

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 ( $\triangle$ LPP2) 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-MB231, 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 ( $\triangle$ LPP2) inhibited proliferation of HEK293 cells. B: Hs578Bst 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 $\pm$ 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


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

## Supplementary Figure 5



Supplementary Figure 4: A : Wild type (WT) and LPP2 knockout ( $\triangle$ LPP2) MDA-MB-231 cells migrated through a $8 \mu \mathrm{~m}$-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 $\alpha$. D: Wild type (WT) and LPP2 knockout ( $\triangle$ LPP2) MDA-MB-231 cells treated with $100 \mathrm{ng} / \mathrm{ml}$ 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.



Upper aerodigestive tract cancer


Urinary tract cancer


Supplementary Figure 6: A: Decrease of c-Myc by LPP2 KO ( $\triangle$ 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: A: LPP activity decreased by $\sim 53 \%$ in 4 T1 mouse breast cancer cells by LPP2 knockout ( $\Delta \mathrm{LPP} 2$ ) . 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 4 T1 cells decreased number of visible nodules on lungs. Results were means $\pm$ 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 | in LPP2 knock | MDA-MB-231 cells | down-regulat | es in LPP2 knock | 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 |
| TERF1 | NM_017489 | 0.992427826 | GSK3B | NM_002093 | -0.073875427 |
| SERPINF1 | NM_002615 | 0.93470192 | ZEB2 | NM_014795 | -0.097764969 |
| PROM1 | NM_006017 | 0.9311409 | TAZ | NM_000116 | -0.118747711 |
| ALDH1A1 | NM_000689 | 0.879224777 | IKBKB | NM_001556 | -0.154550552 |
| TWIST2 | NM_057179 | 0.87663269 | TERF2IP | NM_018975 | -0.156988144 |
| CDH2 | NM_001792 | 0.858652115 | YAP1 | NM_006106 | -0.187217712 |
| FASLG | NM_000639 | 0.856519699 | TGFBR1 | NM_004612 | -0.206331253 |
| ITGA2 | NM_002203 | 0.845849991 | PFKL | NM_002626 | -0.207624435 |
| WNT1 | NM_005430 | 0.843910217 | ITGB1 | NM_002211 | -0.220739365 |
| ANGPT2 | NM_001147 | 0.819452286 | DDIT3 | NM_004083 | -0.222034454 |
| TEK | NM_000459 | 0.814302444 | FZD7 | NM_003507 | -0.223829269 |
| FGF2 | NM_002006 | 0.812753677 | MAML1 | NM_014757 | -0.228210449 |
| POU5F1 | NM_002701 | 0.787111282 | LATS1 | 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 |
| THY1 | 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 |

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 $\quad$| log2 $(\mathbf{n}$-fold) changes |
| :---: |



