The intersection of COVID-19 and autoimmunity

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Acute COVID-19, caused by SARS-CoV-2, is characterized by diverse clinical presentations, ranging from asymptomatic infection to fatal respiratory failure, and often associated with varied longer-term sequelae. Over the past 18 months, it has become apparent that inappropriate immune responses contribute to the pathogenesis of severe COVID-19. Researchers working at the intersection of COVID-19 and autoimmunity recently gathered at an American Autoimmune Related Diseases Association Noel R. Rose Colloquium to address the current state of knowledge regarding two important questions: Does established autoimmunity predispose to severe COVID-19? And, at the same time, can SARS-CoV-2 infection trigger de novo autoimmunity? Indeed, work to date has demonstrated that 10% to 15% of patients with critical COVID-19 pneumonia exhibit autoantibodies against type I interferons, suggesting that preexisting autoimmunity underlies severe disease in some patients. Other studies have identified functional autoantibodies following infection with SARS-CoV-2, such as those that promote thrombosis or antagonize cytokine signaling. These autoantibodies may arise from a predominantly extrafollicular B cell response that is more prone to generating autoantibody-secreting B cells. This Review highlights the current understanding, evolving concepts, and unanswered questions provided by this unique opportunity to determine mechanisms by which a viral infection can be exacerbated by, and even trigger, autoimmunity. The potential role of autoimmunity in post-acute sequelae of COVID-19 is also discussed.

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Introduction

In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan, Hubei Province, China, and caused the coronavirus disease 2019 (COVID-19) pandemic. COVID-19 presentations range from asymptomatic infection to mild flu-like symptoms to fatal respiratory failure. In addition, many patients experience long-term symptoms of COVID-19 persisting weeks to months after the initial onset of symptoms and extending beyond the original organ involvement, known as post-acute sequelae of COVID-19 (PASC) and more commonly called "long COVID."

Over the past 18 months, researchers have sought to determine mechanisms by which an individual's immune system may be helpful or harmful in COVID-19. In the context of vaccination, it is apparent that adaptive immunity can quite effectively negate severe COVID-19. At the same time, it appears that preexisting autoimmunity may influence, often deleteriously, the course of COVID-19 in certain individuals. Of par-

ticular note, work to date has demonstrated that 10% to 15% of patients with critical COVID-19 pneumonia exhibit autoantibodies against type I interferons (IFNs). Meanwhile, in other patients, the virus may contribute to a de novo breakdown in immune tolerance, triggering pathogenic autoantibodies in susceptible individuals. In some reports, more than 50% of patients hospitalized with moderate to severe COVID-19 have circulating autoantibodies; the extent to which these autoantibodies persist after hospital discharge is a question that has for the most part not been addressed.

In the summer of 2021, the Noel R. Rose COVID-19 and Autoimmunity Colloquium, organized by the American Autoimmune Related Diseases Association (AARDA), brought together researchers working at the intersection of COVID-19 and autoimmunity to address the current state of knowledge regarding two important questions: Does established autoimmunity predispose to severe COVID-19? And, at the same time, can SARS-CoV-2 infection trigger de novo autoimmunity? The breadth of expertise reflected the desire to create a colloquium that spanned multiple medical specialties and scientific disciplines. Participants represented diverse fields, including biobanking, cardiovascular medicine, clinical informatics, immunology, pathology, and rheumatology, among others. This Review highlights the current state of knowledge regarding the intersection of COVID-19 and autoimmunity, including work and ideas discussed during the COVID-19 and Autoimmunity Colloquium.

Immunopathology of severe COVID-19

A cardinal histopathological feature of severe COVID-19 is pulmonary microangiopathy with evidence of fibrin thrombi, activated platelets, and neutrophil extracellular traps within vessels (1, 2). Furthermore, infiltrating neutrophils, monocytes, and macrophages are observed in additional organs beyond the lungs, including the heart, central nervous system, and liver (2–4). In addition to cell activation and infiltration, local and systemic complement activation likely contributes to the microangiopathy. In patients with severe COVID-19, exaggerated complement deposition has been detected in various tissues, including the lungs (5). Meanwhile, systemic detection of alternative complement pathway activation has also been appreciated in severe disease (6).

A subset of patients with COVID-19 develop hyperinflammation with high cytokine and chemokine levels in a pattern that is similar to, but still distinct from, the autoinflammatory macrophage activation syndrome that complicates various autoimmune diseases, such as systemic juvenile idiopathic arthritis and systemic lupus erythematosus (SLE) (7–9). It is notable that immunomodulatory medications, especially dexamethasone (10), appear to improve survival in severe COVID-19. Trials of more targeted therapies have also been conducted in COVID-19. These include inhibitors of cytokines (or their receptors), such as IL-6 (11), IL-1 (12), and granulocyte-macrophage colony-stimulating factor (13). Small molecules that block cytokine-mediated signaling, for instance, Janus kinase (JAK) inhibitors (14, 15), have also been studied. The efficacy of these targeted therapies is less proven than that of dexamethasone and is likely highly dependent on the timing of administration and patient selection (16).

Role of preexisting autoimmunity

The clinical manifestations of COVID-19 are variable, ranging from asymptomatic infection in many individuals to critical pneumonia in about 2% to 3% of patients (17). The dominant epidemiological risk factor for life-threatening COVID-19 is age, with the risk of death doubling every 5 years from childhood onward. Male sex and preexisting comorbidities contribute to a lesser extent (odds ratios typically <1.5) (18). We now also know that genetic variants (such as monogenic inborn errors) and — with high relevance to this Review — preexisting immunological abnormalities may underlie the severity of disease in some individuals (19).

The role of type I IFNs in COVID-19. Type I IFNs induce the expression of many IFN-stimulated genes (ISGs) that are essential for antiviral immunity (Figure 1A). For at least a subset of patients, SARS-CoV-2 induces only a limited type I IFN response, leading to poor control of SARS-CoV-2 replication and the transition to severe COVID-19 (20–22). At the same time, other studies have delivered a contrasting message that some patients with severe COVID-19 exhibit robust and sustained type I IFN responses that ultimately contribute to organ damage (23–26). While type I IFNs and ISGs are certainly helpful and protective in early stages of infection, additional work is needed to understand which specific subgroups of patients with severe disease are more likely to be helped or harmed by type I IFNs.

Genetics and autoantibodies that disrupt type I IFN immunity. In an international cohort, about 3.5% of patients with severe COVID-19 carried rare loss-of-function inborn errors of TLR3- and IRF7-dependent type I IFN immunity that have previously been shown to underlie critical influenza pneumonia (27, 28). For example, four previously healthy, unrelated adults between 25 and 50 years of age had autosomal recessive, complete deficiency of the IFNAR1 chain of the type I IFN receptor ($n = 2$) or IFN regulatory factor 7 (IRF7) ($n = 2$; refs. 27, 28).

In the same cohort (but in other patients without these inborn errors), neutralizing autoantibodies against type I IFNs were detected in at least 10% of patients with critical COVID-19 pneumonia, but not in patients with asymptomatic infection (Figure 1B and ref. 29). Importantly, these autoantibodies may be causal and not a consequence of critical COVID-19, as they can be found in at least some patients before infection (29). The autoantibodies of patients with critical COVID-19 primarily targeted IFN-ω and IFN-α, but not IFN-β, IFN-κ, or IFN-ε (29); therefore, patients with these antibodies could potentially still benefit from early administration of IFN-β (30).

Neutralizing autoantibodies against type I IFNs have been identified since the 1980s in patients treated with IFN-α2 and IFN-β (31), patients with SLE (32), patients with thymoma and/or myasthenia gravis (33), and nearly all patients with autoimmune polyendocrinopathy syndrome type 1 (APS-1; refs. 34–36). Although these autoantibodies are typically clinically silent for much of life, most patients with APS-1 who were infected with SARS-CoV-2 developed severe COVID-19, further suggesting that preexisting autoantibodies against type I IFNs predispose to severe manifestations of COVID-19 (37). Moreover, the same autoantibodies against type I IFNs underlie adverse reactions to yellow fever live attenuated viral vaccine in about a third of cases (38). Notably, multiple centers have confirmed that autoantibodies

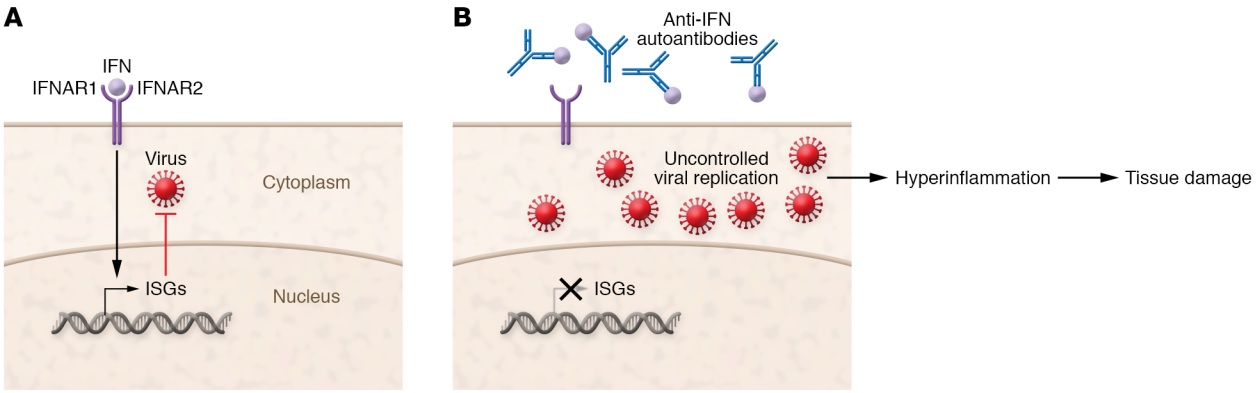

Figure 1. Some patients with severe COVID-19 exhibit autoantibodies antagonizing type I IFN immunity. (**A**) Type I IFNs bind to the IFN-α/β receptor (IFNAR) to induce the expression of IFN-stimulated genes (ISGs) that are essential for antiviral immunity. (**B**) Anti-IFN autoantibodies block IFN binding to its receptor, preventing the upregulation of ISG expression and impairing antiviral immunity. Uncontrolled replication of SARS-CoV-2 may then result in hyperinflammation and tissue damage.

against type I IFNs underlie at least 10% of cases of life-threatening COVID-19 pneumonia in the general population (29, 39–48).

More recently, autoantibodies neutralizing lower, more physiological concentrations of type I IFNs were found in at least 15% of patients with critical COVID-19 pneumonia, including 20% of patients older than 80 years (49). Furthermore, these autoantibodies were found in about 20% of COVID-19 deaths across all ages (49, 50). Analysis of more than 34,000 uninfected individuals demonstrated that these autoantibodies were present in 0.18% of individuals between 18 and 69 years of age, rising to 4% in individuals older than 70 years (49), a pattern that likely contributes to the age-associated risk of life-threatening COVID-19.

In parallel to this recent work, a genome-wide, unbiased approach found that about 1% of male patients younger than 60 years of age with critical COVID-19 pneumonia had X-linked recessive TLR7 deficiency (51). Plasmacytoid dendritic cells isolated from these patients produced negligible amounts of type I IFNs in response to SARS-CoV-2 (51). When combined with the autosomal inborn errors of TLR3-dependent type I IFN immunity that likely impact pulmonary epithelial cells (28), inborn errors may underlie critical COVID-19 in 3% to 4% of patients, especially in those younger than 60 years (whereas autoantibodies are more commonly involved in patients older than 60 years). Collectively, inborn errors (5%) and autoantibodies associated with type I IFN signaling (15%) could account for about 20% of cases of critical COVID-19 pneumonia.

A two-step model seems likely whereby some patients demonstrate inadequate type I IFN immunity during early infection (whether mediated by inborn errors, autoantibodies, or other unknown factors). This contributes to unrestrained viral replication and spread, resulting in pulmonary and systemic hyperinflammation (Figure 1B and ref. 18). Therefore, the timing of therapies enhancing type I IFN signaling is likely to be crucial, and they should be administered in the first few days of SARS-CoV-2 infection.

Role of de novo autoimmunity

Some clinical features of moderate to severe COVID-19 are reminiscent of those seen in autoimmune diseases such as antiphospholipid syndrome, inflammatory arthritis, SLE, and anti-MDA5 syndrome (52–55). In addition, there are numerous case reports of patients developing classifiable autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, and type 1 diabetes, concomitantly with or immediately following SARS-CoV-2 infection (56–64). These various observations have led investigators to question whether de novo autoimmunity may contribute to at least a subset of patients who experience a more severe course with COVID-19.

Other examples of virus-associated autoimmunity. Viruses such as cytomegalovirus, parvovirus B19, and Epstein-Barr virus (EBV) have been postulated to be environmental triggers of autoimmunity in genetically predisposed individuals (65). As one example, serological evidence of EBV reactivation tracks not only with the transition to SLE, but also with increased disease activity in individuals with established SLE (66, 67); indeed, antibodies against EBV nuclear antigen-1 cross-react with the SLE-associated antigens Sm and Ro (68–70), and levels of anti-EBV antibodies correlate with SLE-associated autoantibodies (66, 71–73). Viruses that trigger autoimmunity exhibit several characteristic features (Table 1), including a tendency to cause ubiquitous and/or persistent infection, as well as an ability to tip the host immune response toward loss of tolerance via production of autoreactive lymphocytes. Mechanistically, viruses may contribute to autoimmunity-prone immune responses in various ways. Examples include molecular and functional mimicry, superantigen activity, and stimulation of inflammatory signaling, including production of type I IFNs (74–76).

Profiling the autoantigenome of COVID-19. To determine whether COVID-19 promotes autoantibody production, several groups have endeavored to comprehensively profile the autoantigenome of COVID-19. Using established antigen arrays, Chang et al. identified autoantibodies associated with rheumatological diseases in 49% of patients hospitalized with COVID-19, compared with less than 15% of healthy controls (77). Many of these autoantibodies are traditionally associated with rare autoimmune diseases, such as autoimmune myositis (77). In addition, 60% to 80% of patients hospitalized with COVID-19 had at least one anti-cytokine autoantibody with the potential to modulate

Table 1. SARS-CoV-2 shares some characteristic features with other viruses that trigger autoimmunity

Features of other viruses	Evidence for SARS-CoV-2
Precedes autoimmunity	Case reports of patients developing classifiable autoimmune diseases following SARS-CoV-2 infection (56–64)
Induces type I IFNs	SARS-CoV-2 induces robust type I IFN responses in a subset of patients (23–26)
Breaks tolerance	SARS-CoV-2 induces autoantibody production in patients with severe COVID-19 (42, 77)
Superantigen activity	SARS-CoV-2 spike protein contains a superantigen motif and patients with severe COVID-19 exhibit TCR skewing consistent with superantigen activation (109)
Inhibits apoptosis of infected cells	No evidence to date
Interferes with its own destruction	No evidence to date

immune responses (77).

Wang et al. used a more unbiased approach and screened for autoantibodies against extracellular and secreted proteins, which were theorized to be the main targets for functional autoantibodies. Using rapid extracellular antigen profiling (REAP), in which barcoded human extracellular and secreted proteins are displayed on the surface of yeast (78), they identified a wide range of antibodies targeting immune-related antigens, such as cytokines and chemokines, in the plasma of patients with COVID-19 (42). Mouse surrogates of these autoantibodies increased disease severity in a mouse model of SARS-CoV-2 infection (42). Furthermore, patients with COVID-19 exhibited autoantibodies against tissue-associated antigens that correlated positively with disease severity (42). Importantly, some autoantibodies were clearly induced following SARS-CoV-2 infection, suggesting that COVID-19 contributes to loss of tolerance (42, 77).

Autoantigens can form affinity complexes with the glycosaminoglycan dermatan sulfate (DS). These complexes may then engage B cell receptor signaling in autoreactive B1 cells and thereby induce autoantibody production (79–81). Self-proteins with affinity to DS are therefore more likely to be autoantigens. Wang et al. identified autoantigens with DS affinity from different cell lines and compared them with proteins altered at the protein or transcript level in SARS-CoV-2 infection (82–84). Notably, many of the SARS-CoV-2–altered proteins with DS affinity were associated with COVID-19 disease manifestations, such as neurological symptoms, thrombosis, and possibly PASC (82–84).

Other functional autoantibodies. Abnormal coagulation, along with microvascular and macrovascular thrombosis, is associated with not only severe COVID-19 (85, 86), but also the autoimmune thromboinflammatory disease antiphospholipid syndrome. Antiphospholipid syndrome is characterized by the presence of antiphospholipid autoantibodies (aPLs), which promote thrombosis by activating endothelial cells and platelets while also stimulating neutrophils to release neutrophil extracellular traps (NETs) (Figure 2A and refs. 87–90). Patients hospitalized with COVID-19 exhibit elevated levels of NETs (91), which correlate with disease severity and thrombosis (92). In one study, approximately half of patients hospitalized with COVID-19 had at least one type of aPL, while positive aPL testing was associated with neutrophil activation, more NET release, reduced oxygenation efficiency, and more severe disease (93). Importantly, total IgG fractions from patients with COVID-19 who were positive for aPLs triggered NET release from healthy neutrophils (93), activated endothelial cells to upregulate cell adhesion molecules (94), and accelerated thrombosis when transferred into mice (93). All these phenotypes are similar to those associated with IgG fractions from individuals with established antiphospholipid syndrome.

Patients with antiphospholipid syndrome and other rheumatological diseases have elevated levels of antibodies that bind to NETs, impairing NET degradation and likely activating complement (95, 96). Levels of anti-NET antibodies are also increased in patients hospitalized with COVID-19, with the highest levels in patients requiring mechanical ventilation (97). Anti-NET antibodies correlate with NET remnants in blood, COVID-19 severity, and platelet count and inversely correlate with oxy-

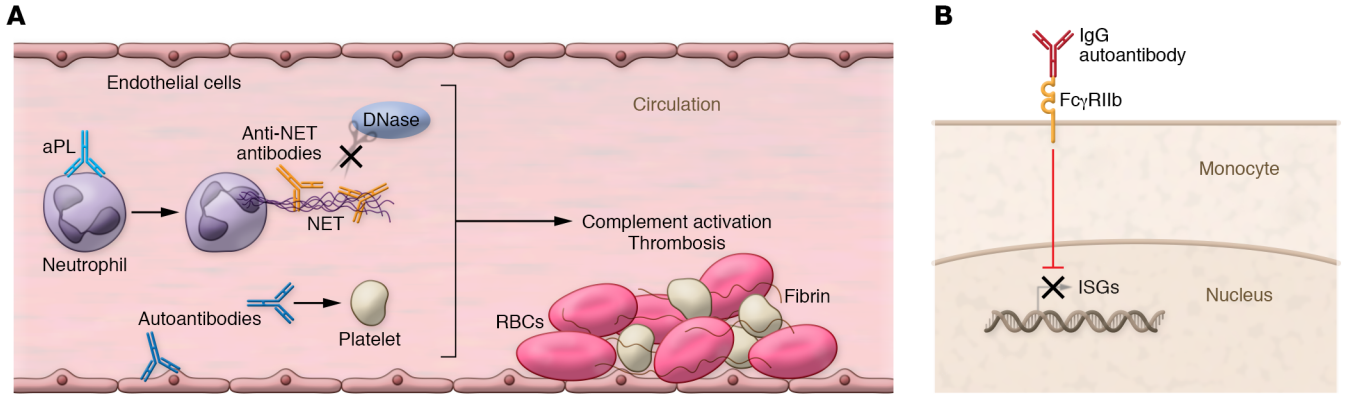

Figure 2. Potential downstream mechanisms of autoantibodies identified in patients with severe COVID-19. (**A**) A subset of patients with severe COVID-19 have anti-phospholipid antibodies (aPLs) and/or anti–neutrophil extracellular trap (anti-NET) autoantibodies. aPLs may activate endothelial cells and platelets and stimulate neutrophils to release NETs. Anti-NET antibodies bind to NETs, impairing NET degradation by DNase. Together, these autoantibodies may activate complement and promote thrombosis. (**B**) In some patients with severe COVID-19, antibodies can prevent the expression of ISGs by antagonizing signaling through the type I IFN receptor in an FcγRIIb-dependent fashion, impairing antiviral immunity.

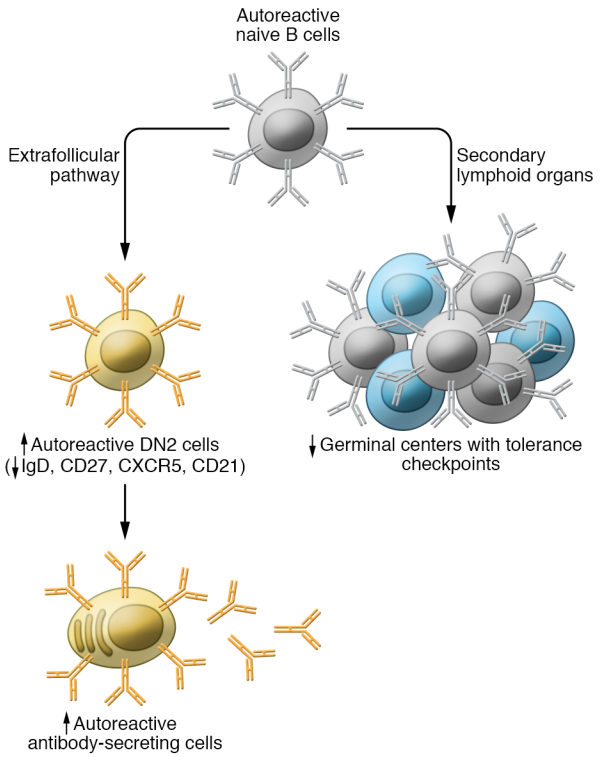

Figure 3. Potential mechanisms of de novo autoimmunity in COVID-19. Naive B cells can be activated via both the germinal center and the extrafollicular pathway. The extrafollicular pathway lacks some tolerance checkpoints that prevent the activation and maturation of autoreactive B cells and is, therefore, more prone to generating autoantibodies. Patients with severe COVID-19 exhibit higher levels of extrafollicular B cells lacking IgD, CD27, CXCR5, and CD21 (known as double-negative [DN2] cells) and plasma cells. They may also lack germinal centers. Red arrows indicate increased or reduced levels in patients with severe COVID-19 compared with patients with mild COVID-19.

genation efficiency and NET clearance (97). Taken together, these findings suggest a potential role in COVID-19–associated thrombosis (Figure 2A).

Another study by Combes et al. found that immune cells from patients with mild COVID-19, including neutrophils and monocytes, expressed a strong ISG signature (98). In contrast, and in line with some of the studies mentioned above (20, 21), ISG-expressing cells were less likely to be found in patients with severe COVID-19 requiring intubation and intensive care (98). In the study, one of seven patients with severe COVID-19 exhibited autoantibodies against IFN-α (98). In the remaining six patients, total IgG fractions antagonized signaling through the monocyte type I IFN receptor in FcγRIIb-dependent fashion (Figure 2B and refs. 98, 99). Although the antigen specificity of these antibodies remains to be determined (which would allow this concept to be tested more broadly in additional cohorts), these data suggest that therapies inhibiting FcγRIIb may have the potential to restore type I IFN responses in some patients with severe COVID-19.

Potential mechanisms of de novo autoimmunity in COVID-19. Effector B cell responses can be activated through the germinal center or extrafollicular pathways. Unlike germinal center reactions, extrafollicular maturation lacks certain checkpoints to prevent autoreactivity and, as such, is more prone to generating autoantibodies (100). In SLE, a large proportion of antibody-secreting cells originate from naive B cells (as opposed to memory B cells), which are activated via the extrafollicular pathway in a TLR7-dependent manner (101, 102). These extrafollicular B cells, known as double-negative (DN2) B cells, lack IgD, CD27, CXCR5, and CD21. They are poised to become antibody-secreting cells, tend to produce pathogenic autoantibodies, and are enriched in patients with active SLE, including patients with lupus nephritis (102).

Reminiscent of SLE, higher levels of both circulating DN2 B cells and circulating plasma cells associate with greater disease severity and poor outcomes in COVID-19 (Figure 3 and ref. 100). In addition, patients who succumb to COVID-19 lack Bcl6$^+$ germinal centers (103), consistent with a predominantly extrafollicular response. Patients with severe COVID-19 also exhibited higher numbers of unmutated SLE-associated, autoimmune-prone IGHV4-34 antibody–secreting cells in circulation (100, 104). The mechanisms contributing to extrafollicular pathway activation in severe COVID-19 are unknown; however, TLR7 drives DN2 cell differentiation (102), and TLR7 recognizes viral single-stranded RNA genomes, such as that of SARS-CoV-2 (105). Furthermore, patients with severe COVID-19 exhibit elevated plasma IL-6 levels (106), which correlate with DN2 cell expansion (107). Notably, patients with high extrafollicular responses exhibit high titers of neutralizing antibodies against the receptor-binding domain of the SARS-CoV-2 spike protein (100), suggesting that a lack of protective antibodies is not the main driver of disease severity in these patients. Together, these studies indicate that autoimmune-prone extrafollicular B cells dominate the B cell response in many patients with severe COVID-19, likely contributing to the loss of tolerance and dysregulated humoral immunity in patients with severe disease.

Some viruses possess superantigen activity, enabling broad nonspecific T cell activation via MHC class II or the T cell receptor (TCR) and contributing to hyperinflammation and autoimmunity (108). Using computational modeling, Cheng et al. demonstrated that the SARS-CoV-2 spike protein contains a high-affinity motif similar to bacterial superantigens that directly interacts with the TCR and may form a ternary complex with MHC class II (109). Interestingly, the authors found that some patients with severe COVID-19 have a skewed TCR repertoire consistent with superantigen activity (109). Multisystem inflammatory syndrome in children (MIS-C) is a severe inflammatory syndrome with multiorgan involvement that occurs in a small percentage of children following SARS-CoV-2 infection (110). One study of 16 children with severe MIS-C found significant expansion of TCR β chain variable gene 11-2 (TRBV11-2), TRBV24-1, and TRBV11-3 in MIS-C patients relative to febrile control patients, such that up to 24% of the clonal T cell space was taken up by clones using TRBV11-2 (111). In silico modeling indicated that polyacidic residues in the Vβ chain encoded by TRBV11-2 strongly interact with the superantigen-like motif of SARS-CoV-2 spike glycoprotein, suggesting that unprocessed SARS-CoV-2 spike may directly mediate TRBV11-2 expansion. Another study found that 24 of 32 patients (75%) with MIS-C (and none in other clinical groups) displayed TRBV11-2 (also known as Vβ21.3$^+$) expansions (112). Notably,

TRBV11-2 T cells correlate with MIS-C cytokine storm and were enriched in a cluster of patients with autoimmunity-associated immunoglobulin heavy chain variable region genes and increased autoantibodies targeting tissue-specific autoantigens (113). Therefore, superantigen-like T cells may trigger hyperinflammation and the production of autoantibodies following SARS-CoV-2 infection, contributing to de novo autoimmunity. The extent to which SARS-CoV-2 spike–mediated superantigen activity contributes to autoimmunity in adults with severe COVID-19 is a topic worthy of further research.

Does autoimmunity play a role in PASC?

Whether autoimmunity contributes to PASC is only beginning to be addressed. Furthermore, as definitions of PASC are still being established, any available data will need to be interpreted in relation to the definition used by the authors. One recent study of 96 patients detected antinuclear antibody (ANA) titers ≥1:160 in 43.6% of patients at 12 months after COVID-19 symptom onset (114). In the cohort, the frequency of neurocognitive symptoms (such as concentration problems) was significantly higher in the group with ANA titers ≥1:160 compared with the group with titers less than 1:160 (107). Outstanding questions that should be systematically considered in the coming months and years include the following: Do preexisting autoantibodies predispose someone with COVID-19 to develop PASC? How commonly do de novo autoantibodies persist beyond the acute phase of SARS-CoV-2 infection, and will these patients transition to a classifiable autoimmune disease? Meanwhile, does virus-induced autoreactivity underlie at least some of the wide spectrum of clinical phenotypes associated with PASC? If so, can patients with acute disease or PASC be immunologically profiled to identify those who might benefit from immune-modulating therapies? Answering these questions will require the generation of multiethnic biospecimen repositories from COVID-19 patients, such as the Collaborative Cohort of Cohorts for COVID-19 Research (C4R), which includes information from before, during, and after SARS-CoV-2 infection that can potentially enable the necessary longitudinal investigations (115). Analysis of large-scale electronic health record (EHR) data (116–118) will likely also be needed to determine clinical associations with COVID-19, such as autoimmune manifestations. This approach has already been used to identify hospitalization trends and clinical and laboratory features and to predict severity in patients with COVID-19 (119–121) through initiatives such as the international Consortium for Clinical Characterization of COVID-19 by EHR (4CE; https://covidclinical.net) and the National COVID Cohort Collaborative (N3C; https://ncats.nih.gov/n3c).

Conclusions

Many of the studies discussed above leveraged patient samples obtained in the early months of the COVID-19 pandemic, before the regular use of dexamethasone, and certainly before the advent of vaccination. Understanding the extent to which these interventions (and hopefully additional interventions to come) change how SARS-CoV-2 interacts with the immune system is one important future direction. It will also be valuable to see additional studies that use affinity purification to characterize downstream mechanisms of specific autoantibody species. Furthermore, longitudinal cohorts that capture patient samples at the time of acute illness and then in follow-up will be important; establishing cohorts that also include pre-COVID samples will be even more valuable.

In conclusion, data to date strongly suggest that some severe COVID-19 cases can be explained by preexisting autoantibodies (which, interestingly, confer a risk similar to that conferred by rare inborn genetic errors in the same pathways). With regard to de novo autoantibody formation, a variety of such antibodies are detected when patients are hospitalized with severe COVID-19; however, there is still work to be done to determine whether these antibodies are important contributors to severe disease or an epiphenomenon of the marked inflammation. Going forward, the COVID-19 pandemic would seem to provide a once-in-a-lifetime opportunity to more precisely determine how a viral infection can be exacerbated by, and even trigger, autoimmunity.

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