARS-CoV-2 S1 protein among non-classical monocytes	(54)

AREG: Amphiregulin; Bcl6: B-cell lymphoma 6; AutoAbs: autoantibodies; CRP: C-reactive protein; E-protein: Envelope protein; ERS: early recovery stage; HC: Healthy Control; HGF: hepatocyte growth factor; LCR: long-time follow up; LRS: late recovery stage; mDCs: myeloid DC; M-protein: Membrane Protein; N.D.: Not determined; N-protein: Nucleocapsid Protein; OXPHOS: oxidative phosphorylation; PBMC: peripheral blood mononuclear cells; pDCs: plasmacytoid DC; POS: post-onset of symptoms; PSGL1: P-selectin glycoprotein ligand-1; SCR: short-time follow up; S-protein: Spike protein; VEGFA: vascular endothelial growth factor A.
[a]ACI (Active COVID-19 Infection): includes acute, severe, hospitalized, and non-hospitalized active cases (i.e.: Nucleic acid tests positive).
[b]Recovered from other mild respiratory infections.
[c]Pregnant Women.
[d]NET marker: citrullinated histone H3, cell-free DNA, neutrophil elastase.
[e]First study visit.
[f]n for autoimmune comparison and n for immunological assessment (in parentheses).
[g] Post-recovery: Persons having recovered after COVID-19.

Among immune mediators, a reduced cortisol level was strongly correlated with PASC (84). Low cortisol levels during COVID-19 have been linked with pulmonary PASC symptoms (10). However, documented long-term hypocortisolism, more than 1 year after infection, raises the possibility that this condition may also account for PASC symptoms, as low cortisol levels are common in persons with encephalomyelistic/chronic fatigue syndrome (138). Adrenal tissue injury and insufficiency likely can be ruled out in PASC, because ACTH levels remain normal (84). However, it remains to be determined if glucocorticoid replacement can have a role in future PASC therapy strategies, as suggested by

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a case-control observational study on persons with PASC receiving oral dexamethasone during hospitalization reported fewer symptoms (n=73, 1.9 per person) than untreated persons (n=152, 3.2 per person) with PASC eight months after recovering from COVID-19 (139).

4. Closing Remarks

PASC-associated pathologies can be linked to several potential pathways. Persistent i) antigenemia, ii) lymphopenia, iii) activation of $CD8^+$ T cells, iv) increased cytokines in the bloodstream, v) autoantibodies, vi) the potential for persistent microbial translocation, vii) the potential role of leukocyte activation driven fibrosis as a tissue remodeling mechanism, and viii) the persistence of dysregulated monocytes. Immune-mediated tissue injury mechanisms during PASC have centered on thrombosis, coagulopathy, and tissue fibrosis, resulting from acute and sustained leukocyte-fibroblast activation mechanisms. To date, the dominant mechanism underlying each specific presentation of PASC remains elusive. However, we posit that the degree of macro-level tissue injury during acute infection or micro-level effects from sustained antigen expression and tissue immune activation after a resolution could be driving these PASC outcomes. In both cases, data suggest that the host's response to persistent antigen (38-41) and/or chronic activation are central determinants in the immunopathology of PASC. Tissue injury during COVID infection that results in organ NETinjury, microthrombosis, and fibrosis, along with subsequent organ dysfunction, could help explain why stubborn symptoms continue to persist. Furthermore, long-term antigenemia, sustained fungal translocation, and cytokine-mediated activation may sustain micro-level tissue injuries, leading to new symptoms as PASC progresses. For example, the premise that long-term cytokine activation, resulting from persistent intestinal injury and microbial translocation, is linked with multi-organ pathology outcomes has already been established in other diseases such as endotoxemia, AIDS-associated dementia, AIDS-associated osteopenia, HCV-related cirrhosis, and pancreatitis (115, 140-143). Promoting a fast recovery from these immunological imbalances after SARS-CoV-2 infection resolves or early in PASC, could be crucial to disrupting the foundational steps that lead to long-term PASC outcomes. Indeed, recent studies indicate that SARS-CoV-2 vaccination associated with a faster recovery can reduce the incidence of PASC (144-146). Likewise, the early use of antivirals might also be used to prevent PASC, given the relationship between high SARS-CoV-2 RNAemia and PASC (147).

Here we have identified some potential common themes and possible research directions to explore the connection between leukocyte biology and PASC in adults. However, it is essential to note that this interpretation may oversimplify PASC conditions. The studies summarized here include several distinct mechanisms, depending on the organ system affected, the specific individuals' PASC immune profiles (148, 149), and whether the studies focused on unique organ systems, such as neurologic or pulmonary PASC (150, 151). For example, neurologic PASC was associated with high levels of glial fibrillary acidic but not neurofilament light chain proteins, together with increases in more general activation markers (i.e., TNF, IL-6, MCP-1) (150). Disease severity and hospitalization/ventilation typically are used as criteria for defining PASC, as reported by the RECOVER Consortium. However, it remains to be determined if immune modulation and leukocyte changes contribute to PASC outcomes in other ways. Those outcomes may be impacted by risk factors that lead to PASC, such as co-occurring depression, chronic lung disease, and obesity, as well as factors that could protect against PASC, such as younger age, male sex, non-Hispanic black race, substance abuse, cardiomyopathy, psychosis, and dementia (152). Current efforts examining larger and more diverse populations should give us a better understanding of PASC than the studies summarized here. For example, the immunopathology of pediatric PASC has not been thoroughly investigated (153, 154). Likewise, it remains to be determined whether emerging variants of concern will result in a different or similar incidence of PASC outcomes as a recent report indicates a lower PASC incidence following Omicron infection (155). A lower incidence of PASC following Omicron infection is

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also suggested in breakthrough infections in vaccinated persons(156). Specifically, although vaccination can reduce (15%-50%) but not completely prevent the risk of developing PASC (144, 146), breakthrough Omicron infections in vaccinated persons are reported to be half as likely to result in PASC when compared with the delta variant (4.5% vs. 10.8%)(156).

Given the heterogeneity of PASC, it will be essential to determine what causes each type of clinical PASC presentation, from short- (<6 months) to long-term symptoms. For example, specific PASC presentations may depend on a selective interaction between a pathogen (viral isolate), host (e.g., HLA, epigenetics, pre-existing comorbidities, age [adult vs. pediatric], etc.), predominant immunopathology mechanisms (e.g., microthrombosis, intestinal leakage, fibrosis, autoimmune, etc.), and sociodemographic factors (e.g., food security, access to medical care). The emergence of potential animal models centered on PASC mechanisms of disease may aid in developing novel therapeutic strategies (157, 158). More significant advances in these areas may lead to treatments to target common pathogenic processes of PASC as well as specific organ-targeted and/or precision-medicine treatment strategies to alleviate specific PASC symptoms (34).

Authorship

M.S.I., Z.W., M.A.M., X.C., and L.J.M. wrote the manuscript. M.S.I and Z.W. contributed equally to this work. L.J.M. created figures. X.C., and L.J.M. conceptualized, revised, and supervised the manuscript.

Disclosure

The authors declare no conflicts of interest.

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