

Supplementary Table S1. Primer sequences used for RT-qPCR.

Gene		Primer sequence 5'-3'	Reactions Conditions
ACTB	Forward	CCAACCGCGAGAAGATGA	95 °C – 10"
	Reverse	CCAGAGGCGTACAGGGATAG	61 °C - 10" 72 °C – 10"
OCT4	Forward	CGCAAGCCCTCATTCAC	95 °C– 10"
	Reverse	CATCACCTCCACCACCTG	60 °C– 06" 72 °C– 06"
PPARG	Forward	GCTTATCTATGACAGATGTGATCT	95 °C– 10"
	Reverse	AGCTTCTCCTTCTCGGC	55 °C– 10" 72 °C– 10"
SIX3	Forward	CCTCCTCCTCTTCCTCCTCT	95 °C – 10"
	Reverse	AGTGGTAGATGGTGGTTGGG	60 °C - 20" 72 °C – 10"
SP7	Forward	ATGAGTGGGAAAAGGGAGGG	95 °C – 10"
	Reverse	TCAACAACCTCTGGGCAAAGC	60 °C - 10" 72 °C – 20"

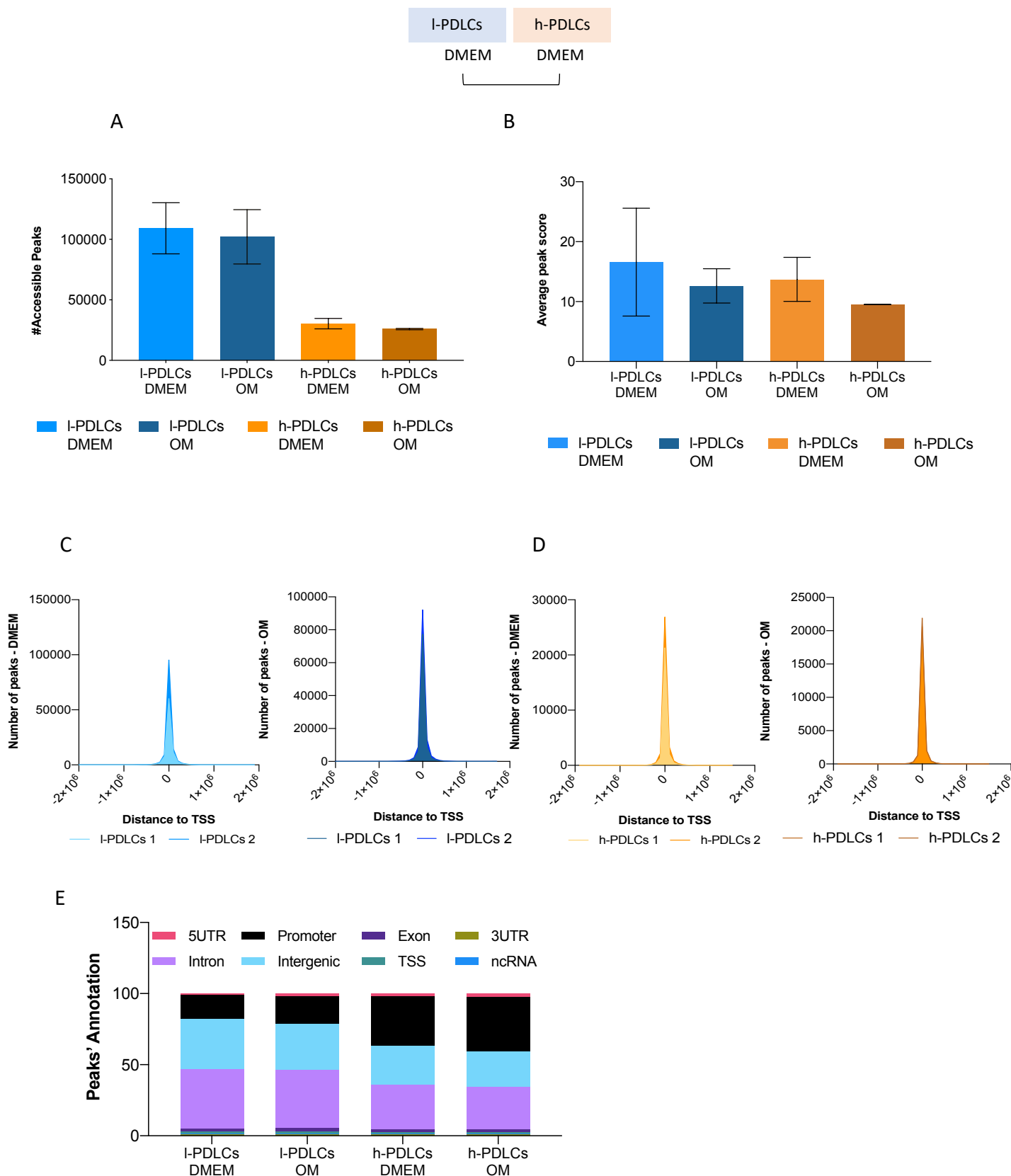
Supplementary Table S2. Top 60 most differentially expressed genes at basal level between l- and h-PDLCs.

Symbol	Log2FC_High	Log2FC_Low	
C1QL3	7.625	-6.019	
CX3CR1	5.019	-5.220	Symbol: gene identification
DLX4	9.064	-7.405	Log2FC_High: log2 fold change in h-PDLCs
EGFLAM	8.784	-5.718	Log2FC_Low: log2 fold change in l-PDLCs
FABP7	5.019	-5.746	Negative Log2FC: gene downregulated
FOXO6	6.893	-5.496	Positive Log2FC: gene upregulated
GRM3	5.996	-5.535	
KRT18	7.231	-5.661	
KRT81	7.441	-5.304	
LRRC18	7.154	-5.384	
PCDH1	5.535	-7.860	
PLD4	6.688	-5.081	
PLEKHN1	7.566	-5.788	
PLVAP	6.450	-5.336	
PSMB9	5.996	-7.824	
SP7	8.370	-6.736	
THNSL2	8.386	-9.274	
TNNC1	5.306	-5.222	
TSPAN18	6.010	-6.372	
ABLIM2	-5.641	5.194	
ACTN3	-7.207	5.628	
ADH1C	-5.055	6.301	
ADORA1	-8.120	6.640	
BCHE	-5.931	8.511	
BEX1	-6.627	5.087	
BMP5	-6.847	5.351	
CASQ1	-7.207	5.663	
CDH18	-8.811	6.780	
CHGB	-7.207	5.556	
DDX25	-5.070	5.158	
DNAJB7	-5.070	5.193	
EPHA6	-6.847	5.058	
ERICH5	-7.207	6.679	
FIBCD1	-8.616	6.901	
GALNT13	-12.680	11.179	
GRID2	-6.847	5.191	
IFNE	-6.627	5.085	
IGFALS	-7.358	5.769	
IGSF3	-7.558	5.722	
IL1RN	-6.847	5.519	
IL4	-6.847	6.034	
IRX6	-7.940	6.395	
JPH1	-7.125	5.697	
L1TD1	-6.627	5.372	
LRRTM1	-5.070	5.511	
MAB21L2	-6.937	7.049	
NKD1	-5.070	7.181	
OCM	-7.207	5.886	
OR5K2	-6.627	5.165	
PCDH10	-5.899	5.883	
PSG1	-7.734	5.329	
PSMA8	-6.627	5.189	
RSPH1	-5.641	5.084	
SCN7A	-7.678	6.244	
SIX3	-9.369	5.630	
SLITRK5	-5.140	5.146	
SMOC1	-6.733	6.101	
TMEM196	-6.627	5.144	
TMEM74	-6.847	5.340	
TP53TG3D	-7.358	5.367	

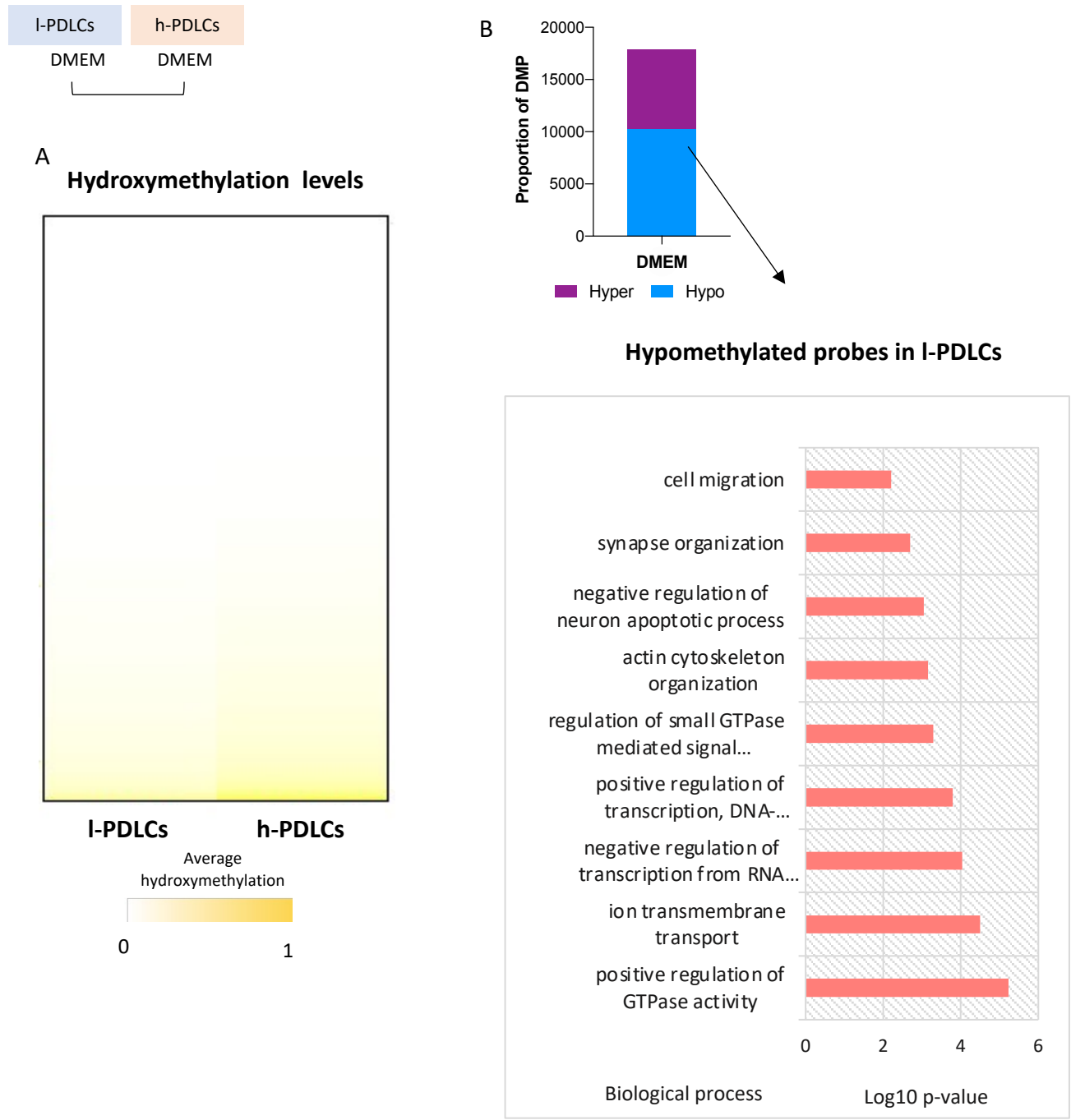
Supplementary Table S3. Top 150 most differentially expressed genes at induced levels in l- and h-PDLCs

Symbol	Log2FC Low	Log2FC High	Symbol	Log2FC Low	Log2FC High	Symbol	Log2FC Low	Log2FC High
BST2	7.196	5.918	AC069368.1	6.340	-2.353	EPHB6	0.174	11.538
CHKB-CPT1B	6.436	5.774	CD101	8.129	-1.489	GOLGA8A	-2.813	12.699
FGL1	4.698	2.577	ASB2	4.445	-2.998	HNRNPAB	5.902	8.637
ART3	8.085	4.343	ATP6AP1	4.401	-3.091	FAM117B	6.236	8.179
COMTD1	7.158	2.758	DLEC1	4.908	-4.146	CEMP1	4.420	9.641
CRABP1	4.860	4.305	CTAGE15	4.561	-4.268	CXCR5	4.826	12.415
FCMR	4.653	4.074	AC004223.3	4.328	-4.160	EXPH5	-2.612	5.034
GPM6B	4.503	3.449	HSD17B11	4.375	-4.287	FUT6	-2.601	4.897
CEMIP	4.321	3.487	CHRFAM7A	5.545	-3.811	AL049844.3	-2.823	5.179
FKBP5	5.762	3.715	AMDHD1	6.250	-4.564	HLA-DOA	-2.826	4.986
ANO3	4.541	2.968	GMNC	8.830	-4.738	CATSPERG	-2.219	5.532
FCHO1	5.449	5.612	ARHGAP20	8.498	-4.993	DRGX	-2.687	5.468
DGKB	4.289	6.676	BORCS8- MEF2B	7.399	-4.885	FOXE3	-3.786	5.844
FBXO43	3.639	6.930	ANKRD26	9.161	-7.281	CRLF2	-3.797	5.754
ADGRF2	4.348	6.116	GNL1	8.281	-7.396	DND1	-3.791	5.254
DPEP1	3.946	5.837	AC012184.2	7.842	-7.396	C1QTNF3-AMACR	-1.725	6.259
CXCL8	3.315	6.063	CORO7- PAM16	6.791	-6.630	GPAT2	-2.709	6.267
INMT-MINDY4	2.813	6.040	AC090527.2	6.118	-5.955	AC104662.2	-4.501	5.009
DKK1	2.550	6.567	AL022318.4	5.650	-6.168	C19ORF67	-5.132	4.898
COMP	3.819	5.213	ITIH5	5.371	-7.351	CKAP2L	-5.383	6.646
DAPP1	3.542	5.073	FAM183A	-0.368	5.432	GCH1	-6.244	6.206
CFAP65	2.980	5.238	GAL3ST3	-0.368	5.391	KIF24	-8.416	8.937
BTLA	4.621	0.199	AC068946.1	-0.368	5.474	FAM213B	-9.038	6.174
AURKA	4.582	0.199	GNLY	-0.368	5.256			
ADRA1A	4.691	0.199	BOP1	-0.368	5.226			
IGHV3-74	4.873	0.169	CYTH4	-0.368	5.068			
HLA-A	4.822	-0.156	FAM166B	-0.368	5.029			
C3	4.570	-0.092	CLDN34	-0.368	4.952			
CHI3L1	4.406	0.199	CTXN3	-0.860	5.095			
FPR2	4.397	0.199	FIBCD1	-0.982	5.131			
FPR1	4.445	0.200	FOXD4L1	-0.697	5.036			
GNGT1	4.378	0.199	FAM189A2	-0.677	5.387			
ATP13A4	4.353	0.250	KIF18B	-0.771	5.406			
IFITM5	4.502	0.199	HYDIN	-1.106	5.829			
ADAMDEC1	4.455	0.199	CENPA	-1.052	5.669			
ALOX15B	5.365	0.199	BLOC1S5- TXNDC5	-0.711	5.980			
AL121758.1	5.245	0.199	AF241726.2	-1.364	5.210			
FMO3	5.119	-0.275	CHRM3	-0.427	5.887			
HLA-B	5.194	-1.021	JSRP1	-0.368	5.811			
ARHGDIG	4.974	-0.990	AGAP2	-0.247	5.683			
GLRA3	5.131	-0.804	ALDOB	-0.417	5.583			
CELA3B	5.134	-1.310	CHGB	-0.042	6.048			
KCNN3	4.718	-1.161	AC008758.4	-0.567	6.896			
GPR17	4.688	-0.785	ELMO3	-0.368	6.649			
CARNS1	4.400	-0.656	CRYM	1.656	5.119			
COMMD3- BMI1	5.942	0.199	GPR82	1.597	5.131			
BIN2	5.888	0.199	ADGRV1	1.565	5.501			
ADH4	6.249	0.199	IGKV2-30	2.087	5.809			
DMKN	6.238	-0.170	AC104109.3	2.057	5.267			
CASC1	6.114	-0.425	C1ORF87	2.374	4.869			
KCNT1	5.617	-0.751	APOBEC3B	0.697	5.478			
CDH5	4.438	1.773	DUXA	0.551	5.471			
HKDC1	4.367	1.499	ASF1B	0.508	5.667			
HPD	4.822	0.974	BLID	0.566	6.014			
FGR	4.419	1.145	CDC45	1.091	5.678			
ABCA2	5.364	0.584	BMP7	0.059	5.225			
ANKDD1A	5.164	0.753	GSY2	0.311	4.899			
CCDC13	5.945	0.965	HNRNPA1L2	-0.700	8.914			
GRIA2	6.679	0.707	KIAA1107	-0.956	9.016			
C17ORF100	6.654	0.346	CNNM1	-0.368	8.265			
ANO2	7.906	0.290	CYP19A1	2.071	7.976			
ABL2	9.535	1.259	CDC25C	1.035	6.983			
ERVMER34-1	6.593	-1.408						
COL26A1	6.227	-1.335						

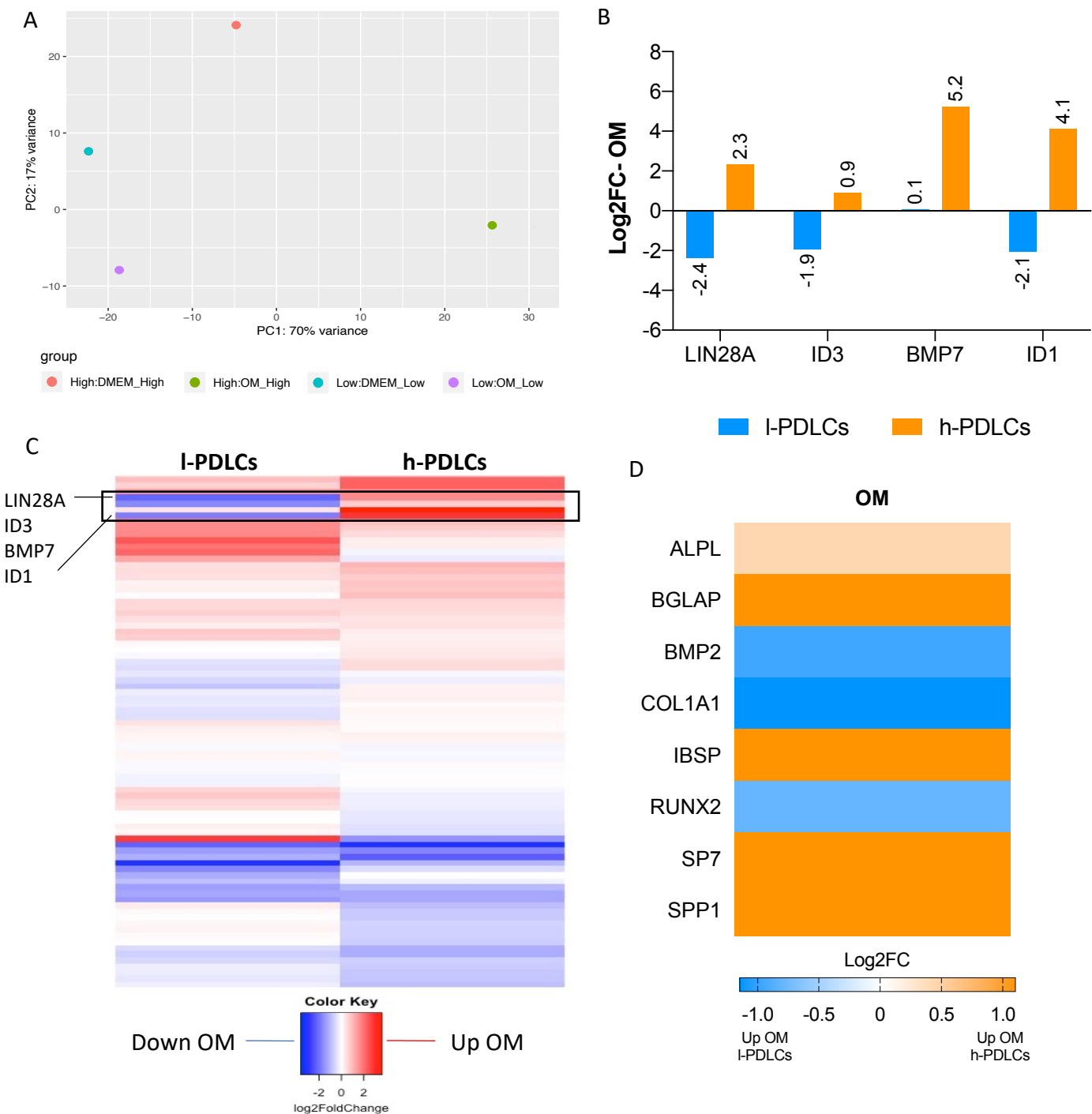
Symbol: gene identification
Log2FC_High: log2 fold change in h-PDLCs
Log2FC_Low: log2 fold change in l-PDLCs
Negative Log2FC: gene downregulated
Positive Log2FC: gene upregulated



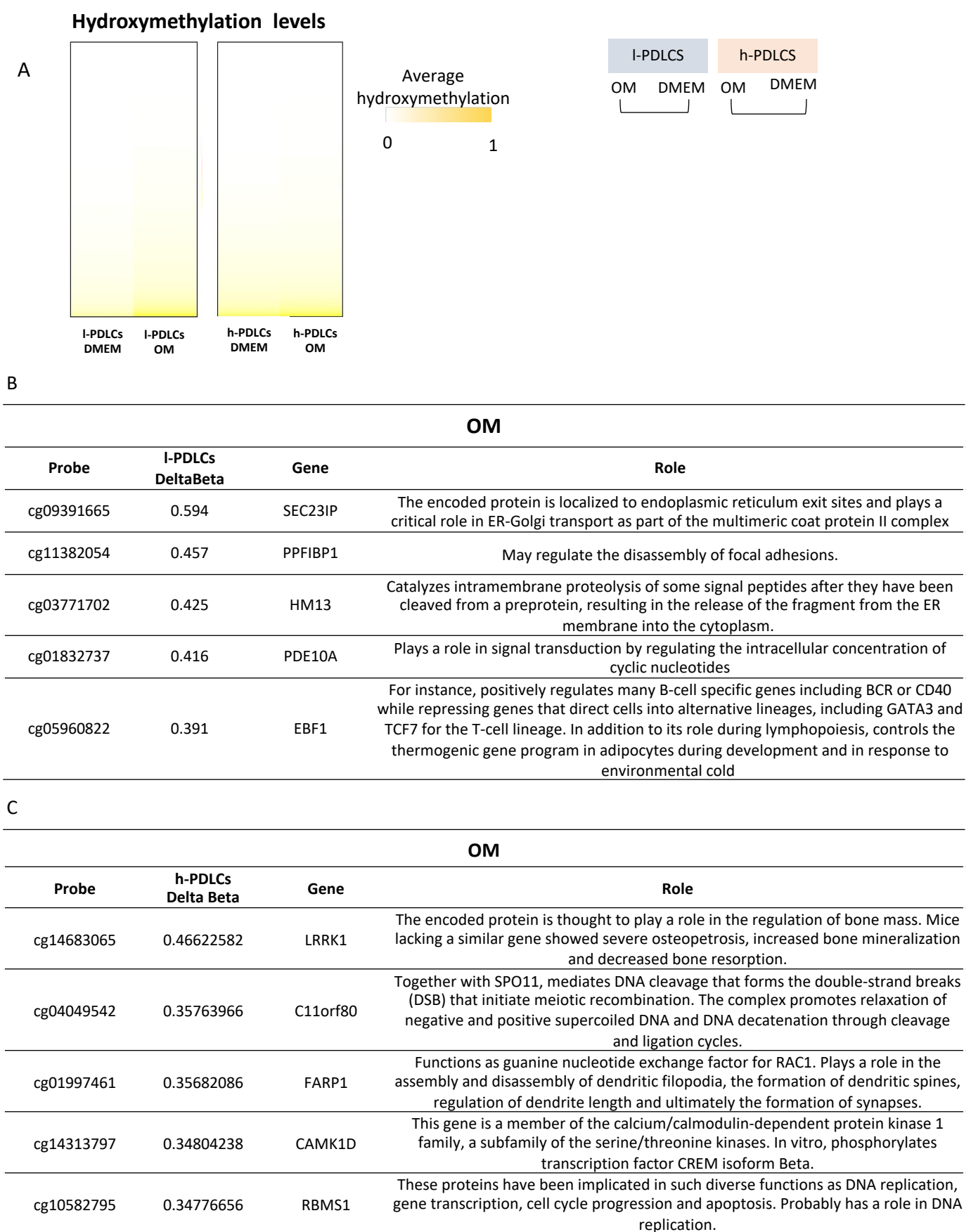
Supplementary figure S1. Chromatin accessibility in PDLCs. (A) Number of accessible chromatin peaks in I-PDLCs and h-PDLCs. (B) Average peak score at basal levels for I-PDLCs and h-PDLCs. (C, D) Distribution of peaks in relation to the nearest transcription start site (TSS) for each ATAC-seq replicate and experimental condition in I-PDLCs (C) and h-PDLCs (D). (E) Peaks' annotations shown as percentage of all peaks and compared between the experimental conditions. I-PDLCs, periodontal ligament cells showing low osteogenic potential *in vitro*; h-PDLCs, periodontal ligament cells showing high osteogenic potential *in vitro*.



Supplementary figure S2. DNA hydroxymethylation of PDLCs at basal levels. (A) Heatmap showing DNA hydroxymethylation levels of all DNA methylation sites. (B) The proportion of 14,194 differentially methylated probes at day 10 of osteogenic stimulations *in vitro* in I-PDLCs (upper graph) and biological processes related to this subset. I-PDLCs, periodontal ligament cells showing low osteogenic potential *in vitro*; h-PDLCs, periodontal ligament cells showing high osteogenic potential *in vitro*.



Supplementary figure S3. Transcriptional analysis of osteogenic markers. (A) PCA plot of RNA-seq data showing the four experimental conditions: h-PDLCs in DMEM, h-PDLCs in OM, I-PDLCs in DMEM and I-PDLCs in OM. For each condition, three independent replicates were first performed and then pooled for sequencing. The variability represented by the first component clearly separates the h-PDLCs after OM stimulation from the other samples. (B) OM-induced gene expression changes in RNA-seq data in I-PDLCs and h-PDLCs. The panel represents genes responsible for controlling osteoblast lineage progression as described in “Genetic and transcriptional control of bone formation” by Javed et al. (2010). (C) Gene expression changes for four genes most differentially up-regulated by OM in h-PDLCs (as highlighted in (B)). (D) Comparison of gene expression levels of classical osteogenic markers between I- and h-PDLCs at day 10 of osteogenic stimulation. I-PDLCs, periodontal ligament cells showing low osteogenic potential *in vitro*; h-PDLCs, periodontal ligament cells showing high osteogenic potential *in vitro*.



Supplementary figure S4. DNA hydroxymethylation in PDLCs following osteogenic induction. (A) Heatmap showing DNA hydroxymethylation levels of 850,000 DNA methylation sites at basal state and after 10 days of osteogenic induction. (B) Top 5 most DNA hydroxymethylated probes in I-PDLCs after osteogenic induction. (C) Top 5 most hydroxymethylated probes in h-PDLCs at induced levels. I-PDLCs, periodontal ligament cells showing low osteogenic potential *in vitro*; h-PDLCs, periodontal ligament cells showing high osteogenic potential *in vitro*. DMEM, standard culture medium; OM, osteogenic medium.