

Supplementary Materials for

Differentiated fibrocytes assume a functional mesenchymal phenotype with regenerative potential

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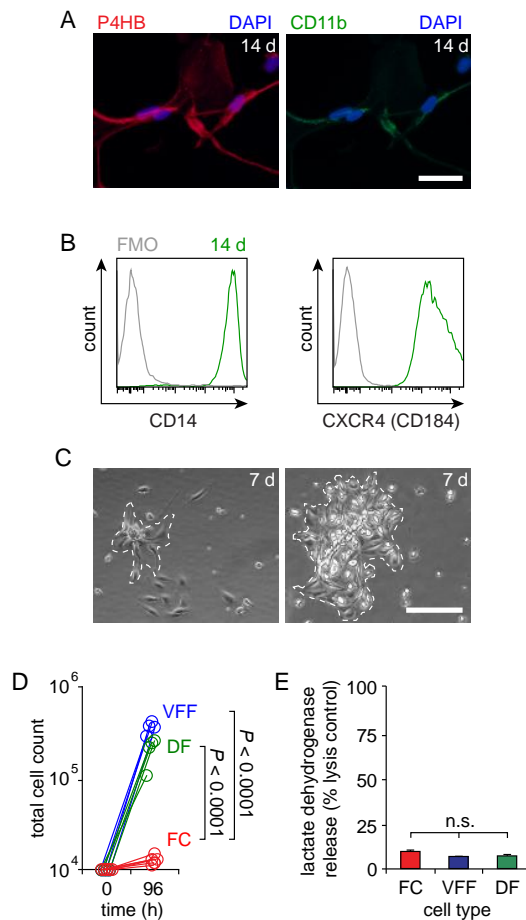


Fig. S1. Additional characterization of human FC differentiation *in vitro*. (A) P4HB and CD11b immunostaining patterns at 14 d. Scale bar, 50 μ m. (B) CD14 and CXCR4 (CD184) expression at 14 d. FMO controls are shown in gray. (C) Phase-contrast images of FC colonies at 7 d. The left image shows a typically sized 10–20 cell colony; the right image shows a rarely observed ~100 cell colony. White dashed lines indicate the boundary of each colony. Scale bar, 100 μ m. (D) Cell count data showing FC proliferation over 96 h, compared to DF and VFF. *P* values were calculated using ANOVA (*n* = 4–6 per condition). (E) Lactate dehydrogenase release by FCs, DFs, and VFFs. Data are shown as mean \pm s.e.m. Statistical testing was performed using ANOVA (*n* = 4 per condition).

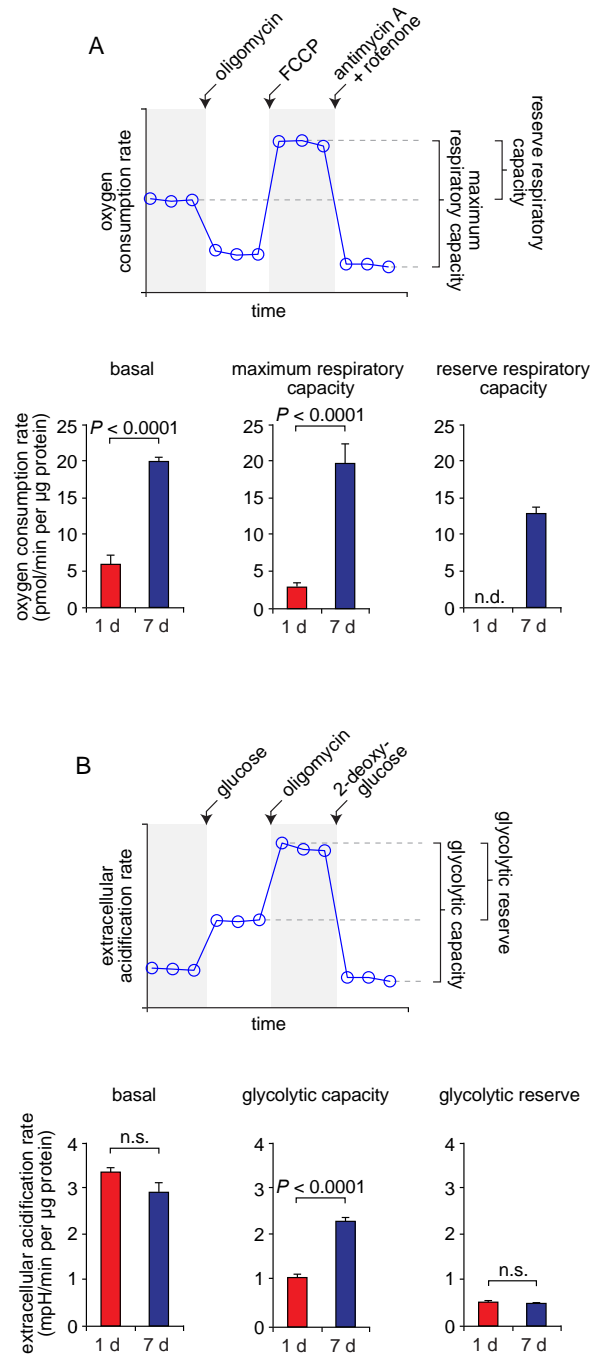


Fig. S2. Bioenergetic profiles of human FCs at 1 and 7 days. (A) Analysis of mitochondrial respiration. The time-course schematic illustrates the calculation of maximum and reserve respiratory capacities from changes in real-time oxygen consumption rate. Data in the bar graphs (derived from the real-time plots in Fig. 2H) are shown as mean \pm s.e.m. P values were calculated using a Student's t test ($n = 10$ per condition). (B) Analysis of glycolysis. The time-course schematic illustrates the calculation of glycolytic capacity and reserve from changes in real-time extracellular acidification rate. Data in the bar graphs (derived from the real-time plots in Fig. 2I) are shown as mean \pm s.e.m. P values were calculated using a Student's t test ($n = 4$ per condition).

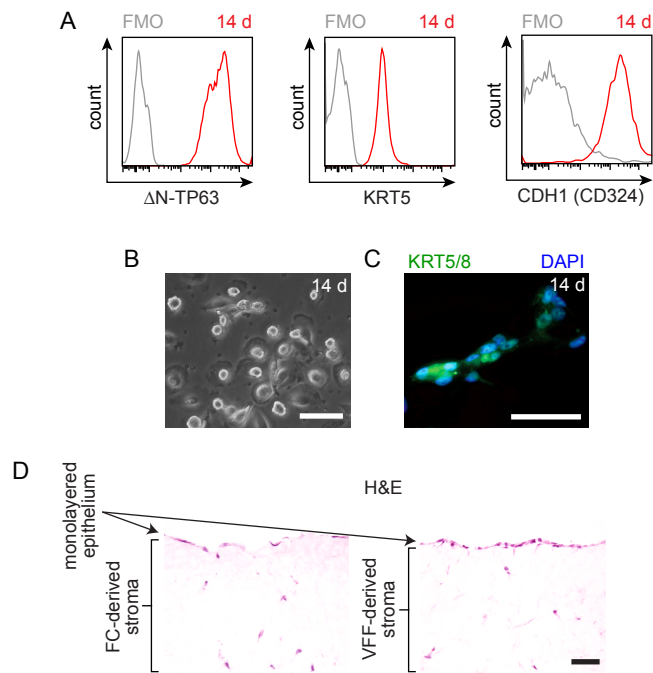


Fig. S3. Characterization of monocytes following epithelial cell-oriented culture. (A) Δ N-TP63, KRT5, and CDH1 (CD324) expression at 14 d. FMO controls are shown in gray. (B) Phase-contrast image showing cell morphology at 14 d. Scale bar, 50 μ m. (C) KRT5/8 immunostaining pattern in a cellular chain at 14 d. Scale bar, 50 μ m. (D) H&E-stained sections showing morphology of engineered tissues generated using monocyte-derived epithelial cells and either FCs or VFFs as the stromal cell source. Scale bar, 50 μ m.

Table S1. Reactome pathways enriched in protein sets associated with FC differentiation. Pathways were identified using the Enrichr algorithm based on a Benjamini Hochberg-adjusted *P* value < 0.01 and minimum of 4 protein identifications per pathway. Pathways are listed in order of ascending adjusted *P* value; significant pathways associated with the initial 7 d differentiation period are also presented in Fig. 2G.

Reactome pathway	Description	Proteins	Adjusted <i>P</i> value
<u>Proteins with increased abundance at 1 d compared to 7 d</u>			
<i>No significantly enriched pathways</i>			
<u>Proteins with increased abundance at 1 d compared to 14 d</u>			
R-HSA-109582	Hemostasis	SERPINB2; ITGA2B; F13A1; HBB; PPBP; HBD	7.93E-03
<u>Proteins with increased abundance at 7 d compared to 1 d</u>			
R-HSA-1430728	Metabolism	POR; ASAH1; NCEH1; ACSL1; GAA; ALDH1A1; EPHX1; ACP5; MAN2B1; FBP1	9.95E-04
R-HSA-71387	Metabolism of carbohydrates	GAA; ALDH1A1; MAN2B1; FBP1	3.54E-03
<u>Proteins with increased abundance at 7 d compared to 14 d</u>			
<i>No significantly enriched pathways</i>			
<u>Proteins with increased abundance at 14 d compared to 1 d</u>			
R-HSA-1430728	Metabolism	GSTM4; ASAH1; GAA; EPHX1; ALDH3A2; GRHPR; PC; NCEH1; SCP2; ALDH1A1; APOE; MGLL; PCK2	3.08E-03
<u>Proteins with increased abundance at 14 d compared to 7 d</u>			
<i>No significantly enriched pathways</i>			

Table S2. Reactome pathways enriched in the protein set overrepresented in VFFs, DFs, and MSCs compared to FCs. Pathways were identified using the Enrichr algorithm based on a Benjamini Hochberg-adjusted *P* value < 0.01 and minimum of 4 protein identifications per pathway. Pathways are listed in order of ascending adjusted *P* value; the top three pathways are also presented in Fig. 3C.

Reactome pathway	Description	Proteins	Adjusted <i>P</i> value
R-HSA-1650814	Collagen biosynthesis and modifying enzymes	CRTAP; COL12A1; PLOD2; PLOD1; COL1A1; COL3A1; COL1A2; P4HA1; COL5A1; P4HA2; COL6A2; COL6A1; SERPINH1; COL6A3	1.87E-11
R-HSA-1474244	Extracellular matrix organization	ITGB1; CRTAP; SPARC; ITGA3; LAMB2; COL12A1; PRKCA; PLOD2; LAMB1; PLOD1; LAMC1; COL1A1; COL3A1; COL1A2; P4HA1; COL5A1; P4HA2; COL6A2; COL6A1; SERPINH1; COL6A3; ITGAV; ITGA5	3.03E-10
R-HSA-1474290	Collagen formation	CRTAP; COL12A1; PLOD2; PLOD1; COL1A1; COL3A1; COL1A2; P4HA1; COL5A1; P4HA2; COL6A2; COL6A1; SERPINH1; COL6A3	5.00E-10
R-HSA-176974	Unwinding of DNA	MCM7; MCM3; MCM4; MCM5; MCM6; MCM2	5.15E-07
R-HSA-68962	Activation of the pre-replicative complex	MCM7; CDK2; MCM3; MCM4; MCM5; MCM6; MCM2	9.05E-06
R-HSA-69190	DNA strand elongation	PCNA; MCM7; MCM3; MCM4; MCM5; MCM6; MCM2	1.22E-05
R-HSA-176187	Activation of ATR in response to replication stress	MCM7; CDK2; MCM3; MCM4; MCM5; MCM6; MCM2	2.66E-05
R-HSA-3000157	Laminin interactions	ITGB1; ITGA3; LAMB2; LAMB1; ITGAV; LAMC1	2.66E-05
R-HSA-422475	Axon guidance	ITGB1; PDGFRB; CAMK2D; LAMB1; AP2B1; LAMC1; RHOC; ENAH; ALCAM; PSME3; COL6A2; DPYSL3; COL6A1; COL6A3; ITGAV; ITGA5; MYL9; SPTAN1; MYH10; SPTBN1; VCL; PFN2	3.31E-05
R-HSA-69206	G1/S transition	PCNA; MCM7; PSME3; CDK2; MCM3; MCM4; MCM5; MCM6; SKP1; MCM2	8.85E-05
R-HSA-1640170	Cell cycle	PPP1R12A; PCNA; MCM7; NUMA1; PRKCA; LEMD3; RANGAP1; SMC2; NUP93; PSME3; RUVBL2; CDK2; MCM3; MCM4; NCAPD2; MCM5; RBBP7; MCM6; TP53BP1; EMD; MCM2; SKP1	1.27E-04
R-HSA-68949	Orc1 removal from chromatin	MCM7; PSME3; CDK2; MCM3; MCM4; MCM5; MCM6; MCM2	1.27E-04
R-HSA-69052	Switching of origins to a post-replicative state	MCM7; PSME3; CDK2; MCM3; MCM4; MCM5; MCM6; MCM2	1.27E-04
R-HSA-69239	Synthesis of DNA	PCNA; MCM7; PSME3; CDK2; MCM3; MCM4; MCM5; MCM6; MCM2	1.32E-04
R-HSA-69300	Removal of licensing factors from origins	MCM7; PSME3; CDK2; MCM3; MCM4; MCM5; MCM6; MCM2	1.32E-04
R-HSA-69242	S Phase	PCNA; MCM7; PSME3; CDK2; MCM3; MCM4; MCM5; MCM6; SKP1; MCM2	1.32E-04
R-HSA-373760	L1CAM interactions	ITGB1; ALCAM; LAMB1; ITGAV; ITGA5; LAMC1; AP2B1; SPTAN1; SPTBN1	1.32E-04
R-HSA-69304	Regulation of DNA replication	MCM7; PSME3; CDK2; MCM3; MCM4; MCM5; MCM6; MCM2	1.55E-04
R-HSA-2022090	Assembly of collagen fibrils and other multimeric structures	COL1A1; COL3A1; COL1A2; COL5A1; COL6A2; COL6A1; COL6A3	1.62E-04
R-HSA-69278	Cell cycle, mitotic	PPP1R12A; PCNA; MCM7; NUMA1; PRKCA; LEMD3; RANGAP1; SMC2; NUP93; PSME3; CDK2; MCM3; MCM4; NCAPD2; MCM5; MCM6; EMD; MCM2; SKP1	1.64E-04
R-HSA-5627123	RHO GTPases activate PAKs	PPP1R12A; CTTN; MYH10; MYL9; MYLK	1.64E-04
R-HSA-69306	DNA replication	PCNA; MCM7; PSME3; CDK2; MCM3; MCM4; MCM5; MCM6; MCM2	1.95E-04
R-HSA-68874	M/G1 transition	MCM7; PSME3; CDK2; MCM3; MCM4; MCM5; MCM6; MCM2	2.19E-04
R-HSA-69002	DNA replication pre-initiation	MCM7; PSME3; CDK2; MCM3; MCM4; MCM5; MCM6; MCM2	2.19E-04
R-HSA-453279	Mitotic G1-G1/S phases	PCNA; MCM7; PSME3; CDK2; MCM3; MCM4; MCM5; MCM6; SKP1; MCM2	2.19E-04
R-HSA-3000171	Non-integrin membrane-ECM interactions	ITGB1; LAMB2; LAMB1; PRKCA; ITGAV; LAMC1	3.31E-04
R-HSA-1266738	Developmental biology	ITGB1; CAMK2D; LAMC1; ALCAM; DPYSL3; CTNNA1; ITGAV; RBBP7; SPTAN1; MYH10; SPTBN1; PDGFRB; LAMB1; AP2B1; RHOC; ENAH; PSME3; COL6A2; COL6A1; CTNNA1; COL6A3; ITGA5; MYL9; VCL; PFN2	3.56E-04
R-HSA-68867	Assembly of the pre-replicative complex	MCM7; PSME3; MCM3; MCM4; MCM5; MCM6; MCM2	4.70E-04
R-HSA-445355	Smooth muscle contraction	CALD1; TPM1; MYL9; VCL; MYLK	1.19E-03
R-HSA-5627117	RHO GTPases activate ROCKs	PPP1R12A; RHOC; MYH10; MYL9	1.19E-03
R-HSA-3000178	ECM proteoglycans	ITGB1; SPARC; LAMB2; LAMB1; ITGAV; LAMC1	1.35E-03

R-HSA-195258	RHO GTPase effectors	ITGB1; PPP1R12A; KLC2; CTTN; CTNNA1; CTNNB1; RHOC; RANGAP1; MYL9; MYH10; PFN2; MYLK	1.77E-03
R-HSA-69481	G2/M checkpoints	MCM7; PSME3; CDK2; MCM3; MCM4; MCM5; TP53BP1; MCM6; MCM2	2.23E-03
R-HSA-5250913	Positive epigenetic regulation of rRNA expression	MYO1C; POLR1C; DDX21; CHD4; DEK; RBBP7	6.00E-03
R-HSA-389957	Prefoldin mediated transfer of substrate to CCT/TriC	TUBB6; TUBB2A; TUBB3; PFDN1	6.65E-03
R-HSA-75153	Apoptotic execution phase	TJP1; CTNNB1; SPTAN1; ADD1; HIST1H1C	8.19E-03
R-HSA-69620	Cell cycle checkpoints	MCM7; PSME3; CDK2; MCM3; MCM4; MCM5; TP53BP1; MCM6; MCM2	8.48E-03

Table S3. Reactome pathways enriched in the protein set overrepresented in FCs compared to VFFs, DFs, and MSCs. Pathways were identified using the Enrichr algorithm based on a Benjamini Hochberg-adjusted *P* value < 0.01 and minimum of 4 protein identifications per pathway. Pathways are listed in order of ascending adjusted *P* value; the top three pathways are also presented in Fig. 3C.

Reactome pathway	Description	Proteins	Adjusted <i>P</i> value
R-HSA-1430728	Metabolism	SLC25A1; CDA; ARF1; ADPGK; HEXB; HEXA; ATP5C1; HBB; AKR1B1; PYGL; SQRDL; HNMT; CNRP2; HK3; IL4I1; CPT2; GM2A; ALDH2; CA2; KYNU; BSG; NAMPT; ME1; ACP5; CYP1B1; CD36; GUSB; GSTK1; G6PD; GPX1; GPX4; GSTO1; ACSL1; GAA; MCCC1; AKR1A1; ACOT13; TALDO1; PGD; ASRGL1; CYP27A1; ALDH3A2; POR; ALDH1A1; PSME1; PLBD1; BLVRB; PLIN2; FBP1; FBP2; PI4K2A; MGLL; BLVRA; CES1; PDXK; ASAH1; MGST3; HSD17B4; GLRX; HSD17B11; UQCRH; PSMB10; PLD3; GNAI2; TYMP; SULT1A1; CYB5R1; ALOX5; INPP5D; PSAP; PGK1; PLCG2; LTA4H; APOE; CYB5A; PDHA1; GK; PTGES3; IDH1; GSR; IDH2; EPHX1; AKR1C3; FAH; PSMB8; DERA; GCLC; PC; FABP5; GLB1; TBXAS1; PPT1; MAN2B1; GLA	2.66E-26
R-HSA-1222556	ROS, RNS production in response to bacteria	ATP6V1A; ATP6V1G1; NCF1; NCF2; NCF4; CYBB; CYBA; TCIRG1; ATP6V1B2; ATP6V1H; ATP6V1E1; ATP6V0C; ATP6V0D2; ATP6V1D; ATP6V1C1; ATP6V0A1	6.71E-19
R-HSA-168256	Immune system	CYFIP1; ARF1; ITGAM; NCF1; NCF2; ARPC1B; ITGB2; NCF4; PEBP1; ARRB1; TCIRG1; ITGAL; IFI30; AP2A2; CTSS; PYCARD; LGALS3; CASP1; CTSH; LGALS9; CD36; ATP6V1E1; CTSD; B2M; CTSB; ACTR3; ATP6V1G1; FCER1G; SYK; PRKCD; AP1B1; HLA-B; CYBB; IL16; CYBA; HLA-A; FGR; HCK; TYROBP; ATP6V1B2; PSME1; ELMO2; EVL; ATP6V0D2; ATP6V0C; RAB7A; ATP6V1A; WAS; SAMHD1; PSMB10; PLD3; HLA-DMB; INPP5D; PLCG2; ATP6V1H; NCKAP1L; CD14; ATG7; ATP6V1D; ATP6V1C1; ATP6V0A1; LYN; CD74; HLA-DRB4; LILRB2; PSMB8; PTPRC; ARPC2; HLA-DPB1; HLA-DRA; PTPN6; HLA-DRB1	4.61E-18
R-HSA-917937	Iron uptake and transport	ATP6V1A; ATP6V1G1; STEAP3; TCIRG1; FTH1; ATP6V1B2; ATP6V1H; ATP6V1E1; ATP6V0C; ATP6V0D2; ATP6V1D; ATP6V1C1; FTL; ATP6V0A1	5.94E-14
R-HSA-917977	Transferrin endocytosis and recycling	ATP6V1A; ATP6V1G1; STEAP3; ATP6V1B2; ATP6V1H; TCIRG1; ATP6V1E1; ATP6V0C; ATP6V0D2; ATP6V1D; ATP6V1C1; ATP6V0A1	2.06E-13
R-HSA-109582	Hemostasis	CD84; ITGAM; ITGB2; PLEK; GNAI3; HBB; ARRB1; PRCP; ITGAL; GNAI2; ABHD12; CYB5R1; INPP5D; PSAP; BSG; PLCG2; ITGAX; RAC2; SIRPA; CD36; LYN; CAP1; CD74; SERPINB2; FCER1G; SYK; PRKCD; RHOG; FGR; P2RX4; PECAM1; CD9; PTPN6; PFN1; DOCK2; MGLL	1.28E-12
R-HSA-77387	Insulin receptor recycling	ATP6V1A; ATP6V1G1; ATP6V1B2; ATP6V1H; TCIRG1; ATP6V1E1; ATP6V0C; ATP6V0D2; ATP6V1D; ATP6V1C1; ATP6V0A1	1.67E-12
R-HSA-556833	Metabolism of lipids and lipoproteins	SLC25A1; ASAH1; ARF1; HEXB; HEXA; AKR1B1; HSD17B4; HSD17B11; PLD3; GM2A; CPT2; ALOX5; INPP5D; PSAP; ME1; CYP1B1; LTA4H; APOE; CD36; GPX1; GK; GPX4; ACSL1; PTGES3; IDH1; AKR1C3; ACOT13; CYP27A1; ALDH3A2; FABP5; GLB1; TBXAS1; PPT1; PLBD1; PLIN2; GLA; PI4K2A; MGLL	8.15E-12
R-HSA-1280218	Adaptive immune system	ARF1; NCF1; NCF2; NCF4; ITGB2; WAS; ITGAL; IFI30; AP2A2; PSMB10; CTSS; HLA-DMB; INPP5D; PLCG2; CTSH; CD36; ATG7; B2M; CTSD; CTSB; LYN; CD74; HLA-DRB4; SYK; AP1B1; HLA-B; CYBB; CYBA; HLA-A; LILRB2; PSMB8; PTPRC; TYROBP; PSME1; HLA-DPB1; HLA-DRA; PTPN6; EVL; HLA-DRB1; RAB7A	3.17E-11
R-HSA-2132295	MHC class II antigen presentation	CD74; ARF1; HLA-DRB4; AP1B1; IFI30; AP2A2; CTSS; HLA-DMB; HLA-DPB1; HLA-DRA; CTSH; CTSD; HLA-DRB1; CTSB; RAB7A	7.87E-10
R-HSA-76002	Platelet activation, signaling and aggregation	LYN; CAP1; FCER1G; SYK; PRKCD; PLEK; RHOG; GNAI3; ARRB1; GNAI2; ABHD12; CYB5R1; PSAP; PLCG2; RAC2; PECAM1; CD9; PTPN6; CD36; PFN1; MGLL	3.59E-09
R-HSA-1236975	Antigen processing-cross presentation	NCF1; NCF2; NCF4; HLA-B; CYBB; CYBA; HLA-A; CTSS; PSMB10; PSMB8; PSME1; CD36; B2M	5.16E-09
R-HSA-1236973	Cross-presentation of particulate exogenous antigens (phagosomes)	NCF1; NCF2; NCF4; CYBB; CYBA; CD36	8.39E-09
R-HSA-71387	Metabolism of carbohydrates	SLC25A1; G6PD; ADPGK; GAA; HEXB; HEXA; AKR1A1; TALDO1; AKR1B1; PYGL; PGD; DERA; HK3; PC; GLB1; ALDH1A1; PGK1; MAN2B1; GUSB; FBP1; FBP2	2.10E-08
R-HSA-2029480	Fc gamma receptor (FCGR) dependent phagocytosis	ACTR3; LYN; CYFIP1; SYK; ARPC1B; PRKCD; WAS; PLD3; FGR; HCK; ARPC2; PLCG2; ELMO2; NCKAP1L	5.19E-08
R-HSA-202733	Cell surface interactions at the vascular wall	LYN; CD74; CD84; FCER1G; ITGAM; ITGB2; ITGAL; INPP5D; BSG; PECAM1; ITGAX; SIRPA; PTPN6	5.59E-08

R-HSA-164952	The role of Nef in HIV-1 replication and disease pathogenesis	HCK; ARF1; AP1B1; ATP6V1H; HLA-A; DOCK2; AP2A2; B2M	1.06E-07
R-HSA-5668599	RHO GTPases activate NADPH oxidases	NCF1; NCF2; NCF4; RAC2; CYBB; CYBA	3.50E-07
R-HSA-3299685	Detoxification of reactive oxygen species	PRDX3; GPX1; TXNRD2; PRDX1; GSR; CYBB; CYBA; SOD2	4.00E-07
R-HSA-168249	Innate immune system	CYFIP1; ITGAM; ARPC1B; ITGB2; WAS; PEBP1; ARRB1; PSMB10; CTSS; PLD3; PYCARD; LGALS3; PLCG2; CASP1; NCKAP1L; CD14; CD36; B2M; CTSB; LYN; ACTR3; FCER1G; SYK; PRKCD; HLA-B; PSMB8; FGR; HCK; TYROBP; ARPC2; PSME1; ELMO2	3.18E-06
R-HSA-195258	RHO GTPase effectors	ACTR3; CYFIP1; NCF1; NCF2; ARPC1B; NCF4; RHOG; WAS; CYBB; CYBA; IQGAP2; FMNL1; ARPC2; RAC2; NCKAP1L; EVL; PFN1	3.27E-06
R-HSA-211859	Biological oxidations	GSTK1; GSTO1; MGST3; EPHX1; AKR1A1; CNDP2; CYP27A1; SULT1A1; POR; GCLC; ALDH2; TBXAS1; ALDH1A1; CYP1B1; CES1	3.59E-06
R-HSA-164938	Nef-mediate down modulation of cell surface receptors by recruiting them to clathrin adaptors	ARF1; AP1B1; ATP6V1H; HLA-A; AP2A2; B2M	7.89E-06
R-HSA-2142753	Arachidonic acid metabolism	GPX1; GPX4; PTGES3; ALOX5; TBXAS1; AKR1C3; CYP1B1; LTA4H	1.58E-05
R-HSA-877300	Interferon gamma signaling	HLA-DRB4; PRKCD; HLA-B; HLA-DPB1; HLA-DRA; PTPN6; HLA-A; IFI30; B2M; HLA-DRB1	1.58E-05
R-HSA-202403	TCR signaling	HLA-DRB4; PTPRC; INPP5D; PSME1; HLA-DPB1; WAS; HLA-DRA; EVL; PSMB10; HLA-DRB1; PSMB8	1.80E-05
R-HSA-194315	Signaling by Rho GTPases	ACTR3; CYFIP1; NCF1; NCF2; ARPC1B; NCF4; RHOG; WAS; CYBB; CYBA; GMIP; IQGAP2; FMNL1; ARPC2; ARHGDI1; RAC2; NCKAP1L; EVL; PFN1	2.28E-05
R-HSA-1660662	Glycosphingolipid metabolism	ASAH1; GM2A; GLB1; HEXB; HEXA; PSAP; GLA	2.91E-05
R-HSA-70326	Glucose metabolism	SLC25A1; HK3; PC; ADPGK; GAA; PGK1; PYGL; FBP1; FBP2	3.04E-05
R-HSA-162909	Host Interactions of HIV factors	HCK; ARF1; AP1B1; PSME1; ATP6V1H; HLA-A; DOCK2; B2M; AP2A2; PSMB10; PSMB8	3.78E-05
R-HSA-71336	Pentose phosphate pathway (hexose monophosphate shunt)	G6PD; TALDO1; PGD; DERA	8.14E-05
R-HSA-199992	Trans-golgi network vesicle budding	VAMP8; ARF1; FTH1; AP1B1; M6PR; DNASE2; ARRB1; FTL	1.00E-04
R-HSA-421837	Clathrin derived vesicle budding	VAMP8; ARF1; FTH1; AP1B1; M6PR; DNASE2; ARRB1; FTL	1.00E-04
R-HSA-5621480	Dectin-2 family	LYN; FCER1G; SYK; PLCG2	1.22E-04
R-HSA-74752	Signaling by insulin receptor	ATP6V1A; ATP6V1G1; PEBP1; ARRB1; TCIRG1; PSMB10; PSMB8; PSME1; ATP6V1B2; ATP6V1H; ATP6V1E1; ATP6V0D2; ATP6V0C; ATP6V1D; ATP6V1C1; ATP6V0A1	1.28E-04
R-HSA-432720	Lysosome vesicle biogenesis	VAMP8; ARF1; AP1B1; M6PR; DNASE2; ARRB1	1.28E-04
R-HSA-202433	Generation of second messenger molecules	HLA-DRB4; HLA-DPB1; WAS; HLA-DRA; EVL; HLA-DRB1	1.28E-04
R-HSA-114604	GPVI-mediated activation cascade	LYN; FCER1G; SYK; RHOG; RAC2; PLCG2; PTPN6	1.28E-04
R-HSA-428157	Sphingolipid metabolism	ALDH3A2; ASAH1; GM2A; GLB1; HEXB; PSAP; HEXA; GLA	1.29E-04
R-HSA-5663213	RHO GTPases activate WASPs and WAVEs	ACTR3; CYFIP1; ARPC2; ARPC1B; WAS; NCKAP1L	1.37E-04
R-HSA-156590	Glutathione conjugation	GSTK1; GCLC; GSTO1; MGST3; AKR1A1; CNDP2	1.85E-04
R-HSA-210990	PECAM1 interactions	LYN; INPP5D; PECAM1; PTPN6	2.23E-04
R-HSA-1236977	Endosomal/vacuolar pathway	HLA-B; HLA-A; B2M; CTSS	2.23E-04
R-HSA-202427	Phosphorylation of CD3 and TCR zeta chains	PTPRC; HLA-DRB4; HLA-DPB1; HLA-DRA; HLA-DRB1	2.26E-04
R-HSA-913531	Interferon signaling	HLA-DRB4; PRKCD; HLA-B; HLA-DPB1; HLA-DRA; PTPN6; HLA-A; IFI30; SAMHD1; B2M; HLA-DRB1; PSMB8	2.66E-04
R-HSA-1280215	Cytokine signaling in immune system	LYN; HLA-DRB4; SYK; PRKCD; HLA-B; PEBP1; ARRB1; IL16; HLA-A; IFI30; SAMHD1; PSMB8; PSMB10; HCK; INPP5D; PSME1; HLA-DPB1; CASP1; HLA-DRA; PTPN6; LGALS9; B2M; HLA-DRB1	2.69E-04

R-HSA-389948	PD-1 signaling	HLA-DRB4; HLA-DPB1; HLA-DRA; PTPN6; HLA-DRB1	3.20E-04
R-HSA-211945	Phase 1 - functionalization of compounds	CYP27A1; POR; ALDH2; EPHX1; ALDH1A1; TBXAS1; CYP1B1; CES1	5.22E-04
R-HSA-5621481	C-type lectin receptors (CLRs)	PYCARD; LYN; FCER1G; SYK; PRKCD; PSME1; PLCG2; PSMB10; PSMB8	6.60E-04
R-HSA-2029482	Regulation of actin dynamics for phagocytic cup formation	ACTR3; CYFIP1; ARPC2; SYK; ARPC1B; WAS; ELMO2; NCKAP1L	7.18E-04
R-HSA-202424	Downstream TCR signaling	HLA-DRB4; INPP5D; PSME1; HLA-DPB1; HLA-DRA; PSMB10; HLA-DRB1; PSMB8	8.12E-04
R-HSA-70263	Gluconeogenesis	SLC25A1; PC; PGK1; FBP1; FBP2	8.12E-04
R-HSA-2173782	Binding and uptake of ligands by scavenger receptors	CD163; FTH1; STAB1; HBB; CD36; APOE; FTL	8.17E-04
R-HSA-432722	Golgi associated vesicle biogenesis	VAMP8; ARF1; FTH1; AP1B1; ARRB1; FTL	1.07E-03
R-HSA-983169	Class I MHC mediated antigen processing & presentation	NCF1; NCF2; NCF4; HLA-B; CYBB; CYBA; HLA-A; PSMB10; CTSS; PSMB8; PSME1; CD36; B2M; ATG7	1.07E-03
R-HSA-114608	Platelet degranulation	CAP1; CYB5R1; PSAP; PLEK; PECAM1; CD9; CD36; PFN1	1.13E-03
R-HSA-983712	Ion channel transport	ATP6V1A; ATP6V1G1; ATP6V1B2; ATP6V1H; TCIRG1; ATP6V1E1; ATP6V0D2; ATP6V0C; ATP6V1D; ATP6V1C1; ATP6V0A1	1.36E-03
R-HSA-76005	Response to elevated platelet cytosolic Ca ²⁺	CAP1; CYB5R1; PSAP; PLEK; PECAM1; CD9; CD36; PFN1	1.51E-03
R-HSA-4420097	VEGFA-VEGFR2 pathway	CYFIP1; NCF1; NCF2; PRKCD; NCF4; PEBP1; CYBB; CYBA; ARRB1; PSMB10; PSMB8; PSME1; ELMO2; NCKAP1L	1.65E-03
R-HSA-202430	Translocation of ZAP-70 to immunological synapse	HLA-DRB4; HLA-DPB1; HLA-DRA; HLA-DRB1	1.72E-03
R-HSA-194138	Signaling by VEGF	CYFIP1; NCF1; NCF2; PRKCD; NCF4; PEBP1; CYBB; CYBA; ARRB1; PSMB10; PSMB8; PSME1; ELMO2; NCKAP1L	2.02E-03
R-HSA-196854	Metabolism of vitamins and cofactors	CYB5A; PDXK; PC; GSTO1; MCCC1; NAMPT; AKR1C3; ACP5; APOE	2.12E-03
R-HSA-6788656	Histidine, lysine, phenylalanine, tyrosine, proline and tryptophan catabolism	IL4I1; KYNU; FAH; HNMT; ASRGL1	2.22E-03
R-HSA-162582	Signal transduction	VPS29; CYFIP1; NCF1; NCF2; ARPC1B; NCF4; PEBP1; ARRB1; TCIRG1; AP2A2; ABHD12; HEBP1; ARHGDI1; RAC2; ATP6V1E1; ACTR3; ATP6V1G1; SYK; PRKCD; RHOG; ADAM10; CYBB; CYBA; GMIP; ALDH1A1; ATP6V1B2; PSME1; ELMO2; EVL; PFN1; ATP6V0D2; ATP6V0C; MGLL; ATP6V1A; GNAI3; WAS; IQGAP2; PSMB10; GNAI2; GPNMB; PSAP; ATP6V1H; NCKAP1L; APOE; ATP6V1D; ATP6V1C1; ATP6V0A1; LYN; PDHA1; AKR1C3; PSMB8; FMNL1; ARPC2; FABP5; PTPN6	2.30E-03
R-HSA-71291	Metabolism of amino acids and derivatives	PDHA1; MCCC1; GSR; SQRDL; FAH; HNMT; ASRGL1; PSMB10; PSMB8; CNDP2; IL4I1; GCLC; KYNU; PSME1	2.36E-03
R-HSA-1236974	ER-phagosome pathway	HLA-B; PSME1; HLA-A; B2M; PSMB10; PSMB8	2.43E-03
R-HSA-162906	HIV infection	HCK; ARF1; AP1B1; PSME1; ATP6V1H; HLA-A; DOCK2; B2M; AP2A2; PSMB10; PSMB8	2.45E-03
R-HSA-216083	Integrin cell surface interactions	ITGAM; BSG; ITGB2; PECAM1; ITGAX; ITGAL	2.75E-03
R-HSA-422475	Axon guidance	LYN; ACTR3; CAP1; ARPC1B; RHOG; ADAM10; PEBP1; ARRB1; AP2A2; PSMB8; PSMB10; PTPRC; TYROBP; ARPC2; PSME1; RAC2; EVL; PFN1	2.80E-03
R-HSA-196849	Metabolism of water-soluble vitamins and cofactors	CYB5A; PDXK; PC; GSTO1; MCCC1; NAMPT; ACP5	3.45E-03
R-HSA-5607764	CLEC7A (Dectin-1) signaling	PYCARD; SYK; PRKCD; PSME1; PLCG2; PSMB10; PSMB8	3.62E-03
R-HSA-109581	Apoptosis	BCAP31; GSN; PRKCD; PSME1; DSG1; CD14; BID; PSMB10; PSMB8	3.64E-03
R-HSA-156580	Phase II conjugation	SULT1A1; GSTK1; GCLC; GSTO1; MGST3; AKR1A1; CNDP2	3.70E-03
R-HSA-388841	Costimulation by the CD28 family	LYN; HLA-DRB4; HLA-DPB1; HLA-DRA; PTPN6; HLA-DRB1	3.70E-03
R-HSA-5357801	Programmed cell death	BCAP31; GSN; PRKCD; PSME1; DSG1; CD14; BID; PSMB10; PSMB8	3.81E-03

Table S4. Cytokine production by FCs and VFFs, cultured under basal conditions for 24 hours. Raw concentrations (pg/mL) are shown as a single value per cytokine, assayed using pooled culture supernatant ($n = 6$ per condition) and a multiplexed protein array. Serum-free medium was used as a negative control. Log₂-transformed fold change data (FC versus VFF) are presented in Fig. 5C.

Cell population	IL5	IL2	IFNG	IL4	IL13	IL6	CSF2	IL10	TNF	CXCL8
FC	0.3	17.4	22.7	1.6	3.4	12.6	2.0	7.8	24.0	77.5
VFF	n.d. ^a	15.1	18.0	1.0	2.0	4.8	0.7	2.7	8.0	0.4
Serum-free medium (no cells)	n.d. ^a	13.4	14.5	1.0	2.2	1.1	1.9	4.4	14.3	0.2

^a n.d., not detected.

Table S5. Antibodies and isotype controls used for flow cytometry.

Item	Clone	Fluorochrome	Dilution	Manufacturer	Catalog number
<i>Primary antibodies</i>					
rabbit anti-human prolyl-4-hydroxylase β	polyclonal	FITC	1:50	Bioss	bs-5090R-FITC
rabbit anti-human prolyl-4-hydroxylase β	polyclonal	PE	1:50	Bioss	bs-5090R-PE
mouse anti-human E-cadherin (CD324)	67A4	PerCP	1:5	Santa Cruz Biotechnology	sc-21791 PerCP
mouse anti-human CD11b	ICRF44	Alexa 488	1:20	BD Biosciences	557701
mouse anti-human CD11b	ICRF44	Alexa 700	1:20	BD Biosciences	557918
mouse anti-human CD11b	ICRF44	APC	1:20	BD Biosciences	550019
mouse anti-human CD14	M5E2	PE-Cy7	1:20	BD Biosciences	557742
mouse anti-human CXCR4 (CD184)	12G5	PE	1:100	Santa Cruz Biotechnology	sc-12764 PE
mouse anti-human CD16	LNK16	FITC	1:20	Santa Cruz Biotechnology	sc-51524 FITC
mouse anti-human CD16	3G8	FITC	1:5	BD Bioscience	555406
mouse anti-human CD29	MAR4	PE-Cy5	1:5	BD Biosciences	559882
mouse anti-human CD105	SN6	PE	1:50	eBioscience	12-1057-41
mouse anti-human CD34	8G12	PE-Cy7	1:20	BD Biosciences	348791
mouse anti-human keratin 5	XM26	none	1:20	Santa Cruz Biotechnology	sc-58732
goat anti-human Δ N-TP63	polyclonal	none	1:100	Santa Cruz Biotechnology	sc-8609
<i>Secondary antibodies</i>					
Alexa 647-conjugated donkey anti-mouse IgG		Alexa 647	1:200	Life Technologies	A-31571
Alexa 594-conjugated donkey anti-goat IgG		Alexa 594	1:200	Life Technologies	A-11058
<i>Isotype controls</i>					
rabbit IgG	EPR25A	none	1:100	Abcam	ab172730
mouse IgG1	ICIGG1	none	1:200	Abcam	ab91353
	MOPC-21	APC	1:20	BioLegend	400121
	MOPC-21	FITC	1:20	BioLegend	400107
	MOPC-21	PE	1:20	BioLegend	400111
mouse IgG2b	MPC-11	APC	1:20	BioLegend	400321
	MPC-11	PE	1:20	BioLegend	400314
goat IgG	polyclonal	FITC	1:20	Abcam	ab37374

Table S6. Antibodies and phalloxin used for immunocytochemistry and immunohistochemistry.

Item	Clone	Dilution	Manufacturer	Catalog number	Positive control
<i>Primary antibodies</i>					
mouse anti-human prolyl-4-hydroxylase β	3-2B12	1:250	Chemicon	MAB2701	vocal fold
Alexa 488-conjugated mouse anti-human CD11b	ICRF44	1:50	BD Biosciences	557701	monocytes
rabbit anti-rat CD3	polyclonal	1:500	Abcam	ab5690	spleen
mouse anti-human Ki67	4A1	1:200	Invitrogen	MA5-15525	fibroblasts
mouse anti-human keratin 5/8	RCK102	1:100	BD Biosciences	550505	skin
mouse anti-human protein tyrosine kinase 2	4.47	1:200	LifeSpan Biosciences	LS-B212	fibroblasts
<i>Secondary antibodies</i> ^a					
Alexa 488-conjugated donkey anti-mouse IgG		1:200	Life Technologies	A-21202	
Alexa 594-conjugated donkey anti-mouse IgG		1:200	Life Technologies	A-21203	
<i>Phalloxin</i>					
rhodamine phalloidin (F-actin)		1:200	Invitrogen	R415	fibroblasts

^a Secondary antibodies used for fluorescent detection are listed here; HRP-based detection is described in Materials and Methods.