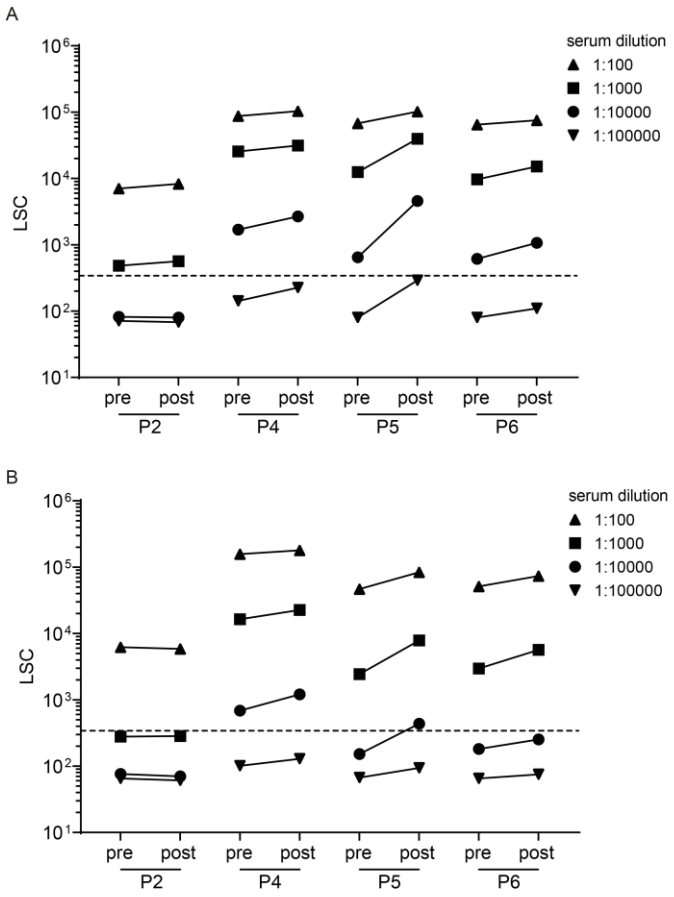
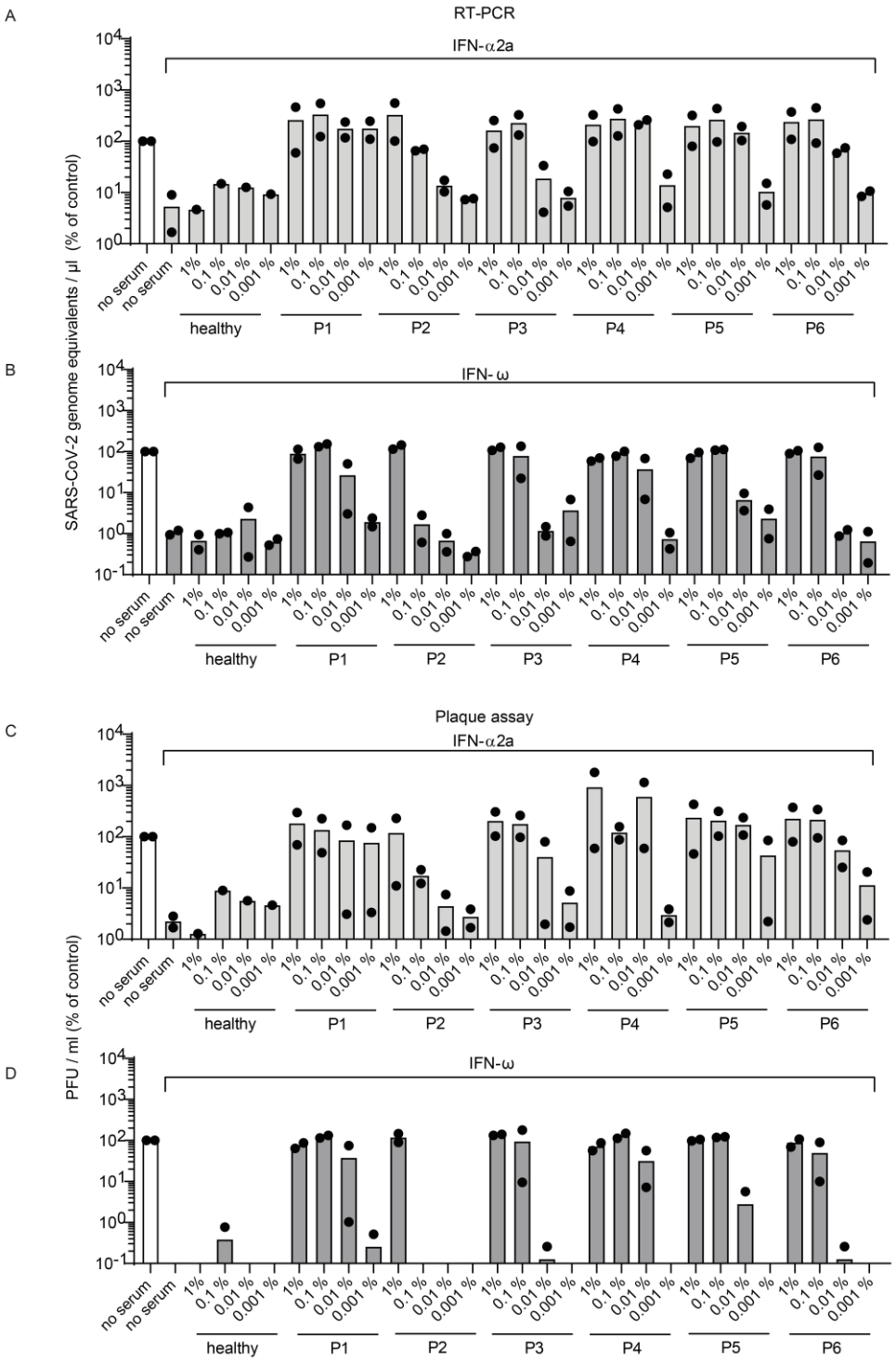
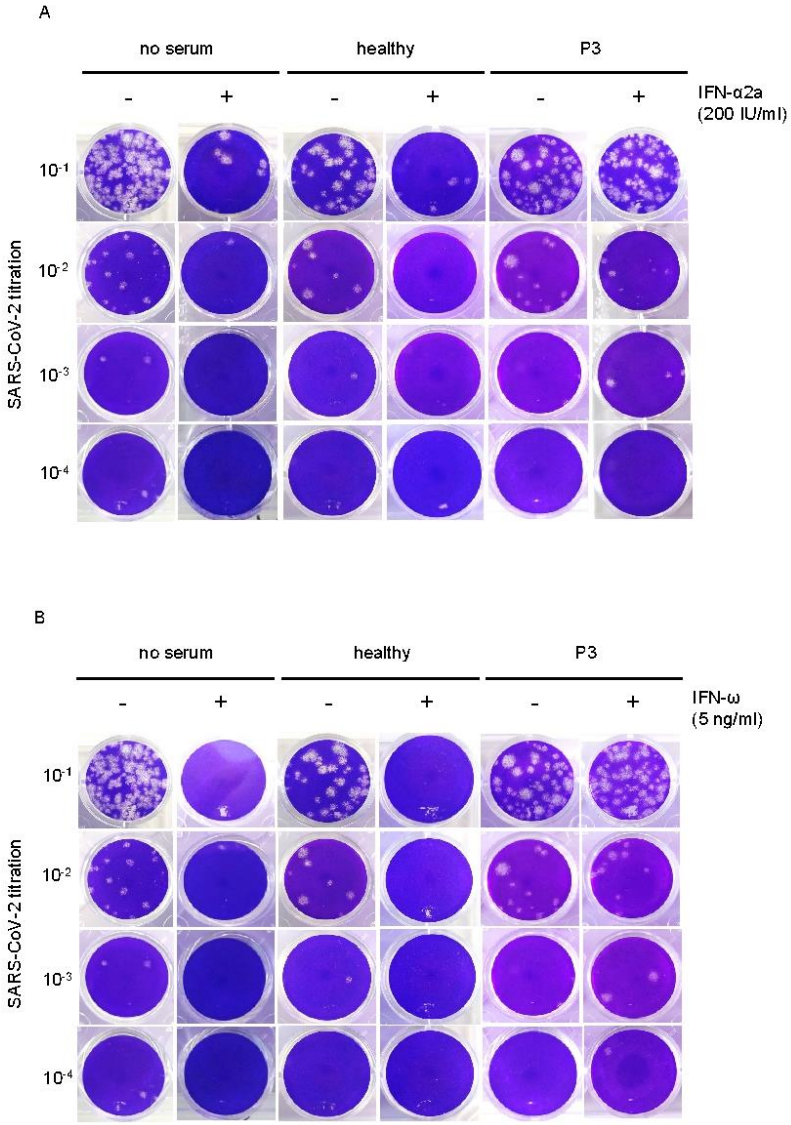


Supplementary Figure 1. Titer of auto-Abs against IFN-α2 and IFN-ω in patients with APS-1 before and after COVID-19: ECLIA based assay for detection of IgG auto-Abs against IFN-α2 (**A**) and IFN-ω (**B**) in serial dilutions of pre- and post-COPVID sera from patients P2, P4, P5, and P6. Dotted lines indicate the maximum LSC signal in the anti-IFN-α2 and anti-IFN-ω assay in the cohort of healthy controls.



Supplementary Figure 2. Neutralization of type I interferons by auto-Abs in patients with APS-1 is concentration-dependent: Neutralization assay was performed as described in Fig 2. **A-B** Viral RNA was extracted from supernatant and SARS-CoV-2 genome equivalents/µl were quantified by Q-RT-PCR using primers targeting the E gene region. **C-D** Supernatants were titrated on Vero E6 cells and incubated for plaque formation for 3 days. Plaques were counted and PFU/ml were determined. Data were generated in two independent assays. Values obtained in the absence of serum and IFN were set to 100%.



Supplementary Figure 3. Auto-Abs in patients with APS-1 neutralize the ability of type I IFNs to inhibit SARS-CoV-2 infection: Neutralization assay was performed as described in Fig. 2. Shown are representative plaque assays from supernatants collected from Calu-3 cells pretreated with mock or 0.1 % human serum in the presence or absence of 200 IU/ml IFN-α2a (**A**) or 5 ng/ml IFN-ω (**B**). The images of the plaques identified in the absence of IFN are identical in (A) and (B). Shown are representative images from two individual experiments.

Supplementary information on methods

Detection of autoantibodies against cytokines by ELISA

We collected sera during routine follow-up visits in 2020 at Charité Universitätsmedizin. In patients who developed SARS-CoV-2 infection, sera were sampled four to ten months before and within one to two months after infection. Autoantibodies were detected with use of an electrochemiluminescence immunoassay-platform (MSD, Rockville, U.S.). MSD GOLD 96-well small spot streptavidin SECTOR Plates were washed with wash buffer (MSD), and blocked with 150µl blocking buffer (Thermo Fisher) per well at 4°C over night. All further incubations were performed for 60 minutes at room temperature. After each incubation step, plates were washed three times with 150µl wash buffer (MSD). After blocking, plates were incubated with IFN-α2 (Merck Sharp & Dohme, Kenilworth, USA), IFN-ω (Peprotech, Rocky Hill, USA), Interleukin (IL)-6 (R&D, Minneapolis, USA), IFN-γ (Imukin, Boehringer Ingelheim) and Granulocyte-macrophage colony-stimulating factor (GM-CSF; Peprotech) linked to biotin (Thermo Scientific, Waltham, USA). Next, plates were incubated with patients´ sera. When not stated otherwise patients´ sera were diluted 1:100 in blocking buffer. Cytokine autoantibodies were detected using a monoclonal mouse antibody to human IgG (D20JL-6, MSD). After incubation and washing, 150µl of read buffer (Read Buffer T (4x), MSD) were added, incubated 10 minutes at room temperature and plates were analyzed using the MESO QuickPlex SQ 120 analyzer (MSD). Data are shown as light signal counts (LSC).

Phosphorylation of STAT1

100 µl of heparinized whole blood (1:2 diluted with AIM V medium) were stimulated with 1 or 10 ng/ml of recombinant human IFN-α2 (Merck Sharp & Dohme) or with 10 ng/ml recombinant human IFN-γ (Boehringer Ingelheim) for 13 min at 37°C. After 8 min of stimulation, a mixture of surface antibodies (CD16-PE, CD56-PE, CD19-PC5.5, CD3-AF750, CD14-ECD, CD4-PacBlue, CD45-KrO; Beckman Coulter) was added. After 5 additional minutes, 50 µl of PerFix EXPOSE buffer 1 (Beckman Coulter) was added for 10 min at room temperature followed by addition of 1 ml of PerFix EXPOSE buffer 2 for 5 min at 37°C, for cell fixation and permeabilization. Cells were stained with AF488-conjugated antibodies against pSTAT1 (pY701, clone 58D6, Cell Signaling Technology) for 30 min at room temperature in the dark. Samples were washed twice and acquired on a 10-color NaviosEX flow cytometer (Beckman Coulter). Navios software was used for data analysis (1). Data are shown as mean fluorescent intensity (MFI) signal of phospho-STAT1 in $CD45^{+}CD14^{+}$ monocytes.

Serology against SARS-COV-2

SARS-CoV-2 specific antibodies (IgG and IgA) to the spike protein were detected using an ELISA kit (Euroimmun, Lübeck, Germany) (2). Samples were tested at a 1:101 dilution and results were considered positive above an optical density (OD) ratio of 1.1. In addition to the S1-IgA/IgG ELISA we applied a microarray-based immunoassay (SeraSpot®Anti-SARS-CoV-2 IgG, Seramun Diagnostica GmbH, Heidesee, Germany), that uses four recombinant SARS-CoV-2 proteins (complete Spike, Spike S1 domain, Spike receptor binding domain (RBD) and nucleocapsid protein), printed in an array arrangement on the bottom of each of a well. Antibodies were detected by use of a horseradish peroxidase-(HRP)-labeled antibody against human IgG. Color intensity at the site of formed immune complexes correlates to the antibody concentration. Results are shown as signal-to-cutoff (S/CO) ratios, obtained by dividing the signal of a specific spot by that of an internal control spot in each well. Samples showing in at least two out of the four antigens S/CO ratio of ≥ 1.0 were regarded as positive (3).

Cell culture

Calu-3 (ATCC HTB-55) and Vero E6 (ATCC CRL-1586) cells were cultured in DMEM (Dulbecco's Modified Eagles Medium, Sigma Aldrich) with 4.5 g/L glucose, supplemented with 10% fetal bovine serum, 1% penicillin/streptomycin, and 1% L-glutamine at 37 °C and 5% CO_2.

Virus infection-based IFN neutralization assays

SARS-CoV-2 strain Munich 984 (strain: SARS-CoV-2/human/DEU/BavPat2-ChVir984, NCBI GenBank Acc. No. MT270112.1) was propagated on Vero E6 cells. Calu-3 cells were seeded at a density of 6 x 10^5 cells/ml and pre-incubated with dilutions of human serum in the presence or absence of 200 IU/ml IFN-α2a (Roferon®-A, Roche) or 5 ng/ml IFN-ω (PeproTech). After 24h, IFN and serum were removed and cells were infected with SARS-CoV-2 at MOI 0.01. Virus inoculum was removed after one hour, cells were washed with PBS and 100 µl medium were added per well. 24 hours post infection, cell culture supernatant was collected for viral RNA quantification and infectious titer determination. For viral RNA extraction, 50 µl of cell culture supernatant were mixed with 300 µl MagNA Pure external lysis buffer (Roche, Penzberg, Germany) and heat-inactivated at 70 °C for 10 minutes. Extraction was performed by automated pipetting using MagNA Pure 96 instrument (Roche). For plaque assays, 30 µl of cell culture supernatant were mixed with 30 µl of 0.5% gelatin in Opti-Pro™ for stabilization of infectious particles during storage at -80°C.

Real-time reverse-transcription PCR

SARS-CoV-2 genome equivalents were quantified by real-time RT-PCR assay targeting SARS-CoV-2 E gene using the following primers (4): E_Sarbeco_F: ACAGGTACGTTAATAGTTAATAGCGT; E_Sarbeco_P1: FAM-ACACTAGCCATCCTTACTGCGCTTCG-BBQ; E_Sarbeco_R: ATATTGCAGCAGTACGCACACA. Real time RT-PCRs were performed using the Superscript III OneStep RT-PCR kit (Invitrogen, Darmstadt, Germany). Reactions were performed in 12.5 µl volume with 6.25 µl of 2x reaction buffer, 0.5 µl of 10 µM forward and reverse primers, 0.25 µl of 10 µM probe, 0.5 µl of SSIII / P. Taq enzyme mix, RNase-free water, and 2.5 µl of RNA template. RNA was reverse transcribed at 55°C for 10 min, followed by initial denaturation at 95°C for 180 s. Cycling and fluorescence signal acquisition was performed for 45 cycles of 95 °C for 15 s and 58 °C for 30 s. Real-time RT-PCR experiment and data processing was conducted using the LightCycler® 480 Real-Time PCR System (Roche). Absolute quantification was performed using SARS-CoV-2-specific *in vitro*-transcribed RNA standards [4].

Plaque assay

Infectious SARS-CoV-2 plaque forming units (PFU) were quantified by plaque titration. Vero E6 cells were seeded at a density of 3.5×10^5 cells/ml and infected with serial dilutions of SARS-CoV-2-containing cell culture supernatants for 1 h at 37 °C. After removing the inoculum, cells were washed with PBS and overlaid with 2.4% Avicel (FMC BioPolymers) 1:2 diluted in 2 × DMEM supplemented with 2% penicillin/streptomycin, 2% L-glutamine, 2% non-essential amino acids, 2% sodium pyruvate and 20% fetal bovine serum. Three days after infection the overlay was discarded, cells were fixed in 6% formaldehyde and stained with a 0.2% crystal violet, 2% ethanol and 10% formaldehyde containing solution. PFU/ml were determined by counting the plaques in the respective dilutions.

Supplementary references:

1. Hanitsch, L.G., et al., *Late-Onset Disseminated Mycobacterium avium intracellulare Complex Infection (MAC), Cerebral Toxoplasmosis and Salmonella Sepsis in a German Caucasian Patient with Unusual Anti-Interferon-Gamma IgG1 Autoantibodies.* J Clin Immunol, 2015. **35**(4): p. 361-5.

2. Okba, N.M.A., et al., *Severe Acute Respiratory Syndrome Coronavirus 2-Specific Antibody Responses in Coronavirus Disease Patients.* Emerg Infect Dis, 2020. **26**(7): p. 1478-1488.

3. Schrezenmeier, E., et al., 2021.

4. Corman, V.M., et al., *Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR.* Euro Surveill, 2020. **25**(3).

Antibody	**Clone**	**Vendor**	**Catalog-No-**
CD16 PE	3G8	Beckman Coulter	A07766
CD56 PE	N901	Beckman Coulter	A07788
CD19 PC5.5	J3-119	Beckman Coulter	B49211
CD3 AF750	UCHT1	Beckman Coulter	A94680
CD14 ECD	RMO52	Beckman Coulter	IM2707U
CD4 Pac-Blue	13B8.2	Beckman Coulter	A82789
CD45 Kr-Orange	J33	Beckman Coulter	B36294
phosphoSTAT1 Alexa Fluor®488	58D6	Cell Signaling	9174S

Supplementary table 1: Clone, vendor and catalog number of all antibodies used in the study.