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

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Interindividual clinical variability in the course of SARS-CoV-2 infection is immense. We report that at least 101 of 987 patients with life-threatening COVID-19 pneumonia had neutralizing IgG auto-Abs against IFN-ω (13 patients), the 13 types of IFN-α (36), or 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 1,227 healthy individuals. Patients with auto-Abs were aged 25 to 87 years and 95 were men. A B cell auto-immune phenocopy of inborn errors of type I IFN immunity underlies 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 IFN-γ, IL-6, and IL-17A/F, respectively, or by their genetically driven auto-immune phenocopies, with the production of neutralizing auto-Abs against these cytokines (*1–8*). Type I IFNs, first described in 1957, are ubiquitously expressed cytokines that contribute to both innate immunity (via 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 (*14*). Neutralizing IgG auto-Abs against type I IFNs can occur in patients treated with IFN-α2 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, 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 bi-allelic, 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 pre-existing anti-type I IFN auto-Abs, and life-threatening COVID-19 pneumonia (*22*) (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-α2 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 SARS-CoV-2 presenting asymptomatic or mild disease, and 1,227 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; >1,500) for IgG auto-Abs against IFN-α2 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 Abs against both IFN-α2 and IFN-ω, whereas 45 were positive only for Abs against IFN-α2, and 41 were positive only for Abs against IFN-ω.

We also performed ELISA and the results obtained were consistent with those obtained with Luminex technology (fig. S1A). We also found that 11 and 14 of 23 patients tested had low levels of IgM and IgA auto-Abs against IFN-ω and IFN-α2, 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, indicating that these antibodies were present before SARS-

CoV-2 infection and were not triggered by this infection. As a control, we confirmed that all 25 APS-1 patients tested had high levels of auto-Abs against IFN-α2 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-α2 and IFN-ω in vitro

We then tested whether auto-Abs against IFN-α2 and IFN-ω were neutralizing in vitro. We incubated PBMCs from healthy controls with 10 ng/mL IFN-α2 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-α2 and/or IFN-ω (table S1). The antibodies detected were neutralizing against both IFN-α2 and IFN-ω in 52 of these 101 patients (51%), against IFN- α2 only in 36 patients (36%), and against IFN-ω only in 13 patients (13%), at the IFN-α2 and IFN-ω concentrations tested (Fig. 1, C and D). IgG depletion from patients with auto-Abs restored normal pSTAT1 induction after IFN-α2 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-α2 (fig. S1E) and were neutralizing at high dilutions (Fig. 1E and fig. S1F). Interestingly, 15 patients with life-threatening COVID-19 and auto-Abs against IFN-α2 and/or IFN-ω also had auto-Abs against other cytokines (IFN-γ, GM-CSF, IL-6, IL-10, IL-12p70, IL-22, IL-17A, IL-17F, and/or TNF-β), only three of which (IL-12p70, IL-22, 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-α2, IFN-β or IFN-γ, in the presence of plasma from healthy individuals or from patients with auto-Abs. With plasma from 8 patients with auto-Abs against IFN-α2, the induction of ISG *CXCL10* was abolished after IFN-α2 stimulation but maintained after stimulation with IFN-γ (Fig. 1F). We then found that plasma from the five patients with neutralizing auto-Abs tested neutralized the protective activity of IFN-α2 in MDBK cells infected with vesicular stomatitis virus (table S2). Overall, we found that 101 of 987 patients (10.2%), including 95 males (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 four of 1,227 healthy controls (0.33%) (Fisher exact test, p-value<10^{-16}) and in none of the 663 patients with asymptomatic or mild SARS-CoV-2 infection tested (Fisher exact test, p-value<10^{-16}).

Auto-Abs against all 13 IFN-α subtypes in patients with auto-Abs to IFN-α2

We investigated whether patients with neutralizing auto-Abs against IFN-α2 only or IFN-α2 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-α2 also had auto-Abs against all 13 IFN-α subtypes (IFN-α1, -α2, -α4, -α5, -α6, -α7, -α8, -α10, -α13, -α14, -α16, -α17, and -α21), whereas only two of the 22 patients tested had auto-Abs against IFN-β, one had auto-Abs against IFN-κ, and two 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 the patients had auto-Abs against all 13 subtypes of IFN-α, by testing the same samples by LIPS (Fig. 2B). For IFN-β, we also screened the whole cohort in a multiplex assay. We found that 19/987 (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-α2, -α5, -α6, α8, -α13, -α14, -α21, -β, -ω and -κ), have undergone strong negative selection, suggesting that they play an essential role in the general population, whereas the 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 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-α2 tested (N=22) had auto-Abs against all 13 IFN-α subtypes, and three of the 22 patients tested (14%) had auto-Abs against 14 or more type I IFNs.

The auto-Abs neutralize IFN-α2 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-α2 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-α2 (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 neutralizing auto-Abs against IFN-α is, therefore,

strongly associated with low serum IFN-α levels (Fisher exact test, p-value<10^{-6}). Consistently, in patients with neutralizing auto-Abs against IFN-α2, the baseline levels of type I IFN-dependent transcripts were low while they were normal for 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.

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

There was a strong excess of male patients (95 of 101, 94%) with critical COVID-19 pneumonia and neutralizing auto-Abs against type I IFNs. This proportion of males was higher than that observed in patients with critical COVID-19 without auto-Abs (75%; Fisher exact test p-value=2.5×10^{-6}), and much higher than that in male patients within the asymptomatic or pauci-symptomatic cohort (28%, Fisher exact test p-value<10^{-6}) (Table 1, Fig. 4A, and fig. S4A). Further evidence for X-linkage was provided by the observation that one of the seven women with auto-Abs and life-threatening COVID-19 had X-linked incontinentia pigmenti (IP), in which cells activate only one 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% (0.015-0.67%) in a sample of 1,227 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), suggesting 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). PCA was performed on 49: 34 European, 5 North Africans, 1 sub-Saharan African, 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 fourth 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, suggesting that the production of auto-Abs against type I IFNs, whether driven by germ line or somatic genome, may be X-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, suggesting a pre-existing 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 one, or even two weeks of infection. Finally, inborn errors of type I IFNs underlying life-threatening COVID-19 in other previously healthy adults, including autosomal recessive IFNAR1 deficiency, are 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 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, which is a poor inducer of type I IFNs (*28*), suggesting 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, resulting 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 trial, or at least tested before their plasma donations are accepted (*29*).

Second, this unexpected finding paves the way for 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.

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 1127 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. "Life-threatening COVID-19 pneumonia" is pneumonia in patients with critical disease, whether pulmonary, with mechanical ventilation (CPAP, BIPAP, intubation, high-flow oxygen), septic shock, or damage to any other organ requiring admission in the ICU. The individuals with asymptomatic or mild SARS-CoV-2 infection we 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 luciferase immunoprecipitation systems (LIPS) assay was used to determine the levels of antibodies against the SARS-CoV-2 nucleoprotein and spike protein, as previously described (*31*).

Detection of anti-cytokine autoantibodies

Multiplex particle-based assay

Serum/plasma samples were screened for autoantibodies 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 a fluorescence intensity (FI) of > 1500 for IFN-α2, IFNβ, or > 1000 IFNω were tested for blocking activity; as were patients positive for another cytokine.

ELISA

Enzyme-linked immunosorbent assays (ELISA) was performed as previously described (*5*). In brief, ELISA plates were coated with 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 autoantibodies against IFN-α subtypes were measured with luciferase-based immunoprecipitation assay (LIPS), as previously described (*32*). IFN-α1, I IFN-α2, I IFN-α4, IFN-α5, IFN-α6, I IFN-α7, IFN-α8, IFN-α10, IFN-α14, IFN-α16, IFN-α17 and IFN-α21 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 $2x10^6$ 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 autoantibodies

The blocking activity of anti-IFNα and anti-IFNω autoantibodies was determined by assessing STAT1 phosphorylation in healthy control cells following stimulation with the appropriate cytokines in the presence of 10% healthy control or patient serum/plasma.

We demonstrated that the IFNα/ω blocking activity observed was due to autoantibodies 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 to total plasma in the phospho-STAT1 assay.

The blocking activity of anti-IFNγ, -GM-CSF, -IFNλ1, -IFNλ2, -IFNλ3, -IL-6, -IL-10, -IL-12p70, -IL-22, -IL-17A, -IL-17F, -TNFα, and -TNFβ antibodies was assessed with the assays outlined in the table in online supplementary materials, as previously reported (*21*).

For the neutralization of ISG induction, peripheral blood mononuclear cells (PBMCs) were left unstimulated or were stimulated for two hours with 10 ng/mL IFNα or 10 ng/mL IFNγ in a final volume of 100 μL. Quantitative real-time PCR (RT-qPCR) was performed with Applied Biosystems *Taq*man assays for *CXCL10*, and the β-glucuronidase (GUS) housekeeping gene for normalization. Results are expressed according to the ΔΔCt 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-IFNα concentrations were determined with Simoa technology, as previously described (*40*, *41*), with reagents and procedures obtained from Quanterix Corporation.

VSV assay

The seroneutralization assay was performed as previously described (*42*). In brief, the incubation of IFN-α2 with Madin–Darby bovine kidney (MDBK) cells protects the cultured cells against the cytopathic effect of vesicular stomatitis virus (VSV). The titer of anti IFN alpha 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 Huh-7.5 hepatoma cells at 33°C. Viral titers were measured on Huh-7.5 cells in a standard plaque assay. Huh-7.5 cells (*H. sapiens*) were cultured. Plasma samples or a commercial anti-IFN-α2 antibody were serially diluted and incubated with 20 pM recombinant IFN-α2 for 1 hour at 37°C (starting concentration: plasma samples = 1/100 and anti-IFN-α2 antibody = 1/,1000). The cell culture medium was then removed and replaced with the plasma/antibody-IFN-α2 mixture. The plates were incubated overnight and the plasma/antibody-IFN-α2 mixture was removed by aspiration. The cells were washed once with 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 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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COVID Human Genetic Effort

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SUPPLEMENTARY MATERIALS

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Supplementary Materials and Methods
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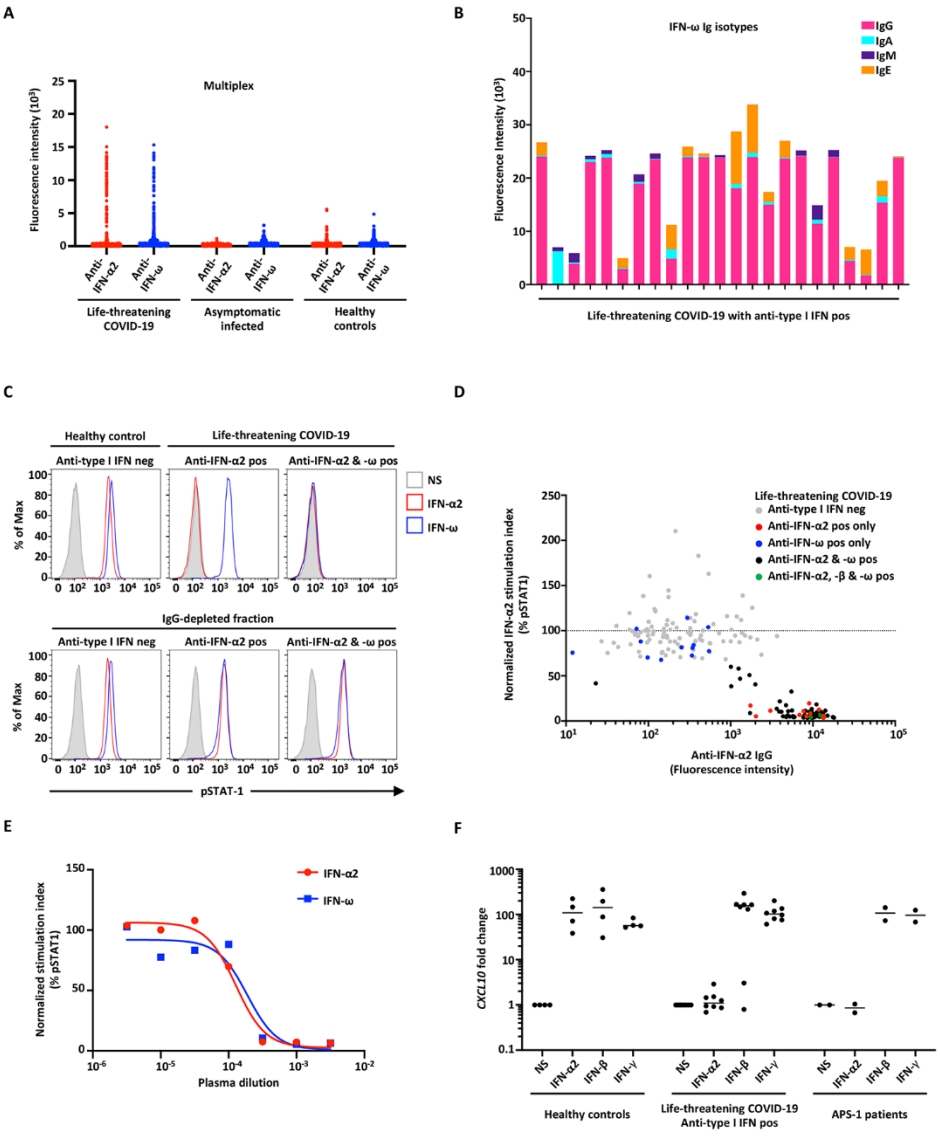

Fig. 1. Neutralizing auto-Abs against IFN-α2 and/or IFN-ω in patients with life-threatening COVID-19. (**A**) Multiplex particle-based assay for auto-Abs against IFN-α2 and IFN-ω in patients with life-threatening COVID-19 (*N*=782), or asymptomatic or mild SARS-CoV-2 infection (N=443), and in healthy controls not infected with SARS-CoV2 (*N*=1160). (**B**) Anti-IFN-ω Ig isotypes in 23 patients with life-threatening COVID-19 and auto-Abs to type 1 IFNs. (**C**) Representative FACS plots depicting IFN-α2- or IFN-ω-induced pSTAT1 in healthy control cells (gated on $CD14^+$ monocytes) in the presence of 10% healthy control or anti-IFN-α2/ω- auto-Abs-containing patient plasma (top panel) or an IgG-depleted plasma fraction (bottom panel). (**D**) Plot of anti-IFN-α2 auto-Ab levels against their neutralization capacity. The stimulation index (stimulated/unstimulated conditions) for the plasma from each was normalized against that of healthy control plasma from the same experiment. Spearman's rank correlation coefficient = −0.6805, *p*-value <0.0001. (**E**) IC_{50} curves representing IFN-α2- and IFN-ω-induced pSTAT1 levels in healthy donor cells in the presence of serial dilutions of patient plasma. The stimulation index (stimulated/unstimulated conditions) for patient plasma was normalized against that of 10% healthy control plasma. IFN-α2: IC_{50}= 0.016%, R^2= 0.985; IFN-ω: IC_{50}=0.0353%, R^2 = 0.926. (**F**) Neutralizing effect on *CXLC10* induction after stimulation with IFN-α2, IFN-β or IFN-γ, of plasma from healthy controls (*N*=4), patients with life-threatening COVID-19 and auto-Abs against IFN-α2 (*N*=8) and APS-1 patients (*N*=2).

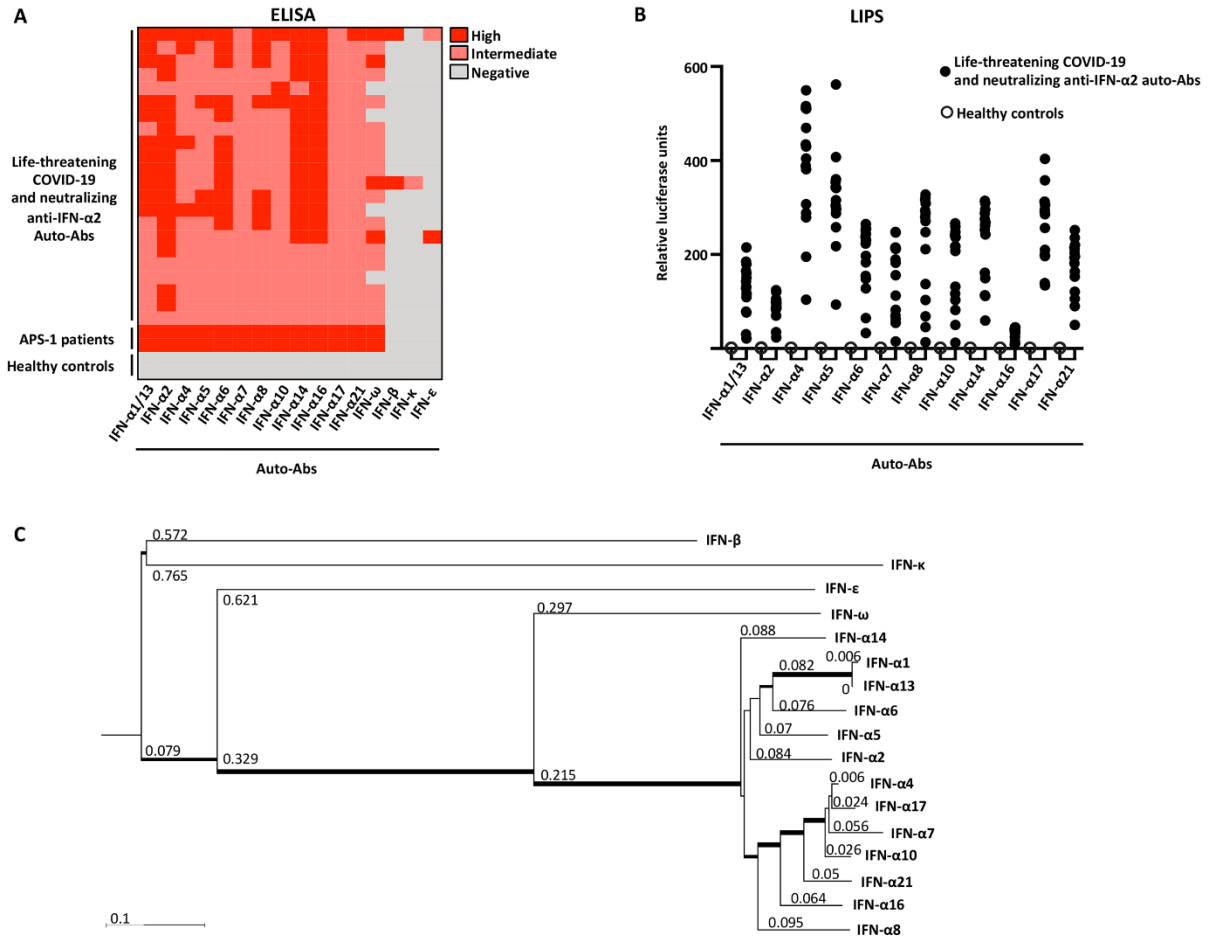

Fig. 2. Auto-Abs against the different type I IFN subtypes. (**A**) Enzyme-linked immunosorbent assay (ELISA) for auto-Abs against the 13 different IFN-α subtypes, IFN-ω, -β, -κ, and -ε in patients with life-threatening COVID-19 and auto-Abs against IFN-α2 (*N*=22), APS-1 patients (*N*=2) and healthy controls (*N*=2). (**B**) Luciferase-based immunoprecipitation assay (LIPS) for the 12 different IFN-α subtypes tested in patients with auto-Abs against IFN-α2 (*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 <50%, ≥50 and >80%, respectively. The bootstrap value for the branch separating IFN-ω from all IFN-α is 100%.

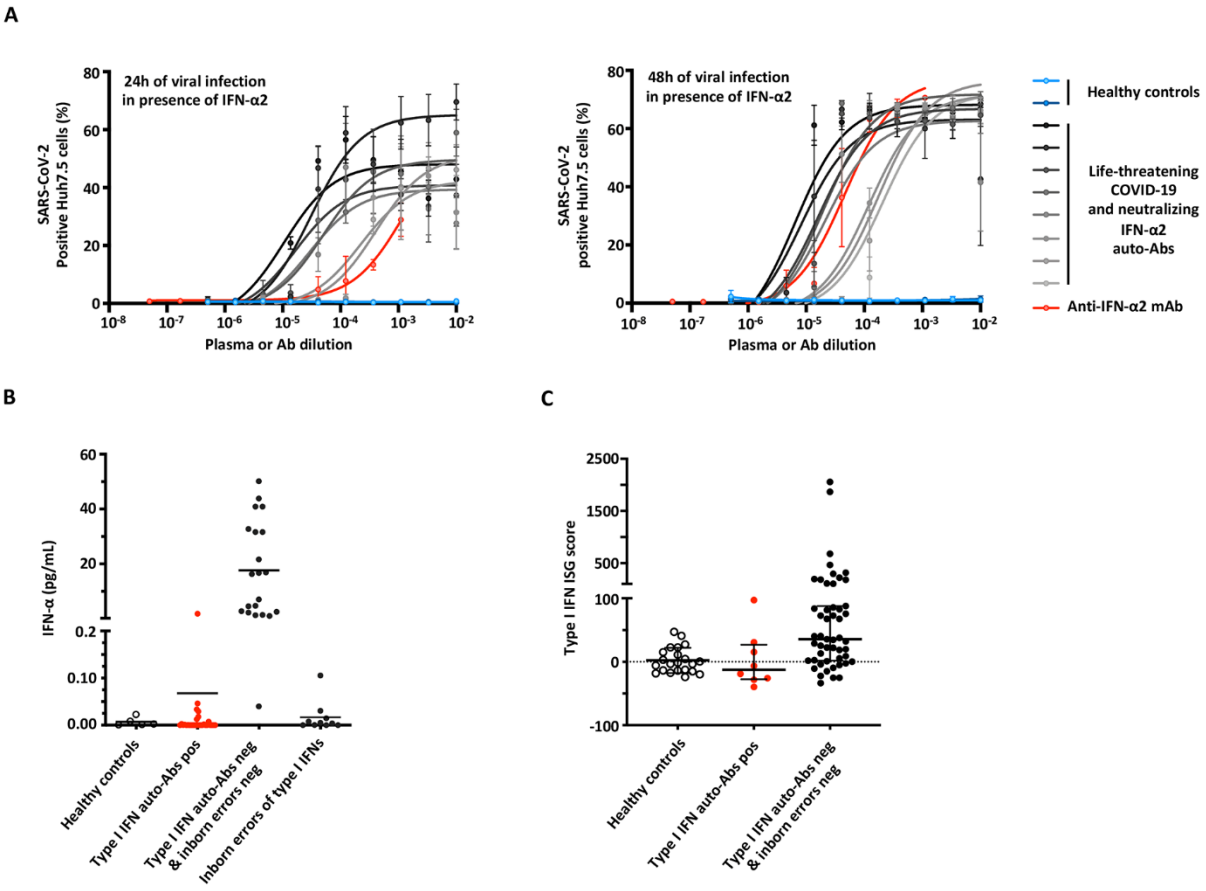

Fig. 3. Enhanced SARS-CoV-2 replication, despite the presence of IFN-α2, in the presence of plasma from patients with auto-Abs against IFN-α2 and low in vivo levels of IFN-α. (**A**) SARS-CoV-2 replication, measured 24h (left panel) and 48h (right panel) after infection, in Huh7.5 cells treated with 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 neutralizing Auto-Abs (N=51), or healthy uninfected controls (N=22). The median ± 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).

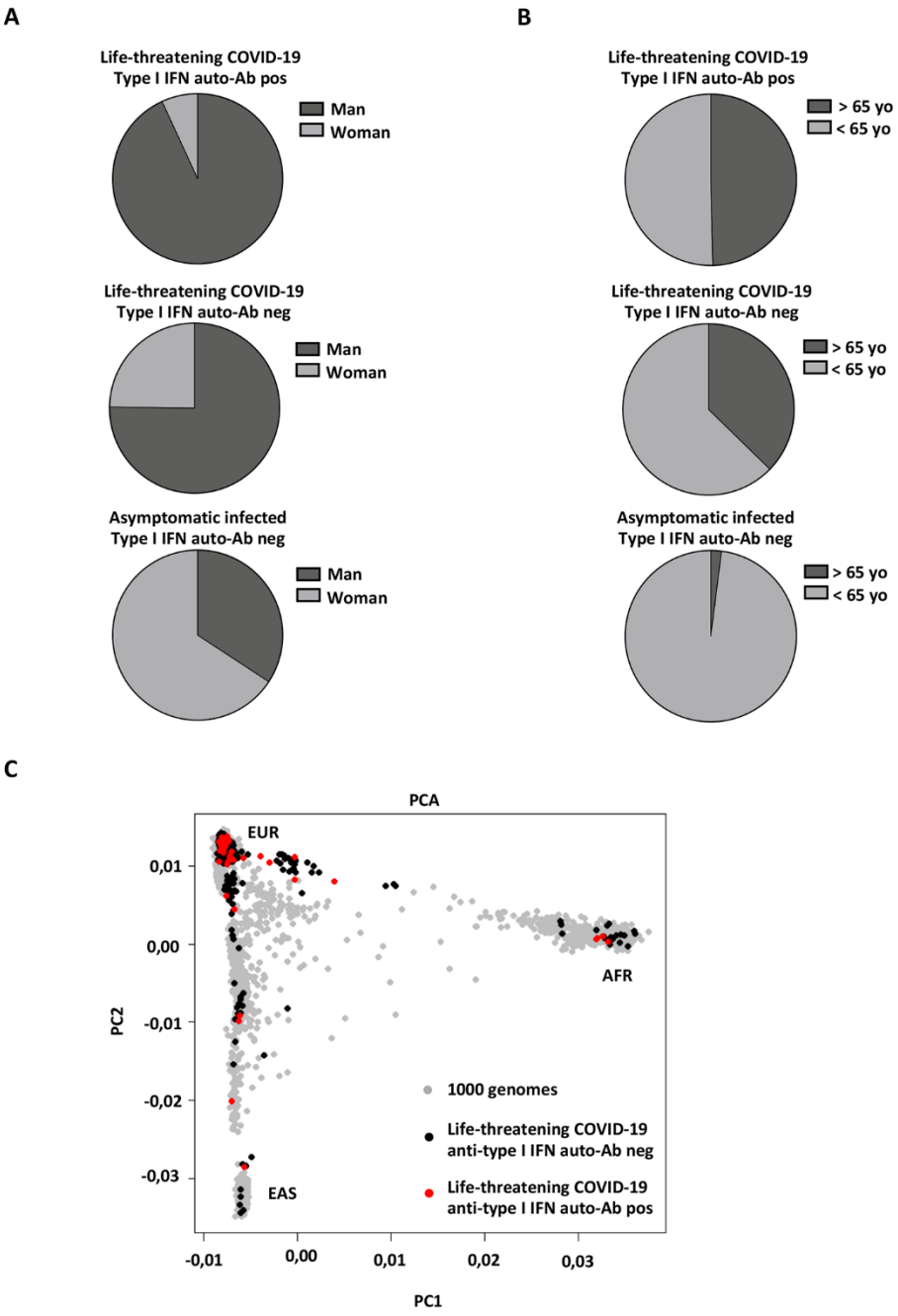

Fig. 4. Demographic and ethnic information about the patients and controls. (**A**) Gender distribution in patients with life-threatening COVID-19 and auto-Abs to type I IFNs, patients with life-threatening COVID-19 and without auto-Abs to type I IFNs and individuals with asymptomatic or mild SARS-CoV-2. (**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**) Principal component analysis (PCA) on 49 patients with life-threatening COVID-19 and auto-Abs against type 1 IFNs.

Table 1. Sex and age distribution of patients with critical COVID-19 with and without autoAbs.
Age and sex of the patients and controls, and information about auto-Abs against IFN-α2 and IFN-ω by age and sex. OR: odds ratio.

Life-threatening COVID-19	N total	N auto-Abs positive (%)	OR [95% CI]	p-value*
		Sex		
Female	226	6 (2.7%)	1	
Male	761	95 (12.5%)	5.22 [2.27-14.80]	$2.5\,10^{-6}$
		Age		
<65 years	602	51 (8.5%)	1	
≥65 years	385	50 (13.0%)	1.61 [1.04 - 2.49]	0.024

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