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EDITORIAL

SARS-CoV-2 infection provoking autoimmunity

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For decades, infections have been recognized as strong stimulators of the immune system and subsequently serve as a trigger for autoimmunity and autoimmune diseases. While infection is a very broad term, infectious agents such as bacteria, viruses and parasites, but particularly viruses present a key player in this regard and have been considered a classical example for this correlation.

Recently, the severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19), was no different from other potent triggers of the immune system in terms of producing autoimmune reactions secondary to infection. Having said that, during the early days of the COVID-19 pandemic, the immune and autoimmune manifestations of SARS-CoV-2 were underestimated. A fact that, if it is to be analysed in depth, necessitates closer focus on the potential of the correlation between infection in general and autoimmunity, and viruses in particular and autoimmunity.

Unsurprisingly, SARS-CoV-2 was called the 'autoimmune virus' by leading researchers as well as during an international congress on autoimmunity discussing various aspects of the autoimmune nature of SARS-CoV-2 [1]. Therefore, nowadays, whilst millions have already been infected with SARS-CoV-2 around the globe, the strong bond between SARS-CoV-2 and autoimmunity is a matter that still needs to be analyzed and presented.

PROPOSED MECHANISMS OF AUTOIMMUNITY IN SARS-COV-2 INFECTION

Various mechanisms have been proposed regarding the ways infections contribute to autoimmunity such as molecular mimicry and the bystander effect, among others. Nevertheless, the following can be summarized in correlation with SARS-CoV-2 infection:

(i) Immune dysregulation: SARS-CoV-2 was shown to cause several disturbances and dysregulation in the immune response in patients with COVID-19, especially those patients with severe disease. For instance, T cells were found to be significantly decreased and impaired in patients with severe COVID-19 [2]. In this regard, all subtypes of T cells including helper T cells, suppressor and regulatory T cells, showed a similar pattern.

(ii) Autoantibodies: the production of autoantibodies is considered the core of autoimmunity. Autoantibodies in autoimmunity serve as a complement to diagnosis, prognosis and response to treatment in a vast majority of diseases. Of significant importance, patients with SARS-CoV-2 infection demonstrate tens of autoantibodies directed against various auto-antigens [3]. For example, among others, autoantibodies against the G protein–coupled receptors in the autonomic nervous system were described in patients with COVID-19 [4]. In terms of the implication of these autoantibodies, though still under extensive investigations, the autoantibodies were linked to the severe manifestations of COVID-19 as well as the long recovery period following SARS-CoV-2 infection, what was called later on during the pandemic, 'post-COVID syndrome'.

(iii) Hyperferritinaemic syndrome and cytokine storm: since the start of the pandemic, patients with severe COVID-19 demonstrated high levels of ferritin. The finding was proposed to serve as a prognostic sign due to the fact that COVID-19 patients with high ferritin levels showed higher rates of morbidity and mortality [5]. The correlation with ferritin was the base for the reason behind categorizing COVID-19 as a fifth member of the 'hyperferritinemic syndrome' which includes: adult-onset Still's disease, macrophage activation syndrome, catastrophic antiphospholipid syndrome and septic shock [6]. All of these have in common a severe disease course, an extremely elevated level of inflammatory markers, and high morbidity and mortality rates. In fact, the cytokine storm shed light on the pathogenetic processes involved in severe COVID-19.

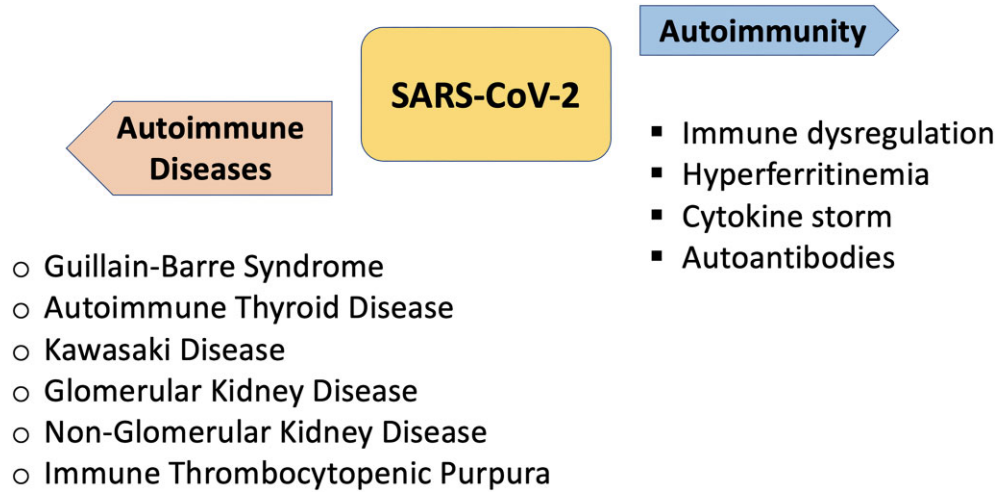

Figure 1: Autoimmunity, presented by mechanisms, and autoimmune diseases associated with SARS-CoV-2.

(iv) The role of biological agents in SARS-CoV-2 infection: following the aforementioned severe immune and autoimmune reactions illustrated, it is of no surprise that biological agents have been used in different treatment regimens for patients with severe COVID-19—those requiring oxygen, together with mechanically ventilated patients [7]. Patients treated with such agents showed better outcomes in some studies.

AUTOIMMUNE MANIFESTATIONS OF SARS-COV-2 INFECTION

To address autoimmunity first, autoimmune diseases can involve any organ system or tissue. For instance, Guillain–Barré syndrome points to the correlation between infection and autoimmunity manifested in the central nervous system; type 1 diabetes mellitus concerning autoantibodies against pancreatic insulin-producing cells; and primary biliary cholangitis in terms of liver involvement in autoimmune processes. Accordingly, the autoimmune phenomena reported in association with SARS-CoV-2 infection are numerous and concern many organ systems [3]. Among others, type 1 diabetes mellitus, Guillain–Barré syndrome, celiac disease, autoimmune thyroid disease, immune thrombocytopenic purpura and Kawasaki disease were all reported in patients with SARS-CoV-2 infection [8].

Moreover, of importance is the involvement of the kidneys in the autoimmune processes seen in SARS-CoV-2 infection. We have previously reported extensively on the kidney's role in autoimmunity [9]. The kidneys are involved in a wide range of autoimmune diseases including glomerular and non-glomerular kidney structures. In turn, infectious agents, bacteria and viruses alike have been associated with autoimmune kidney disease such as streptococcal and staphylococcal infections, hepatitis B virus, hepatitis C virus, human immunodeficiency virus and others. In terms of pathogenetic mechanisms related to kidney involvement, kidney injury can result from direct damage to the kidney by the infectious agent, molecular mimicry by which kidney-related structures are recognized as antigens by the immune system, and hyperstimulation of B cells leading to the production of autoantibodies.

In regard to SARS-CoV-2 and COVID-19 and the kidneys, glomerular diseases—those related to infections—are a classic example of infectious-related autoimmune kidney disorder. For instance, during the COVID-19 pandemic, glomerular lesions such as focal segmental glomerulosclerosis and ANCA-associated vasculitis were reported secondary to SARS-CoV-2 infection. Furthermore, a histological analysis of kidney biopsies from 17 patients with COVID-19, 15 out of 17 (88%) presented with acute kidney injury, and showed various forms of kidney injury patterns including podocytopathies with minimal or sclerotic lesions collapsing glomerulopathy, membranous nephropathy and anti-glomerular basement membrane glomerulonephritis in patients with native kidneys [10]. However, transplanted kidneys demonstrated T cell–mediated rejection, cortical infarction and acute tubular injury.

Autoimmune mechanisms related to SARS-CoV-2 infection and reported autoimmune diseases associated with the infection are presented in Fig. 1.

CONCLUSION

SARS-CoV-2 has been involved in autoimmunity and autoimmune manifestations since the start of the COVID-19 pandemic. Autoimmune diseases in the context of SARS-CoV-2 infection were consistently reported to affect every organ system. This was shown to be expressed by various patterns of autoimmunity, including immune dysregulation, autoantibody production and cytokine storm, among others. In terms of kidney disease, both glomerular and non-glomerular diseases were described with higher rates of the former including collapsing glomerulonephritis and membranous nephropathy. Such an implication of autoimmunity in SARS-CoV-2 infection, including kidney and non-kidney involvement, is critical and of paramount importance, as it serves as a basis for diagnosis, therapy, and prognosis.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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