Review article

Autoimmunity in long COVID

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Long COVID (also termed postacute sequelae of SARS-CoV-2, or PASC) affects up to 10% of people recovering from infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Diagnosis is hampered by diffuse symptomatology, lack of biomarkers, incomplete understanding of pathogenesis, and lack of validated treatments. In terms of pathogenesis, hypothesized causes include virus persistence, the legacy of endotheliitis and thrombosis, low-grade tissue-based inflammation and/or scarring, perturbation of the host virome/microbiome, or triggering of autoimmunity. Several studies show preexisting and/or *de novo* production of autoantibodies after infection with SARS-CoV-2, but the persistence of these antibodies and their role in causing long COVID is debated. Here, we review the mechanisms through which autoimmune responses can arise during and after viral infection, focusing on the evidence for B-cell dysregulation and autoantibody production in acute and long COVID. (J Allergy Clin Immunol 2025;155:1082-94.)

Key words: *Long COVID, autoimmunity, B-cell dysregulation, autoantibodies*

Abbreviations used

ANA:	Antinuclear antibody
aPL:	Antiphospholipid
CCL:	Chemokine C-C motif ligand
COVID-19:	Coronavirus disease 2019
CXCL:	C-X-C motif chemokine ligand
EBV:	Epstein-Barr virus
ENA:	Extractable nuclear antigen antibody
GPCR:	G protein–coupled receptor
IFN-I:	Type I interferon
LCMV:	Lymphocytic choriomeningitis virus
ME/CFS:	Encephalomyelitis/chronic fatigue syndrome
MS:	Multiple sclerosis
NET:	Neutrophil extracellular trap
PASC:	Postacute sequelae of SARS-CoV-2
REAP:	Rapid extracellular antigen profiling
SARS-CoV-2:	Severe acute respiratory syndrome coronavirus 2
SLE:	Systemic lupus erythematosus

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the coronavirus disease 2019 (COVID-19) pandemic, resulting in more than 14 million deaths worldwide.[1] The continued emergence of new variants with enhanced transmission or immune escape has resulted in further waves of infection. Although most individuals recover quickly after a mild infection, the burden of the pandemic is still evident, as over 65 million people globally suffer from persistent symptoms. The definition of long COVID or postacute sequelae of SARS-CoV-2 (PASC) is yet to be established, although recent proposals are approaching a consensus (Table I).[2-4] The definitions require new-onset symptoms, typically diverse but commonly including breathlessness, brain fog, dysautonomia, and fatigue. Over 200 symptoms have been described.[5]

The estimated prevalence of long COVID can vary depending on study design and target populations. For example, 2 recent studies aimed at studying the prevalence of long COVID in the Scottish adult population reported estimates from 1.7% to 10.4%, respectively.[6,7] Another meta-analysis estimated that 45% of individuals have at least one unresolved symptom, regardless of hospitalization status.[8] Although the number of individuals with long COVID is striking, the phenomenon of postacute viral syndromes is also seen with other infections, including Ebola,[9-11] Epstein-Barr virus (EBV),[12] dengue,[13,14] and severe acute respiratory syndrome.[15] The underlying pathophysiology of these conditions remains poorly understood; however, one hypothesized mechanism is the development of autoimmunity.[16]

Here we review the interplay between viruses and autoimmunity, with a particular focus on the potential role of autoantibodies in acute COVID-19 and long COVID. Additionally, we discuss the importance of measuring tissue-specific immunity and the advances in this field so far.

MECHANISMS THROUGH WHICH VIRAL INFECTIONS CAN TRIGGER AUTOIMMUNITY

Autoimmunity is a result of dysregulated immune responses to self-antigens, which can manifest into chronic autoimmune conditions (Fig 1). Although the mechanisms through which a breakdown in tolerance occurs remain mostly unknown, factors such as sex, age, and infection history can predispose an individual to autoimmunity.[17] A common feature of autoimmune disease is the presence of autoantibodies, which can cause damage through a range of mechanisms (Fig 1).

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TABLE I. Key definitions of long COVID

Characteristic	NICE (2022)	WHO (2022)	NASEM (2024)
Definition	"Long COVID is a multi-system condition with a range of debilitating symptoms—signs and symptoms continue or develop after acute COVID-19, continue for more than 4 weeks, and are not explained by an alternative diagnosis."	"It is defined as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation."	"Long Covid is an infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems."
Key features	Defines long COVID as a multisystem condition lasting for at least 4 weeks.	Requires positive identification of SARS-CoV-2 infection.	Defines long COVID as infection-associated chronic condition affecting single or multiple organs, regardless of initial severity.

Definitions are from National Institute for Health and Care Excellence (NICE, 2022),[2] World Health Organization (WHO, 2022),[3] and National Academies of Sciences, Engineering, and Medicine (NASEM, 2024).[4]

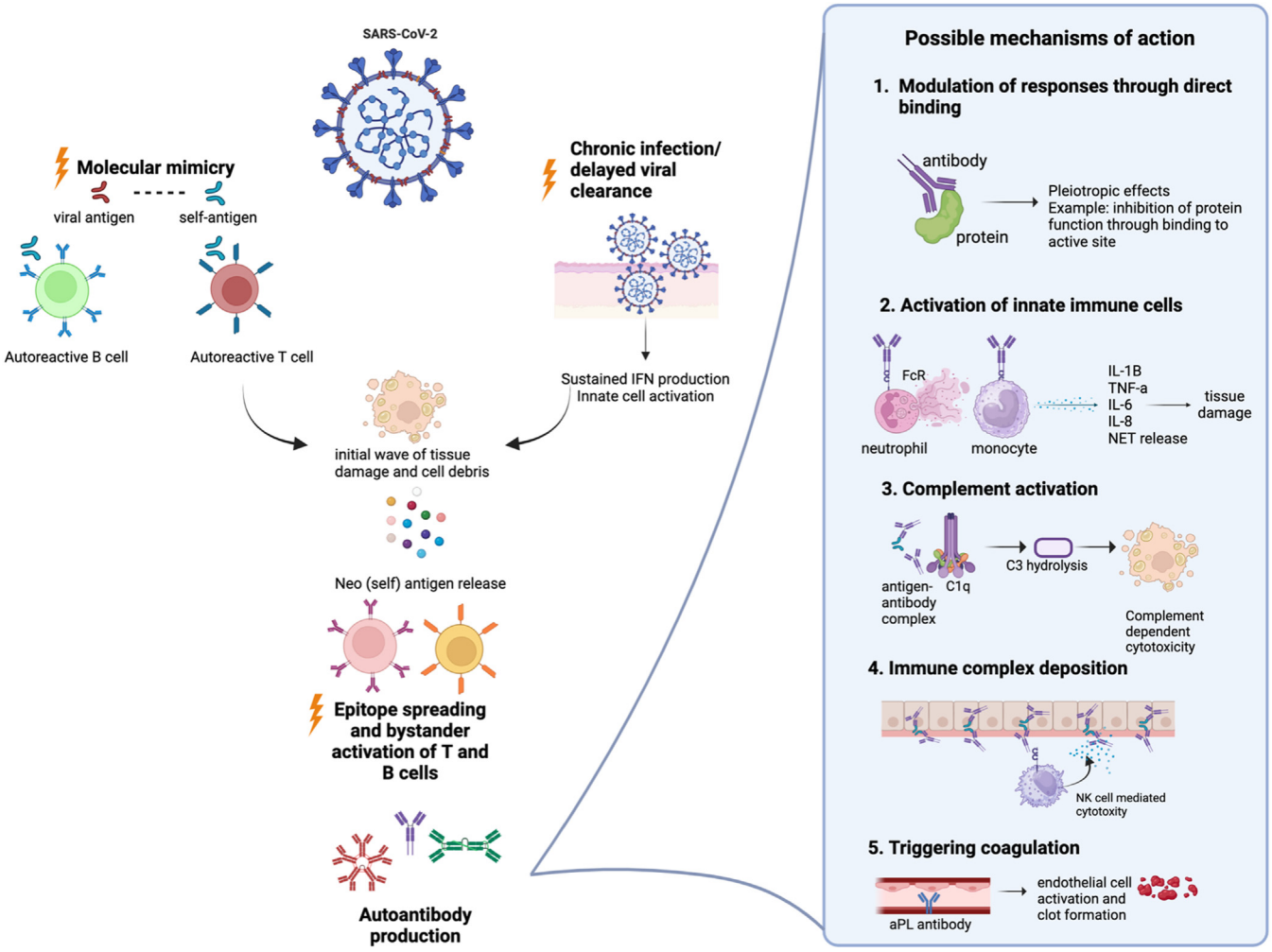


FIG 1. Autoimmunity after virus challenge. Infection with virus (here, SARS-CoV-2) can result in tissue damage and neoantigen release through direct molecular mimicry with self-antigen and/or sustained interferon production. This can then lead to activation of bystander T and B cells and autoantibody production, triggering a loop of autoimmune responses and further tissue damage. *1,* Direct binding of autoantibodies to different sites on a protein can exhibit varying effects on function (eg, prevent binding to target receptor/ligand). *2,* Fc receptor engagement on immune cells such as neutrophils and monocytes can trigger cytokine and NET release, potentially contributing to surrounding tissue damage. *3,* Autoantibody–antigen immune complexes can trigger the classical complement pathway, leading to C3 hydrolysis and complement deposition/cytotoxicity. *4,* Immune complex deposition in tissue can trigger antibody-mediated cellular cytotoxicity. *5,* Specific autoantibodies such as those specific to phospholipids can induce endothelial cell activation, facilitating vascular thrombosis. Created with BioRender.com.

TABLE II. Key studies characterizing autoantibodies in acute COVID-19 and long COVID

Study	Acute COVID-19/ long COVID	Methodology	Key findings	Relevant concepts
Bastard, Science, 2020[37]	Severe acute COVID-19	ELISA, magnetic particle–based assay, autoantibody functionality (blocking assays)	10.2% of patients with severe COVID-19 had neutralizing anti-IFN IgG autoantibodies, relative to 0.33% of healthy prepandemic individuals. These autoantibodies were present before infection.	Preexisting autoantibodies
Briquez, Sci Adv, 2022[38]	Severe acute COVID-19	ELISA	63% of cohort had anti-AngII autoantibodies relative to 1.7% of controls. Cross-binding of anti-AngII antibodies to RBD and Spike.	Molecular mimicry
Jernbom, Nat Commun, 2024[39]	Mild and severe COVID-19, neurologic long COVID	Proteome wide planar and bead assays	New-onset autoantibodies were found in 55% of individuals, which persisted up to 12 months. These autoantibodies were associated with neurologic symptoms after COVID-19 and shared epitopes with Spike protein.	*De novo* autoantibodies, molecular mimicry
Wang, Nature, 2021[40]	Severe and mild/ asymptomatic COVID-19	REAP; 2770 autoantibodies measured	Increase in autoantibody reactivity in severe COVID-19 patients relative to mild/uninfected controls. Immune targeting autoantibodies were functional and increased disease burden in mouse model of long COVID.	Broad autoantibody production, general breakdown in tolerance
Woodruff, Nature, 2022[41]	Mild and severe COVID-19	Single B-cell repertoire analysis, Luminex	Patients with severe COVID-19 had expanded naïve-derived, low-mutation IgG_1 population of antibody-secreting cells. Some overlap between autoreactive and antiviral clones.	Extrafollicular B-cell activation
Shi, Arthritis Rheum, 2022[42]	Severe COVID-19	ELISA	Surface expression of cell adhesion molecules on human endothelial cells was increased when cultured with plasma from severe COVID-19 patients, relative to controls and non–COVID-19 sepsis patients.	Endothelial dysfunction and clotting
Woodruff, Nat Commun, 2023[43]	Long COVID	Proteomics screening and machine learning	Subset of "inflong COVID" group demonstrated sustained ANA reactivity and active B-cell profiles, and was not distinguishable based solely on typical inflammatory mediators.	Sustained B-cell activation and autoantibody production
Su, Cell, 2022[44]	Long COVID	ELISA	Patients with autoantibodies at long COVID time point showed class-switched antibodies at diagnosis, suggesting their preexisting nature. Specific clinical autoantibodies correlated with distinct long COVID entities.	Preexisting autoantibodies, early determinants of long COVID
Klein, Nature, 2023[45]	Long COVID	REAP, 6000 autoantibodies measured	Individual autoantibodies were identified, but no significant differences were noted in number of autoreactivities observed between long COVID patients versus recovered controls.	No evidence of autoantibodies in long COVID
Muri, Nat Immunol, 2023[46]	Long COVID	ELISA	Anti-CXCL13, anti-CCL21, and anti-CXCL16 correlate with a lower likelihood of developing long COVID.	Protective role for autoantibodies

(Continued)

TABLE II. *(Continued)*

Study	Acute COVID-19/ long COVID	Methodology	Key findings	Relevant concepts
Son, Eur Respir J, 2023[47]	Long COVID	Microarray autoantibody profiling	Persistent positive ANA titers were associated with dyspnea, fatigue, and cough severity. Anti-La/SSB and anti–U1-SnRNP levels positively correlated with fatigue and dyspnea.	Specific autoantibodies correlating with long COVID symptoms
Wallukat, J Transl Autoimmun, 2021[48]	Long COVID	Cardiomyocyte-based cellular bioassay	Anti-GPCR individuals found in all individuals with primarily neurologic symptoms, with both agonistic and antagonistic effects.	Specific autoantibodies correlating with long COVID symptoms
Chen, bioRxiv, 2024[49]	Long COVID	MSD, Olink, mouse IgG transfer model	Mice injected with IgG from individuals with long COVID replicated some neurologic symptoms.	Specific autoantibodies correlating with long COVID symptoms
Santos Guedes de Sa, medRxiv, 2024[50]	Long COVID	Microarray screening and mouse IgG transfer model	Plasma from long COVID patients showed increased reactivity to neural antigens. Transfer of IgG from long COVID group replicated some neurologic symptoms in mice.	Specific autoantibodies correlating with long COVID symptoms

AngII, Angiotensin II; *MSD,* Meso-Scale Discovery (www.mesoscale.com); *RBD*, receptor-binding domain.

Molecular mimicry

Molecular mimicry between viral and self-antigens is one of the mechanisms through which autoimmune responses can arise. This occurs when there is structural similarity between self and foreign antigens, directing the production of autoantibodies. The best-documented examples of this phenomenon are multiple sclerosis (MS) and EBV infection, where cross-reactive T cells in MS patients recognize both myelin basic protein and EBV nuclear antigen 1,[18,19] leading to the production of anti–myelin basic protein autoantibodies.[20] Individuals with an EBV infection are 30 times more likely to develop MS.[21] Another example is Guillain-Barré syndrome; a subtype of the disease is linked to recent *Campylobacter jejuni* infection.[22]

Although there is convincing evidence for molecular mimicry using *in vitro* and *in vivo* models, it is unlikely that this mechanism acts in isolation. Indeed, the rate of autoimmunity would be far higher if molecular mimicry alone led to an autoimmune response every time.[23] Additional factors such as host MHC restriction (eg, HLA-DRB1*15:01 is associated with EBV-linked development of MS[24]) and the presence of secondary inflammatory signals are essential for the development of autoimmunity.

Epitope spreading

Epitope spreading occurs when immune responses develop to additional epitopes or proteins that are secondary to the original antigen. Epitope spreading can occur dependently or independently of molecular mimicry, with the initial autoimmune response triggered by the recognition of a similar antigen or because of damage during antiviral immune responses, respectively.[25] A canonical example of this principle is demonstrated by lymphocytic choriomeningitis virus (LCMV) mouse model studies, wherein LCMV GP protein was expressed by islet cells in the mouse pancreas. On infection with LCMV, transgenic mice develop diabetes within 2 weeks of infection, demonstrating the spread of response from the initial viral target (LCMV GP) to self-antigens (islet cells).[26]

A recent study has also highlighted the role B cells play in epitope spreading through presenting antigens to different MHC restricted T cells in a mouse model of systemic lupus erythematosus (SLE),[27] which is a systemic autoimmune disease characterized by autoantibodies to nuclear and extranuclear antigens.[28] Epitope spreading is facilitated by bystander activation of T cells (and subsequently B cells), where activation occurs independent of TCR specificity. This is therefore a key mechanism that could lead to sustained autoimmune responses even after the initial virus challenge has passed.

Role of innate immune responses

Much research on autoimmunity has focused on T and B cells, but recent studies have also highlighted the emerging roles of innate immunity in activating these cells.

One of the earliest innate immune responses after encountering a virus is the production of type I interferon (IFN-I) and interferon-related cytokines, which leads to the maturation of dendritic cells and macrophages, followed by T- and B-cell activation.[29,30] Overproduction and/or dysregulation of the IFN-I response is implicated in several autoimmune conditions such as SLE,[31] with interferon signatures correlating with autoantibody profiles.[32] Although the finding that inducing IFN-I production worsens disease in a mouse model of SLE was published in 1969,[33] the trigger for continued IFN-I production is unknown. One proposed mechanism is EBV infection/reactivation driving IFN-I production,[34] which is supported by increased levels of anti-EA (early antigen) antibodies in SLE patients.[35] Chronic viral infection or even a delay in virus clearance can therefore trigger sustained release of IFN-I, potentially causing activation of bystander T and B cells and production of autoantibodies.

The concept that autoimmunity is triggered by viral infection via a range of interconnected mechanisms has been termed the

fertile field hypothesis.[36] This could explain why one mechanism in isolation is not sufficient to trigger autoimmunity, but rather a fertile field is present in some individuals that enables autoimmune or autoaggressive responses.

AUTOIMMUNITY AND ACUTE COVID-19 DISEASE

Preexisting versus *de novo* autoantibody responses

To understand the totality of evidence for autoimmunity in long COVID pathogenesis, it is helpful to first consider studies which reported evidence for autoantibodies in severe acute COVID-19. Table II lists the key studies describing autoantibodies.[37-50] There are 2 arms when considering autoimmunity and COVID-19: the presence of preexisting autoantibodies that can lead to severe disease, or *de novo* induction of autoantibodies that could exacerbate acute COVID-19 and potentially inhibit full recovery. One of the first studies to report evidence for preexisting autoantibodies found neutralizing anti-IFN autoantibodies in 10% of patients with severe COVID-19, compared to 0.33% of healthy prepandemic individuals.[37] These preexisting autoantibodies can be due to inborn errors of immunity[51,52] or due to a breakdown in tolerance with age. A study of 1,876 individuals living with human immunodeficiency virus for over 35 years found anti–IFN-I autoantibodies developed with age in 1.9% of the cohort, lasted lifelong, and increased the risk of severe COVID-19.[53]

Direct molecular mimicry between SARS-CoV-2 and self-antigens has also been reported.[38,54] Conversely, larger autoantibody screens reveal a broad autoimmune response in patients with severe COVID-19, more suggestive of a general breakdown in tolerance rather than specific mimicry. One such study using rapid extracellular antigen profiling (REAP) measured autoantibodies to 2,770 extracellular proteins in patients with severe COVID-19 relative to mild and asymptomatic controls,[40] finding a high prevalence of autoantibodies against chemokines, cytokines, complement proteins, and tissue-specific antigens in patients with severe COVID-19.

Innate responses and autoantibodies in acute COVID-19

Another key feature of severe acute COVID-19 is neutrophil/monocyte-derived inflammation. Several studies have reported increased neutrophil counts in the upper airway,[55] lower airway,[56] and blood[57,58] to correlate with disease severity. Neutrophil extracellular traps (NETs; fragments of DNA decorated with enzymes released on activation) are also elevated in severe acute COVID-19,[59,60] as well as other diseases such as acute respiratory distress syndrome,[61-63] immunothrombosis,[64] and autoimmune conditions.[65] Interestingly, autoantibodies to NETs or neutrophil components can further stabilize NETs and prevent their degradation,[66] leading to greater surrounding tissue damage, neoantigen release, and complement activation.[67] Antiphospholipid (aPL) antibodies activate neutrophils and trigger thrombosis, with several studies reporting increased aPL antibodies in severe COVID-19.[68-70] Notably, a meta-analysis describing 1,159 patients hospitalized with COVID-19 showed aPL antibodies in nearly half of their cohort, with higher levels in critically ill patients.[71] The persistence of aPL and other autoantibodies arising from (and further triggering) sustained innate responses requires further study.

All pathways of the complement system can be activated during SARS-CoV-2 infection,[72,73] supported by histologic staining of complement proteins in heart, kidney, and lung tissue from patients with severe COVID-19.[74-76] Excessive complement activation is thought contribute to COVID-19–associated thrombosis, partly through the C5a-mediated recruitment and activation of neutrophils, macrophages, and monocytes via upregulation of integrins such as intercellular adhesion molecule 1.[77] The complement cascade also drives NET production, which then induces platelet aggregation and further NET release.[78] This process is a rich source for neoantigens, which may support autoantibody production.[79] In turn, autoantibodies can also trigger complement deposition. One study analyzed autoantibodies to the SARS-CoV-2 entry receptor angiotensin-converting enzyme 2 and found anti–angiotensin-converting enzyme 2 IgM autoantibodies in 27% of patients with severe COVID-19 (relative to 7.1% of patients with mild disease), which bound C1q and C3 proteins to trigger deposition.[80] IgM autoantibodies are likely not specific to severe COVID-19 and could rather be a feature of severe inflammatory diseases. Indeed, another study found broadly reactive IgM autoantibodies in severe COVID-19 and non–COVID-19 patients in the intensive care unit.[81] Although autoantibody frequencies between the 2 groups were similar, plasma from COVID-19 patients showed greater ability to fix complement and increased binding to human small airway epithelial cells.[81] Despite the small number of patients, this highlights the potential preponderance of SARS-CoV-2 to trigger production of autoantibodies that mediate complement activation.

In summary, several studies report the expansion/initiation of autoimmune responses in severe COVID-19. The fertile field hypothesis can be applied here, wherein certain individuals predisposed to a break in tolerance can develop autoantibodies after SARS-CoV-2 infection. These autoantibodies can be preexisting (likely at low levels before infection) or *de novo* (due to heightened inflammation).

AUTOIMMUNITY AND LONG COVID

Whether autoantibodies last after acute SARS-CoV-2 infection, and more importantly contribute to long COVID, is only beginning to be investigated. One of the impediments in answering this question accurately is the variance in long COVID definitions used by different studies. For example, the World Health Organization and National Institute for Health and Care Excellence definitions for long COVID differ, with the latter including symptoms persisting 4 weeks after infection.[82] Additionally, many studies use the presence of one or more self-reported persistent symptoms as inclusion criteria, lacking objective symptom data and assessment of symptom severity, which prevents an understanding of symptom-specific pathophysiology. For this discussion, studies referenced here include individuals with defined long COVID (rather than convalescent follow-up), unless specified otherwise.

B-cell dysregulation and autoantibodies in long COVID

B-cell dysregulation has been reported in severe acute COVID-19[41] and long COVID.[43] One study sampled 97 individuals with long COVID (including both hospitalized and outpatient groups) and 26 individuals with an uncomplicated recovery after infection. Proteomics screening and flow cytometry, combined with

machine learning approaches, revealed 2 clusters within the long COVID group. One cluster (termed *inflPASC*) showed increased markers of inflammation, such as complement and clotting pathway activation and neutrophil degranulation, alongside B-cell dysregulation and increased DN2 B-cell frequencies. A subset of these patients had autoantibody titers that steadily increased up to 1 year after infection.[43] Interestingly, the inflPASC group was not distinguishable on the basis of typical inflammatory mediators (eg, IL-6 and C-X-C motif chemokine ligand [CXCL] 8), emphasizing the need for broader inflammatory profiling and autoreactivity screening to identify these patients. Another key takeaway from this study is the incomplete association between symptom burden and inflammation because the 2 long COVID groups are not well distinguishable solely using symptom presentation. These findings are in contrast with another study of 807 individuals followed up at 5 months and 1 year after hospital discharge after COVID-19, where Olink (Thermo Fisher Scientific, Waltham, Mass) analysis revealed distinct inflammatory signatures such as IL-6 to be associated with severe physical and mental health impairment.[83] An important difference between these studies is the patient cohort, with the first being predominantly outpatients and the second exclusively hospitalized individuals. Taken together, these data suggest that chronic inflammation and autoreactivity are a feature of at least a subset of individuals with long COVID; however, their association with specific symptoms needs further study with careful consideration of patient heterogeneity.

One possible explanation for sustained B-cell activation is the persistence of a reservoir of SARS-CoV-2 virus or antigen. A recent large-scale study used digital-droplet PCR, immunohistochemistry, and RNA *in situ* hybridization to demonstrate viral RNA in 11% of solid tissue samples (including lung, gut, brain, and kidney samples) collected at 4 months after mild SARS-CoV-2 infection. Virus RNA levels were significantly positively associated with long COVID symptoms. Additionally, transcriptomics demonstrated B-cell activation at sites of virus persistence in the lung.[84] Continued somatic hypermutation was also seen in receptor binding domain–specific memory B cells at ≤6 months after infection, even after virus-specific antibody titers declined.[85] Taken together, these data suggest virus antigen persistence in tissue as a possible cause for B-cell activation and autoantibody production, which could then contribute to continued inflammation.

Multiomics studies are invaluable in understanding long COVID. One study found that half of their long COVID cohort positive for autoantibodies such as anti–IFN-α-2 and antinuclear antibodies (ANAs) at 2 to 3 months after infection already had class-switched autoantibodies during acute COVID-19.[44] This suggests that specific autoantibodies might precede severe disease and long COVID, as has been shown before with preexisting anti-IFN IgG antibodies in 10% of patients with severe COVID-19.[37] In addition to autoantibodies, the detection of EBV at acute infection predicted the development of fatigue at a later time point.[44] Another study reported 66.7% of their long COVID cohort to be EBV positive, relative to 10% of healthy controls.[86] This suggests a potential role for EBV reactivation in driving long COVID symptoms, possibly through its role in reprogramming the B-cell response.[87] The observation that autoantibodies and EBV viremia during acute COVID-19 correlate to the same factors at long COVID time points strengthens the argument that early measurement may identify future long COVID cases. However, this study was limited by the breadth of antibodies measured, and establishing a causal role requires validation and functional assessment.

Another approach to profile autoantibodies is staining tissue sections with plasma from acute/convalescent COVID-19 patients. One study used plasma from 84 individuals infected with SARS-CoV-2 of various severities.[88] When compared to a non–COVID-19 intensive therapy unit group, the COVID-19 group showed greater autoantibody frequency, which persisted for 3 to 5 months after infection. Additionally, the staining pattern was more specific in the COVID-19 group (restricted to skin, skeletal muscle, and cardiac muscle) compared to the non–COVID-19 intensive therapy unit group. A follow-up study on the same cohort focused on a specific autoantibody, anti–desmoglein-2, which was significantly increased in convalescent COVID-19 individuals but not convalescent influenza or healthy control groups. Desmoglein maintains cardiomyocyte integrity and connects them at intercalated discs. They also found disrupted intercalated disc formation when staining postmortem cardiac tissue from patients with severe COVID-19.[89] Although this study did not have a clinically defined long COVID group, the findings are valuable given the evidence for these autoantibodies' binding to tissues and potentially causing damage.

However, some studies of long COVID symptoms find no relationship between symptoms and autoantibodies. One study using REAP measurement of autoantibodies to 6,000 human extracellular and secreted proteins found no significant differences in the number of autoantibody reactivities between the long COVID, recovered, and healthy control groups.[45] Although they found individual reactivities to G protein–coupled receptor (GPCR), which has been previously reported,[48,90] these did not differ between long COVID and control groups. Although a universal autoantibody signature was not found, analysis of soluble mediators in the plasma revealed increased levels of APRIL (a key mediator of B-cell activation and autoimmunity[91]) and reduced cortisol levels (which has been found in some autoimmune conditions such as psoriasis[92]) in patients with long COVID. These findings suggest that broadly reactive autoantibodies might not be a shared feature in all individuals with long COVID. Similar findings were reported by a study using phage immunoprecipitation sequencing, where an autoantibody signature separated previously infected individuals from prepandemic controls (with anti-ARHGAP31 being a key hit). However, no differences were observed between individuals with long COVID and recovered controls.[93] Phage immunoprecipitation sequencing offers several advantages such as broad coverage and high-throughput outcomes. However, these are linear epitopes, which limits its use in detecting autoantibodies to conformational and posttranslational epitopes. Both studies have some shared features such as self-reported symptom long COVID groups and large numbers of autoantigens screened, a design that only allows for very common autoantibodies with large effect sizes to be detected.

Although most reports of autoantibodies suggest a detrimental role, a recent study challenged this concept by suggesting a potentially protective role for autoantibodies in developing long COVID.[46] Specifically, anti–chemokine C-C motif ligand (CCL) 21, anti-CXCL13, and anti-CXCL16 were increased in individuals without persistent symptoms compared to individuals with long COVID. These chemokines recruit and activate T and B

cells, and autoantibodies that bind to the N loop of these chemokines could inhibit their binding to cognate receptors, thus modulating the immune response. Chronic inflammation is evident in long COVID,[83,94,95] and these findings suggest some autoantibodies could dampen this inflammation and steer the immune response toward uncomplicated recovery after infection. Establishing functionality of these autoantibodies from observational studies is not plausible; however, they highlight the importance of further *in vitro* and *in vivo* research to untangle the multiple ways in which autoantibodies can modulate the immune response.

Together, these studies suggest that pathogenic autoantibodies against a single antigen are uncommon in long COVID, although individual reactivities might better define long COVID subtypes and associate with specific symptoms.

Autoantibodies in symptom-specific long COVID subgroups

Long COVID is an umbrella term covering a breadth of symptom types. Commonly reported symptom groups include cardiorespiratory (pooled because cardiac inflammation is a potential driver of respiratory symptoms), musculoskeletal, gastrointestinal, and neurologic symptoms.[96,97] Although most studies have focused on long COVID cohorts with diverse symptoms, differential mechanisms have been reported to contribute to specific long COVID symptom groups. For instance, in a posthospitalization study, we used clinical data on different symptoms (such as the Modified Medical Research Council Dyspnea Scale and the Montreal Cognitive Assessment [MoCA] for neurologic symptoms) to define 426 individuals with long COVID and 233 fully recovered controls, with myeloid inflammation and complement activation prevalent in most long COVID subgroups.[98] Even though the role of autoimmunity was not directly studied, autoantibodies could drive both myeloid inflammation and complement activation. Broadly, this study emphasizes the need for studying clinically defined long COVID subgroups to understand the biological underpinnings of symptoms.

Respiratory symptoms

Breathlessness is reported by over 50% of patients after discharge from the hospital following COVID-19,[99] and by up to 37.5% of individuals with long COVID who had mild initial infection.[100] The primary tropism of SARS-CoV-2 to the respiratory epithelium drives inflammation and, in some cases, prolonged changes to the lung parenchyma, which has been suggested to be a separate disease entity known as post–COVID-19 interstitial lung disease, or PC-ILD.[101,102] Given the heterogenous nature of respiratory long COVID symptoms, there remains a need to differentiate between post–COVID-19 lung disease (which is mostly seen in patients who were hospitalized and is characterized by changes in the lung morphology visible by computed tomography) and respiratory long COVID (which is not restricted to hospitalized individuals and changes are not visible by computed tomography in some cases[103]).

Autoantibodies have been implicated in this range of post–COVID-19 respiratory sequelae. One study of 106 individuals at 3, 6, and 12 months after acute COVID-19 used a microarray panel to detect ANAs and extractable nuclear antigen antibodies (ENAs), with anti–U1-SnRNP and anti–SS-B/La significantly increased at 12 months after infection.[47] These autoantibodies also positively predicted fatigue and dyspnea in these individuals.[47] Interestingly, the titers of ANAs/ENAs showed a proportional increase with disease severity only at 3 months but not at later time points, suggesting that autoantibodies persist in some individuals regardless of acute COVID-19 severity. It is crucial to note that different studies have found contrasting results, with some reporting almost 50% of their cohort to be ANA positive at 12 months[104] and others reported negligible positivity.[105] ANAs/ENAs have been described in acute COVID-19[88,106] and autoinflammatory diseases such as SLE[107] and rheumatoid arthritis.[108] Although they serve as diagnostic markers for some autoimmune diseases, their exact role in pathology is mostly unknown. Proposed mechanisms include the formation of immune complexes that activate other immune cells, or complement deposition causing tissue damage, with necroptosis of more cells then triggering further ANA/ENA production. Whether ANA/ENA positivity is restricted to specific symptoms or can be used as a diagnostic marker for long COVID warrants large-scale studies with well-matched control groups (because 5% of the healthy population is positive for ANAs/ENAs).[105]

Distinct mechanisms could underpin the range of presentations of respiratory sequelae after COVID-19. A recent preprint study used the Tracking Responders Expending (T-REX) machine-learning approach to combine lung function measures and immunophenotyping data to identify different phenotypes of restrictive lung disease in 110 patients previously hospitalized with severe COVID-19. This identified 2 clusters with the greatest degree of restrictive lung disease and a clear distinction from the healthy control group, with anti-CCL3 and anti-IFN autoantibodies being some of the key discriminants,[109] supporting findings from other studies.[44] Another hallmark observation was elevated levels of CXCL13 in clusters with greater disease severity. In the context of autoimmunity, elevated CXCL13 has been reported widely in a plethora of diseases such as SLE,[110,111] rheumatoid arthritis,[112,113] and Sjögren syndrome.[114-116] CXCL13 facilitates the development of ectopic lymphoid tissues, which are known to facilitate autoantigen-specific B-cell activation and autoantibody production,[117] and which can be present in post–COVID-19 lung tissue up to 15 weeks after infection,[118] alluding to a possible role in pathology. Another study showed markedly increased $IL17^+$ CD4 T cells in individuals with pulmonary sequelae.[119] $IL17^+$ T cells can induce inflammation and drive autoimmune disease;[120,121] however, their contribution to long COVID requires validation. Taken together, the evidence suggests that the persistence of an autoimmune response (potentially localized to the lung) could in part explain respiratory sequelae after COVID-19.

Neurologic symptoms

One striking observation after the COVID-19 pandemic has been the burden of neurologic sequelae. These include difficulty concentrating (aka brain fog), sleep disturbances, anxiety, depression, and neuromuscular disorders. A study of 154,000 patients reported a 42% increased risk of neurologic disorders 1 year after infection.[122] There is also evidence of physical changes in the brain structure (such as reduction in gray-matter thickness and overall reduction in brain size) on infection with SARS-CoV-2, even in individuals with mild initial disease.[123]

Several groups reported antineuronal antibodies in both the serum and cerebrospinal fluid of COVID-19 patients with acute

neurologic manifestations.[124-126] To understand the persistence of the acute autoimmune response, a study included 50 individuals with self-reported cognitive defects 8 months after infection (although MoCA abnormalities were only seen in 18 of 50 individuals) and measured autoantibodies in the serum and cerebrospinal fluid. Fifty-two percent of individuals had at least one antineuronal antibody, with 6% of individuals autoantibody positive exclusively in the cerebrospinal fluid.[127] This aligns with the documented ability of SARS-CoV-2 to replicate in the brain, and even persist for up to 230 days,[128] potentially triggering the production of local neuroautoantibodies. However, this study used postmortem tissues from individuals who died of COVID-19 and may not relate to individuals with neurologic long COVID.

Autoantibodies targeting GPCRs have also been implicated in neurologic long COVID. An exploratory study of 80 individuals with long COVID reported anti–β_2-adrenoceptor autoantibodies to significantly correlate with severity of fatigue and vasomotor symptoms.[129] A study with 31 individuals with primarily neurologic symptoms found anti-GPCR autoantibodies in all individuals, with a combination of agonistic and antagonistic effects. Of note, anti–β_2-adrenoceptor and anti–M2-receptor autoantibodies were increased and exhibited the respective effects *in vitro*.[48] These autoantibodies have also been found in patients with postural orthostatic tachycardia syndrome, or POTS,[130,131] a condition characterized by a steep increase in heart rate when standing upright and can be accompanied by fatigue, dizziness, brain fog, and chest pain. Survey data suggests that 66% of patients with long COVID have moderate to severe POTS.[132] Anti-GPCR autoantibodies can modulate the autonomic nervous system and mediate these symptoms through various mechanisms. For example, anti–α-adrenoceptor autoantibodies can exert an antagonistic effect on the cognate receptor, resulting in vasoconstriction and tachycardia when present in tandem with anti–β-adrenoceptor autoantibodies.[131] There are over 800 GPCRs in humans,[133] so further studies are crucial to understand how different autoantibodies can affect GPCR function and potentially contribute to dysautonomia in long COVID.

The similarities in symptoms and immunologic profile of individuals with neurologic long COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) patients have garnered significant attention and research.[134-136] Autoantibodies targeting β_2-adrenoceptor have been shown to be significantly increased in up to 30% of patients with ME/CFS.[137-139] However, establishing a causal link has been challenging because of the lack of prospective studies of ME/CFS onset. Additionally, even though classically viewed as antagonizing, autoantibodies exhibit pleiotropic effects *in vivo,* which might explain why some GPCR-specific autoantibodies were found to be lower in individuals with long COVID[128] and other studies showed that depleting anti-GPCR autoantibodies alleviated neurologic long COVID symptoms.[140] Untangling the relationship between autoantibodies and the autonomic nervous system therefore requires large-scale *in vitro* and *in vivo* studies, building on foundational ME/CFS research.

Influence of sex on autoimmunity and long COVID

Even though men are at greater risk of severe COVID-19 and mortality, a greater proportion of women experience debilitating long COVID symptoms.[141,142] The autoimmune hypothesis for long COVID is strengthened by the fact that many autoimmune diseases are more common in women,[143] an observation variously attributed to genetic differences, incomplete silencing of the second X chromosome,[144] or the influence of sex hormones on the immune system.[145-147]

Even though female sex has been identified as a risk factor for long COVID in multiple studies, we lack data on the relationship between autoantibodies and long COVID specifically in female patients. One preprint study used machine learning to identify sex-specific immune features in individuals with long COVID. Lower testosterone level in both sexes was associated with reduced long COVID symptom burden.[148] Although this study did not measure autoantibodies, the authors reported increased levels of antibodies to EBV, herpes simplex virus type 2, and cytomegalovirus in female long COVID patients, which have been associated with other postacute infection syndromes[16] and autoimmune conditions such as MS.[21] Notably, another preprint study reported transcriptomic and proteomic signatures specific to female long COVID patients, including increased expression of *XIST,*[149] previously described in driving autoimmune susceptibility in female subjects.[150]

This area of research in long COVID is moving swiftly, and further studies with broader cohorts (including individuals from Black, Asian, and minority ethnic backgrounds as well as trans men and women) will shed invaluable light onto the complex interplay between sex and the regulation of immune responses in long COVID. Additionally, this could guide the potential use of hormone replacement therapy as a treatment for long COVID, and maybe even other conditions such as ME/CFS, which has been associated with sex hormones.[151]

In vivo models to study the role of autoimmunity in long COVID

The development of suitable *in vivo* animal models would aid the mechanistic study of long COVID. However, these have been hard to develop; mice are not a natural host for SARS-CoV-2 and require high doses of adapted virus or host humanization. Additionally, long COVID is a heterogenous multisymptom condition in humans, which makes it difficult to accurately define and study in animals. Few studies have successfully recapitulated features of acute and postacute sequelae in mice, either by using a mouse-adapted SARS-CoV-2[152] model or humanized mice expressing hACE2 receptor in their lungs.[153] A common finding from these studies was a proinflammatory lung fibrotic signature that persisted up to 120 days after virus challenge. Additionally, high levels of $CD11c^+$ B cells were reported late in infection—a profile that resembles EF B-cell activation in SLE[154] and severe COVID-19 in humans.[155]

Two recent preprints add to our understanding of whether autoantibodies could directly contribute to long COVID symptoms (as best recapitulated in a mouse model). The first study categorized a group of 34 individuals with long COVID (with mild initial SARS-CoV-2 infection) into 3 clusters on the basis of their glial fibrillary acidic protein and IFN-I levels in plasma. Purified human IgG was pooled from each cluster, along with IgG from healthy controls (individuals with an uncomplicated recovery after infection). Mice injected with IgG from individuals with long COVID demonstrated increased mechanical sensitivity, thermal hypersensitivity, and reduced motor function compared to mice injected with IgG from controls. Some correlations between levels of neurodegenerative proteins (such as glial

fibrillary acidic protein) in a patient cluster and respective neurologic symptoms in mice were also reported.[49] The second preprint study focused on a subset of 55 individuals with primarily neurologic sequelae and performed microarray screening and mass spectrometry analysis on patient plasma to profile autoantibodies. Plasma from individuals with long COVID showed increased diversity in autoimmune targets, along with a specific increase in reactivity against neurologic antigens such as MED20 and USP5. Like the previous study, purified IgG from long COVID and recovered control subjects were passively transferred into mice; 85% of mice with enhanced pain sensitivity were recipients of IgG from individuals with chronic pain. This was accompanied by a reduction in intraepidermal nerve fibres (a marker for chronic pain associated neuropathy) in mice that received plasma from individuals with long COVID compared to controls.[50]

It is important to consider the crucial limitations to these models. The use of purified and/or pooled human IgG suggests, but does not directly implicate, the role of specific autoantibodies in driving these symptoms in mice, which would only be possible with the injection of antigen-purified autoantibodies. Additionally, autoantigens and Fc receptors in mice and humans differ in structure and distribution. Future studies aimed at validating these findings and identifying specific autoantibodies could pave the way toward biomarker discovery and treatment in this subset of long COVID patients.

FUTURE DIRECTIONS

In parallel with the building evidence of an autoimmune response after COVID-19 and its role in driving long COVID symptoms, there are now multiple large-scale studies that consistently report a much higher incidence (up to 43%) of new-onset autoimmune disease in individuals after COVID-19 compared to uninfected controls.[156-158]

There are several limitations in deducing viral infections as causes for autoimmunity and/or long COVID. For instance, preinfection immunologic data rarely exist for individuals with long COVID and other autoimmune diseases, making it difficult to exclude the possibility of preexisting autoantibodies. Outcomes can also significantly differ depending on the individual, virus strain, and timing of infection. Additionally, even though most studies measure autoantibodies in the plasma, it is well established that they can be produced locally and result in tissue damage in many (auto)inflammatory diseases.[98,159-161] There have now been several reports supporting tissue-specific inflammation in long COVID,[98,162,163] the signs of which can be absent in plasma.[164] Therefore, understanding immune responses at tissue sites can be invaluable in providing mechanistic insights and enabling biomarker discovery. Recent studies have shown that nasal swabbing[165] and nasopharyngeal biopsies[166] can sample adenoid lymphoid tissue, which is a main site of early adaptive responses in the upper respiratory tract. This offers a route toward bridging the knowledge gap in tissue-specific autoimmunity in long COVID.

There are currently no diagnostic tests for long COVID.[2,3] As some definitions suggest, the diagnosis is therefore formed by excluding other conditions that might explain the symptoms.[167] Biomarker discovery and diagnostic tests for not only long COVID but even other infection-associated syndromes is challenging as a result of the varied symptomology and poor clinical definitions. Despite this, there have been a range of studies reporting markers at acute and convalescent time points that are associated with the development of long COVID.[168] Canonical markers of inflammation such C-reactive protein and fibrinogen ratios measured at acute time points were predictive of neurologic long COVID symptoms; however, measuring these at long COVID time points was not informative.[167] Despite the breadth of evidence for autoantibodies in long COVID, they are currently not useful diagnostic markers. This is due to the lack of consistent evidence using standardized tests, variability in autoantibody titers in healthy individuals preventing definition of disease thresholds, and lack of sufficiently sensitive and specific targets. Larger studies are needed to test the feasibility of using any of the autoantibodies implicated so far as effective biomarkers, which is likely to be symptom dependent.

The overarching common goal is to develop effective treatments for long COVID, which may then inform treatments for other chronic conditions such as ME/CFS. There are multiple clinical trials underway for the treatment of long COVID,[167] some of which include GPCR autoantibody antagonists (BC007) and Fc receptor blockers (Efgartigimod). These are conceptually based on clinical data showing reduced long COVID symptom burden on therapeutic apheresis, which reduced levels of anti-GPCR and anti–acetylcholine receptor autoantibodies.[140] Anti–IL-1, anti–IL-6, and anti-TNF therapies are also currently in clinical trials, which have been previously used for the treatment of other autoimmune diseases such as rheumatoid arthritis.[167] Ultimately, there may be a need to stratify treatment approaches according to the specific endotype presented by different long COVID patients.

The fact that it is unlikely for there to be a single cause for long COVID is now well accepted, and evidence for a few mechanisms has emerged. However, although our understanding of the immunologic basis of long COVID has advanced, this remains to be translated to the specific tests and treatments so urgently needed to diagnose and manage this important and debilitating condition.

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