Faculty Opinions

Anti-type I interferon antibodies as a cause of severe COVID-19

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EVALUATION OF

Landmark

Autoantibodies against type I IFNs in patients with life-threatening COVID-19.

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COVID-19 ranges from asymptomatic through to respiratory failure and death. Although specific pre-existing conditions such as age and male sex have been associated with poor outcomes, we remain largely ignorant of the mechanisms predisposing to severe disease. In this study, the authors discovered that approximately 10% of 987 patients with life-threatening COVID-19 harbored neutralizing antibodies to Type I interferons (IFNs)[1]. They demonstrated that these antibodies could neutralize high concentrations of the corresponding IFN and could rescue SARS-CoV-2 infection from inhibition by IFN *in vitro*. Importantly, anti-IFN antibodies were associated with low levels of serum IFN. These observations suggest that disease severity in these individuals results from a failure to control SARS-CoV-2 replication because of antibody-mediated IFN inhibition. The study suggests specific treatments and diagnostics for this class of severe COVID-19.

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Competing interests: Adrian Hayday is a co-author and/or ongoing collaborator with Kai Kisand and Pärt Peterson, authors who contributed to the evaluated paper. He is also a Board Member and equity holder in ImmunoQure AG, a company that has identified naturally occurring human anti-cytokine antibodies targeting Type I interferon for potential use in the clinic.

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Background

COVID-19 is a severe acute respiratory syndrome (SARS) which emerged in late 2019 in China and was quickly associated with infection by a novel coronavirus named SARS-CoV-2. This virus rapidly spread globally in early 2020 causing large numbers of hospitalizations, with many patients requiring respiratory support in intensive care. It soon became clear that COVID-19 ranged from completely asymptomatic through to respiratory failure, multi-organ failure, and death. This suggested large differences between individuals in their susceptibility to SARS-CoV-2-driven disease. At this time, it became evident that being elderly, male or having other specific medical conditions (e.g., cardiovascular disease) was associated with poor outcome, but the reasons underlying these differences are clearly complex and remain poorly understood today. Most significantly, there is debate over whether severe pathology reflects an immunodeficient failure to control the virus or an exuberant immune response that attacks tissues, or a combination of both.

Type I IFN, including IFNα, is a critical line of defense against infection, and viruses have evolved complex mechanisms to evade and antagonize its effects. Antibodies to Type I IFN are found in many individuals with thymic dysfunction—for example, patients with Autoimmune Polyglandular Syndrome Type 1 (APS1; also known as APECED)—but, excepting rare examples, have not been found in the general population. If neutralizing anti-IFN antibodies are associated with increased disease severity, it would seem to imply that immunodeficient failure to control the virus is a primary driver of pathology in this subset of patients.

Main contributions and importance

In sampling almost one thousand patients hospitalized for life-threatening COVID-19 pneumonia within a 3-month period in early 2020, this study presents a Herculean logistical undertaking, particularly considering the impacts on infrastructure of the global pandemic. It is the first study to link autoantibodies directed against Type I IFNs with severe-to-critical COVID-19. The authors hypothesize that these autoantibodies functionally induce a primary immunodeficiency that prevents proper control of SARS-CoV-2 replication. Thus, this study offers a plausible explanation for the variability in disease severity of COVID-19 in a subset of patients. The overwhelming preponderance of these antibodies in men is striking and surprising. The association of anti-IFN antibodies with severe COVID-19 suggests the potential for future screening and stratification strategies, patient risk assessments and precision treatments based on serology; for example, therapeutic use of IFNβ in patients who have autoantibodies against IFNα (see Figure 1). Moreover, autoantibodies may reflect only one mechanism for impairing type I IFN, suggesting the utility of measuring Type I IFN levels in infected individuals more generally. For example, there is published association of severe COVID-19 with depletion of plasmacytoid dendritic cells (pDC), the body's main IFN-producing cell type[2].

Open questions

Given that no one factor will explain poor patient outcomes and given that the underlying biology may differ significantly across individuals, identifying disease causation in 10% of the severest cases is an important achievement, particularly since it includes increased disease predisposition of males. Nonetheless, the study segregated patients into extreme categories (severe versus mild/asymptomatic) to permit the clearest interpretation. It remains unclear whether there is any association between anti-IFN antibodies and moderate disease, which is a more common outcome, displaying only some features of severe disease.

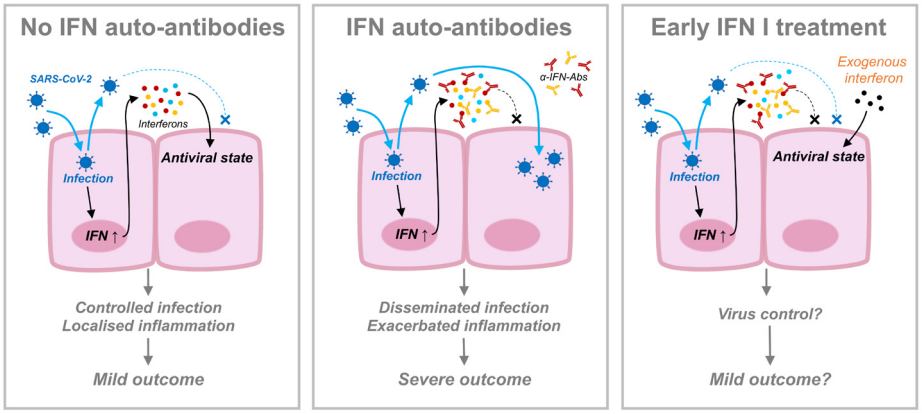

Figure 1. The impact of anti-Type I IFN antibodies on COVID-19 outcomes

The left-hand panel depicts virus-stimulated induction of Type I IFN that upon secretion protects neighboring cells from productive infection, limiting disease to a mild state. In the middle panel, the presence of Type I IFN-specific neutralizing antibodies prevents IFN engagement of neighboring cells, permitting virus infection to disseminate. Neutralization may also block immunoregulatory impacts of Type I IFN (not shown). Individually or jointly, these two impacts promote severe disease. In the right-hand panel, it is proposed that early Type I IFN supplementation (e.g., with β- or λ-IFN) can overcome the impacts of the antibodies, restoring a mild disease prognosis. It is expected that the events depicted occur in the context of Type III IFN (blue dots), and why that does not limit virus dissemination (middle panel) remains unresolved. Image credit: Ann-Kathrin Reuschl.

The origin of anti-IFN antibodies remains unknown. Were they present before disease or has disease contributed to *de novo* induction? Suggesting autoantibody pre-existence, the autoantibodies were primarily IgG versus IgM, and may have been restimulated by infection. Moreover, follow-up studies have found higher percentages of patients with pre-existing autoantibodies[3]. Strikingly, most autoantibodies are apparently specific for particular Type I IFNs, IFNα2 and IFNΩ, with far fewer patients displaying autoantibodies against IFNβ. Interestingly, this mirrors the situation in APS1 that is attributable to defective central tolerance. Indeed, IFNα is produced in the thymus, whereas IFNβ is not. This in turn raises a profound question as to whether continuous interindividual variation in the efficacy of central tolerance underpins varying propensities to generate autoantibodies and autoreactive T cells specific for various targets that may influence responses to infection in different ways. Thus, APS1 patients show susceptibility to mucocutaneous candidiasis, reflecting their high titres of anti-interleukin (IL)-17 antibodies[4]. Moreover, by neutralizing immune effectors, anti-cytokine antibodies can also protect against autoimmune disease[5]. This is an understudied area. At the same time, there is no obvious male bias to anti-IFN antibodies in APS1, so that aspect of the COVID-19 study remains intriguing, serving to highlight another understudied area, namely the sexual dimorphism of innate and adaptive immune mechanisms.

It is unclear why IFNβ does not substitute for IFNs lost due to antibody-mediated neutralization. One possibility is that the thirteen genes encoding IFNα isotypes reflect the amount of Type I IFN made during an infection and that, by comparison, the single IFNβ gene cannot produce enough IFN to mitigate this deficit. There is also the prospect that Type III IFNs, which are encoded by four genes in humans, might also contribute anti-viral effects against

SARS-CoV-2, so why this is not the case remains wholly unexplained (see Figure 1).

It is unclear why it has taken so long for anti-IFN antibodies to be detected in the general population; for example, they were not picked up in control cohorts examined in studies of APS1. Moreover, why did clinical susceptibility not emerge from prior virus infections or other inflammatory diseases or cancer? Perhaps the elderly have typically seen a full complement of viral infections and therefore, particularly elderly males, rely on classical adaptive memory responses to control infection. Thus, it is only when a new virus infects elderly patients that Type I IFN becomes so important and anti-IFN antibodies can have such a strong impact. We note that previous studies found that inborn errors leading to Type I IFN receptor loss, or STAT2 defects, did not impact the outcome of classical childhood infections, leading the authors to propose that Type I IFN was most important for recently zoonotic infections[6,7]. It will be interesting to examine patients with other infectious diseases (e.g., severe influenza) for the presence of IFN antibodies or for other impairments to Type I IFN activity (e.g., pDC depletions, as considered above).

The simplest explanation for the role of anti-IFN antibodies is that virus replication, and therefore virus-driven disease, is enhanced by IFN blockade. However, although the study demonstrated that patient-derived anti-IFN antibodies reduced effective Type I IFN responses against SARS-CoV-2 replication *in vitro*, the authors did not test whether the antibodies were associated with high virus replication in the patients, or even a change in the anatomical sites most virulently targeted by the virus. Another, non-mutually exclusive, possibility is that anti-IFN antibodies contribute to hyperinflammation by inhibiting the immunoregulatory effects of IFNα, manifest in the induction of IL-10, PD-L1, and other molecules[8–10]. Thus, the study does not formally resolve whether disease severity reflects higher levels of viral replication, or different viral distribution, or immunopathology driven by exuberant immune activation.

Conclusion

This logistical tour-de-force is an important and thought-provoking study which raises many questions. It highlights the occurrence of anti-Type I IFN antibodies as a possible cause of severe COVID-19, with the implication that they, or other autoantibodies, may influence the pathogenicity of other infections to a greater degree than has been appreciated.

The study aligns with the perspective that disease severity reflects poor control of viral replication, but it clearly does not exclude immunoregulatory impacts of the antibodies on inflammatory responses. Indeed, data from randomized controlled trials demonstrating improved outcomes in hospitalized patients treated with immunosuppressive agents such as dexamethasone and tocilizumab[11] versus trends towards worsening outcomes in hospitalized patients treated with intravenous IFN[12] suggest that excessive inflammation late in the disease course is a major contributor to mortality. Possibly, severity reflects immunodeficiency in some patients, and over-exuberant immune activity in others. Moreover, the two may be linked, in that failure to control any virus infection might lead to downstream immune dysregulation. Either way, this study absolutely underlines how important Type I IFN can be in regulating disease outcomes following infection.

Importantly, this study has direct clinical implications for COVID-19 disease stratification and treatment. For example, can patients making anti-IFN antibodies be

treated with inhaled IFNs to which the patient does not make antibodies? Moreover, other treatments, including antivirals and dexamethasone, might be found to differentially benefit patients stratified by their levels of anti-IFN antibodies and/or by their serum IFN levels more generally, in which regard, improved methods of directly measuring Type I IFN have recently been developed[13].

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