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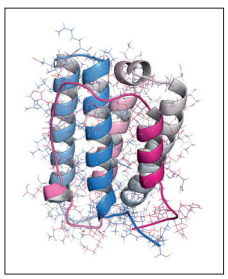
# Type I interferon, anti-interferon antibodies, and COVID-19



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In the past year, considerable gains in our understanding of the immunobiology of COVID-19 have provided key insights into the centrality of interferons in the immune response against severe acute respiratory syndrome coronavirus 2. Several studies attest to the involvement of interferons. For instance, Zhang and colleagues[1] screened a large cohort of patients with severe COVID-19 for the presence of predicted loss-of-function variants in 13 genes associated with Toll-like receptor signaling molecules and the type I interferon pathway identified in cases of severe influenza and other viral infections. Of 659 patients with severe COVID-19, 23 (3·5%) harbored known or new mutations in eight of the genes, attesting to the importance of these pathways in viral defense. In a second study, Bastard and colleagues[2] reported a remarkable finding that 135 (13·7%) of 987 patients with life-threatening COVID-19 harboured autoantibodies against type I interferons (mostly against interferon [IFN]-α2 and IFN-ω) with most showing neutralising capacity in vitro. Such antibodies were only detected in 4 (0·3%) of 1227 unexposed, healthy individuals.

These papers add to a growing body of literature affirming the importance of interferons in COVID-19, which has direct and indirect implications for the field of rheumatology. Of particular and immediate importance is how these data might affect the development programme of a new class of biological agents designed to therapeutically target the type I interferon pathway in patients with systemic lupus erythematosus (SLE) and allied conditions.

The documentation of naturally occurring autoantibodies against a cytokine is not remarkable, as low concentrations of such antibodies have been reported in studies of healthy blood donors, which showed most of the donors to have trace amounts.[3] In the largest study examining the prevalence of antibodies against five cytokines including type I interferons in 8972 blood donors, high concentrations of antibodies to type I interferons were found in less than 1% of participants, with no epidemiological associations with variables such as age, sex, or smoking,[3] similar to findings in control populations (type I interferon antibodies in <1%) in the COVID-19 study.[2] These autoantibodies have also been found in intravenous immunoglobulin preparations and in patients undergoing therapy with type I interferon for infections such as hepatitis C.[4] The biological role of such antibodies is uncertain, and whether they are deterministic (ie, have an immunoregulatory function) or stochastic (ie, appear in response to physiological elevations) is debated. Under some circumstances, naturally occurring anti-cytokine antibodies have been shown to be pathogenic across a range of haematological, pulmonary, and infectious diseases.[5] Such immune dysregulatory syndromes can be monogenic (eg, defects in the *AIRE* gene) or polygenic (eg, antibodies against interleukin [IL]-17, IL-22, IFN-γ, and granulocyte-macrophage colony-stimulating factor), with polygenic syndromes now classified as inborn errors of immunity, although no specific genes have been identified.[6] Autoantibodies against type I interferon might be clinically important, as they have been associated with a history of severe viral infections in patients with *RAG1/2* gene deficiency, an inborn error of immunity associated with diseases with prominent autoimmune features.[7]

Autoantibodies against one or more cytokines have been reported in a number of rheumatological conditions, but their biological role remains undefined. The notable exception is SLE, in which autoantibodies against numerous cytokines, including type 1 interferon, have been reported in 27% and 42% of individuals in two studies.[8] These antibodies have varying capacity to neutralise type I interferon bioactivity, depending on the study and assay used, but their presence has been associated with reduced type I interferon in serum and lowered disease activity.[9] However, no clear evidence shows that in the absence of immunosuppression or comorbidities, patients with SLE are at increased risk of developing severe COVID-19 due to subclinical immunodeficiency, and more robust epidemiological studies are needed.[10]

Absence of evidence of de novo vulnerability to viral infections in patients with SLE, despite the high prevalence of neutralising autoantibodies to type I interferons, perhaps should not be surprising. In the study by Bastard and colleagues,[2] the presence of such antibodies appeared to antedate illness with COVID-19, and none of the patients had a history of severe influenza or other severe viral illnesses before COVID-19. This observation suggests that in individuals with subclinical immunodeficiency and anti-type I interferon antibodies, infection with COVID-19 might, in some unique way, tip

the balance to the advantage of the pathogen, whereas this might not happen in response to other common viral infections. Prospective studies examining the potential influence of autoantibodies against type I interferons on the incidence and severity of viral infection in patients with SLE and other rheumatological disorders is needed.

Finally, what might these data forecast regarding the development programmes for biological therapeutics targeting type 1 interferons? Previous clinical trials of monoclonal antibodies directed against type 1 interferons have largely been unsuccessful on the basis of efficacy. By contrast, anifrolumab, an IgG1 monoclonal antibody that targets the type I interferon receptor—allowing it to neutralise the entire family of type I interferons, including IFN-α, IFN-β, IFN-δ, and IFN-ω—has completed two large phase 3 trials (NCT02446912, NCT02446899). Despite some inconsistency in trial outcomes, anifrolumab showed efficacy across clinical, laboratory, and quality of life domains in SLE.[11] One limitation is that all drugs directed at type I interferons share a safety concern of increased risk of herpes zoster infection, which has been as high or higher than that seen with Janus kinase (JAK) inhibitors. However, most infections observed in clinical trials have been non-serious.[12] Although risk of simple upper respiratory infections might also be increased with anifrolumab, no evidence to date shows an increased risk of other serious viral infections. Careful monitoring of outcomes in patients on this drug (and other drugs capable of inhibiting type I interferon) who contract COVID-19 should be of the highest priority. Small molecules, particularly JAK inhibitors, are also of concern given their capacity to broadly inhibit interferon signaling and associated risk of herpes zoster infection. Many JAK inhibitors are currently in clinical trials for COVID-19, a logical step given their potent anti-inflammatory capacity, and baricitinib was granted emergency use authorisation in the USA (Nov 19, 2020) in combination with the antiviral drug remdesivir for hospitalised patients with COVID-19. Yet concerns remain over the countervailing effects of these drugs on interferon pathways.[12]

Moving forward, if drugs targeting interferons and interferon pathways advance to approval in SLE and other autoimmune diseases, clinicians should consider the broader implications of anti-type I interferon therapies on protective immune responses to other viral infections. Ultimately, some form of heightened risk mitigation might be required. Monitoring for viral complications will be wise with the future use of these drugs. As new immune-based therapeutics are developed that target new molecules and pathways for immune diseases, clinicians should return to lessons learned from inborn errors of immunity, which might help us to prepare for future discoveries.

We declare no competing interests.

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1 Zhang Q, Bastard P, Liu Z, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science* 2020; **370:** eabd4570.
2 Bastard P, Rosen LB, Zhang Q, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* 2020; **370:** eabd4585.
3 von Stemann JH, Rigas AS, Thørner LW, et al. Prevalence and correlation of cytokine-specific autoantibodies with epidemiological factors and C-reactive protein in 8972 healthy individuals: results from the Danish blood donor study. *PLoS One* 2017; **12:** e017981.
4 Merkel PA, Lebo T, Knight V. Functional analysis of anti-cytokine autoantibodies using flow cytometry. *Front Immunol* 2019; **10:** 1517.
5 Knight V, Merkel PA, O'Sullivan MD. Anticytokine autoantibodies. *Antibodies (Basel)* 2016; **5:** 3.
6 Bousfiha A, Jeddane L, Picard C, et al. Human inborn errors of immunity: 2019 update of the IUIS phenotypical classification. *J Clin Immunol* 2020; **40:** 66–81.
7 Walter JE, Rosen LB, Csomos K, et al. Broad-spectrum antibodies against self-antigens and cytokines in RAG deficiency. *J Clin Invest* 2015; **125:** 4135–48.
8 Howe HS, Leung BPL. Anti-cytokine autoantibodies in systemic lupus erythematosus. *Cells* 2019; **9:** 72.
9 Morimoto AM, Flesher DT, Yang J, et al. Association of endogenous anti-interferon-α autoantibodies with decreased interferon-pathway and disease activity in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011; **63:** 2407–15.
10 Gianfrancesco M, Yazdany J, Robinson PC. Epidemiology and outcomes of novel coronavirus 2019 in patients with immune-mediated inflammatory diseases. *Curr Opin Rheumatol* 2020; **32:** 434–40.
11 Anderson E, Furie R. Anifrolumab in systemic lupus erythematosus: current knowledge and future considerations. *Immunotherapy* 2020; **12:** 275–86.
12 Calabrese LH, Lenfant T, Calabrese C. Cytokine storm release syndrome and the prospects for immunotherapy with COVID-19, part 4: the role of JAK inhibition. *Cleve Clin J Med* 2020; published online Aug 28. https://doi.org/10.3949/ccjm.87a.ccc060.