

Supplementary Figure 1: A-C: Disease-free survival curves from patients with high (Z score > 0) and low (Z score < 0) mRNA levels of LPP2 (*PLPP2*) were plotted using data extracted from TCGA database. Results were analyzed by log rank test.



Supplemeraty Figure 2: Confirmation of LPP2 knockout. **A:** PCR of LPP2 using cDNA of wild type (WT) and LPP2 knockout (ΔLPP2) MCF7 cells. One of the primers is complimentary with the Cas9 cleavage site in exon 3 of human LPP2 gene. The predicted size of the amplification product is 208 bp. LPP2 knockout cells did not have the PCR product because the sequence at the Cas9 cleavage site has been disrupted by the indels. **B:** The indel (marked with red box) at the Cas9 cleavage site of human LPP2 gene was confirmed by genomic sequencing. **C:** LPP activity decreased by 75%, 27%, and 19% in MCF7, MDA-MB-231, and HEK293 cells by LPP2 knockout . The remaining LPP2 activity is due to other LPP isoforms e.g. LPP1 and LPP3. **D and E:** Levels of LPP1 and LPP3 mRNA in MCF7 cells were not affected by LPP2 knockout.

Supplemeraty Figure 3: A: Knockout of LPP2 (Δ LPP2) inhibited proliferation of HEK293 cells. **B:** Hs-578Bst cells expressing GFP-tagged LPP2 (LPP2) showed an increased proliferation compared with cells expressing GFP (Control). **C and D:** Expressing GFP-tagged LPP2 in HEK293 and MDA-MB-231 cells decreased the percentage of cells in G1/0 phase. Results are means ± SE from three experiments per group and analyzed by ANOVA followed by Tukey test. **P* < 0.05, ***P* < 0.01 compared with control.

Supplementary Figure 4

В

D

С

HEK293

Supplemeraty Figure 4: A: Expressions of PARP, caspase-9, caspase-3 and bcl-2 in wild type (WT) and LPP2 knockout (Δ LPP2) MCF7 and MDA-MB-231 cells. **B:** Time courses of AKT and ERK phosphorylation induced by IGF (50 ng/ml), EGF (50 ng/ml) and LPA (10 μ M) in wild type (WT) and LPP2 knockout (Δ LPP2) MDA-MB-231 cells. **C:** Expressions of PARP, caspase-9, caspase-3 and bcl-2 in wild type (WT) and LPP2 knockout (Δ LPP2) HEK293 cells. **D:** Time courses of AKT and ERK phosphorylation induced by IGF (50 ng/ml) and LPA (10 μ M) in wild type (WT) and LPP2 knockout (Δ LPP2) HEK293 cells. **D:** Time courses of AKT and ERK phosphorylation induced by IGF (50 ng/ml), EGF (50 ng/ml) and LPA (10 μ M) in wild type (WT) and LPP2 knockout (Δ LPP2) HEK293 cells.

Supplementary Figure 4: A : Wild type (WT) and LPP2 knockout (Δ LPP2) MDA-MB-231 cells migrated through a 8µm-pore filter in a Boyden chamber assay were fixed with methanol. The round bands of cells were stained with crystal violet. **B:** The intensity of cell bands were quantified by LI-COR infra-red imaging system. **C:** The decrease of CCL2 mRNA expression was proved by measuring cytokines in the conditioned media of MDA-MB-231 cells. Secretion of CCL2 was almost completely suppressed by LPP2 knockout. LPP2 knockout also significantly inhibit the secretions of GM-CSF and increased IL-10 and TNF α . **D:** Wild type (WT) and LPP2 knockout (Δ LPP2) MDA-MB-231 cells treated with 100 ng/ml CCL2 for 24 h did not show changes in cell cycle relative to cells without CCL2 treatment. Results were analyzed by two-tail t-test or ANOVA followed by Tukey test. ***P* < 0.01 compared with WT.

Supplementary Figure 6: A: Decrease of c-Myc by LPP2 KO (Δ LPP2) in nuclear portions of HEK293 and MCF7 cells. Phospho-c-Myc (S62 and T58) in LPP2 KO cells also decreased compared with the wild type (WT) cells. B: Positive correlation between LPP2 (*PLPP2*) and c-Myc (*MYC*) mRNA in cell lines of lung, upper aerodigestive tract, and urinary tract cancer. Data were extracted from Cancer Cell Line Encyclopedia (CCLE) of the Broad Institute and Novartis and Pearson correlation coefficient was determined.

Supplementary Figure 7

Supplementary Figure 7: A: LPP activity decreased by ~53% in 4T1 mouse breast cancer cells by LPP2 knockout (Δ LPP2). **B:** Decrease of c-Myc by LPP2 KO in nuclear portions of 4T1 cells. **C:** LPP2 KO in 4T1 cells decreased tumor growth and tumor weight in a syngeneic mouse model of breast cancer. **D:** LPP2 KO in 4T1 cells decreased number of visible nodules on lungs. Results were means ± SE from n = 5 per group. Results were analyzed by two-tail t-test or ANOVA followed by Tukey test. * *P* < 0.05 compared with WT.

Supplementary table 1: changes of gene expression in LPP2 knockout MDA-MB-231 cells relative to wild-type cells

up-regulated genes in LPP2 knockout MDA-MB-231 cells		down-regulated genes in LPP2 knockout MDA-MB-231 cells			
Symbol	Genbank	log2 (n-fold) changes	Symbol	Genbank	log2 (n-fold) changes
LPL	NM 000237	1.254634857	CASP7	NM 001227	-0.002742767
IGFBP5	NM_000599	1.241355896	MAP2K1	NM_002755	-0.003427505
KIT	NM_000222	1.212060928	ADM	NM_001124	-0.014028549
FGFR2	NM_000141	1,152915955	IGFBP7	NM 001553	-0.018899918
EPO	NM 000799	1.019714355	PTCH1	NM 000264	-0.05238533
HMOX1	NM_002133	0.999263763	ATM	NM_000051	-0.05688858
TERE1	NM_017489	0.992427826	GSK3B	NM_002093	-0.073875427
SERPINE1	NM_002615	0.93470192	ZEB2	NM 014795	-0.097764969
PROM1	NM_006017	0.9311409	TAZ	NM_000116	-0 118747711
	NM_000689	0.879224777	IKBKB	NM_001556	-0 154550552
TWIST2	NM_057179	0.87663269	TERE2IP	NM_018975	-0 156988144
CDH2	NM_001792	0.858652115	VAP1	NM_006106	-0 187217712
FASIG	NM 000639	0.856519699	TGEBR1	NM_004612	-0.206331253
	NM_002203	0.845840001		NM 002626	-0.200031203
	NM 005430	0.843010217		NM 002020	0.220730365
	NM 001147	0.043910217		NIM 004092	-0.220739303
	NM 000450	0.019402200	EZD7	NIVI_004003	-0.222034454
	NM_0000459	0.812752677		NIVI_003307	-0.223829209
	NM_002006	0.812/030//		NIVI_014757	-0.228210449
P005F1	NM_002701	0.787111282	LAIST	NM_004690	-0.233034134
SMO	NM_005631	0.769031525	ABCG2	NM_004827	-0.243246078
LIN28B	NM_001004317	0.768035889	COX5A	NM_004255	-0.24379158
LIN28A	NM_024674	0.756601334	CASP9	NM_001229	-0.244665146
IHY1	NM_006288	0.712741852	CD44	NM_000610	-0.288244247
DLL1	NM_005618	0.6901474	CASP2	NM_032982	-0.290599823
CD38	NM_001775	0.688327789	NOTCH2	NM_024408	-0.291160583
BIRC3	NM_001165	0.664369583	ACLY	NM_001096	-0.299726486
SNAI3	NM_178310	0.661207199	JAG1	NM_000214	-0.302106857
ANGPT1	NM_001146	0.651576996	ALCAM	NM_001627	-0.303314209
FOXP1	NM_032682	0.624868393	NOTCH1	NM_017617	-0.303665161
ITGA4	NM_000885	0.595752716	FOXC2	NM_005251	-0.313022614
ID1	NM_002165	0.589834213	WEE1	NM_003390	-0.323949814
GADD45G	NM_006705	0.589595795	E2F4	NM_001950	-0.324035645
SOX10	NM_006941	0.589097977	GPD2	NM_000408	-0.326490402
SOX2	NM_003106	0.561719894	HDAC1	NM_004964	-0.326719284
SNAI2	NM_003068	0.547794342	CCND3	NM_001760	-0.337615967
NOS2	NM_000625	0.5260849	TEP1	NM_007110	-0.35941124
CCND2	NM_001759	0.522829056	ERCC5	NM_000123	-0.364494324
PTPRC	NM_002838	0.518320084	MKI67	NM_002417	-0.364543915
ENG	NM_000118	0.518217087	KITLG	NM_003994	-0.367141724
CD34	NM_001773	0.438417435	MUC1	NM_001018016	-0.367591858
FLT1	NM_002019	0.424293518	PINX1	NM_017884	-0.3705616
KLF17	NM_173484	0.41472435	SOD1	NM_000454	-0.397607803
MS4A1	NM_021950	0.413740158	CPT2	NM_000098	-0.398511887
ATXN1	NM_000332	0.406332016	MAP2K3	NM_002756	-0.410093307
KRT14	NM_000526	0.403690338	OCLN	NM_002538	-0.421339035
XIAP	NM_001167	0.393486023	DDB2	NM_000107	-0.421834946
TWIST1	NM_000474	0.391210556	PLAUR	NM_002659	-0.458185196
KDR	NM_002253	0.378587723	VEGFC	NM_005429	-0.461988449
NANOG	NM 024865	0.353549957	JAK2	NM 004972	-0.466907501
PGF	NM_002632	0.34327507	STMN1	NM_005563	-0.470554352
ZEB1	NM_030751	0.330713272	WEE1	NM_003390	-0.472980499
CA9	NM_001216	0.324865341	TINF2	NM_012461	-0.480195999
G6PD	NM_000402	0.314731598	GATA3	NM_002051	-0.48400116
GSC	NM 173849	0.298522949	ATP5A1	NM 004046	-0.484085083
ABCB5	NM 178559	0.289064407	SKP2	NM 005983	-0.485609055
APAF1	NM 001160	0.272527695	PPP1R15A	NM 014330	-0.512840271
BMP7	NM 001719	0.272285461	ETFA	NM 000126	-0.521837234
DLL4	NM 019074	0.262916565	AURKA	NM 003600	-0.535881042
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Supplementary table 1: changes of gene expression in LPP2 knockout MDA-MB-231 cells relative to wild-type cells

up-regulated genes in LPP2 knockout MDA-MB-231 cells							
Symbol	Genbank	log2 (n-fold) changes					
SNAI1	NM_005985	0.260686874					
TNKS	NM_003747	0.248916626					
DACH1	NM_004392	0.219028473					
TBX2	NM_005994	0.217012405					
DDR1	NM_001954	0.199293137					
IGFBP3	NM_000598	0.159706116					
BCL2L11	NM_006538	0.14899826					
LDHA	NM_005566	0.13892746					
MYCN	NM_005378	0.127464294					
TNKS2	NM_025235	0.100011826					
MAPK14	NM_001315	0.095556259					
EGF	NM_001963	0.042631149					
MERTK	NM_006343	0.036523819					
ARNT	NM_001668	0.031070709					
NOL3	NM_003946	0.021102905					

down-regulated genes in LPP2 knockout MDA-MB-231 cell					
Symbol	Genbank	log2 (n-told) changes			
UQCREST	NM_006003	-0.537349701			
	NM_001379	-0.545078278			
CFLAR	NM_003879	-0.546897888			
FLOT2	NM_004475	-0.548576355			
SIRT1	NM_012238	-0.554803848			
AXL	NM_001699	-0.577075958			
SAV1	NM_021818	-0.588003159			
POLB	NM_002690	-0.592323303			
ETS2	NM_005239	-0.600931168			
ERCC3	NM_000122	-0.611265182			
SLC2A1	NM_006516	-0.661832809			
CHEK1	NM_001274	-0.682130814			
LIG4	NM_002312	-0.688751221			
ERBB2	NM_004448	-0.696914673			
NFKB1	NM_003998	-0.69950676			
DKC1	NM_001363	-0.702711105			
BMI1	NM_005180	-0.72023201			
STAT3	NM_003150	-0.72908783			
FOXA2	NM_021784	-0.735729218			
ACSL4	NM_004458	-0.754804611			
ITGA6	NM_000210	-0.756126404			
MCM2	NM_004526	-0.76002121			
DSP	NM_004415	-0.784818649			
CDC20	NM_001255	-0.866754532			
KLF4	NM_004235	-0.940618515			
EPCAM	NM_002354	-0.951040268			
MYC	NM_002467	-1.110683441			
WWC1	NM_015238	-1.114034653			
PECAM1	NM_000442	-1.303861618			
CXCL8	NM_000584	-1.436033249			
SERPINB2	NM_002575	-1.590080261			
DKK1	NM_012242	-1.640377045			
CD24	NM_013230	-1.961645126			
PLAT	NM_000930	-2.01742363			
CCL2	NM_002982	-3.887592316			