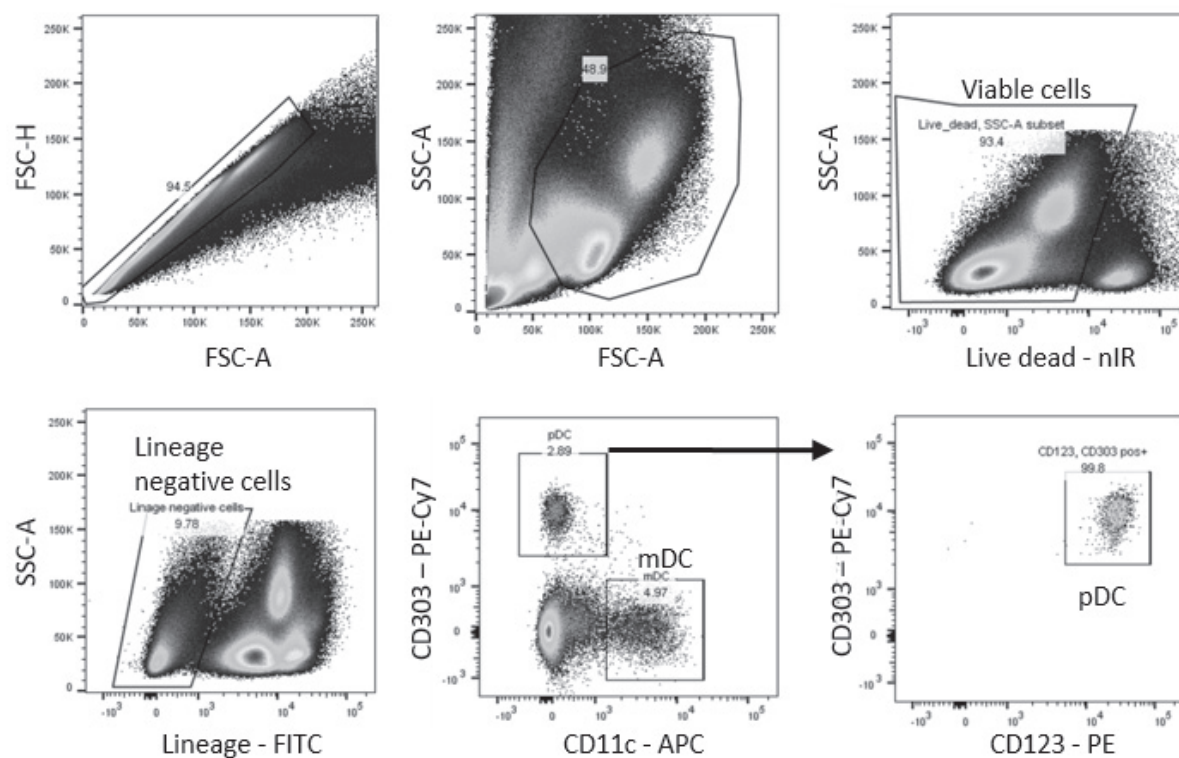
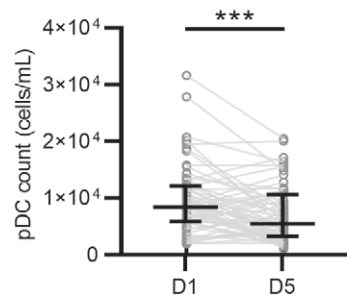


Expanded View Figures

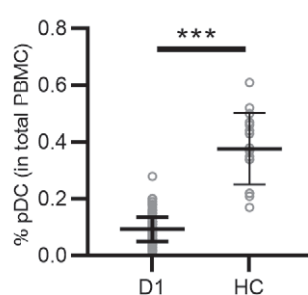
A



B



C



D

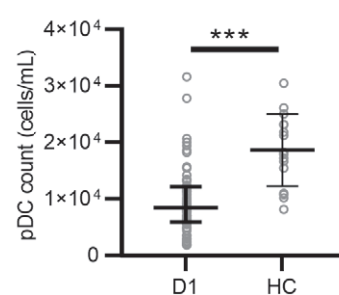


Figure EV1. SARS-CoV-2 infection reduces pDC frequency in peripheral blood.

A Overview of the flow cytometric gating strategy to determine the percentage of mDC and pDC from total PBMCs obtained from COVID-19 patients.

B pDC counts/ml of blood collected at time of hospitalization (D1) and 5 days thereafter (D5) ($n = 62$).

C, D Percentage of pDC from total PBMC (C) and pDC counts/ml blood (D) from COVID-19 patients at D1 of hospitalization ($n = 93$ and 62 , respectively) compared to healthy controls (HC, $n = 16$).

Data information: Each dot represents a patient, line with error bar shows median value with interquartile range. Statistical significance was determined with the Wilcoxon matched pairs signed rank test (B) and the unpaired nonparametric Mann-Whitney test (C, D). *** $P < 0.001$.

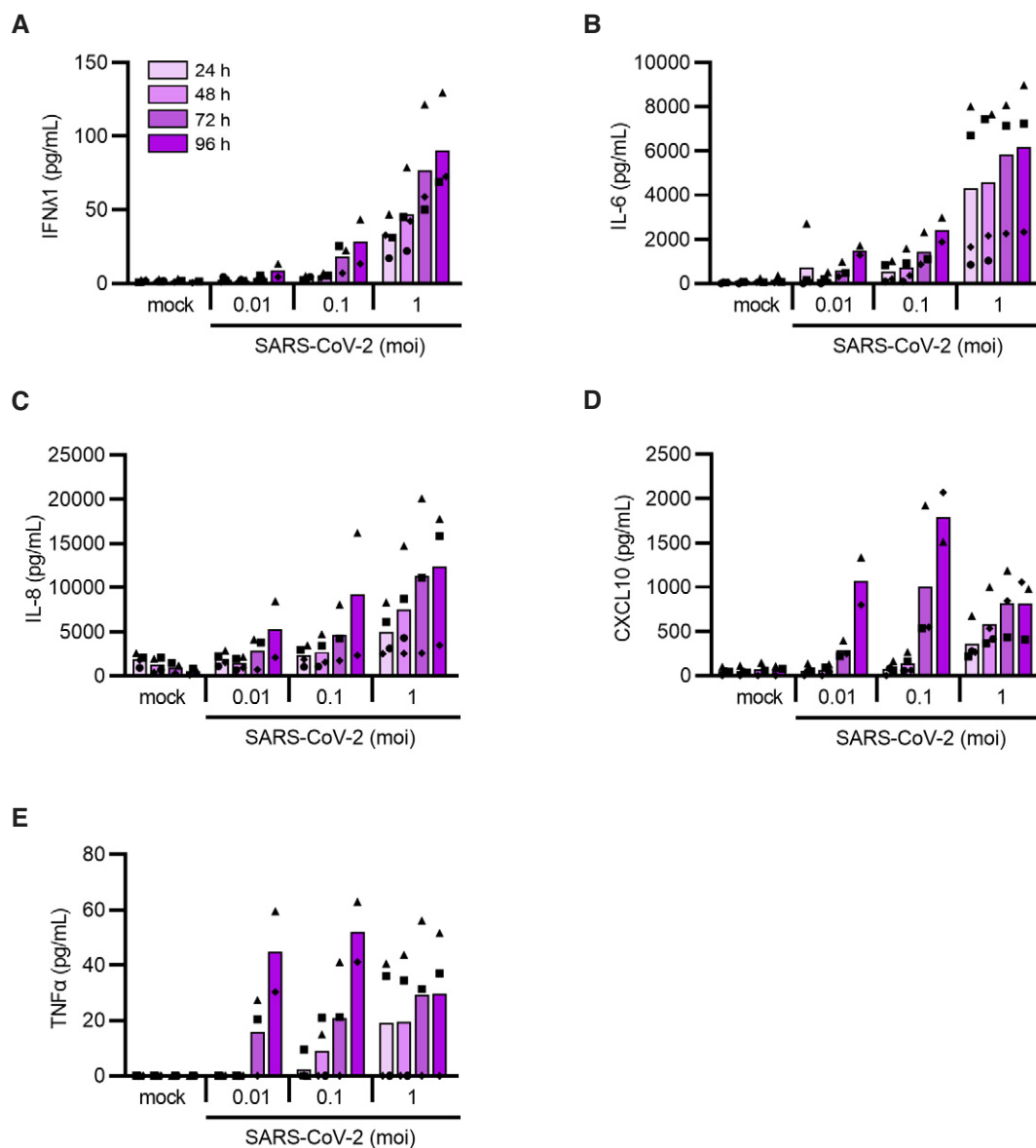


Figure EV2. Induction of inflammatory cytokines enhances with increasing viral titers and duration of exposure.

A–E HSPC-pDCs were either mock treated (mock) or inoculated with increasing SARS-CoV-2 titers (MOI of 0.01, 0.1, or 1). Supernatant was collected after 24 h, 48 h, 72 h, and 96 h for the quantification of type III IFNλ1 (A), IL-6 (B), IL-8 (C), CXCL10 (D), and TNFα (E) proteins.

Data information: Bars represent mean values, symbols represent individual HSPC-pDC donors ($n = 2-4$). Equal symbols represent equal donors.

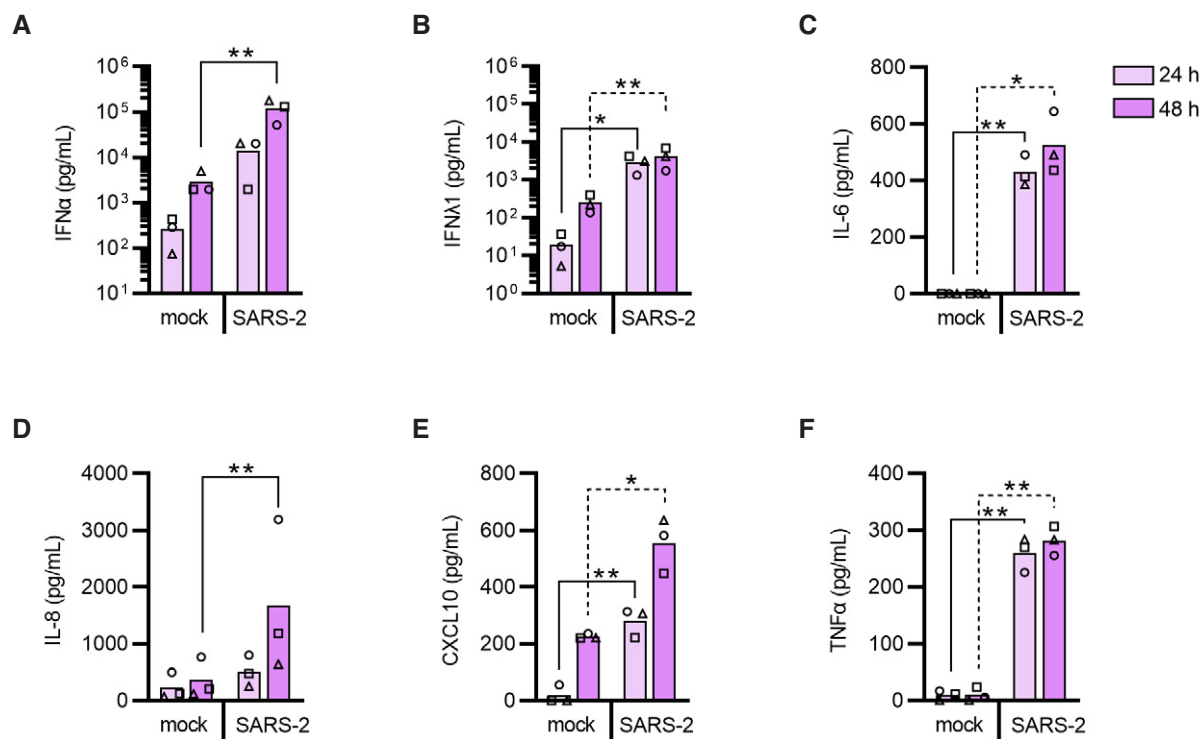


Figure EV3. pDCs isolated from peripheral blood sense SARS-CoV-2 and produce inflammatory cytokines similar to stem cell-generated pDCs.

A–F pDCs were isolated from PBMCs using negative selection and either mock treated (mock) or exposed to SARS-CoV-2 (1 MOI, SARS-2). Supernatants were collected at indicated time points and the production of type I IFN α (A), type III IFN λ 1 (B), IL-6 (C), IL-8 (D), CXCL10 (E), and TNF α (F) was quantified by ELISA.

Data information: Bars and lines represent mean values and symbols represent individual donors ($n = 3$). Statistical significance was determined using the ratio-paired student *T* test by comparing virus-exposed cell culture supernatant to the mock control of the matched time point. * $P < 0.05$, ** $P < 0.01$.

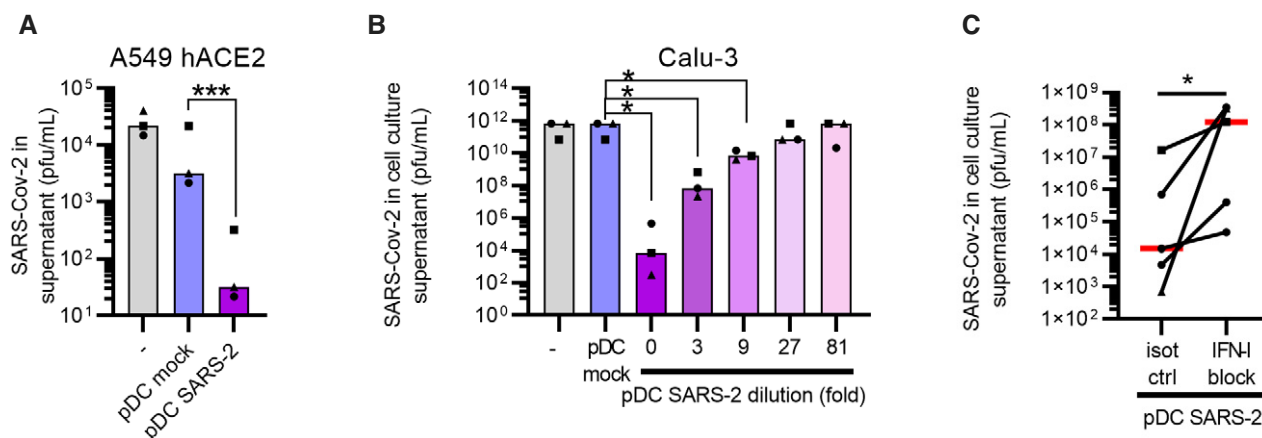


Figure EV4. Plasmacytoid DC-secreted cytokines produced post SARS-CoV-2 sensing, protect epithelial cells from infection.

A–C To assess whether pDCs could mount protection against SARS-CoV-2, conditioned medium from SARS-CoV-2-exposed pDC cultures (d3 post inoculation with 1 MOI) was added to A549 hACE2 lung epithelial cells (A) or Calu-3 (B) cultures followed by SARS-CoV-2 inoculation. The cell cultures were conditioned with normal medium (–, grey), pDC supernatant (pDC mock, blue), or SARS-CoV-2-inoculated pDC supernatant (pDC SARS-2, purple), prior to infection with SARS-CoV-2 (0.1 MOI). Supernatants were collected and viral outgrowth was determined 48 h post infection. To investigate a potential dose-response, SARS-CoV-2-inoculated pDC supernatant was 3-fold serially diluted prior to addition to Calu-3 cells (purple-pink gradient, B). To determine the involvement of type I IFNs, Calu-3 cells and SARS-CoV-2-inoculated pDC supernatants were pre-treated with antibodies blocking the type I IFN receptor and antibodies neutralizing type I IFN α (IFN-I block) or isotype control antibodies (isot ctrl), prior to the addition of conditioned medium to the cells and infection (C). All antibodies were used at a final concentration of 10 μ g/ml.

Data information: Bars and lines represent median values and symbols represent individual HSPC-pDC donors ($n = 3–5$). Equal symbols represent equal donors. Statistical significance was determined using the ratio paired student *T* test (A, B) and one-tailed paired student *T* test (C). * $P < 0.05$, *** $P < 0.001$.

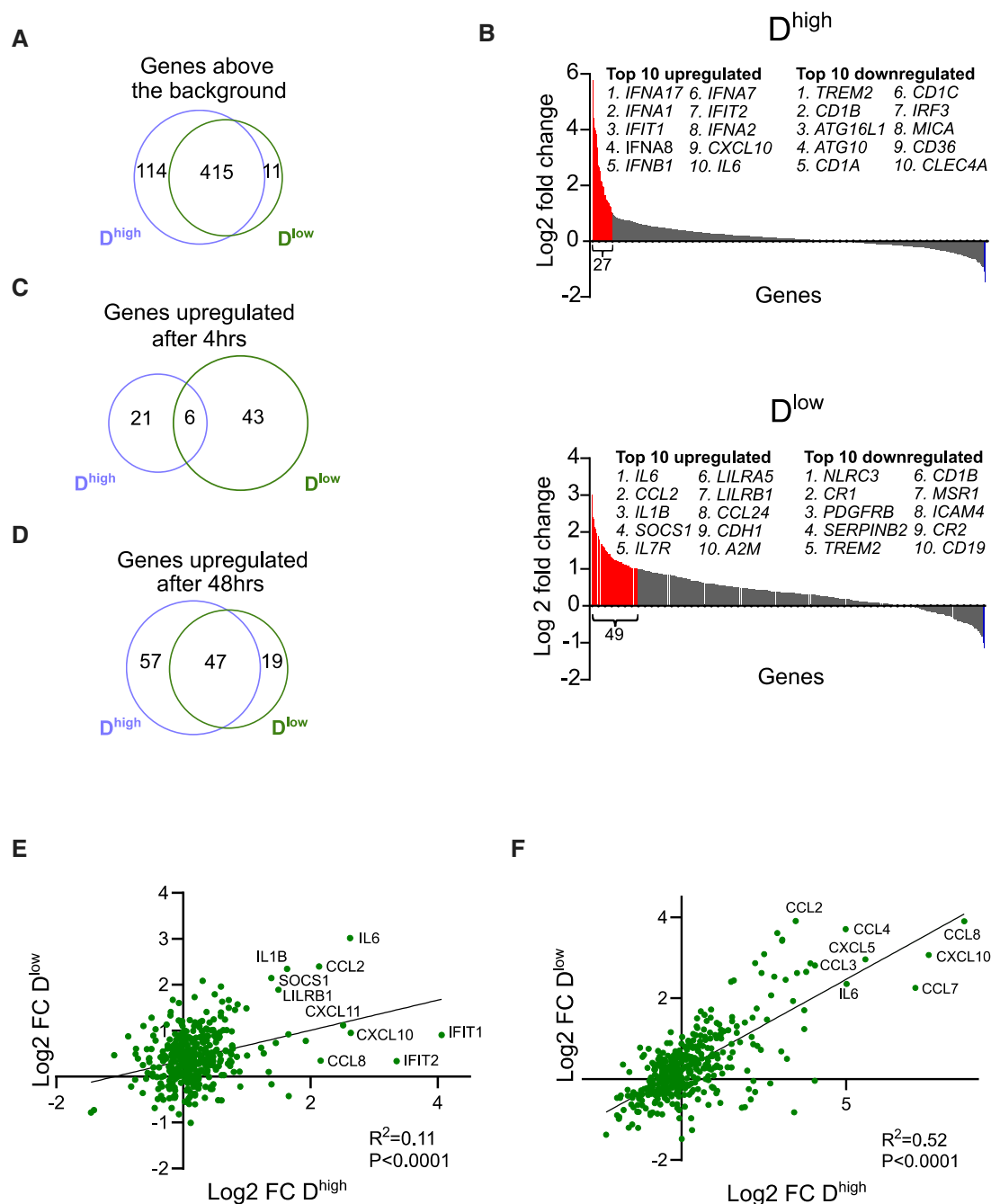


Figure EV5. SARS-CoV-2-induced gene expression changes in pDCs.

- A Venn diagram illustrating the large overlap in gene expression detected above background levels in D^{high} and D^{low} , measured using a NanoString nCounter (A).
- B Waterfall plots illustrating gene expression changes in pDCs 4 h after SARS-CoV-2 exposure relative to mock-treated cells from two donors; D^{high} (B, top) and D^{low} (B, bottom).
- C, D Venn diagrams illustrating the number of genes that were > 2-fold upregulated after 4 h (C) and 48 h (D) in D^{high} and D^{low} post SARS-CoV-2 exposure.
- E, F Scatter plots of log₂ fold changes (FC) in gene expression in D^{high} and D^{low} after 4 h (E) and 48 h (F) post SARS-CoV-2 inoculation with corresponding linear regression statistics and R-squared values. Note that the genes, which were not detected above background levels in any of the donors, could not be displayed due to division by zero.