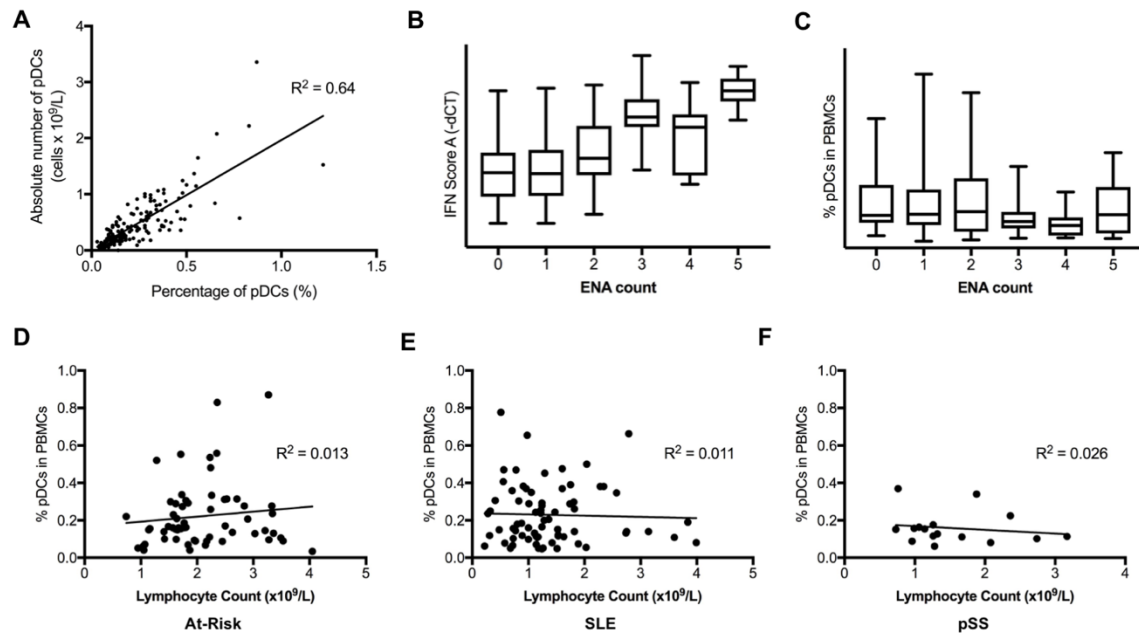


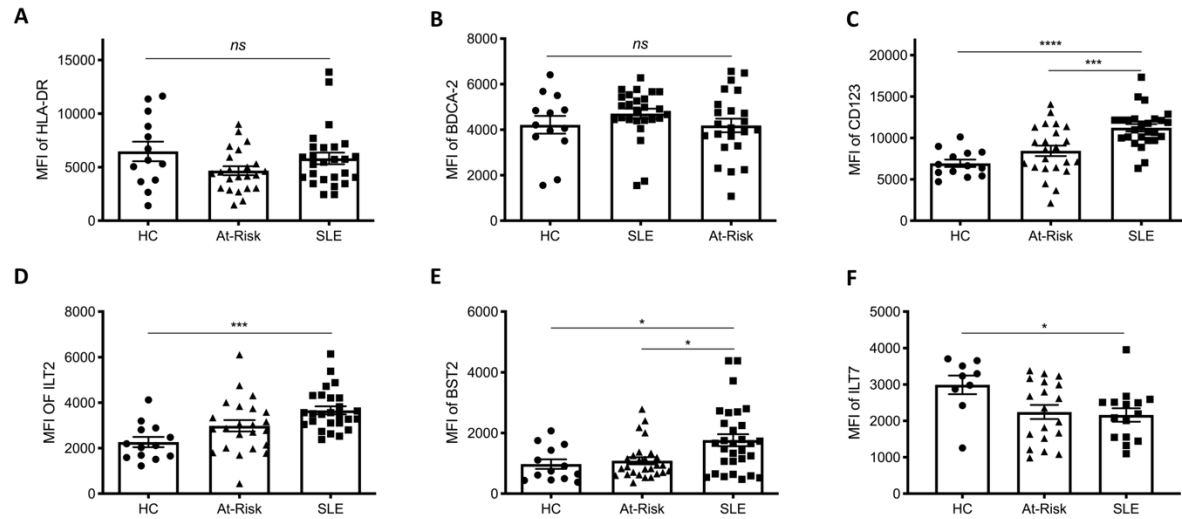
SUPPLEMENTARY INFORMATION FILE

Functionally impaired plasmacytoid dendritic cells and non-haematopoietic sources of type I interferon dominate human autoimmunity

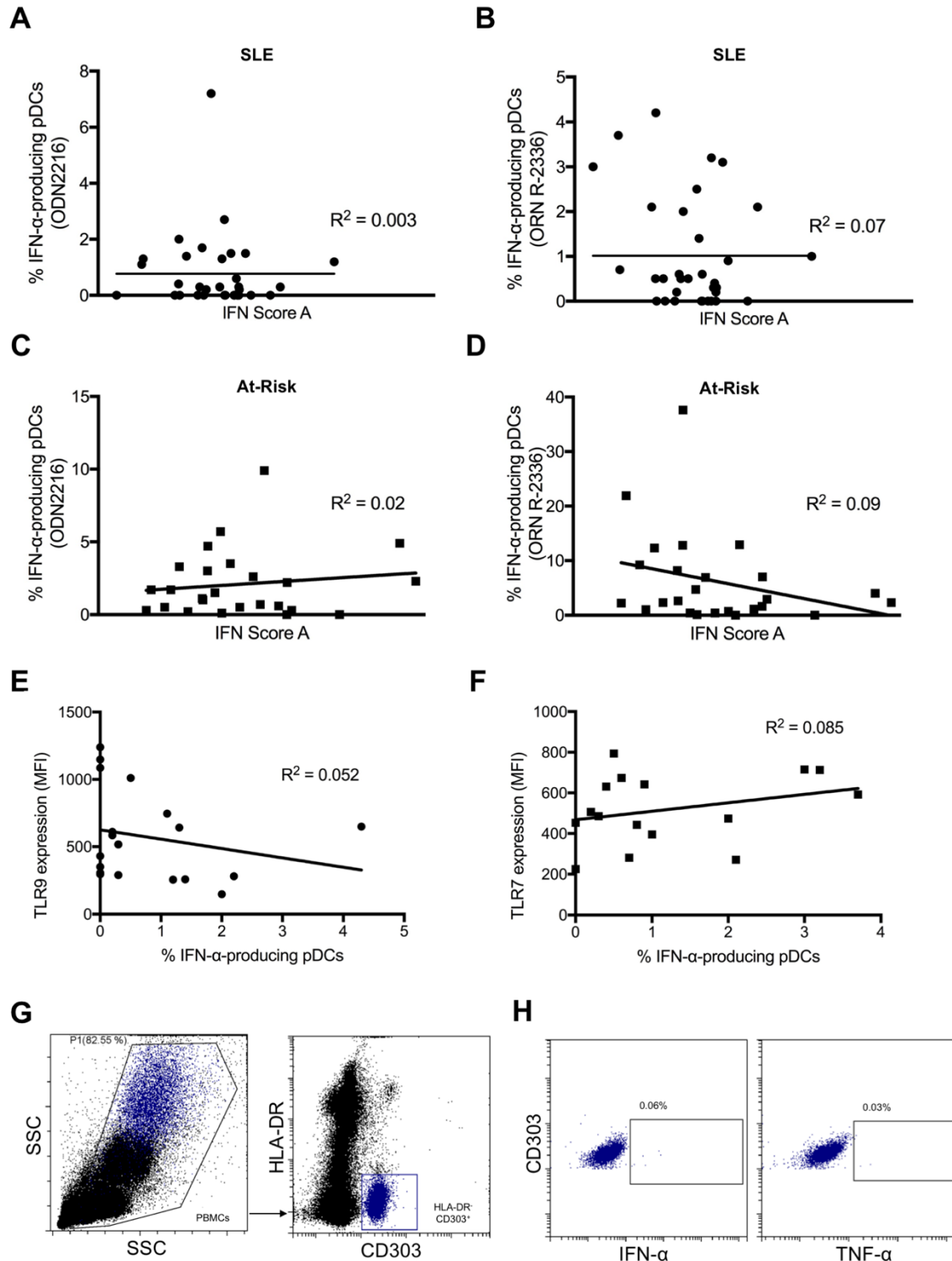
Antonios Psarras^{1,2,3}, Adewonuola Alase¹, Agne Antanaviciute⁴, Ian M. Carr⁴, Md Yuzaiful Md Yusof^{1,2}, Miriam Wittmann^{1,2}, Paul Emery^{1,2}, George C. Tsokos³, Edward M. Vital^{1,2}



Supplementary Figure 1. Association of peripheral pDCs with other immunological parameters. **(A)** Percentage and absolute numbers of pDCs are closely correlated (results merged from healthy controls, At-Risk individuals, patients with SLE and pSS). **(B)** Higher IFN Score A was correlated to a higher ENA count. **(C)** The percentage of pDCs in peripheral blood showed no correlation with ENA count. **(D)** Association of percentage of pDCs in peripheral blood and lymphocyte count in At-Risk individuals. **(E)** Association of percentage of pDCs in peripheral blood and lymphocyte count in patients with SLE. **(F)** Association of percentage of pDCs in peripheral blood and lymphocyte count in patients with pSS. Data are represented as mean $\pm$ SEM. Nonlinear regression **(A-F)**.

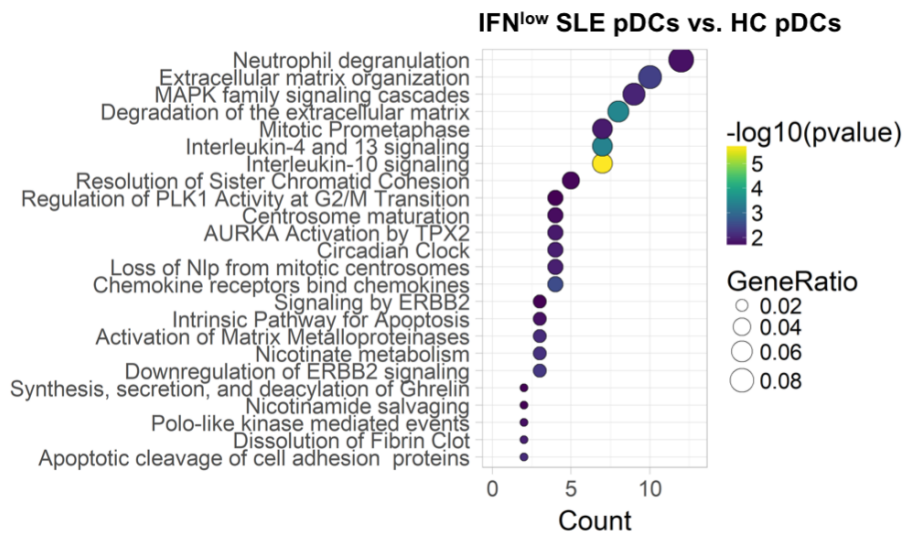


Supplementary Figure 2. Phenotyping peripheral pDCs in At-Risk individuals and patients with SLE in comparison with healthy controls (HC) for the expression of HLA-DR (**A**), BDCA-2 (**B**), CD123 (**C**), ILT2 (**D**), BST2 (**E**), and ILT7 (**F**). Data are represented as mean $\pm$ SEM. * $P < 0.05$; *** $P < 0.001$. 2-way ANOVA (**A-F**).

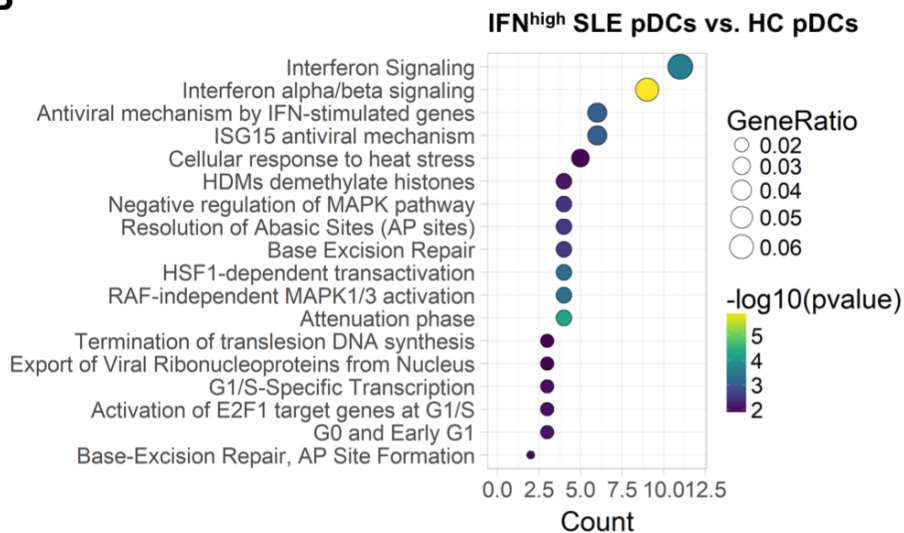


Supplementary Figure 3. (A-D) No association between TLR-mediated IFN- α production and IFN Score A in SLE patients and at-risk individuals. **(E)** Association of percentage of IFN- α production by pDCs and TLR9 expression in patients with SLE. **(F)** Association of percentage of IFN- α production by pDCs and TLR7 expression in patients with SLE. **(G)** Gating of HLA-DR⁺CD303⁺ cells from cultured PBMCs. **(H)** No production of IFN- α or TNF- α was detected by HLA-DR⁺CD303⁺ cells after TLR9 stimulation (ODN 2216). Data are represented as mean $\pm$ SEM. Nonlinear regression **(A-F)**.

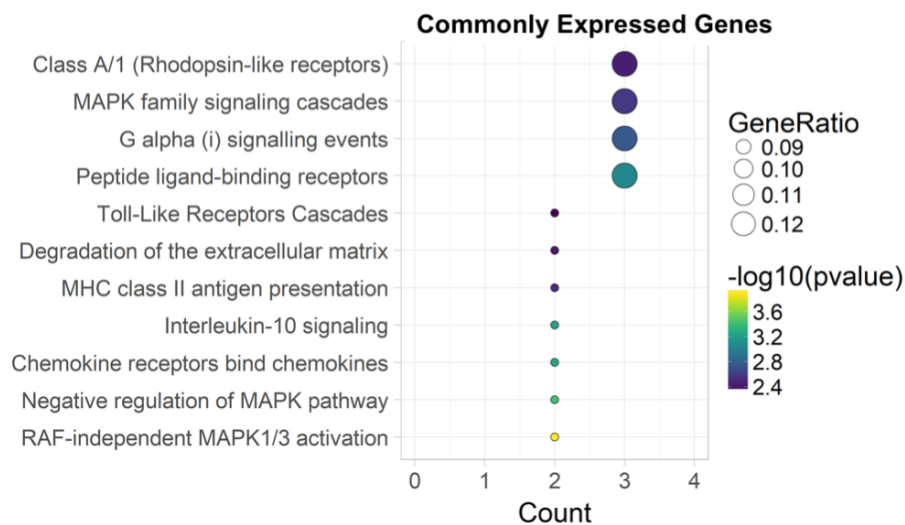
A



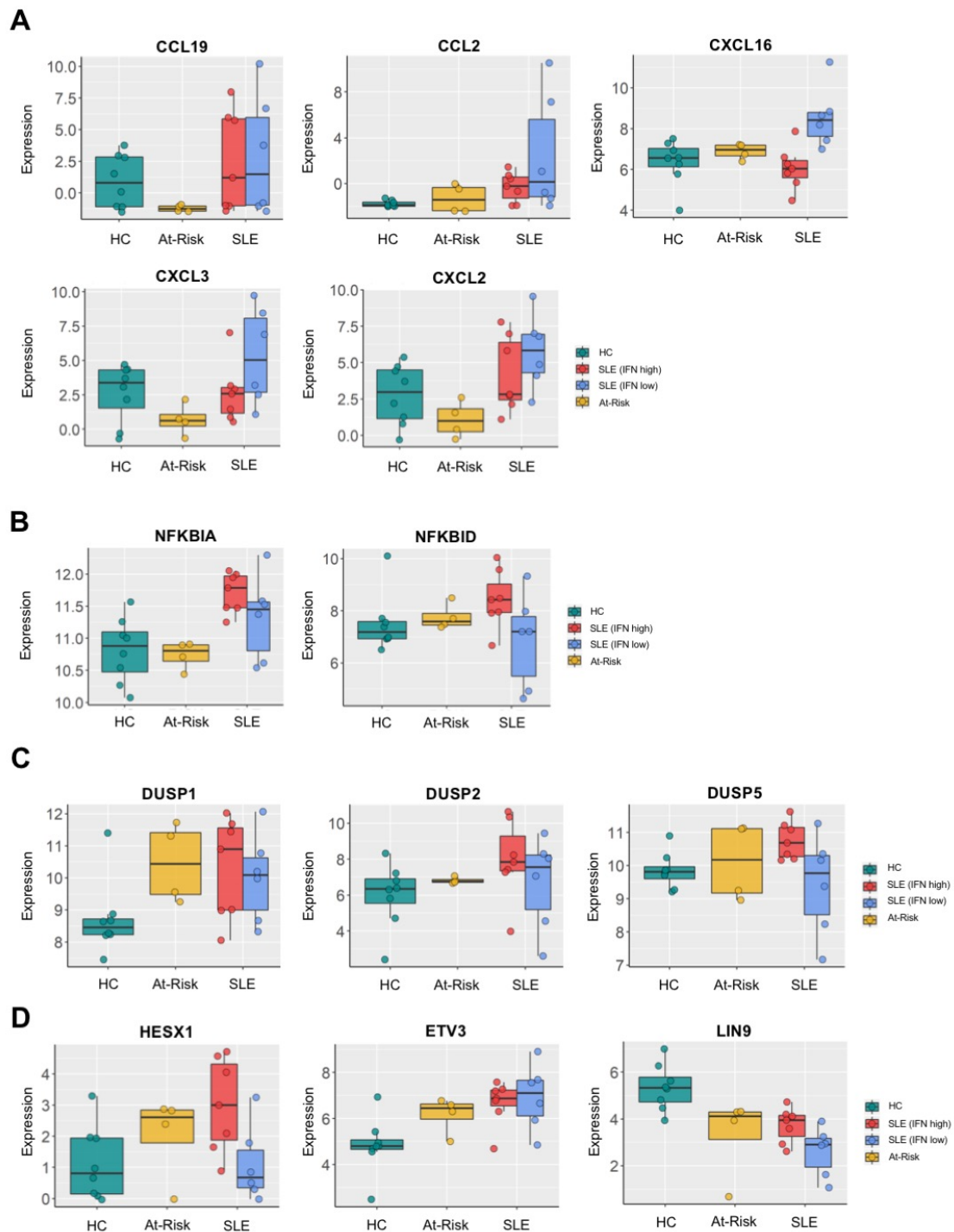
B



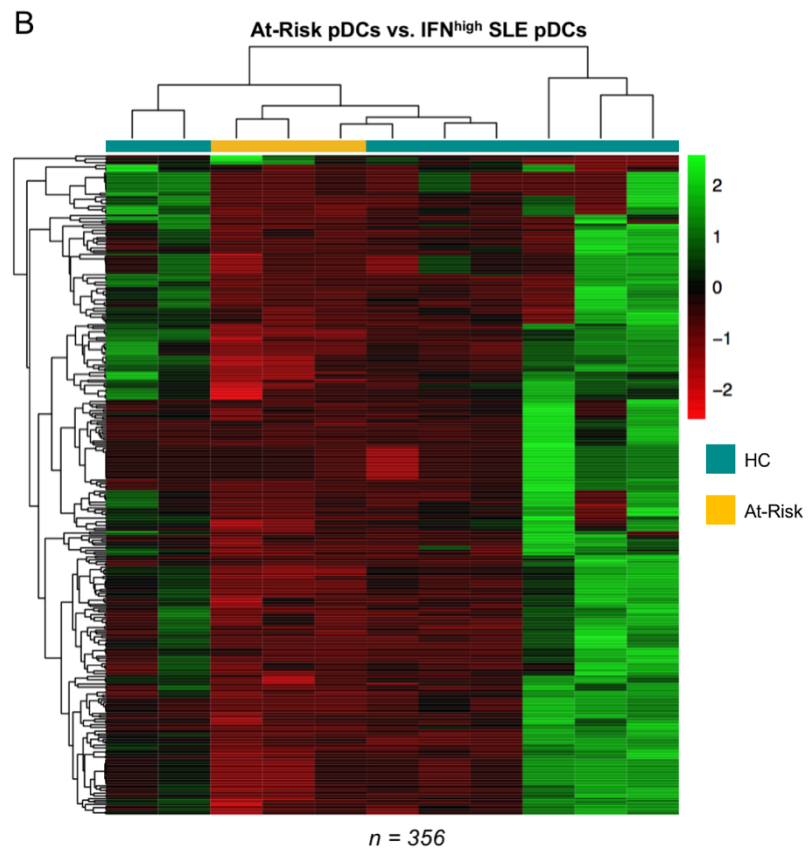
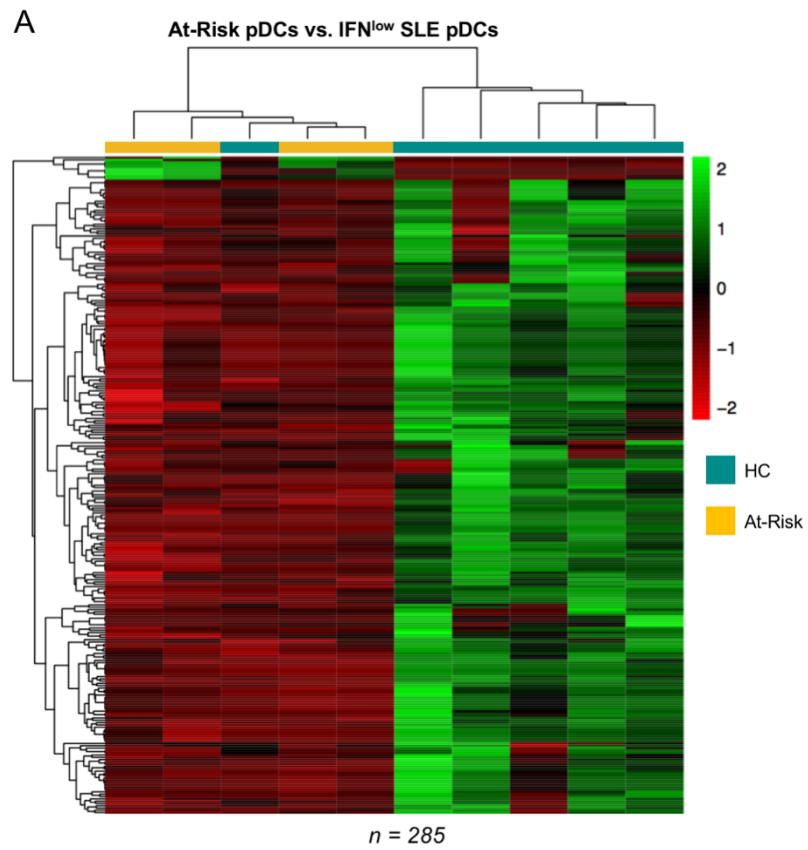
C



Supplementary Figure 4. Reactome Pathway Enrichment in differentially expressed genes in pDCs of IFN^{low} SLE patients (**A**), IFN^{high} SLE patients (**B**) and genes commonly expressed to both (**C**) in comparison with pDCs from healthy controls.

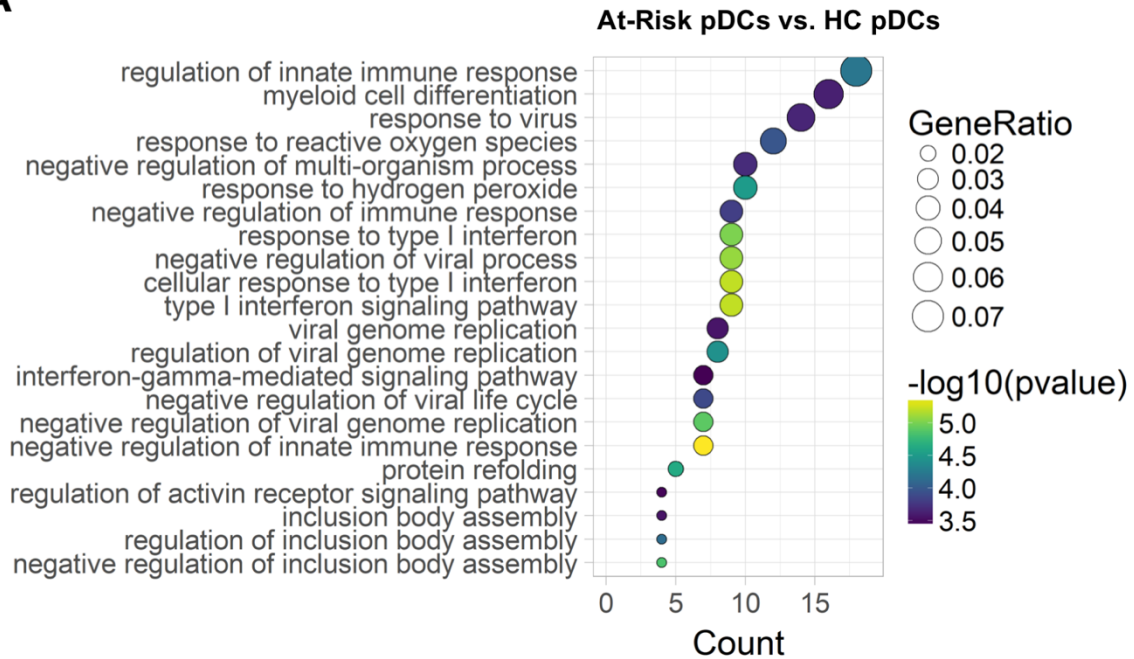


Supplementary Figure 5. Differentially expressed genes in pDCs of healthy controls (HC), at-risk individuals (At-Risk), IFN^{low} SLE and IFN^{high} SLE patients: **(A)** Chemokines; **(B)** NF-κB inhibitors; **(C)** Phosphatases; **(D)** Transcriptional repressors.

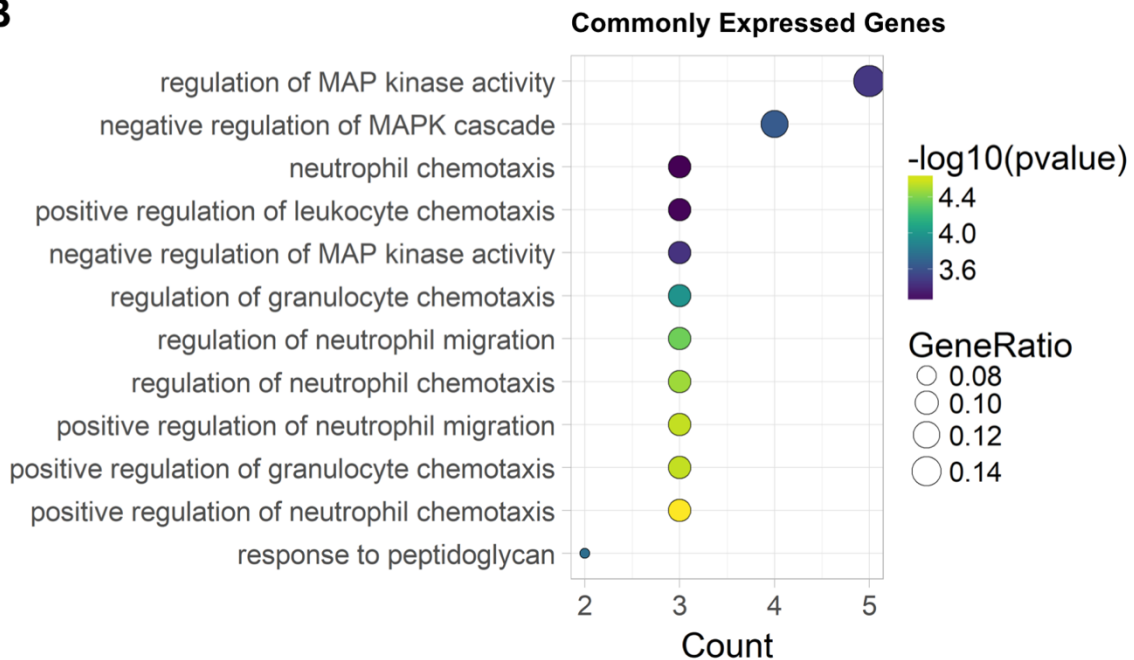


Supplementary Figure 6. Differentially expressed transcripts in At-Risk pDCs compared to IFN^{low} SLE pDCs (A) and IFN^{high} SLE pDCs (B).

A

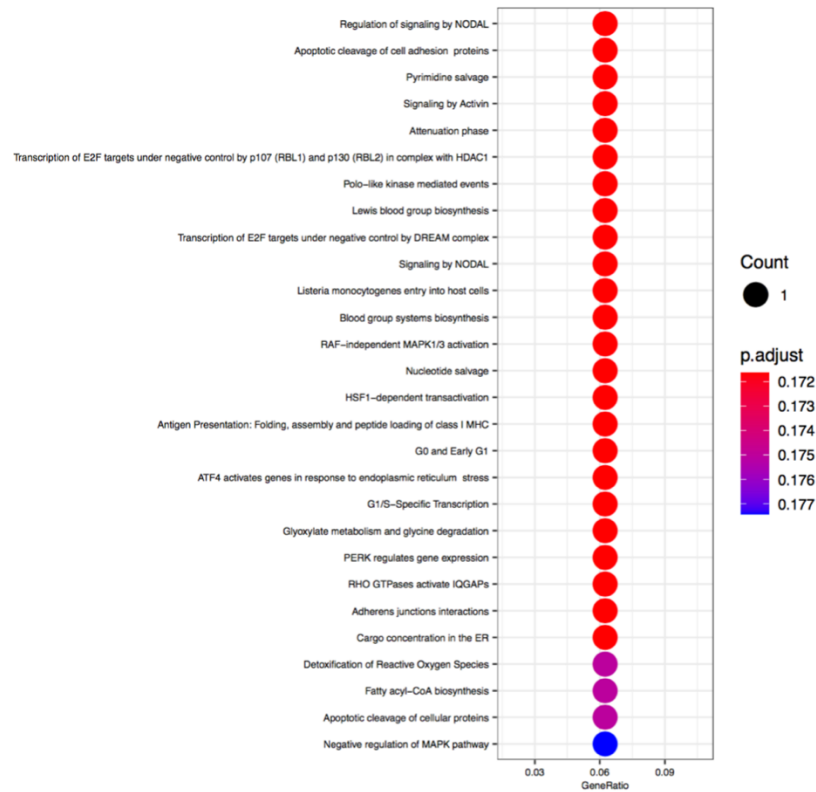


B

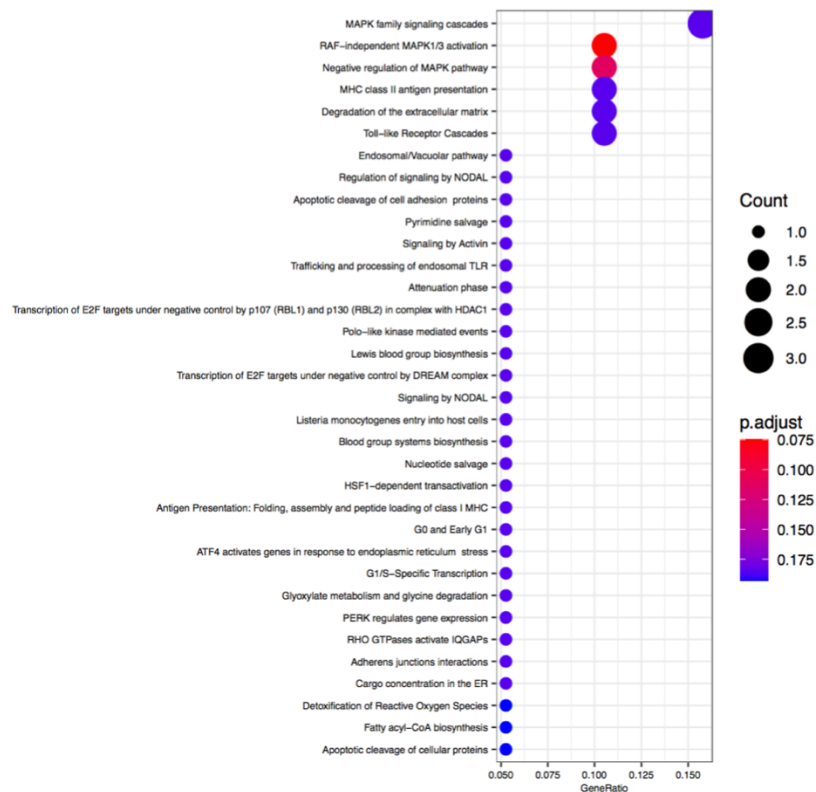


Supplementary Figure 7. Reactome Pathway Enrichment in differentially expressed genes in pDCs of At-Risk individuals in comparison with pDCs from healthy controls. **(A)**, Enriched pathways for genes commonly expressed in pDCs of At-Risk individuals and SLE patients in comparison with pDCs from healthy controls.

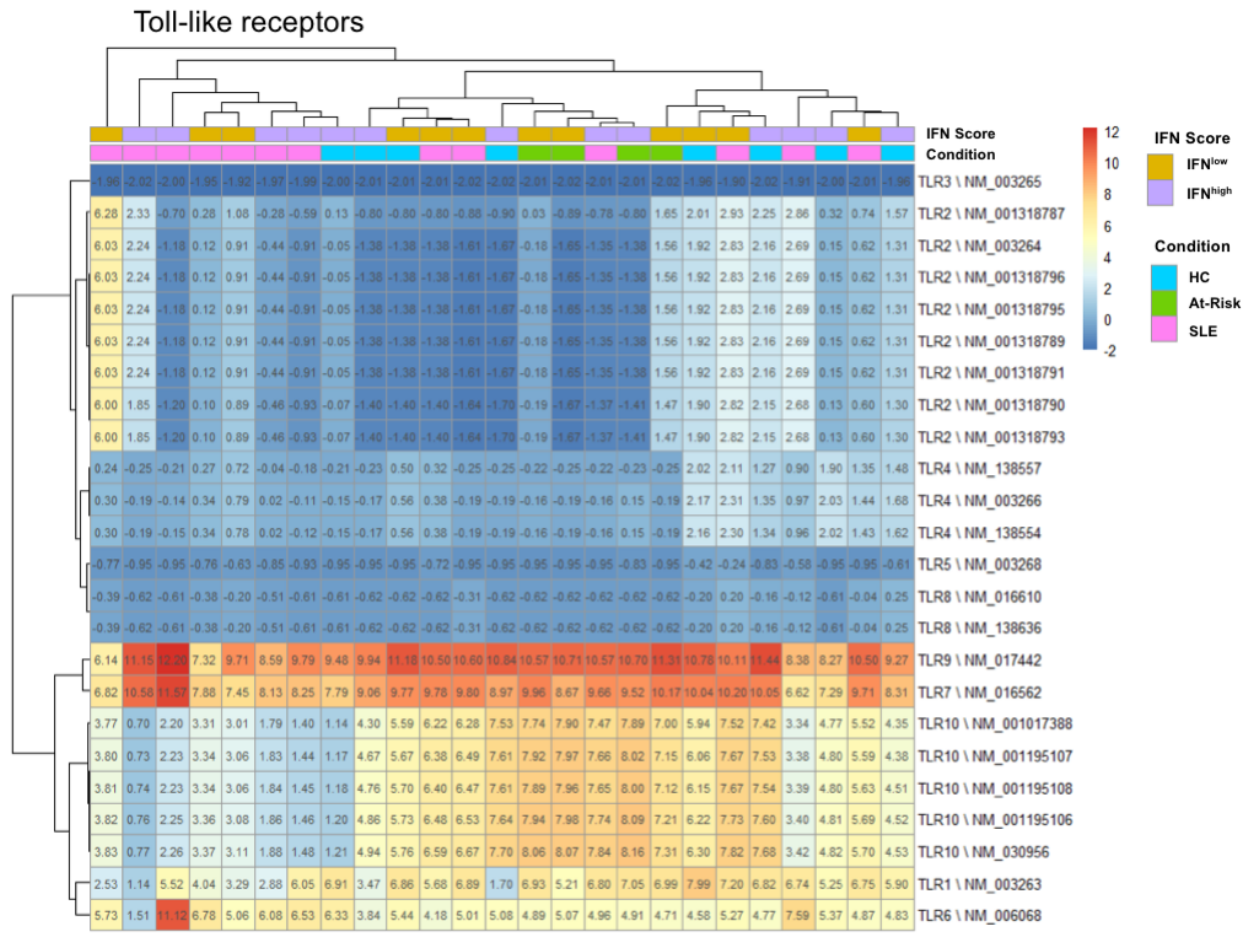
A



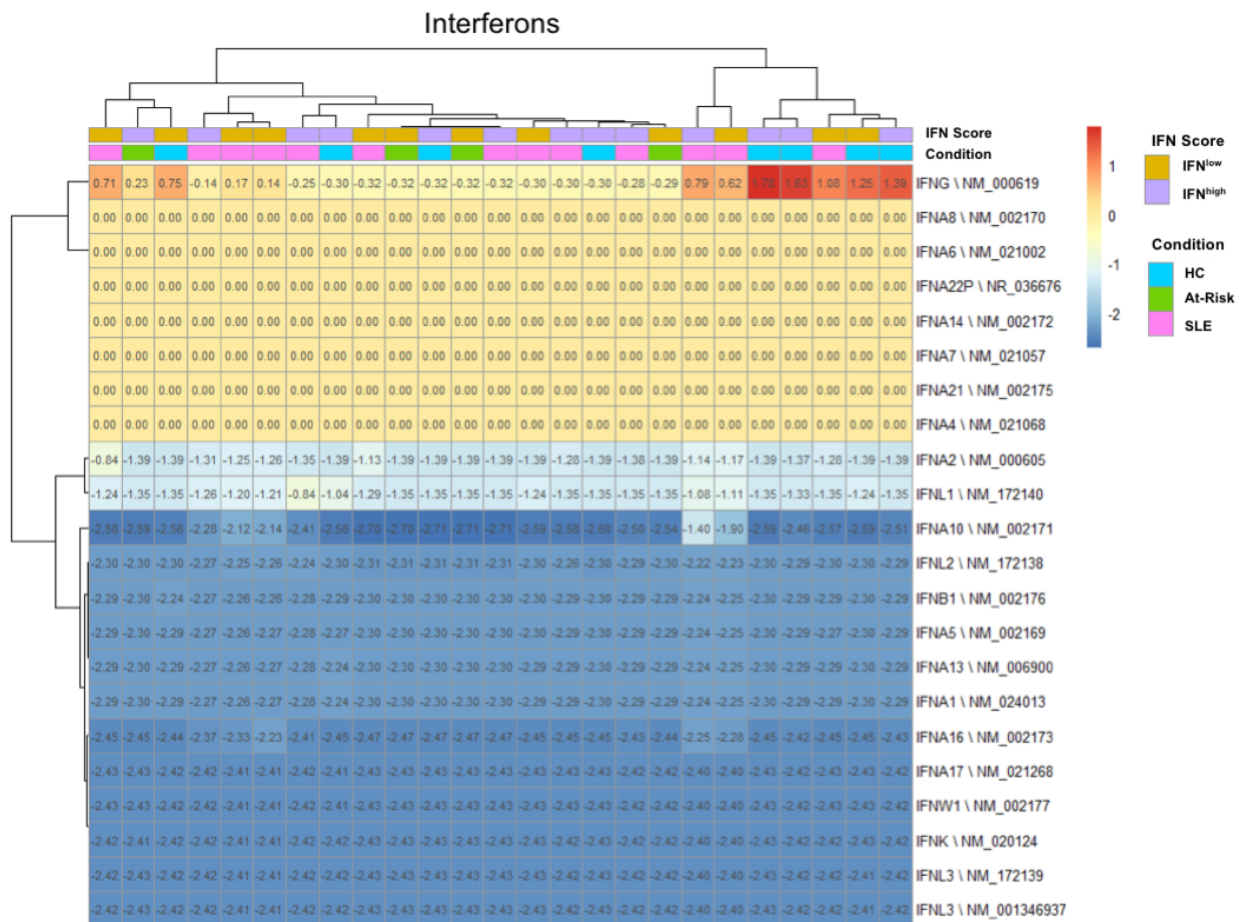
B



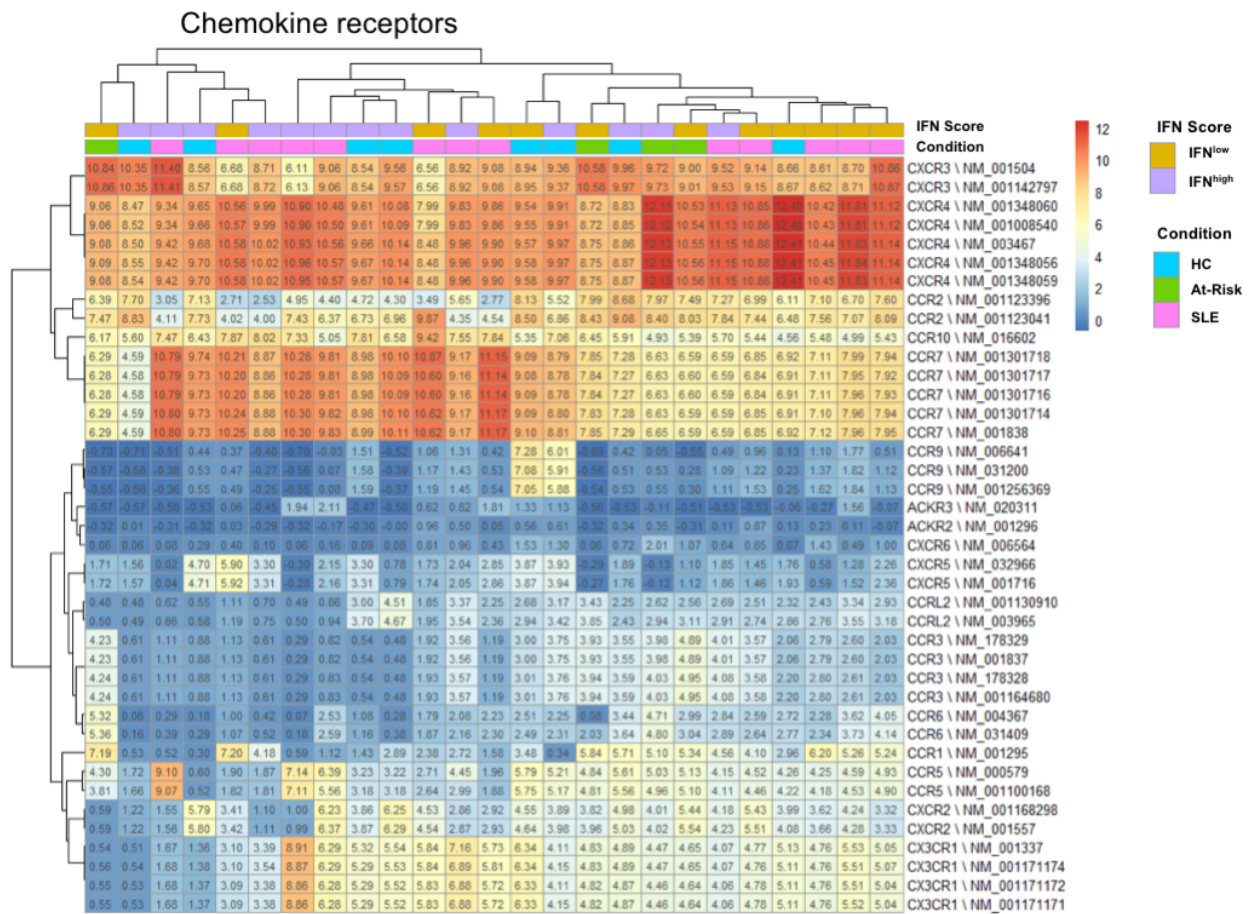
Supplementary Figure 8. Reactome Pathway Enrichment in the commonly differentially expressed genes in pDCs of IFN^{low} SLE (**A**) and IFN^{high} SLE patients (**B**) in comparison with pDCs from At-Risk individuals.



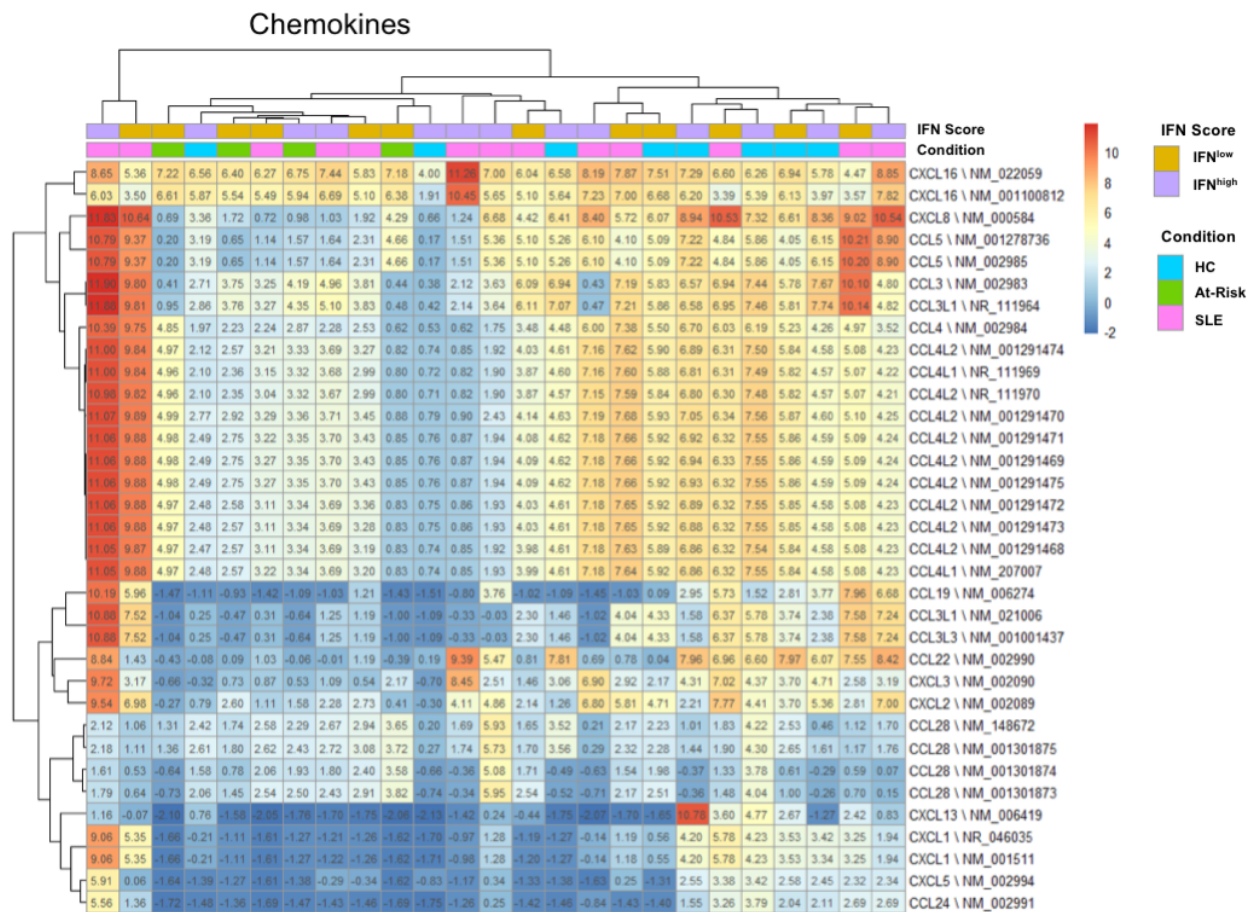
Supplementary Figure 9. Differential expression of Toll-like receptors (TLRs) in pDCs of healthy controls (HC), at-risk individuals (At-Risk), and SLE patients.



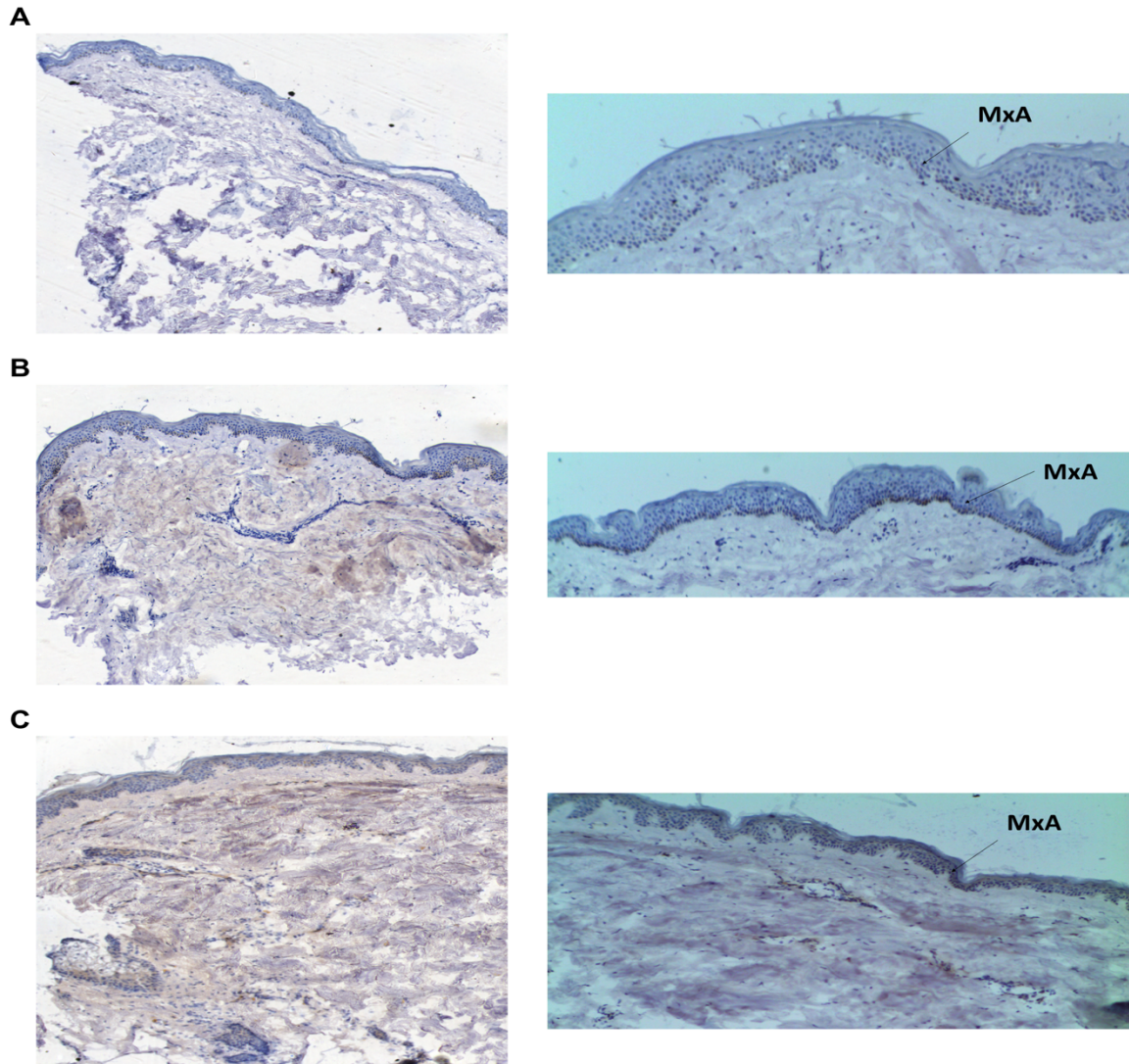
Supplementary Figure 10. Differential expression of type I, II, and III IFNs in pDCs of healthy controls (HC), At-risk individuals (At-Risk), and SLE patients.



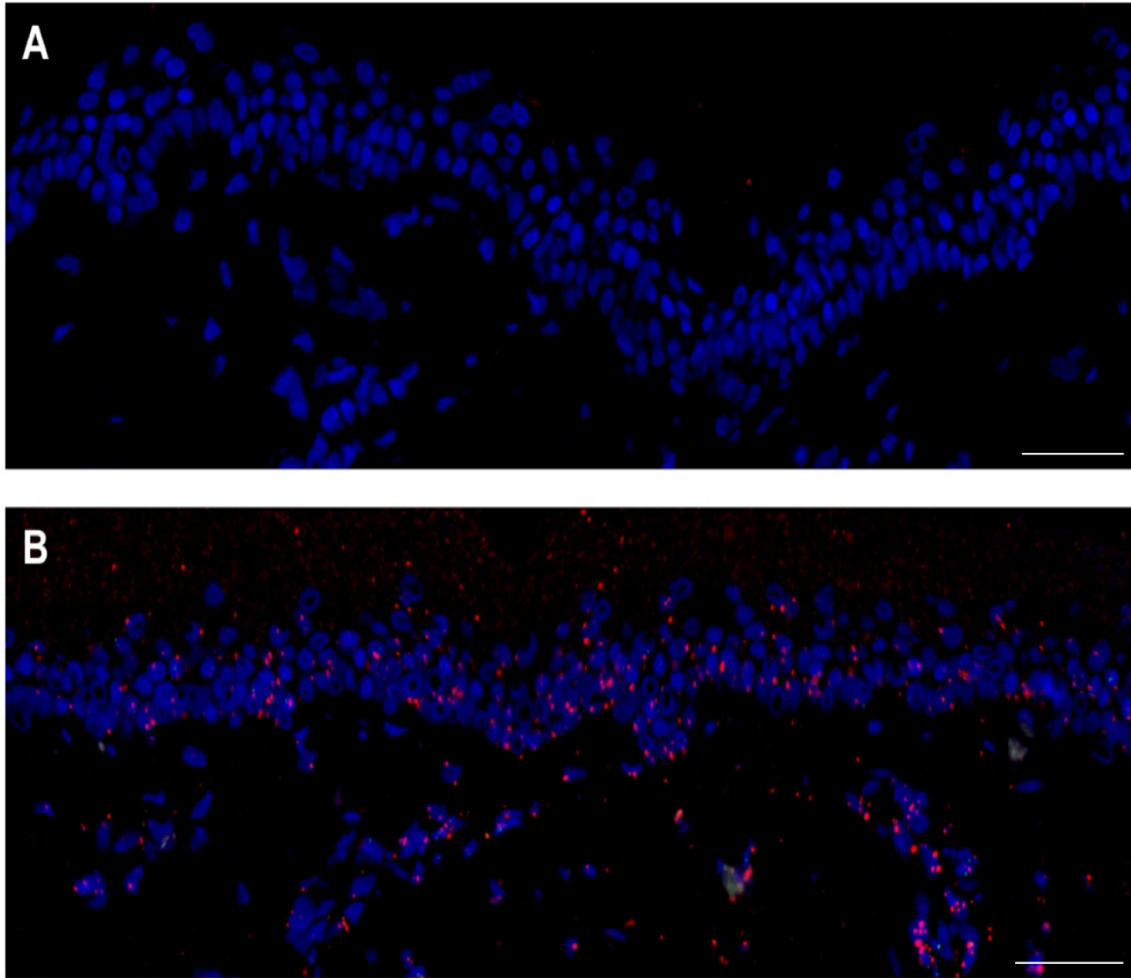
Supplementary Figure 11. Differential expression of chemokine receptors in pDCs of healthy controls (HC), At-risk individuals (At-Risk), and SLE patients.



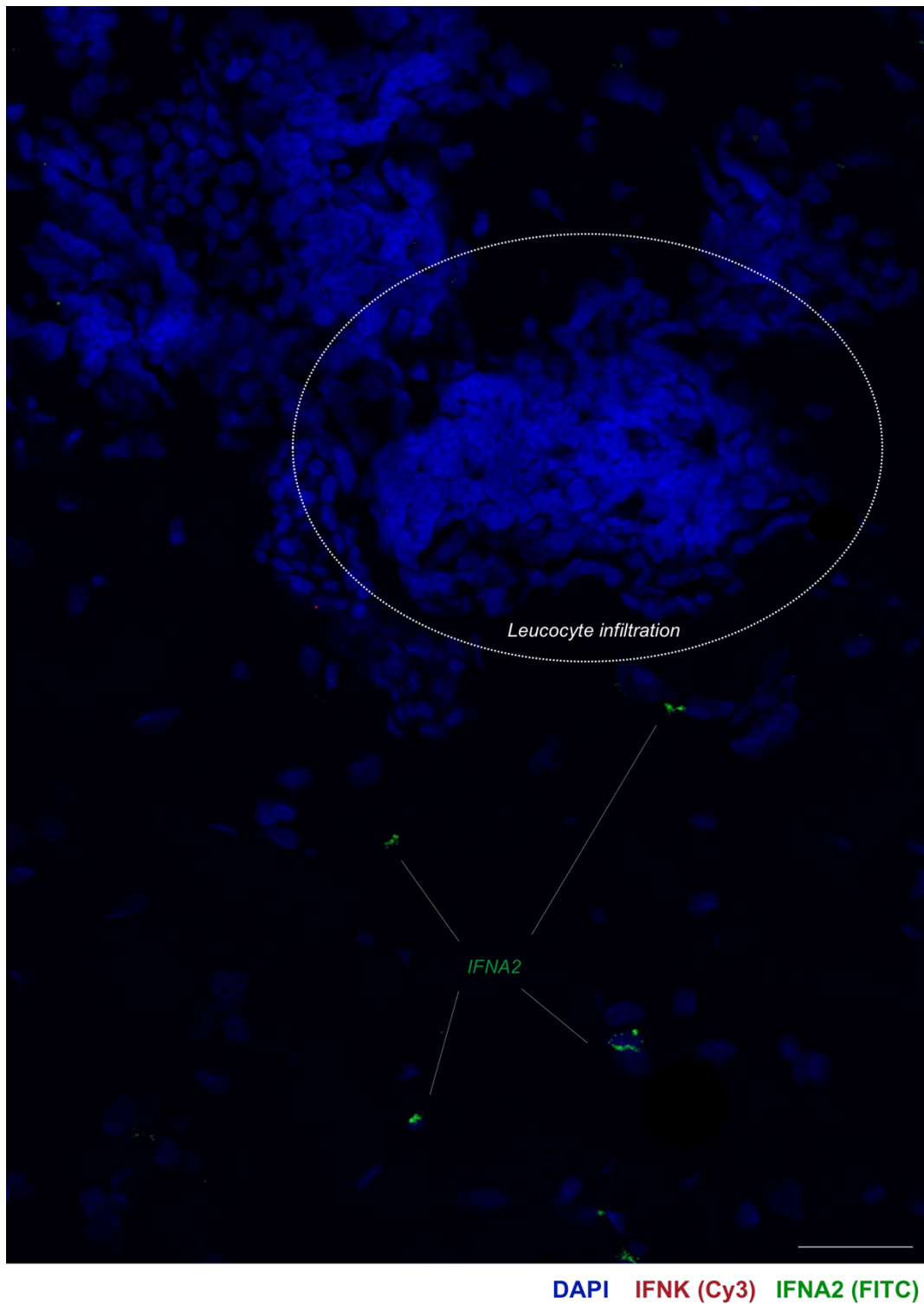
Supplementary Figure 12. Differential expression of chemokines in pDCs of healthy controls (HC), At-risk individuals (At-Risk), and SLE patients.



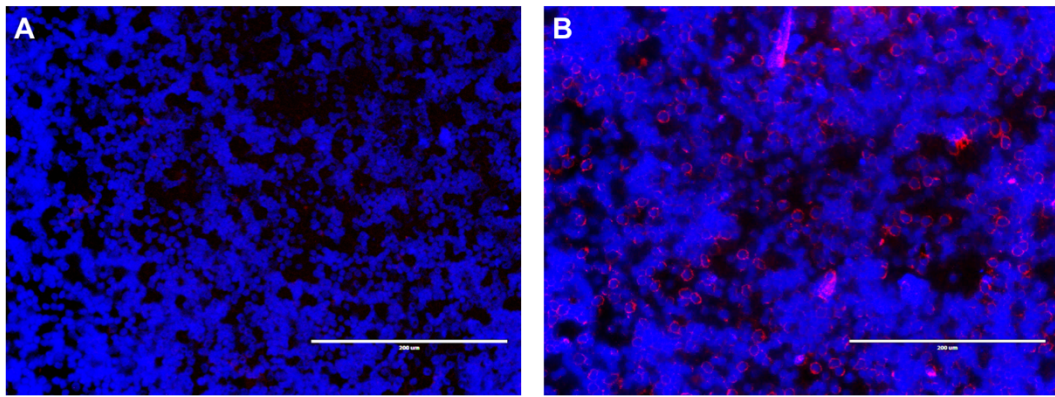
Supplementary Figure 13. Expression of interferon-induced GTP-binding protein MxA in the epidermis from skin biopsies of healthy controls ($n = 3$), skin biopsies of At-Risk individuals ($n = 3$), and non-lesional skin biopsies of SLE patients ($n = 3$) using immunohistochemistry (IHC). MxA positivity is indicated accordingly by the intensity of brown staining. Representative IHC images of: **(A)** healthy control, **(B)** At-Risk, and **(C)** SLE.



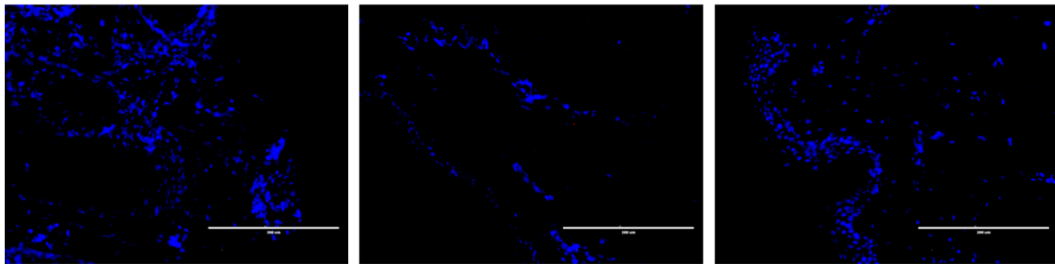
Supplementary Figure 14. Representative pictures of *in situ* hybridization using RNAscope Multiplex Fluorescent Reagent Kit v2 (Advanced Cell Diagnostics): **(A)** negative control; **(B)** positive control (proprietary probes provided by the manufacturer). Scale bars: 100 μ m.



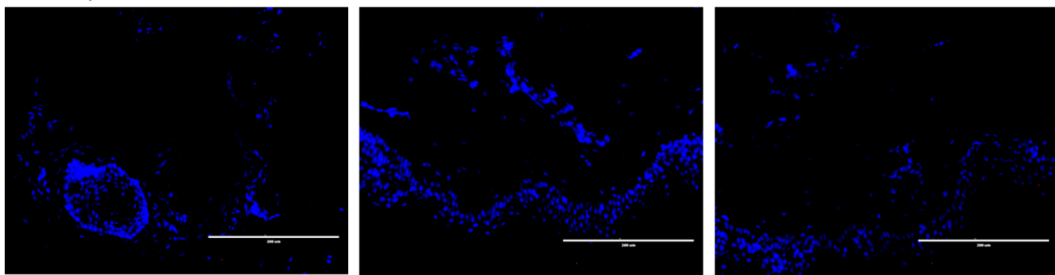
Supplementary Figure 15. Area of leucocyte infiltration and connective tissue of a patient with SLE with active skin lesion. Skin biopsies were hybridized using RNAscope *in situ* hybridization technology with custom-designed target probes for *IFNA2* and *IFNK*. Hybridization signals were amplified and detected using TSA Plus fluorescein (FITC) for *IFNA2* and TSA Plus Cyanine 3 (Cy3) for *IFNK*. Nuclei were highlighted using DAPI. *IFNA2* expression was detected in cells within the connective tissue but not in infiltrating leucocytes. Scale bars: 100 μ m.



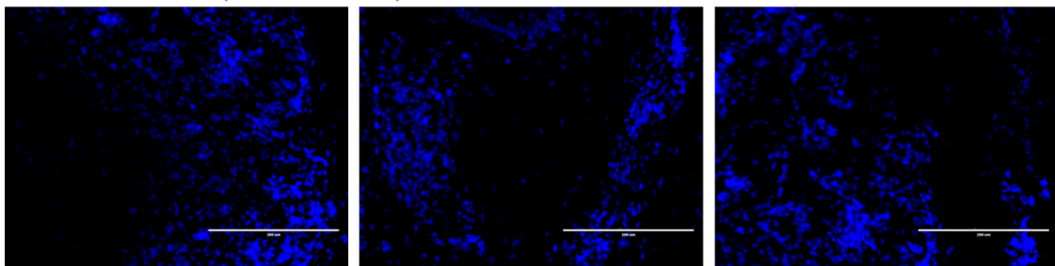
C *Skin biopsies from Healthy Controls*



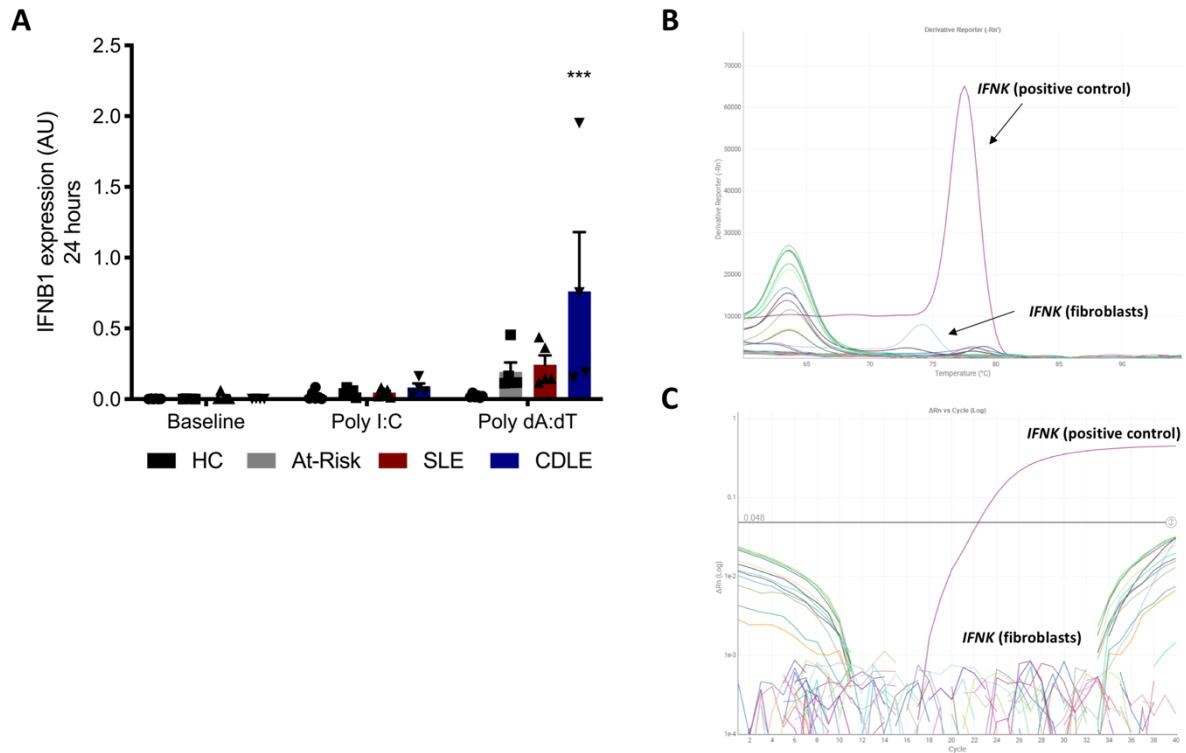
D *Skin biopsies from At-Risk individuals*



E *Non-lesional skin biopsies from SLE patients*



Supplementary Figure 16. Expression of BDCA-4 positive cells in skin biopsies from of healthy controls ($n = 3$), skin biopsies of At-Risk individuals ($n = 3$), and non-lesional skin biopsies of SLE patients ($n = 3$) using immunofluorescence. Isolated pDCs by negative selection were used as positive control: **(A)** unstained, **(B)** BDCA-4 stained. BDCA-4 positivity is indicated by the red fluorescence. No expression of BDCA-4 was identified in any of the skin biopsies acquired from healthy controls **(C)**, At-Risk individuals **(D)**, and SLE patients **(E)**.



Supplementary Figure 17. Human dermal fibroblasts were isolated from fresh skin biopsies and were then cultured in the absence or presence of Poly I:C (1 μ g/mL) or Poly dA:dT (100 ng/mL). **(A)** Expression level of *IFNB1* in dermal fibroblasts from healthy controls (HC), At-Risk individuals (At-Risk), SLE patients (SLE), and patients with cutaneous discoid lupus erythematosus (CDLE) after in vitro culture for 24 hours. **(B and C)** Raw qPCR data for *IFNK* expression of dermal fibroblasts from all samples; no expression detected. Data are represented as mean $\pm$ SEM. *** $P < 0.001$. 2-way ANOVA **(A)**.

Age, median (range) years	44 (18 -76)
Female patients (%)	94
Ethnicity (%)	
Caucasian	74
South Asian	16
East Asian	5
African/Caribbean	5
Clinical symptoms: BILAG Score A/B (%)	
Mucocutaneous	23
Musculoskeletal	23
Haematological	3
Renal	16
Neurological	3
Cardiorespiratory	2
Gastrointestinal	3
Ophthalmic	0
General	0
Hydroxychloroquine (%)	83
Other immunosuppressants (%)	
Methotrexate	14
Azathioprine	18
Mycophenolate mofetil	27
Cyclophosphamide	1
Oral steroids (%)	47

Supplementary Table 1. Clinical characteristics and treatment of SLE patients.

Gene	IFN ^{low} SLE pDCs vs. HC pDCs		
	Fold Change (log2)	P value	FDR
<i>ULBP2</i>	19.757	< 0.001	< 0.001
<i>C10orf35</i>	18.302	< 0.001	< 0.001
<i>TPSB2</i>	18.228	< 0.001	< 0.001
<i>TMEM216</i>	-4.981	< 0.001	< 0.001
<i>CXCL2</i>	6.379	< 0.001	< 0.001
<i>PLA2G7</i>	9.712	< 0.001	< 0.001
<i>DNAJB4</i>	1.965	< 0.001	0.001
<i>ZBP1</i>	-7.254	< 0.001	0.001
<i>LUCAT1</i>	6.207	< 0.001	0.006
<i>LOC100861532</i>	2.839	< 0.001	0.007
<i>LGALS1</i>	6.161	< 0.001	0.007
<i>SNORD95</i>	4.390	< 0.001	0.007
<i>LOC100008587</i>	3.428	< 0.001	0.007
<i>BBC3</i>	2.962	< 0.001	0.011
<i>SPR</i>	6.792	< 0.001	0.015
<i>FN1</i>	4.352	< 0.001	0.015
<i>PHF3</i>	1.125	< 0.001	0.015
<i>HSPB1</i>	1.527	< 0.001	0.015
<i>CLEC5A</i>	8.287	< 0.001	0.015
<i>CKAP4</i>	-6.563	< 0.001	0.015
<i>IRAIN</i>	5.493	< 0.001	0.015
<i>FAM157C</i>	3.945	< 0.001	0.015
<i>DNAJB1</i>	2.108	< 0.001	0.015
<i>ETV3</i>	3.037	< 0.001	0.017
<i>TPSAB1</i>	9.650	< 0.001	0.020
<i>SLC6A6</i>	3.758	< 0.001	0.020
<i>NPAS1</i>	5.880	< 0.001	0.020
<i>GADD45B</i>	2.245	< 0.001	0.021
<i>IFITM1</i>	-3.619	< 0.001	0.022
<i>COCH</i>	-7.844	< 0.001	0.022
<i>ANO8</i>	3.516	< 0.001	0.022
<i>LINC00623</i>	3.718	< 0.001	0.022
<i>HSPA4</i>	-2.406	< 0.001	0.023
<i>AOAH</i>	-6.704	< 0.001	0.023
<i>HOXB3</i>	4.793	< 0.001	0.023
<i>SLC8A2</i>	5.243	< 0.001	0.023
<i>NPL</i>	4.663	< 0.001	0.025
<i>ZNF678</i>	4.063	< 0.001	0.025
<i>CNST</i>	2.130	< 0.001	0.025
<i>RNY5</i>	3.224	< 0.001	0.025
<i>PLEKHA8P1</i>	-4.947	< 0.001	0.025
<i>DUSP1</i>	2.903	< 0.001	0.027
<i>LOC100008589</i>	2.695	< 0.001	0.028
<i>NRP2</i>	6.969	< 0.001	0.028
<i>EGR2</i>	7.175	< 0.001	0.029
<i>FCGR2B</i>	-6.697	< 0.001	0.033
<i>NRG2</i>	5.224	< 0.001	0.033
<i>LOC221946</i>	5.139	< 0.001	0.033
<i>PLCXD1</i>	3.230	< 0.001	0.033
<i>LACC1</i>	4.975	< 0.001	0.033

Supplementary Table 2. Top 50 genes that are differentially expressed in pDCs of IFN^{low} SLE patients in comparison with pDCs from healthy controls (HC).

Gene	IFN ^{high} SLE pDCs vs. HC pDCs		
	Fold Change (log2)	P value	FDR
<i>IFI44</i>	5.403	< 0.001	< 0.001
<i>CAMP</i>	7.261	< 0.001	< 0.001
<i>OASL</i>	6.812	< 0.001	< 0.001
<i>SLC8A2</i>	5.644	< 0.001	< 0.001
<i>ATF3</i>	5.870	< 0.001	< 0.001
<i>CMPK2</i>	7.710	< 0.001	< 0.001
<i>BCL2</i>	5.485	< 0.001	< 0.001
<i>LGALS1</i>	6.240	< 0.001	< 0.001
<i>ORM1</i>	8.011	< 0.001	< 0.001
<i>NCMAP</i>	4.931	< 0.001	< 0.001
<i>HCG11</i>	-3.108	< 0.001	< 0.001
<i>PARP14</i>	3.402	< 0.001	< 0.001
<i>MSL2</i>	2.238	< 0.001	0.001
<i>DDX60L</i>	6.470	< 0.001	0.001
<i>PPDPF</i>	1.798	< 0.001	0.001
<i>IER2</i>	2.552	< 0.001	0.001
<i>NR4A1</i>	5.230	< 0.001	0.002
<i>TFB1M</i>	-2.213	< 0.001	0.002
<i>GFOD1</i>	4.279	< 0.001	0.002
<i>TP53INP2</i>	5.236	< 0.001	0.002
<i>TMEM177</i>	-3.452	< 0.001	0.002
<i>LIPT1</i>	-2.499	< 0.001	0.002
<i>JUND</i>	2.486	< 0.001	0.002
<i>THG1L</i>	-2.089	< 0.001	0.002
<i>CCDC121</i>	6.073	< 0.001	0.002
<i>SNORD14C</i>	4.151	< 0.001	0.002
<i>C2orf74</i>	-2.833	< 0.001	0.002
<i>CISD1</i>	-2.392	< 0.001	0.002
<i>HIST1H4F</i>	-2.531	< 0.001	0.002
<i>SEMA7A</i>	3.150	< 0.001	0.002
<i>ETV3L</i>	3.865	< 0.001	0.002
<i>CEACAM1</i>	5.448	< 0.001	0.002
<i>L3MBTL2</i>	-1.887	< 0.001	0.002
<i>ETV3</i>	2.959	< 0.001	0.002
<i>NPAS1</i>	5.469	< 0.001	0.002
<i>QRICH2</i>	4.336	< 0.001	0.002
<i>LTC4S</i>	5.089	< 0.001	0.003
<i>ARID5A</i>	1.781	< 0.001	0.003
<i>EIF2AK2</i>	2.358	< 0.001	0.003
<i>HES4</i>	4.895	< 0.001	0.003
<i>LINC00847</i>	-2.487	< 0.001	0.003
<i>NSUN7</i>	5.334	< 0.001	0.003
<i>DNAJB1</i>	4.229	< 0.001	0.003
<i>KLF8</i>	-4.556	< 0.001	0.003
<i>RSAD2</i>	4.959	< 0.001	0.003
<i>JUN</i>	2.582	< 0.001	0.003
<i>MON1A</i>	-2.248	< 0.001	0.003
<i>IFI44L</i>	3.195	< 0.001	0.004
<i>WDR87</i>	6.155	< 0.001	0.004
<i>IRAIN</i>	4.774	< 0.001	0.004

Supplementary Table 3. Top 50 genes that are differentially expressed in pDCs of IFN^{high} SLE patients in comparison with pDCs from healthy controls (HC).

Gene	IFN ^{low} SLE pDCs vs. HC pDCs			IFN ^{high} SLE pDCs vs. HC pDCs		
	Fold Change (log2)	P value	FDR	Fold Change (log2)	P value	FDR
ETV3	3.037	< 0.001	0.017	2.959	< 0.001	0.002
ATF3	3.914	< 0.001	0.052	5.209	< 0.001	0.000
LIN9	-3.716	< 0.001	0.058	-2.423	< 0.001	0.031
LGALS1	6.161	< 0.001	0.007	6.240	< 0.001	< 0.001
ZNF2	-4.108	< 0.001	0.058	-2.907	< 0.001	0.020
LIPT1	-3.224	< 0.001	0.050	-2.499	< 0.001	0.002
SEC24D	-2.559	< 0.001	0.051	-1.605	0.001	0.038
CXCL2	6.379	< 0.001	< 0.001	4.163	< 0.001	0.019
CBR4	-3.260	< 0.001	0.052	-1.546	< 0.001	0.011
DUSP1	2.903	< 0.001	0.027	2.386	< 0.001	0.021
LTC4S	5.509	< 0.001	0.033	5.089	< 0.001	0.003
SNORD95	4.390	< 0.001	0.007	3.106	< 0.001	0.016
PHF3	1.125	< 0.001	0.015	1.531	< 0.001	0.028
LOC441242	-2.798	0.001	0.068	-2.494	< 0.001	0.015
FUT10	-3.275	0.002	0.100	-2.388	< 0.001	0.016
LOC102724580	3.699	0.001	0.088	4.080	< 0.001	0.004
CCL19	4.468	< 0.001	0.057	3.828	< 0.001	0.020
CTSL	6.460	< 0.001	0.040	4.114	< 0.001	0.020
PUDP	-2.632	< 0.001	0.058	-2.752	< 0.001	0.008
ATP7A	-4.215	< 0.001	0.035	-2.853	< 0.001	0.020
SAT1	1.642	< 0.001	0.036	1.805	< 0.001	0.009
MIR6087	2.376	< 0.001	0.050	2.411	< 0.001	0.028
ZFP91	2.619	< 0.001	0.046	2.147	0.001	0.043
PAAF1	-3.453	0.001	0.066	-1.973	< 0.001	0.033
DUSP8	6.050	0.001	0.085	6.392	< 0.001	0.006
IRAK3	6.179	< 0.001	0.045	4.152	< 0.001	0.007
PLEKHA8P1	-4.947	< 0.001	0.025	-2.810	< 0.001	0.009
ACVR1B	5.196	0.001	0.059	4.169	< 0.001	0.017
RN7SL1	2.867	< 0.001	0.049	2.648	< 0.001	0.034
RN7SL2	3.107	< 0.001	0.033	2.806	< 0.001	0.021
ATG14	2.520	< 0.001	0.058	1.640	< 0.001	0.028
REREP3	3.757	< 0.001	0.046	3.672	< 0.001	0.019
IRAIN	5.493	< 0.001	0.015	4.774	< 0.001	0.004
CDH1	3.795	0.001	0.061	2.895	< 0.001	0.028
SCARNA21	2.549	0.001	0.074	2.980	0.001	0.041
C5AR1	6.724	0.002	0.098	5.210	< 0.001	0.031
SLC8A2	5.243	< 0.001	0.023	5.644	< 0.001	< 0.001
IER2	2.416	< 0.001	0.050	2.552	< 0.001	0.001
DNAJB1	2.108	< 0.001	0.015	4.097	< 0.001	0.005
NPAS1	5.880	< 0.001	0.020	5.469	< 0.001	0.002
LOC100008589	2.695	< 0.001	0.028	2.969	< 0.001	0.006
MIR3687-1	3.321	0.002	0.098	3.448	< 0.001	0.007
MIR3687-2	3.321	0.002	0.098	3.448	< 0.001	0.007
LOC100861532	2.839	< 0.001	0.007	2.930	< 0.001	0.005
WRB	-2.306	0.001	0.068	-2.027	< 0.001	0.008
pDC-specific transcription factors						
E2-2 (TCF4)	0.691	0.118	0.537	0.313	0.578	0.852
SPIB	0.657	0.279	0.719	0.235	0.744	0.922

Supplementary Table 4. Genes that are differentially expressed in pDCs of both IFN^{low} and IFN^{high} SLE patients in comparison with pDCs from healthy controls (HC).

Gene	At-Risk pDCs vs. HC pDCs		
	Fold Change (log2)	P value	FDR
<i>DNAJB4</i>	-1.938	< 0.001	0.008
<i>ATF3</i>	-2.990	< 0.001	0.008
<i>RNU6-1</i>	2.960	< 0.001	0.004
<i>RNU6-9</i>	2.957	< 0.001	0.004
<i>RNU6-7</i>	2.960	< 0.001	0.004
<i>RNU6-8</i>	2.960	< 0.001	0.004
<i>RNU6-2</i>	2.957	< 0.001	0.004
<i>GSTM1</i>	1.941	< 0.001	0.005
<i>GLRX2</i>	2.736	< 0.001	0.005
<i>MIR4435-2HG</i>	2.529	< 0.001	0.006
<i>STAT1</i>	-2.113	< 0.001	0.004
<i>COL4A4</i>	2.891	< 0.001	0.009
<i>CYTOR</i>	3.023	< 0.001	0.002
<i>ANKRD36BP2</i>	3.771	< 0.001	< 0.001
<i>CD38</i>	2.778	< 0.001	0.007
<i>TXNDC15</i>	2.401	< 0.001	0.003
<i>DUSP1</i>	-2.774	< 0.001	< 0.001
<i>HIST1H2BB</i>	3.194	< 0.001	< 0.001
<i>HIST1H3A</i>	2.916	< 0.001	0.002
<i>BET1</i>	2.043	< 0.001	0.010
<i>SNORA109</i>	3.523	< 0.001	0.001
<i>MECP2</i>	1.951	< 0.001	0.006
<i>EIF1AY</i>	-3.234	< 0.001	0.006
<i>DDX3Y</i>	-4.419	< 0.001	< 0.001
<i>KDM5D</i>	-3.804	< 0.001	< 0.001
<i>CSKMT</i>	3.363	< 0.001	< 0.001
<i>EHD1</i>	1.389	< 0.001	0.010
<i>RAB30</i>	2.610	< 0.001	0.005
<i>ERBB3</i>	3.265	< 0.001	0.004
<i>FKBP11</i>	3.086	< 0.001	0.002
<i>CNPY2</i>	2.266	< 0.001	0.001
<i>CKAP4</i>	3.181	< 0.001	0.006
<i>C12orf65</i>	2.252	< 0.001	0.009
<i>MRPS31</i>	2.589	< 0.001	< 0.001
<i>RPPH1</i>	2.977	< 0.001	0.001
<i>FOS</i>	-3.826	< 0.001	0.000
<i>CRIP2</i>	3.717	< 0.001	0.000
<i>SLCO3A1</i>	3.129	< 0.001	0.008
<i>IGHV1OR15-1</i>	3.725	< 0.001	< 0.001
<i>LOC102724760</i>	3.725	< 0.001	< 0.001
<i>TNFRSF17</i>	3.643	< 0.001	< 0.001
<i>NPIP8</i>	3.034	< 0.001	0.002
<i>NPIP9</i>	3.073	< 0.001	0.002
<i>PHF23</i>	2.419	< 0.001	0.009
<i>HEXIM1</i>	2.342	< 0.001	0.009
<i>KANSL1-AS1</i>	2.967	< 0.001	0.002
<i>LSR</i>	2.955	< 0.001	0.002
<i>FTL</i>	2.684	< 0.001	0.003
<i>BCL2L12</i>	2.367	< 0.001	0.003
<i>SNORD12C</i>	3.257	< 0.001	0.003

Supplementary Table 5. Top 50 genes that are differentially expressed in pDCs of At-Risk individuals in comparison with pDCs from healthy controls (HC).

At-Risk pDCs vs. IFN ^{low} SLE pDCs			
Gene	Fold Change (log2)	P value	FDR
<i>COL24A1</i>	4.046	< 0.001	0.002
<i>CDK11A</i>	4.130	< 0.001	0.001
<i>FAM72C</i>	4.744	< 0.001	0.003
<i>LMNA</i>	5.449	< 0.001	< 0.001
<i>TNFRSF4</i>	5.748	< 0.001	< 0.001
<i>CDK11B</i>	4.207	< 0.001	0.001
<i>RNU6-1</i>	5.202	< 0.001	< 0.001
<i>RNU6-9</i>	5.196	< 0.001	< 0.001
<i>RNU6-7</i>	5.202	< 0.001	< 0.001
<i>RNU6-8</i>	5.202	< 0.001	< 0.001
<i>RNU6-2</i>	5.196	< 0.001	< 0.001
<i>ID3</i>	6.455	< 0.001	< 0.001
<i>IFI6</i>	4.682	< 0.001	0.003
<i>SNORA16A</i>	5.022	< 0.001	0.005
<i>POU3F1</i>	7.210	< 0.001	< 0.001
<i>SNORD46</i>	4.793	< 0.001	< 0.001
<i>HIST2H3D</i>	5.510	< 0.001	< 0.001
<i>HIST2H3A</i>	4.801	< 0.001	< 0.001
<i>HIST2H3C</i>	4.801	< 0.001	< 0.001
<i>TNFAIP8L2</i>	3.967	< 0.001	0.001
<i>LMNA</i>	5.894	< 0.001	< 0.001
<i>IGSF9</i>	6.193	< 0.001	< 0.001
<i>GAS5-AS1</i>	4.061	< 0.001	0.003
<i>NPL</i>	4.650	< 0.001	0.003
<i>FAM72A</i>	4.297	< 0.001	0.008
<i>ID2</i>	5.343	< 0.001	< 0.001
<i>FBXO48</i>	4.007	< 0.001	0.003
<i>ANKRD36BP</i>			
<i>2</i>	4.160	< 0.001	0.002
<i>SCARNA5</i>	5.077	< 0.001	0.003
<i>RSRC1</i>	3.969	< 0.001	0.002
<i>CACNA1D</i>	5.556	< 0.001	0.002
<i>TNFSF10</i>	-4.893	< 0.001	0.001
<i>HES1</i>	5.766	< 0.001	< 0.001
<i>TNK2-AS1</i>	3.486	< 0.001	0.002
<i>PCDH10</i>	7.397	< 0.001	< 0.001
<i>ARHGAP10</i>	5.957	< 0.001	< 0.001
<i>SCARNA22</i>	4.668	< 0.001	0.007
<i>MSX1</i>	5.869	< 0.001	0.001
<i>CXCL3</i>	6.537	< 0.001	< 0.001
<i>PCDH10</i>	7.397	< 0.001	< 0.001
<i>ELL2</i>	5.151	< 0.001	< 0.001
<i>CCDC127</i>	4.327	< 0.001	0.001
<i>BRD9</i>	3.428	< 0.001	0.006
<i>PTGER4</i>	4.681	< 0.001	< 0.001
<i>CDC20B</i>	7.824	< 0.001	< 0.001
<i>ENC1</i>	5.279	< 0.001	< 0.001
<i>LUCAT1</i>	5.804	< 0.001	< 0.001
<i>EGR1</i>	3.934	< 0.001	0.001
<i>SNORD95</i>	5.194	< 0.001	< 0.001
<i>NQO2</i>	4.500	< 0.001	0.001

Supplementary Table 6. Top 50 genes that are differentially expressed in pDCs of At-Risk individuals in comparison with pDCs from IFN^{low} SLE patients.

At-Risk pDCs vs. IFN ^{high} SLE pDCs			
Gene	Fold Change (log2)	P value	FDR
<i>NUP210L</i>	4.718	< 0.001	0.009
<i>LMNA</i>	5.127	< 0.001	0.002
<i>PCNX2</i>	5.859	< 0.001	0.001
<i>PLEKHN1</i>	4.941	< 0.001	0.009
<i>HES4</i>	5.030	< 0.001	0.002
<i>TNFRSF4</i>	4.667	< 0.001	0.004
<i>TNFRSF25</i>	4.450	< 0.001	0.007
<i>TNFRSF9</i>	6.082	< 0.001	0.001
<i>ID3</i>	4.972	< 0.001	0.001
<i>NCMAP</i>	4.261	< 0.001	0.005
<i>IFI6</i>	6.506	< 0.001	0.000
<i>SNORA16A</i>	5.387	< 0.001	0.003
<i>GBP2</i>	5.083	< 0.001	0.002
<i>FAM46C</i>	4.362	< 0.001	0.003
<i>LMNA</i>	5.203	< 0.001	0.001
<i>FCGR2C</i>	4.781	< 0.001	0.007
<i>SNORD74</i>	4.855	< 0.001	0.004
<i>GLRX2</i>	4.303	< 0.001	0.008
<i>LAX1</i>	4.786	< 0.001	0.009
<i>DUSP10</i>	4.680	< 0.001	0.010
<i>RNA5S4</i>	4.762	< 0.001	0.005
<i>RNA5S2</i>	4.762	< 0.001	0.005
<i>RNA5S3</i>	4.762	< 0.001	0.005
<i>RNA5S1</i>	4.762	< 0.001	0.005
<i>RNA5S15</i>	4.762	< 0.001	0.005
<i>RNA5S16</i>	4.762	< 0.001	0.005
<i>RNA5S14</i>	4.762	< 0.001	0.005
<i>RNA5S5</i>	4.762	< 0.001	0.005
<i>RNA5S12</i>	4.762	< 0.001	0.005
<i>RNA5S6</i>	4.762	< 0.001	0.005
<i>RNA5S8</i>	4.762	< 0.001	0.005
<i>RNA5S13</i>	4.762	< 0.001	0.005
<i>RNA5S7</i>	4.762	< 0.001	0.005
<i>RNA5S10</i>	4.762	< 0.001	0.005
<i>RNA5S9</i>	4.736	< 0.001	0.005
<i>RNA5S11</i>	4.762	< 0.001	0.005
<i>RNA5S17</i>	4.762	< 0.001	0.005
<i>EXO1</i>	6.374	< 0.001	< 0.001
<i>RASGRP3</i>	4.696	< 0.001	0.005
<i>EML6</i>	5.493	< 0.001	0.003
<i>ITGA6</i>	4.334	< 0.001	0.005
<i>TMEM198</i>	5.427	< 0.001	0.004
<i>SERPINE2</i>	-4.011	< 0.001	0.009
<i>SP140</i>	4.826	< 0.001	0.002
<i>RAMP1</i>	5.191	< 0.001	0.006
<i>CENPA</i>	5.367	< 0.001	0.003
<i>CDC42EP3</i>	5.704	< 0.001	< 0.001
<i>ANKRD36BP</i>			
2	5.174	< 0.001	0.001
<i>IL1B</i>	4.827	< 0.001	0.007
<i>TUBA4A</i>	4.224	< 0.001	0.002

Supplementary Table 7. Top 50 genes that are differentially expressed in pDCs of At-Risk individuals in comparison with pDCs from IFN^{high} SLE patients.

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
Anti-human CD3 clone BW264/56, VioBlue	Miltenyi Biotec	Cat# 130-094-363
Anti-human CD3 clone BW264/56, VioGreen	Miltenyi Biotec	Cat# 130-096-910
Anti-human CD4 clone M-T466, APC-Vio770	Miltenyi Biotec	Cat# 130-100-457
Anti-human CD19 clone LT19, VioBlue	Miltenyi Biotec	Cat# 130-098-598
Anti-human CD14 clone TÜK4, VioBlue	Miltenyi Biotec	Cat# 130-094-364
Anti-human CD56 clone B159, BV450	BD Biosciences	Cat# 560360
Anti-human CD11c clone MJ4-27G12, VioBlue	Miltenyi Biotec	Cat# 130-097-328
Anti-human HLA-DR clone AC122, APC-Vio770	Miltenyi Biotec	Cat# 130-104-200
Anti-human CD123 clone AC145, PerCP-Vio700	Miltenyi Biotec	Cat# 130-103-802
Anti-human CD303 (BDCA-2) clone AC144, FITC	Miltenyi Biotec	Cat# 130-090-510
Anti-human CD304 (BDCA-4) clone AD5-17F6, VioBright FITC	Miltenyi Biotec	Cat# 130-104-272
Anti-human CD85g clone REA100, PE-Vio770	Miltenyi Biotec	Cat# 130-099-009
Anti-human CD85j clone GHI/75, PE-Vio770	Miltenyi Biotec	Cat# 130-101-552
Anti-human CD69 clone FN50, FITC	Miltenyi Biotec	Cat# 130-092-166
Anti-human CD25 clone 4E3, PE	Miltenyi Biotec	Cat# 130-091-024
Anti-human CD317 clone RS38E, PE	BioLegend	Cat# 348406
Anti-human IFN- α clone LT27:295, APC	Miltenyi Biotec	Cat# 130-092-602
Anti-human TNF- α cA2, PE-Vio770	Miltenyi Biotec	Cat# 130-096-755
Anti-human IL-6 clone MQ2-13A5, PE	Miltenyi Biotec	Cat# 130-096-086
Anti-human IFN- γ clone 45-15, APC	Miltenyi Biotec	Cat# 130-091-640
Anti-human IL-10 clone JES3-9D7, PE	Miltenyi Biotec	Cat# 130-096-043
Anti-human TNF- α clone Mab11, APC/Cy7	BioLegend	Cat# 502944
Anti-human IFN- γ clone 4S.B3, PE/Cy7	BioLegend	Cat# 502528
Anti-human IL-17A clone BL168, APC	BioLegend	Cat# 512334
Anti-human TLR9 clone eB72-1665, APC	BD Biosciences	Cat# 560428
Anti-human TLR7 clone 533707, PE	R&D	Cat# IC5875P
Anti-human FoxP3 clone 3G3, APC	Miltenyi Biotec	Cat# 130-093-013
Human TNF alpha antibody clone 1825	R&D Systems	Cat# MAB210-SP
Anti-Mx1 rabbit polyclonal	Abcam	Cat# ab95926
Anti-BDCA-4 rabbit monoclonal	Abcam	Cat# ab81321

Anti-rabbit polyclonal biotin-conjugated secondary antibody	Sigma-Aldrich	Cat# SAB3700930
AffiniPure Donkey Anti-Rabbit IgG (H+L), PE	Jackson ImmunoResearch	Cat# 711-005-152
Chemicals, Peptides, and Recombinant Proteins		
ODN 2216	Miltenyi Biotec	Cat# 130-100-243
ORN R-2336	Miltenyi Biotec	Cat# 130-104-431
Human IL-3, premium grade	Miltenyi Biotec	Cat# 130-095-071
Human TNF- α , premium grade	Miltenyi Biotec	Cat# 130-094-014
Hydrogen peroxide solution [30% (w/w) in H ₂ O ₂]	Sigma-Aldrich	Cat# H1009
Prolong Gold Antifade Mountant	ThermoFischer Scientific	Cat# P36930
Poly(I:C) LMW	InvivoGen	Cat# 31852-29-6
Poly(dA:dT)	InvivoGen	Cat# 86828-69-5
TaqMan Universal PCR master Mix	ThermoFischer Scientific	Cat# 4304437
SYBR Green PCR Master Mix	ThermoFischer Scientific	Cat# 4309155
T cell activation/expansion kit	Miltenyi Biotec	Cat# 130-091-441
7-AAD Staining Solution	Miltenyi Biotec	Cat# 130-111-568
Annexin V-FTIC kit	Miltenyi Biotec	Cat# 130-092-052
DQ Ovalbumin	Molecular Probes	Cat# D-12053
Streptavidin peroxidase	Sigma-Aldrich	Cat# S2438
Critical Commercial Assays		
Diamond Plasmacytoid Dendritic Cell Isolation Kit II	Miltenyi Biotec	Cat# 130-097-240
Naive CD4 ⁺ T Cell Isolation Kit II	Miltenyi Biotec	Cat# 130-094-131
Intracellular Fixation & Permeabilization Buffer Set	eBioscience	Cat# 88-8824-00
FoxP3 Staining Buffer Set	Miltenyi Biotec	Cat# 130-093-142
CellTrace Violet Cell Proliferation Kit	ThermoFischer Scientific	Cat# C34571
Total RNA Purification Kit	Norgen Biotek	Cat# 17200
PicoPure RNA Isolation Kit	ThermoFischer Scientific	Cat# KIT0204

Qubit RNA HS Assay Kit	ThermoFisher Scientific	Cat# Q32852
SMART-Seq V4 ultra low Input RNA Kit	Takara Bio	Cat# 634888
Nextera XT DNA Library Preparation Kit	Illumina	Cat# FC-131-1024
Telomere PNA Kit/FITC for Flow Cytometry	Agilent	Cat# K532711-8
Superfrost plus slides	ThermoFisher Scientific	Cat# J1800AMNT
RNAscope Multiplex Fluorescent Reagent Kit v2	Advanced Cell Diagnostics	Cat# 323100
TSA Cy 3, Cy 5, TMR, Fluorescein Evaluation Kit	Perkin Elmer	Cat# NEL760001KT
RevertAid First Strand cDNA Synthesis Kit	ThermoFisher Scientific	Cat# K1622
QuantiFast SYBR Green PCR Kit	Qiagen	Cat# 204054
Quick-RNA MiniPrep Kit	Zymo Research	Cat# R1055A
Human IFN alpha Platinum ELISA	Invitrogen	Cat# BMS216
Experimental Models: Cell Lines		
Human: 1301 cell line	Sigma-Aldrich	Cat# 0105161
Oligonucleotides		
U6snRNA Primer: Forward 5'-CTCGCTTCGGCAGCACCA-3' Reverse 5'-AACGCTTCACGAATTTGC-3'	Sigma-Aldrich	N/A
IFNK Primer	Qiagen	Cat# QT00197512
IFNA Primer	Qiagen	Cat# QT00212527
IFNB1 Primer	Qiagen	Cat# QT00203763
IFNL1 Primer	Qiagen	Cat# QT00222495
Software and Algorithms		
Prism 7	Graphpad Software, Inc.	https://www.graphpad.com/
FACS DiVA	BD Biosciences	http://www.bdbiosciences.com/
CytExpert 2.0	Beckman Coulter	https://www.beckman.com/
Fluidigm Real Time PCR Analysis	Fluidigm	https://www.fluidigm.com/software
FastQC	BaseSpace Labs	https://www.illumina.com/

Cutadapt	Cutadapt	http://cutadapt.readthedocs.io/en/stable/index.html/
Table Browser	UCSC Genome Browser	https://genome.ucsc.edu/
QualiMap 2.0	QualiMap	http://qualimap.bioinfo.cipf.es/
Picard tools	Broad Institute	https://broadinstitute.github.io/picard/
ReactomePA	Bioconductor	https://www.bioconductor.org/
KEGG	Kyoto University	https://www.genome.jp/kegg/
Nikon NIS Elements	Nikon Instruments	https://www.nikoninstruments.com/
Other		
50mL Leucosep Tubes	Greiner Bio-One	Cat# 89048-938

Supplementary Table 8. Key resources.