

RESEARCH ARTICLE SUMMARY

CORONAVIRUS

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

Paul Bastard*† and Lindsey B. Rosen† *et al.*

INTRODUCTION: Interindividual clinical variability is vast in humans infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), ranging from silent infection to rapid death. Three risk factors for life-threatening coronavirus disease 2019 (COVID-19) pneumonia have been identified—being male, being elderly, or having other medical conditions—but these risk factors cannot explain why critical disease remains relatively rare in any given epidemiological group. Given the rising toll of the COVID-19 pandemic in terms of morbidity and mortality, understanding the causes and mechanisms of life-threatening COVID-19 is crucial.

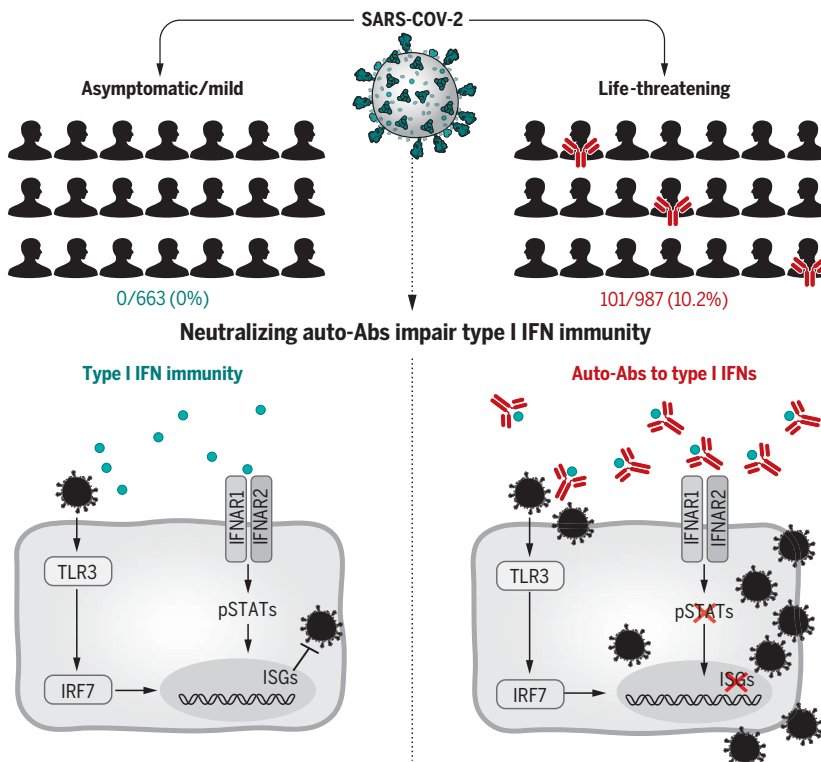
RATIONALE: B cell autoimmune infectious phenocopies of three inborn errors of cyto-

kine immunity exist, in which neutralizing autoantibodies (auto-Abs) against interferon- γ (IFN- γ) (mycobacterial disease), interleukin-6 (IL-6) (staphylococcal disease), and IL-17A and IL-17F (mucocutaneous candidiasis) mimic the clinical phenotypes of germline mutations of the genes that encode the corresponding cytokines or receptors. Human inborn errors of type I IFNs underlie severe viral respiratory diseases. Neutralizing auto-Abs against type I IFNs, which have been found in patients with a few underlying noninfectious conditions, have not been unequivocally shown to underlie severe viral infections. While searching for inborn errors of type I IFN immunity in patients with life-threatening COVID-19 pneumonia, we also tested the hypothesis that neutralizing auto-Abs against type I IFNs

may underlie critical COVID-19. We searched for auto-Abs against type I IFNs in 987 patients hospitalized for life-threatening COVID-19 pneumonia, 663 asymptomatic or mildly affected individuals infected with SARS-CoV-2, and 1227 healthy controls from whom samples were collected before the COVID-19 pandemic.

RESULTS: At least 101 of 987 patients (10.2%) with life-threatening COVID-19 pneumonia had neutralizing immunoglobulin G (IgG) auto-Abs against IFN- ω (13 patients), against the 13 types of IFN- α (36), or against both (52) at the onset of critical disease; a few also had auto-Abs against the other three individual type I IFNs. These auto-Abs neutralize high concentrations of the corresponding type I IFNs, including their ability to block SARS-CoV-2 infection *in vitro*. Moreover, all of the patients tested had low or undetectable serum IFN- α levels during acute disease. These auto-Abs were present before infection in the patients tested and were absent from 663 individuals with asymptomatic or mild SARS-CoV-2 infection ($P < 10^{-16}$). They were present in only 4 of 1227 (0.33%) healthy individuals ($P < 10^{-16}$) before the pandemic. The patients with auto-Abs were 25 to 87 years old (half were over 65) and of various ancestries. Notably, 95 of the 101 patients with auto-Abs were men (94%).

CONCLUSION: A B cell autoimmune phenocopy of inborn errors of type I IFN immunity accounts for life-threatening COVID-19 pneumonia in at least 2.6% of women and 12.5% of men. In these patients, adaptive autoimmunity impairs innate and intrinsic antiviral immunity. These findings provide a first explanation for the excess of men among patients with life-threatening COVID-19 and the increase in risk with age. They also provide a means of identifying individuals at risk of developing life-threatening COVID-19 and ensuring their enrolment in vaccine trials. Finally, they pave the way for prevention and treatment, including plasmapheresis, plasmablast depletion, and recombinant type I IFNs not targeted by the auto-Abs (e.g., IFN- β). ■



Neutralizing auto-Abs to type I IFNs underlie life-threatening COVID-19 pneumonia. We tested the hypothesis that neutralizing auto-Abs against type I IFNs may underlie critical COVID-19 by impairing the binding of type I IFNs to their receptor and the activation of the downstream responsive pathway. Neutralizing auto-Abs are represented in red, and type I IFNs are represented in blue. In these patients, adaptive autoimmunity impairs innate and intrinsic antiviral immunity. ISGs, IFN-stimulated genes; TLR, Toll-like receptor; IFNAR, IFN- α/β receptor; pSTAT, phosphorylated signal transducers and activators of transcription; IRF, interferon regulatory factor.

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

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Interindividual clinical variability in the course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is vast. We report that at least 101 of 987 patients with life-threatening coronavirus disease 2019 (COVID-19) pneumonia had neutralizing immunoglobulin G (IgG) autoantibodies (auto-Abs) against interferon- ω (IFN- ω) (13 patients), against the 13 types of IFN- α (36), or against both (52) at the onset of critical disease; a few also had auto-Abs against the other three type I IFNs. The auto-Abs neutralize the ability of the corresponding type I IFNs to block SARS-CoV-2 infection in vitro. These auto-Abs were not found in 663 individuals with asymptomatic or mild SARS-CoV-2 infection and were present in only 4 of 1227 healthy individuals. Patients with auto-Abs were aged 25 to 87 years and 95 of the 101 were men. A B cell autoimmune phenocopy of inborn errors of type I IFN immunity accounts for life-threatening COVID-19 pneumonia in at least 2.6% of women and 12.5% of men.

Mycobacteriosis, staphylococcosis, and candidiasis can be driven by monogenic inborn errors of interferon- γ (IFN- γ), interleukin-6 (IL-6), and IL-17A and IL-17F, respectively, or they can be driven by their genetically driven autoimmune phenocopies, with the production of neutralizing autoantibodies (auto-Abs) against these cytokines (1–8). Type I IFNs, first described in 1957, are ubiquitously expressed cytokines that contribute to both innate immunity (through their secretion by plasmacytoid dendritic cells and other leukocytes) and cell-intrinsic immunity (in most if not all cell types) against viral infections (9–13). Their receptors are ubiquitously expressed and trigger the induction of IFN-stimulated genes (ISGs) via phosphorylated STAT1-STAT2-IRF9

trimers (STAT, signal transducers and activators of transcription; IRF, interferon regulatory factor) (14). Neutralizing immunoglobulin G (IgG) auto-Abs against type I IFNs can occur in patients treated with IFN- α 2 or IFN- β (15) and exist in almost all patients with autoimmune polyendocrinopathy syndrome type I (APS-1) (16). They are also seen in women with systemic lupus erythematosus (17).

These patients do not seem to suffer from unusually severe viral infections, although human inborn errors of type I IFNs can underlie severe viral diseases, both respiratory and otherwise (18). In 1984, Ion Gresser described a patient with unexplained auto-Abs against type I IFNs suffering from severe chickenpox and shingles (19, 20). More recently, auto-Abs against type I IFNs have been found in a few

patients with biallelic, hypomorphic *RAG1* or *RAG2* mutations and viral diseases including severe chickenpox and viral pneumonias (21). Our attention was drawn to three patients with APS-1, with known preexisting anti-type I IFN auto-Abs, who had life-threatening coronavirus disease 2019 (COVID-19) pneumonia (22) (see detailed case reports in Methods). While searching for inborn errors of type I IFNs (18, 23), we hypothesized that neutralizing auto-Abs against type I IFNs might also underlie life-threatening COVID-19 pneumonia.

Auto-Abs against IFN- α 2 and/or IFN- ω in patients with critical COVID-19

We searched for auto-Abs against type I IFNs in 987 patients hospitalized for life-threatening COVID-19 pneumonia. We also examined 663 individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presenting asymptomatic infection or mild disease and 1227 healthy controls whose samples were collected before the COVID-19 pandemic. Plasma or serum samples were collected from patients with critical COVID-19 during the acute phase of disease. Multiplex particle-based flow cytometry revealed a high fluorescence intensity (FI) (>1500) for IgG auto-Abs against IFN- α 2 and/or IFN- ω in 135 patients (13.7%) with life-threatening COVID-19 (Fig. 1A). We found that 49 of these 135 patients were positive for auto-Abs against both IFN- α 2 and IFN- ω , whereas 45 were positive only for auto-Abs against IFN- α 2, and 41 were positive only for auto-Abs against IFN- ω .

We also performed enzyme-linked immunosorbent assay (ELISA), and the results obtained were consistent with those obtained with Luminex technology (fig. S1A). We found that 11 and 14 of 23 patients tested had low levels of IgM and IgA auto-Abs against IFN- ω and IFN- α 2, respectively (Fig. 1B and fig. S1B). Auto-Abs against type I IFNs were detected in two unrelated patients for whom we had plasma samples obtained before SARS-CoV-2 infection, which indicates that these antibodies were present before SARS-CoV-2 infection and were not triggered by the infection. As a control, we confirmed that all 25 APS-1 patients tested had high levels of auto-Abs against IFN- α 2 and IFN- ω (fig. S1C). Overall, we found that 135 of 987 patients (13.7%) with life-threatening COVID-19 pneumonia had IgG auto-Abs against at least one type I IFN.

The auto-Abs neutralize IFN- α 2 and IFN- ω in vitro

We then tested whether auto-Abs against IFN- α 2 and IFN- ω were neutralizing in vitro. We incubated peripheral blood mononuclear cells (PBMCs) from healthy controls with 10 ng/mL IFN- α 2 or IFN- ω in the presence of plasma from healthy individuals or from patients with auto-Abs. A complete abolition of STAT1 phosphorylation was observed in 101 patients

with auto-Abs against IFN- α 2 and/or IFN- ω (table S1). The antibodies detected were neutralizing against both IFN- α 2 and IFN- ω in 52 of these 101 patients (51%), against only IFN- α 2 in 36 patients (36%), and against only IFN- ω in 13 patients (13%) at the IFN- α 2 and IFN- ω concentrations tested (Fig. 1, C and D). IgG depletion from patients with auto-Abs restored normal pSTAT1 induction after IFN- α 2 and IFN- ω stimulation, whereas the purified IgG fully neutralized this induction (Fig. 1C and fig. S1D). Furthermore, these auto-Abs neutralized high amounts of IFN- α 2 (fig. S1E) and were neutralizing at high dilutions (Fig. 1E and fig. S1F). Notably, 15 patients with life-threatening COVID-19 and auto-Abs against IFN- α 2 and/or IFN- ω also had auto-Abs against other cytokines [IFN- γ , granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6, IL-10, IL-12p70, IL-22, IL-17A, IL-17F, and/or tumor necrosis factor- β (TNF β)], only three of which (IL-12p70, IL-22, and IL-6) were neutralizing (in four patients) (fig. S2, A to C). Similar proportions were observed in the other cohorts (fig. S2, D to L).

We also analyzed ISG induction after 2 hours of stimulation with IFN- α 2, IFN- β , or IFN- γ in

the presence of plasma from healthy individuals or from patients with auto-Abs. With plasma from eight patients with auto-Abs against IFN- α 2, the induction of ISG *CXCL10* was abolished after IFN- α 2 stimulation but maintained after stimulation with IFN- γ (Fig. 1F). We then found that plasma from the five patients with neutralizing auto-Abs neutralized the protective activity of IFN- α 2 in Madin-Darby bovine kidney (MDBK) cells infected with vesicular stomatitis virus (VSV) (table S2). Overall, we found that 101 of 987 patients (10.2%)—including 95 men (94%)—with life-threatening COVID-19 pneumonia had neutralizing IgG auto-Abs against at least one type I IFN. By contrast, auto-Abs were detected in only 4 of 1227 healthy controls (0.33%) (Fisher exact test, $P < 10^{-16}$) and in none of the 663 patients with asymptomatic or mild SARS-CoV-2 infection tested (Fisher exact test, $P < 10^{-16}$).

Auto-Abs against all 13 IFN- α subtypes in patients with auto-Abs to IFN- α 2

We investigated whether patients with neutralizing auto-Abs against IFN- α 2 only or those with neutralizing auto-Abs against IFN- α 2 and IFN- ω also had auto-Abs against the other 15

type I IFNs. ELISA showed that all patients tested ($N = 22$) with auto-Abs against IFN- α 2 also had auto-Abs against all 13 IFN- α subtypes (IFN- α 1, - α 2, - α 4, - α 5, - α 6, - α 7, - α 8, - α 10, - α 13, - α 14, - α 16, - α 17, and - α 21), whereas only 2 of the 22 patients tested had auto-Abs against IFN- β , 1 had auto-Abs against IFN- κ , and 2 had auto-Abs against IFN- ϵ (Fig. 2A). The auto-Abs against IFN- β had neutralizing activity against IFN- β (Fig. 1D). We confirmed that all of the patients had auto-Abs against all 13 subtypes of IFN- α by testing the same samples using luciferase-based immunoprecipitation assay (LIPS) (Fig. 2B). For IFN- β , we also screened the whole cohort in a multiplex assay. We found that 19 of 987 (1.9%) patients had auto-Abs against IFN- β and that all of them were in our cohort of severe COVID-19 individuals with neutralizing auto-Abs against IFN- α and/or IFN- ω . Of these patients with auto-Abs against IFN- β , only two were neutralizing against IFN- β (Fig. 1, D and F).

Ten of the 17 genes encoding type I IFNs (IFN- α 2, - α 5, - α 6, - α 8, - α 13, - α 14, - α 21, - β , - ω , and - κ), have undergone strong negative selection, which suggests that they play an essential role in the general population. By contrast, the

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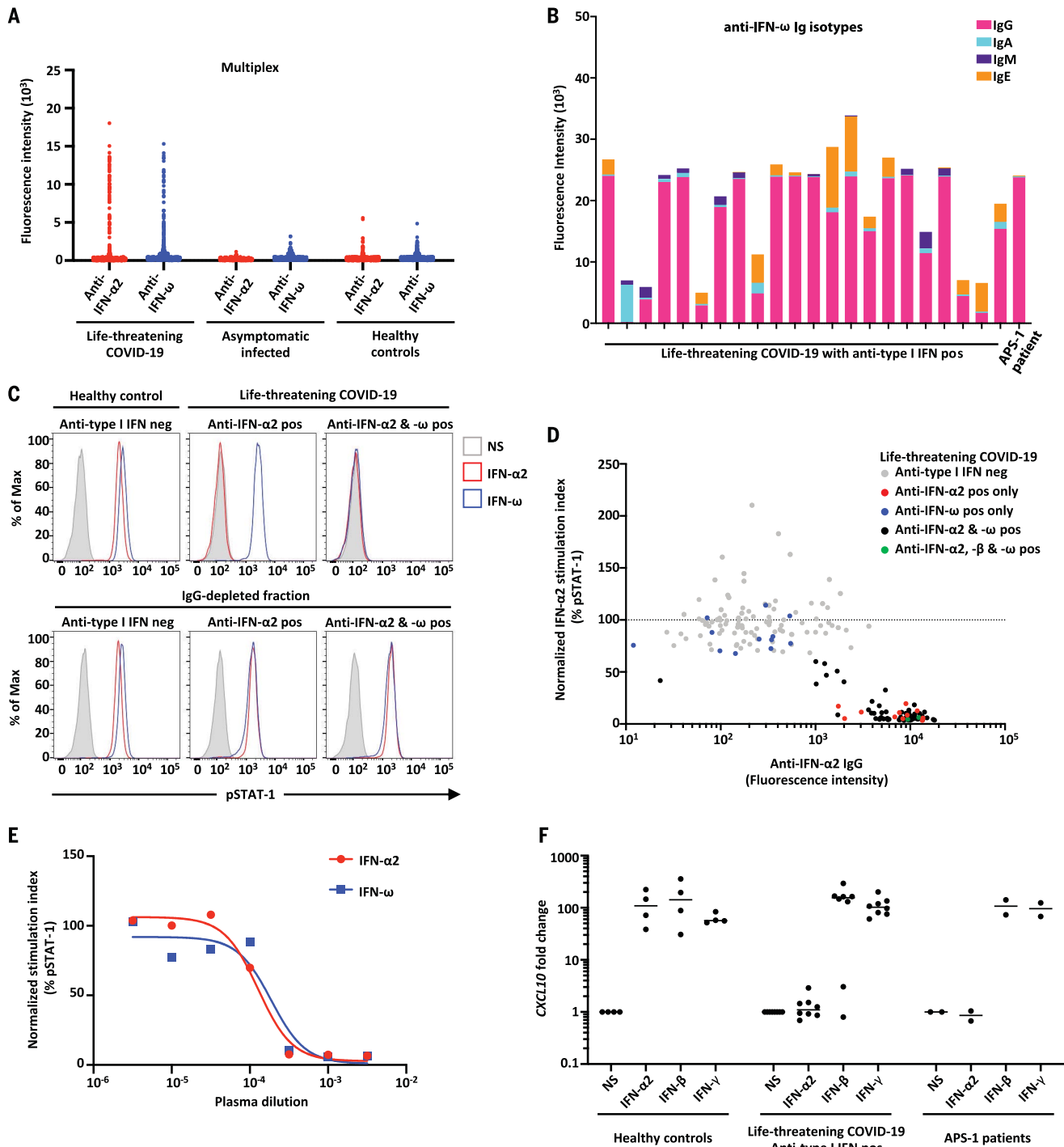


Fig. 1. Neutralizing auto-Abs against IFN- $\alpha 2$ and/or IFN- ω in patients with life-threatening COVID-19.

(A) Multiplex particle-based assay for auto-Abs against IFN- $\alpha 2$ and IFN- ω in patients with life-threatening COVID-19 ($N = 782$), in patients with asymptomatic or mild SARS-CoV-2 infection ($N = 443$), and in healthy controls not infected with SARS-CoV-2 ($N = 1160$). (B) Anti-IFN- ω Ig isotypes in 23 patients with life-threatening COVID-19 and auto-Abs to type I IFNs. (C) Representative fluorescence-activated cell sorting (FACS) plots depicting IFN- $\alpha 2$ - or IFN- ω -induced pSTAT1 in healthy control cells (gated on CD14⁺ monocytes) in the presence of 10% healthy control or anti-IFN- $\alpha 2$ or anti-IFN- ω auto-Abs-containing patient plasma (top panel) or an IgG-depleted plasma fraction (bottom panel). Max, maximum; neg, negative; pos, positive; NS, not stimulated. (D) Plot of anti-IFN- $\alpha 2$ auto-Ab levels against their

neutralization capacity. The stimulation index (stimulated over unstimulated condition) for the plasma from each patient was normalized against that of healthy control plasma from the same experiment. Spearman's rank correlation coefficient = -0.6805 ; $P < 0.0001$. (E) Median inhibitory concentration (IC_{50}) curves representing IFN- $\alpha 2$ - and IFN- ω -induced pSTAT1 levels in healthy donor cells in the presence of serial dilutions of patient plasma. The stimulation index (stimulated over unstimulated condition) for patient plasma was normalized against that of 10% healthy control plasma. IFN- $\alpha 2$: $IC_{50} = 0.016\%$, $R^2 = 0.985$; IFN- ω : $IC_{50} = 0.0353\%$, $R^2 = 0.926$. R^2 , coefficient of determination. (F) Neutralizing effect on CXCL10 induction, after stimulation with IFN- $\alpha 2$, IFN- β , or IFN- γ , in the presence of plasma from healthy controls ($N = 4$), patients with life-threatening COVID-19 and auto-Abs against IFN- $\alpha 2$ ($N = 8$), and APS-1 patients ($N = 2$).

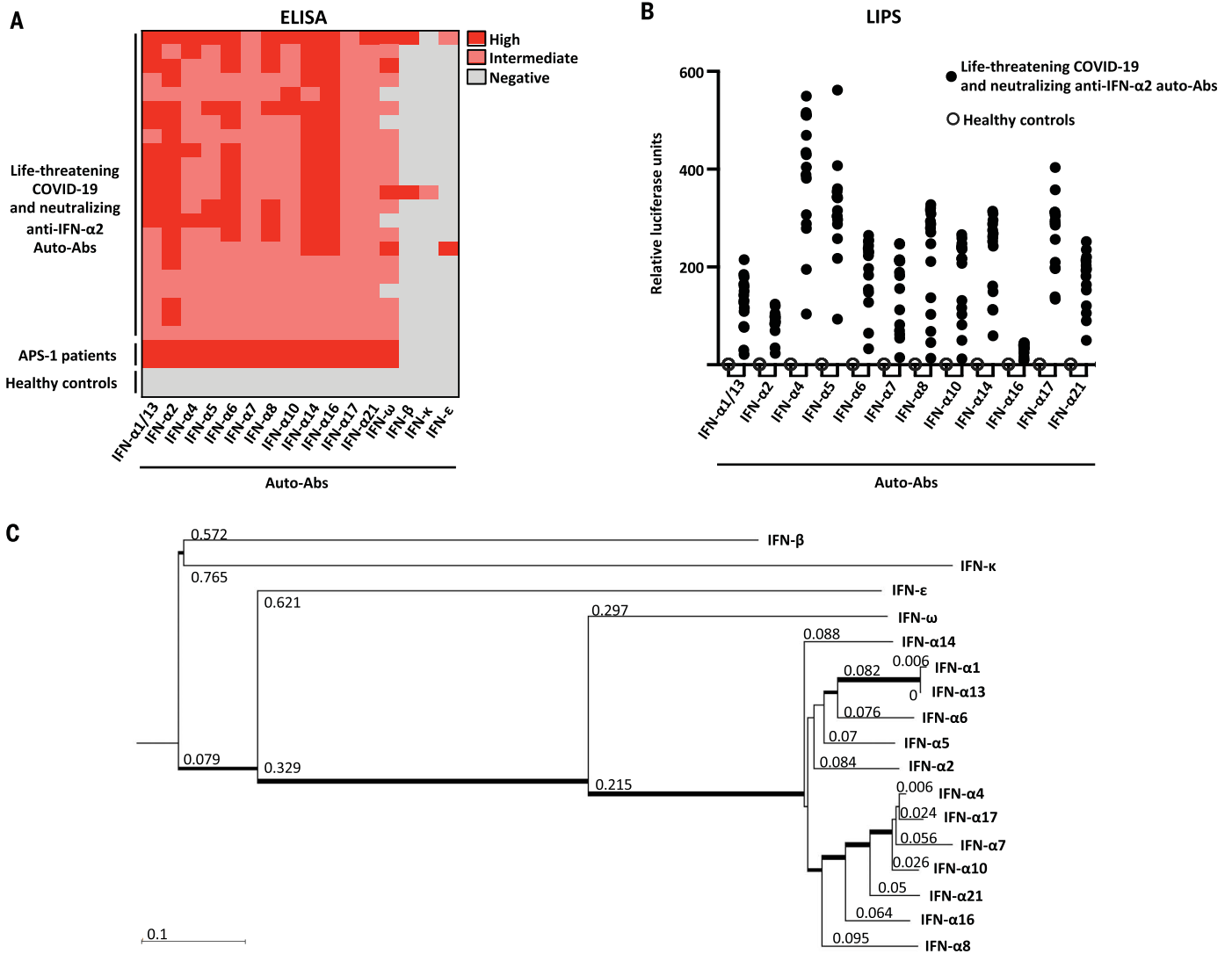


Fig. 2. Auto-Abs against the different type I IFN subtypes. (A) ELISA for auto-Abs against the 13 different IFN- α subtypes, IFN- ω , IFN- β , IFN- κ , and IFN- ϵ in patients with life-threatening COVID-19 and auto-Abs against IFN- $\alpha 2$ ($N = 22$), APS-1 patients ($N = 2$), and healthy controls ($N = 2$). (B) LIPS for the 12 different IFN- α subtypes tested in patients with auto-Abs against IFN- $\alpha 2$ ($N = 22$) and

healthy controls ($N = 2$). (C) Neighbor-joining phylogenetic tree of the 17 human type I IFN proteins. Horizontal branches are drawn to scale (bottom left, number of substitutions per site). Thinner, intermediate, and thicker internal branches have bootstrap support of <50 , ≥ 50 , and $>80\%$, respectively. The bootstrap value for the branch separating IFN- ω from all IFN- α subtypes is 100%.

other seven IFN loci in the human genome often carry loss-of-function alleles (24). Moreover, the 13 IFN- α subtypes and IFN- ω are more-closely related to each other than they are to the other three IFNs (IFN- β , IFN- ϵ , and IFN- κ), which are structurally and phylogenetically more distant (Fig. 2C). Thus, all patients with neutralizing auto-Abs against IFN- $\alpha 2$ that we tested ($N = 22$) had auto-Abs against all 13 IFN- α subtypes, and 3 of the 22 patients tested (14%) had auto-Abs against 14 or more type I IFNs.

The auto-Abs neutralize IFN- $\alpha 2$ against SARS-CoV-2 in vitro and IFN- α in vivo

Plasma from eight patients with neutralizing auto-Abs against type I IFN also neutralized the ability of IFN- $\alpha 2$ to block the infection of

Huh7.5 cells with SARS-CoV-2 (Fig. 3A). Plasma from two healthy controls or from seven SARS-CoV-2-infected patients without auto-Abs did not block the protective action of IFN- $\alpha 2$ (Fig. 3A and fig. S3A). These data provide compelling evidence that the patients' blood carried sufficiently large amounts of auto-Abs to neutralize the corresponding type I IFNs and block their antiviral activity in vitro, including that against SARS-CoV-2.

We also found that all 41 patients with neutralizing auto-Abs against the 13 types of IFN- α tested had low (one patient) or undetectable (40 patients) levels of the 13 types of IFN- α in their plasma during the course of the disease (Fig. 3B) (25, 26). Type I IFNs may be degraded and/or bound to the corresponding circulating auto-Abs. The presence of circulating neutral-

izing auto-Abs against IFN- α is, therefore, strongly associated with low serum IFN- α levels (Fisher exact test, $P < 10^{-6}$). Consistently in patients with neutralizing auto-Abs against IFN- $\alpha 2$, the baseline levels of type I IFN-dependent transcripts were low, whereas they were normal for nuclear factor κB (NF- κB)-dependent transcripts (Fig. 3C and fig. S3B). Overall, our findings indicate that the auto-Abs against type I IFNs present in patients with life-threatening COVID-19 were neutralizing in vitro and in vivo.

Pronounced excess of men in patients with auto-Abs against type I IFNs

There was a pronounced excess of male patients (95 of 101; 94%) with critical COVID-19 pneumonia and neutralizing auto-Abs against type I

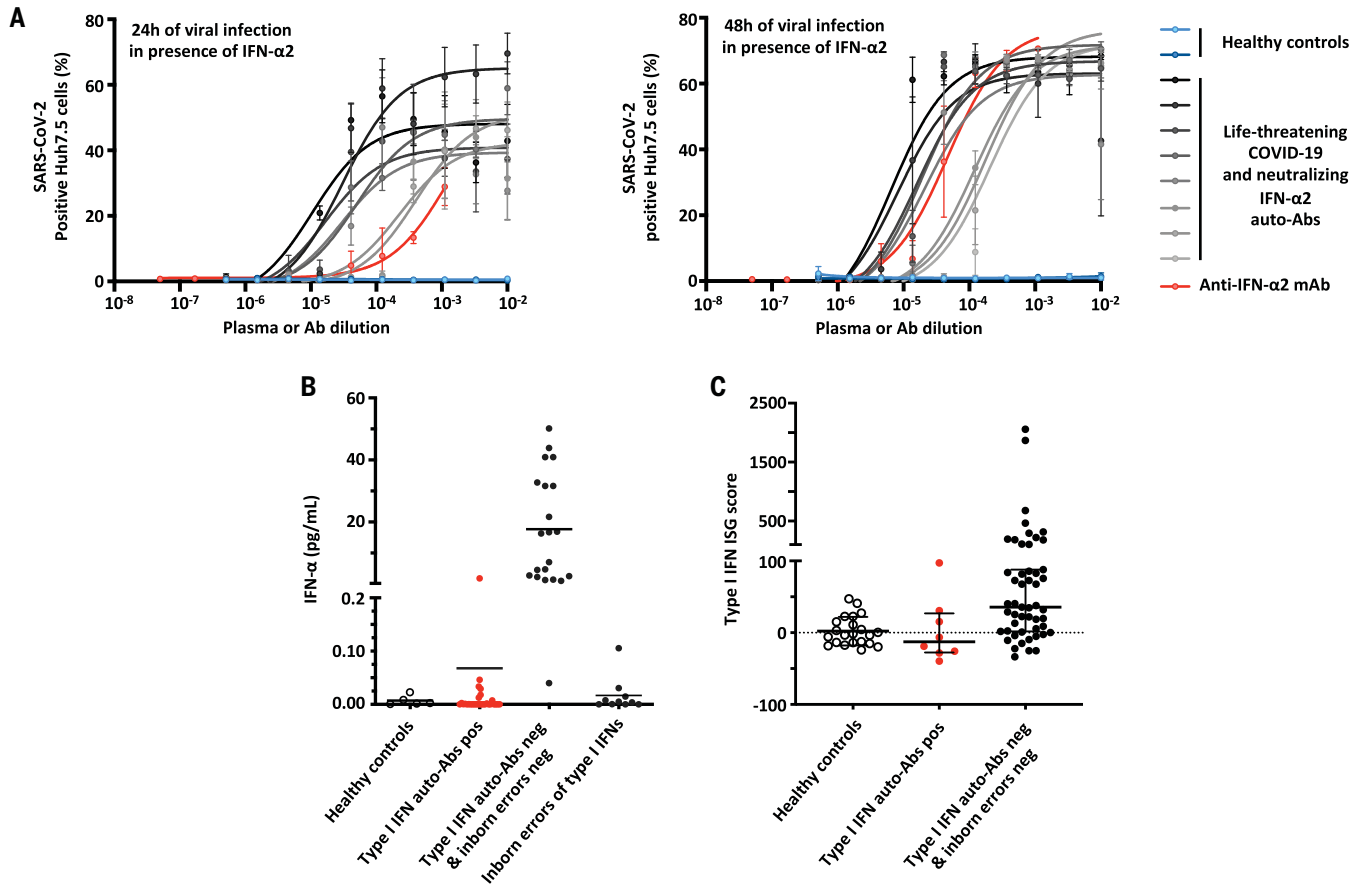


Fig. 3. Enhanced SARS-CoV-2 replication, despite the presence of IFN-α2, in the presence of plasma from patients with auto-Abs against IFN-α2 and low in vivo levels of IFN-α. (A) SARS-CoV-2 replication—measured 24 hours (left) and 48 hours (right) after infection—in Huh7.5 cells treated with IFN-α2 in the presence of plasma from patients with life-threatening COVID-19 and neutralizing auto-Abs against IFN-α2 ($N = 8$); a commercial anti-IFN-α2 antibody; or control plasma ($N = 2$). (B) IFN-α levels in the plasma or serum of patients with neutralizing auto-Abs

($N = 41$), healthy controls ($N = 5$), COVID-19 patients without auto-Abs ($N = 21$), and patients with life-threatening COVID-19 and loss-of-function (LOF) variants ($N = 10$), as assessed by Simoa ELISA. (C) z-scores for type I IFN gene responses in whole blood of COVID-19 patients with ($N = 8$) or without ($N = 51$) neutralizing auto-Abs, or healthy uninfected controls ($N = 22$). The median \pm interquartile range is shown. z-scores were significantly lower for patients with neutralizing auto-Abs compared with patients without auto-Abs (Mann-Whitney test, $P = 0.01$).

Table 1. Sex and age distribution of patients with critical COVID-19 with and without auto-Abs. Ages and sexes of the patients and controls and information about auto-Abs against IFN-α2 and IFN-α, presented by age and sex. Dashes in rightmost column indicate data not available. OR, odds ratio; CI, confidence interval.

Life-threatening COVID-19	<i>N</i> total	<i>N</i> auto-Abs positive (percentage)	OR [95% CI]	<i>P</i> value*
<i>Sex</i>				
Female	226	6 (2.6%)	1	—
Male	761	95 (12.5%)	5.22 [2.27 – 14.80]	2.5×10^{-6}
<i>Age</i>				
<65 years	602	51 (8.5%)	1	—
≥65 years	385	50 (13.0%)	1.61 [1.04 – 2.49]	0.024

**P* values were derived from Fisher's exact test, as implemented in R (<https://cran.r-project.org/>).

IFNs. This proportion of males was higher than that observed in patients with critical COVID-19 without auto-Abs (75%; Fisher exact test, $P = 2.5 \times 10^{-6}$), and the proportion was much higher than that in male patients in the asymptomatic

or pauci-symptomatic cohort (28%; Fisher exact test, $P < 10^{-6}$) (Table 1, Fig. 4A, and fig. S4A). Further evidence for X-chromosome linkage was provided by the observation that one of the seven women with auto-Abs and life-

threatening COVID-19 had X chromosome-linked incontinentia pigmenti (IP), in which cells activate only a single X chromosome (cells having activated the X chromosome bearing the null mutation in *NEMO* dying in the course of development) (27). The prevalence of auto-Abs against type I IFNs in the general population was estimated at 0.33% (0.015 to 0.67%) in a sample of 1227 healthy individuals—a value much lower than that in patients with life-threatening COVID-19 pneumonia, by a factor of at least 15.

The patients with auto-Abs were also slightly older than the rest of our cohort (49.5% of patients positive for auto-Abs were over 65 years of age versus 38% for the rest of the cohort; $P = 0.024$), which suggests that the frequency of circulating anti-type I IFNs auto-Abs increases with age (Table 1 and Fig. 4B). However, auto-Abs were found in patients aged from 25 to 87 years (fig. S4B). Principal components analysis (PCA) was performed on data from

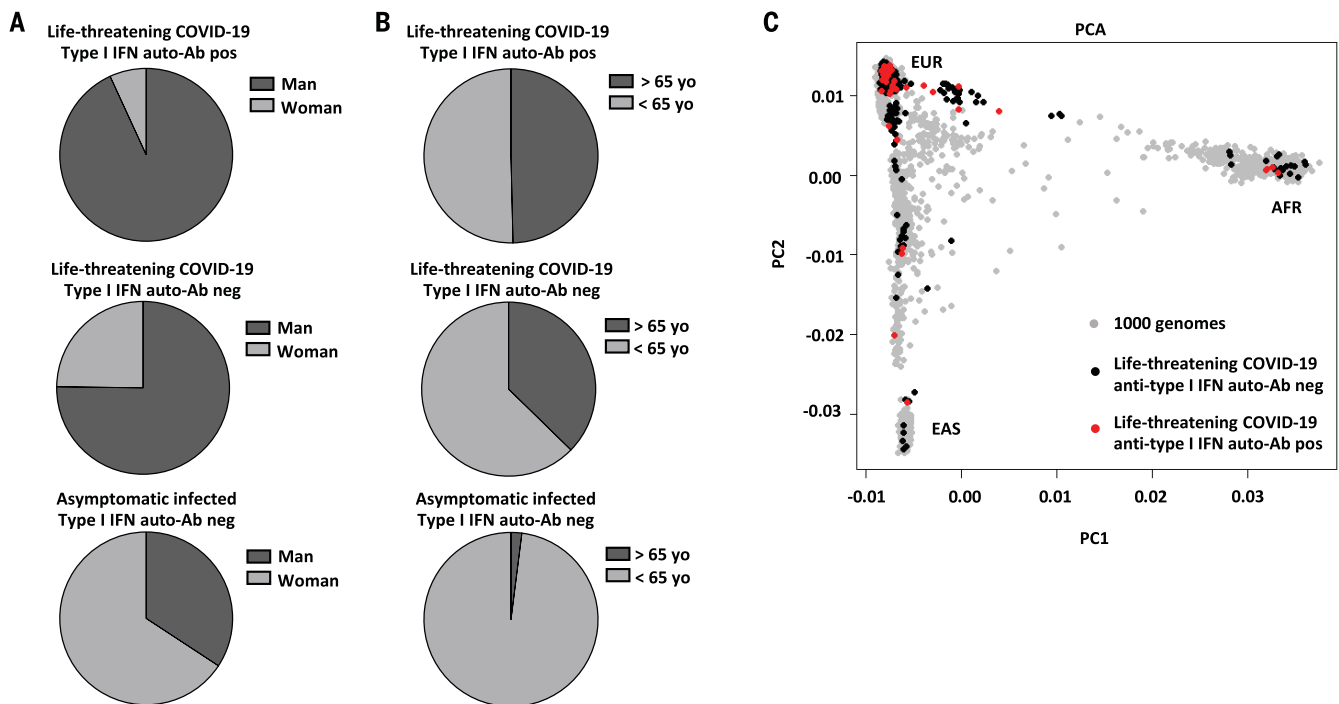


Fig. 4. Demographic and ethnic information about the patients and controls. (A) Gender distribution in patients with life-threatening COVID-19 and auto-Abs to type I IFNs, patients with life-threatening COVID-19 and without auto-Abs to type I IFNs, and individuals with asymptomatic or mild SARS-CoV-2. (B) Age distribution in patients with life-threatening COVID-19

and auto-Abs to type I IFNs, patients with life-threatening COVID-19 and without auto-Abs to type I IFNs, and individuals with asymptomatic or mild SARS-CoV-2. (C) PCA on 49 patients with life-threatening COVID-19 and auto-Abs against type I IFNs. EUR, Europeans; AFR, Africans; EAS, East-Asians.

49 patients: 34 Europeans, 5 North Africans, 4 sub-Saharan Africans, 2 patients from the Middle East, 2 South Asians, 1 East Asian, and 1 South American (Fig. 4C). Large-scale studies will be required to determine the frequency of such auto-Abs in humans of different sexes, ages, and ancestries. Finally, the presence of auto-Abs was associated with a poor outcome, with death occurring in 37 of the 101 patients (36.6%) (table S1).

Neutralizing auto-Abs to type I IFNs are causative of critical COVID-19

There are multiple lines of evidence to suggest that the neutralizing auto-Abs against type I IFNs observed in these 101 patients preceded infection with SARS-CoV-2 and accounted for the severity of disease. First, the two patients for whom testing was performed before COVID-19 were found to have auto-Abs before infection. Second, three patients with APS-1 known to have neutralizing auto-Abs against type I IFN immunity before infection also had life-threatening COVID-19 (22) (supplementary methods). Third, we screened a series of 32 women with IP and found that a quarter of them had auto-Abs against type I IFNs, including one who developed critical COVID-19 (fig. S1C). Fourth, there is a marked bias in favor of men, which suggests that the production of auto-Abs against type I IFNs—whether

driven by germ line or somatic genome—may be X chromosome-linked and therefore pre-existing to infection.

Moreover, IFN- α subtypes were undetectable during acute disease in the blood of patients with auto-Abs against IFN- α , which suggests a preexisting or concomitant biological impact in vivo. It is also unlikely that patients could break self-tolerance and mount high titers of neutralizing IgG auto-Abs against type I IFN within only 1 or even 2 weeks of infection. Finally, inborn errors of type I IFNs underlying life-threatening COVID-19 in other previously healthy adults—including autosomal recessive IFN- α/β receptor subunit 1 (IFNAR1) deficiency—have also been reported in an accompanying paper (18). Collectively, these findings suggest that auto-Abs against type I IFNs are a cause and not a consequence of severe SARS-CoV-2 infection, although their titers and affinity may be enhanced by the SARS-CoV-2-driven induction of type I IFNs. They also provide an explanation for the major sex bias seen in patients with life-threatening COVID-19 and perhaps also for the increase in risk with age.

Conclusion

We report here that at least 10% of patients with life-threatening COVID-19 pneumonia have neutralizing auto-Abs against type I IFNs. With our accompanying description of patients

with inborn errors of type I IFNs and life-threatening COVID-19 (18), this study highlights the crucial role of type I IFNs in protective immunity against SARS-CoV-2. These auto-Abs against type I IFNs were clinically silent until the patients were infected with SARS-CoV-2—a poor inducer of type I IFNs (28)—which suggests that the small amounts of IFNs induced by the virus are important for protection against severe disease. The neutralizing auto-Abs against type I IFNs, like inborn errors of type I IFN production, tip the balance in favor of the virus, which results in devastating disease with insufficient, and even perhaps deleterious, innate and adaptive immune responses.

Our findings have direct clinical implications. First, SARS-CoV-2-infected patients can be screened to identify individuals with auto-Abs at risk of developing life-threatening pneumonia. Such patients recovering from life-threatening COVID-19 should also be excluded from donating convalescent plasma for ongoing clinical trials, or at least they should be tested before their plasma donations are accepted (29). Second, this finding paves the way for preventive or therapeutic intervention, including plasmapheresis, monoclonal Abs depleting plasmablasts, and the specific inhibition of type I IFN-reactive B cells (30). Finally, in this patient group, early treatment with IFN- α is unlikely to be beneficial; however, treatment

with injected or nebulized IFN- β may have beneficial effects, as auto-Abs against IFN- β appear to be rare in patients with auto-Abs against type I IFNs.

Materials and methods

Subjects and samples

We enrolled 987 patients with proven life-threatening (critical) COVID-19, 663 asymptomatic or pauci-symptomatic individuals with proven COVID-19, and 1227 healthy controls in this study. All subjects were recruited following protocols approved by local Institutional Review Boards (IRBs). All protocols followed local ethics recommendations and informed consent was obtained when required.

COVID-19 disease severity was assessed in accordance with the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia. The term life-threatening COVID-19 pneumonia describes pneumonia in patients with critical disease, whether pulmonary, with mechanical ventilation [continuous positive airway pressure (CPAP), bilevel positive airway pressure (BIPAP), intubation, or high-flow oxygen], septic shock, or damage to any other organ requiring admission in the intensive care unit (ICU). The individuals with asymptomatic or mild SARS-CoV-2 infection were individuals infected with SARS-CoV-2 who remained asymptomatic or developed mild, self-healing, ambulatory disease with no evidence of pneumonia. The healthy controls were individuals who had not been exposed to SARS-CoV-2.

Plasma and serum samples from the patients and controls were frozen at -20°C immediately after collection. The fluid-phase LIPS assay was used to determine the levels of antibodies against the SARS-CoV-2 nucleoprotein and spike protein, as has been previously described (31).

Detection of anti-cytokine auto-Abs Multiplex particle-based assay

Serum and plasma samples were screened for auto-Abs against 18 targets in a multiplex particle-based assay, in which magnetic beads with differential fluorescence were covalently coupled to recombinant human proteins. Patients with an FI of >1500 for IFN- $\alpha 2$ or IFN- β or >1000 for IFN- ω were tested for blocking activity, as were patients positive for another cytokine.

ELISA

ELISA was performed as previously described (5). In brief, ELISA plates were coated with recombinant human interferon- α (rhIFN- α) or rhIFN- ω and incubated with 1:50 dilutions of plasma samples from the patients or controls. A similar protocol was used when testing for 12 subtypes of IFN- α .

LIPS

Levels of auto-Abs against IFN- α subtypes were measured with LIPS, as previously described

(32). IFN- $\alpha 1$, IFN- $\alpha 2$, IFN- $\alpha 4$, IFN- $\alpha 5$, IFN- $\alpha 6$, IFN- $\alpha 7$, IFN- $\alpha 8$, IFN- $\alpha 10$, IFN- $\alpha 14$, IFN- $\alpha 16$, IFN- $\alpha 17$, and IFN- $\alpha 21$ sequences were transfected in HEK293 cells, and the IFN- α -luciferase fusion proteins were collected in the tissue culture supernatant. For autoantibody screening, serum samples were incubated with protein G agarose beads, and we then added 2×10^6 luminescence units (LU) of antigen and incubated. Luminescence intensity was measured. The results are expressed in arbitrary units (AU), as a fold-difference relative to the mean of the negative control samples.

Functional evaluation of anti-cytokine auto-Abs

The blocking activity of anti-IFN- α and anti-IFN- ω auto-Abs was determined by assessing STAT1 phosphorylation in healthy control cells after stimulation with the appropriate cytokines in the presence of 10% healthy control or patient serum or plasma.

We demonstrated that the IFN- α and IFN- ω blocking activity observed was due to auto-Abs and not another plasma factor, by depleting IgG from the plasma with a protein G column. Without eluting the IgG, the flow-through fraction (IgG-depleted) was then collected and compared with total plasma in the phospho-STAT1 assay.

The blocking activity of anti-IFN- γ , -GM-CSF, -IFN- $\lambda 1$, -IFN- $\lambda 2$, -IFN- $\lambda 3$, -IL-6, -IL-10, -IL-12p70, -IL-22, -IL-17A, -IL-17F, -TNF α , and -TNF β antibodies was assessed with the assays outlined in table S3, as previously reported (21).

For the neutralization of ISG induction, PBMCs were left unstimulated or were stimulated for 2 hours with 10 ng/mL IFN- α or 10 ng/mL IFN- γ in a final volume of 100 μL . Real-time quantitative polymerase chain reaction (RT-qPCR) analysis was performed with Applied Biosystems Taqman assays for *CXCL10*, and the β -glucuronidase (GUS) housekeeping gene for normalization. Results are expressed according to the $\Delta\Delta\text{Ct}$ method, as described by the manufacturer's kit.

Phylogenetic reconstruction

Protein sequences were aligned with the online version of MAFFT v7.471 software (33), using the L-INS-i strategy (34) and the BLOSUM62 scoring matrix for amino acid substitutions. Phylogenetic tree reconstruction was performed by the neighbor-joining method (35) with the substitution model (36). Low-confidence branches ($<50\%$) are likely to be due to gene conversion events between *IFNA* genes, as previously reported (24, 37). The tree was then visualized (38). Very similar results were obtained with the corresponding DNA sequences (37, 39).

Statistical analysis

Comparison of proportions were performed using a Fisher exact test, as implemented in R

(<https://cran.r-project.org/>). PCA was performed with Plink v1.9 software on whole-exome and whole-genome sequencing data with the 1000 Genomes (1kG) Project phase 3 public database as a reference.

Simoa

Serum IFN- α concentrations were determined with Simoa technology, as previously described (40, 41), with reagents and procedures obtained from the Quanterix Corporation.

VSV assay

The seroneutralization assay was performed as previously described (42). In brief, the incubation of IFN- $\alpha 2$ with MDBK cells protects the cultured cells against the cytopathic effect of VSV. The titer of anti-IFN- α antibodies was defined as the last dilution causing 50% cell death.

SARS-CoV-2 experiment

SARS-CoV-2 strain USA-WA1/2020 was obtained from BEI Resources and amplified in Huh7.5 hepatoma cells at 33°C . Viral titers were measured on Huh7.5 cells in a standard plaque assay. Plasma samples or a commercial anti-IFN- $\alpha 2$ antibody were serially diluted and incubated with 20 pM recombinant IFN- $\alpha 2$ for 1 hour at 37°C (starting concentrations: plasma samples = 1/100 and anti-IFN- $\alpha 2$ antibody = 1/1000). The cell culture medium was then removed and replaced with the plasma- or antibody-IFN- $\alpha 2$ mixture. The plates were incubated overnight, and the plasma- or antibody-IFN- $\alpha 2$ mixture was removed by aspiration. The cells were washed once with phosphate-buffered saline (PBS) to remove potential anti-SARS-CoV-2 neutralizing antibodies, and fresh medium was then added. Cells were then infected with SARS-CoV-2 by directly adding the virus to the wells. Cells infected at a high multiplicity of infection (MOI) were incubated at 37°C for 24 hours, whereas cells infected at a low MOI were incubated at 33°C for 48 hours. The cells were fixed with 7% formaldehyde, stained for SARS-CoV-2 with an anti-N antibody, imaged, and analyzed as previously described (43).

Nanostring

For the NanoString assay, total RNA was extracted from whole blood samples collected in PaxGene tubes. The expression of selected genes was determined by NanoString methods and a 28-gene type I IFN score was calculated (44).

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SUPPLEMENTARY MATERIALS

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Supplementary Materials and Methods

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

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The genetics underlying severe COVID-19

The immune system is complex and involves many genes, including those that encode cytokines known as interferons (IFNs). Individuals that lack specific IFNs can be more susceptible to infectious diseases. Furthermore, the autoantibody system dampens IFN response to prevent damage from pathogen-induced inflammation. Two studies now examine the likelihood that genetics affects the risk of severe coronavirus disease 2019 (COVID-19) through components of this system (see the Perspective by Beck and Aksentijevich). Q. Zhang¹ used a candidate gene approach and identified patients with severe COVID-19 who have mutations in genes involved in the regulation of type I and III IFN immunity. They found enrichment of these genes in patients and conclude that genetics may determine the clinical course of the infection. Bastard² identified individuals with high titers of neutralizing autoantibodies against type I IFN- α 2 and IFN- β in about 10% of patients with severe COVID-19 pneumonia. These autoantibodies were not found either in infected people who were asymptomatic or had milder phenotype or in healthy individuals. Together, these studies identify a means by which individuals at highest risk of life-threatening COVID-19 can be identified.

¹, this issue p. eabd4570, p. eabd4585; see also p. 404

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