Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Association of IFNAR1 and IFNAR2 with COVID-19 severity

Type I interferons propagate and amplify the antiviral response at the start of an infection and are crucial for effective antiviral immunity. Type I interferons bind interferon alpha/beta receptors 1 (IFNAR1) and 2 (IFNAR2), which are ubiquitous, but expressed differentially depending on the cell type.[1]

Interferon pathways have been identified as involved in COVID-19 and are associated with disease severity.[2] Genome-wide association studies, transcriptomic studies, and single-cell studies, have identified IFNAR2 as a risk factor for severe COVID-19.[3] However, the correlation between serum amounts of soluble forms of IFNAR in individuals with COVID-19 at early stages of infection and COVID-19 disease severity has not been investigated.

In this Correspondence, we compared serum IFNAR1 and IFNAR 2 amounts (quantified by two commercial sandwich ELISA kits: LS-F17211 and ab264610) in 77 individuals. This study included ten individuals who were PCR-negative for SARS-CoV-2 and 67 who were PCR-positive (ten asymptomatic patients, 20 patients with mild disease, 17 hospitalised patients [not intensive care unit], and 16 patients in the intensive care unit). Written informed consent for participation was obtained from all participants and ethics approval was obtained from Comité Protection des Personnes Ile de France V (NCT04648709). All samples were collected at the time of patient inclusion in the study (days 3–7 after symptom onset).

Although we found no differences in IFNAR1 concentrations between groups separated by disease severity, IFNAR1 amounts seemed to be inversely correlated to COVID-19 severity (appendix p 1). These results are in concordance with findings from other studies that associated autosomal recessive IFNAR1 deficiency with severe COVID-19.[4] By contrast, IFNAR2 concentrations were significantly higher in patients with severe COVID-19 (appendix p 1). IFNAR2 is expressed in three isoforms, two of which are soluble but cannot activate signalling after interaction with type I interferon. Therefore, the action of type I interferon might depend on the relative abundances of IFNAR2 isoforms, as suggested by Aliaga-Gaspar and colleagues in 2021.[5] The higher amounts of soluble IFNAR2 in serum observed in our study might underlie an impairment of the immune response in patients with severe COVID-19, which decreases sensitivity to interferon beta and therefore antiviral activity. Our results contrast with the genome-wide association studies or transcriptomic studies. However, these studies did not quantify the soluble IFNAR isoforms in the serum of individuals with COVID-19. Our study contributes to a better understanding of the interferon response damage during SARS-CoV-2 infection. Whether the increased serum concentrations of soluble IFNAR2 in patients with COVID-19 are due to splicing mechanisms, as is the case in patients with multiple sclerosis,[5] remains unclear and requires further studies. We believe serum IFNAR1 and IFNAR2 concentrations in patients with COVID-19 can be used as predictors of disease severity and response to interferon treatment outcomes.

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1 Takaoka A. Interferons. In: Ando H, Ukena K, Nagata S, eds. Handbook of hormones: comparative endocrinology for basic and clinical research, 2nd edn. London: Elsevier, 2021: 447–52.

2 Bastard P, Gervais A, Le Voyer T, et al. Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths. *Sci Immunol* 2021; **6:** eabl4340.

3 Pairo-Castineira E, Clohisey S, Klaric L, et al. Genetic mechanisms of critical illness in COVID-19. *Nature* 2021; **591:** 92–98.

4 Zhang Q, Bastard P, Cobat A, Casanova JL. Human genetic and immunological determinants of critical COVID-19 pneumonia. *Nature* 2022; **603:** 587–98.

5 Aliaga-Gaspar P, Hurtado-Guerrero I, Ciano-Petersen NL, et al. Soluble receptor isoform of IFN-beta (sIFNAR2) in multiple sclerosis patients and their association with the clinical response to IFN-beta treatment. *Front Immunol* 2021; **12:** 778204.

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