

Editorial

Potential Mechanisms Linking SARS-CoV-2 to Autoimmunity

Tooba Ghazanfari¹ *1. Immunoregulation Research Center, Shahed University, Tehran, Iran.***Citation** Ghazanfari T. Potential Mechanisms Linking SARS-CoV-2 to Autoimmunity. *Immunoregulation*. 2025; 8:E1.<http://dx.doi.org/10.32598/Immunoregulation.8.1> <http://dx.doi.org/10.32598/Immunoregulation.8.1>

Viral infections such as COVID-19 are significant environmental triggers for autoimmune diseases [1]. After infection with COVID-19, many autoimmune disorders that can potentially impact diverse organ systems may emerge [2]. The processes underlying the onset of autoimmunity in post-COVID-19 patients are complex and varied. Recent research has proposed several plausible mechanisms and theories to elucidate the molecular basis of immune dysregulation associated with COVID-19. These include molecular mimicry by viral proteins, systemic manifestations and multi-organ involvement due to the extensive expression of the SARS-CoV-2 receptor ACE2, bystander activation of immune cells, the release of autoantigens from virus-damaged tissues, superantigen-mediated lymphocyte activation, and epitope spreading. Several host factors, including age, comorbidities, and genetic predispositions, may also play a role [3].

Various studies have reported that individuals with severe COVID-19 exhibit autoantibodies targeting various proteins in some tissues and organs, including the lungs, heart, blood vessels, brain, and components of the immune system [4, 5]. A possible reason is molecular mimicry, in which viral proteins resemble self-antigens, leading to cross-reactivity and autoimmune responses [6]. The cross-reactivity between viral and host proteins

is attributed to the structural or sequence similarities between COVID-19 viral proteins and self-antigens. This cross-reactivity can lead to an autoimmune reaction, wherein the immune system mistakenly identifies and attacks host tissues and organs. A study on 104 patients with COVID-19, including 40 with heart failure and 20 with severe aortic stenosis, used a protein microarray method and identified cross-reactivity between host proteins, including those present in immune cells, blood vessels, and lung tissue, and autoantibodies that targeted the spike protein of SARS-CoV-2. It was suggested that autoantibodies may inadvertently target and damage host tissues, leading to tissue injury and the development of autoimmune responses [7].

Bystander activation is another proposed mechanism that illustrates how COVID-19 infection triggers an overreaction of the immune system, resulting in collateral damage to healthy tissues [8]. The production of self-antigens and the activation of autoreactive immune cells may facilitate the development of autoimmunity. Exposure of self-antigens can activate autoreactive immune cells, leading to an immunological response against these self-antigens [9, 10]. Thus, the heightened immune response elicited by COVID-19 infection may result in collateral damage to healthy tissues, potentially leading to autoimmunity.

*** Corresponding Author:***Tooba Ghazanfari, Professor.**Address: Immunoregulation Research Center, Shahed University, Tehran, Iran.**Phone: +98 (21) 66418216**E-mail: ghazanfari@shahed.ac.ir*

Copyright © 2025 The Author(s);

This is an open access article distributed under the terms of the Creative Commons Attribution License (CC-BY-NC; <https://creativecommons.org/licenses/by-nc/4.0/legalcode.en>), which permits use, distribution, and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

A dysregulated immunological response induced by COVID-19 may lead to an imbalance in cytokine production, immune cell activation, and the generation of autoantibodies. SARS-CoV-2 infection may cause an exaggerated immune response, marked by the secretion of pro-inflammatory cytokines, commonly referred to as a “cytokine storm.” The development of autoimmunity in patients following COVID-19 may also be induced by the dysregulation of immune responses, cytokine secretion [9], immunological checkpoints, and the depletion of immune cells [11], which can consequently lead to loss of self-tolerance and development of autoimmune responses.

Persistent immune cell activation, including T and B cells, even after the infection, may facilitate the development of autoimmunity through the promotion of autoantibody production and the activation of autoreactive T cells. The development of autoimmunity may also be influenced by viral persistence and the establishment of viral reservoirs in specific organs. SARS-CoV-2 has been detected in multiple organs, such as the kidneys, brain, heart, and lungs. Prolonged viral persistence in these tissues may lead to continuous immunological activation and inflammation, potentially resulting in autoimmune reactions [12].

While emerging evidence implicates molecular mimicry, bystander activation, and viral persistence in post-COVID autoimmunity, critical questions also remain. The interplay of genetic susceptibility (e.g. HLA haplotypes and ACE2 polymorphisms) and epigenetic modifiers (e.g. DNA methylation changes induced by prolonged inflammation) remains poorly mapped. Furthermore, the pathophysiology of transient versus chronic autoimmune manifestations requires clarification; does it represent distinct pathways or a spectrum of immune dysregulation?

References

- [1] Hileman CO, Malakooti SK, Patil N, Singer NG, McComsey GA. New-onset autoimmune disease after COVID-19. *Frontiers in Immunology*. 2024; 15:1337406. [DOI:10.3389/fimmu.2024.1337406] [PMID]
- [2] Mohan A, Iyer VA, Kumar D, Batra L, Dahiya P. Navigating the post-COVID-19 immunological era: Understanding long COVID-19 and immune response. *Life*. 2023; 13(11):2121. [DOI:10.3390/life13112121]
- [3] Sharma C, Bayry J. High risk of autoimmune diseases after COVID-19. *Nature Reviews Rheumatology*. 2023; 19(7):399-400. [DOI:10.1038/s41584-023-00964-y] [PMID]
- [4] Meffre E, Iwasaki A. Interferon deficiency can lead to severe COVID. *Nature*. 2020; 587(7834):374-376. [DOI:10.1038/d41586-020-03070-1] [PMID]
- [5] Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann H-H, Zhang Y, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science*. 2020; 370(6515):eabd4585. [PMID]
- [6] Fagyas M, Nagy Jr B, Ráduly AP, Mányiné IS, Mártha L, Erdősi G, et al. The majority of severe COVID-19 patients develop anti-cardiac autoantibodies. *Geroscience*. 2022; 44(5):2347-60. [DOI:10.1007/s11357-022-00649-6]
- [7] Cunningham MW. Molecular mimicry, autoimmunity, and infection: the cross-reactive antigens of group A streptococci and their sequelae. *Microbiology Spectrum*. 2019; 7(4):10-1128. [DOI:10.1128/microbiolspec.GPP3-0045-2018]
- [8] Mobasheri L, Nasirpour MH, Masoumi E, Azarnaminy AF, Jafari M, Esmaili S-A. SARS-CoV-2 triggering autoimmune diseases. *Cytokine*. 2022; 154:155873. [DOI:10.1016/j.cyto.2022.155873]
- [9] Peng M-Y, Liu W-C, Zheng J-Q, Lu C-L, Hou Y-C, Zheng C-M, et al. Immunological aspects of SARS-CoV-2 infection and the putative beneficial role of vitamin-D. *International Journal of molecular sciences*. 2021; 22(10):5251. [DOI:10.3390/ijms22105251]
- [10] Vahabi M, Ghazanfari T, Sepehrnia S. Molecular mimicry, hyperactive immune system, and SARS-COV-2 are three prerequisites of the autoimmune disease triangle following COVID-19 infection. *International Immunopharmacology*. 2022;112:109183. [DOI:10.1016/j.intimp.2022.109183] [PMID]
- [11] Zhou Y, Han T, Chen J, Hou C, Hua L, He S, et al. Clinical and autoimmune characteristics of severe and critical cases of COVID-19. *Clinical and Translational Science*. 2020; 13(6):1077-86. [DOI:10.1111/cts.12805] [PMID]
- [12] Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. *Nature Medicine*. 2021; 27(4):601-15. [DOI:10.1038/s41591-021-01283-z]