Supplementary Materials

In Vitro Culture Expansion Shifts the Immune Phenotype of Human Adipose-derived Mesenchymal Stem Cells

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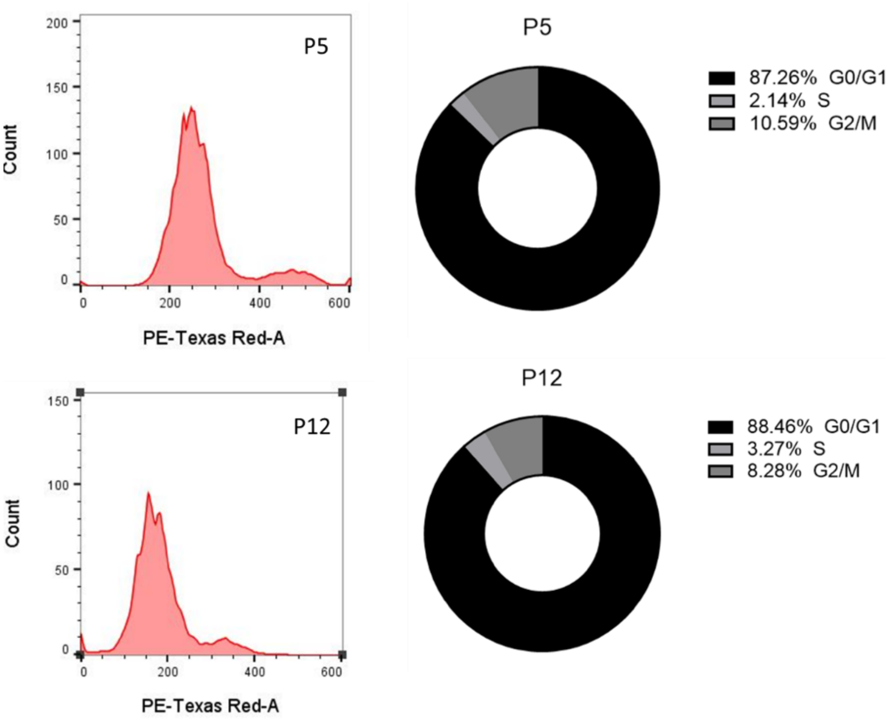
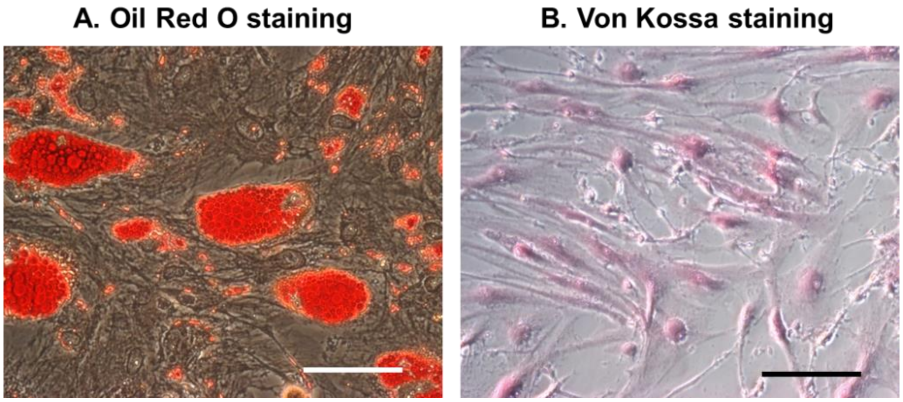
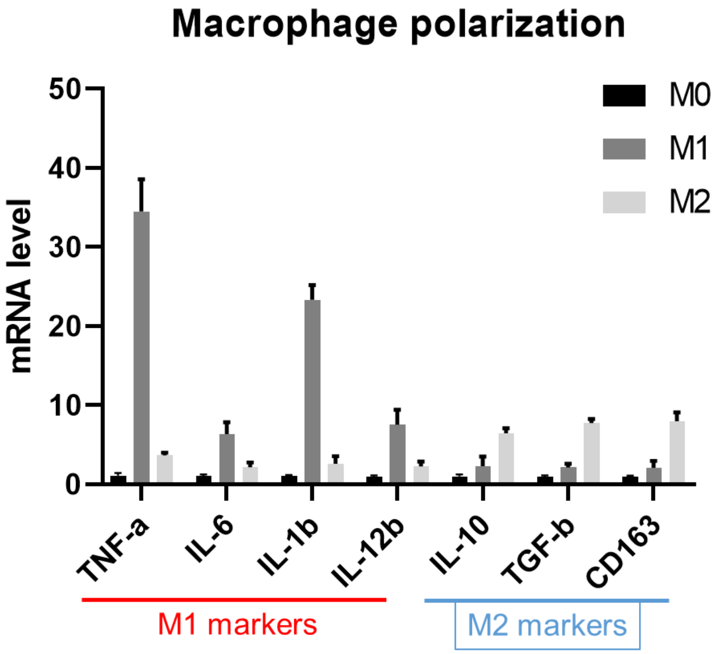
Supplementary Figure S1. Flow cytometry analysis of cell cycle distribution of hASCs at P5 and P12.



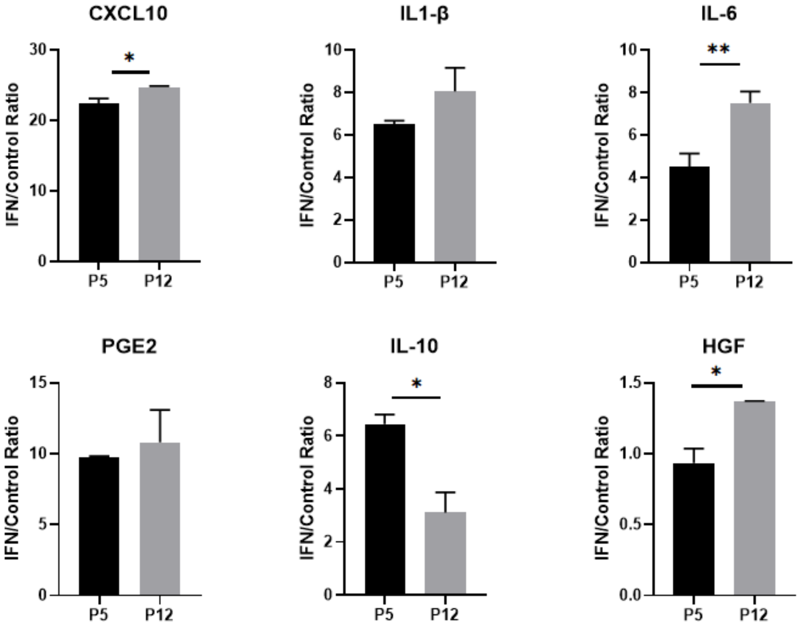
Supplementary Figure S2. Representative images for adipogenic differentiation and osteogenic differentiation. (A) Oil red O staining for adipogenic differentiation; and (B) Von Kossa staining for osteogenic differentiation. Scale bar: 100 µm.



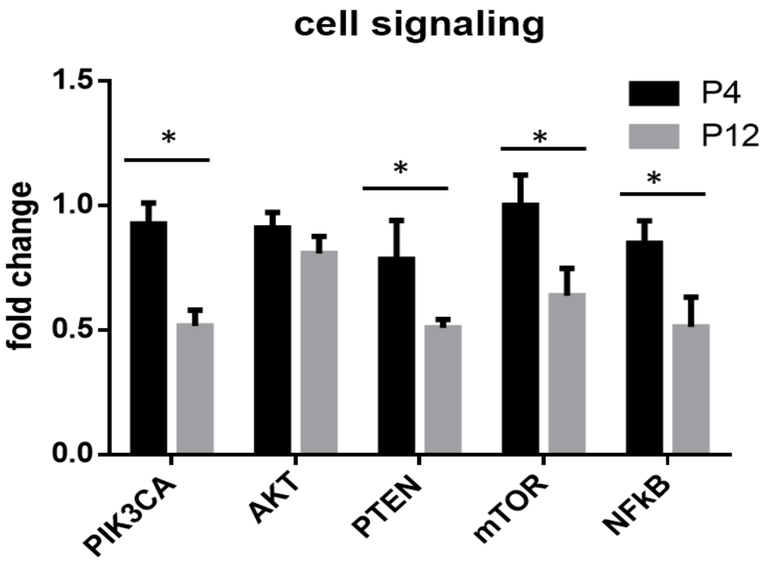
Supplementary Figure S3. Comparison of M1/M2 macrophages with M0 macrophages to confirm the successful polarization. The relative mRNA levels of M1 and M2 markers were determined by RT-PCR.



Supplementary Figure S4. The fold change in cytokine secretion when treated with IFN-γ compared to the control (without IFN-γ treatment) (corresponding to Figure 4D and 4E).

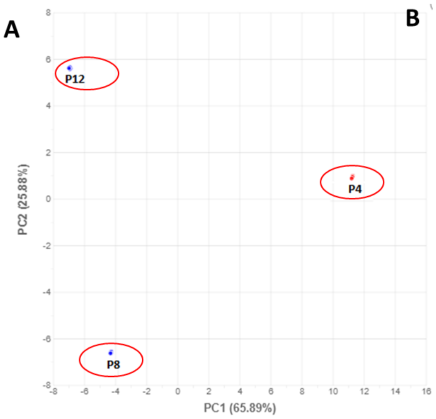


Supplementary Figure S5. Relative mRNA expression of cell signaling genes for P12 vs. P4 hASCs. * indicates *p*<0.05.



Supplementary Figure S6. Additional results from transcriptome analysis for P4 vs. P12 differentially expressed genes (DEGs). (A) Principal component analysis (PCA) demonstrated the separation of hMSCs at P4, P8, and P12 as categorized with the genes identified in transcriptomics. (B) Pericyte-related genes for P4 vs. P12 group. (C) Astrocyte-related genes for P4 vs. P12 group. (D) Microglia-related genes (highly expressed in P4 group or similarly expressed for P4 vs. P12 group). (E) Microglia-related genes (significantly upregulated in P12 group) for P4 vs. P12 group. (F). Extracellular matrix (ECM)-related genes differentially expressed in P4 and P12 groups. The numbers are the Log2 values of ratios of P12 cells to P4 cells. Negative values indicate that the genes are present in higher amounts in the P4 group, while positive values indicate that the genes are present in higher amounts in the P12 group. The number 1 indicates two-fold increase.

A



B

Pericyte genes	baseMean	log2(P12/P4)
ENG (CD105)	38723.145	**-1.241**
ABCC9	1561.067	**-0.895**
TBX18	1716.458697	**-0.882**
FOXF2	929.2241212	**-0.875**
THY1 (CD90)	40450.069	**-0.561**
KCNJ8	882.153	**-0.503**
ANPEP (CD13)	26186.308	**-0.470**
ZIC1	700.062	**-0.433**
PDGFRB	22146.14871	**-0.162**
TAGLN	3.102	**-0.122**
MCAM (CD146)	1242.046	**0.120**
FOXC1	977.156	**0.161**
VTN	138.6162746	**0.168**
ACTA2	23344.235	**0.346**
CNN1 (Calponin	4748.632	**0.373**
NT5E (CD73)	26038.684	**0.738**

C

Astrocyte gene	baseMean	log2(P12/P4)
S100B	0.811308246	**-3.046**
GFAP	12.90551414	**-1.974**
KCNJ10	2.332570528	**-1.753**
TNC	43632.6892	**-1.363**
NFIA	1339.162	**-0.888**
NFIB	2193.258	**-0.824**
NFIX	25634.959	**-0.714**
CD44	33709.79159	**-0.389**
SOX9	530.2990605	**-0.388**
VIM	267859.151	**-0.312**
RYR3	27.037	**0.116**
WIF1	0.256	**0.191**
SLC1A2	45.65872059	**0.228**
SLC1A3	348.615	**0.275**
GJA1	14403.97849	**1.153**
HEPACAM	0.661	**2.948**
ALDH1L1	1.414	**3.198**

D

Microglia genes	baseMean	log2(P12/P4)	Microglia genes	baseMean	log2(P12/P4)
ITM2A	48.865	**-4.371**	ENTPD1	682.088	**0.028**
TYROBP	1.074	**-3.440**	CD200R1	1.477	**0.325**
SPI1	1.092	**-1.592**	RGS10	666.143	**0.330**
OLFML3	10478.583	**-1.566**	GPR34	2.012	**0.436**
PROS1	956.090	**-1.495**	RUNX1	6437.255	**0.467**
TMEM119	9546.277	**-1.234**	ITM2B	19809.288	**0.476**
SELPLG	181.319	**-0.942**	SIRPA (CD172a)	8163.333	**0.574**
MERTK	4.970	**-0.935**	AIF1	0.139	**0.917**
CD74 (HLA-DR)	16.147	**-0.786**	P2RY14	6.258	**-5.993**
GAS6-AS1	8.779	**-0.782**	P2RY11	1.242	**-3.660**
CSF1R	26.666	**-0.703**	P2RY4	1.529	**-3.103**
PTPRC	8.483	**-0.648**	P2RY6	171.702	**-1.375**
ITGAM	0.356	**-0.512**	P2RY12	5.943	**-0.940**
CD68	5385.799	**-0.432**	P2RY2	14.502	**-0.392**
TLR3	263.816	**-0.145**	P2RY1	1.439	**3.210**

E

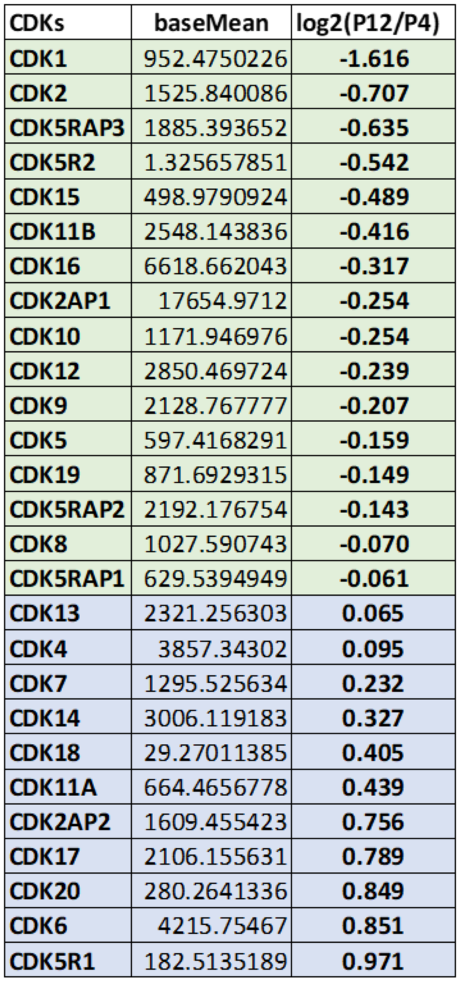
Microglia genes	baseMean	log2(P12/P4)
CSF1	10355.638	**0.989**
TLR4	1983.246	**1.169**
CTSD	25569.058	**1.328**
SIGLEC11	0.265	**1.639**
CX3CR1	3.259	**1.843**
CD274	128.116	**1.869**
IL34	83.639	**2.313**
GAS6	55906.156	**2.402**
CD14	136.674	**2.622**
TLR2	17.550	**3.770**
CSF3	89.908	**3.882**
CD200	130.574	**4.206**
CD163	53.477	**5.990**
CSF2	121.965	**10.471**
SIGLEC15	51.082	**0.439**
SIGLEC16	2.810	**1.003**
SIGLEC10	0.909	**1.542**
SIGLEC9	1.311	**3.066**

F

ECM gene	baseMean	log2(P12/P4)
LAMA2	8741.126955	**-0.931**
LAMC1-AS1	1.221379206	**-0.444**
LAMB4	1.688337388	**-0.404**
LAMA4	20597.24486	**-0.393**
LAMB1	23003.98907	**-0.333**
LAMB2P1	3.668089791	**-0.110**
LAMC1	107128.6094	**0.181**
LAMB2	42504.57215	**0.186**
LAMC3	0.74983529	**0.208**
LAMA1	1016.707871	**1.055**
LAMC2	1479.088708	**1.177**
LAMA5	2910.295926	**1.414**
LAMA3	187.7129631	**1.731**
LAMB3	792.1194837	**1.937**
FN1	3152597.472	**0.996**
VTN	138.6162746	**0.168**
CSPG4	4631.65873	**-1.215**
CSPG5	2.243898211	**0.494**

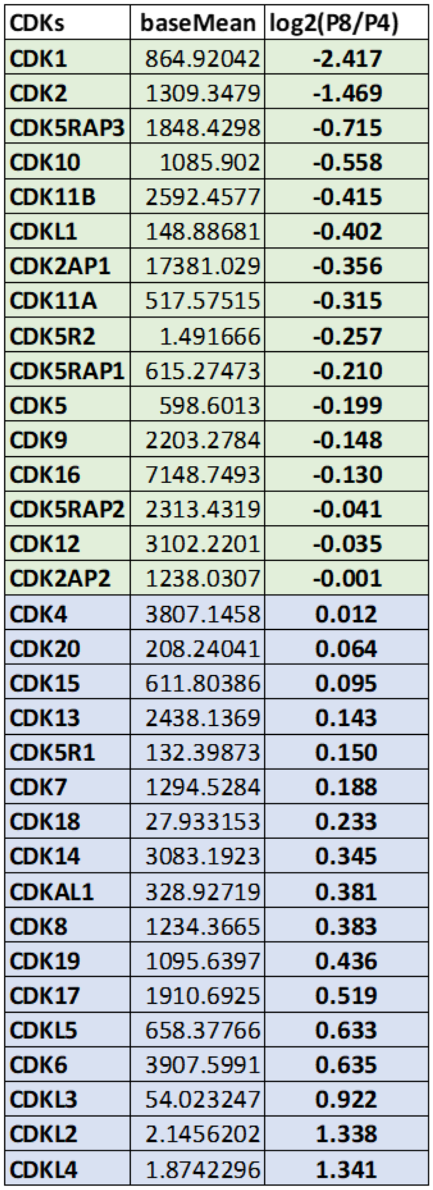
Supplementary Figure S7. The differential expression of CDK related genes. (A) P12 vs P4 comparison. (B) P8 vs. P4 comparison. The numbers are the Log2 values of ratios of P12 or P8 cells to P4 cells. Negative values indicate that the genes are present in higher amounts in the P4 group, while positive values indicate that the genes are present in higher amounts in the P12 or P8 group. The number 1 indicates two-fold increase.

A



CDKs	baseMean	log2(P12/P4)
CDK1	952.4750226	**-1.616**
CDK2	1525.840086	**-0.707**
CDK5RAP3	1885.393652	**-0.635**
CDK5R2	1.325657851	**-0.542**
CDK15	498.9790924	**-0.489**
CDK11B	2548.143836	**-0.416**
CDK16	6618.662043	**-0.317**
CDK2AP1	17654.9712	**-0.254**
CDK10	1171.946976	**-0.254**
CDK12	2850.469724	**-0.239**
CDK9	2128.767777	**-0.207**
CDK5	597.4168291	**-0.159**
CDK19	871.6929315	**-0.149**
CDK5RAP2	2192.176754	**-0.143**
CDK8	1027.590743	**-0.070**
CDK5RAP1	629.5394949	**-0.061**
CDK13	2321.256303	**0.065**
CDK4	3857.34302	**0.095**
CDK7	1295.525634	**0.232**
CDK14	3006.119183	**0.327**
CDK18	29.27011385	**0.405**
CDK11A	664.4656778	**0.439**
CDK2AP2	1609.455423	**0.756**
CDK17	2106.155631	**0.789**
CDK20	280.2641336	**0.849**
CDK6	4215.75467	**0.851**
CDK5R1	182.5135189	**0.971**

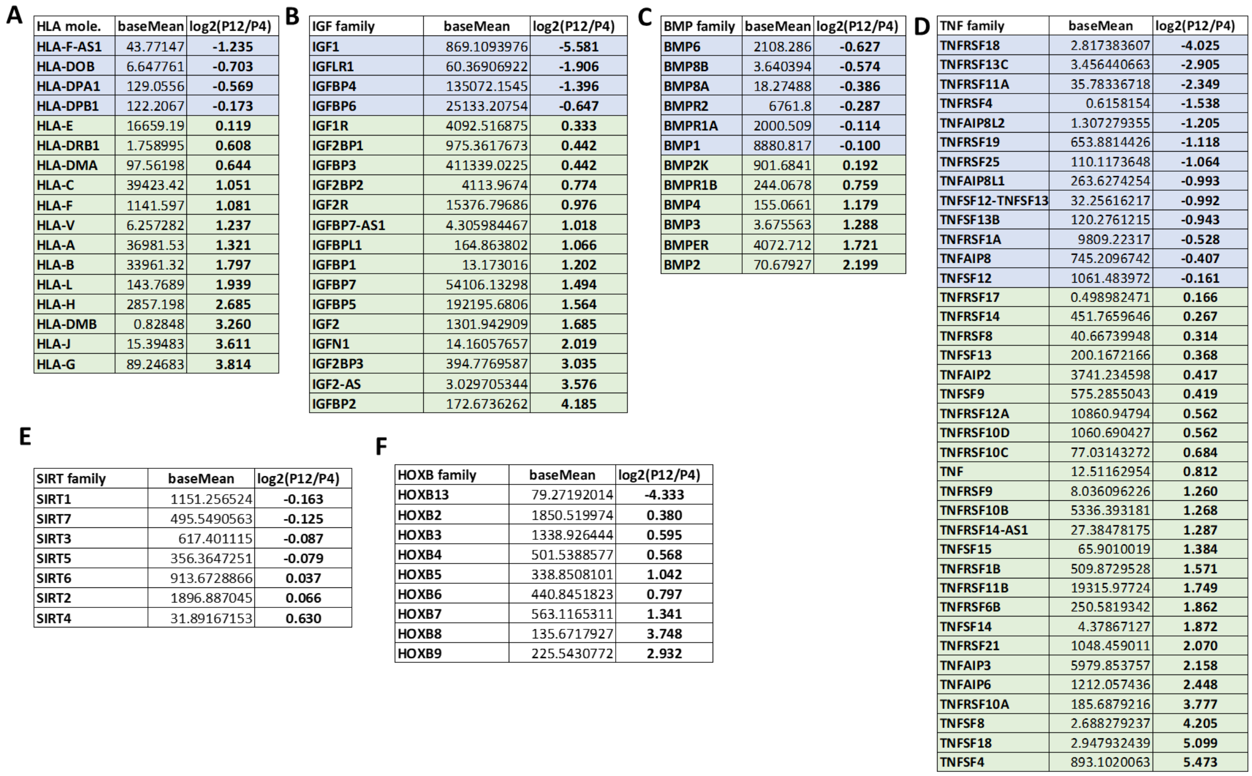
B



CDKs	baseMean	log2(P8/P4)
CDK1	864.92042	**-2.417**
CDK2	1309.3479	**-1.469**
CDK5RAP3	1848.4298	**-0.715**
CDK10	1085.902	**-0.558**
CDK11B	2592.4577	**-0.415**
CDKL1	148.88681	**-0.402**
CDK2AP1	17381.029	**-0.356**
CDK11A	517.57515	**-0.315**
CDK5R2	1.491666	**-0.257**
CDK5RAP1	615.27473	**-0.210**
CDK5	598.6013	**-0.199**
CDK9	2203.2784	**-0.148**
CDK16	7148.7493	**-0.130**
CDK5RAP2	2313.4319	**-0.041**
CDK12	3102.2201	**-0.035**
CDK2AP2	1238.0307	**-0.001**
CDK4	3807.1458	**0.012**
CDK20	208.24041	**0.064**
CDK15	611.80386	**0.095**
CDK13	2438.1369	**0.143**
CDK5R1	132.39873	**0.150**
CDK7	1294.5284	**0.188**
CDK18	27.933153	**0.233**
CDK14	3083.1923	**0.345**
CDKAL1	328.92719	**0.381**
CDK8	1234.3665	**0.383**
CDK19	1095.6397	**0.436**
CDK17	1910.6925	**0.519**
CDKL5	658.37766	**0.633**
CDK6	3907.5991	**0.635**
CDKL3	54.023247	**0.922**
CDKL2	2.1456202	**1.338**
CDKL4	1.8742296	**1.341**

Supplementary Figure S8. Additional results from transcriptome analysis for P4 vs. P12 DEGs. (A) Genes related to HLA molecules. (B) Genes related to IGF family; (C) Genes related to BMP family; (D) Genes related to TNF family; (E) Genes related to Sirt family; (F) Genes related to HOXB family.

The numbers are the Log2 values of ratios of P12 cells to P4 cells. Negative values indicate that the genes are present in higher amounts in the P4 group, while positive values indicate that the genes are present in higher amounts in the P12 group. The number 1 indicates two-fold increase.



A

HLA mole.	baseMean	log2(P12/P4)
HLA-F-AS1	43.77147	-1.235
HLA-DOB	6.647761	-0.703
HLA-DPA1	129.0556	-0.569
HLA-DPB1	122.2067	-0.173
HLA-E	16659.19	0.119
HLA-DRB1	1.758995	0.608
HLA-DMA	97.56198	0.644
HLA-C	39423.42	1.051
HLA-F	1141.597	1.081
HLA-V	6.257282	1.237
HLA-A	36981.53	1.321
HLA-B	33961.32	1.797
HLA-L	143.7689	1.939
HLA-H	2857.198	2.685
HLA-DMB	0.82848	3.260
HLA-J	15.39483	3.611
HLA-G	89.24683	3.814

B

IGF family	baseMean	log2(P12/P4)
IGF1	869.1093976	-5.581
IGFLR1	60.36906922	-1.906
IGFBP4	135072.1545	-1.396
IGFBP6	25133.20754	-0.647
IGF1R	4092.516875	0.333
IGF2BP1	975.3617673	0.442
IGFBP3	411339.0225	0.442
IGF2BP2	4113.9674	0.774
IGF2R	15376.79686	0.976
IGFBP7-AS1	4.305984467	1.018
IGFBPL1	164.863802	1.066
IGFBP1	13.173016	1.202
IGFBP7	54106.13298	1.494
IGFBP5	192195.6806	1.564
IGF2	1301.942909	1.685
IGFN1	14.16057657	2.019
IGF2BP3	394.7769587	3.035
IGF2-AS	3.029705344	3.576
IGFBP2	172.6736262	4.185

C

BMP family	baseMean	log2(P12/P4)
BMP6	2108.286	-0.627
BMP8B	3.640394	-0.574
BMP8A	18.27488	-0.386
BMPR2	6761.8	-0.287
BMPR1A	2000.509	-0.114
BMP1	8880.817	-0.100
BMP2K	901.6841	0.192
BMPR1B	244.0678	0.759
BMP4	155.0661	1.179
BMP3	3.675563	1.288
BMPER	4072.712	1.721
BMP2	70.67927	2.199

D

TNF family	baseMean	log2(P12/P4)
TNFRSF18	2.817383607	-4.025
TNFRSF13C	3.456440663	-2.905
TNFRSF11A	35.78336718	-2.349
TNFRSF4	0.6158154	-1.538
TNFAIP8L2	1.307279355	-1.205
TNFRSF19	653.8814426	-1.118
TNFRSF25	110.1173648	-1.064
TNFAIP8L1	263.6274254	-0.993
TNFSF12-TNFSF13	32.25616217	-0.992
TNFSF13B	120.2761215	-0.943
TNFRSF1A	9809.22317	-0.528
TNFAIP8	745.2096742	-0.407
TNFSF12	1061.483972	-0.161
TNFRSF17	0.498982471	0.166
TNFRSF14	451.7659646	0.267
TNFRSF8	40.66739948	0.314
TNFSF13	200.1672166	0.368
TNFAIP2	3741.234598	0.417
TNFSF9	575.2855043	0.419
TNFRSF12A	10860.94794	0.562
TNFRSF10D	1060.690427	0.562
TNFRSF10C	77.03143272	0.684
TNF	12.51162954	0.812
TNFRSF9	8.036096226	1.260
TNFRSF10B	5336.393181	1.268
TNFRSF14-AS1	27.38478175	1.287
TNFSF15	65.9010019	1.384
TNFRSF1B	509.8729528	1.571
TNFRSF11B	19315.97724	1.749
TNFRSF6B	250.5819342	1.862
TNFSF14	4.37867127	1.872
TNFRSF21	1048.459011	2.070
TNFAIP3	5979.853757	2.158
TNFAIP6	1212.057436	2.448
TNFRSF10A	185.6879216	3.777
TNFSF8	2.688279237	4.205
TNFSF18	2.947932439	5.099
TNFSF4	893.1020063	5.473

E

SIRT family	baseMean	log2(P12/P4)
SIRT1	1151.256524	-0.163
SIRT7	495.5490563	-0.125
SIRT3	617.401115	-0.087
SIRT5	356.3647251	-0.079
SIRT6	913.6728866	0.037
SIRT2	1896.887045	0.066
SIRT4	31.89167153	0.630

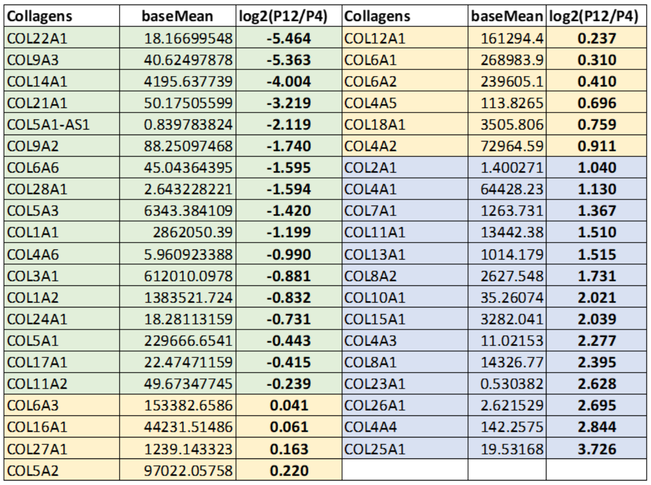
F

HOXB family	baseMean	log2(P12/P4)
HOXB13	79.27192014	-4.333
HOXB2	1850.519974	0.380
HOXB3	1338.926444	0.595
HOXB4	501.5388577	0.568
HOXB5	338.8508101	1.042
HOXB6	440.8451823	0.797
HOXB7	563.1165311	1.341
HOXB8	135.6717927	3.748
HOXB9	225.5430772	2.932

Supplementary Figure S9. Additional results from transcriptome analysis for P4 vs. P12 DEGs. (A) Genes related to collagen molecules. (B) Genes related to metabolism; (C) Genes related to CD markers; (D) Additional genes related to CD markers.

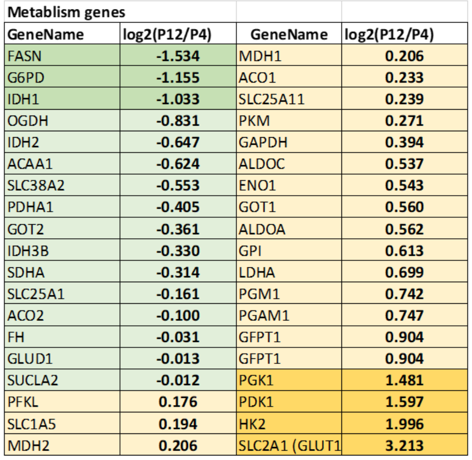
The numbers are the Log2 values of ratios of P12 cells to P4 cells. Negative values indicate that the genes are present in higher amounts in the P4 group, while positive values indicate that the genes are present in higher amounts in the P12 group. The number 1 indicates two-fold increase.

A



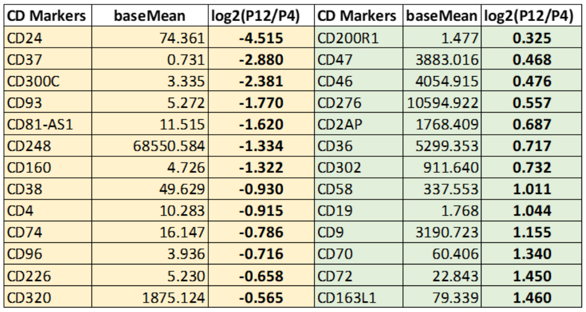
Collagens	baseMean	log2(P12/P4)	Collagens	baseMean	log2(P12/P4)
COL22A1	18.16699548	**-5.464**	COL12A1	161294.4	**0.237**
COL9A3	40.62497878	**-5.363**	COL6A1	268983.9	**0.310**
COL14A1	4195.637739	**-4.004**	COL6A2	239605.1	**0.410**
COL21A1	50.17505599	**-3.219**	COL4A5	113.8265	**0.696**
COL5A1-AS1	0.839783824	**-2.119**	COL18A1	3505.806	**0.759**
COL9A2	88.25097468	**-1.740**	COL4A2	72964.59	**0.911**
COL6A6	45.04364395	**-1.595**	COL2A1	1.400271	**1.040**
COL28A1	2.643228221	**-1.594**	COL4A1	64428.23	**1.130**
COL5A3	6343.384109	**-1.420**	COL7A1	1263.731	**1.367**
COL1A1	2862050.39	**-1.199**	COL11A1	13442.38	**1.510**
COL4A6	5.960923388	**-0.990**	COL13A1	1014.179	**1.515**
COL3A1	612010.0978	**-0.881**	COL8A2	2627.548	**1.731**
COL1A2	1383521.724	**-0.832**	COL10A1	35.26074	**2.021**
COL24A1	18.28113159	**-0.731**	COL15A1	3282.041	**2.039**
COL5A1	229666.6541	**-0.443**	COL4A3	11.02153	**2.277**
COL17A1	22.47471159	**-0.415**	COL8A1	14326.77	**2.395**
COL11A2	49.67347745	**-0.239**	COL23A1	0.530382	**2.628**
COL6A3	153382.6586	**0.041**	COL26A1	2.621529	**2.695**
COL16A1	44231.51486	**0.061**	COL4A4	142.2575	**2.844**
COL27A1	1239.143323	**0.163**	COL25A1	19.53168	**3.726**
COL5A2	97022.05758	**0.220**			

B



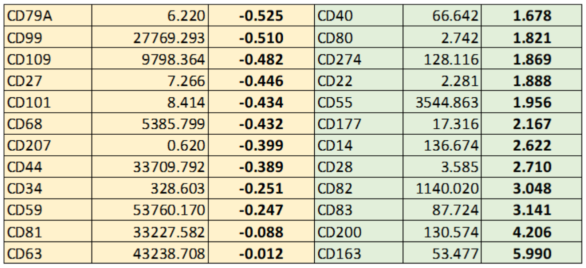
Metablism genes			
GeneName	**log2(P12/P4)**	**GeneName**	**log2(P12/P4)**
FASN	**-1.534**	MDH1	**0.206**
G6PD	**-1.155**	ACO1	**0.233**
IDH1	**-1.033**	SLC25A11	**0.239**
OGDH	**-0.831**	PKM	**0.271**
IDH2	**-0.647**	GAPDH	**0.394**
ACAA1	**-0.624**	ALDOC	**0.537**
SLC38A2	**-0.553**	ENO1	**0.543**
PDHA1	**-0.405**	GOT1	**0.560**
GOT2	**-0.361**	ALDOA	**0.562**
IDH3B	**-0.330**	GPI	**0.613**
SDHA	**-0.314**	LDHA	**0.699**
SLC25A1	**-0.161**	PGM1	**0.742**
ACO2	**-0.100**	PGAM1	**0.747**
FH	**-0.031**	GFPT1	**0.904**
GLUD1	**-0.013**	GFPT1	**0.904**
SUCLA2	**-0.012**	PGK1	**1.481**
PFKL	**0.176**	PDK1	**1.597**
SLC1A5	**0.194**	HK2	**1.996**
MDH2	**0.206**	SLC2A1 (GLUT1	**3.213**

C



CD Markers	baseMean	log2(P12/P4)	CD Markers	baseMean	log2(P12/P4)
CD24	74.361	**-4.515**	CD200R1	1.477	**0.325**
CD37	0.731	**-2.880**	CD47	3883.016	**0.468**
CD300C	3.335	**-2.381**	CD46	4054.915	**0.476**
CD93	5.272	**-1.770**	CD276	10594.922	**0.557**
CD81-AS1	11.515	**-1.620**	CD2AP	1768.409	**0.687**
CD248	68550.584	**-1.334**	CD36	5299.353	**0.717**
CD160	4.726	**-1.322**	CD302	911.640	**0.732**
CD38	49.629	**-0.930**	CD58	337.553	**1.011**
CD4	10.283	**-0.915**	CD19	1.768	**1.044**
CD74	16.147	**-0.786**	CD9	3190.723	**1.155**
CD96	3.936	**-0.716**	CD70	60.406	**1.340**
CD226	5.230	**-0.658**	CD72	22.843	**1.450**
CD320	1875.124	**-0.565**	CD163L1	79.339	**1.460**

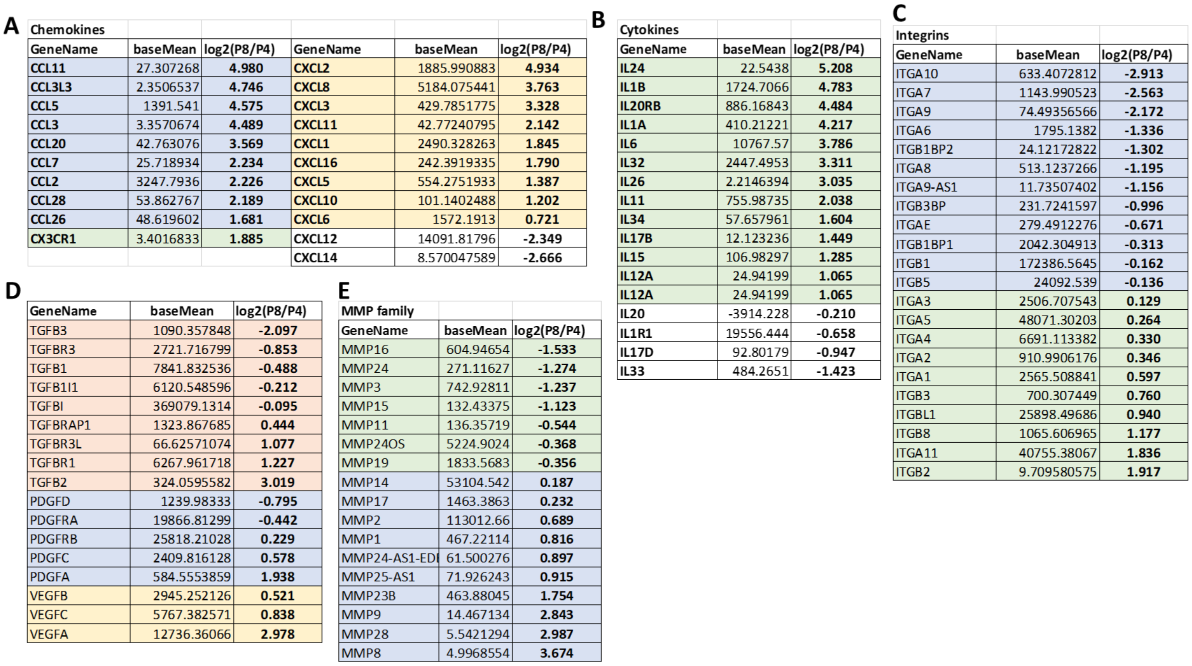
D



CD79A	6.220	**-0.525**	CD40	66.642	**1.678**
CD99	27769.293	**-0.510**	CD80	2.742	**1.821**
CD109	9798.364	**-0.482**	CD274	128.116	**1.869**
CD27	7.266	**-0.446**	CD22	2.281	**1.888**
CD101	8.414	**-0.434**	CD55	3544.863	**1.956**
CD68	5385.799	**-0.432**	CD177	17.316	**2.167**
CD207	0.620	**-0.399**	CD14	136.674	**2.622**
CD44	33709.792	**-0.389**	CD28	3.585	**2.710**
CD34	328.603	**-0.251**	CD82	1140.020	**3.048**
CD59	53760.170	**-0.247**	CD83	87.724	**3.141**
CD81	33227.582	**-0.088**	CD200	130.574	**4.206**
CD63	43238.708	**-0.012**	CD163	53.477	**5.990**

Supplementary Figure S10. Corresponding to Figure 5: results from transcriptome analysis for P4 vs. P8 DEGs. (A) Interleukin mRNA expression (shown in fold change) for P8 vs. P4 hASCs, showing upregulation at P8. (B) Chemokine mRNA expression (shown in fold change) for P8 vs. P4 hASCs, showing upregulation at P8. (C) Integrin mRNA expression for P8 vs. P4 hASCs. (D) Growth factor mRNA expression (TGF, PDGF, and VEGF) for P8 vs. P4 hASCs. (E) Matrix metalloproteinase (MMP) mRNA expression for P8 vs. P4 hASCs.

The numbers are the Log2 values of ratios of P12 cells to P4 cells. Negative values indicate that the genes are present in higher amounts in the P4 group, while positive values indicate that the genes are present in higher amounts in the P12 group. The number 1 indicates two-fold increase.



A

Chemokines					
GeneName	baseMean	log2(P8/P4)	GeneName	baseMean	log2(P8/P4)
CCL11	27.307268	4.980	CXCL2	1885.990883	4.934
CCL3L3	2.3506537	4.746	CXCL8	5184.075441	3.763
CCL5	1391.541	4.575	CXCL3	429.7851775	3.328
CCL3	3.3570674	4.489	CXCL11	42.77240795	2.142
CCL20	42.763076	3.569	CXCL1	2490.328263	1.845
CCL7	25.718934	2.234	CXCL16	242.3919335	1.790
CCL2	3247.7936	2.226	CXCL5	554.2751933	1.387
CCL28	53.862767	2.189	CXCL10	101.1402488	1.202
CCL26	48.619602	1.681	CXCL6	1572.1913	0.721
CX3CR1	3.4016833	1.885	CXCL12	14091.81796	-2.349
			CXCL14	8.570047589	-2.666

B

Cytokines		
GeneName	baseMean	log2(P8/P4)
IL24	22.5438	5.208
IL1B	1724.7066	4.783
IL20RB	886.16843	4.484
IL1A	410.21221	4.217
IL6	10767.57	3.786
IL32	2447.4953	3.311
IL26	2.2146394	3.035
IL11	755.98735	2.038
IL34	57.657961	1.604
IL17B	12.123236	1.449
IL15	106.98297	1.285
IL12A	24.94199	1.065
IL12A	24.94199	1.065
IL20	-3914.228	-0.210
IL1R1	19556.444	-0.658
IL17D	92.80179	-0.947
IL33	484.2651	-1.423

C

Integrins		
GeneName	baseMean	log2(P8/P4)
ITGA10	633.4072812	-2.913
ITGA7	1143.990523	-2.563
ITGA9	74.49356566	-2.172
ITGA6	1795.1382	-1.336
ITGB1BP2	24.12172822	-1.302
ITGA8	513.1237266	-1.195
ITGA9-AS1	11.73507402	-1.156
ITGB3BP	231.7241597	-0.996
ITGAE	279.4912276	-0.671
ITGB1BP1	2042.304913	-0.313
ITGB1	172386.5645	-0.162
ITGB5	24092.539	-0.136
ITGA3	2506.707543	0.129
ITGA5	48071.30203	0.264
ITGA4	6691.113382	0.330
ITGA2	910.9906176	0.346
ITGA1	2565.508841	0.597
ITGB3	700.307449	0.760
ITGBL1	25898.49686	0.940
ITGB8	1065.606965	1.177
ITGA11	40755.38067	1.836
ITGB2	9.709580575	1.917

D

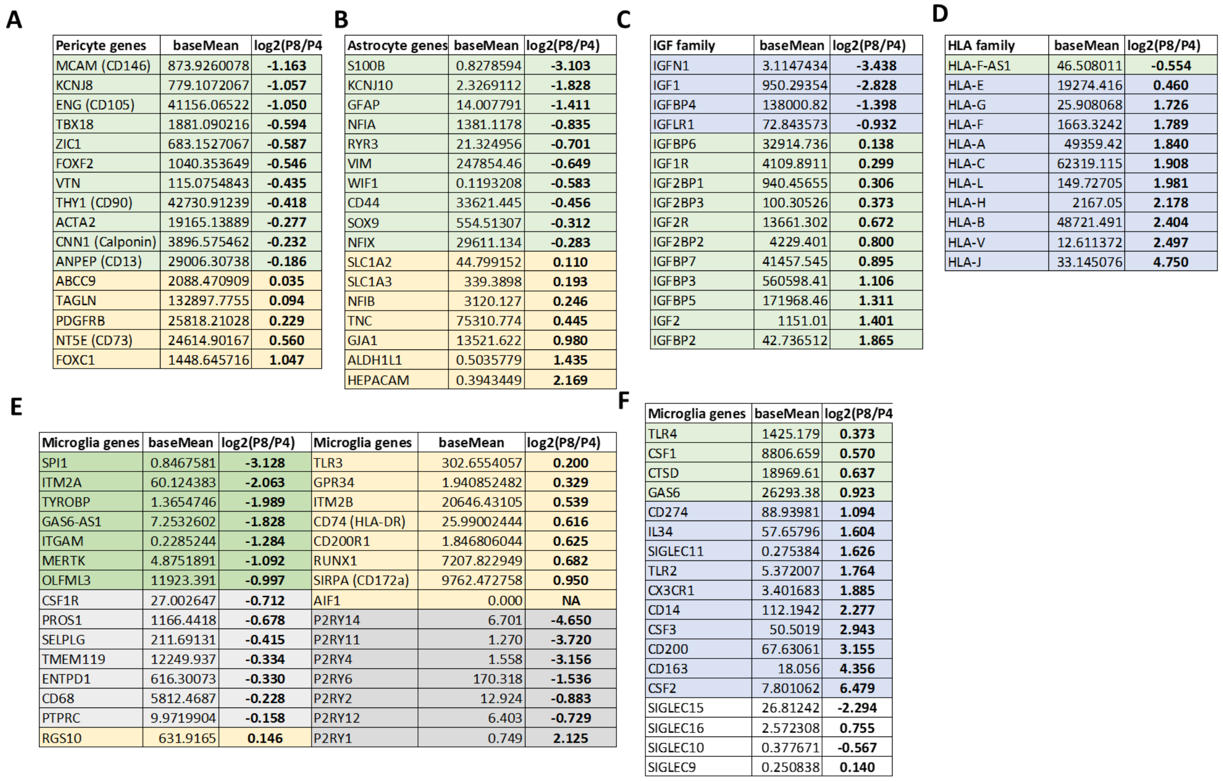
GeneName	baseMean	log2(P8/P4)
TGFB3	1090.357848	-2.097
TGFBR3	2721.716799	-0.853
TGFB1	7841.832536	-0.488
TGFB1I1	6120.548596	-0.212
TGFBI	369079.1314	-0.095
TGFBRAP1	1323.867685	0.444
TGFBR3L	66.62571074	1.077
TGFBR1	6267.961718	1.227
TGFB2	324.0595582	3.019
PDGFD	1239.98333	-0.795
PDGFRA	19866.81299	-0.442
PDGFRB	25818.21028	0.229
PDGFC	2409.816128	0.578
PDGFA	584.5553859	1.938
VEGFB	2945.252126	0.521
VEGFC	5767.382571	0.838
VEGFA	12736.36066	2.978

E

MMP family		
GeneName	baseMean	log2(P8/P4)
MMP16	604.94654	-1.533
MMP24	271.11627	-1.274
MMP3	742.92811	-1.237
MMP15	132.43375	-1.123
MMP11	136.35719	-0.544
MMP24OS	5224.9024	-0.368
MMP19	1833.5683	-0.356
MMP14	53104.542	0.187
MMP17	1463.3863	0.232
MMP2	113012.66	0.689
MMP1	467.22114	0.816
MMP24-AS1-EDI	61.500276	0.897
MMP25-AS1	71.926243	0.915
MMP23B	463.88045	1.754
MMP9	14.467134	2.843
MMP28	5.5421294	2.987
MMP8	4.9968554	3.674

Supplementary Figure S11. Additional results from transcriptome analysis for P4 vs. P8 DEGs). (A) Pericyte-related genes for P4 vs. P8 group. (B) Astrocyte-related genes for P4 vs. P8 group. (C) Genes related to IGF family; (D) Genes related to HLA molecules; (E) Microglia-related genes (highly expressed in P4 group or similarly expressed for P4 vs. P8 group). (F) Additional microglia-related genes (significantly upregulated in P8 group) for P4 vs. P8 group.

The numbers are the Log2 values of ratios of P12 cells to P4 cells. Negative values indicate that the genes are present in higher amounts in the P4 group, while positive values indicate that the genes are present in higher amounts in the P12 group. The number 1 indicates two-fold increase.



A

Pericyte genes	baseMean	log2(P8/P4
MCAM (CD146)	873.9260078	-1.163
KCNJ8	779.1072067	-1.057
ENG (CD105)	41156.06522	-1.050
TBX18	1881.090216	-0.594
ZIC1	683.1527067	-0.587
FOXF2	1040.353649	-0.546
VTN	115.0754843	-0.435
THY1 (CD90)	42730.91239	-0.418
ACTA2	19165.13889	-0.277
CNN1 (Calponin)	3896.575462	-0.232
ANPEP (CD13)	29006.30738	-0.186
ABCC9	2088.470909	0.035
TAGLN	132897.7755	0.094
PDGFRB	25818.21028	0.229
NT5E (CD73)	24614.90167	0.560
FOXC1	1448.645716	1.047

B

Astrocyte genes	baseMean	log2(P8/P4)
S100B	0.8278594	-3.103
KCNJ10	2.3269112	-1.828
GFAP	14.007791	-1.411
NFIA	1381.1178	-0.835
RYR3	21.324956	-0.701
VIM	247854.46	-0.649
WIF1	0.1193208	-0.583
CD44	33621.445	-0.456
SOX9	554.51307	-0.312
NFIX	29611.134	-0.283
SLC1A2	44.799152	0.110
SLC1A3	339.3898	0.193
NFIB	3120.127	0.246
TNC	75310.774	0.445
GJA1	13521.622	0.980
ALDH1L1	0.5035779	1.435
HEPACAM	0.3943449	2.169

C

IGF family	baseMean	log2(P8/P4)
IGFN1	3.1147434	-3.438
IGF1	950.29354	-2.828
IGFBP4	138000.82	-1.398
IGFLR1	72.843573	-0.932
IGFBP6	32914.736	0.138
IGF1R	4109.8911	0.299
IGF2BP1	940.45655	0.306
IGF2BP3	100.30526	0.373
IGF2R	13661.302	0.672
IGF2BP2	4229.401	0.800
IGFBP7	41457.545	0.895
IGFBP3	560598.41	1.106
IGFBP5	171968.46	1.311
IGF2	1151.01	1.401
IGFBP2	42.736512	1.865

D

HLA family	baseMean	log2(P8/P4)
HLA-F-AS1	46.508011	-0.554
HLA-E	19274.416	0.460
HLA-G	25.908068	1.726
HLA-F	1663.3242	1.789
HLA-A	49359.42	1.840
HLA-C	62319.115	1.908
HLA-L	149.72705	1.981
HLA-H	2167.05	2.178
HLA-B	48721.491	2.404
HLA-V	12.611372	2.497
HLA-J	33.145076	4.750

E

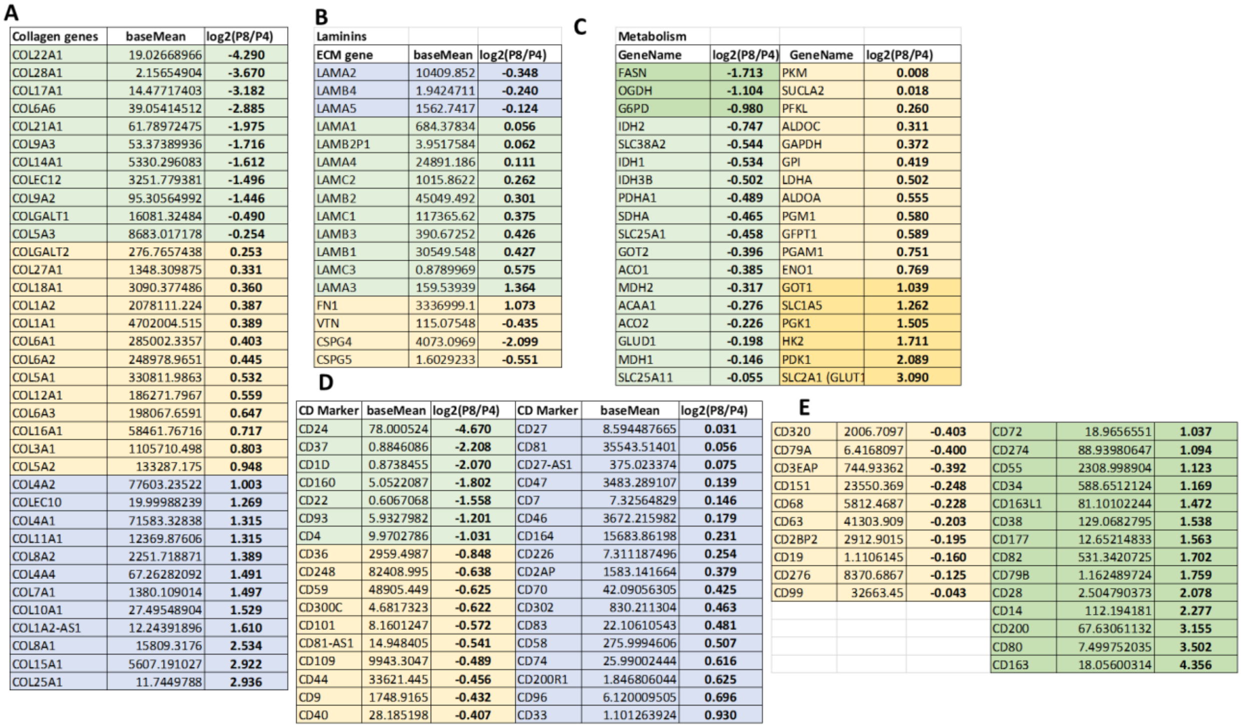
Microglia genes	baseMean	log2(P8/P4)	Microglia genes	baseMean	log2(P8/P4)
SPI1	0.8467581	-3.128	TLR3	302.6554057	0.200
ITM2A	60.124383	-2.063	GPR34	1.940852482	0.329
TYROBP	1.3654746	-1.989	ITM2B	20646.43105	0.539
GAS6-AS1	7.2532602	-1.828	CD74 (HLA-DR)	25.99002444	0.616
ITGAM	0.2285244	-1.284	CD200R1	1.846806044	0.625
MERTK	4.8751891	-1.092	RUNX1	7207.822949	0.682
OLFML3	11923.391	-0.997	SIRPA (CD172a)	9762.472758	0.950
CSF1R	27.002647	-0.712	AIF1	0.000	NA
PROS1	1166.4418	-0.678	P2RY14	6.701	-4.650
SELPLG	211.69131	-0.415	P2RY11	1.270	-3.720
TMEM119	12249.937	-0.334	P2RY4	1.558	-3.156
ENTPD1	616.30073	-0.330	P2RY6	170.318	-1.536
CD68	5812.4687	-0.228	P2RY2	12.924	-0.883
PTPRC	9.9719904	-0.158	P2RY12	6.403	-0.729
RGS10	631.9165	0.146	P2RY1	0.749	2.125

F

Microglia genes	baseMean	log2(P8/P4
TLR4	1425.179	0.373
CSF1	8806.659	0.570
CTSD	18969.61	0.637
GAS6	26293.38	0.923
CD274	88.93981	1.094
IL34	57.65796	1.604
SIGLEC11	0.275384	1.626
TLR2	5.372007	1.764
CX3CR1	3.401683	1.885
CD14	112.1942	2.277
CSF3	50.5019	2.943
CD200	67.63061	3.155
CD163	18.056	4.356
CSF2	7.801062	6.479
SIGLEC15	26.81242	-2.294
SIGLEC16	2.572308	0.755
SIGLEC10	0.377671	-0.567
SIGLEC9	0.250838	0.140

Supplementary Figure S12. Additional results from transcriptome analysis for P4 vs. P8 DEGs). (A) Collagen-related genes for P4 vs. P8 group. (B) Laminin-related genes for P4 vs. P8 group. (C) Genes related to metabolism (no significant change); (D) Genes related to HLA molecules; (E) Genes related to CD markers for P4 vs. P8 group. (F) Additional genes related to CD markers for P4 vs. P8 group.

The numbers are the Log2 values of ratios of P12 cells to P4 cells. Negative values indicate that the genes are present in higher amounts in the P4 group, while positive values indicate that the genes are present in higher amounts in the P12 group. The number 1 indicates two-fold increase.



A

Collagen genes	baseMean	log2(P8/P4)
COL22A1	19.02668966	-4.290
COL28A1	2.15654904	-3.670
COL17A1	14.47717403	-3.182
COL6A6	39.05414512	-2.885
COL21A1	61.78972475	-1.975
COL9A3	53.37389936	-1.716
COL14A1	5330.296083	-1.612
COLEC12	3251.779381	-1.496
COL9A2	95.30564992	-1.446
COLGALT1	16081.32484	-0.490
COL5A3	8683.017178	-0.254
COLGALT2	276.7657438	0.253
COL27A1	1348.309875	0.331
COL18A1	3090.377486	0.360
COL1A2	2078111.224	0.387
COL1A1	4702004.515	0.389
COL6A1	285002.3357	0.403
COL6A2	248978.9651	0.445
COL5A1	330811.9863	0.532
COL12A1	186271.7967	0.559
COL6A3	198067.6591	0.647
COL16A1	58461.76716	0.717
COL3A1	1105710.498	0.803
COL5A2	133287.175	0.948
COL4A2	77603.23522	1.003
COLEC10	19.99988239	1.269
COL4A1	71583.32838	1.315
COL11A1	12369.87606	1.315
COL8A2	2251.718871	1.389
COL4A4	67.26282092	1.491
COL7A1	1380.109014	1.497
COL10A1	27.49548904	1.529
COL1A2-AS1	12.24391896	1.610
COL8A1	15809.3176	2.534
COL15A1	5607.191027	2.922
COL25A1	11.7449788	2.936

B

Laminins

ECM gene	baseMean	log2(P8/P4)
LAMA2	10409.852	-0.348
LAMB4	1.9424711	-0.240
LAMA5	1562.7417	-0.124
LAMA1	684.37834	0.056
LAMB2P1	3.9517584	0.062
LAMA4	24891.186	0.111
LAMC2	1015.8622	0.262
LAMB2	45049.492	0.301
LAMC1	117365.62	0.375
LAMB3	390.67252	0.426
LAMB1	30549.548	0.427
LAMC3	0.8789969	0.575
LAMA3	159.53939	1.364
FN1	3336999.1	1.073
VTN	115.07548	-0.435
CSPG4	4073.0969	-2.099
CSPG5	1.6029233	-0.551

C

Metabolism

GeneName	log2(P8/P4)	GeneName	log2(P8/P4)
FASN	-1.713	PKM	0.008
OGDH	-1.104	SUCLA2	0.018
G6PD	-0.980	PFKL	0.260
IDH2	-0.747	ALDOC	0.311
SLC38A2	-0.544	GAPDH	0.372
IDH1	-0.534	GPI	0.419
IDH3B	-0.502	LDHA	0.502
PDHA1	-0.489	ALDOA	0.555
SDHA	-0.465	PGM1	0.580
SLC25A1	-0.458	GFPT1	0.589
GOT2	-0.396	PGAM1	0.751
ACO1	-0.385	ENO1	0.769
MDH2	-0.317	GOT1	1.039
ACAA1	-0.276	SLC1A5	1.262
ACO2	-0.226	PGK1	1.505
GLUD1	-0.198	HK2	1.711
MDH1	-0.146	PDK1	2.089
SLC25A11	-0.055	SLC2A1 (GLUT1	3.090

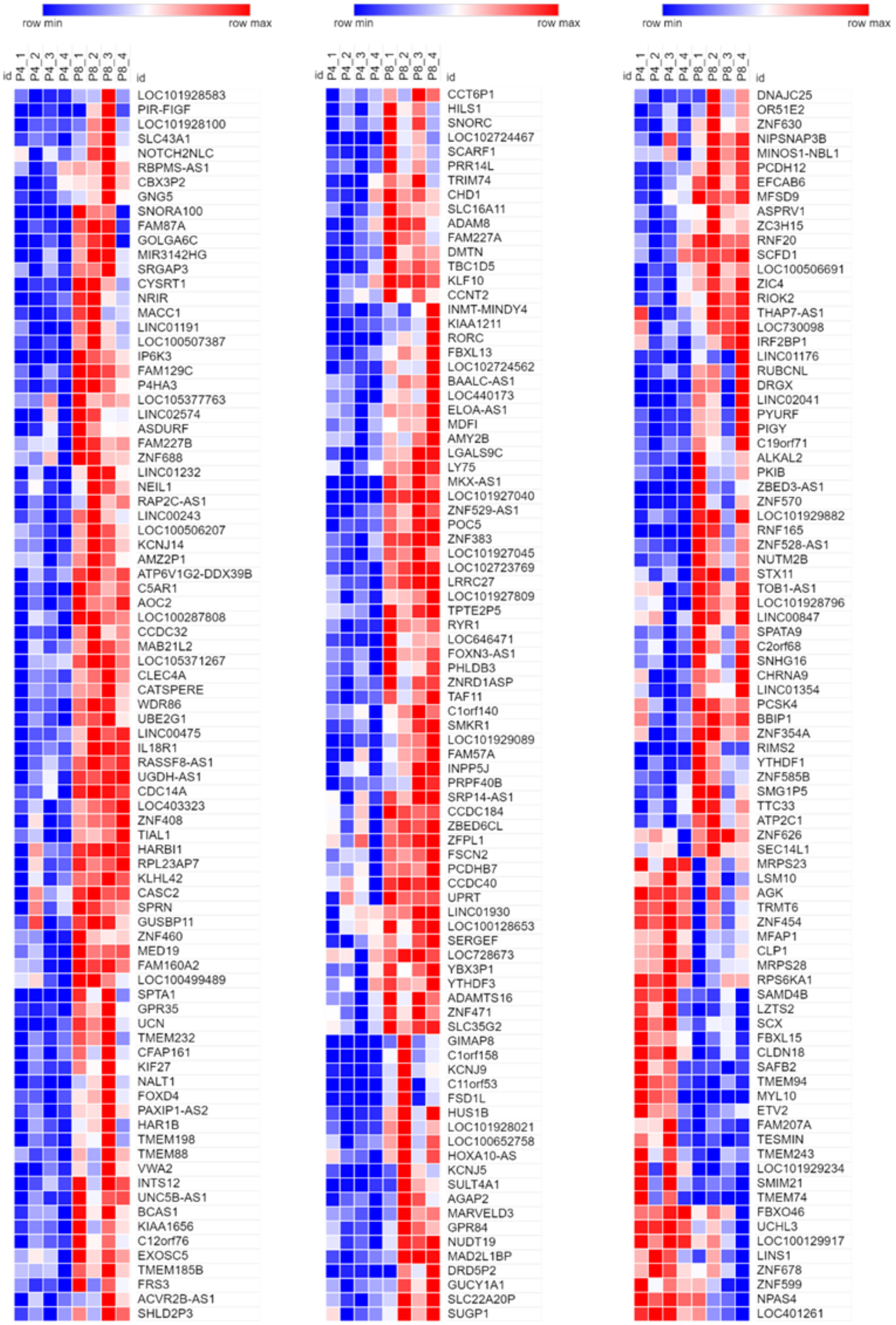
D

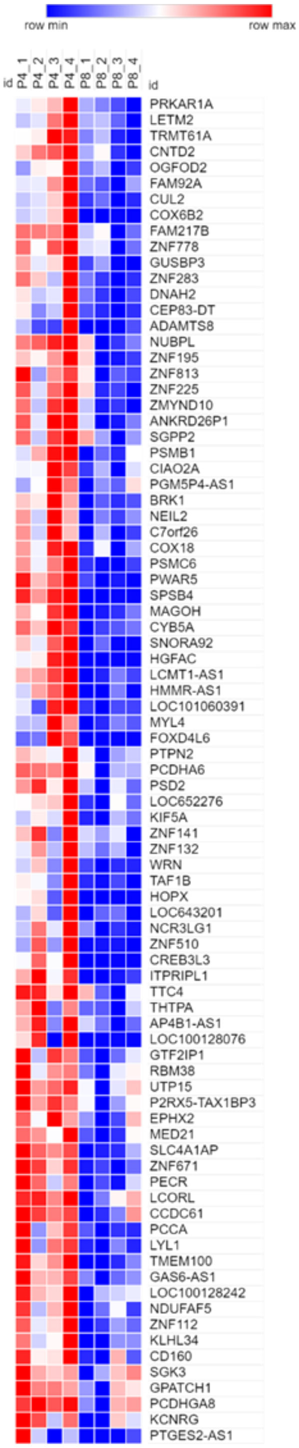
CD Marker	baseMean	log2(P8/P4)	CD Marker	baseMean	log2(P8/P4)
CD24	78.000524	-4.670	CD27	8.594487665	0.031
CD37	0.8846086	-2.208	CD81	35543.51401	0.056
CD1D	0.8738455	-2.070	CD27-AS1	375.023374	0.075
CD160	5.0522087	-1.802	CD47	3483.289107	0.139
CD22	0.6067068	-1.558	CD7	7.32564829	0.146
CD93	5.9327982	-1.201	CD46	3672.215982	0.179
CD4	9.9702786	-1.031	CD164	15683.86198	0.231
CD36	2959.4987	-0.848	CD226	7.311187496	0.254
CD248	82408.995	-0.638	CD2AP	1583.141664	0.379
CD59	48905.449	-0.625	CD70	42.09056305	0.425
CD300C	4.6817323	-0.622	CD302	830.211304	0.463
CD101	8.1601247	-0.572	CD83	22.10610543	0.481
CD81-AS1	14.948405	-0.541	CD58	275.9994606	0.507
CD109	9943.3047	-0.489	CD74	25.99002444	0.616
CD44	33621.445	-0.456	CD200R1	1.846806044	0.625
CD9	1748.9165	-0.432	CD96	6.120009505	0.696
CD40	28.185198	-0.407	CD33	1.101263924	0.930

E

CD320	2006.7097	-0.403	CD72	18.9656551	1.037
CD79A	6.4168097	-0.400	CD274	88.93980647	1.094
CD3EAP	744.93362	-0.392	CD55	2308.998904	1.123
CD151	23550.369	-0.248	CD34	588.6512124	1.169
CD68	5812.4687	-0.228	CD163L1	81.10102244	1.472
CD63	41303.909	-0.203	CD38	129.0682795	1.538
CD2BP2	2912.9015	-0.195	CD177	12.65214833	1.563
CD19	1.1106145	-0.160	CD82	531.3420725	1.702
CD276	8370.6867	-0.125	CD79B	1.162489724	1.759
CD99	32663.45	-0.043	CD28	2.504790373	2.078
			CD14	112.194181	2.277
			CD200	67.63061132	3.155
			CD80	7.499752035	3.502
			CD163	18.05600314	4.356

Supplementary Figure S13. Heatmaps for DEGs of P4 vs. P8 only in Venn Diagram.

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COX6B2
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ZNF283
DNAH2
CEP83-DT
ADAMTS8
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ZNF195
ZNF813
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ZMYND10
ANKRD26P1
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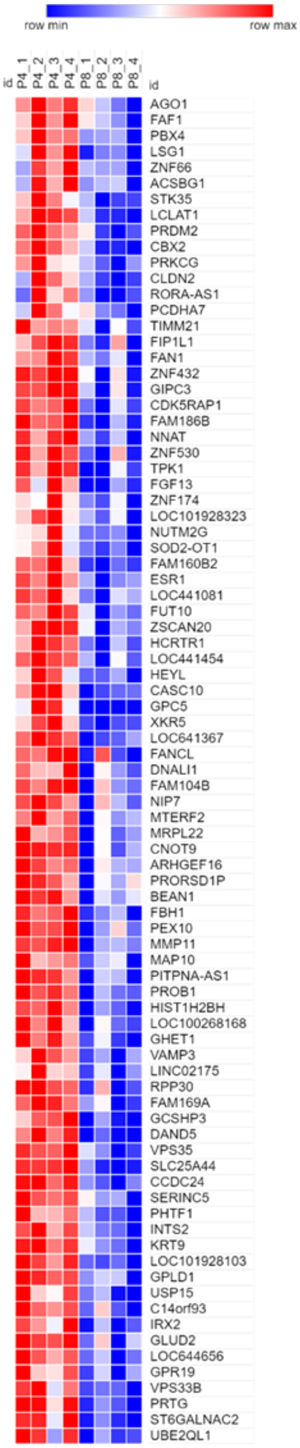
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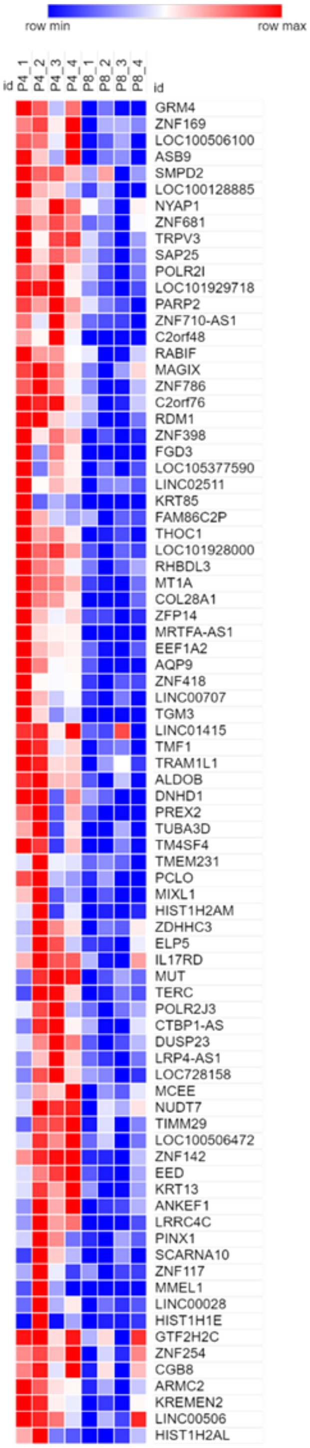
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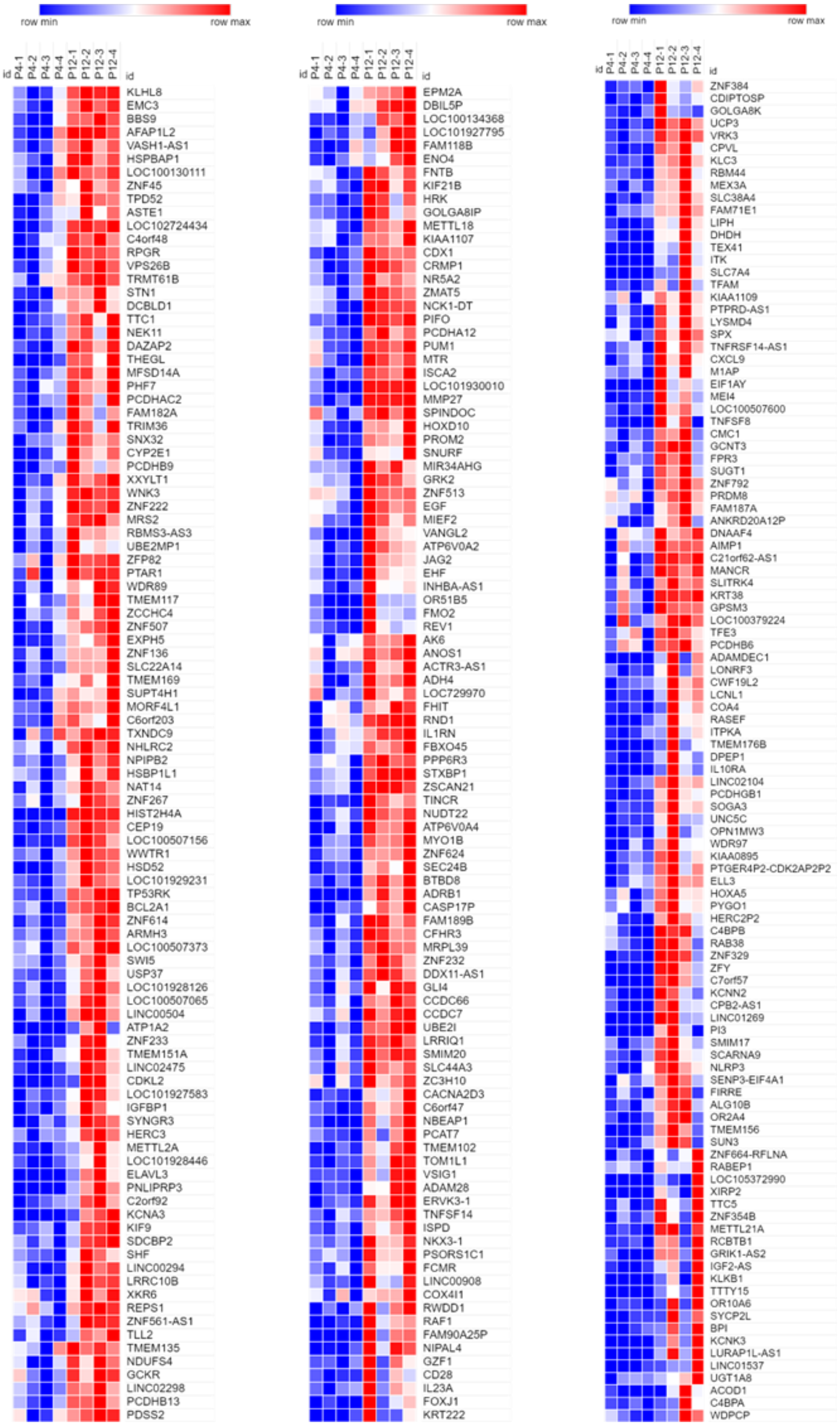
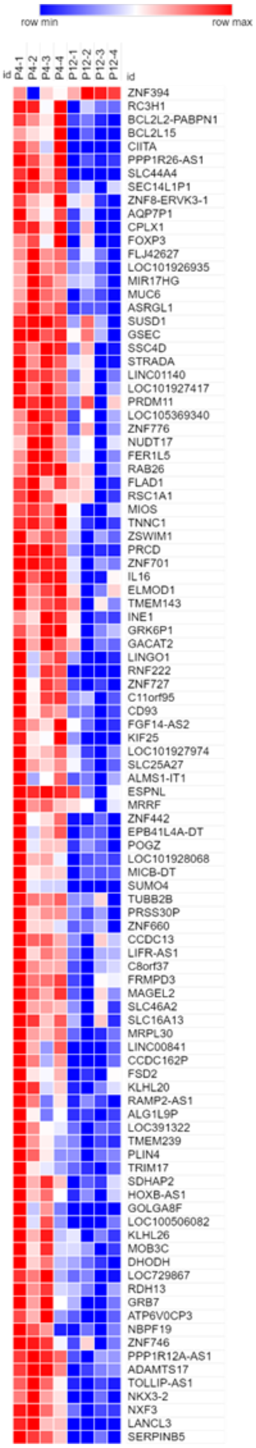
Supplementary Figure S14. Heatmaps for DEGs of P4 vs. P12 only in Venn Diagram.

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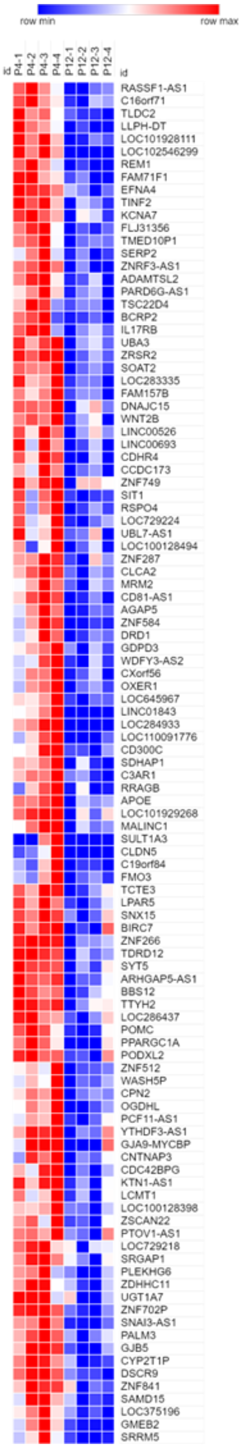
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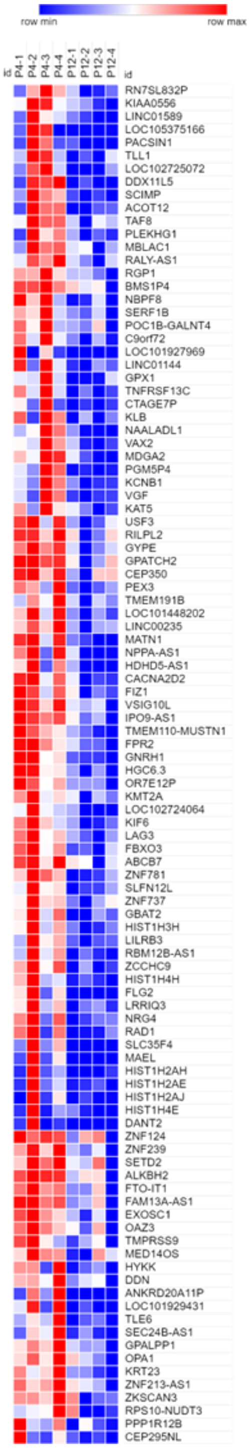
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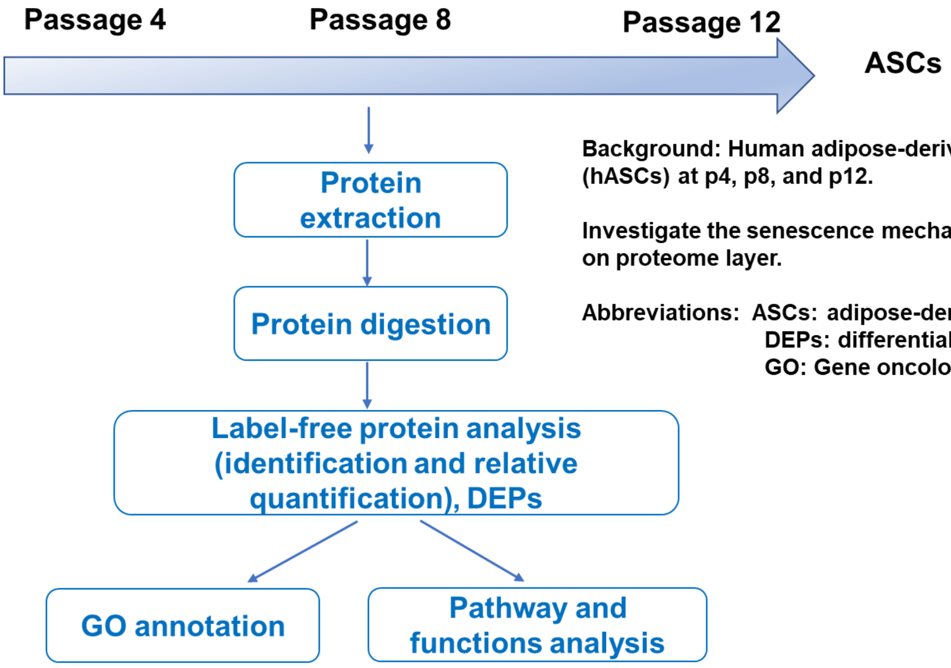
Supplementary Figure S15. Schematic of proteomics analysis work flow for hASCs at P4, P8, and P12.

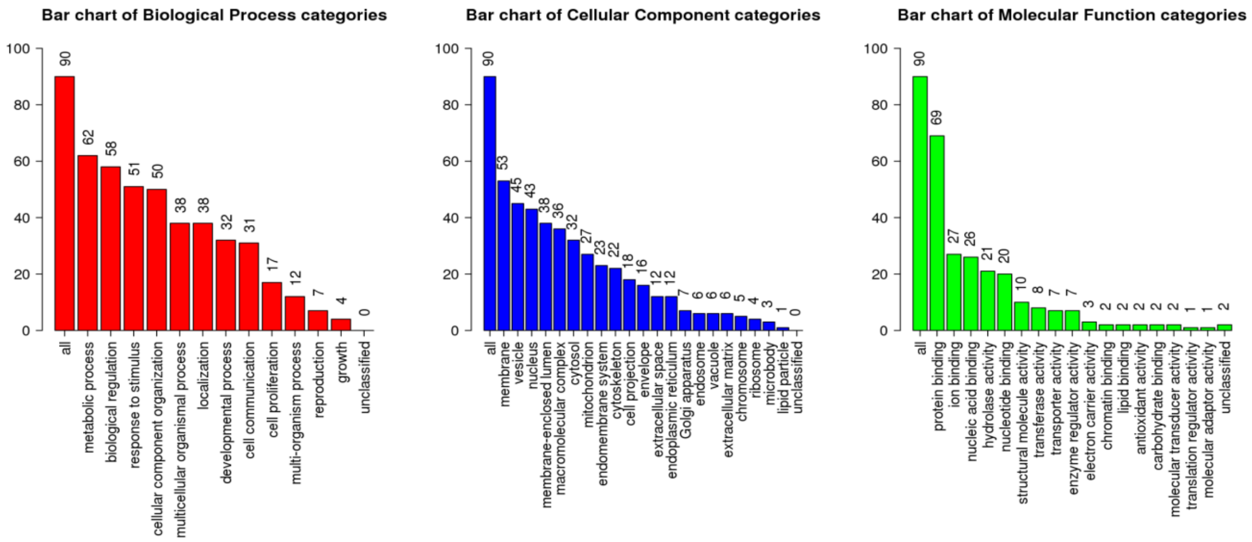


Background: Human adipose-derived stem cells (hASCs) at p4, p8, and p12.

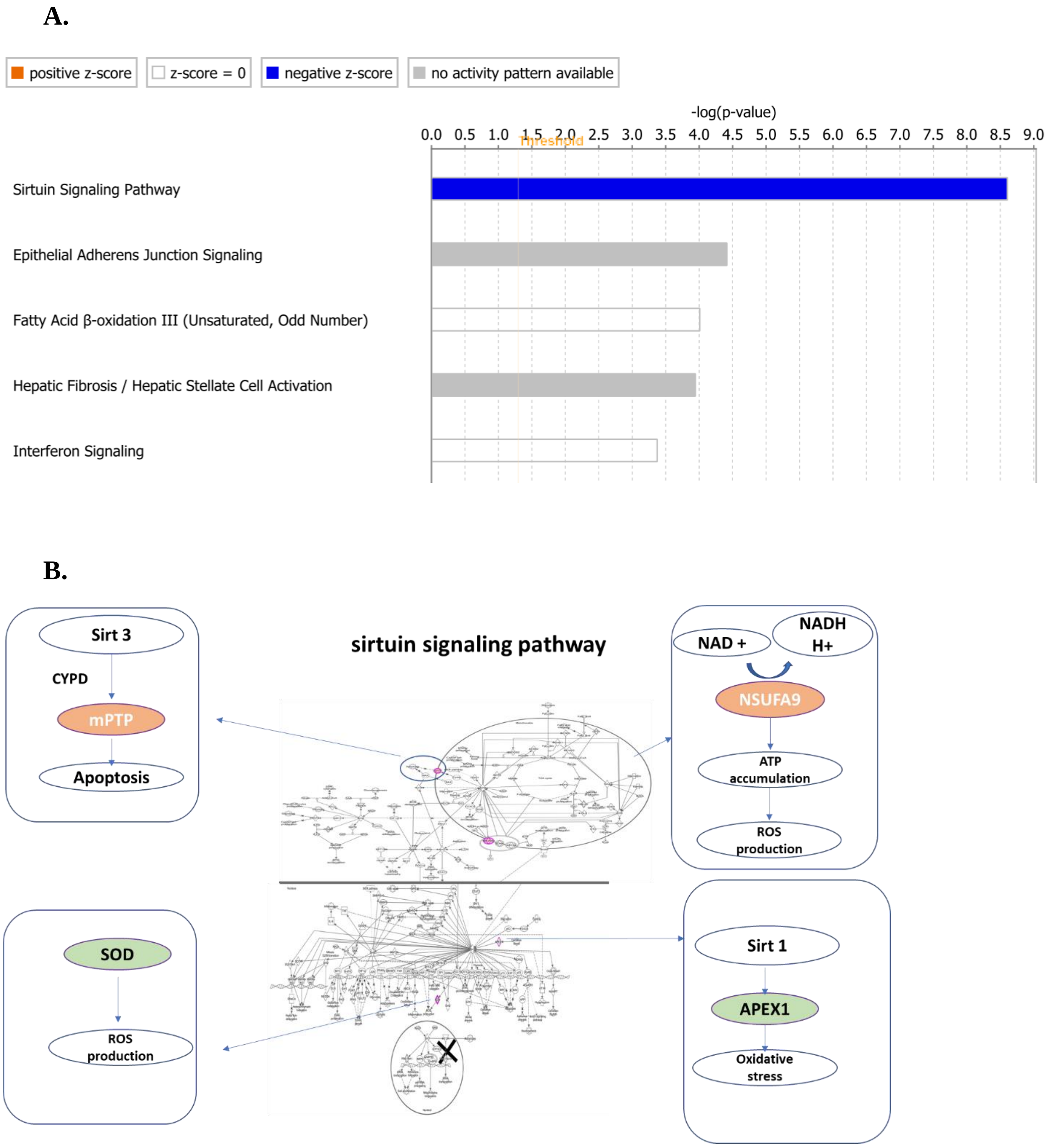
Investigate the senescence mechanism of hASCs based on proteome layer.

Abbreviations: ASCs: adipose-derived stem cells
DEPs: differentially expressed proteins
GO: Gene oncology

Supplementary Figure S16. GO analysis of DEPs (P8/P4 hASCs with 90 DEPs)



Supplementary Figure S17. Pathway enrichment analysis of DEPs (P8/P4)



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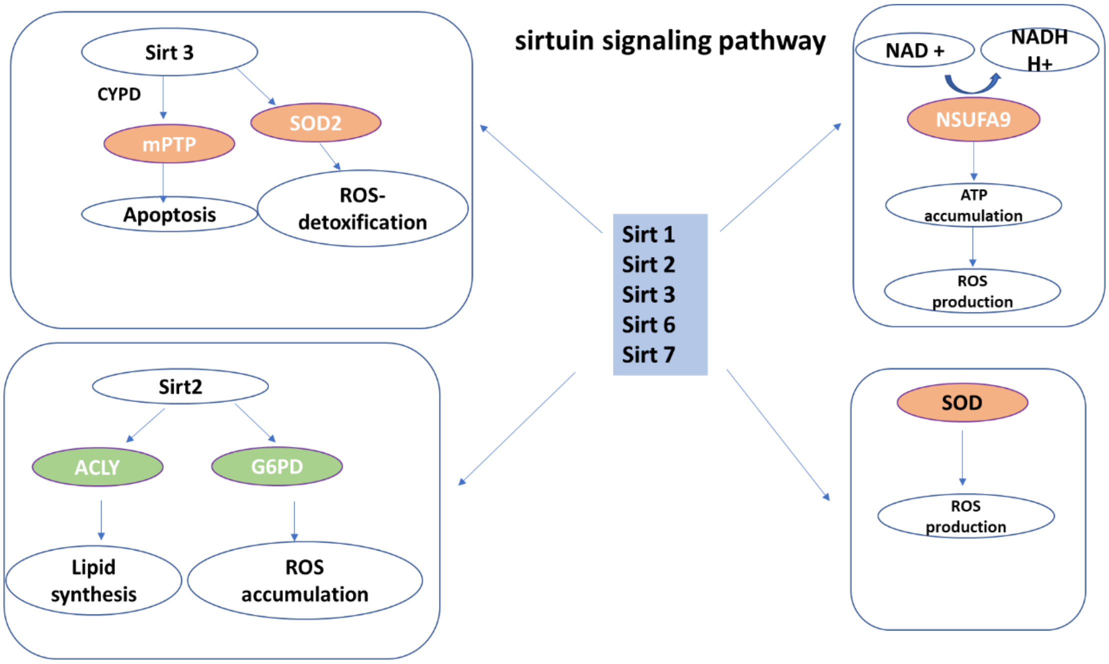
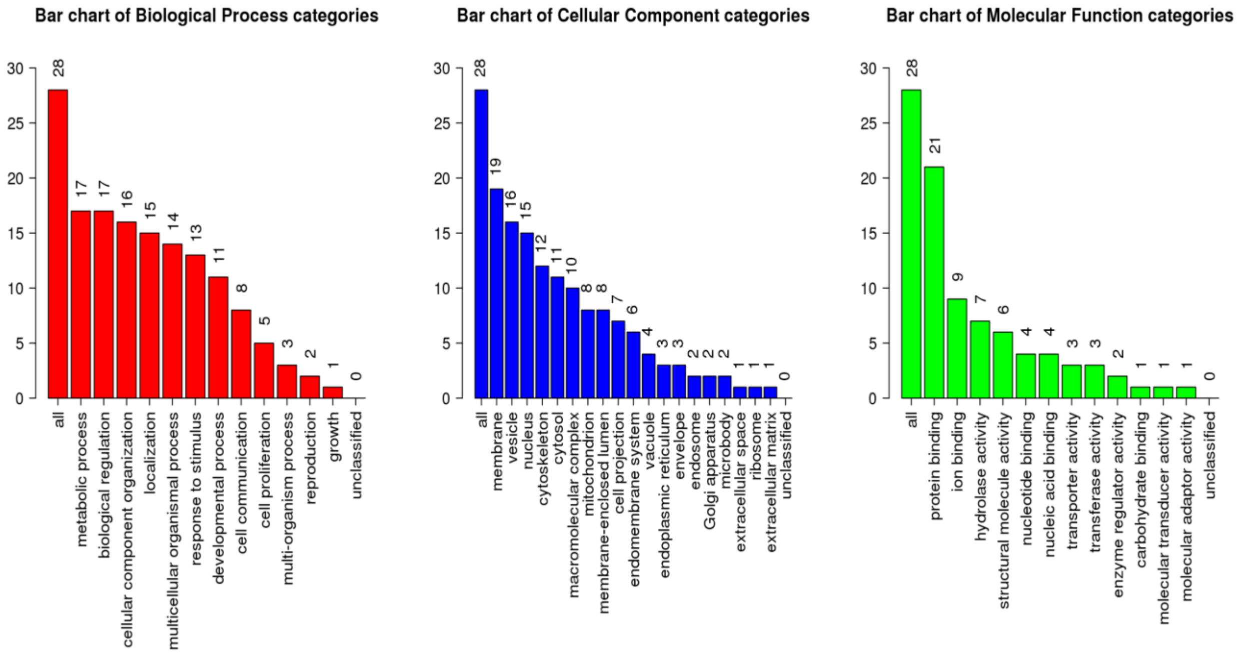


Supplementary Figure S18. GO analysis of DEPs overlapped between P8/P4 and P12/P4 hASCs.



Supplementary materials for RNA-Seq data analysis

Supplementary Spreadsheet 1. “P4_vs_P12_Deseq2_Plus” for RNA-Seq data analysis.

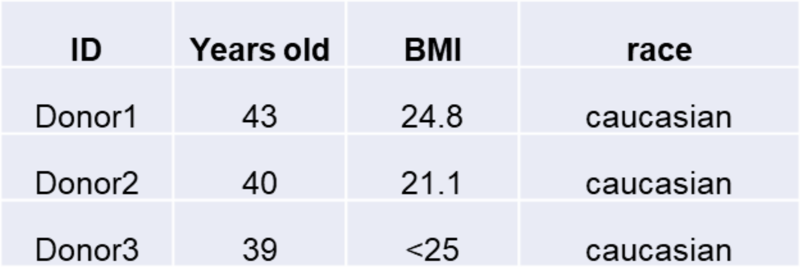
DEGs for P4 and P12 comparison.

Supplementary Spreadsheet 2. “P4_vs_P8_Deseq2_Plus” for RNA-Seq data analysis.

DEGs for P4 and P8 comparison.

Supplementary Tables

Supplementary Table S1. The donor information for the derived hASCs used in this study.



ID	Years old	BMI	race
Donor1	43	24.8	caucasian
Donor2	40	21.1	caucasian
Donor3	39	<25	caucasian

Supplementary Table S2. Primer sequences for target genes in RT-PCR analysis.

Gene	Forward primer 5' to 3'	Reverse primer 5' to 3'
Oct-4	CAGCAGATCAGCCACATCGCC	TGAGAAAGGAGACCCAGCAGCC
Nanog	CCTGTGATTTGTGGGCCTG	GACAGTCTCCGTGTGAGGCAT
SOX2	GTATCAGGAGTTGTCAAGGCAGAG	TCCTAGTCTTAAAGAGGCAGCAAAC
P53	CTGGACGACAGGCAGACTTT	GCACAAACACGAACCTCAAA
P15 (CDKN2B)	GCTGTTTCATCAGCAGCCTAA	TTCCACAATGGAGCTAGAAGCA
P21	GAGACTCTCAGGGTCGAAAACG	GGATTAGGGCTTCCTCTTGGAG
NFKB	GACGAGCTCCGAGACAGTGAC	GAGGCACCACTGGTCAGAGAC
mTOR	GCCTGGATGGCAACTACAGAA	CCAGTTCAGCAAGGGGTCATA
PIK3CA	TTGGAGAACTTGGCCTTCATCT	ACCCAATTAGGTCTGAGGACTGAA
AKT1	TATCGTGTGGCAGCACGTGTA	GCCGTGAACTCCTCATCAAAAT
PTEN	GGCTGCTGTTGGCTTATCAGT	AAACGCGGTAATTTTCAGAGC
SIRT1	TCGCAACTATACCCAGAACATAGACA	CTGTTGCAAAGGAACCATGACA
SIRT3	GCATCCCTGCCTCAAAGC	CGTCAGCCCGAATGTCCTC
CD38	TTCCCGCAGTTTTTCTTTGAA	GCACCTCTCAGCTGCCTACTG
CD73	GCCTGGGAGCTTACGATTTTG	TAGTGCCCTGGTACTGGTCG
NAMPT	CTCCATTCTGAGCACCAAACG	ATGCCATTTGCTTTTGTCTGG
PDK1	AAACAGGGGAGCTTTGTCTGG	CTGCCCATTCACATCCCTCTA
PKM2	AAAAATGGATGCCCAGAGGAC	GAGTCGGCTTCAATGGAACAA
LDHA	CCTTGAGCCAGGTGGATGTTT	CACTGGATCCCAGGATGTGAC
G6PD (GL6PD)	CTACCCGAGCCCAGCTACATT	TTCTGTTGGGCTGGAGTGAGT

6PGD (6PGLD)	CCATGCCCTGTTTTACCACTG	AGGTGTGAGCCCCGAAGTAAT
TALDO1	CTGTCATCAACCTGGGAAGGA	GGGCGAAGGAGAAGAGTAACG
TKTL1	ACCTTGGGATTCTGTGTGCTG	CCTAACAAGCTTTCGCTGCTG
TNFα	TGGCCAATGGCGTGGAGCTG	GTAGGAGACGGCGATGCGGC
IL-6	GAACTCCTTCTCCACAAGCG	TTTTCTGCCAGTGCCTCTTT
IL-1β	CCACAGACCTTCCAGGAGAATG	GTGCAGTTCAGTGATCGTACAGG
IL-12β	CCAAGGGGTGACGTGCGGAG	GGTGGGTCAGGTTTGATGATGTCCC
IL-10	AAGCCTGACCACGCTTTCTA	ATGAAGTGGTTGGGGAATGA
TGF- β	CCTACATTTGGAGCCTGGAC	TGTCCTTAAATACAGCCCCC
CD163	*CCAGTCCCAAACACTGTCCT*	*ATGCCAGTGAGCTTCCCGTTCAGC*
ALP	CAGTCTGCTGTGCCCCTGC	GTAGTTCTGCTCGTGGACGCC
BMP2	TTCCCCGTGACCAGACTTTTGG	GCCACTTCCACCACGAATCCAT
Osteocalcin	GGCAGCGAGGTAGTGAAGAGAC	GAAAGCCGATGTGGTCAGCCAA
Osteopontin	AGCGGAAAGCCAATGATGAGAGC	ACTTTTGGGGTCTACAACCAGCAT
Runx2	CCAACCCACGAATGCACTATC	TAGTGAGTGGTGGCGGACATAC
CEBPA	AGCCTTGTTTGTACTGTATG	AAAATGGTGGTTTAGCAGAG
FABP4	ACGAGAGGATGATAAACTGGTGG	GCGAACTTCAGTCCAGGTCAAC
LPL	CTGACCAAGGATAGTGGGATATAG	GGTAACTGAGCGAGACTGTGTCT
PPARG	AGCCTGCGAAAGCCTTTTGGTG	GGCTTCACATTCAGCAAACCTGG
TFEB	CCTGGTGGAGATTCCCTGTCT	CAGGACCAGTTGCCTCAGATG
BECN1	ACTGTGTTGCTGCTCCATGCT	AACGGCAGCTCCTTAGATTTGT
LAMP1	TCACACGTAGGACGCATGAAG	GAAGCGCTCCAGACACTCATC
MFN1	AAATGCTCAAAGGGTGCTCCT	GATGCATTATCTGGCGTTGCT
MFN2	GATGCCTGTCACCAAGGTGTT	TGCTTTTTGGGAGAGGTGTTG
FIS1	CTGGTGCGGAGCAAGTACAAT	CACGGCCAGGTAGAAGACGTA
DNM1L	CGATGCACTTTTCTCCAGCAC	TTCCGTTGTTTCTTGCCTCTG
GAPDH	TCACTGCCACCCAGAAGACTG	GGATGACCTTGCCCACAGC
TUB1a (TUBA1A)	TGAGGAGGTTGGTGTGGATTC	AAAAGCAGCACCTTTGTGACG

Supplementary Table S3. DEPs between P8 and P4 hASCs. For a total of 90 DEPs, 44 were up regulated and 46 were down regulated.

Protein name	Gene	Molecular Weight	Fold Change (p8 vs p4)
Protein AHNAK2	AHNAK2	617 kDa	8
Keratin, type I cytoskeletal 14	KRT14	52 kDa	6.6
Enoyl-CoA delta isomerase 2, mitochondrial	ECI2	44 kDa	5.2
Desmin	DES	54 kDa	5.2
Delta(3,5)-Delta(2,4)-dienoyl-CoA isomerase, mitochondrial	ECH1	36 kDa	3.8
Fibrillin-1	FBN1	312 kDa	3.3
Keratin, type II cytoskeletal 8	KRT8	54 kDa	3.3
Collagen alpha-3(VI) chain	COL6A3	344 kDa	3.3
Paraspeckle component 1	PSPC1	59 kDa	3.2
Nuclear mitotic apparatus protein 1	NUMA1	238 kDa	3.1
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 12	NDUFA12	17 kDa	3
Probable 28S rRNA (cytosine(4447)-C(5))-methyltransferase	NOP2	89 kDa	2.9
Acyl-coenzyme A thioesterase 9, mitochondrial	ACOT9	50 kDa	2.8
Lysosomal protective protein	CTSA	54 kDa	2.7
NAD-dependent malic enzyme, mitochondrial	ME2	65 kDa	2.7
Ribosome production factor 2 homolog	RPF2	36 kDa	2.7
Early endosome antigen 1	EEA1	162 kDa	2.7
Pyrroline-5-carboxylate reductase 1, mitochondrial	PYCR1	33 kDa	2.7
Ferrochelatase, mitochondrial	FECH	48 kDa	2.6
Lon protease homolog, mitochondrial	LONP1	106 kDa	2.6
Serine/arginine repetitive matrix protein 2	SRRM2	300 kDa	2.5
Mitochondrial import inner membrane translocase subunit Tim13	TIMM13	11 kDa	2.5
Monofunctional C1-tetrahydrofolate synthase, mitochondrial	MTHFD1L	106 kDa	2.5
Heat shock protein beta-7	HSPB7	19 kDa	2.5
Ras-related protein R-Ras2	RRAS2	23 kDa	2.4
Mitochondrial import receptor subunit TOM40 homolog	TOMM40	38 kDa	2.4
Semaphorin-7A	SEMA7A	75 kDa	2.4
Transmembrane emp24 domain-containing protein 5	TMED5	26 kDa	2.4
U1 small nuclear ribonucleoprotein C	SNRPC	17 kDa	2.4
NADH dehydrogenase [ubiquinone] flavoprotein 1, mitochondrial	NDUFV1	51 kDa	2.3

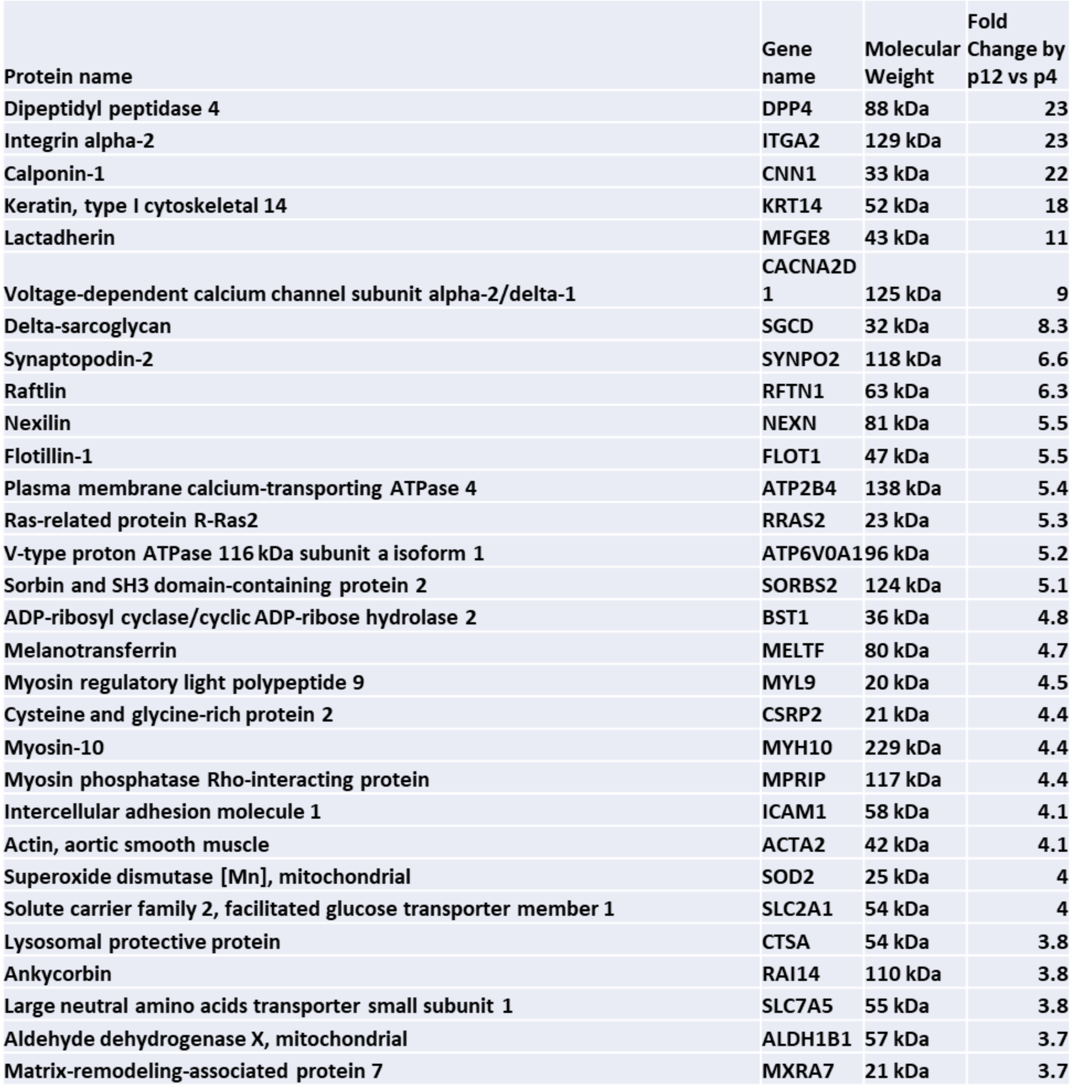
Adenosine deaminase	ADA	41 kDa	2.3
Heterogeneous nuclear ribonucleoprotein F	HNRNPF	46 kDa	2.2
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 9, mitochondrial	NDUFA9	43 kDa	2.2
40S ribosomal protein S27-like	RPS27L	9 kDa	2.2
Collagen alpha-2(VI) chain	COL6A2	109 kDa	2.2
Flotillin-1	FLOT1	47 kDa	2.2
Voltage-dependent anion-selective channel protein 3	VDAC3	31 kDa	2.2
Polycystin-2	PKD2	110 kDa	2.1
Epidermal growth factor receptor	EGFR	134 kDa	2.1
Isochorismatase domain-containing protein 2	ISOC2	22 kDa	2.1
ADP/ATP translocase 2	SLC25A5	33 kDa	2.1
Mitochondrial import inner membrane translocase subunit TIM50	TIMM50	40 kDa	2
Enoyl-CoA delta isomerase 1, mitochondrial	ECI1	33 kDa	2
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 8	NDUFA8	20 kDa	2
Acid ceramidase	ASAH1	45 kDa	-2
Protein S100-A4	S100A4	12 kDa	-2
60S ribosomal protein L26	RPL26	17 kDa	-2
Exportin-1	XPO1	123 kDa	-2
Glutamine--fructose-6-phosphate aminotransferase [isomerizing] 1	GFPT1	79 kDa	-2
Isocitrate dehydrogenase [NADP] cytoplasmic	IDH1	47 kDa	-2
Prostaglandin G/H synthase 1	PTGS1	69 kDa	-2
Bcl-2-associated transcription factor 1	BCLAF1	106 kDa	-2
DNA-(apurinic or apyrimidinic site) lyase	APEX1	36 kDa	-2
Peptidyl-tRNA hydrolase 2, mitochondrial	PTRH2	19 kDa	-2
Interferon-induced protein with tetratricopeptide repeats 3	IFIT3	56 kDa	-2
ATP-dependent DNA helicase Q1	RECQL	73 kDa	-2
60 kDa SS-A/Ro ribonucleoprotein	TROVE2	61 kDa	-2
Peptidase inhibitor 16	PI16	49 kDa	-2.5
Aldose reductase	AKR1B1	36 kDa	-2.5
High mobility group protein B1	HMGB1	25 kDa	-2.5
Microtubule-associated protein RP/EB family member 1	MAPRE1	30 kDa	-2.5

ATP-dependent 6-phosphofructokinase, platelet type	**PFKP**	**86 kDa**	**-2.5**
EH domain-containing protein 1	**EHD1**	**61 kDa**	**-2.5**
Malignant T-cell-amplified sequence 1	**MCTS1**	**21 kDa**	**-2.5**
Ubiquitin carboxyl-terminal hydrolase 5	**USP5**	**96 kDa**	**-2.5**
Cysteine and glycine-rich protein 2	**CSRP2**	**21 kDa**	**-2.5**
Drebrin-like protein	**DBNL**	**48 kDa**	**-2.5**
Actin-related protein 2/3 complex subunit 3	**ARPC3**	**21 kDa**	**-2.5**
ADP/ATP translocase 1	**SLC25A4**	**33 kDa**	**-2.5**
Bifunctional purine biosynthesis protein PURH	**ATIC**	**65 kDa**	**-2.5**
Hepatoma-derived growth factor	**HDGF**	**27 kDa**	**-2.5**
Sorbin and SH3 domain-containing protein 2	**SORBS2**	**124 kDa**	**-2.5**
Interferon-induced GTP-binding protein Mx2	**MX2**	**82 kDa**	**-2.5**
Puromycin-sensitive aminopeptidase	**NPEPPS**	**103 kDa**	**-2.5**
Protein YIF1B	**YIF1B**	**34 kDa**	**-2.5**
Interferon-induced protein with tetratricopeptide repeats 1	**IFIT1**	**55 kDa**	**-2.5**
A-kinase anchor protein 12	**AKAP12**	**191 kDa**	**-2.5**
1,4-alpha-glucan-branching enzyme	**GBE1**	**80 kDa**	**-2.5**
NAD(P)H dehydrogenase [quinone] 1	**NQO1**	**31 kDa**	**-2.5**
Calponin-1	**CNN1**	**33 kDa**	**-3.3**
Myosin-10	**MYH10**	**229 kDa**	**-3.3**
Phosphoglucomutase-1	**PGM1**	**61 kDa**	**-3.3**
Purine nucleoside phosphorylase	**PNP**	**32 kDa**	**-3.3**
Integrin alpha-1	**ITGA1**	**131 kDa**	**-3.3**
Kinesin-1 heavy chain	**KIF5B**	**110 kDa**	**-3.3**
Dihydropyrimidinase-related protein 3	**DPYSL3**	**62 kDa**	**-3.3**
Myosin light chain 1/3, skeletal muscle isoform	**MYL1**	**21 kDa**	**-5**
Interferon-induced GTP-binding protein Mx1	**MX1**	**76 kDa**	**-5**
Protein-glutamine gamma-glutamyltransferase 2	**TGM2**	**77 kDa**	**-10**
Myosin-7	**MYH7**	**223 kDa**	**-14.3**

Supplementary Table S4. Upstream analysis of DEPs (P8/P4 hASCs)

Upstream Regulator	Molecule Type	Predicted Activation State	Activation z-score	p-value of overlap	Target molecules in dataset
MAPK1	kinase	Activated	2.236	0.0157	EHD1,IFIT1,IFIT3,MX2,MYH7
SB203580	chemical - kinase inhibitor	Activated	2.213	0.0413	IFIT1,IFIT3,MX1,NQO1,TGM2
fluticasone propionate	chemical drug	Activated	2	0.00578	IFIT1,MX1,PTGS1,TGM2
mir-122	microRNA	Activated	2	0.000531	KIF5B,MAPRE1,NPEPPS,TGM2
BTK	kinase	Activated	2	0.00012	CTSA,IFIT1,IFIT3,MX1,MX2
oblimersen	biologic drug	Inhibited	-2	7.91E-05	IFIT1,IFIT3,MX1,MX2
TLR7	transmembrane receptor	Inhibited	-2	0.00366	IFIT1,IFIT3,MX1,MX2
CREB1	transcription regulator	Inhibited	-2	0.00916	ARPC3,CNN1,CSRP2,MYH10,NDUFV1,RRAS2,SEMA7A
lipopolysaccharide	chemical drug	Inhibited	-2.033	0.00129	ADA,APEX1,EHD1,FBN1,HDGF,HMGB1,IDH1,IFIT1,IFIT3,MCTS1,MX1,MX2,MYH7,NQO1,PFKP,PTGS1,TGM2
Interferon alpha	group	Inhibited	-2.082	0.0378	EGFR,IFIT1,IFIT3,MX1,MX2
IFNA2	cytokine	Inhibited	-2.18	0.00314	IFIT1,IFIT3,MX1,MX2,TGM2
IL1B	cytokine	Inhibited	-2.551	0.00174	AKR1B1,HMGB1,IFIT1,IFIT3,ITGA1,MX1,NQO1,PFKP,PTGS1,SLC25A4,TGM2
tretinoin	chemical - endogenous mammalian	Inhibited	-2.636	1.73E-06	ADA,AKAP12,APEX1,COL6A3,DPYSL3,ECI2,EGFR,EHD1,HDGF,HNRNPF,IFIT1,IFIT3,ITGA1,KRT14,MYH7,NDUFV1,PNP,PTGS1,RPF2,SEMA7A,TGM2

Supplementary Table S5. DEPs between P12 and P4 hASCs. For a total of 318 DEPs, 86 were up regulated, and 232 were down regulated.



Protein name	Gene name	Molecular Weight	Fold Change by p12 vs p4
Dipeptidyl peptidase 4	DPP4	88 kDa	23
Integrin alpha-2	ITGA2	129 kDa	23
Calponin-1	CNN1	33 kDa	22
Keratin, type I cytoskeletal 14	KRT14	52 kDa	18
Lactadherin	MFGE8	43 kDa	11
Voltage-dependent calcium channel subunit alpha-2/delta-1	CACNA2D 1	125 kDa	9
Delta-sarcoglycan	SGCD	32 kDa	8.3
Synaptopodin-2	SYNPO2	118 kDa	6.6
Raftlin	RFTN1	63 kDa	6.3
Nexilin	NEXN	81 kDa	5.5
Flotillin-1	FLOT1	47 kDa	5.5
Plasma membrane calcium-transporting ATPase 4	ATP2B4	138 kDa	5.4
Ras-related protein R-Ras2	RRAS2	23 kDa	5.3
V-type proton ATPase 116 kDa subunit a isoform 1	ATP6V0A1	96 kDa	5.2
Sorbin and SH3 domain-containing protein 2	SORBS2	124 kDa	5.1
ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase 2	BST1	36 kDa	4.8
Melanotransferrin	MELTF	80 kDa	4.7
Myosin regulatory light polypeptide 9	MYL9	20 kDa	4.5
Cysteine and glycine-rich protein 2	CSRP2	21 kDa	4.4
Myosin-10	MYH10	229 kDa	4.4
Myosin phosphatase Rho-interacting protein	MPRIP	117 kDa	4.4
Intercellular adhesion molecule 1	ICAM1	58 kDa	4.1
Actin, aortic smooth muscle	ACTA2	42 kDa	4.1
Superoxide dismutase [Mn], mitochondrial	SOD2	25 kDa	4
Solute carrier family 2, facilitated glucose transporter member 1	SLC2A1	54 kDa	4
Lysosomal protective protein	CTSA	54 kDa	3.8
Ankycorbin	RAI14	110 kDa	3.8
Large neutral amino acids transporter small subunit 1	SLC7A5	55 kDa	3.8
Aldehyde dehydrogenase X, mitochondrial	ALDH1B1	57 kDa	3.7
Matrix-remodeling-associated protein 7	MXRA7	21 kDa	3.7

Cell migration-inducing and hyaluronan-binding protein	**CEMIP**	**153 kDa**	**3.7**
Plasma membrane calcium-transporting ATPase 1	**ATP2B1**	**135 kDa**	**3.4**
Endoplasmic reticulum junction formation protein lunapark	**LNPK**	**48 kDa**	**3.2**
HLA class I histocompatibility antigen, B-44 alpha chain	**HLA-B**	**40 kDa**	**3.2**
BAG family molecular chaperone regulator 2	**BAG2**	**24 kDa**	**3.1**
ADP/ATP translocase 1	**SLC25A4**	**33 kDa**	**3.1**
Glutaredoxin-1	**GLRX**	**12 kDa**	**3**
Integrin beta-1	**ITGB1**	**88 kDa**	**2.9**
Selenoprotein M	**SELENOM**	**16 kDa**	**2.9**
Stromal interaction molecule 1	**STIM1**	**77 kDa**	**2.9**
Gamma-glutamyl hydrolase	**GGH**	**36 kDa**	**2.9**
Acid ceramidase	**ASAH1**	**45 kDa**	**2.9**
Mitochondrial import inner membrane translocase subunit Tim13	**TIMM13**	**11 kDa**	**2.8**
Peroxisomal acyl-coenzyme A oxidase 1	**ACOX1**	**74 kDa**	**2.8**
Guanine nucleotide-binding protein subunit beta-4	**GNB4**	**38 kDa**	**2.7**
Delta(3,5)-Delta(2,4)-dienoyl-CoA isomerase, mitochondrial	**ECH1**	**36 kDa**	**2.7**
Utrophin	**UTRN**	**394 kDa**	**2.7**
Retinol dehydrogenase 10	**RDH10**	**38 kDa**	**2.7**
Microtubule-associated protein 1A	**MAP1A**	**305 kDa**	**2.6**
DnaJ homolog subfamily C member 5	**DNAJC5**	**22 kDa**	**2.6**
Polycystin-2	**PKD2**	**110 kDa**	**2.6**
Multidrug resistance-associated protein 4	**ABCC4**	**150 kDa**	**2.6**
Perilipin-2	**PLIN2**	**48 kDa**	**2.6**
GRAM domain-containing protein 2B	**GRAMD2B**	**48 kDa**	**2.6**
Cysteine and glycine-rich protein 1	**CSRP1**	**21 kDa**	**2.5**
N-acetylglucosamine-6-sulfatase	**GNS**	**62 kDa**	**2.5**
Copine-3	**CPNE3**	**60 kDa**	**2.5**
Polypeptide N-acetylgalactosaminyltransferase 2	**GALNT2**	**65 kDa**	**2.5**
Annexin A7	**ANXA7**	**53 kDa**	**2.5**
Enoyl-CoA delta isomerase 2, mitochondrial	**ECI2**	**44 kDa**	**2.5**

Heterogeneous nuclear ribonucleoprotein H3	HNRNPH3	37 kDa	0.5
Septin-7	SEPT7	51 kDa	0.5
Heterogeneous nuclear ribonucleoprotein A1	HNRNPA1	39 kDa	0.5
Procollagen galactosyltransferase 1	COLGALT1	72 kDa	0.5
Eukaryotic translation initiation factor 4 gamma 1	EIF4G1	175 kDa	0.5
Peptidyl-prolyl cis-trans isomerase FKBP3	FKBP3	25 kDa	0.5
Collagen alpha-1(XII) chain	COL12A1	333 kDa	0.5
Peptidyl-prolyl cis-trans isomerase FKBP7	FKBP7	26 kDa	0.5
ADP-ribosylation factor-like protein 1	ARL1	20 kDa	0.5
40S ribosomal protein S28	RPS28	8 kDa	0.5
Elongation factor 2	EEF2	95 kDa	0.5
Nuclear transport factor 2	NUTF2	14 kDa	0.5
Heterogeneous nuclear ribonucleoprotein U	HNRNPU	91 kDa	0.5
E3 ubiquitin/ISG15 ligase TRIM25	TRIM25	71 kDa	0.5
Proteasome subunit beta type-1	PSMB1	26 kDa	0.5
Coiled-coil domain-containing protein 47	CCDC47	56 kDa	0.5
Vigilin	HDLBP	141 kDa	0.5
Far upstream element-binding protein 1	FUBP1	68 kDa	0.5
Splicing factor 3A subunit 3	SF3A3	59 kDa	0.5
26S proteasome non-ATPase regulatory subunit 4	PSMD4	41 kDa	0.5
ATP-dependent RNA helicase A	DHX9	141 kDa	0.5
RNA-binding protein Raly	RALY	32 kDa	0.5
Serine hydroxymethyltransferase, mitochondrial	SHMT2	56 kDa	0.5
Guanine nucleotide-binding protein subunit alpha-13	GNA13	44 kDa	0.5
Cytoplasmic dynein 1 heavy chain 1	DYNC1H1	532 kDa	0.5
60S ribosomal protein L36	RPL36	12 kDa	0.5
Elongation factor 1-alpha 1	EEF1A1	50 kDa	0.5
RNA-binding protein 3	RBM3	17 kDa	0.5
26S proteasome regulatory subunit 7	PSMC2	49 kDa	0.5

Leucyl-cystinyl aminopeptidase	LNPEP	117 kDa	2.4
Reticulon-3	RTN3	113 kDa	2.4
Neudesin	NENF	19 kDa	2.4
Multidrug resistance-associated protein 1	ABCC1	172 kDa	2.4
Solute carrier family 12 member 4	SLC12A4	121 kDa	2.3
Dynamin-like 120 kDa protein, mitochondrial	OPA1	112 kDa	2.3
Tropomyosin alpha-3 chain	TPM3	33 kDa	2.3
PDZ and LIM domain protein 5	PDLIM5	64 kDa	2.3
Plasminogen activator inhibitor 1	SERPINE1	45 kDa	2.2
Lysosome membrane protein 2	SCARB2	54 kDa	2.2
MICOS complex subunit MIC19	CHCHD3	26 kDa	2.2
Connective tissue growth factor	CTGF	38 kDa	2.2
V-type proton ATPase subunit d 1	ATP6V0D1	40 kDa	2.2
Procollagen-lysine,2-oxoglutarate 5-dioxygenase 2	PLOD2	85 kDa	2.2
Lysosomal acid glucosylceramidase	GBA	60 kDa	2.2
Protein O-mannosyl-transferase TMTC3	TMTC3	104 kDa	2.1
ATP synthase subunit gamma, mitochondrial	ATP5F1C	33 kDa	2.1
Guanine nucleotide-binding protein G(q) subunit alpha	GNAQ	42 kDa	2.1
Thy-1 membrane glycoprotein	THY1	18 kDa	2.1
Calpain-1 catalytic subunit	CAPN1	82 kDa	2.1
Glia-derived nexin	SERPINE2	44 kDa	2.1
Lysyl oxidase homolog 2	LOXL2	87 kDa	2.1
Inorganic pyrophosphatase	PPA1	33 kDa	2.1
CD166 antigen	ALCAM	65 kDa	2.1
Tropomyosin beta chain	TPM2	33 kDa	2
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 9, mitochondrial	NDUFA9	43 kDa	2
Moesin	MSN	68 kDa	0.5
Nascent polypeptide-associated complex subunit alpha, muscle-specific form	NACA	205 kDa	0.5
Poly(U)-binding-splicing factor PUF60	PUF60	60 kDa	0.5
Interleukin enhancer-binding factor 3	ILF3	95 kDa	0.5
Nucleolar protein 58	NOP58	60 kDa	0.5
Oligoribonuclease, mitochondrial	REXO2	27 kDa	0.5
Caprin-1	CAPRIN1	78 kDa	0.5
Ribosomal L1 domain-containing protein 1	RSL1D1	55 kDa	0.5
RNA-binding protein FUS	FUS	53 kDa	0.5
Insulin-like growth factor 2 mRNA-binding protein 2	IGF2BP2	66 kDa	0.5
Keratin, type II cytoskeletal 8	KRT8	54 kDa	0.5
Neutral amino acid transporter B(0)	SLC1A5	57 kDa	0.5
Alpha-enolase	ENO1	47 kDa	0.5
Collagen alpha-1(I) chain	COL1A1	139 kDa	0.5
Sorting nexin-9	SNX9	67 kDa	0.5
26S proteasome regulatory subunit 6A	PSMC3	49 kDa	0.5
Plectin	PLEC	532 kDa	0.4
Spliceosome RNA helicase DDX39B	DDX39B	49 kDa	0.4
40S ribosomal protein S10	RPS10	19 kDa	0.4
Glucose-6-phosphate isomerase	GPI	63 kDa	0.4
Rab GDP dissociation inhibitor beta	GDI2	51 kDa	0.4
Dynein light chain 1, cytoplasmic	DYNLL1	10 kDa	0.4
Proteasome subunit alpha type-7	PSMA7	28 kDa	0.4
Glutamine--fructose-6-phosphate aminotransferase [isomerizing] 1	GFPT1	79 kDa	0.4
Non-POU domain-containing octamer-binding protein	NONO	54 kDa	0.4
Poly(rC)-binding protein 2	PCBP2	39 kDa	0.4
Creatine kinase B-type	CKB	43 kDa	0.4
Alpha-centractin	ACTR1A	43 kDa	0.4
Emerin	EMD	29 kDa	0.4
26S proteasome non-ATPase regulatory subunit 2	PSMD2	100 kDa	0.4
Heterogeneous nuclear ribonucleoprotein R	HNRNPR	71 kDa	0.4
Eukaryotic translation initiation factor 5A-1	EIF5A	17 kDa	0.4
Probable ATP-dependent RNA helicase DDX17	DDX17	80 kDa	0.4
Actin-related protein 2/3 complex subunit 3	ARPC3	21 kDa	0.4
Histone H2B type 1-B	HIST1H2BB	14 kDa	0.4

Serine/arginine-rich splicing factor 9	SRSF9	26 kDa	0.4
Histone H4	HIST1H4A	11 kDa	0.4
Myristoylated alanine-rich C-kinase substrate	MARCKS	32 kDa	0.4
Proteasome subunit beta type-4	PSMB4	29 kDa	0.4
Heterogeneous nuclear ribonucleoprotein L	HNRNPL	64 kDa	0.4
Drebrin-like protein	DBNL	48 kDa	0.4
Serine/threonine-protein phosphatase PP1-alpha catalytic subunit	PPP1CA	38 kDa	0.4
Transforming growth factor beta-1-induced transcript 1 protein	TGFB1I1	50 kDa	0.4
Splicing factor U2AF 65 kDa subunit	U2AF2	54 kDa	0.4
Microtubule-associated protein RP/EB family member 1	MAPRE1	30 kDa	0.4
U1 small nuclear ribonucleoprotein 70 kDa	SNRNP70	52 kDa	0.4
Integrin-linked protein kinase	ILK	51 kDa	0.4
Signal recognition particle subunit SRP72	SRP72	75 kDa	0.4
U1 small nuclear ribonucleoprotein A	SNRPA	31 kDa	0.4
26S proteasome non-ATPase regulatory subunit 14	PSMD14	35 kDa	0.4
Nesprin-1	SYNE1	1011 kDa	0.4
Protein NOXP20	FAM114A1	61 kDa	0.4
Eukaryotic translation initiation factor 3 subunit F	EIF3F	38 kDa	0.4
Alpha-parvin	PARVA	42 kDa	0.4
TAR DNA-binding protein 43	TARDBP	45 kDa	0.4
Nucleoside diphosphate kinase B	NME2	17 kDa	0.4
Phenylalanine--tRNA ligase alpha subunit	FARSA	58 kDa	0.4
Eukaryotic translation initiation factor 3 subunit D	EIF3D	64 kDa	0.4
Far upstream element-binding protein 3	FUBP3	62 kDa	0.4
Sorting nexin-3	SNX3	19 kDa	0.4
X-ray repair cross-complementing protein 6	XRCC6	70 kDa	0.4
Protein transport protein Sec24D	SEC24D	113 kDa	0.4
THO complex subunit 4	ALYREF	27 kDa	0.4
Pre-mRNA-processing-splicing factor 8	PRPF8	274 kDa	0.4
Nuclease-sensitive element-binding protein 1	YBX1	36 kDa	0.4
Fermitin family homolog 2	FERMT2	78 kDa	0.4
Arginine--tRNA ligase, cytoplasmic	RARS	75 kDa	0.4
Importin subunit alpha-4	KPNA3	58 kDa	0.4
Erythrocyte band 7 integral membrane protein	STOM	32 kDa	0.4
Glutathione S-transferase P	GSTP1	23 kDa	0.4
Heat shock protein HSP 90-beta	HSP90AB1	83 kDa	0.4
Tensin-1	TNS1	186 kDa	0.4
Elongin-C	ELOC	12 kDa	0.4
UV excision repair protein RAD23 homolog B	RAD23B	43 kDa	0.4
Ubiquitin-like modifier-activating enzyme 1	UBA1	118 kDa	0.4
E3 UFM1-protein ligase 1	UFL1	90 kDa	0.4
Poly(rC)-binding protein 1	PCBP1	37 kDa	0.4
Plasminogen activator inhibitor 1 RNA-binding protein	SERBP1	45 kDa	0.4
Serpin B6	SERPINB6	43 kDa	0.4
Importin-5	IPO5	124 kDa	0.4
Alpha-adducin	ADD1	81 kDa	0.4
Branched-chain-amino-acid aminotransferase, cytosolic	BCAT1	43 kDa	0.4
Multiple coagulation factor deficiency protein 2	MCFD2	16 kDa	0.4
Splicing factor, proline- and glutamine-rich	SFPQ	76 kDa	0.4
Valine--tRNA ligase	VARS	140 kDa	0.4
40S ribosomal protein S15	RPS15	17 kDa	0.4
Calcium-binding mitochondrial carrier protein SCaMC-1	SLC25A24	53 kDa	0.4
Eukaryotic peptide chain release factor subunit 1	ETF1	49 kDa	0.4
Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A alpha isoform	PPP2R1A	65 kDa	0.4
ATP-dependent 6-phosphofructokinase, liver type	PFKL	85 kDa	0.4
Interleukin enhancer-binding factor 2	ILF2	43 kDa	0.4
Proteasome subunit alpha type-5	PSMA5	26 kDa	0.4
DNA damage-binding protein 1	DDB1	127 kDa	0.4
Adenylate kinase isoenzyme 1	AK1	22 kDa	0.4
T-complex protein 1 subunit theta	CCT8	60 kDa	0.4

Niban-like protein 1	FAM129B	84 kDa	0.4
HLA class I histocompatibility antigen, A-3 alpha chain	HLA-A	41 kDa	0.4
Aspartate--tRNA ligase, cytoplasmic	DARS	57 kDa	0.4
60S ribosomal protein L35	RPL35	15 kDa	0.4
GTPase NRas	NRAS	21 kDa	0.4
Proteasome subunit alpha type-1	PSMA1	30 kDa	0.4
Transketolase	TKT	68 kDa	0.4
Nucleoprotein TPR	TPR	267 kDa	0.4
Probable ATP-dependent RNA helicase DDX5	DDX5	69 kDa	0.3
ATP-citrate synthase	ACLY	121 kDa	0.3
Apoptosis inhibitor 5	API5	59 kDa	0.3
T-complex protein 1 subunit gamma	CCT3	61 kDa	0.3
Glutathione S-transferase omega-1	GSTO1	28 kDa	0.3
60S ribosomal protein L26	RPL26	17 kDa	0.3
Golgi resident protein GCP60	ACBD3	61 kDa	0.3
ATP-dependent 6-phosphofructokinase, platelet type	PFKP	86 kDa	0.3
DNA-dependent protein kinase catalytic subunit	PRKDC	469 kDa	0.3
Pyrroline-5-carboxylate reductase 1, mitochondrial	PYCR1	33 kDa	0.3
Eukaryotic translation initiation factor 3 subunit B	EIF3B	92 kDa	0.3
Tyrosine--tRNA ligase, cytoplasmic	YARS	59 kDa	0.3
SUN domain-containing protein 2	SUN2	80 kDa	0.3
Dolichol-phosphate mannosyltransferase subunit 1	DPM1	30 kDa	0.3
Apolipoprotein L2	APOL2	37 kDa	0.3
LIM domain and actin-binding protein 1	LIMA1	85 kDa	0.3
Peroxiredoxin-6	PRDX6	25 kDa	0.3
Nucleolar RNA helicase 2	DDX21	87 kDa	0.3
T-complex protein 1 subunit beta	CCT2	57 kDa	0.3
T-complex protein 1 subunit epsilon	CCT5	60 kDa	0.3
26S proteasome regulatory subunit 6B	PSMC4	47 kDa	0.3
Eukaryotic initiation factor 4A-I	EIF4A1	46 kDa	0.3
Eukaryotic translation initiation factor 5	EIF5	49 kDa	0.3
Histone deacetylase 2	HDAC2	55 kDa	0.3
40S ribosomal protein S30	FAU	7 kDa	0.3
Matrix metalloproteinase-14	MMP14	66 kDa	0.3
ATP-binding cassette sub-family F member 2	ABCF2	71 kDa	0.3
Purine nucleoside phosphorylase	PNP	32 kDa	0.3
Lupus La protein	SSB	47 kDa	0.3
Inactive C-alpha-formylglycine-generating enzyme 2	SUMF2	34 kDa	0.3
Puromycin-sensitive aminopeptidase	NPEPPS	103 kDa	0.3
CDK5 regulatory subunit-associated protein 3	CDK5RAP3	57 kDa	0.3
NADPH--cytochrome P450 reductase	POR	77 kDa	0.3
Serine/arginine-rich splicing factor 1	SRSF1	28 kDa	0.3
Hsp90 co-chaperone Cdc37	CDC37	44 kDa	0.3
Lysosomal alpha-glucosidase	GAA	105 kDa	0.3
Interferon-induced, double-stranded RNA-activated protein kinase	EIF2AK2	62 kDa	0.3
Lon protease homolog, mitochondrial	LONP1	106 kDa	0.3
Double-stranded RNA-specific adenosine deaminase	ADAR	136 kDa	0.3
ATPase family AAA domain-containing protein 3A	ATAD3A	71 kDa	0.3
26S proteasome regulatory subunit 8	PSMC5	46 kDa	0.3
D-3-phosphoglycerate dehydrogenase	PHGDH	57 kDa	0.3
Transportin-1	TNPO1	102 kDa	0.3
X-ray repair cross-complementing protein 5	XRCC5	83 kDa	0.3
Coatomer subunit delta	ARCN1	57 kDa	0.3
Splicing factor 3A subunit 1	SF3A1	89 kDa	0.3
Serine-threonine kinase receptor-associated protein	STRAP	38 kDa	0.3

Protein SEC13 homolog	SEC13	36 kDa	0.2
Coatomer subunit gamma-1	COPG1	98 kDa	0.2
Thyroid hormone receptor-associated protein 3	THRAP3	109 kDa	0.2
Constitutive coactivator of PPAR-gamma-like protein 1	FAM120A	122 kDa	0.2
Proteasome subunit alpha type-4	PSMA4	29 kDa	0.2
Pentraxin-related protein PTX3	PTX3	42 kDa	0.2
Transforming growth factor-beta-induced protein ig-h3	TGFBI	75 kDa	0.2
HLA class I histocompatibility antigen, Cw-7 alpha chain	HLA-C	41 kDa	0.2
Golgi-associated plant pathogenesis-related protein 1	GLIPR2	17 kDa	0.2
GTP-binding nuclear protein Ran	RAN	24 kDa	0.2
Fascin	FSCN1	55 kDa	0.2
Eukaryotic translation initiation factor 3 subunit C	EIF3C	105 kDa	0.2
Splicing factor 3B subunit 2	SF3B2	100 kDa	0.2
Eukaryotic initiation factor 4A-III	EIF4A3	47 kDa	0.2
Bifunctional glutamate/proline--tRNA ligase	EPRS	171 kDa	0.2
26S proteasome non-ATPase regulatory subunit 13	PSMD13	43 kDa	0.2
T-complex protein 1 subunit delta	CCT4	58 kDa	0.2
Stress-induced-phosphoprotein 1	STIP1	63 kDa	0.2
Translationally-controlled tumor protein	TPT1	20 kDa	0.2
Tryptophan--tRNA ligase, cytoplasmic	WARS	53 kDa	0.2
Glucose-6-phosphate 1-dehydrogenase	G6PD	59 kDa	0.2
Histone H1.2	HIST1H1C	21 kDa	0.2
T-complex protein 1 subunit alpha	TCP1	60 kDa	0.2
RuvB-like 1	RUVBL1	50 kDa	0.2
Coatomer subunit beta	COPB1	107 kDa	0.2
Isoleucine--tRNA ligase, cytoplasmic	IARS	145 kDa	0.2
Serine--tRNA ligase, cytoplasmic	SARS	59 kDa	0.2

Myosin light chain 1/3, skeletal muscle isoform	MYL1	21 kDa	0.2
EH domain-containing protein 4	EHD4	61 kDa	0.2
Band 4.1-like protein 3	EPB41L3	121 kDa	0.2
Asparagine--tRNA ligase, cytoplasmic	NARS	63 kDa	0.2
Ras suppressor protein 1	RSU1	32 kDa	0.2
Coatomer subunit alpha	COPA	138 kDa	0.2
Far upstream element-binding protein 2	KHSRP	73 kDa	0.2
Lamin-B1	LMNB1	66 kDa	0.2
Platelet-derived growth factor receptor beta	PDGFRB	124 kDa	0.2
Eukaryotic translation initiation factor 3 subunit A	EIF3A	167 kDa	0.2
Glycine--tRNA ligase	GARS	83 kDa	0.1
Threonine--tRNA ligase, cytoplasmic	TARS	83 kDa	0.1
Splicing factor 3B subunit 1	SF3B1	146 kDa	0.1
High mobility group protein HMG-I/HMG-Y	HMGA1	12 kDa	0.1
Phosphoserine aminotransferase	PSAT1	40 kDa	0.1
14-3-3 protein eta	YWHAH	28 kDa	0.1
T-complex protein 1 subunit eta	CCT7	59 kDa	0.1
Transcription intermediary factor 1-beta	TRIM28	89 kDa	0.08

Supplementary Table S6. Upstream analysis of DEPs (P12/P4 hASCs)

Upstream Regulator	Molecule Type	Predicted Activation State	Activation z-score	p-value of overlap	Target molecules in dataset
ST1926	chemical drug	Activated	4.69	1.06E-14	ARPC3,CCT2,CCT3,CCT6A,DYNLL1,EEF2,EIF3D,EIF4A1,EIF5A,ENO1,ILF2,NACA,NARS,PCBP2,PSMA4,PSMB1,RPS10,RPS15,SEPT7,SRP72,TPT1,YBX1
CD 437	chemical drug	Activated	4.6	2.01E-15	API5,ARPC3,ATP5F1C,CCT2,CCT3,CCT6A,EEF2,EIF3D,EIF4A1,EIF5A,ENO1,FSCN1,HLA-C,HNRNPA1,ILF2,NACA,NARS,PCBP1,PCBP2,PSMA4,PSMB1,RPS10,RPS15,SEPT7,YBX1
5-fluorouracil	chemical drug	Activated	4.14	1.57E-10	ATP5F1C,CCT3,CCT4,CCT6A,EEF2,EIF3C,EIF4A1,GARS,HNRNPA1,HSP90AB1,IARS,ILF2,NACA,PCBP1,PSMA7,PSMB1,PSMD2,RPL35,RPS28,SERPINB6,SSB,YBX1
valproic acid	chemical drug	Activated	3.534	6.3E-09	ATP2B4,BAG2,FSCN1,HNRNPA1,ICAM1,LIMA1,PDGFRB,PSMA1,PSMA4,PSMA5,PSMA7,PSMB1,PSMB4,PSMC2,PSMC3,PSMC4,PSMC5,PSMD13,PSMD14,PSMD2,PSMD4,PTX3,SERPINE1,SRSF1,TNS1,UTRN,YWHAH
CST5	other	Activated	2.982	8.61E-08	ABCC1,CEMIP,COL12A1,DDX21,DHX9,HNRNPU,MSN,MYL9,PCBP1,PDLIM5,PRPF8,PUF60,RBM3,RSL1D1,RTN3,SRSF1,SRSF9,TARDBP,VARS
sirolimus	chemical drug	Activated	2.878	5.59E-16	ACTA2,ATP2B4,ATP5F1C,COL1A1,CTGF,EEF1A1,EEF2,EIF2AK2,EIF4A1,EIF5,ENO1,FSCN1,FUS,G6PD,GSTP1,HIST1H4A,HLA-B,HNRNPU,HSP90AB1,ICAM1,MMP14,NDUFA9,PDGFRB,PFKP,PLIN2,PSMA4,PSMB1,PSMB4,RAN,RPL35,RPS10,RPS15,SERPINE1,SLC1A5,SLC2A1,TARS,TPM3,TRIM25,UBA1
mir-122	microRNA	Activated	2.714	1.62E-07	ACTR1A,CSRP1,G6PD,MAPRE1,NPEPPS,NUTF2,RBM3,SERPINB6,SLC1A5,WARS,YARS
KLF3	transcription regulator	Activated	2.714	0.0131	CCT3,EIF5A,EPRS,GLIPR2,GSTP1,MSN,PFKP,PSMC5,RUVBL1,SEC24D,TPM3
RICTOR	other	Activated	2.711	1.17E-11	ATP5F1C,ATP6V0A1,ATP6V0D1,FAU,NDUFA9,PPA1,PSMA1,PSMA4,PSMA5,PSMA7,PSMB1,PSMB4,PSMC2,PSMC3,PSMC4,PSMC5,PSMD13,PSMD14,PSMD2,PSMD4,RPL26,RPS10,RPS15
EDN1	cytokine	Activated	2.542	3.28E-06	ACTA2,BAG2,CTGF,ICAM1,ITGA2,ITGB1,MPRIP,MSN,SERPINE1,SF3B2,SLC2A1,TPM2,TPM3,TPT1
cigarette smoke	chemical toxicant	Activated	2.434	0.000513	ACTA2,CCT5,CKB,G6PD,GSTP1,HDAC2,ICAM1,SERPINE1,SLC2A1,SOD2,TCP1,UGDH
fatty acid	chemical - endogenous mammalian	Activated	2.414	0.00566	ACOX1,ATP5F1C,PLIN2,PPA1,SERPINE1,SLC2A1
SRF	transcription regulator	Activated	2.394	0.0061	ACTA2,CAPRIN1,CNN1,CSRP1,CSRP2,CTGF,FERMT2,ITGB1,MYL1,MYL9,SLC2A1,TGFB1I1
sphingosine-1-phosphate	chemical - endogenous mammalian	Activated	2.366	0.0026	ACTA2,CTGF,HDAC2,ICAM1,MMP14,SERPINE1
tretinoin	chemical - endogenous mammalian	Activated	2.327	3.89E-07	ACOX1,ADAR,CCT5,COL1A1,CTGF,DPP4,DYNLL1,ECI2,EEF1A1,EIF2AK2,EIF3B,EIF3C,EIF4A1,EIF4G1,EIF5,ELOC,FUBP3,GARS,GNA13,GSTP1,HLA-A,HLA-B,HLA-C,HMGA1,ICAM1,ILF3,ITGA2,ITGB1,KRT14,LOXL2,MMP14,NME2,PDGFRB,PLIN2,PNP,POR,PSMC4,PTX3,RAD23B,RAI14,RAN,RUVBL1,SERPINE1,SERPINE2,TGFBI,TPR,TPT1,UBA1,XRCC5,XRCC6,YBX1
RELA	transcription regulator	Activated	2.302	0.0146	ACTA2,ALCAM,COL1A1,CTGF,FSCN1,HLA-B,ICAM1,KRT8,PRDX6,PTX3,SERPINE2,SOD2,STIM1
IND S7	chemical - kinase inhibitor	Activated	2.236	6.68E-05	ENO1,HNRNPL,KHSRP,PSMA1,STIP1
MEL S3	chemical - kinase inhibitor	Activated	2.236	7.97E-05	ENO1,HNRNPL,KHSRP,PSMA1,STIP1
4-hydroxytamoxifen	chemical drug	Activated	2.228	0.00786	CTGF,DDX21,DYNLL1,EIF5A,GLRX,SLC25A4,SLC2A1,TNPO1
eicosapentenoic acid	chemical drug	Activated	2.213	0.0148	ECH1,PLIN2,PSMC2,SERPINE1,SLC2A1
MRTFA	transcription regulator	Activated	2.204	0.0161	ACTA2,CNN1,HLA-A,ICAM1,ITGB1,MYL9
ITGB1	transmembrane receptor	Activated	2.184	0.0599	ABCC1,ACTA2,COL1A1,ICAM1,SERPINE1

CDKN2A	transcription regulator	Activated	2.158	0.0145	AK1,CTGF,DDX5,EEF1A1,GNA13,PDGFRB,PSMA5,PTX3,SERPINE1,TRIM28
SMAD2	transcription regulator	Activated	2.116	0.00206	ACTA2,CTGF,ITGB1,SERPINE1,TPM2,TPM3
SFRP1	transmembrane receptor	Activated	2	0.00886	ACLY,ACTA2,COL1A1,SERPINE1
CD3	complex	Inhibited	-2.024	6.71E-09	ATP5F1C,DPP4,EIF4A3,FKBP3,G6PD,GDI2,HDAC2,HNRNPA1,HNRNPR,ICAM1,ILF2,KRT14,LNPEP,LONP1,PCBP2,PLEC,PLIN2,PNP,PPA1,PSMA5,RAD23B,RARS,RBM3,SRSF1,SSB,STIM1,STOM,TARDBP,THY1,TRIM25,XRCC6,YARS
RUNX2	transcription regulator	Inhibited	-2.074	0.0394	ACTA2,COL1A1,MMP14,NEXN,SERPINE1
EGFR	kinase	Inhibited	-2.093	2.44E-07	ACTA2,ATAD3A,CCT5,COL1A1,CTGF,EIF5A,HMGA1,HNRNPA1,ICAM1,ITGA2,MARCKS,MMP14,NUTF2,PSMB1,PSMB4,RAI14,SERBP1,SERPINE1,SERPINE2,SLC2A1,SRSF1,UBA1
tunicamycin	chemical - endogenous non-mammalian	Inhibited	-2.099	0.00101	ACOX1,HDLBP,ICAM1,ILK,LONP1,NARS,PLIN2,SEC24D,SLC2A1,WARS
XBP1	transcription regulator	Inhibited	-2.137	0.00517	ARCN1,COPB1,COPG1,FKBP7,ICAM1,MCFD2,SEC24D,SELENOM,XRCC6
ATF4	transcription regulator	Inhibited	-2.148	2.74E-09	BCAT1,GARS,IARS,NARS,PHGDH,PRKDC,PSAT1,PTX3,PYCR1,SARS,SHMT2,SLC1A5,SLC7A5,SOD2,TKT,WARS
pimagedine	chemical drug	Inhibited	-2.219	2.97E-05	ACTA2,CNN1,CTGF,ICAM1,OPA1,SERPINE1
DDIT3	transcription regulator	Inhibited	-2.236	0.0348	ITGA2,PLEC,SARS,SRSF1,WARS
bortezomib	chemical drug	Inhibited	-2.261	7.03E-05	ABCF2,HDAC2,ICAM1,PSMA1,PSMA5,PSMA7,PSMB4,PSMC4,PSMD13,PSMD14,PSMD2,PSMD4,UFD1
simvastatin	chemical drug	Inhibited	-2.341	0.044	ACTA2,CTGF,HIST1H1C,ICAM1,MYH10,NONO,SERPINE1
STAT6	transcription regulator	Inhibited	-2.619	0.191	ACOX1,COL1A1,FSCN1,GNB4,MMP14,SERPINB6,SERPINE1,THY1
NFE2L1	transcription regulator	Inhibited	-2.646	5.21E-07	GSTP1,PSMA1,PSMA7,PSMB1,PSMC2,PSMC3,PSMD14
beta-estradiol	chemical - endogenous mammalian	Inhibited	-2.71	6.66E-10	ACOX1,ACTA2,ALCAM,ATP2B1,BCAT1,CCT2,CKB,CNN1,COL1A1,CTGF,DDX17,DYNLL1,ECH1,EIF3A,EIF3B,EIF3D,ELOC,ENO1,EPB41L3,FARSA,FLOT1,G6PD,GARS,GDI2,GNS,GSTP1,HDAC2,HDLBP,HLA-A,HNRNPA1,HSP90AB1,IARS,ICAM1,ILF3,ITGA2,KRT8,LIMA1,NARS,NOP58,PDGFRB,PFKL,PLIN2,PNP,PSAT1,PSMA1,PSMB1,PSMC3,PTX3,PYCR1,RAN,RARS,RDH10,SLC12A4,SLC2A1,SLC7A5,SRSF1,STIP1,SYNE1,TARDBP,TARS,TIMM13,TPR,TRIM25,YARS,YWHAH
HSF1	transcription regulator	Inhibited	-2.789	4.79E-05	CCT2,CCT3,CCT4,CCT5,CCT6A,CCT7,CCT8,CSRP2,HSP90AB1,ICAM1,STIP1,TCP1
UCP1	transporter	Inhibited	-2.961	0.000968	EEF1A1,G6PD,GARS,GSTO1,PHGDH,PSAT1,PYCR1,SERPINE1,SHMT2
2-amino-1-methyl-6-phenylimidazo-4-5-b-pyridine	chemical toxicant	Inhibited	-3	1.79E-08	CCT2,CCT4,CCT5,CCT7,CCT8,PSMB1,PSMB4,RAN,UBA1
MYCN	transcription regulator	Inhibited	-3.044	6.71E-14	ABCC1,ABCC4,ABCF2,COL1A1,CTGF,EEF1A1,EEF2,EIF3C,EIF4A1,EIF5A,FAU,HDAC2,HLA-A,HMGA1,HSP90AB1,ITGA2,ITGB1,NACA,NME2,PHGDH,PSMA7,RPL26,RPL35,RPS15,RPS28,SERPINE1,SLC2A1
MYC	transcription regulator	Inhibited	-3.242	4.71E-18	ABCC1,ABCC4,ABCF2,ADD1,ALCAM,ATAD3A,BCAT1,CCT3,COL1A1,CSRP2,DDX21,DDX39B,DDX5,EEF2,EIF3D,EIF4A1,EIF4G1,ENO1,G6PD,GAA,GDI2,GFPT1,GGH,GPI,HDAC2,HLA-A,HLA-B,HMGA1,HNRNPA1,HNRNPU,ICAM1,ITGB1,KRT14,LIMA1,MSN,MYL9,NARS,NME2,NOP58,PDGFRB,PFKL,PFKP,PSAT1,PYCR1,RARS,RPL26,RPL35,RUVBL1,SERPINE1,SERPINE2,SHMT2,SLC1A5,SLC2A1,SLC7A5,SOD2,SRSF1,THY1,TKT,VARS,YBX1
HSF2	transcription regulator	Inhibited	-3.317	6.98E-12	CCT2,CCT3,CCT4,CCT5,CCT6A,CCT7,CCT8,PSMA1,PSMA5,PSMC4,TCP1
NFE2L2	transcription regulator	Inhibited	-4.431	1.08E-19	ABCC1,ABCC4,CCT3,CCT7,COL1A1,CTGF,DDX39B,DYNLL1,EIF3C,G6PD,GSTO1,GSTP1,HSP90AB1,MCFD2,NARS,PCBP1,PHGDH,PLIN2,PSAT1,PSMA1,PSMA4,PSMA5,PSMA7,PSMB1,PSMB4,PSMC3,PSMD13,PSMD14,PSMD4,RAN,RARS,RUVBL1,SERPINE1,SHMT2,SLC2A1,SOD2,STIP1,TKT,UGDH
1,2-dithiol-3-thione	chemical reagent	Inhibited	-4.965	7.18E-19	CCT3,CCT7,DDX39B,DYNLL1,EIF3C,EIF3D,GSTP1,HSP90AB1,MCFD2,NARS,PCBP1,PSAT1,PSMA1,PSMA4,PSMA5,PSMA7,PSMB1,PSMB4,PSMC2,PSMC3,PSMD13,PSMD14,PSMD4,RAN,RARS,RUVBL1,SOD2,STIP1

Supplementary Table S7. DEPs overlapped between P8/P4 and P12/P4 hASCs. A total of 28 DEPs were overlapped with P4, P8 and P12 hASCs, 19 DEPs have the same changing trend between P8/P4 and P12/P4 comparisons.

Protein name	Gene name	Molecular Weight	Fold Change by p8/p4	Fold Change by p12/p4
ADP/ATP translocase 1 OS=Homo sapiens OX=9606 GN=SLC25A4 PE=1 SV=4	ARPC3	21 kDa	-2.5	-2.5
Actin-related protein 2/3 complex subunit 3 OS=Homo sapiens OX=9606 GN=ARPC3 PE=1 SV=3	ASAH1	45 kDa	-2	2.9
Acid ceramidase OS=Homo sapiens OX=9606 GN=ASAH1 PE=1 SV=5	CNN1	33 kDa	-3.3	22
Calponin-1 OS=Homo sapiens OX=9606 GN=CNN1 PE=1 SV=2	CSRP2	21 kDa	-2.5	4.4
Cysteine and glycine-rich protein 2 OS=Homo sapiens OX=9606 GN=CSRP2 PE=1 SV=3	CTSA	54 kDa	2.7	3.8
Drebrin-like protein OS=Homo sapiens OX=9606 GN=DBNL PE=1 SV=1	DBNL	48 kDa	-2.5	-2.5
Delta(3,5)-Delta(2,4)-dienoyl-CoA isomerase, mitochondrial OS=Homo sapiens OX=9606 GN=ECH1 PE=1 SV=2	ECH1	36 kDa	3.8	2.7
Enoyl-CoA delta isomerase 2, mitochondrial OS=Homo sapiens OX=9606 GN=ECI2 PE=1 SV=4	ECI2	44 kDa	5.2	2.5
Flotillin-1 OS=Homo sapiens OX=9606 GN=FLOT1 PE=1 SV=3	FLOT1	47 kDa	2.2	5.5
Glutamine--fructose-6-phosphate aminotransferase [isomerizing] 1 OS=Homo sapiens OX=9606 GN=GFPT1 PE=1 SV=3	GFPT1	79 kDa	-2	-2.5
Keratin, type I cytoskeletal 14 OS=Homo sapiens OX=9606 GN=KRT14 PE=1 SV=4	KRT14	52 kDa	6.6	18
Keratin, type II cytoskeletal 8 OS=Homo sapiens OX=9606 GN=KRT8 PE=1 SV=7	KRT8	54 kDa	3.3	-2
Lon protease homolog, mitochondrial OS=Homo sapiens OX=9606 GN=LONP1 PE=1 SV=2	LONP1	106 kDa	2.6	-3.3
Microtubule-associated protein RP/EB family member 1 OS=Homo sapiens OX=9606 GN=MAPRE1 PE=1 SV=3	MAPRE1	30 kDa	-2.5	-2.5
Myosin-10 OS=Homo sapiens OX=9606 GN=MYH10 PE=1 SV=3	MYH10	229 kDa	-3.3	4.4
Myosin light chain 1/3, skeletal muscle isoform OS=Homo sapiens OX=9606 GN=MYL1 PE=2 SV=3	MYL1	21 kDa	-5	-5
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 9, mitochondrial OS=Homo sapiens OX=9606 GN=NDUFA9 PE=1 SV=2	NDUFA9	43 kDa	2.2	2
Pyrroline-5-carboxylate reductase 1, mitochondrial OS=Homo sapiens OX=9606 GN=PYCR1 PE=1 SV=2	NPEPPS	103 kDa	-2.5	-3.3
ATP-dependent 6-phosphofructokinase, platelet type OS=Homo sapiens OX=9606 GN=PFKP PE=1 SV=2	PFKP	86 kDa	-2.5	-3.3
Polycystin-2 OS=Homo sapiens OX=9606 GN=PKD2 PE=1 SV=3	PKD2	110 kDa	2.1	2.6
Purine nucleoside phosphorylase OS=Homo sapiens OX=9606 GN=PNP PE=1 SV=2	PNP	32 kDa	-3.3	-3.3
Lysosomal protective protein OS=Homo sapiens OX=9606 GN=CTSA PE=1 SV=2	PYCR1	33 kDa	2.7	-3.3
Puromycin-sensitive aminopeptidase OS=Homo sapiens OX=9606 GN=NPEPPS PE=1 SV=2	RPL26	17 kDa	-2	-3.3
60S ribosomal protein L26 OS=Homo sapiens OX=9606 GN=RPL26 PE=1 SV=1	RRAS2	23 kDa	2.4	5.3
Ras-related protein R-Ras2 OS=Homo sapiens OX=9606 GN=RRAS2 PE=1 SV=1	SLC25A4	33 kDa	-2.5	3.1
Sorbin and SH3 domain-containing protein 2 OS=Homo sapiens OX=9606 GN=SORBS2 PE=1 SV=3	SORBS2	124 kDa	-2.5	5.1
Mitochondrial import inner membrane translocase subunit Tim13 OS=Homo sapiens OX=9606 GN=TIMM13 PE=1 SV=1	TIMM13	11 kDa	2.5	2.8
Ubiquitin carboxyl-terminal hydrolase 5 OS=Homo sapiens OX=9606 GN=USP5 PE=1 SV=2	USP5	96 kDa	-2.5	-3.3