SUPPLEMENTARY MATERIAL AND METHODS

cDC2s isolation and RNA isolation

cDC2s were isolated from peripheral blood mononuclear-cells (PBMCs) by magnetic-activated cell sorting (MACS) using CD1c (BDCA-1)$^+$ Dendritic Cell Isolation Kit (Miltenyi Biotec) according to the manufacturer's instructions. In brief, CD19+ cells were depleted using anti-CD19-coated magnetic beads, and after CD1c+ cells were isolated using biotinylated anti-CD1c and anti-biotin-beads. cDC2s purity measured by flow cytometry (**Supplementary Table 2** and **Supplementary Figure 1**) was 90% [83–97%] (median [interquartile range]), and there were no significant differences between groups.

Cells were lysed in RLTplus buffer (Qiagen) supplemented with 1% beta-mercaptoethanol for transcriptional analyses. Total RNA was purified using AllPrep Universal Kit (Qiagen), according to the manufacturer's instructions. RNA concentration was assessed with Qubit RNA Kit (Thermo Fisher Scientific) and RNA integrity was measured by capillary electrophoresis using the RNA 6000 Nano Kit (Agilent Technologies); all samples had a RIN-score >7.0.

RNA sequencing analysis

RNA sequencing was performed at the Beijing genomics institute, at two different time points, using a NextSeq 500 sequencer (Illumina) for the discovery cohort and an Illumina HiSeq 4000 sequencer (Illumina) for the replication cohort, following the standard manufacturer's protocols. For both cohorts about 20 million paired-end (91 bp for discovery; 100 bp for replication) reads were generated for each sample. RNA-sequencing data analysis was performed as previously described [1]. Briefly, FastQC tool (https://www.bioinformatics.babraham.ac.uk/projects/fastqc/), was used to assess the quality control of the reads. All samples passed the quality check. Next, reads were aligned to the human genome assembly (GRCh38 build 79) [2] using STAR aligner [3]. The aligned reads (mapping quality > 30) were used to calculate the read counts using Python package HTSeq [4] for each annotated gene. To remove unwanted variance (k=1 parameter) related with technical aspects RUVSeq was used [5]. A total of 65217 genes were analyzed in both cohorts. Differentially expressed genes (DEGs) were identified using Bioconductor/R package DESeq2 [6]; Wald's test was used to identify DEGs in each pair-wise comparison performed

between the three groups (HC, nSS, and pSS) and likelihood ratio test to identify DEGs considering multiple groups. Differences in gene expression with a nominal p-value <0.05 were considered differentially expressed. Variance stabilizing transformation was applied to obtain normalized gene counts (variance stabilized data), which were used for subsequent analyses. Raw and processed RNA sequencing data are available in NCBI's Gene Expression Omnibus under the following accession number GSE200020.

Pathway enrichment analysis

Pathway enrichment analysis, was performed for the consistently DEGs in both cohorts using the R/Bioconductor package ReactomePA [7] to identify the processes and pathways dysregulated between patients and HC.

Flow cytometry

For validation of the selected targets identified by RNA sequencing, PBMCs were cryopreserved in complete medium (RPMI glutamax (Thermo Fisher Scientific) supplemented with 10% heat-inactivated FCS (Sigma-Aldrich) and 1% penicillin/streptomycin (Thermo Fisher Scientific)) and freezing medium (20% (v/v) DMSO in FCS) at a 1:1 ratio. PBMCs were thawed and washed prior to incubation with the fixable viability dye eFluor506 (eBioscience) to allow exclusion of dead cells and blocked with Fc receptor blocking reagent (Miltenyi Biotech). Hereafter cells were stained for 20min at 4°C with the fluorochome-conjugated monoclonal antibodies described in **supplementary Table 2** and measured by flow cytometry. cDC2s were identified based on the expression of HLA-DR, CD1c, CD11c and FcεR1 (**Supplementary Figure 4A**).

Antigen processing and uptake by cDC2s

To study processing by cDC2s, PBMCs were thawed as previously described and directly incubated in complete medium with 0.5 µg/mL of DQ-green bovine serum albumin (BSA; Biovision) for 10 min at 37°C. Next, cells were washed, resuspended in complete medium and chased for 10, 30, 60 and 120 min. At the specific time points, samples were placed on ice and when all time points were collected, cells were washed twice with cold phosphate-buffered saline (PBS) (Sigma) with 0.1% FCS and 0.05% NaN3 (Immunosource), stained on ice for 15 min with the antibodies described in **supplementary Table 2** and measured by flow cytometry (**Supplementary Figure 4A**). BSA

processing by cDC2s was calculated as the median fluorescence intensity (MFI) of DQ-BSA normalized to T=0.

For BSA uptake assay, PBMCs were incubated in complete medium with 0.5µg/mL of BSA conjugated with Alexa Fluor 647 (Invitrogen) at 37°C. In addition, HC-PBMCs were primed with 1000U/mL of IFNα2a (Cell Sciences) or left in complete medium for 3h before BSA exposure. BSA uptake was monitored at 10, 30, 60 and 120 minutes. At the specific time point, samples were placed on ice and after all time points were collected, cells were washed twice with cold PBS (Sigma) with 0.1% FCS and 0.05% NaN3 (Immunosource), stained on ice for 15 min with the antibodies described in **supplementary Table 2** and measured by flow cytometry (**Supplementary Figure 4A**). BSA uptake was calculated as the median fluorescence intensity (MFI) of BSA-AF647 on cDC2s.

Interferon signature assessment

To determine the type I IFN-score, PBMCs were lysed in RLTPlus buffer (Qiagen) and total RNA was purified using AllPrep DNA/RNA/miRNA Universal Kit (Qiagen) according to the manufacturer's instructions. cDNA was synthesized using Superscript IV kit and quantitative-PCRs were performed on the QuantStudio 12k flex system (both Thermo Fisher Scientific). The expression of each IFN-induced genes (*IFI44L*, *IFI44*, *IFIT3*, *LY6E*, and *MX1*) was normalized to that of the endogenous *GAPDH* (**Supplementary Table 3**). The average IFN-score was calculated as previously described [8].

Uptake of apoptotic salivary gland epithelial cells by cDC2s

The human submandibular salivary gland (HSG) epithelial cell line (HTB-41) was kindly provided by Dr. Lynne Bingle (School of Clinical Dentistry, University of Sheffield). HSG cells were cultured in McCoy's 5A media (Thermo Fisher Scientific) supplemented with 1% penicillin/streptomycin (Thermo Fisher Scientific) and 10% FCS (Sigma-Aldrich).

HSG cells were stained with 0.1 µM of carboxyfluorescein succinimidyl ester (CFSE) (Thermo Fisher Scientific) and induced to apoptosis during 24h with 1 µM of staurosporine (Merck Chemicals BV), as previously described [9]. After that, supernatant was collected to preserve floating cells and adherent cells were rinsed with PBS (Sigma-Aldrich) and harvested by standard trypsinization. The

frequency of apoptotic HSG cells was assessed by annexin V staining according to the manufacturer's protocol. Cryopreserved PBMCs were thawed, rested and then either primed with or without IFNα2a, as previouly described, or co-cultured at a 1:1 ratio with apoptotic HSG cell suspension for 2h at 37°C. Cells were washed twice with cold PBS (Sigma) with 0.1% FCS and 0.05% NaN3 (Immunosource), stained on ice for 15 min with the antibodies described in **supplementary Table 2** and measured by flow cytometry (**Supplementary Figure 7**). Uptake of apoptotic HSG cells was quantified using the CFSE median fluorescence intensity (MFI).

cDC2s and CD4$^+$ T cell allogenic co-cultures

CD4$^+$ T cells were isolated from buffy coats (Sanquin) of 3 different donors by MACS using CD4$^+$ T Cell Isolation Kit (Miltenyi Biotec) according to the manufacturer's protocol. To ensure consistent purity and comparable T cell compartments of the isolated CD4$^+$ T cell, cells were stained with the antibodies described in **supplementary Table 2**. The purity of the isolated CD4$^+$ T cells was consistently above 90% for all the donors (**Supplementary Figure 8A**). cDC2s were isolated as described before and co-cultured in complete medium with allogenic CD4$^+$ T cells at a 1:5 ratio (cDC2s: T cells) for 3 days. To assess the proliferation rate of CD4$^+$ T cells, cells were labelled with 1.5 μM of CellTrace Violet (CTV) dye (Invitrogen), prior to co-culture. After 3 days of co-culture, cells were stained at 4°C for 10 min with fixable viability dye eFluor780 (eBioscience) to allow exclusion of dead cells, washed and stained at 4°C for 15 min with the antibodies described in **supplementary Table 2** and measured by flow cytometry (**Supplementary Figure 8B**). The percentage of proliferating CD4$^+$ T cells was measured as the proportion of CTV negative cells, and the expression of chemokine receptors on the cell-surface was evaluated within the proliferating CD4$^+$ T cells.

Flow cytometry data acquisition of all experiments was performed using a BD LSR Fortessa (BD Biosciences) and data were analyzed using FlowJo software (Tree Star).

Cytokine analysis

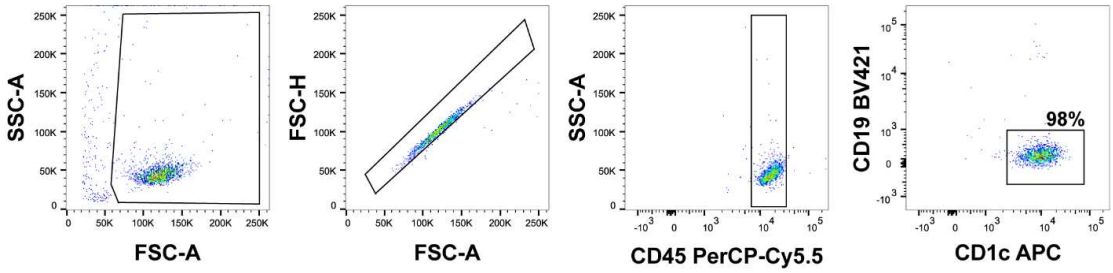
TNFα (Diaclone) and IFNγ (Thermo Fisher Scientific) levels were measured in cell-free supernatant of cDC2s-CD4$^+$ T cell co-culture using enzyme-linked immunosorbent assay following the manufacturer's instructions.

Phospho-Epitope Staining for Flow Cytometry

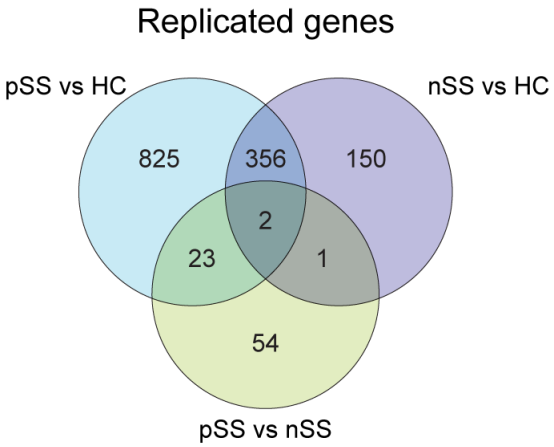
Peripheral blood mononuclear cells (PBMCs) were isolated and directly stained (T=0) or cultured at 1 × 10^6 cells/mL in complete medium. Cells were left unstimulated or were stimulated with toll-like receptor (TLR)4 ligand [Lipopolysaccharide (Invivogen)] for 15, 30 and 60 minutes. Next, PBMC were washed with phosphate-buffered saline (PBS) and fixed with 2% paraformaldehyde for 15 minutes at room temperature. After washing with cold PBS, cells were resuspended in cold PBS before drop wise addition of ice-cold methanol (ratio PBS: methanol; 1:9) and incubated on ice for 30min. Next, cells were washed with FACS Buffer and stained for 30min on ice with the antibodies described in **supplementary Table 2**. Data acquisition was performed using a BD LSR Fortessa (BD Biosciences) and data were analysed using FlowJo software (Tree Star). cDC2s were identified based on the expression of HLA-DR, CD1c, CD11c and FcεR1 (**Supplementary Figure 4A**).

Statistical Analysis

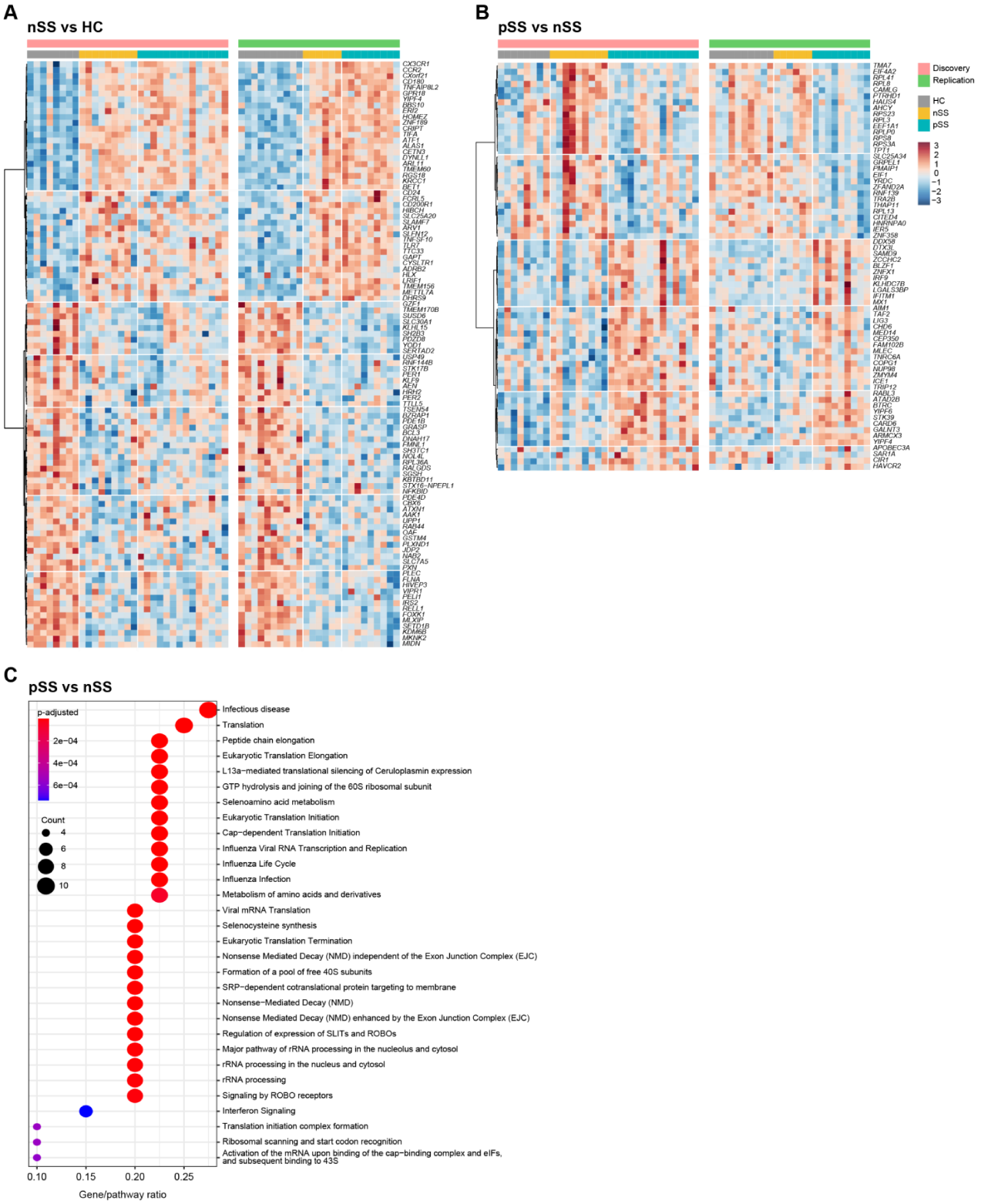
For RNA sequencing analysis, the Wald's test was used to identify DEGs in each pair-wise comparison performed between HC, nSS and pSS and the likelihood ratio test to identify DEGs considering multiple groups. Differences between the groups were analyzed by non-parametric test Mann-Whitney U-test and Kruskal-Wallis test, when appropriate. For the uptake and processing experiments at multiple time points the multiple comparison 2way ANOVA test with FDR correction was used. For the uptake experiments after IFNα priming at a single time point the paired t test was used. Statistical analyses and data visualization were performed using Python and R language, Graphpad Prism (GraphPad Software), MetaboAnalyst 4.0 [10] and ClustVis software [11]. Differences were considered to be statistically significant at $p < 0.05$.



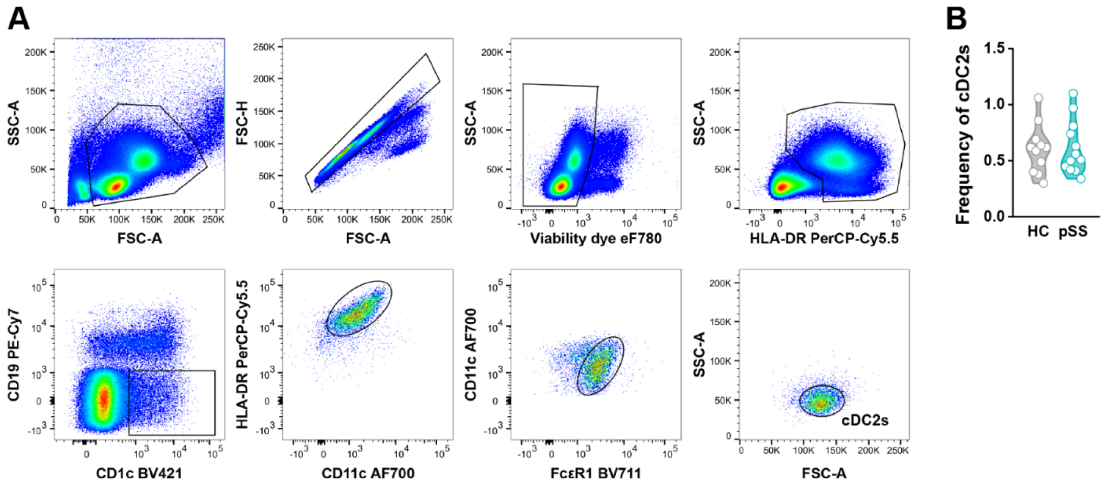
Supplementary Figure 1. Analysis strategy used to assess cDC2s purity. Flow cytometry gating strategy analysis to assess cDC2s purity after MACS isolation.



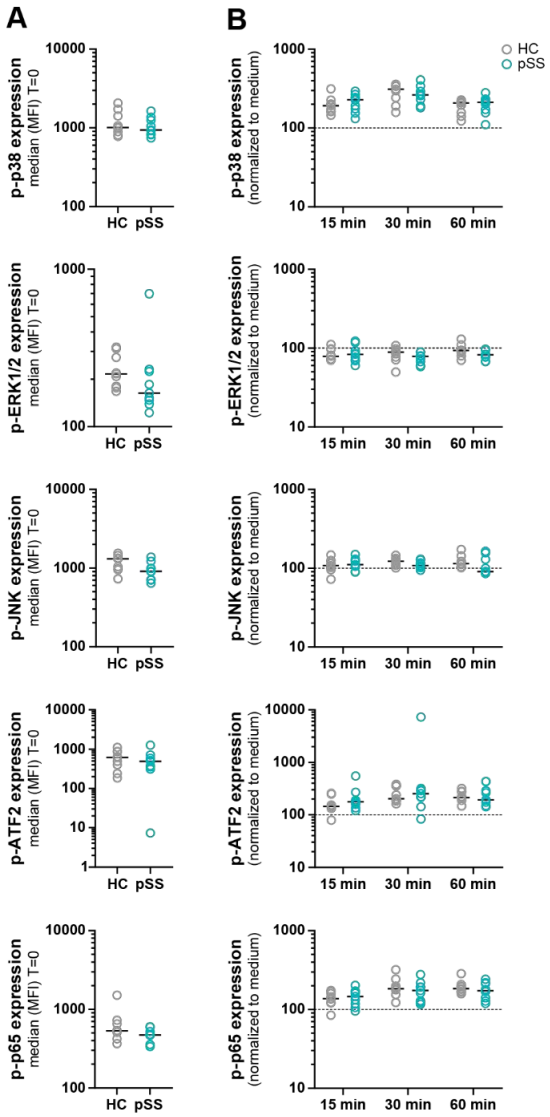
Supplementary Figure 2. Overlap of the replicated differentially expressed genes between pSS, nSS and HC. RNA sequencing of circulating cDC2s was performed independently for both discovery and replication cohort. Differentially expressed genes (DEGs) with a nominal p-value <0.05, average base mean expression >100 and with the same directionality in both cohorts were considered to be replicated. Venn diagrams show the overlap of the replicated differentially expressed genes (DEGs).


A
nSS vs HC
B
pSS vs nSS
Discovery
Replication
HC
nSS
pSS
C
pSS vs nSS
p-adjusted
2e−04
4e−04
6e−04
Count
4
6
8
10
Infectious disease
Translation
Peptide chain elongation
Eukaryotic Translation Elongation
L13a−mediated translational silencing of Ceruloplasmin expression
GTP hydrolysis and joining of the 60S ribosomal subunit
Selenoamino acid metabolism
Eukaryotic Translation Initiation
Cap−dependent Translation Initiation
Influenza Viral RNA Transcription and Replication
Influenza Life Cycle
Influenza Infection
Metabolism of amino acids and derivatives
Viral mRNA Translation
Selenocysteine synthesis
Eukaryotic Translation Termination
Nonsense Mediated Decay (NMD) independent of the Exon Junction Complex (EJC)
Formation of a pool of free 40S subunits
SRP−dependent cotranslational protein targeting to membrane
Nonsense−Mediated Decay (NMD)
Nonsense Mediated Decay (NMD) enhanced by the Exon Junction Complex (EJC)
Regulation of expression of SLITs and ROBOs
Major pathway of rRNA processing in the nucleolus and cytosol
rRNA processing in the nucleus and cytosol
rRNA processing
Signaling by ROBO receptors
Interferon Signaling
Translation initiation complex formation
Ribosomal scanning and start codon recognition
Activation of the mRNA upon binding of the cap−binding complex and eIFs, and subsequent binding to 43S
0.10
0.15
0.20
0.25
Gene/pathway ratio

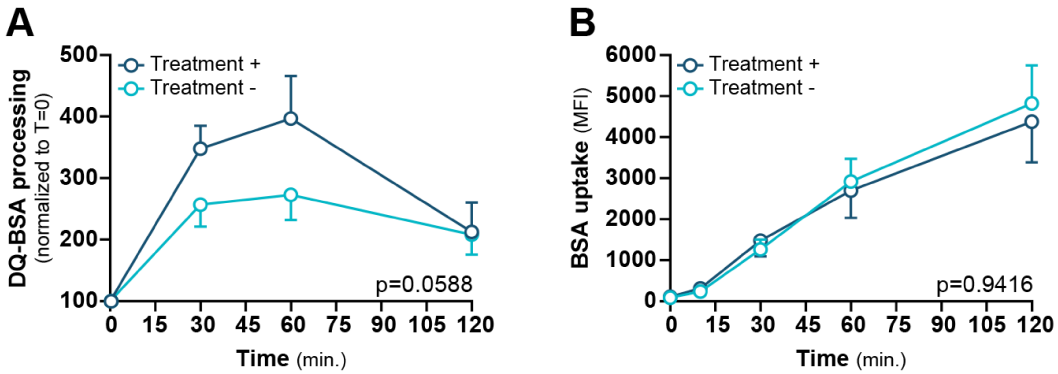
Supplementary Figure 3. Transcriptomic characterization of circulating cDC2s from nSS patients. RNA sequencing of circulating cDC2s was performed independently for both cohorts. Heatmap shows the top 100 protein coding differentially expressed genes (DEGs) in both cohorts between nSS vs. HC in both cohorts (A). Heatmap of protein coding DEGs with a nominal p-value < 0.05 between pSS vs. nSS in both cohorts (B). Pathway enrichment analysis of the DEGs between pSS vs. nSS depicted in Supplementary Figure 3B. Columns show the number of DEGs found within the pathway over the total number of pathway components (ratio), dot-size depicts the number of genes used for enrichment analysis and color indicates the statistical significance (C).



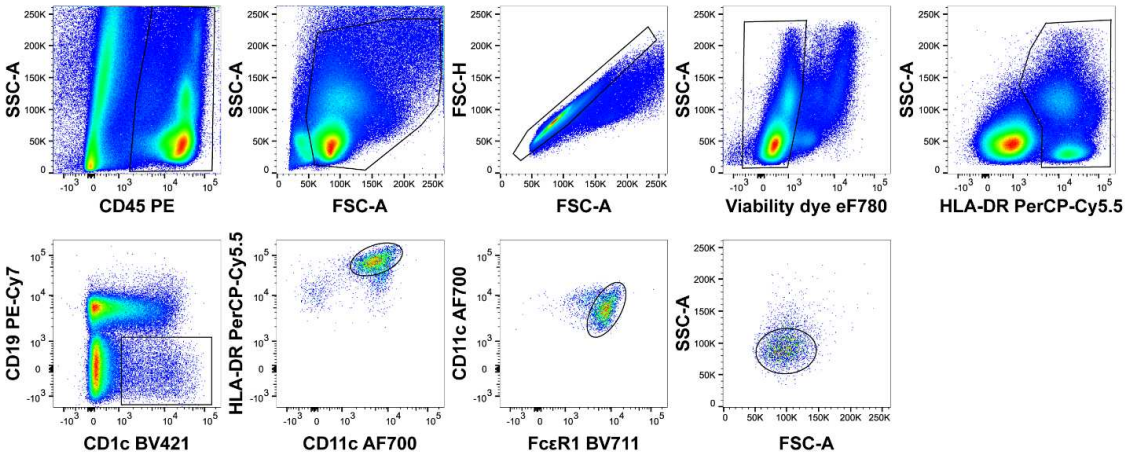
Supplementary Figure 4. Analysis strategy used to identify cDC2s in PBMCs. Representative flow cytometry gating strategy analysis to identify cDC2s in peripheral blood mononuclear cells (A). Violin plots depicts the frequency of circulating cDC2 in HC (n=11) and pSS patients (n=13) determined by flow cytometry (B).



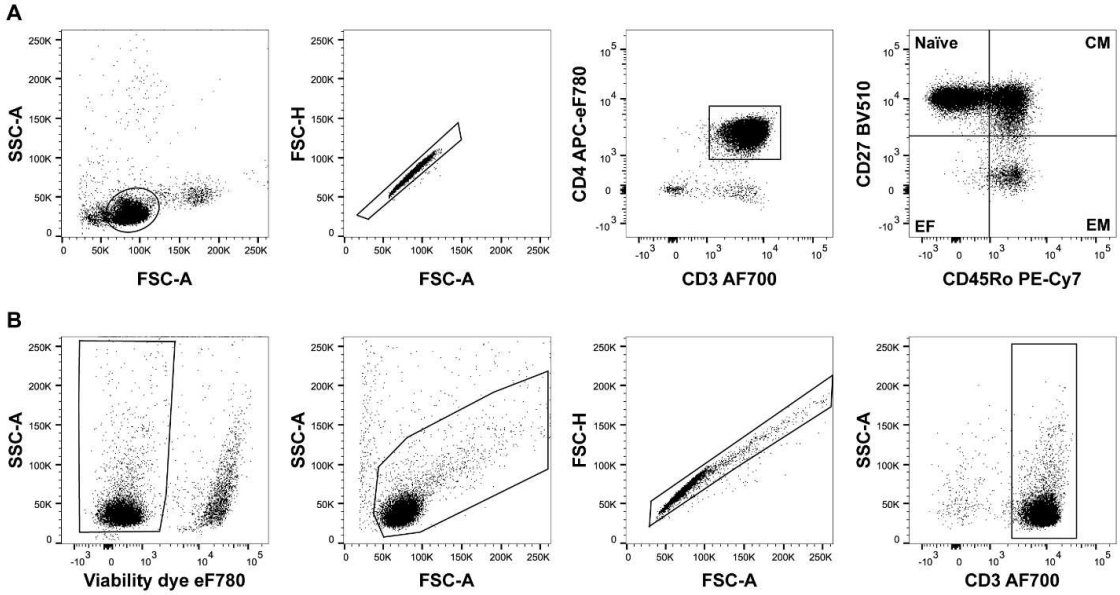
Supplementary Figure 5. Phosphorylation profile of cDC2s upon TLR4 activation. Phosphorylation levels of P38, ERK1/2, JNK, ATF2 and NF-kB were analyzed by flow cytometry in cDC2s of HC (n=9) and pSS patients (n=9) *ex-vivo* (basal level; T=0) (B) and after TLR4 stimulation at different time points. Phosphorylation results at the different time points was normalized to the respective medium condition (C).



Supplementary Figure 6. Influence of pSS treatment on antigen processing and uptake by cDC2s. Peripheral blood mononuclear cells (PBMCs) were incubated with DQ–BSA for 10 minutes and the antigen processing by cDC2s was followed at the indicated time points. DQ-BSA processing represented as median fluorescence intensity (MFI) normalized to T=0, in treated pSS patients (Treatment +; n=7) and non-treated pSS patients (Treatment -; n=6) at different time points assessed by flow cytometry (A). Isolated PBMCs were incubated with AF647–BSA for the indicated time points and the uptake by cDC2s was assessed by flow cytometry. BSA uptake in treated pSS patients (Treatment +; n=8) and non-treated pSS patients (Treatment -; n=6) at different time points assessed by flow cytometry (B).



Supplementary Figure 7. Analysis strategy used to identify cDC2s in co-culture with apoptotic salivary gland (HSG)-epithelial cells. Representative flow cytometry gating strategy analysis to identify cDC2s in peripheral blood mononuclear cells after co-culture with apoptotic salivary gland (HSG)-epithelial cells.



Supplementary Figure 8. Analysis strategy used to identify CD4$^+$ T cells subsets after MACS isolation and after co-culture with cDC2s. Representative flow cytometry gating strategy analysis of the different CD4$^+$ T cell subsets: naïve (CD27$^+$CD45Ro$^-$); CM: central memory (CD27$^+$CD45Ro$^+$); EM: effector memory (CD27$^-$CD45Ro$^+$); EF: effector (CD27$^-$CD45Ro$^-$) (A). Representative flow cytometry gating strategy analysis to identify CD3$^+$ T cells in cDC2s co-cultures (B).

Supplementary Table 1. Characteristics of the patients and controls enrolled in the validation experiments.

	Protein validation		**BSA uptake and processing**		**cDC2 – CD4⁺ T cell co-culture**	
	(n=44)		**(n=29)**		**(n=6)**	
	HC	pSS	HC	pSS	HC	pSS
N (M/F)	22 [1/21]	22 [1/21]	13 [0/13]	16 [0/16]	3 [0/3]	3 [0/3]
Age (yr.)	56 [25-78]	56 [21-76]	58 [35-63]	58 [41-78]	55 [43-60]	60 [56-65]
LFS (foci/4 mm^2)	-	3.0 [1.0-7.0]	-	1.7 [1.0-7.0]	-	1.4 [1.1-1.6]
ESSDAI	-	5.5 [1.0-15]	-	8.0 [0.0-16]	-	7.0 [0.0-7.0]
ESSPRI	-	7.0 [1.0-8.0]	-	7.0 [3.0-8.0]	-	6.0 [4.0-7.0]
Schirmer (mm/5 min)	-	3.0 [0.0-28]	-	1.5 [0.0-26]	-	12 [0.0-24]
ANA (no. positive [%])	-	18 [86%]	-	12 [75%]	-	2 [67%]
SSA (no. positive [%])	-	18 [82%]	-	12 [75%]	-	2 [67%]
SSB (no. positive [%])	-	13 [59%]	-	10 [63%]	-	1 [33%]
RF (no. positive [%])	-	12 [71%]	-	7 [78%]	-	2 [100%]
Serum IgG (g/L)	-	14 [7.0-33]	-	15 [8.4-26]	-	15 [9.0-16]
ESR (mm/hour)	-	15 [2.0-54]	-	18 [3.0-75]	-	10 [5.0-28]
C3 (g/L)	-	1.1 [0.8-1.6]	-	1.1 [0.9-1.4]	-	1.3 [1.2-1.4]
C4 (g/L)	-	0.2 [0.0-0.4]	-	0.2 [0.2-0.4]	-	0.3 [0.2-0.3]
Not treated (no. [%])	-	13 [59%]	-	8 [50%]	-	3 [100%]
Only HCQ (no. [%])	-	2 [9%]	-	3 [19%]	-	-
Other (no. [%])	-	7 [32%]	-	5 [31%]	-	-

HC: healthy control; pSS: primary Sjögren's syndrome; LFS: lymphocyte focus score; ESSDAI: EULAR Sjögren's syndrome disease activity index; ESSPRI: EULAR Sjögren's syndrome patient reported index; ANA: anti-nuclear antibodies; SSA: anti-SSA/Ro; SSB: anti-SSB/La; RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein, HCQ: hydroxychloroquine. Other treatment group includes for protein validation: azathioprine, alone (n=2) or in combination with prednisone (n=1); prednisone in combination with HCQ (n=2); methotrexate (n=2). For BSA uptake and processing: azathioprine (n=1), methotrexate, alone (n=1) or in combination with

hydroxychloroquine (n=1), hydroxychloroquine in combination with leflunomide (n=1) and hydroxychloroquine in combination with azathioprine and prednisone (n=1). Values are median [range] unless stated otherwise.

Supplementary Table 2. List of antibodies used for the flow cytometry stainings

Target	Label	Manufacturer	Clone	cDC2s Purity	Protein validation	Phospho flow	BSA uptake	DQ-BSA processing	CD4⁺ T cell purity	cDC2s-CD4⁺ T cell
BDCA1	APC	eBioscience	L161	x						
CD14	FITC	Miltenyi	TÜK4	x						
CD19	BV421	Biolegend	HIB19	x						
CD20	PE	eBioscience	2H7	x						
CD45	PerCP	Biolegend	HI30	x						
FceR1	BV711	Biolegend	AER-37		x					
CX3CR1	FITC	Biolegend	2A9-1		x					
BAFF	PE	Biolegend	T7-241		x					
CD18 (ITGB2)	FITC	Biolegend	TS1/18		x					
IFNAR1	PE	Thermo Scientific	85228		x					
PLXND1	FITC	FAB4160G			x					
PLXNB2	APC	FAB53291A			x					
HLA-DR	PerCP-Cy5.5	Biolegend	L243		x	x	x	x		
CD11c	AF700	eBioscience	3.9		x			x		
CD14	APC-eF780	eBioscience	61D3		x		x	x		
CD19	PE-Cy7	Beckman Coulter	J3-119		x		x	x		
BDCA1	BV421	Biolegend	L161		x		x	x		
BDCA1	AF488	Sony Biotechnology	L161			x				
CD14	APC-H7	BD Biosciences	MϕP9			x				
CD11c	PE-CF594	BD Biosciences	B-ly6			x				
CD19	BV711	Biolegend	HIB19			x				
Phospho-p38	AF647	Cell signaling Techn	28B10			x				
Phospho-ATF2	PE	Anbnova	G3			x				
P-p44/42 (ERK1/2)	PB	Cell signaling Techn	197G2			x				
P-NF-kB p65	AF647	BD Biosciences	K10-895			x				
Phospho-JNK	PE	BD Biosciences	N9-66			x				
CD16	V500	BD Biosciences	3G8				x	x		
FceR1	FITC	eBioscience	AER-37				x			
CD11c	PE	BD Biosciences	B-LY6				x			
FcεR1	PE	eBioscience	AER-37					x		
CD8	PerCP-Cy5.5	Biolegend	RPA-T8						x	
CD4	APC-eF780	eBioscience	RPA-T4						x	
CD56	PE-CF594	BD Biosciences	B159						x	
CD27	BV510	BD Biosciences	L128						x	
CXCR3	FITC	Biolegend	G025H7							x
CXCR5	PerCP-Cy5.5	Biolegend	J252D4							x
CD27	APC	BD Biosciences	L128							x
CD3	AF700	Biolegend	UCHT1						x	x
Viability dye	eF780	eBioscience	n.a.							x
CCR4	PE	BD Biosciences	1G1							x
CD45Ro	PE-Cy7	BD Biosciences	UCHL1						x	x

Supplementary Table 3. Sequences of primers used for RT-qPCR

Gene	Primer forward 5′ – 3′	Primer reverse 5′ – 3′
IFI44L	CCACCGTCAGTATTTGGAATGT	ATTTCTGTGCTCTCTGGCTT
IFI44	TTTGCTCTTTCTGACATCTCGGT	TCCTCCCTTAGATTCCCTATTTGC
IFIT3	ACTGTTTCAACGGGTGTTGG	CCTTGTAGCAGCACCCAATC
LY6E	ATCTGTACTGCCTGAAGCCG	GTCACGAGATTCCCAATGCC
MX1	GCATCCCACCCTCTATTACTG	CGCACCTTCTCCTCATACTG
GAPDH	GCCAGCCGAGCCACATC	TGACCAGGCGCCCAATAC

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