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Editorial: Autoantibodies to Components of the Immune System, Including Type 1 Interferons, and the Risk of Severe COVID-19

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Abstract During the past two years, clinical studies have attempted to identify risk factors to predict clinical outcomes following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In July 2021, a study using a high-throughput technique detected autoantibodies to chemokines, cytokines, and complement components in patients with symptomatic coronavirus disease 2019 (COVID-19). In August 2021, a study identified pre-existing autoantibodies to type 1 interferons (IFNs) in 10% of patients with severe COVID-19 but not asymptomatic individuals. Autoantibodies may be the long-awaited markers of clinical risk for severe COVID-19 in patients with SARS-CoV-2 infection. This Editorial aims to present some recent findings of autoantibodies to components of the immune system, including type 1 IFNs, and the risk of severe COVID-19.

Keywords: **Editorial • Autoantibodies • Interferons • Risk • Severe Acute Respiratory Syndrome Coronavirus 2 • COVID-19**

During the past two years, observational clinical studies and population studies have attempted to identify risk factors to predict clinical outcomes following infection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1-4]. However, the risk factors for severe coronavirus disease 2019 (COVID-19) and the clinical outcomes are likely to vary between individuals [3-5]. These associations or general risk factors are not absolute, as severe disease and mortality from COVID-19 have been reported in young patients and previously healthy individuals [3,4].

In July 2021, the US National COVID Cohort Collaborative (N3C) Consortium reported the findings from a retrospective cohort study on the predictive factors associated with the development of severe COVID-19 [5]. The N3C study cohort included 174,568 adults with confirmed SARS-CoV-2 infection diagnosed between January 1, 2020, and December 7, 2020, the largest COVID-19 cohort currently evaluated [5]. In the study cohort, 18.6% of patients were hospitalized, and 20.2% required invasive ventilation [5]. Patient mortality, or discharge to hospice care, was reported in 11.6% of hospitalized patients with COVID-19 [5].

Therefore, there is still a need to understand why age and certain underlying health conditions increase the severity of COVID-19 and patient mortality [1]. Identifying risk factors or profiles for both susceptibility and severity of COVID-19 is of global importance for allocating healthcare resources during the COVID-19 pandemic [5,6].

In a publication in the journal *Nature*, in July 2021, Wang and colleagues reported using a high-throughput technique to detect autoantibodies to screen a cohort of 194 individuals with confirmed SARS-CoV-2 [7]. In this study, 172 patients had COVID-19, and 22 healthcare staff were asymptomatic or had mild symptoms [7]. The high-throughput screening method screened for autoantibodies to 2,770 secreted and extracellular proteins [7]. Patients with symptomatic COVID-19 had a significant increase in autoantibody reactivity compared with non-infected individuals [7]. The screening method detected autoantibodies to chemokines, cytokines, and complement components, which are all immune modulators [7].

In August 2021, an international team of immunologists identified pre-existing autoantibodies to type 1 interferons (IFNs) in 10% of patients with severe COVID-19, but not in individuals with asymptomatic infection [8]. Immunologists at the Rockefeller University, New York City, led this international research team [8]. The study included 3,595 patients from 38 countries with confirmed severe COVID-19 admitted to intensive care units (ICUs) [8]. Of these critically ill patients, 13.6% had autoantibodies, and of the patients who died while in the ICU, 18% had autoantibodies [8]. In critically ill patients under 40 years of age, autoantibodies were present in 21% [8]. These neutralizing autoantibodies were to either IFN-α or IFN-ω, and 1.3% of patients with critical COVID-19 and 0.9% of patients who died had autoantibodies to IFN-β. [8]. The autoantibodies to IFNs were identified as a cause rather than a consequence of the development of severe COVID-19 [8]. In October 2020,

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this research group previously showed that autoantibodies were present in only 4 in 1,000 healthy people who had blood samples collected before the COVID-19 pandemic [9].

Several studies have reported an association between the reduced activity of IFNs and increased susceptibility to severe COVID-19 [10,11]. In October 2020, Zhang and colleagues reported that inborn errors of TLR3-dependent and IRF7-dependent type I IFN immunity were associated with severe and life-threatening COVID-19 pneumonia [10]. In August 2021, Asano and colleagues showed that individuals with genetic mutations that alter the activity of type 1 interferons were at increased risk of developing severe COVID-19 [11]. Type I IFNs have a key role in innate and adaptive immune cell responses during infection from organisms that include viruses [12]. Also, type I IFNs are involved in complex immuno-regulatory networks that usually, but not always, protect the host from infection, with minimal immunological damage to the host [12].

Conclusions

Ongoing studies have identified a possible role for autoantibodies in the development of clinically severe COVID-19. It is possible that autoantibodies to components of the immune system, which are either pre-existing or develop after infection, impair immune control of SARS-CoV-2. The role of autoantibodies to components of the immune system in the pathogenesis of COVID-19 may involve inhibition of immunoreceptor signaling or directly affect immune cells. There is the possibility that newly identified autoantibodies may be the long-awaited markers for clinical risk of severe COVID-19 in patients with SARS-CoV-2 infection.

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