Crimson Publishers
Wings to the Research

Opinion

A Potential Mechanism for Triggering Cytokine Storm in Covid-19 Patients

Harald Butterweck and Alfred Weber*

Baxalta Innovations GmbH, Vienna, Austria

***Corresponding author:** Alfred Weber, Baxalta Innovations GmbH, Vienna, Austria

Submission: August 29, 2020

Published: September 03, 2020

Volume 1 - Issue 2

How to cite this article: Harald Butterweck, Alfred Weber. A Potential Mechanism for Triggering Cytokine Storm in Covid-19 Patients. COJ Biomedical Science & Research. 1(2). COJBSR. 000508. 2020.

Copyright@ Alfred Weber. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License, which permits unrestricted use and redistribution provided that the original author and source are credited.

Abstract

Infection with SARS-CoV-2 can result in severe disease characterized by cytokine storm and systemic inflammation. Despite huge efforts, there is only initial evidence that the humoral immune response and particularly the development of antibodies targeting SARS-CoV-2 nucleoprotein could play a decisive role for disease severity. Here, we present the opinion that severe Covid-19 disease could be co-triggered by anti-SARS-Cov-2 nucleoprotein antibodies, which are cross-reactive with human interleukin-11 and inhibit its anti-inflammatory and tissue protective function.

Keywords: Autoantibodies; Covid-19; SARS-CoV-2; Cytokine storm; Interleukin-11; Nucleoprotein

Opinion

After the Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV) outbreak in 2003, the Covid-19 pandemic spread worldwide in 2019/2020 affecting 24 million of people with a considerable mortality rate [1]. While many patients experience a mild to moderate disease course, for unknown reasons a single digit percentage of patients progresses to severe or even life-threatening conditions. However, successful convalescent plasma therapy has been reported demonstrating the beneficial effect of regulated immune response to SARS-CoV-2 [2]. The medicinal, societal, and economical criticality of the crisis has prompted the community to an unprecedent solidarity. Alliances have been built between competitive Pharma companies and all findings are open to access for the whole scientific community. Most scientists believe it is an obligation to contribute to the resolution of the crisis by developing treatments and vaccines. Knowledge about the virus and of its interaction with human cells and tissues triggering occasionally (excessive) human defense mechanisms is an indispensable prerequisite to reach this target. The present opinion merges the findings from studies regarding SARS, SARS-CoV-2, interleukin 11 (IL-11) and autoimmune diseases.

Covid-19 is often asymptomatic but in mild cases symptoms at the onset are sore throat, coughing and fatigue. Some days after onset anosmia and dysgeusia are reported frequently. Fever follows in moderate to severe cases. The disease may than progress to pneumoniae and acute respiratory distress syndrome [3]. Interestingly, this state is already characterized by the presence of an adaptive immune response. In severe cases, mechanical ventilation is required. Life- threatening conditions triggered by a cytokine storm are lung and heart failure, thrombocytopenia, and lymphopenia. Even complications affecting the nervous system are reported. Like SARS, SARS-CoV-2 targets the host epithelial cells in the respiratory tract by binding of its surface protein to the angiotensin-converting enzyme 2 (ACE2) which is part of the renin-angiotensin system. ACE2 is known to mediate anti-inflammatory responses through generation of Angiotensin 1-7. This MAS receptor agonist was shown to decrease TNF-α and IL-1β levels and neutrophil recruitment in an antibody-induced arthritis mouse model. Thus, through ACE2 binding SARS-CoV-2 already inhibits the anti-inflammatory arm

of the renin angiotensin system during cell entry and thereby enhances the pro-inflammatory response in the host. After cell entry SARS virus was found to interfere with the JAK/STAT signaling pathway [4]. Especially STAT 3 is dephosphorylated in infected cells. The IL-6 cytokine family regulates the immune system and cell apoptosis by STAT 3 activation [5]. Furthermore, antibody-dependent enhancement (ADE) was reported for the SARS virus [6]. This probably explains the excessive activation of macrophages, resulting in devastating pro-inflammatory conditions. Of note, it was shown recently that IgG antibodies with a distinct Fc glycosylation pattern drive macrophage activation [7]. Serum from severely ill Covid-19 patients was incubated with SARS-Cov-2 spike (S) protein in vitro to form immune complexes which triggered excessive macrophage activation. The authors concluded that neutralizing anti-S protein antibodies could trigger a pronounced inflammatory response in macrophages without infection of the cells. These data seemed to confirm that there is no evidence for ADE during SARS-Cov-2 infection. Surprisingly, it was not investigated, if native serum samples could activate macrophages as it is likely that serum from severely ill Covid-19 patients could contain immune complexes containing other SARS-Cov-2 antigens.

Severe Covid-19 disease form is characterized by a cytokine storm as described for other conditions including macrophage activating syndrome [8], catastrophic antiphospholipid syndrome and septic shock. Among other cytokines, especially IL -1, IL -6 and TNF-α are reported to be elevated. Similarly, the adverse reaction occurring during a phase I trial for an anti-CD28 monoclonal antibody [9] was associated with a significant increase of the proinflammatory cytokines TNF-α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-12p and IFN-γ. Cytokine storm is also known to potentially cause multiorgan failure with fatal outcome in several autoimmune diseases [10].

As exemplified, SARS-CoV-2 promotes a strong inflammatory response and elicits a solid neutrophil, macrophage and T cell response accompanied by elevated pro-inflammatory cytokine levels. The disease seems to be clearly Th1 driven but the severe disease form is characterized by a strong S protein neutralizing antibody response. Early and pronounced IgG and IgM responses correlate with disease severity. Even more, disease severity has recently been described to be linked to a stronger antibody response against the N protein of SARS-CoV-2 [11]. Grifoni, et al. [12] investigated prediction models for SARS-CoV-2 immune response and identified possible immunodominant regions and epitopes for the SARS.CoV-2 proteins. Not unexpectedly, the majority of B and T cell epitopes was found on S protein (64% and 47% of total epitopes), followed by B and T cell epitopes on N protein making up 26% and 33%, respectively. In another publication [13] the responses against several viral proteins were associated to CD4+ and CD8+ T cells revealing that CD8+ T cell response is more likely to be directed against SARS-CoV-2 N protein and by far not as strong as CD4+ response against S protein. These findings are in line with higher production of N protein by the host cell, estimated to be 10-times higher than that of S protein [14]. Cheng, et al. [15] described the cross-reactivity of a mouse scFv directed against N protein with human recombinant IL-11. The IL-11-binding scFv also inhibited IL-11-induced STAT3 phosphorylation. In line with this observation is the finding that STAT3 phosphorylation is suppressed in SARS-CoV-infected Vero E6 cells [4]. Significant N-specific antibody levels were detected in SARS patients 1 to 2 weeks after infection. Severe cases were associated with an early and strong response to the SARS N protein [16,17]. Interestingly, Wang, et al. [18] reported positive results for non-exposed patients with various autoimmune diseases using SARS-CoV IgG and IgM ELISAs with antigens from SARS-CoV Vero E6 cell lysates and an immunofluorescence test with SARS-CoV-infected Vero E6 cells. The authors concluded that these antibodies are cross-reactive with Vero cell antigen. Unfortunately, the possibility that antibodies from autoimmune patients could cross react with SARS-CoV antigens was not investigated. Viral infections have been reported to induce autoantibodies and to potentially trigger autoimmune diseases in humans. Generation of autoantibodies has been described after infection with human immunodeficiency virus, hepatitis C virus, enterovirus and Epstein-Barr virus. Independently, Italy's most Covid-19 affected region Lombardia reported a dramatically increase in Kawasaki disease-similar symptoms in children and adolescents after SARS-CoV-2 exposure with mild or asymptomatic symptoms weeks after infection [19]. A similar increase was reported for New York. Molecular mimicry was proposed as the mechanism to explain neuronal complications seen in Covid-19 patients [20], but also autoimmune hemolytic anemia [21]. Just recently, the occurrence of false positive anti-SARS-CoV-2 antibodies directed against the N protein has been described in two of three Kawasaki patients. This raises the question if autoantibodies from Kawasaki patients can cross-react with SARS-CoV-2 antigens [22].

Overall genetic homology between SARS and SARS-CoV-2 is 85-90%, the same is true for N protein homology. Based on these findings related to SARS and SARS-CoV-2, we hypothesize that one possible mechanism for developing a severe form of Covid-19 might be an early, strong antibody response against SARS-Cov-2 N protein. This could possibly be related to an initial high viral load or an impaired first immune barrier on the mucosa of the upper respiratory tract allowing the virus to massively infect lung epithelial cells. Certain anti-N antibodies could cross-react with IL-11, thus impairing immune regulation, inhibiting STAT 3 phosphorylation pathway signaling and triggering cell apoptosis. IL-11 was reported to regulate Th1/Th2 polarization in antigen presenting cells, to trigger differentiation of naïve CD4+ T-cells into IL-4-producing Th2 cells and to inhibit IFN-γ producing Th1 T cells [23]. Inhibition of proinflammatory cytokine production by macrophages was also described [24]. In normal healthy individuals,

Copyright © Alfred Weber

IL-11 levels are hardly detectable in blood. IL-11 is expressed in fibroblasts, epithelial cells, in the heart, lung, thymus, spleen, bone marrow, brain, intestine, testis and ovary. Overall, IL-11 has been described as a pleiotropic cytokine with biological activity on many different cell types. Recombinant IL-11 has been approved for the treatment of chemotherapy-induced thrombocytopenia [25]. IL-11 is also known as an anti-inflammatory factor. In addition, there is sparse data on its potential antiviral activity. In 2019, Li, et al. [26] investigated the antiviral activity of IL-11 using porcine epidemic diarrhea virus-infected Vero cell. They found that following viral infection IL-11 expression was clearly upregulated. IL-11 knockdown promoted virus infection in Vero cells, while porcine IL-11 administration resulted in prevention of apoptosis caused by the virus. The authors concluded that IL-11, generated as a response to epidemic diarrhea virus infection, inhibited apoptosis via the STAT3 signaling pathway as STAT3 inhibitors obviously antagonized the anti-apoptosis function of porcine IL-11. The multiple functions of IL-11 could therefore interfere in many aspects with the pro-inflammatory Th1 response triggered by SARS-CoV-2. Thus, IL-11 would counteract tissue and cell damage as seen in severe Covid -19 cases through binding of IL -11 receptor on epithelial cells and the classical JAK/STAT3 signaling. Alternatively, IL-11 signaling is also possible via trans signaling and trans presentation [27]. Trans signaling is described to be mediated by a complex of IL-11 and soluble IL-11 receptor which binds to gp130 expressing cells. Trans presentation occurs between adjacent cells, one expressing IL-11 receptor, the other expressing gp130. IL-11 signaling thus is not limited to IL-11 receptor bearing cells but allows regulation of all cell types expressing gp130. The presence of anti-IL-11 antibodies will interfere with the classical and both alternate signaling pathways.

Uncontrolled, upregulated inflammatory response leading to cytokine storm could be an inadvertent consequence or a cumulative effect of anti-N antibodies cross-reacting with IL-11. This would impair IL-11-driven tissue protection or cell proliferation. This hypothesis could well fit as additional puzzle piece in the complex mosaic depicted in the comprehensive, holistic immunological model of COVID-19 [28]. Verification of this hypothesis would have implications for the design of vaccines and provide an additional diagnostic tool for patients at risk to develop severe disease. Potentially, this is also a unique opportunity to elucidate the mechanism of autoimmune Kawasaki disease.

References

1. WHO (2020) Coronavirus disease (COVID-19) weekly epidemiological update data.
2. Joyner MJ, Wright RS, Fairweather D, Senefeld JW, Bruno KA, et al. (2020) Early safety indicators of COVID-19 convalescent plasma in 5,000 patients. J Clin Invest 130: 4791-4797.
3. Siordia JA (2020) Epidemiology and clinical features of COVID-19: A review of current literature. J Clin Virol 127: 104357.
4. Mizutani T, Fukushi S, Murakami M, Hirano T, Saijo M, et al. (2004) Tyrosine de-phosphorylation of STAT3 in SARS coronavirus-infected Vero E6 cells. FEBS Lett 577: 187-192.
5. Takeda KK, Kaisho T, Yoshida N, Takeda J, Kishimoto T, et al. (1998) Stat3 activation is responsible for IL-6-dependent T Cell proliferation through preventing apoptosis: Generation and characterization of T cell-specific Stat3-deficient mice. The Journal of Immunology 161: 4652-4660.
6. Yip MS, Leung HL, Li PH, Cheung CY, Dutry I, et al. (2016) Antibody-dependent enhancement of SARS coronavirus infection and its role in the pathogenesis of SARS. Hong Kong Med J 22: S25-S31.
7. Hoepel W, Chen HJ, Allahverdiyeva S, Manz X, Aman J, et al. (2020) Anti-SARS-CoV-2 IgG from severely ill COVID-19 patients promotes macrophage hyper-inflammatory responses.
8. Rosario C, Goddard ZG, Holtz MEG, D'Cruz DP, Shoenfeld Y (2013) The hyperferritinemic syndrome: Macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. BMC Med 11: 185-196.
9. Suntharalingam G, Perry MR, Ward S, Brett SJ, Cortes CA, et al. (2000) Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412N. Engl J Med 355: 1-11.
10. Caricchio R (2019) Systemic lupus erythematosus and cytokine storm. In: Cron R, Behrens E (Eds.), Cytokine Storm Syndrome. Springer, Cham.
11. Atyeo C, Fischinger S, Zohar T, Slein MD, Burke J, et al. (2020) Distinct early serological signatures track with SARS-CoV-2 survival. Immunity 53: 1-9.
12. Grifoni A, Sidney J, Zhang Y, Scheuermann RH, Peters B, et al. (2020) A sequence homology and bioinformatic approach can predict candidate targets for immune responses to SARS-CoV-2. Cell Host & Microbe 27: 671-680.
13. Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, et al. (2020) Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. Cell 181: 1489-1501.
14. On BYM, Flamholz A, Phillips R, Milo R (2020) SARS-Cov-2 (COVID-19) by the numbers. eLife 9: e57309.
15. Cheng M, Chan CWL, Cheung RCF, Cheung RCF, Bikkavilli RK, et al. (2005) Cross-reactivity of antibody against SARS-coronavirus nucleocapsid protein with IL-11. Biochemical and Biophysical Research Communications 33: 1654-1660.
16. Leung DT, Tam FC, Ma CH, Chan PKS, Cheung JLK (2004) Antibody response of patients with severe acute respiratory syndrome (SARS) targets the viral nucleocapsid. J Infect Dis 190: 379-386.
17. Liu X, Shi Y, Li P, Li L, Yi Y, et al. (2004) Profile of antibodies to the nucleocapsid protein of the severe acute respiratory syndrome (SARS)-associated coronavirus in probable SARS patients. Clin Diagn Lab Immunol 11: 227-228.
18. Wang Y, Sun S, Shen H, Jiang L, Zhang M, et al. (2004) Cross-reaction of SARS-CoV antigen with autoantibodies in autoimmune Diseases. Cellular & Molecular Immunology 1: 304-307.
19. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, et al. (2020) An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: An observational cohort study. The Lancet 395: 1771-1778.
20. Lucchese G, Flöel A (2020) Molecular mimicry between SARS-CoV-2 and respiratory pacemaker neurons. Autoimmunity Reviews 19: 102556.
21. Angileri F, Legare S, Gammazz AM, Macario EC, Macario AJL, et al. (2020) Is molecular mimicry the culprit in the autoimmune hemolytic anemia affecting COVID-19 patients? British Journal of Haematology.
22. To KKW, Chua GT, Kwok LK, Wong JSC, Au DCY, et al. (2020) False-positive SARS-CoV-2 serology in 3 children with Kawasaki disease. Diagnostic Microbiology and Infectious Disease 98: 115141.

Copyright © Alfred Weber

23. Curti A, Ratta M, Corinti S, Girolomoni G, Ricci F, et al. (2001) Interleukin-11 induces Th2 polarization of human CD41 T cells. Blood 97: 2758-2563.

24. Trepicchio WL, Bozza M, Pedneault G, Dorner AJ (1996) Recombinant human IL-11 attenuates the inflammatory response through down-regulation of proinflammatory cytokine release and nitric oxide production. J Immunol 157: 3627-3634.

25. Schwertschlag US, Trepicchio WL, Dykstra KH, Keith JC, Turner KJ, et al. (1999) Hematopoietic, immunomodulatory and epithelial effects of interleukin-11. Leukemia 13: 1307-1315.

26. Li Y, Wu Q, Jin Y, Yang Q (2019) Antiviral activity of interleukin-11 as a response to porcine epidemic diarrhea virus infection. Vet Res 50: 111.

27. Murakami M, Kamimura D, Hirano T (2019) Pleiotropy and specificity: Insights from the interleukin 6 family of cytokines. Immunity 50: 812-831.

28. Matricardi PM, Negro DRW, Nisini R (2020) The first, holistic immunological model of COVID-19: Implications for prevention, diagnosis, and public health measure. Pediatr Allergy Immunol 31: 454-470.

For possible submissions Click below:

Submit Article

Copyright © Alfred Weber