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NOVEL HYPOTHESIS

Will the COVID-19 pandemic trigger future occurrence of autoimmunity like Sjögren's syndrome?

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new RNA virus that is homologous with the previously known SARS-CoV-2 and Middle East respiratory syndrome (MERS) coronaviruses. SARS-CoV-2 binds to various cell types, including lung epithelial cells, via the angiotensin-converting enzyme (ACE)-2 molecules expressed on the cell surface. After binding, viral RNA enters the cytosol of the infected cells and stimulates intracellular signals to activate intranuclear gene transcriptions of multiple pro-inflammatory cytokines, including tumor necrosis factor alpha, interleukin (IL)-6, and IL-1, causing substantial inflammatory reactions.[1,2] In susceptible patients, the complex inflammatory responses, the so-called cytokine storm, would lead to severe acute respiratory distress syndrome.[2]

SARS-CoV-2 infection triggers autoimmunity aside from inflammation. The clinical features of the coronavirus disease 2019 (COVID-19) may include ground-glass opacity on chest radiography, coagulopathy, and other hematological abnormalities that resemble those found in autoimmune diseases.[3,4] Autoantibodies, including anti-nuclear, anti-Sjögren's syndrome (SS)-A/Ro, anti-neutrophilic cytoplasmic, anti-cyclic peptide containing citrulline, and anti-interferon were detected in COVID-19 patients.[5-7] As for T cell immunity, long-term antigenic stimulation by SARS-CoV2 would induce T cell activation and exhaustion in both CD4+ and CD8+ T cells.[8,9] Furthermore, a T-helper 17 (Th17) phenotype has been shown in COVID-19, as the T cells of patients with COVID-19 produce more IL-17 than those of controls.[9] T cell exhaustion and Th17 phenotype are characteristics found in autoimmune rheumatic diseases, such as in systemic lupus erythematosus (SLE).[10] In fact, a considerable number of COVID-19 patients were diagnosed as having autoimmune rheumatic diseases as they fulfilled the respective criteria.[4,11,12]

In general, infection, either viral or bacterial, is recognized as the most critical factor to accelerate the incidence and/or disease activity of autoimmune diseases. For example, parvovirus, hepatitis virus, and Epstein-Barr virus (EBV) have been significant candidates as pathogens in autoimmune diseases such as SLE and SS.[13,14] The precise mechanisms by which infection would accelerates autoimmunity are unclear; however, it may be plausible that infection evokes antiviral or antibacterial immune responses and activates inflammatory cytokines, which lead to a dysregulation of innate and adaptive immunity. Pusch et al[15] described that viruses induce "heterologous immunity" to the infected host, altering adaptive immune responses to viral and self-antigens. Moreover, EBV evokes B lymphocyte activation associated with overproduction of autoantibodies.[16]

A "molecular mimicry" may exist between the viral antigen and autoantigen(s).[17,18] Coxsackie virus, for example, has sequence homologies between the viral protein and an autoantigen, Ro60 peptide, which is often found in SS and other autoimmune diseases.[12]

In addition, infections themselves, or the administration of anti-pathogenic agents, may alter the host's intestinal homeostasis, causing dysbiosis in the gut flora. Recent investigations suggest that the alteration of gut homeostasis, or dysbiosis, is crucial in the induction of autoimmune diseases.[19] For instance, the potential role of a species of Gram negative bacteria in oral and gut microbiota, that is, *Prevotella* spp., in the pathogenesis of rheumatoid arthritis is attracting widespread interest.[19,20] As for SS, researchers have suggested an association between gut dysbiosis and the severity of dry eye.[21]

Of note, in 2011, Shoenfeld et al[22] identified the concept of ASIA syndrome (autoimmune/inflammatory syndrome induced by adjuvants). The proposed syndrome encompasses a broad spectrum of autoimmunity that is induced after exposure to external factors such as infections.[22] Considering the time gap between exposure to an infection and autoimmune disease diagnosis, the authors hypothesized that "the non-antigenic activation" of immunity might determine the degree of autoimmune reaction after the infection. In the

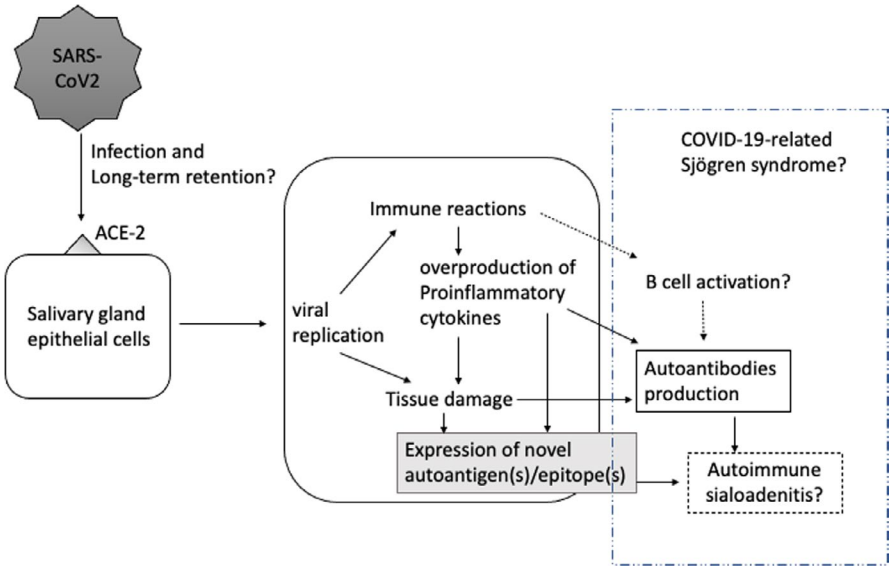

FIGURE 1 Severe acute respiratory syndrome coronavirus 2 infection with potential of developing Sjögren's syndrome

proposed entities for the diagnosis of "ASIA," "exposure to external stimuli" is one of the major criteria. According to the concept, SS is a typical example of "ASIA".[23]

Considering these findings, the current pandemic of COVID-19 would evoke the occurrence of autoimmune rheumatic diseases such as SLE or SS,[24] which may constitute the ASIA syndrome.[12] To support this notion, it was observed that a significant number of patients with COVID-19 show clinical and laboratory findings similar to those in autoimmune rheumatic diseases.[24] The sequence homology between SARS-CoV-2 spike and nuclear proteins and human peptides has been demonstrated.[17,18] Moreover, altered gut dysbiosis after SARS-CoV-2 infection has been reported,[25] suggesting its implication in dysregulated immunity in COVID-19.

Regarding other coronaviruses, only few reports have described the occurrence of autoimmune diseases after SARS-CoV or MERS-CoV infection, owing to the relatively small-scale pandemic compared with the current COVID-19 pandemic. However, MERS-CoV was reported to induce pro-inflammatory reactions and Th17 cytokine profile,[26] suggesting a possibility that it triggers autoimmunity.

Brito-Zerón et al[27] reported that patients who developed primary SS after contracting SARS-COV-2 infection manifested clinical presentation similar to those in the general population. Nevertheless, Fernandez-Gutierrez et al[28] demonstrated a slight but significant difference in the crude incidence of COVID-19-related hospital admission among different rheumatologic diseases, with SS being one of the conditions with a higher risk. This finding may support the implication of viral infection in the pathophysiology of SS.

Therefore, I propose that autoimmunity against the salivary glands should be carefully monitored, as SARS-CoV-2 infects human salivary glands as abundantly so that the saliva could be used as an excellent clinical sample for COVID-19 diagnosis.[29] The expression of ACE2, the SARS-CoV-2 receptor, was even higher in minor salivary glands than in the lungs.[30] After the infection, saliva may cultivate the live virus, and the salivary glands would act as a long-term viral reservoir of SARS-CoV-2.[30] Hence, autoimmune sialoadenitis, which is or at least mimics SS, might become apparent even after susceptible individuals recover from COVID-19 (Figure 1). The well-known complaint of altered taste and smell functions in patients with COVID-19[31] may reflect in a part a clinical manifestation of salivary dysfunction.

Conversely, because of the mimicry between viral spike protein and human cells, whether the messenger RNA (mRNA)-based anti-SARS-CoV-2 vaccines might stimulate an unwanted immune reaction in individuals with immune dysfunctions is controversial.[32] The speculation may not be limited to mRNA vaccines, as an association between specific vaccination (eg, influenza vaccine) and SS or the production of anti-Ro/anti-La antibodies has been reported.[23] Thus, the infection and/or vaccination might trigger or accelerate autoimmune responses against the spike protein of the SARS-CoV-2 in genetically susceptible individuals or patients with immune dysfunction. In this concern, not only autoimmune rheumatic diseases but also other autoimmunity entities such as hepatitis[33] and thyroiditis[34] have been reported to emerge after vaccination against SARS-CoV-2. Therefore, the potential stimulatory effect of SARS-CoV-2 vaccines (regardless of mRNA, virus vectored, or protein subunit) to brake immunological tolerance should be examined for both short- and long-term events. Nevertheless, considering the severe outcome of COVID-19, vaccinations should be processed under a balance between the risk and the benefit for each individual in this pandemic.[32]

CONFLICT OF INTEREST

None.

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