Coronavirus Infection 2019 (COVID-19) and Autoimmunity

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Abstract—The pandemic of coronavirus disease 2019, etiologically associated with the SARS-CoV-2 virus, has drawn the attention of the medical community to new clinical and fundamental problems of the immunopathology of human diseases. During a detailed analysis of the clinical manifestations and immunopathological disorders in COVID-19, it became apparent that SARS-CoV-2 infection is accompanied by the development of a wide range of extrapulmonary clinical and laboratory disorders, some of which are characteristic of immunoinflammatory rheumatic diseases and other human autoimmune and autoinflammatory diseases. All this taken together served as a theoretical justification for the repositioning of anti-inflammatory drugs in COVID-19, previously specifically designed for the treatment of immunoinflammatory rheumatic diseases. The prospects for studying the autoimmune mechanisms of COVID-19 and the possibility of anti-inflammatory therapy are discussed.

Keywords: COVID-19, immunoinflammatory rheumatic diseases, autoimmunity, autoinflammation

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The pandemic of coronavirus disease 2019 (COVID-19), etiologically associated with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus, has drawn the attention of the medical community to new clinical and fundamental problems of the immunopathology of human diseases [1]. In the two years that have passed since the beginning of the pandemic, an unprecedented number of clinical and fundamental studies have been carried out in the world on the problems of epidemiology, virology, immunology, molecular biology, clinical polymorphism, and diagnostics and pharmacotherapy of COVID-19, bringing together scientists and doctors of all biological and medical specialties. These efforts culminated in the creation of several types of vaccines against the new infection, antiviral drugs, monoclonal antibodies that neutralize SARS-CoV-2, and, in general, the development of more rational approaches to managing patients with COVID-19 [2].

Rheumatology has made a significant contribution to the fight against the COVID-19 pandemic [1, 3]. Back in early 2020, the first publications concerning the rheumatological problems of COVID-19 formulated the position [1] that the experience gained in rheumatology over the past 70 years of studying the pathogenetic mechanisms and pharmacotherapy of immunoinflammatory rheumatic diseases as the most frequent and severe forms of autoimmune and autoinflammatory human pathology will be in demand to decipher the nature of the pathological processes underlying COVID-19 and develop approaches to effective pharmacotherapy.

Considering the history of science, recall that in 1950 T. Reichstein (Switzerland) and E. Kendall and P. Hench (United States) were awarded the Nobel Prize in Physiology or Medicine “for their discoveries related to adrenal cortex hormones and their structure...
and biological activity” [4]. A year earlier, at the American Mayo Clinic, the glucocorticoid hormone cortisone was first successfully used to treat patients with rheumatoid arthritis. Seventy years after the breakthrough in the treatment of inflammatory diseases, the use of synthetic glucocorticoids (GCs) in patients with severe COVID-19 not only saved the lives of tens of thousands of people but also contributed to the concept of the fundamental role of virus-induced inflammation in the pathogenesis of this disease. The next important step in the fight against the severe consequences of COVID-19 was the reposi-
tioning of genetically engineered biological drugs, which are monoclonal antibodies that block the activ-
itvity of proinflammatory cytokines (or their cellular receptors), as well as targeted anti-inflammatory drugs that modulate intracellular signaling of cytokines, special-
dy developed to treat immunoinflammatory rheu-
matic diseases, primarily rheumatoid arthritis [5].

Although SARS-CoV-2 infection is usually mild/moderately severe and results in recovery, some patients develop severe pneumonia or, less commonly, acute respiratory distress syndrome, coagulopathy, and potentially fatal multiple organ failure (1–2%). The pathogenesis of COVID-19 rests on a kind of virus-induced dysregulation (asynchronization) of innate and acquired immunity, leading to hyperpro-
duction of a wide range of proinflammatory, anti-
inflammatory, and immunoregulatory cytokines and other inflammatory mediators [6]. The course and outcome of the disease are determined both by the unique properties of the SARS-CoV-2 virus itself and by the synergistic (and amplifying) effects of age, gen-
der (male), and genetic factors; comorbid pathology; and the addition of a secondary bacterial infection (Fig. 1). The activation of transcription of inflamma-
tory mediator genes and an increase in the concentra-
tion of cytokines in the blood, including interleukins IL-1, IL-6, IL-8, IL-10, IL-17, and IL-18, the granu-
locyte-macrophage colony-stimulating factor, and the

chemokines CXCL10 and CCL2 are viewed as an “immunological signature” of pathological activation of immunity, the severity of which to a certain extent correlates with the severity of COVID-19 and an unfa-
forable prognosis. The climax of the immunopatho-
logical process is the “cytokine storm” syndrome, a heterogeneous clinical and laboratory symptom com-
plex that includes several pathological conditions: hemophagocytic lymphohistiocytosis, macrophage activation syndrome, and cytokine release syndrome induced by CAR-T-cell therapy (chimeric antigen receptor T-Cell) [7]. Presumably, with COVID-19, the specificity of the associated cytokine storm syn-
drome subtype manifests itself in a combination of immnosuppression, leading to a weakening of the antiviral immune response and slowing down of the elimination of SARS-COV-2 (viral sepsis), and hyper-
inflammation, the intensity of which may be expressed to a lesser extent than in other cytokine storm forms [8, 9].

Detailed analysis of the spectrum of clinical manifesta-
tions and immunopathological disorders in COVID-19 revealed that SARS-CoV-2 infection leads to the development of a wide range of extrapulmonary clinical and laboratory disorders, some of which are characteristic of immunoinflammatory rheumatic and other autoimmune and autoinflammatory human diseases [10]. These include fever, fatigue, arthralgia and arthritis, myalgia, skin “vasculitic” rash, alopecia, thrombosis, clinical and laboratory manifestations of hyperinflammation, and cytopenia. In addition, against the background of infection with the SARS-CoV-2 virus, the development of diseases classified as autoimmune and/or autoinflammatory (rheumatoid arthritis, reactive arthritis, systemic lupus erythemato-
sus, systemic vasculitis, inflammatory myopathies, Guillain–Barré syndrome, IgA nephropathy, Still’s disease, autoimmune cytopenia, etc.) is recorded, and more than 50 types of organ-specific and organ-non-
specific autoantibodies characteristic of these diseases.
are found in the serum of patients with COVID-19 [11, 12]. All this taken together made it possible to discuss the pathogenetic significance of SARS-CoV-2 infection as a trigger factor for human autoimmune pathology [13–15].

When considering the common (partially intersecting) mechanisms of COVID-19 and autoimmune diseases, noteworthy is the close pathogenetic relationship between inflammation, activation of the complementary system, and hypercoagulability, which forms the basis of the pathological process called thrombotic inflammation (immunothrombosis) and viewed as a universal mechanism of pathogenesis both in COVID-19 (the so-called COVID-19-associated coagulopathy) and in immunoinflammatory rheumatic diseases [16–18]. A certain specificity of thromboinflammation in COVID-19 is due to the mechanism of infection with the SARS-CoV-2 virus, which, using angiotensin-converting enzyme 2 as a receptor, induces dysregulation of the renin–angiotensin–aldosterone system, characterized by excessive formation of angiotensin II, which has proinflammatory, vasoconstrictor, and profibrotic effects [19].

Important evidence of the development of autoimmune pathology in COVID-19 is the hyperproduction of autoantibodies—diagnostic markers of autoimmune diseases, which simultaneously play a significant role in the development of autoimmune inflammation. Among them, the most important are antibodies to phospholipid-binding proteins and antibodies to the components of the nucleus and cytoplasm, cytokines, and extracellular and secreted proteins.

In the spectrum of autoimmune manifestations of COVID-19, special attention is drawn to the antiphospholipid syndrome (APS)—a symptom complex that manifests itself in recurrent thrombosis (arterial and/or venous), obstetric pathology, and the presence of antiphospholipid antibodies [20]. As part of the antiphospholipid syndrome, the so-called catastrophic APS stands out—a rare potentially lethal form, characterized by widespread intravascular microthrombosis, resembling COVID-19 coagulopathy [18]. With COVID-19, antiphospholipid antibodies are detected in about half of patients; they are associated with a severe course of the disease and thrombosis of cerebral vessels and can persist in the blood after recovery. Note that antiphospholipid antibodies isolated from the serum of patients with COVID-19, systemic lupus erythematosus, and antiphospholipid syndrome in vitro cause activation of endothelial cells, which is manifested by overexpression of adhesion molecules on their membranes [21].

Recently, lipid-binding antibodies of a new type have been discovered in patients with COVID-19, which, reacting with a complex of lysobisphosphatidic acid and the protein C receptor, induce prothrombotic and proinflammatory activation of monocytes and endothelial cells and thrombus formation, and their detection is associated with a critical disease course and poor prognosis [22]. Of interest are data on the detection of antibodies to the phospholipid-binding protein annexin A2 in the serum of patients with severe COVID-19 and antiphospholipid syndrome [23, 24].

Another autoantigenic target in COVID-19 and antiphospholipid syndrome is autoantibodies to ADAMTS-13 (a metalloproteinase belonging to the Adams peptidase protein family), which are associated with disease severity and mortality in COVID-19, and in patients with antiphospholipid syndrome, with a high risk of thrombosis [25]. An important autoimmune mechanism of their occurrence in COVID-19 is associated with the synthesis of antibodies that induce antibody-dependent activation, apoptosis, and procoagulant activity of platelets [26] and antibodies to platelet factor 4 (PF4) [27]. Presumably, thrombotic thrombocytopenia that develops in COVID-19 or after vaccination against SARS-CoV-2 may be associated with the induction of the synthesis of antibodies to PF4 [28].

The common mechanism of thromboinflammation in both COVID-19 and immunoinflammatory rheumatic diseases may be due to the formation of neutrophil extracellular traps, the detection of components of which (free DNA, DNA-myeloperoxidase complex, citrullinated histone H3) in the serum of patients with COVID-19 correlates with disease severity and the development of thrombotic disorders [29]. All the data make it possible to discuss the pathogenetic significance of various types of autoantibodies to phospholipid-binding proteins in the development of coagulopathy and the existence of the so-called COVID-19-induced APS-like syndrome. Isolation of the autoimmune subtype of COVID-19, associated coagulopathy, may be of great clinical importance in terms of personalizing anticoagulant and anti-inflammatory therapy [18].

Another type of autoantibodies detected in the serum of patients with COVID-19 is antinuclear antibodies characteristic of immunoinflammatory rheumatic diseases, which, just like antiphospholipid antibodies, are associated with severe COVID-19, inflammation activity, and the risk of thrombosis. The pathogenetic significance of these autoantibodies is evidenced by the “crossover” of clinical, serological, radiological, and morphological manifestations of COVID-19 pneumonia and interstitial lung disease in immunoinflammatory rheumatic diseases, which are characterized by the presence of a wide range of antinuclear antibodies [30]. An interesting example of similarities between COVID-19 and immunoinflammatory rheumatic diseases is a subtype of inflammatory myopathy, the so-called anti-MDA-5 syndrome. Its characteristic laboratory biomarker is antibodies to the MDA-5 protein, which acts as an intracellular sensor of viral RNA (including coronaviruses). Clinically, anti-MDA5 syndrome reveals itself in rapidly pro-
progressing interstitial lung disease radiographically similar to COVID-19 pneumonia, muscle weakness, typical skin rash, fever, thrombotic disorders, and other systemic manifestations. In patients with COVID-19, the detection and titers of antibodies to MDA5 significantly correlate with disease severity and mortality [31].

Given the fundamental role of angiotensin-converting enzyme-2 (ACE2) as a receptor for SARS-CoV-2, the detection of antibodies to ACE2 in patients with COVID-19 and immunoinflammatory rheumatic disease has attracted attention [32]. They are supposed to be anti-idiotypic antibodies to the SARS-CoV-2 S-protein [33]. This corresponds to the “network” concept of immunity, formulated by N. Jerne, a Nobel Prize winner in Physiology and Medicine in 1984, and subsequently developed by P. Plotz, according to which autoantibodies are actually anti-idiotypic antibodies against antiviral antibodies, and their synthesis is one of the important mechanisms of virus-induced autoimmunity.

Autoantibodies to a wide range of proteins, previously undetectable in human autoimmune diseases, were detected in the serum of patients with COVID-19 using autoantigen analysis. Wang et al. [34], using the rapid extracellular antigen profiling (REAP) method, which makes it possible to determine simultaneously autoantibodies to 2770 extracellular and secreted proteins, found in the serum of patients with COVID-19 autoantibodies that interact with a variety of protein molecules with immunomodulatory activity (cytokines, chemokines, complement components) and membrane proteins of various cells. These antibodies can disrupt the function of cells of the immune system and weaken the control of viral infection by inhibiting immunoreceptor signaling and disrupting the composition of peripheral immune cells. Chang et al. [35] studied the inhibition of autoantibodies to cytokines and antibodies to SARS-CoV-2 in the serum of patients with severe COVID-19 using specially designed protein microarrays. Antibacterial antibodies were found in more than half of the patients, their overproduction correlating with high titers of antibodies to structural (S1, S2, N) SARS-CoV-2 proteins. These data allow us to draw attention to the role of the phenomenon of “molecular mimicry” in the development of autoimmune disorders in COVID-19, associated with cross-reactivity observed between antibodies to SARS-CoV-2 viral epitopes and self-tissue proteins.

With regard to deciphering the mechanisms of the association between SARS-CoV-2 infection and the development of autoimmune pathology, of particular interest are data indicating dysregulation of type I interferon synthesis in patients with COVID-19 [36] and systemic lupus erythematosus. In COVID-19, a decrease in type I interferon synthesis is observed, which is associated with a severe course of the disease, a slowdown in SARS-CoV-2 clearance, and hyperproduction of proinflammatory cytokines associated with autosomal recessive gene defects with a loss of function of type I interferons involved in TLR3/7-dependent signaling. In addition, neutralizing antibodies to interferons α2 and w are detected in the serum of patients with severe COVID-19. Note that the detection of these antibodies in patients with systemic lupus erythematosus who subsequently fell ill with COVID-19 is associated with a severe course.

Important results, to some extent revealing the mechanisms of the relationship between SARS-CoV-2 and autoimmune pathology, were obtained in the process of in-depth immunophenotyping of B cells [37]. It has been established that, in patients with severe COVID-19, the extrafollicular pathway of the B-cell immune response, which is typical of patients with severe systemic lupus erythematosus, was activated. It remains unclear whether the extrafollicular pathway of the B-cell immune response is a cause or a consequence of the severe course of COVID-19 and systemic lupus erythematosus and how its involvement affects the overproduction of proinflammatory mediators and autoantibodies.

At present, despite the colossal number of open and randomized controlled trials, the management of patients with COVID-19 remains empirical in nature and needs to be improved. Obviously, the main trend of pharmacotherapy of COVID-19, as well as other viral infections, is associated with the implementation of a preventive strategy (vaccination) and the use of antiviral drugs with proven efficacy, and in patients with COVID-19-associated hyperinflammatory syndrome, rational anti-inflammatory therapy. It can be assumed that, in COVID-19, anti-inflammatory therapy is most effective during the short period between the end of the viremia phase, when the cytopathic effect of the virus determines the formation of the early (protective but not always effective) antiviral immune response, and the beginning of the transformation of the immune response in some patients into the hyperimmune phase progressing towards COVID-19-associated hyperinflammatory syndrome (cytokine storm). Drugs that have both antiviral and immunomodulatory effects may be optimal for the treatment of those patients who are at risk of developing hyperinflammation. In the context of improving immunomodulatory personalized therapy based on the concept of taxonomy of cytokine-dependent diseases [38], intensive research is ongoing aimed at finding leading molecular and therapeutic targets in COVID-19.

The first drugs officially recommended for the treatment of severe/critical COVID-19 were glucocorticoids [2]. In rheumatology, vast experience has been accumulated in their use, including for the treatment of life-threatening complications of immunoinflammatory rheumatic diseases. However, many theoretical and practical problems of glucocorticoid therapy in patients with COVID-19 require further study. In the spectrum of cytokines involved in the pathogenesis...
of immunoinflammatory rheumatic diseases and COVID-19, interleukin-6 is of great importance [39]. Inhibition of IL-6 using monoclonal antibodies to IL-6 receptors (tocilizumab, sarilumab, the Russian drug levulimab) or to IL-6 (the Russian drug ololizumab) is considered one of the most important trends in the pharmacotherapy of COVID-19-associated hyperinflammatory syndrome. IL-1β, a key mediator of human autoinflammatory diseases, is considered as a promising target [40]. Certain hopes are associated with the use of Janus kinase inhibitors (baricitinib and tofacitinib) [41], which suppress the signaling of a wide range of proinflammatory cytokines (IL-6, IL-10, granulocyte-macrophage colony-stimulating factor, etc.) involved in the development of hyperinflammatory syndrome in patients with COVID-19.

In conclusion, let us emphasize that the COVID-19 pandemic has drawn attention to the problems of virus-induced autoimmunity and in a short time has accumulated many areas of scientific and clinical research related to the study of the mechanisms of immunopathogenesis and the treatment of human autoimmune and autoinflammatory diseases. A hypothetical model for the development of autoimmune pathology in patients with COVID-19, summarizing the proven (or putative) factors and mechanisms of hyperinflammation in COVID-19 and AIIRD, is shown in Fig. 1.

Hopefully, the efforts of scientists and doctors around the world will not only improve the prognosis for COVID-19 and help gain new knowledge to combat epidemics of viral infections that humanity may face in the future successfully but will also contribute to the improvement of pharmacotherapy for widespread autoimmune and autoinflammatory human diseases.

TRANSPARENCY

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. E. L. Nasonov, “Coronavirus disease 2019 (COVID-19): Reflections of a rheumatologist,” Nauch.-Prakt. Revmatol. 58 (2), 123–132 (2020). https://doi.org/10.14412/1995-4484-2020-123-132

2. F. L. van de Veerdonk, E. Giamarellos-Bourboulis, P. Pickkers, et al., “A guide to immunotherapy for COVID-19,” Nat. Med. 28 (1), 39–50 (2022).

3. G. Schett, B. Manger, D. Simon, and R. Caporali, “COVID-19 revisiting inflammatory pathways of arthritis,” Nat. Rev. Rheumatol. 16 (8), 465–470 (2020).

4. T. N. Raju, “The Nobel chronicles. 1950: Edward Calvin Kendall (1886–1972); Philip Showalter Hench (1896–1965); and Tadeus Reichstein (1897–1996),” Lancet 353 (9161), 1370 (1999).

5. C. B. Nissen, S. Sciascia, D. de Andrade, et al., “The role of antirheumatics in patients with COVID-19,” Lancet Rheumatol. 3 (6), e447–e459 (2021).

6. Y. Wang and S. Perlmutter, “COVID-19: Inflammatory profile,” Annu. Rev. Med. 73, 65–80 (2022).

7. D. C. Faigenbaum and C. H. June, “Cytokine storm,” New Engl. J. Med. 383, 2255–2273 (2020).

8. D. E. Leisman, L. Ronner, R. Pinotti, et al., “Cytokine elevation in severe and critical COVID-19: A rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes,” Lancet Respir. Med. 8 (12), 1233–1244 (2020).

9. J. E. Weatherhead, E. Clark, T. P. Vogel, et al., “Inflammatory syndromes associated with SARS-CoV-2 infection: Dysregulation of the immune response across the age spectrum,” J. Clin. Invest. 130 (12), 6194–6197 (2020).

10. M. Ramos-Casals, P. Brito-Zerón, and X. Mariette, “Systemic and organ-specific immune-related manifestations of COVID-19,” Nat. Rev. Rheumatol. 17 (6), 315–332 (2021).

11. A. E. Gracia-Ramos, E. Martin-Nares, and G. Hernández-Molina, “New onset of autoimmune diseases following COVID-19 diagnosis,” Cells 10 (12), 3592 (2021).

12. J. Damoiseaux, A. Dotan, M. J. Fritzler, et al., “Autoantibodies and SARS-CoV2 infection: The spectrum from association to clinical implication. Report of the 15th Dresden Symposium on Autoantibodies,” Autoimmun. Rev. 21 (3), 103012 (2021).

13. Y. Liu, A. H. Sawalha, and Q. Lu, “COVID-19 and autoimmune diseases,” Curr. Opin. Rheumatol. 33 (2), 155–162 (2021).

14. J. S. Knight, R. Caricchio, J. L. Casanova, et al., “The intersection of COVID-19 and autoimmunity,” J. Clin. Invest. 131 (24), e154886 (2021).

15. G. Halpert and Y. Shoenfeld, “SARS-CoV-2, the autoimmune virus,” Autoimmun. Rev. 19 (12), 102695 (2020).

16. A. Bonaventura, A. Vecchié, L. Dagna, et al., “Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19,” Nat. Rev. Immunol. 21 (5), 319–329 (2021).

17. J. T. Merrill, D. Erkan, J. Winakur, and J. A. James, “Emerging evidence of a COVID-19 thrombotic syndrome has treatment implications,” Nat. Rev. Rheumatol. 16 (10), 581–589 (2020).

18. E. L. Nasonov, T. V. Beketova, T. M. Reshetnyak, et al., “Coronavirus disease 2019 (COVID-19) and immunoinflammatory rheumatic diseases: At the crossroads of thromboinflammation and autoimmunity,” Nauch.-Prakt. Revmatol. 58 (4), 353–367 (2020). https://doi.org/10.47360/1995-4484-2020-353-367

19. B. M. Henry, J. Vikse, S. Benoît, et al., “Hyperinflammation and derangement of renin-angiotensin-aldoste-
ron system in COVID-19: A novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis,” Clin. Chim. Acta. 507, 167–173 (2020).

20. Antiphospholipid Syndrome, Ed. by E. L. Nasonov (Littera, Moscow, 2004) [in Russian].

21. H. Shi, Y. Zuo, S. Navaz, et al., “Endothelial cell-activating antibodies in COVID-19,” Arthritis Rheumatol. 2022. https://doi.org/10.1002/art.42094

22. A. Hollerbach, N. Müller-Calleja, D. Pedrosa, et al., “Pathogenic lipid-binding antiphospholipid antibodies are associated with severity of COVID-19,” J. Thromb. Haemost. 19 (9), 2335–2547 (2021).

23. M. Zuniga, C. Gomes, S. E. Carsons, et al., “Autoimmunity to annexin A2 predicts mortality among hospitalised COVID-19 patients,” Eur. Respir. J. 58 (4), 2100918 (2021).

24. F. Cañas, L. Simonin, F. Couturaud, et al., “Annexin A2 autoantibodies in thrombosis and autoimmune diseases,” Thromb. Res. 135 (2), 226–230 (2015).

25. A. A. N. Doevelaar, M. Bachmann, B. Hölzer, et al., “Generation of inhibitory autoantibodies to ADAMTS13 in Coronavirus disease 2019,” medRxiv. 2021.03.18.21253869. https://doi.org/10.1101/2021.03.18.21253869

26. K. Althaus, I. Marini, J. Zlamal, et al., “Antibody-induced procoagulant platelets in severe COVID-19 infection,” Blood. 137 (8), 1061–1071 (2021).

27. J. Brodard, J. A. Kremer Hovinga, P. Fontana, et al., “COVID-19 patients often show high-titer non-platelet-activating anti-PF4/heparin IgG antibodies,” J. Thromb. Haemost. 19 (5), 1294–1298 (2021).

28. A. Greinacher, T. Thiele, T. E. Warkentin, et al., “Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination,” New Engl. J. Med. 384 (22), 2092–2101 (2021).

29. Y. Zuo, M. Zuo, S. Yalavarthi, et al., “Neutrophil extracellular traps and thrombosis in COVID-19,” J. Thromb. Thrombolyis 51 (2), 446–453 (2021).

30. D. Gagiannis, J. Steinestel, C. Hackenbroch, et al., “Clinical, serological, and histopathological similarities between severe COVID-19 and acute exacerbation of connective tissue disease-associated interstitial lung disease (CTD-ILD),” Front. Immunol. 11, 587517 (2020).

31. G. Wang, Q. Wang, Y. Wang, et al., “Presence of anti-MDA5 antibody and its value for the clinical assessment in patients with COVID-19: A retrospective cohort study,” Front. Immunol. 12, 791348 (2021).

32. J. M. Arthur, J. C. Forrest, K. W. Boehme, et al., “Development of ACE2 autoantibodies after SARS-CoV-2 infection,” PLoS One 16 (9), e0257016 (2021).

33. W. J. Murphy and D. L. Longo, “A possible role for anti-idiotype antibodies in SARS-CoV-2 infection and vaccination,” New Engl. J. Med. 386 (4), 394–396 (2022).

34. E. Y. Wang, T. Mao, J. Klein, et al., “Diverse functional autoantibodies in patients with COVID-19,” Nature 595 (7866), 283–288 (2021).

35. S. E. Chang, A. Feng, W. Meng, et al., “New-onset IgG autoantibodies in hospitalized patients with COVID-19,” Natura Com. 12, 5417 (2021).

36. P. Bastard, Q. Zhang, S. Y. Zhang, et al., “Type I interferons and SARS-CoV-2: from cells to organisms,” Curr. Opin. Immunol. 74, 172–182 (2022).

37. M. C. Woodruff, R. P. Ramonell, D. C. Nguyen, et al., “Extrafollicular B cell responses correlate with neutralizing antibodies and morbidity in COVID-19,” Nat. Immunol. 21 (12), 1506–1516 (2020).

38. G. Schett, I. B. McInnes, M. F. Neurath, “Reframing immune-mediated inflammatory diseases through signature cytokine hubs,” New Engl. J. Med. 385 (7), 628–639 (2021).

39. E. Nasonov and M. Samsonov, “The role of interleukin 6 inhibitors in therapy of severe COVID-19,” Biomed. Pharmacother. 131, 110698 (2020).

40. Y. Wang, K. Zhu, R. Dai, et al., “Specific interleukin-1 inhibitors, specific interleukin-6 inhibitors, and GM-CSF blockades for COVID-19 (at the edge of sepsis): A systematic review,” Front. Pharmacol. 12, 804250 (2022).

41. B. K. Gajjela and M. M. Zhou, “Calming the cytokine storm of COVID-19 through inhibition of JAK2/STAT3 signaling,” Drug Discov. Today 27 (2), 390–400 (2022).

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