

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

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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 unprecedented 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 then 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-1 β 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-1 β , 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,

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.

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