

Supplementary Materials: CCAAT/Enhancer-Binding Protein Delta (C/EBP δ): A Previously Unrecognized Tumor Suppressor That Limits the Oncogenic Potential of Pancreatic Ductal Adenocarcinoma Cells

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Table 1. Fold change of leading edge genes from GSEAs between CEBPD-high and CEBPD-low groups. GSEAs using the PDAC dataset GSE62452 [33] and proliferative gene sets provided by Ben-Porath [35] and Chiang [36] show generally higher expression of proliferation-associated genes in patients with relatively low CEBPD mRNA expression.

BEN-PORATH [35]				
Gene	Average Gene Expression in Group		CORR. <i>p</i> -Value	Fold Change (CEBPD-Low vs. CEBPD-High Group)
	CEBPD-High	CEBPD-Low		
<i>AGFG1</i>	7.936	8.320	1.13×10 ⁻⁴	1.30
<i>ANKRD27</i>	5.743	5.981	1.67×10 ⁻⁵	1.18
<i>ANLN</i>	3.580	4.299	1.97×10 ⁻³	1.65
<i>ASF1A</i>	5.181	6.007	1.64×10 ⁻¹³	1.77
<i>ASPM</i>	3.131	3.945	1.20×10 ⁻⁵	1.76
<i>ATAD2</i>	4.760	5.382	1.14×10 ⁻⁶	1.54
<i>AVL9</i>	5.388	5.761	3.33×10 ⁻⁹	1.29
<i>BUB1</i>	3.111	3.843	4.59×10 ⁻⁷	1.66
<i>C1ORF112</i>	3.125	3.717	1.09×10 ⁻¹¹	1.51
<i>CCNB2</i>	3.228	3.815	4.58×10 ⁻⁴	1.50
<i>CDCA7</i>	3.882	4.275	1.62×10 ⁻³	1.31
<i>CDKN3</i>	2.417	2.818	1.73×10 ⁻⁴	1.32
<i>CDT1</i>	3.473	3.248	2.98×10 ⁻⁴	0.86
<i>CEBPG</i>	5.834	6.031	1.95×10 ⁻³	1.15
<i>CENPE</i>	2.162	2.384	4.11×10 ⁻³	1.17
<i>CENPF</i>	3.665	4.513	1.99×10 ⁻⁵	1.80
<i>CENPM</i>	4.493	4.123	1.76×10 ⁻⁸	0.77
<i>CENPN</i>	3.823	4.114	1.05×10 ⁻³	1.22
<i>CHAF1B</i>	4.191	4.409	3.24×10 ⁻⁴	1.16
<i>CKS1B</i>	6.635	6.442	6.24×10 ⁻³	0.87
<i>CNIH4</i>	6.130	6.433	8.68×10 ⁻⁴	1.23
<i>COX5A</i>	6.875	7.148	2.84×10 ⁻⁴	1.21
<i>CSE1L</i>	6.372	6.849	4.08×10 ⁻⁸	1.39

<i>CSNK1G1</i>	3.814	4.061	3.08×10 ⁻⁶	1.19
<i>CSTB</i>	8.575	9.086	1.40×10 ⁻⁴	1.43
<i>DAP3</i>	6.886	7.217	2.56×10 ⁻⁸	1.26
<i>DCUN1D5</i>	5.484	5.860	3.61×10 ⁻⁶	1.30
<i>DTL</i>	3.244	3.768	6.45×10 ⁻⁵	1.44
<i>EXO1</i>	3.177	3.564	1.18×10 ⁻³	1.31
<i>EZH2</i>	4.740	5.291	7.77×10 ⁻⁹	1.47
<i>FAM3C</i>	7.705	8.338	3.17×10 ⁻⁹	1.55
<i>FAM49B</i>	6.410	6.914	1.53×10 ⁻⁵	1.42
<i>GART</i>	6.382	6.652	2.87×10 ⁻⁶	1.21
<i>GNB4</i>	5.706	6.238	1.97×10 ⁻³	1.45
<i>GTPBP4</i>	6.469	6.837	5.75×10 ⁻⁵	1.29
<i>HDAC2</i>	7.029	7.580	4.38×10 ⁻¹³	1.47
<i>HSPA14</i>	4.575	4.879	6.17×10 ⁻⁸	1.24
<i>ILF2</i>	7.853	8.011	7.89×10 ⁻³	1.12
<i>KDELRL2</i>	7.663	8.356	1.07×10 ⁻¹¹	1.62
<i>LBR</i>	7.054	7.491	6.39×10 ⁻⁷	1.35
<i>LGALS8</i>	3.918	3.696	2.55×10 ⁻⁷	0.86
<i>MAD2L1</i>	3.382	3.813	8.49×10 ⁻⁶	1.35
<i>MAGOHB</i>	5.327	5.741	1.65×10 ⁻⁸	1.33
<i>MCM3</i>	5.156	5.468	5.86×10 ⁻⁵	1.24
<i>MND1</i>	2.366	2.555	6.43×10 ⁻⁴	1.14
<i>MSH2</i>	4.580	5.373	2.75×10 ⁻¹⁶	1.73
<i>NDC80</i>	3.099	3.630	2.47×10 ⁻⁶	1.44
<i>NDUFB5</i>	7.051	7.456	9.21×10 ⁻⁸	1.32
<i>NEK2</i>	3.427	4.021	4.33×10 ⁻⁶	1.51
<i>NFE2L3</i>	4.603	4.933	6.71×10 ⁻⁴	1.26
<i>NMI</i>	4.333	5.195	5.06×10 ⁻⁸	1.82
<i>NUDT5</i>	4.741	5.414	1.75×10 ⁻¹²	1.59
<i>NUF2</i>	3.405	3.954	2.61×10 ⁻⁴	1.46
<i>PARP1</i>	6.211	6.664	1.65×10 ⁻⁸	1.37
<i>PBK</i>	2.490	2.900	1.67×10 ⁻³	1.33
<i>PCNA</i>	5.660	6.096	3.43×10 ⁻⁸	1.35
<i>PDCD10</i>	4.830	5.317	3.48×10 ⁻⁸	1.40
<i>PDSS1</i>	5.504	6.126	2.45×10 ⁻⁷	1.54
<i>PKMYT1</i>	3.813	3.538	6.94×10 ⁻⁸	0.83
<i>PRC1</i>	4.432	5.051	6.54×10 ⁻⁶	1.54
<i>PRIM2</i>	3.471	3.901	1.74×10 ⁻⁸	1.35
<i>PRPF18</i>	6.058	6.588	3.39×10 ⁻¹³	1.44
<i>PSMA3</i>	6.250	6.837	2.63×10 ⁻⁸	1.50
<i>PSMB4</i>	8.348	8.765	1.16×10 ⁻⁷	1.33

<i>PTS</i>	5.488	6.062	1.67×10 ⁻⁸	1.49
<i>PTTG1</i>	4.724	5.081	1.28×10 ⁻³	1.28
<i>RACGAP1</i>	4.991	5.743	1.72×10 ⁻⁸	1.68
<i>RAD51</i>	2.607	2.995	8.03×10 ⁻⁸	1.31
<i>RAD51AP1</i>	3.354	3.962	9.02×10 ⁻⁷	1.52
<i>RANBP1</i>	6.634	6.830	6.27×10 ⁻³	1.15
<i>RBM8A</i>	4.949	5.527	1.89×10 ⁻⁹	1.49
<i>RFC4</i>	4.683	5.400	4.70×10 ⁻¹²	1.64
<i>RRAGD</i>	5.383	5.800	1.69×10 ⁻⁵	1.34
<i>RRM2</i>	2.824	3.344	8.46×10 ⁻⁶	1.43
<i>SLC25A5</i>	8.219	8.504	1.91×10 ⁻³	1.22
<i>SMAD2</i>	6.829	7.245	1.24×10 ⁻⁸	1.33
<i>SNRPD1</i>	4.935	5.798	1.65×10 ⁻¹⁰	1.82
<i>SNRPG</i>	4.122	4.401	5.67×10 ⁻⁶	1.21
<i>SRPK1</i>	6.478	6.825	5.53×10 ⁻⁵	1.27
<i>STMN1</i>	5.451	5.855	4.57×10 ⁻⁴	1.32
<i>TMEM14A</i>	5.461	6.269	4.55×10 ⁻¹⁴	1.75
<i>TOP2A</i>	4.397	5.199	9.01×10 ⁻⁵	1.74
<i>TP53BP2</i>	6.034	6.364	1.60×10 ⁻³	1.26
<i>TTK</i>	2.246	2.704	1.20×10 ⁻⁵	1.37
<i>TYMS</i>	4.626	5.472	5.07×10 ⁻⁸	1.80
<i>UBE2T</i>	3.262	3.909	8.31×10 ⁻⁶	1.57
<i>UGGT1</i>	7.150	7.540	5.26×10 ⁻¹¹	1.31
<i>WDR26</i>	7.360	7.812	1.06×10 ⁻⁸	1.37

CHIANG [36]				
Gene	Average Gene Expression in Group		Corr. <i>p</i> -Value	Fold Change (CEBPD-Low vs. CEBPD-High Group)
	CEBPD-High	CEBPD-Low		
<i>ANLN</i>	3.580	4.299	2.59×10 ⁻³	1.65
<i>ARID3A</i>	5.173	4.805	2.65×10 ⁻⁹	0.77
<i>ASPM</i>	3.131	3.945	1.91×10 ⁻⁵	1.76
<i>BACE2</i>	6.533	6.849	7.94×10 ⁻⁴	1.25
<i>BARD1</i>	4.551	5.051	4.40×10 ⁻⁷	1.41
<i>BUB1B</i>	3.381	3.827	2.91×10 ⁻⁴	1.36
<i>CCNA2</i>	4.225	4.731	1.34×10 ⁻⁴	1.42
<i>CCNB1</i>	4.415	5.122	8.01×10 ⁻⁵	1.63
<i>CCNB2</i>	3.228	3.815	6.48×10 ⁻⁴	1.50
<i>CCNE1</i>	4.108	4.486	5.94×10 ⁻⁷	1.30
<i>CDC6</i>	3.183	3.761	3.05×10 ⁻⁴	1.49
<i>CDC7</i>	3.142	3.517	3.33×10 ⁻⁴	1.30
<i>CDCA7</i>	3.882	4.275	2.16×10 ⁻³	1.31
<i>CDCA7L</i>	5.027	5.580	8.24×10 ⁻⁸	1.47
<i>CDKN3</i>	2.417	2.818	2.50×10 ⁻⁴	1.32
<i>CENPE</i>	2.162	2.384	5.23×10 ⁻³	1.17
<i>CENPF</i>	3.665	4.513	3.11×10 ⁻⁵	1.80
<i>CENPK</i>	3.233	3.912	2.72×10 ⁻⁵	1.60
<i>CEP55</i>	3.441	3.864	1.34×10 ⁻³	1.34
<i>CKAP4</i>	6.872	6.648	1.90×10 ⁻⁵	0.86
<i>CMTM3</i>	5.787	6.176	2.25×10 ⁻³	1.31
<i>CYBA</i>	5.056	4.590	4.52×10 ⁻⁷	0.72
<i>DDR1</i>	6.177	6.463	6.04×10 ⁻³	1.22

DEPDC1	2.045	2.287	7.04×10 ⁻³	1.18
DEPDC1B	3.322	4.016	1.05×10 ⁻⁶	1.62
DLGAP5	2.895	3.565	2.23×10 ⁻⁴	1.59
DSCC1	2.769	3.254	7.27×10 ⁻⁸	1.40
DTL	3.244	3.768	9.96×10 ⁻⁵	1.44
DUSP9	5.718	5.318	2.94×10 ⁻⁶	0.76
ECT2	4.525	5.357	1.38×10 ⁻⁵	1.78
ELOVL7	6.009	6.652	9.81×10 ⁻⁶	1.56
EZH2	4.740	5.291	1.10×10 ⁻⁸	1.47
FANCI	4.212	4.817	7.40×10 ⁻⁶	1.52
FBXO5	4.508	4.834	1.27×10 ⁻⁶	1.25
FEN1	4.367	4.711	5.92×10 ⁻⁷	1.27
FLVCR1	4.130	4.792	8.51×10 ⁻⁹	1.58
FMNL2	6.025	6.474	2.26×10 ⁻⁵	1.37
FUNDC1	6.137	6.648	4.45×10 ⁻¹⁴	1.43
G6PD	5.501	5.201	3.63×10 ⁻⁴	0.81
GALNT7	6.089	6.658	1.33×10 ⁻⁷	1.48
HDAC2	7.029	7.580	9.60×10 ⁻¹³	1.47
HELLS	3.215	3.841	2.24×10 ⁻⁷	1.54
HMGB2	5.085	5.469	2.15×10 ⁻³	1.31
IGF2BP3	3.113	3.676	2.57×10 ⁻³	1.48
KIF11	2.750	3.235	1.91×10 ⁻⁴	1.40
KIF14	2.814	3.253	1.08×10 ⁻³	1.36
KIF20A	2.901	3.152	5.55×10 ⁻³	1.19
KIF4A	3.284	3.626	6.45×10 ⁻³	1.27
LDLRAD3	5.678	5.369	1.57×10 ⁻⁷	0.81
LRRC1	5.798	6.266	6.66×10 ⁻⁷	1.38
MAD2L1	3.382	3.813	1.34×10 ⁻⁵	1.35
MAPK13	5.773	6.003	2.48×10 ⁻³	1.17
MARCKSL1	8.190	7.332	2.82×10 ⁻¹⁵	0.55
MECOM	6.176	6.598	2.61×10 ⁻³	1.34
MKI67	4.263	4.843	1.52×10 ⁻³	1.50
MMP12	3.589	5.041	1.40×10 ⁻⁶	2.74
MTMR2	6.458	6.855	5.00×10 ⁻⁵	1.32
NCEH1	6.201	7.014	3.20×10 ⁻⁸	1.76
NDC80	3.099	3.630	4.14×10 ⁻⁶	1.44
NEK2	3.427	4.021	7.29×10 ⁻⁶	1.51
NT5DC2	5.147	5.524	2.06×10 ⁻⁴	1.30
NUF2	3.405	3.954	3.60×10 ⁻⁴	1.46
NUSAP1	4.172	4.457	4.74×10 ⁻³	1.22
PBK	2.490	2.900	2.26×10 ⁻³	1.33
PLBD1	6.764	7.560	1.89×10 ⁻⁹	1.74
PLP2	8.155	8.884	2.13×10 ⁻⁹	1.66
PRC1	4.432	5.051	1.06×10 ⁻⁵	1.54
PRKCD	6.119	6.358	5.53×10 ⁻³	1.18
PRR11	3.488	3.854	2.51×10 ⁻³	1.29
PTTG1	4.724	5.081	1.74×10 ⁻³	1.28
RACGAP1	4.991	5.743	3.12×10 ⁻⁸	1.68
RAD51AP1	3.354	3.962	1.53×10 ⁻⁶	1.52
RFC4	4.683	5.400	1.08×10 ⁻¹¹	1.64
SASS6	2.906	3.408	1.39×10 ⁻¹¹	1.42
SEL1L3	7.032	7.759	1.75×10 ⁻¹¹	1.66
SHCBP1	3.709	4.441	7.05×10 ⁻⁶	1.66
SLC38A1	7.219	7.537	1.07×10 ⁻³	1.25
SLC39A10	6.062	6.459	5.58×10 ⁻³	1.32
SLC7A7	4.951	5.646	8.20×10 ⁻⁶	1.62
SMC4	5.315	5.843	1.11×10 ⁻⁵	1.44
SPHK1	4.703	4.332	6.36×10 ⁻⁵	0.77
SYNJ2	5.200	5.498	1.11×10 ⁻⁴	1.23
TMEM51	4.957	5.242	2.88×10 ⁻³	1.22
TMEM65	5.411	5.878	2.19×10 ⁻¹⁰	1.38
TOP2A	4.397	5.199	1.36×10 ⁻⁴	1.74
TPX2	3.414	3.901	6.14×10 ⁻³	1.40
TRIP13	3.516	3.837	2.39×10 ⁻³	1.25

<i>TRNP1</i>	6.114	5.555	5.05×10^{-11}	0.68
<i>TSC1</i>	5.364	5.711	3.27×10^{-8}	1.27
<i>TTF2</i>	4.848	5.362	2.09×10^{-9}	1.43
<i>TTK</i>	2.246	2.704	1.90×10^{-5}	1.37
<i>VEGFB</i>	6.530	6.318	5.85×10^{-4}	0.86
<i>WASF1</i>	3.490	3.721	1.46×10^{-3}	1.17
<i>WSB1</i>	8.498	8.826	6.81×10^{-4}	1.26
<i>ZNF532</i>	5.946	6.271	9.91×10^{-3}	1.25
<i>ZWINT</i>	4.379	4.573	8.26×10^{-4}	1.14

Table S2. Pearson correlation of *CEBPD* mRNA with stromal scores. Stromal gene signatures were derived from ESTIMATE analysis [44] and are correlated to *CEBPD* mRNA expression in different publicly available gene sets (Figure S1).

Gene Set	Person's r	p-Value
GSE15471_Badea [38]	0.4869	0.0017
GSE50827_Grimond [39]	0.2761	0.0048
TCGA_Raphael [40]	0.08705	0.2479
GSE16515_Wang [41]	0.3567	0.0327
GSE62452_Hussain [42]	0.2597	0.0312
E-MTAB-6830_Xin [43]	0.2558	0.0150

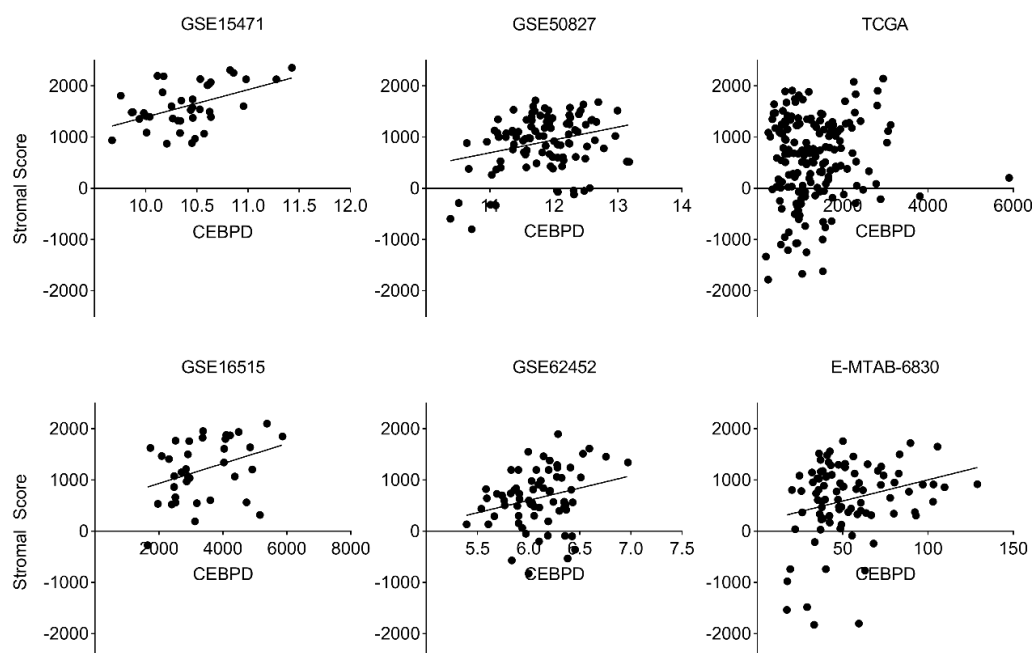


Figure S1. *C/EBPδ* correlates with stromal scores in public datasets. Stromal scores were calculated according to Yoshihara et al. [44] and strongly correlate with *CEBPD* mRNA expression in five out of six publicly available datasets.

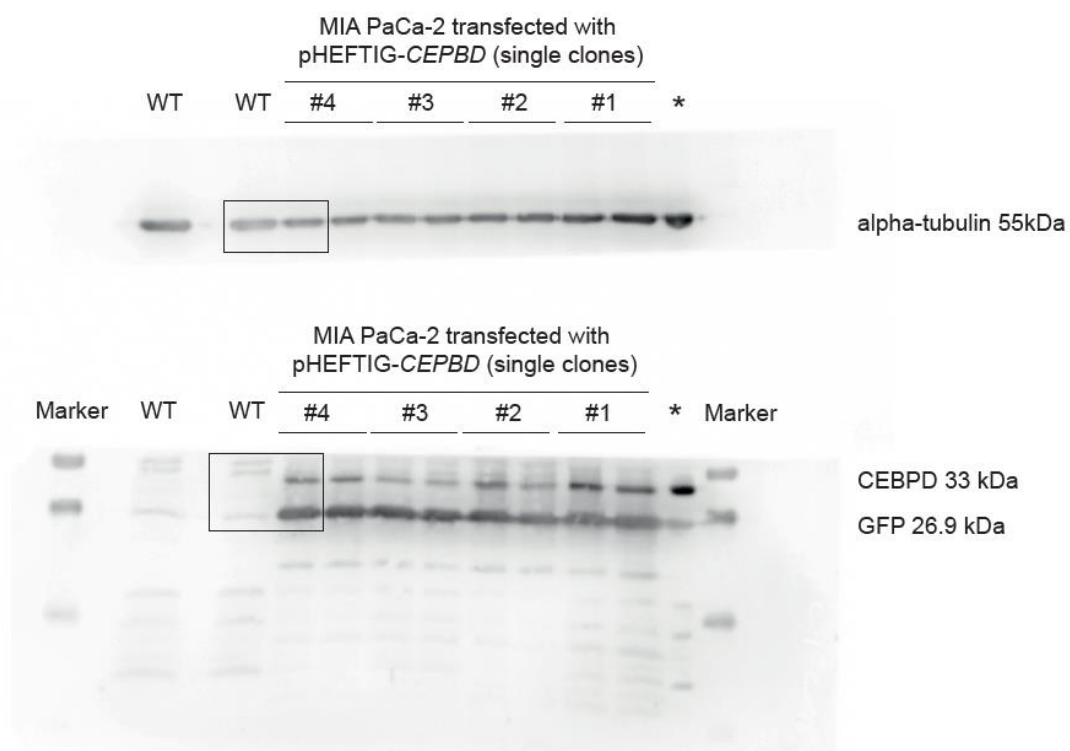
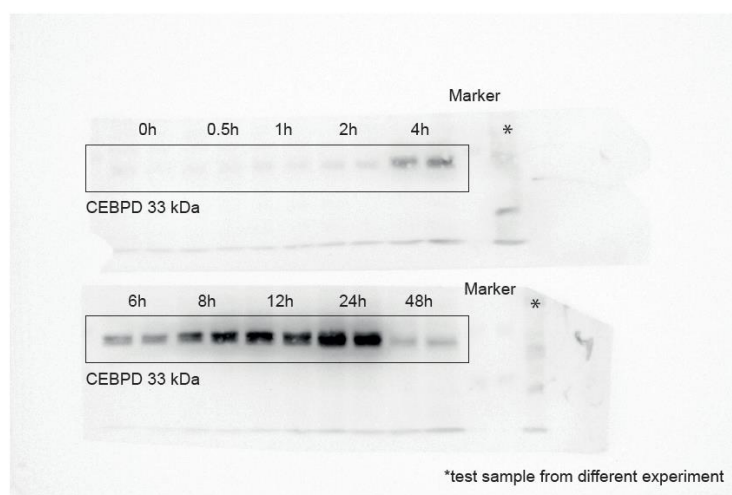
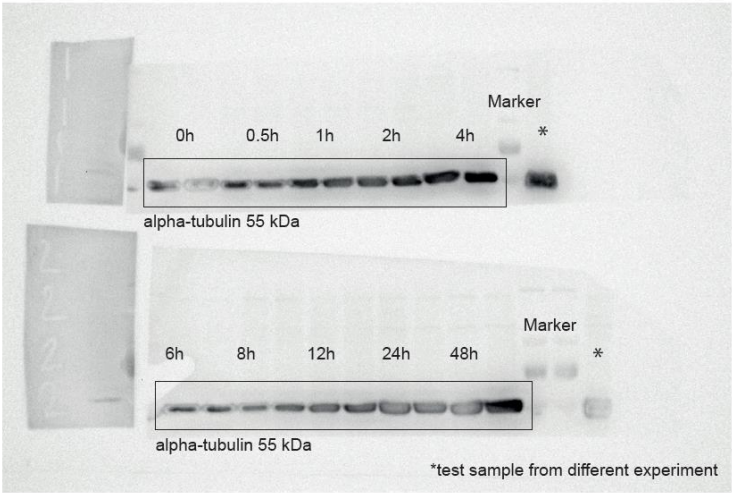
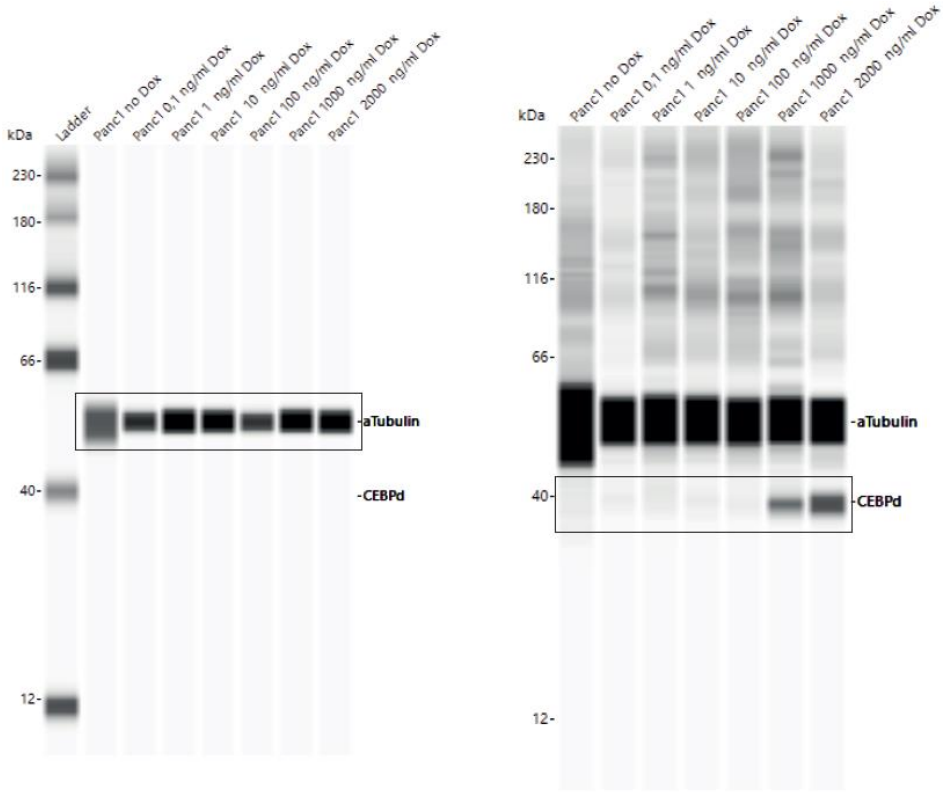


Figure S2. Uncropped Western blot membrane corresponding to Figure 4C. Black boxes indicate the samples of interest as shown in the main text.





A



B

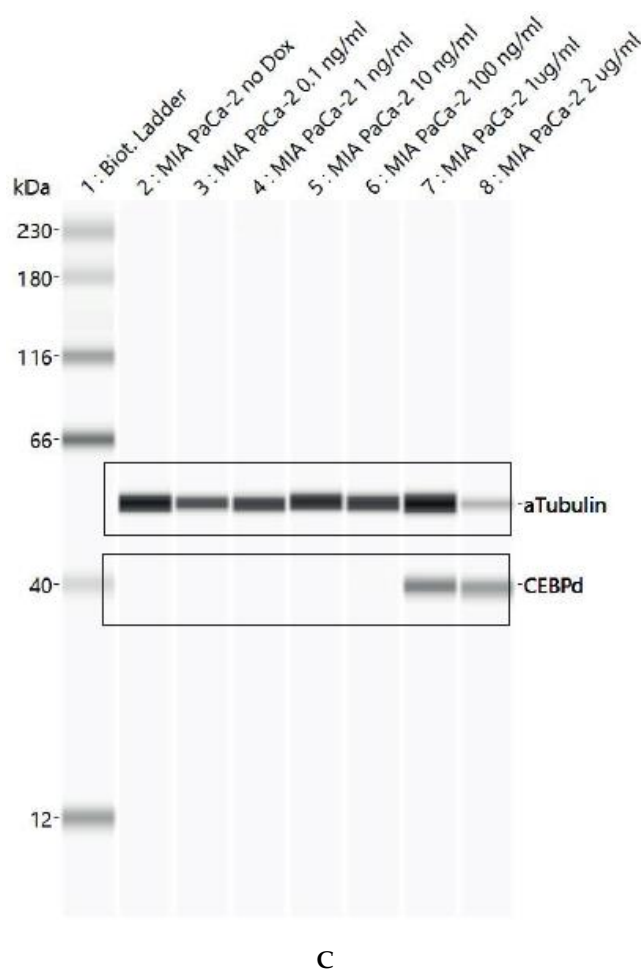


Figure S3. Uncropped Western blot membranes and WESTTM Simple Western images. (A). Uncropped Western blot membrane corresponding to Figure 5B. Black boxes indicate the samples of interest as shown in the main text. (B). WESTTM Simple Western images corresponding to Figure 5D. Both images are taken from the same samples and the same run but in the right image, the intensity was adjusted to visualize C/EBPδ in a representable manner. Black boxes indicate the samples of interest as shown in the main text. (C). WESTTM Simple Western images corresponding to Figure 5F.

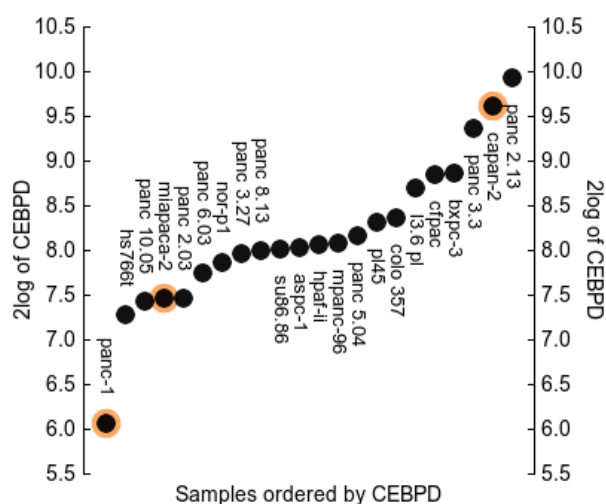


Figure S4. mRNA expression of *CEBPD* across PDAC cell lines. Data and figure are derived from Maupin et al. [46] using R2: Genomics and Visualization Platform [47].

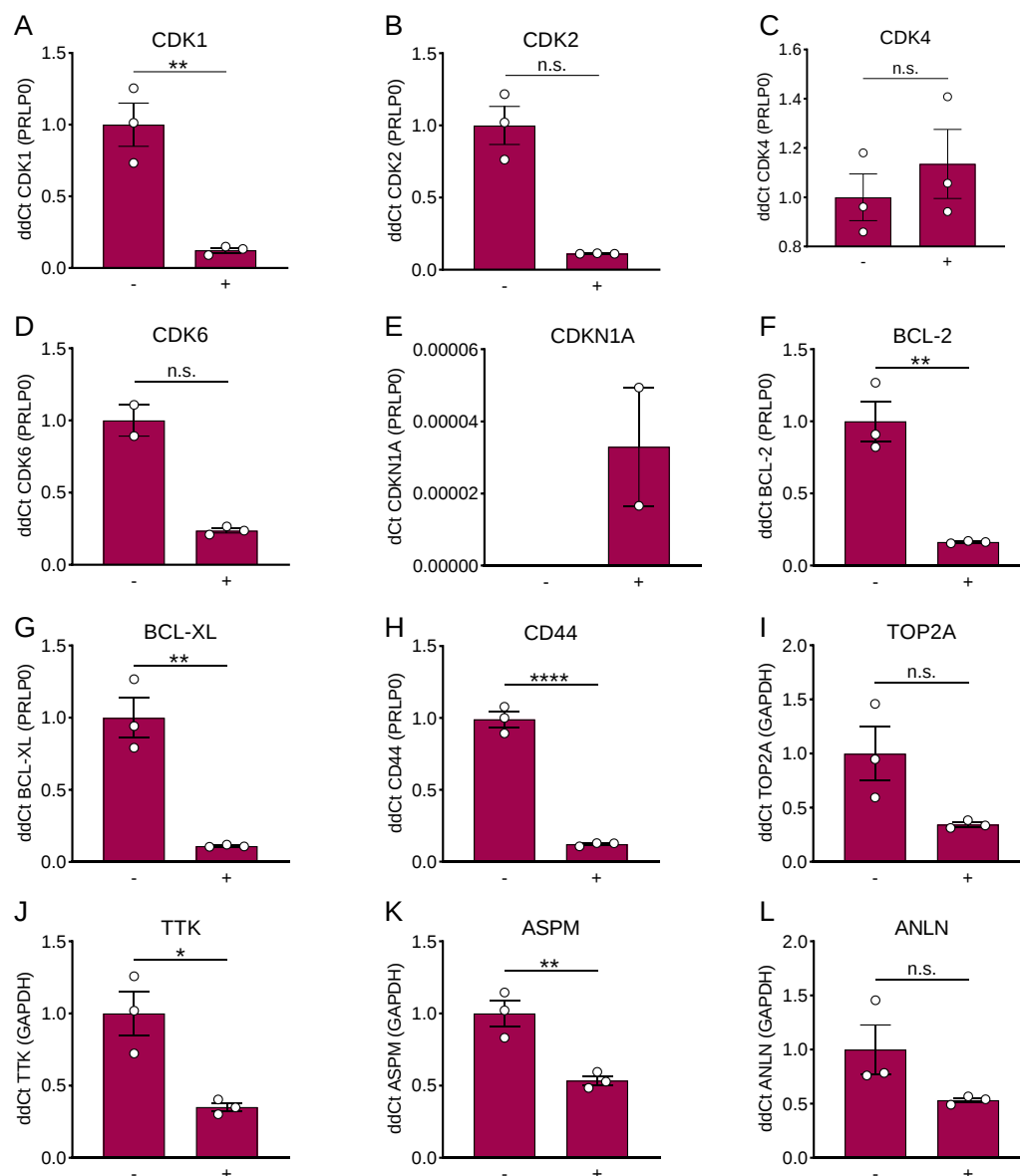


Figure S5. mRNA expression of putative targets of *CEBPD*. Bars represent MIA PaCa-2 cells inducible for *CEBPD* over-expression without (-) or with (+) doxycycline. Data are normalized to their non-induced controls. Genes are involved in: cell cycle progression (A–E), whereby CDKN1A/p21 was only detected in two samples of induced MIA PaCa-2 cells, apoptosis (F–G), stemness (H) and proliferation (I–L, from proliferative genesets by Ben-Porath and Chiang). Notably, in MIA PaCa-2 cells *C/EBPδ* affects a multitude of pathways which in concurrence might account for reduced proliferation and clonogenicity of *C/EBPδ*-high PDAC cells. n.s.: not significant, * $p < 0.05$, ** $p < 0.01$, **** $p < 0.0001$. CDK1: Cyclin Dependent Kinase 1; CDK2: Cyclin Dependent Kinase 2; CDK4: Cyclin Dependent Kinase 4; CDK6: Cyclin Dependent Kinase 6; CDKN1A: Cyclin Dependent Kinase Inhibitor 1A; BCL-2: B-Cell Lymphoma 2 Apoptosis Regulator; BCL-XL: B-Cell Lymphoma-Extra Large; CD44: CD44 Molecule; TOP2A: DNA Topoisomerase II Alpha; TTK: TTK Protein Kinase; ASPM: Assembly Factor For Spindle Microtubules; ANLN: Anilin Actin Binding Protein.

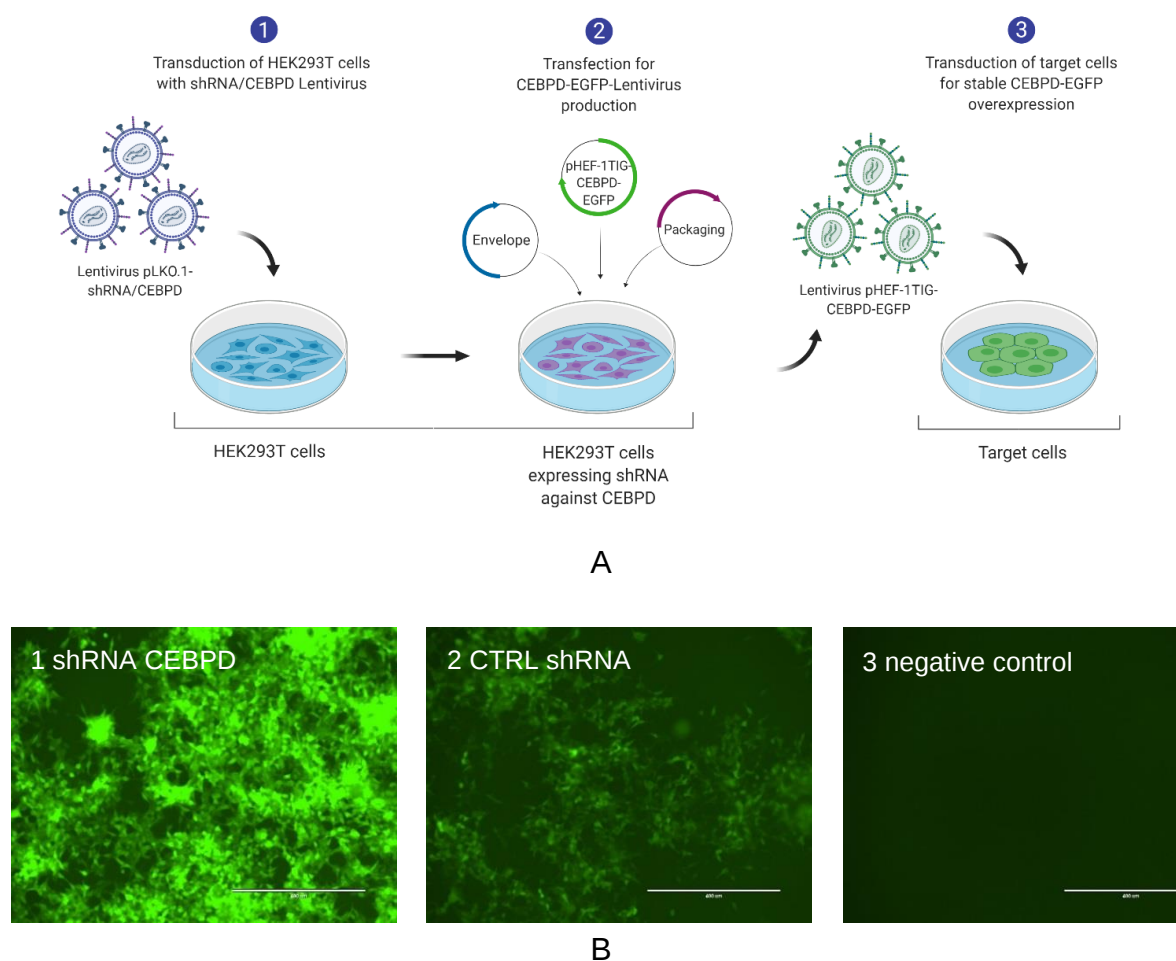


Figure S6. Knocking down *CEBPD* in lentivirus producing cells enhances virus production. **(A)** Schematic representation of pHEF-1TIG-*CEBPD*-IRES-*EGFP* lentivirus production. (1) Establishment of HEK293T cells stably expressing an shRNA against *CEBPD*. (2) Transfection of lentiviral pHEF-1TIG-*CEBPD*-IRES-*EGFP* or pHEF-1TIG-*EGFP* plasmids for virus production and collection of viral particles. (3) Transduction of HEK293T cells to determine lentivirus titer. Knocking down *CEBPD* in the producer cells has markedly enhanced lentivirus production resulting in higher virus titer, as is shown by eGFP expression in HEK293T target cells (panel B). **(B)** (1) Lentivirus titer as marked by eGFP-expression when producer cells stably expressed an shRNA against *CEBPD* (2) or a control shRNA. (3) Untransduced HEK293T cells. Scale bar is 400 μ m.

References

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