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Review

Similarity in Immune Response Between Sars-Cov-2 Infection and Autoimmune Diseases

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ABSTRACT:

Autoimmune diseases are characterized by persistent inflammatory reactions that lead to organ damage and dysfunction in various organs due to the presence of autoantibodies and a deregulated immune system. Disorders of the immune system are also present in COVID-19. Autoantibody production is an important feature of autoimmune diseases. However, the underlying mechanisms are complex and still not fully understood. Infectious pathogens are believed to mimic the molecular mechanisms that trigger autoimmune diseases. The viral infection can impair immunological tolerance by exposure of antigen epitopes that elicit cross-reactive antibodies. There are numerous studies showing antigenic mimicry between viral and human proteins. Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human immunodeficiency virus (HIV) are viruses that inhibit these autoimmune abilities. Similarly, there are numerous studies showing the possibility that patients with SARS-CoV-2, COVID-19 will develop multiple types of autoantibodies and autoimmune diseases. Patients have a tendency to develop more than 15 different types of autoantibodies and more than 10 different autoimmune diseases. COVID-19 has been described along with other autoimmune conditions such as the synthesis of various autoantibodies, Kawasaki disease, anti-phospholipid syndrome, and Guillain-Barre syndrome. Since loss of smell has been described and linked to many autoimmune conditions, it is possible that hyposmia/anosmia in COVID-19 patients is at least partially induced by autoimmune mechanisms. The main mechanisms that may contribute to the development of autoimmunity in the disease are mechanisms: SARS-CoV-2's ability to overstimulate the immune system, induce neutrophil-related cytokine responses and excessive neutrophil extracellular trap formation, and molecular similarity between the host's own components and the virus. In addition, there are potential risks of COVID-19 on new-onset autoimmune diseases such as antiphospholipid syndrome, Guillain-Barré syndrome, Kawasaki disease and others. Recognizing these autoimmune manifestations of COVID-19 is essential in order to properly deal with the ongoing pandemic and its long-term post-pandemic consequences.

Keywords : Autoimmunity, COVID-19, COVID-19 structure, Post COVID, SARS-CoV-2

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1. INTRODUCTION

In December 2019, a new infection called coronavirus disease 2019 (COVID-19) emerged in Wuhan, China, and was officially declared a pandemic by WHO on March 11, 2020 [1]. The disease is caused by the newly defined severe acute respiratory syndrome (SARS)-related coronavirus strain, named SARS-CoV-2 after SARS-CoV that caused the SARS epidemic in 2002 [2]. SARS-CoV-2 belongs to the coronavirus family, which consists of enveloped viruses with a spherical morphology and a single-stranded RNA (ssRNA) genome [3]. Spike glycoproteins (S protein) cross the peplo of the virus and form a crown-like surface [4]. Via the Receptor Binding Domain (RBD) located in the S1 subunit of the S protein, the virus can bind to the host cell receptor Angiotensin Converting Enzyme 2 (ACE2) and invade the cell [5-7]. In most cases, hosts infected with SARS-CoV-2 show flu-like symptoms such as fever, fatigue, and dry cough. Headache, myalgia, sore throat, nausea and diarrhea may also be seen in patients with COVID-19 [8,9]. In severe cases, shortness of breath and hypoxemia occur. In critical cases, the disease progresses rapidly and patients may develop septic shock and multi-organ dysfunction [10]. Therefore, COVID-19 can affect multiple organ systems, including the skin, kidneys, respiratory system, cardiovascular system, digestive system, nervous system, and hematological system [11]. The dysregulated immune response and increased proinflammatory cytokines induced by SARS-CoV-2 contribute to disease pathogenesis and organ damage, which draws attention to immunomodulatory therapy in the treatment of COVID-19 [12]. Drugs used to treat autoimmune diseases are widely used in critical cases of COVID-19 [13]. In addition, some autoantibodies can be detected in patients with COVID-19 [14]. These observations suggest that examining the pathways known to contribute to the pathogenesis of autoimmunity may provide clues to better understand and treat COVID-19.

1.1 Relationship Of Autoimmune Diseases And Covid-19

Autoimmune diseases are characterized by persistent inflammatory reactions that lead to target organ damage and dysfunction due to the presence of autoantibodies and loss of immune tolerance and dysregulated immune system [15]. Infection with SARS-CoV-2 induces immune reactions that may have important implications for the development of vaccine strategies against this virus [16]. T-cell immunity plays a central role in controlling SARS-CoV-2 infection. Antigen-specific CD4 + and CD8 + T cells and neutralizing antibody responses play protective roles against SARS-CoV-2, while impaired adaptive immune responses such as scarcity of naive T cells can lead to poor disease outcomes [17]. In clinical laboratory tests, lymphopenia (lymphocyte count ≤1000) is associated with severe disease in COVID-19 patients and may be a prognostic factor for disease severity and mortality [18-21]. Another notable haemocytological change is neutrophilia and associated excess neutrophil extracellular entrapments parallel to lung injury in severe COVID-19 patients [12]. Therefore, the immune response is a double-edged sword in COVID-19, the consequences of which are affected by the degree of cytokine imbalance and activation of immune cells.

Overproduction and release of proinflammatory cytokines and chemokines can cause severe organ damage, which is also seen in autoimmune diseases in critical situations. Proinflammatory cytokines and chemokines, including interleukin (IL)-1, IL-2, IL-6, IL-8, IL-10, IL-17, IL-18, CXCL10, and CCL2, and chemokines are increased in COVID-19 patients. Expression levels of some of these cytokines, such as IL-10 and IL-18, have been shown to be associated with disease severity [22-25]. Similar to autoimmune diseases, Damage-Associated Molecular Patterns (DAMPs) are also involved in the pathogenesis of COVID-19 and are associated with the disease. Chen et al. [26] revealed that serum S100A8/A9 and HMGB1 levels were significantly increased in patients with severe COVID-19, and a significant increase in two DAMPs was associated with higher mortality.

Activation and infiltration of immune cells are involved in the pathogenesis of organ damage in patients with COVID-19. Macrophage Activation Syndrome (MAS) may be a continuation of the cytokine storm syndrome, which leads to life-threatening complications in COVID-19 [27]. In this case, activated macrophages will produce excessive proinflammatory cytokines, polarize to the inflammatory M1 phenotype, and exhibit cytotoxic dysfunction [28]. Recently, Conti et al. [29] suggested that mast cells activated by SARS-CoV-2 may release histamine to increase IL-1 levels to initiate cytokine storm and exacerbate lung injury. Woodruff et al. [30] found extrafollicular B-cell activation in critically ill patients with COVID-19, similar to that observed in autoimmunity. Moreover, extrafollicular B-cell activation was strongly associated with the production of high concentrations of SARS-CoV-2-specific neutralizing antibodies and poor disease outcome [30]. Peripheral blood B cell subpopulations change during COVID-19. In COVID-19 patients, atypical memory B cells (CD21 lo /CD27 - /CD10 -) were significantly enlarged, while classical memory B cells (CD21 + /CD27 + /CD10 -) were significantly reduced [31]. Analysis of the immune profiles of severe COVID-19 patients revealed that the proportion of mature natural killer (NK) cells increased and the proportion of T-cell numbers decreased [32]. Neutrophil activation and Neutrophil Extracellular Trap production (NETosis) appear to have a pathogenic role in COVID-19, similar to some autoimmune and immune-mediated thromboinflammatory diseases, including lupus, antiphospholipid syndrome, and ANCA-associated vasculitis. Zuo et al. [33] reported that Neutrophil Extracellular Trap (NET) markers were increased in the serum of patients with COVID-19 and were significantly higher in patients requiring mechanical ventilation. In vitro experiments have shown that sera from patients with COVID-19 induce NETosis in normal neutrophils, similar to sera from patients with antiphospholipid syndrome [33, 34]. In severe and critical cases, immunomodulatory drugs and biologic agents targeting proinflammatory cytokines have been administered to contain the robust immune response in COVID-19. Corticosteroids, JAK inhibitors, IL-1 blockade and IL-6 receptor antagonists familiar to rheumatologists have been used to treat patients with COVID-19 [35–38]. The similarities in the immunopathogenesis of COVID-19 and autoimmune diseases are summarized in Table 1.

Table 1. Similarities in the immunopathogenesis of COVID-19 and autoimmune diseases

	COVID-19 immunological features similar to autoimmune diseases	**References**
COVID-19 immunological features similar to autoimmune diseases	Excessive activation of monocytes, macrophages, mast cells and neutrophils. Increasing proportion of mature natural killer (NK) cells.	[12, 27, 29, 32, 33]
Adaptive immune cells	Decreased T-cell numbers, altered B-cell subsets, dysregulation of T cells and B cells.	[17, 30, 31]
Cytokines and chemokines	Increased levels of IL-1, IL-2, IL-6, IL-8, IL-10, IL-17, IL-18, CXCL10, CCL2.	[22-24]
Autoantibodies	ANA, APL, lupus anticoagulant, cold agglutinins, anti-Ro/SSA antibodies, anti-Caspr2 antibody, anti GD1b antibody, anti-MOG antibody	[14, 51-58]
Clinical conditions	Immune-mediated hemolysis, decreased white blood cell count, cytokine storm syndrome, macrophage activation syndrome, a procoagulant state	[25, 28, 57]
Other immunopathogenesis	Increased DAMP levels, molecular mimicry	[26, 46]

1.2. Molecular Mimicry and SARS-CoV-2

Autoantibody production is an important feature of autoimmune diseases. However, the underlying mechanisms are complex and still not fully understood. Molecular mimicry of infectious pathogens is believed to be one of the mechanisms [39]. The viral infection can impair immunological tolerance by exposure of antigen epitopes that elicit cross-reactive antibodies. There are numerous reports of antigenic mimicry between viral and human proteins. Perhaps one of the most established examples of molecular mimicry in autoimmunity is the immune response to Epstein-Barr virus (EBV) in lupus patients [40]. An abnormal immune response to Epstein-Barr virus Nuclear Antigen-1 (EBNA-1) can induce an autoimmune response targeting the Sm and Ro autoantigen systems [41]. Cross-reactivity has also been shown between anti-EBNA-1 antibodies and myelin basic protein in patients with multiple sclerosis [42]. In addition, EBNA-1 shows structural similarity to β synuclein, a brain protein involved in multiple sclerosis, and is predicted to bind HLA class II DR2b (HLA-DRB1∗15:01) [43]. In-silicon analysis revealed that an envelope protein of human endogenous retroviruses (HERV) shares a similar sequence with three myelin proteins that induce an autoimmune response in multiple sclerosis and are predicted to bind to HLA-DRB1~15:01. Basavalingappa et al. [44] showed that Coxsackievirus B3 (CVB3) infection can induce the generation of autoreactive T cells for multiple antigens.

Studies have revealed that some epitopes from SARS-CoV-2 exhibit cross-reactivity with autoantigens. Anand et al. [45] reported that a unique S1/S2 cleavage site in SARS-CoV-2 similarly mimics a FURIN-cleavable peptide on the human epithelial sodium channel α-subunit (ENaC-α) that plays a critical role in airway homeostasis. .

Mimicry between SARS-CoV-2 and three proteins found in the human brainstem pre-Bötzinger Complex (preBötC), DAB1, AIFM, and SURF1, may contribute to respiratory failure in COVID-19 [46]. In addition, SARS-CoV-2 infection can elicit autoimmune responses through molecular mimicry. Marino Gammazza et al. [47] compared viral proteins with human molecular chaperones and suggested that chaperones, most of which are heat shock proteins, may participate in the molecular mimicry phenomenon after SARS-CoV-2 infection. In addition, Lucchese and Flöel [48] compared the viral amino acid sequence to human autoantigens associated with immune-mediated Guillain-Barré syndrome and other autoimmune disease-associated polyneuropathies, and found that peptides embedded in the immunoreactive epitopes of SARS-CoV-2, human heat shock proteins 90 and 60 They showed that they share the same series with. Venkatakrishnan et al. [49] reported 33 different 8-mer/ 9-mer peptides with potential cross-reactivity between SARS-CoV-2 and the human reference proteome; among them, 20 human peptides have not been observed in any previous strain of coronavirus. In addition, four of these human 8-mer/9-mer peptides mimicked by SARS-CoV-2 showed similarity to host pulmonary artery peptides and HLA-B∗40:01, HLA-B∗40:02 and HLA-B∗ It was predicted to connect with 35 : 01 [49]. A recent study analyzed the sharing between hexapeptides that define minimal epitopic sequences of the virus and the human proteome and documented numerous immunoreactive epitopes shared with human proteins [50]. The results of this study imply the possibility of SARS-CoV-2 causing cross-reactivity with host autoantigens and provide clues to possibly explain various clinical manifestations and pathologies involving different organs and systems after SARS-CoV-2 infection.

Autoantibodies known to occur in a number of autoimmune diseases have been identified in patients with COVID-19 (Table 2). Pascolini et al. [14] determined the presence of antinuclear antibodies (ANA), anticytoplasmic neutrophil antibodies (ANCA), and antiantiphospholipid (APL) antibodies in 33 consecutive COVID-19 patients. Results showed that 45% of patients were positive for at least one autoantibody, and patients with positive autoantibodies tended to have a worse prognosis and the significantly higher respiratory rate at presentation. The ANA positive rate was 33%, the positive rate for anticardiolipin antibodies (IgG and/or IgM) was 24%, and the three patients were positive for antiβ2-glycoprotein-I antibodies (IgG and/or IgM) 9%. However, ANCA was negative in all patients [14]. Coagulopathy is a threatening complication of SARS-CoV-2 infection. Recently, a cohort study was conducted at Montefiore Medical Center to evaluate lupus anticoagulant positivity in COVID-19 patients. The researchers found an increased incidence of lupus anticoagulant positivity in COVID-19 patients compared with controls that tested negative by COVID-19 reverse transcriptase-PCR. In addition, there was an increased rate of thrombosis in COVID-19 patients with positive lupus anticoagulant [51]. Amezcua-Guerra et al. [52] also showed a higher frequency of APL antibodies in severe and critical COVID-19 patients, and the presence of APL antibodies was associated with a hyperinflammatory state with pulmonary thromboembolism with

extremely high levels of ferritin, C-reactive protein and IL-6. The data discussed above provide a possible explanation for the hypercoagulable state in severe and critical COVID-19 cases and demonstrate that SARS-CoV-2 can induce autoimmune responses.

Table 2. Autoantibodies detected in COVID-19 patients

Autoantibodies	**Clinical Significance**	**References**
ANA	Poor prognosis and significantly higher respiratory rate	[14]
APL	Poor prognosis and markedly elevated respiratory rate Hyperinflammatory state and possible association with thrombosis and thromboembolism	[14, 52]
Lupus anticoagulant	Higher thrombosis rate	[51]
Cold Agglutinins	Hemolytic anemia. Complex laboratory evaluation and renal replacement therapy	[55, 58]
Anti-Ro/SSA antibodies	Possible association with severe pneumonia	[56]
Anti-CASPR2 antibodies	Uncertain	[54]
Anti-GD1b antibodies	Uncertain	[54]
Anti-MOG antibodies	Uncertain	[53]
Erythrocyte bound antibody	Associated with severity of anemia	[57]

The presence of autoantibodies against contactin-associated protein 2 (anti-Caspr2), ganglioside GD1b (anti-GD1b), and myelin oligodendrocyte glycoprotein (anti-MOG) in COVID-19 patients presenting with neurological symptoms has been shown in case reports or retrospectively [53, 54]. However, the clinical significance of these antibodies remains unclear. In addition, case reports showing the presence of cold agglutinins and autoantibodies against RBC antigens in critically ill patients with COVID-19 [55] and the presence of anti-Ro/SSA antibodies in patients with severe COVID-19 pneumonia have been demonstrated [56]. A study involving 113 samples examined red cell antibodies by direct and indirect antiglobulin testing (DAT or IAT). Positive DAT was found in 46% of COVID-19 patients, which was significantly higher than in non-COVID-19 controls. The presence of red cell membrane-bound immunoglobulins contributes to hemolytic anemia and correlates with the severity of anemia in COVID-19.

1.3. Development Of Autoimmune Diseases After Sars-Cov-2 Infection

Since the SARS-CoV-2 infection can impair immune tolerance and trigger autoimmune responses, it is likely to trigger clinical autoimmunity as well. Indeed, many reports have confirmed the development of autoimmune diseases after SARS-CoV-2 infection.

Cold agglutinin syndrome (CAS) and autoimmune hemolytic anemia have been reported as a complication of COVID-19 [55, 58, 59]. Meanwhile, Guillain--Barré syndrome (GBS) is also emerging as an autoimmune disease that can occur in patients with COVID-19. In most cases of COVID-19, GBS SARS-CoV-2 antibodies are undetectable in the cerebrospinal fluid (CSF). Besides that, Gigli et al. [60] recently reported a case of GBS with a positive test for SARS-CoV-2 antibodies in the CSF [61, 6]. The mechanisms of how SARS-CoV-2 triggers GBS are discussed. However, immune cross-reactivity between epitopes and host antigens may be a possible explanation [62]. Recently, a case of systemic lupus erythematosus has also been reported to be triggered by SARS-CoV-2 [63]. Additional autoimmune diseases caused by SARS-CoV-2 are likely to be reported in the future.

2. CONCLUSION

COVID-19 is a new pandemic with significant global health consequences. Similar to systemic autoimmune diseases, COVID-19 may present with heterogeneous and systemic clinical manifestations. There are similarities in immune response in both disease states, and organ damage in COVID-19 appears to be largely immune-mediated, similar to autoimmune diseases. The SARS-CoV-2 virus can, at least in part, impair the self-tolerance of host antigens through molecular mimicry. The development of autoantibodies and sometimes organ-specific (eg GBS) or systemic (eg SLE-like disease) autoimmunity has been observed in COVID-19. Further research will shed light on this issue.

Conflict of Interest

Author has no personal financial or non-financial interests.

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