Supplementary Information

**LCDR** maintains the integrity of lysosomal membrane by hnRNP K-stabilized **LAPTM5** transcript and promotes cell survival

Xiwang Yang\(^a,b,c,1\), Ya Wen\(^a,c,1\), Shaomin Liu\(^d,1\), Liqiang Duan\(^c\), Tongfeng Liu\(^a,b\), Zhou Tong\(^c\), Zhuo Wang\(^c\), Yinmin Gu\(^b\), Yibo Xi\(^c\), Xiaodong Wang\(^b\), Dingsan Luo\(^b\), Ruobing Zhang\(^b\), Yajuan Liu\(^c\), Yang Wang\(^c\), Tianyou Cheng\(^c\), Siyuan Jiang\(^b\), Xiaofeng Zhu\(^a,c\), Xiaohui Yang\(^b\), Yongbo Pan\(^c\), Shuwen Cheng\(^c\), Qinong Ye\(^l\), Jinfei Chen\(^b,2\), Xiaoding Xu\(^d,2\) and Shan Gao\(^b,c,h,2\)

\(^a\)Medical School of Guizhou University, Guiyang, 550025, China; \(^b\)CAS Key Laboratory of Bio-medical Diagnostics, Suzhou Institute of Biomedical Engineering and Technology, Chinese Academy of Sciences, Suzhou 215163, China; \(^c\)Shanxi Academy of Advanced Research and Innovation, Taiyuan 030032, China; \(^d\)Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Medical Research Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, 510120, China; \(^e\)Cancer Center, Taikang Xianlin Drum Tower Hospital, Nanjing University School of Medicine, Nanjing, 210046, China; \(^f\)Department of Medical Molecular Biology, Beijing Institute of Biotechnology, Collaborative Innovation Center for Cancer Medicine, Beijing, 100850, China; \(^g\)Department of Oncology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, 325000, Zhejiang, China; \(^h\)Zhongda Hospital, Southeast University, 87 Dingjiaqiao, Nanjing, China, 210096.

1These authors contribute equally

\(^2\)Corresponding author: Shan Gao, Xiaoding Xu, Jinfei Chen

Email: gaos@sibet.ac.cn, xuxiaod5@mail.sysu.edu.cn, jinfeichen@sohu.com

This supplementary information contains:

- 51 Pages
- Supplementary Materials and Methods
- Supplementary Figures (18 Figures)
• Supplementary Tables (6 Tables)
• References
Supplementary Materials and Methods

Data collection
Differentially expressed lncRNAs were analysed in 7 cancer types from TCGA Pan-Cancer project, including cholangiocarcinoma (CHOL), head and neck squamous cell carcinoma (HNSC), kidney renal clear cell carcinoma (KIRC), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC) and stomach adenocarcinoma (STAD).

LncRNAs with $p < 0.05$ and log$_2$ Fold change (FC) > 0 between tumor and adjacent tissues were identified as up-regulated lncRNAs, and lncRNAs with $p < 0.05$ and log$_2$ Fold change (FC) < 0 were identified as down-regulated lncRNAs. The public database Gene Expression Omnibus (GEO) [1]: The hnRNP K CLIP-sequence data on K562 cell line was downloaded from GSE91621. The hnRNP K RIP-sequence data on MCF10A cell line was downloaded from the GSE119800. The c-Jun ChIP-sequence data on A549 cell line was downloaded from GSE92783. The H3K27ac ChIP-sequence data on NCI-H1299 cell line was downloaded from GSE109591. The data of histone modifications (H3K4me, H3K9ac, H3K9me, H3K27ac, H3K36me) of LCDR promoter on A549 cell line were downloaded from GSE29611 of ENCODE.

RNA-sequence and analysis
RNA-sequence was performed by Novogene (Beijing, China). Raw read counts were used for differential gene expression analysis by DESeq2 [2]. Gene expression levels were measured by the number of uniquely mapped fragments per kilobase of transcript per million mapped reads (FPKM). Differential expression genes (DEGs) between 300nM trichostain A (TSA) or dimethyl sulfoxide (DMSO)-treated cells were defined based on the criteria: $p < 0.05$ and $|\text{log2FC}| > 0.58$. DEGs between sh-LCDR or si-hnRNP K and control cells were defined by $p < 0.05$. Pathway analysis of DEGs was performed using the KEGG database. The RNA sequence data from this study have been deposited in the GEO (GSE173849).
**5′- And 3′-rapid amplification of cDNA ends (RACE)**

We used the 5′- and 3′-RACE analyses to determine the transcriptional initiation and termination sites of *LCDR* using a SMARTer RACE cDNA Amplification Kit (Clontech, Palo Alto, CA, USA), according to the manufacturer's instructions. The gene-specific primers used for the PCR of the RACE analysis are given in follows:

5′RACE, 5′-GATTACGCCAAGCTTAGACACGTGT-3′;

3′RACE, 5′-TCCGTCCTTCTCCTCTGCGCATTA-3′.

Nucleotide sequences of *LCDR* were shown in Table S1.

**shRNAs and siRNAs**

The sequences of shRNA and siRNA for KD used are listed in Table S2.

**Immunoblot (IB)**

Whole cell lysates were prepared using Radio Immunoprecipitation Assay (RIPA) lysis buffer (Beyotime Biotechnology Inc.) containing 1% protease and phosphatase inhibitor cocktails (sigma). After quantification using a BCA protein assay kit (Beyotime Biotechnology Inc.), protein samples were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene fluoride (PVDF) membranes (General Electric, Fairfield, CT, USA). Membranes were blocked with 5% milk in Tris-buffered saline–Tween 20 (TBST) and incubated overnight at 4°C with the indicated antibodies. After extensive washing, the membrane was incubated with secondary antibody for 1.5 hours in blocking buffer. Membranes were washed again, and bands were visualized with Immobilon Western Chemilum HRP Substrate from Millipore (Merck KGaA, Darmstadt, Germany). The antibodies used were given in Table S3.

**qRT-PCR**

Total RNA was isolated from cultured cells using RNAiso Plus (TAKARA, Shiga,
Japan), and complementary DNA (cDNA) was synthesized using PrimeScript RT Master Mix (TAKARA, Shiga, Japan). qRT-PCR was performed using SYBR premix EX Taq (TaKaRa) and analysed with QuantStudio 7 Flex Real-Time PCR System (Thermo Fisher). Relative gene expression was determined by $2^{-\Delta\Delta CT}$ normalized to GAPDH [3]. The primers used were listed in Table S4.

**Northern blotting analysis**

Total RNA was isolated from NCI-H1299 cells and ribosomal RNA was depleted using Ribo-off rRNA Depletion Kit (Vazyme, Jiangsu, China) according to the manufacturer’s instructions. Then the isolated RNA was dissolved in 2× RNA loading buffer (95% formamide, 0.025% lauryl sodium sulfate, 0.025% bromophenol blue, 0.025% xylene cyanol, 0.025% ethidium bromide and 0.5 mM edetic acid). Samples were loaded onto 15% denaturing TBE-urea gels and then transferred onto positively charged nylon membranes (Roche, Basel, Switzerland). The blotted membranes were prehybridized at 65°C for 1 hours using hybridization buffer (Roche) and subjected to hybridization with DIG-labelled DNA probe targeted against LCDR (Exiqon, Vedbaek, Danmark) overnight at RT. Probe detection was performed using a DIG Luminescent Detection Kit (Roche) according to the manufacturer’s protocol.

**Quantification of LCDR copy numbers**

The copy numbers of LCDR transcript per cell in the indicated cells were quantified using qRT-PCR assay. In this assay, serially diluted pcDNA3.1-LCDR-expressing plasmids were used as templates to formulate standard curves, and then the exact copies of LCDR per cell were calculated by relating the CT value to standard curve [4].

**Nuclear/cytosolic fractionation**

Cell nucleus/cytoplasm fraction isolation was performed according to previously described protocol [5]. $1 \times 10^7$ NCI-H1299 cells were incubated with hypotonic
buffer (25 mM Tris-HCl, PH 7.4, 1 mM MgCl₂, 5 mM KCl) on ice for 5 minutes.

An equal volume of hypotonic buffer containing 1% NP-40 was then added, and each sample was left on ice for another 5 minutes. After centrifugation at 5000 g for 5 minutes, the supernatant was collected as the cytosolic fraction. The pellets were resuspended in nucleus resuspension buffer (20 mM HEPES, PH 7.9, 400 mM NaCl₂, 1 mM EDTA, 1 mM EGTA, 1 mM DTT, 1 mM PMSF), and incubated at 4°C for 30 minutes. Nuclear fraction was collected after removing insoluble membrane debris by centrifugation at 12000 g for 10 minutes.

**Fluorescence in situ hybridization**

Antisense probes targeting *LCDR* were transcribed in vitro and labelled using the DIG RNA LABELING KIT (SP6/T7). Cells were fixed in 4% paraformaldehyde at room temperature (RT) for 15 minutes and after washing with phosphate buffer saline (PBS), permeabilized in TritonX-100 for 5 minutes, and then washed by diethyl pyrocarbonate (DEPC)-PBS. Cells were hybridized with the digoxin (DIG)-labelled probe at 50°C for 16 hours, and then washed and incubated overnight at 4°C with Alexa Fluor 647-conjugated IgG Fraction Monoclonal Mouse anti-DIG antibody (#140118, 1:400, Jackson) and/or anti-hnRNP K antibody. Cells were then washed and incubated overnight at 4°C with Alexa Fluor 488 anti-rabbit IgG (#4412, 1:500, CST). Nuclei were stained by DAPI (4’,6-diamidino-2-phenylindole). Fluorescence images were obtained from confocal microscope (ANDOR, Oxford Instruments).

In situ hybridization assay was performed on a LUAD tissue array was purchased from Shanghai Outdo Biotech CO. Before prehybridized in prehybridization solution at 55 °C for 2 hours, the array was deparaffinized and deproteinated, then incubated with a DIG-labeled probe solution at 37 °C overnight. The next day, the array were then washed three times for 5 minutes at 37 °C with 5×/1×/0.2×sodium citrate buffer (SSC), successively, and then incubated overnight at 4°C with anti-DIG-Alkaline Phosphatase (AP) antibody (Boster).
Cell nuclei were re-stained by 0.1% Nuclear Fast Red solution (Solarbio).
Specific probe sequences were shown in Table S5.

**Cell proliferation assay**
The cells were seeded in 96-well plates with a density of $1 \times 10^3$ or $2 \times 10^3$ cells per well. Cell proliferation was determined using CellTiter-Glo Luminescent™ Cell Viability Assay assays (Promega) and then measured using a multi-mode microplate reader (Synergy HTX, BioTek, Winooski, United States).

**Colony formation assay**
Cells were transfected with the indicated shRNAs or siRNAs. Twenty-four hours later, $1 \times 10^3$ cells were cultured in a six-well plate at 37°C in a 5% CO$_2$ humidified environment. Two weeks later, cells were fixed, stained with crystal violet, and photographed.

**Luciferase reporter assay**
Cells were seeded in triplicate in 24-well plates and allowed to settle down for 24 hours. 300 ng indicated plasmids were transfected into the cells using JetPRIME® DNA and siRNA Transfection Reagent (Polyplus transfection, New York, NY). The luciferase activities were detected by Dual-Luciferase Reporter Assay System (Promega, USA) after 48 hours of transfection. Renilla luciferase activities were normalized against firefly luciferase activities.

**Flow cytometric analysis**
Annexin V staining in combination with viable dye exclusion (7-Aminoactinomycin D-7-AAD) was used to measure apoptosis. Briefly, $1 \times 10^5$ cells were harvested and transferred to Falcon polystyrene tubes, washed with cold PBS for twice and resuspended with 100 µl 1×Annexin V binding buffer. 5 µl Annexin V-FITC-7-AAD solution was added to each tube and a further 400 µl of 1×Annexin V binding buffer added after 15 minutes incubation in the dark.
Samples were subjected to flow cytometry analysis within 1 hours using a BD FACS Canto II instrument.

**Chromatin Immunoprecipitation (ChIP)**

Briefly, $1 \times 10^7$ cells were cross-linked with a final concentration of 1% formaldehyde in growth medium for 15 minutes at room temperature, and cross-linking was quenched by the addition of glycine to a final concentration of 125 mM and incubation for 5 minutes at RT. Cells were sonicated to shear the chromatin to yield DNA fragment sizes of 0.4 to 0.7 kb. Then, approximately 5 ug of Flag antibody or rabbit IgG was added to the remainder of the samples and incubated for 1 hours at 4°C, 40 ul of protein A/G agarose beads (Millipore) were added, and the mixture was incubated for 4 hours at 4°C. Beads were washed six times with cold. The binding of Flag to \textit{LCDR} promoter was quantified using qRT-PCR. The primers used were listed in Table S4.

**RNA pull-down assay**

RNAs were transcribed \textit{in vitro} using a Biotin RNA Labeling Mix Kit (Roche) and T7 RNA polymerase (Roche) according to the manufacturer’s instructions, then treated with RNase-free DNase I (TransGen Biotech), and then precipitate the RNAs by adding 0.1 volumes of 3 M sodium acetate (pH 5.2) (Thermo Scientific™), 2.2 volumes of 100% ethanol (ice cold), and 1μl glycogen (Thermo Scientific™), mix thoroughly, and store at −20°C overnight. Biotinylated RNA was folded in RNA structure buffer (10 mM Tris-HCl pH 7.0, 0.1 M KCl, 10 mM MgCl$_2$) at 95°C for 5 minutes, immediately left on ice for another 2 minutes, and then transferred to RT for 20 minutes to allow proper RNA secondary structure formation. Cell lysates were prepared using RIPA lysis buffer (Beyotime Biotechnology Inc.) containing 1% protease inhibitor cocktail (Sigma). The \textit{in vitro} binding assay of biotin-labeled \textit{LCDR} RNA and cell lysates was performed at RT for 1 hours. Then, 30 ml of washed streptavidin-conjugated magnetic beads were added to each reaction, and the mixtures were incubated at RT for
30 minutes. Beads were washed five times and boiled in 1× SDS loading buffer, and the retrieved protein was analyzed using silver-staining.

**RNA immunoprecipitation (RIP)**

RIP was performed using EZ-Magna RIP™ RNA-Binding Protein Immunoprecipitation Kit (merckmillipore) according to the manufacturer’s instructions. 2 × 10^7 cells were lysed in 100 μl RIP lysis buffer with 0.5 μl of protease inhibitor cocktail and 0.25 μl of RNase inhibitor, and supernatants were collected after centrifugation. Ten microliters of supernatant of the RIP lysate were saved as input. For each RIP, 50 μl protein G magnetic beads with 5 μg anti-hnRNP K, anti-Flag, or IgG (Abcam) were prepared in a microfuge tube as instructed. One hundred microliters of supernatant of the RIP lysate were added to each beads-antibody complex in 900 μl RIP immunoprecipitation buffer (containing 860 μl RIP wash buffer, 35 μl 0.5 M EDTA and 5 μl RNase inhibitor). The samples were mixed by rotation overnight at 4°C, and the beads were then washed six times with the RIP wash buffer. Each immunoprecipitation or input sample was resuspended in 150 μl of proteinase K buffer (107 μl of RIP Wash Buffer, 15 μl of 10% SDS, and 18 μl of proteinase K) and incubated at 55°C for 30 minutes with shaking to digest the protein. Samples were centrifuged, and the supernatants were collected for RNA extraction. Samples were centrifuged, and the supernatants were used to extract RNA by RNeasy Mini Kit (QIAGEN). Purified RNAs were subjected to cDNA synthesis and then qRT-PCR analysis. The primers used were listed in Table S4.

**Lysotracker red staining**

Cells were seeded in confocal plates in growth medium. After more than 24 hours incubation, the cells were 70-90% confluent. Discard the culture media, wash dishes with PBS twice and add the staining solution onto glass bottom. Incubate the cells in a 5% CO₂ atmosphere at 37°C for 30 minutes - 1 hour. Remove the staining solution, wash dishes with PBS twice and incubate the
cells in a 5% CO\textsubscript{2} atmosphere at 37°C for 30 minutes. Image cells by confocal microscope.

**Electron microscopy**

Samples were fixed in solution containing 2% paraformaldehyde, 2.5% glutaraldehyde, and 0.1 mol/L sodium cacodylate for 1 hour. Fixed cells were washed three times with 0.1 mol/L sodium cacodylate and suspended in buffered solution containing 1% osmic acid for 1 hour. Samples were washed three times with 0.1 mol/L sodium cacodylate followed by dehydration in a graded ethanol series, washed with acetone, and embedded into resin. Ultrathin sections were prepared using an ultramicrotome and double-stained with uranyl acetate and lead citrate. Samples were examined and images obtained under electron microscope.

**Electrophoretic mobility shift assay (EMSA)**

Fill an electrophoresis unit with 0.5× Tris borate-EDTA buffer (TBE) to just above the bottom of the wells. Flush wells and pre-electrophorese the gel for 30-60 minutes. Apply 100 V for an 8 × 8 × 0.1 cm gel. Incubate binding reactions at RT for 20-30 minutes. Add 5 μL of 5× Loading Buffer to each 20 μL binding reaction, pipetting up and down several times to mix. Electrophorese samples until the bromophenol blue dye has migrated approximately 2/3 to 3/4 down the length of the gel and then transfer of Binding Reactions to Nylon Membrane. Crosslink Transferred RNA to Membrane. Detect Biotin-labelled RNA by Chemiluminescence. Nucleotide sequences of EMSA probe were shown in Table S6.

**Immunohischemistry (IHC)**

IHC was conducted according to previously described protocol [6]. hnRNP K and LAPTM5 LUAD tissue array was purchased from Shanghai Outdo Biotech CO. Paraffin-embedded sections were dewaxed and rehydrated, then the
samples were treated with proteinase K, fixed in 4% paraformaldehyde. IHC assays were performed using the following primary antibodies: anti-hnRNP K and anti-LAPTM5. The staining intensity was graded using Image J as follows: 0, no staining; 1, weak staining (light yellow); 2, moderate staining (yellow–brown); 3, strong staining (brown). The percentage of cells at each staining intensity level is calculated, and finally, an H-score is assigned using the following formula: $[1 \times (\% \text{ cells } 1+) + 2 \times (\% \text{ cells } 2+) + 3 \times (\% \text{ cells } 3+)] \times 100$.

Animal experiments

All protocols involving animals were previously approved by the Ethics Committee for the Use of Experimental Animals of the Suzhou Institute of Biomedical Engineering and Technology, Chinese Academy of Sciences (Suzhou, Jiangsu, China). NSG (NOD/SCID/IL2Rγnull) mice of 4–6-week-old were purchased from Beijing VitalRiver Laboratory Animal Technology Co. Ltd. Monitoring Institute approved all animal protocols used in this study. Mice were bred in specific pathogen free (SPF) animal house with 28 °C and 50% humidity. Indicated cells were injected subcutaneously into the flanks of recipient mouse. Tumor formation/growth was assessed every 2-4 days as a time course until the experimental endpoint, and tumor volume was calculated by the formula: $(\text{width}) \times \text{length}/2$. Mice were euthanized 30 days after cell inoculation or if the longest dimension of the tumors reached 2.0 cm before 30 days.

Preparation of Nucleus-targeting nanoparticles (NT-NPs)

The amphiphilic polymer Meo-PEG-b-PDPA was synthesized according to our previous study [7] and then dissolved in $N,N'$-dimethylformamide (DMF) to form a homogenous solution with a concentration of 20 mg/mL. Subsequently, a mixture of 1 nmol siRNA of LCDR (0.1 nmol/μL aqueous solution), 50 μL of G0-C14 (5 mg/mL in DMF), and 10 μL of amphiphilic nucleus-targeting peptide (5 mg/mL in DMSO) was prepared and then mixed with 100 μL of Meo-PEG-b-PDPA solution. Under vigorously stirring (1000 rpm), the mixture was added
dropwise to 5 mL of deionized water. The NP dispersion was transferred to an ultrafiltration device (EMD Millipore, MWCO 100 kDa) and centrifuged to remove the organic solvent and free compounds. After washing with ultrapure water twice, the obtained NPs were dispersed in 1 mL of ultrapure water. The size and zeta potential were determined by dynamic light scattering (DLS, Malvern Zetasizer). The morphology of the saporin-loaded NPs was visualized on a Tecnai G² Spirit BioTWIN transmission electron microscope (TEM). Before observation, the sample was stained with 1% uranyl acetate and dried under air. To determine siRNA encapsulation efficiency (EE%), commercially available Cy5-labeled si-LCDR was encapsulated into the NPs according to the method described above. Subsequently, 5 μL of the NP solution was mixed with 20-fold DMSO. The standard was prepared by mixing 5 μL of naked Cy5-labeled siRNA (1 nmol/mL) with 20-fold DMSO. The fluorescence intensity was measured using a multimode microplate reader (TECAN SPARK 10M), and the vector encapsulation efficiency was calculated as EE % = (FI_{NP}/FI_{Standard}) × 100. The NPs with the EE% greater than 80% were adopted for further experiments.

**In vitro siRNA release**

The NT-NPs loading Cy5-labeled si-LCDR were prepared as described above. Subsequently, the NPs were dispersed in 1 mL of PBS (pH 7.4) and then transferred to a Float-a-lyzer G2 dialysis device (MWCO 100 kDa, Spectrum) that was immersed in PBS buffer (pH 7.4 or 6.0) at 37 °C. At a predetermined interval, 5 μL of the NP solution was withdrawn and mixed with 20-fold DMSO. The fluorescence intensity of Cy5-labeled si-LCDR was determined using a microplate reader.

**Confocal-laser scanning microscopy**

NCI-H1299 cells (50,000 cells) were seeded in a round disc and incubated in 2 mL of RPMI 1640 medium (pH 7.4) containing 10% FBS for 24 hours. After replacing the medium with 2 mL of fresh medium, the NT-NPs loading Cy5-
labeled si-LCDR were added at a siRNA concentration of 50 nM, and the cells were allowed to incubate for 4 hours. After removing the medium and subsequently washing with PBS buffer (pH 7.4) thrice, the nuclei were stained by Hoechst 33342 and the cellular uptake was viewed under a FV1000 CLSM (Olympus). The NPs composed of the Meo-PEG-b-PDPA polymer and an amphiphilic cationic lipid-like compound without nucleus-targeting ability were used as a control.

**In vitro gene silencing**

NCI-H1299 cells were seeded in 96-well plates (5,000 cells per well) and incubated in 2 mL of RPMI 1640 medium (pH 7.4) with 10% FBS for 24 hours. Thereafter, the medium was replaced by fresh medium, and then the NT-NPs loading si-LCDR were added at a siRNA concentration of 50 nM. After 24 hours incubation, the cells were washed with PBS buffer (pH 7.4) and allowed to incubate in fresh medium (pH 7.4) for another 48 hours. After removing the medium and subsequently washing with PBS buffer (pH 7.4) thrice, the cells were digested by trypsin and collected for q-PCR analysis of the LCDR expression. The NPs composed of the Meo-PEG-b-PDPA polymer and an amphiphilic cationic lipid-like compound without nucleus-targeting ability were used as a control.

**Pharmacokinetics study**

Healthy male NSG mice were randomly divided into two groups (n = 5) and given an intravenous injection of either naked cy5-siRNA or cy5-siRNA loaded NPs at a 1-nmol siRNA dose per mouse. At predetermined time intervals, orbital vein blood (20 µL) was withdrawn using a tube containing heparin, and the wound was pressed for several seconds to stop the bleeding. The fluorescence intensity of cy5-labeled siRNA in the blood was determined by microplate reader.

**Biodistribution**
Tumor-bearing NSG mice were randomly divided into two groups (n = 5) and given an intravenous injection of either naked Cy5-siRNA or cy5-siRNA-loaded NPs at a 1-nmol siRNA dose per mouse. Twenty-four hours after the injection, the mice were imaged using the Maestro 2 In-Vivo Imaging System (Cri Inc). Organs and tumors were then harvested and imaged. To quantify the accumulation of NPs in tumors and organs, the tissues were homogenated and fluorescence intensity of the Cy5-si-LCDR in each organ was examined by microplate reader.

**Immune response**
Healthy female BALB/c mice were randomly divided into three groups (n = 5) and given an intravenous injection of either (i) PBS, (ii) Control NPs, or (iii) NT-NPs si-LCDR-1 (1 nmol siRNA dose per mouse). After three consecutive injections, the blood was collected at 24 h post the final injection and serum isolated for measurements of representative cytokines (TNF-α, IL-6, IL-12, and IFN-γ) by enzyme-linked immunosorbent assay or ELISA (PBL Biomedical Laboratories and BD Biosciences) according to the manufacturer's instructions.

**Blood and histological analysis**
Healthy female BALB/c mice were randomly divided into three groups (n = 5) and given an intravenous injection of either of either (i) PBS, (ii) Control NPs, or (iii) NT-NPs si-LCDR-1 (1 nmol siRNA dose per mouse). After three consecutive injections, the blood was collected 24 h post the final injection and serum isolated for measurements of representative blood parameters (aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (ALB), blood urine nitrogen (BUN), creatinine, and total protein). Simultaneously, the main organs were collected, fixed with 4% formaldehyde, and embedded in paraffin. Tissue sections were stained with hematoxylin-eosin (H&E) and then viewed under an optical microscope.

**Statistical analyses**
Data are expressed as the mean ± standard error of the mean (SEM) or standard deviation (SD). The significance of differences between groups was assessed by two-tailed unpaired Student’s t-test. p< 0.05 was considered as statistically significant. Spearman’s correlation was used for analyzing the correlation of LCDR/hnRNP K/LAPTM5. Receiver operating characteristic (ROC) curves were generated using “pROC” package in R software. Statistical analysis was performed on GraphPad Prism5 software or R 3.5.2 software.
Supplementary Figures

Figure S1. Gene expression profiles regulated by TSA in lung cancer.

(A-B) Heatmap showing the differentially expressed coding genes (A) and the differentially expressed IncRNAs (B) in BEAS-2B (left) and NCI-H1299 (right) cells after treated with 300nM TSA or DMSO. (C-D) Venn diagram (C) and volcano plot (D) showing the overlapping DEGs between TSA-treated and DMSO-treated BEAS-2B or NCI-H1299 cells. The red dots indicate upregulated genes, the green dots indicate downregulated genes. (E) The top 10 enriched KEGG pathways of the overlapping DEGs from (D). (F-G) Venn diagram (F) and heatmap (G) showing the 24 commonly dysregulated IncRNAs in BEAS-2B and NCI-H1299 cell lines and 7 cancer types of TCGA. Heatmap plotted according to the Z-score of FC of 24 IncRNAs in BEAS-2B and NCI-H1299 cell lines and 7 cancer types of TCGA (G). (H) Immunoblot analysis of H3K27ac and H4K16ac in the indicated cell lines after treatment with 300 nM TSA for 24 hours. These data are presented as mean ± SD. *p < 0.05, **p < 0.01 and ***p < 0.001. ns, not significant, Student’s t test.
Figure S2. LCDR expression regulated by histone acetylation.

(A) Heatmap showing the 7 commonly dysregulated and H3K27ac-regualted lncRNAs and plotted according to the Z-score of Log2 (Fold Change) (Log2 (FC)) of 7 lncRNAs in 2 indicated lung cell lines and 7 cancer types of TCGA. stomach adenocarcinoma (STAD), kidney renal clear cell carcinoma (KIRC), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), head and neck squamous cell carcinoma (HNSC) andcholangiocarcinoma (CHOL). (B) The relative binding enrichment of H3K27ac from the database of GSE109591. TSS represents transcriptional starting site. Number indicates enrichment scale. (C-E) qRT-PCR analysis of LCDR expression in the indicated cell cells treated with the indicated concentration of TSA for 24 hours. (F-H) ChIP qRT-PCR analysis of the relative occupancy levels of H3K27ac on LCDR promoter after treatment with the indicated concentration of TSA in the indicated cell lines. These data are presented as mean ± SD from three independent experiments. *p < 0.05, **p <
0.01 and **p < 0.001. ns, not significant, Student's t test.
Figure S3. The molecular characteristics of LCDR. (A) The 5'- and 3'-RACE analysis of LCDR sequence. Sequence of PCR products reveals the boundaries between universal anchor primers and LCDR sequences. Arrows
indicate transcriptional directions (left). Gel electrophoresis of PCR products from 5'- and 3'-RACE (right). Terminal (ter). (B) Northern blot analysis of \textit{LCDR} transcript in NCI-H1299 cell line. (C) The protein coding potential of \textit{LCDR} predicted by the Coding Potential Calculator (http://cpc.cbi.pku.edu.cn/). \textit{GAPDH} and \textit{ACTB} served as the positive controls of protein coding genes, \textit{PCSEAT} and \textit{HOTAIR} served as the positive controls of non-coding genes. (D) qRT-PCR analysis of \textit{LCDR} expression (top) and immunoblot for the indicated proteins (bottom) in subcellular fractions. \textit{GAPDH} and \textit{U1} served as markers for the cytoplasmic and nuclear genes, respectively. Histone H3 and GAPDH served as the nuclear and cytoplasmic markers for the whole-cell lysates (WCL), cytoplasmic (Cyto) and nuclear (Nuc) fraction, respectively. (E) Representative confocal images showing the localization of \textit{LCDR} in NCI-H1299 cells. The nuclear were stained with DAPI. NC represents siRNA negative control. Scale bars, 10 µm. (F-G) qRT-PCR analysis of \textit{LCDR} relative levels (F) and copy numbers of \textit{LCDR} (G) in the indicated cell lines. (H) The relative occupancy levels of H3K4me, H3K9ac, H3K9me, H3K27ac, H3K36me on \textit{LCDR} promoter and coding regions from the dataset of ENCODE GSE29611. These data are presented as mean ± SD from three independent experiments. *p < 0.05, **p < 0.01 and ***p < 0.001. ns, not significant, Student's \textit{t} test.
Figure S4. **LCDR is transcribed by c-Jun.** (A) ENCODE ChIP-sequence data for c-Jun were displayed in A549 cells across the University of California Santa Cruz (UCSC) Genome Browser illustrations. (B-C) The qRT-PCR analysis of c-Jun and LCDR in c-Jun OE (B) and KD (C) NCI-H1299 cells (top) (n = 3).
Immunoblot of FLAG or c-Jun (bottom). (D) ChIP qRT-PCR analysis of the relative occupancy levels of c-Jun on *LCMDR* promoter. (E) Schematic diagram of the predicted potentially c-Jun-binding sites (BS) in the *LCMDR* promoter. (F) Schematic diagram of mutated sequences of the predicated c-Jun-BSs. (G) The dual-luciferase reporter assay assessing the predicted BSs cluster transcriptionally responsive to c-Jun OE in NCI-H1299 cells. (H) ChIP qRT-PCR analysis of the relative occupancy levels of c-Jun on *LCMDR* promoter after treatment with 300nM TSA in NCI-H1299 cells. These data are presented as mean ± SD from three independent experiments. *p < 0.05, **p < 0.01 and ***p < 0.001. ns, not significant, Student's *t* test.
Figure S5. KD *LCDR* induces cell death in NCI-H1299 cells. (A) The KD efficiency of *LCDR* was verified by qRT-PCR analysis of NCI-H1299 cells transfected with the indicated siRNAs for 48 hours. (B) The CTG assay for the cell proliferation in NCI-H1299 cells transfected with the indicated siRNAs. (C) The quantification data (top) and representative images of colony formation assay (down) in NCI-H1299 cells transfected with the indicated siRNAs. (D-E) Microscopic images of NCI-H1299 cells transfected with the indicated shRNAs (D) or siRNAs (E). (F-G) Representative flow cytometry plots (F) and quantifications (G) of the cell death of NCI-H1299 cells transfected with the indicated siRNAs for 48 hours. 7-amino-actinomycin D, 7-AAD. Fluorescein Isothiocyanate, FITC. (H) Representative cytochrome c confocal images of NCI-H1299 cells transfected with the indicated siRNAs. Scale bars, 25 μm. (I) Immunoblot analysis of the indicated proteins of NCI-H1299 cells transfected with the indicated siRNAs. These data are presented as mean ± SD from three independent experiments. **p < 0.01 and ***p < 0.001, Student’s *t* test.
Figure S6. KD hnRNP K induces cell death in NCI-H1299 cells. (A) The KD efficiency of hnRNP K was verified by qRT-PCR analysis of NCI-H1299 cells transfected with the indicated siRNAs for 48 hours. (B) The CTG assay for the cell proliferation in NCI-H1299 cells transfected with the indicated siRNAs. (C) The quantification data (top) and representative images of colony formation assay (down) in NCI-H1299 cells transfected with the indicated siRNAs. (D) Microscopic images of NCI-H1299 cells transfected with the indicated siRNAs. (E-F) Representative flow cytometry plots (E) and quantifications (F) of the cell death of NCI-H1299 cells transfected with the indicated siRNAs for 48 hours.
(G) Representative cytochrome c confocal images of NCI-H1299 cells transfected with the indicated siRNAs. Scale bars, 25 µm. (H) Immunoblot analysis of the indicated proteins of NCI-H1299 cells transfected with the indicated siRNAs. These data are presented as mean ± SD from three independent experiments. *p < 0.05 and ***p < 0.001, Student's t test.
Figure S7. **LCDR** and **hnRNP K** do not affect each other's expression, cellular localization and function. (A-B) qRT-PCR analysis of **hnRNP K** mRNA levels (A) and immunoblot of **hnRNP K** (B) in NCI-H1299 cells transfected with the indicated siRNAs. (C-D) qRT-PCR analysis of **LCDR** RNA levels (C) and immunoblot of **hnRNP K** (D) in NCI-H1299 cells transfected with the indicated siRNAs. (E) Confocal images showing the colocalization and expression of **LCDR** and **hnRNP K** in NCI-H1299 cells transfected with the
indicated siRNAs. Scale bars, 10 µm. (F-G) The relative cell proliferation in NCI-H1299 cells transfected with the indicated plasmids and siRNAs. These data are presented as mean ± SD from three independent experiments. **p < 0.01 and ***p < 0.001. ns, not significant, Student's t test.
Figure S8. **LCDR** and **hnRNP K** do not affect the expression of apoptosis-related genes. (A-B) qRT-PCR analysis of the relative expression levels of the indicated genes in the **LCDR KD** (A) and **hnRNP K KD** (B) NCI-H1299 cells. (C-D) Immunoblot analysis of the indicated protein levels in the **LCDR KD** (C) and **hnRNP K KD** (D) NCI-H1299 cells. These data are presented as mean ± SD from three independent experiments. *p < 0.05. ns, not significant, Student's *t* test.
Figure S9. KEGG pathways enriched by LCDR and hnRNP K.

(A-B) Heatmap (A) and volcano plot (B) showing the DEGs in LCDR KD NCI-H1299 cell. (C) The top 20 enriched KEGG pathways enriched by DEGs from (B). (D-E) Heatmap (D) and volcano plot (E) showing the DEGs in hnRNP K KD NCI-H1299 cells. (F) The top 20 enriched KEGG pathways enriched by DEGs from (E).
Figure S10. **LCDR and hnRNP K affect LAPTM5 expression.** (A-B) Immunoblot of the indicated proteins in NCI-H1299 cells with KD of either **LCDR** (A) or **hnRNP K** (B). (C-D) qRT-PCR analysis of **LAPTM5** mRNA levels (C) and immunoblot of LAPTM5 (D) in **LCDR OE** of NCI-H1299 cells. (E-F) qRT-PCR analysis of **LAPTM5** mRNA levels (E) and immunoblot of LAPTM5 and **hnRNP K** (F) in **hnRNP K OE** of NCI-H1299 cells. (G) Confocal images showing the colocalization of LAPTM5 and LAMP1 in NCI-H1299 cells. Scale bars, 10 μm. (H) Confocal images showing the colocalization of LAPTM5 and LAMP1 in NCI-H1299 cells with LAPTM5 OE. Scale bars, 10 μm. These data are presented as mean ± SD from three independent experiments. *p < 0.05 and **p < 0.01, Student's t test.
**Figure S11.** LAPTM5 KD induces cell death in NCI-H1299 cells. (A) The KD efficiency of LAPTM5 was verified by qRT-PCR analysis in NCI-H1299 cells transfected with the indicated siRNAs for 48 hours. (B) The CTG assay for the cell proliferation in NCI-H1299 cells transfected with the indicated siRNAs. (C) The quantification data (top) and representative images of colony formation assay (down) in NCI-H1299 cells transfected with the indicated siRNAs. (D) Microscopic images of NCI-H1299 cells transfected with the indicated siRNAs. (E-F) Representative flow cytometry plots (E) and quantifications (F) of the cell death of NCI-H1299 cells transfected with the indicated siRNAs for 48 hours.
(G) Representative cytochrome c confocal images of NCI-H1299 cells transfected with the indicated siRNAs. Scale bars, 25 µm. (H) Immunoblot analysis of the indicated proteins of NCI-H1299 cells transfected with the indicated siRNAs. These data are presented as mean ± SD from three independent experiments. *p < 0.05 and ***p < 0.001, Student's t test.
Figure S12. The effects of lysosome gene knockdown on cell death.

(A-D) The knockdown efficiency of ACP2, ARSB, ASAH1 and HGSNAT was verified by qRT-PCR analysis of NCI-H1299 cells transfected with the indicated siRNAs for 48 hours. (E-L) Representative flow cytometry plots (E, G, I and K) and percentages (F, H, J and L) of the apoptosis of NCI-H1299 cells transfected with the indicated siRNAs for 48 hours. Cell apoptosis was measured by staining of Annexin V and 7-AAD. These data are presented as mean ± SD.
from three independent experiments. *$p < 0.05$ and ***$p < 0.001$. ns, not significant, Student's t test.
Figure S13. LCDR and hnRNP K maintain cell survival through LAPTM5.

(A-B) Representative micrographs of colony formation (A and B) in indicated plasmids. Vector represents empty vector as OE negative control. (C-F) Representative flow cytometry plots (C and E) and quantification (D and F) of
the apoptosis cells after NCI-H1299 cells transfected with the indicated plasmids for 48 hours. (G-L) Representative flow cytometry plots (G, I and K) and quantification (H, J and L) of the apoptosis cells after NCI-H1299 cells transfected with indicated siRNA or plasmids and followed treatment with CA-074-Me (2.86 µM) or DMSO for 24 hours. These data are presented as mean ± SD from three independent experiments. *p < 0.05 and ***p < 0.001, Student's t test.
Figure S14. LAPTM5 is expressed and regulated in the nucleus.

(A) qRT-PCR analysis of LAPTM5 expression in subcellular fractions. GAPDH and U1 served as markers for the cytoplasmic and nuclear genes, respectively. 

(B-E) qRT-PCR analysis of the LAPTM5 half-life after treatment with 5 μM actinomycin D for indicated time in subcellular fractions of NCI-H1299 cells with indicated conditions. (F-G) The analysis of LAPTM5 expression in subcellular fractions with indicated conditions from the above experiments (B-E). These data are presented as mean ± SD from three independent experiments. *p < 0.05 and ***p < 0.001. ns, not significant, Student's t test.
Figure S15. The correlation between *LCPR*, hnRNP K and LAPTM5 in LUAD tissues. (A-C) Correlation analysis of hnRNP K and *LCPR* (A), LAPTM5 and *LCPR* (B), LAPTM5 and hnRNP K (C). (D) ROC curves of the indicated genes or combination for predicting the clinical diagnostic value based on our samples.
Figure S16. The characterization of NT-NPs.

(A) Representative transmission electron microscopic images and size distribution of the NT-NPs. Scale bars, 100 nm. (B) Cumulative siRNA release profile of the complexes at different pH. (C) CLSM images of NCI-H1299 cells incubated with the NP-NPs si-LCDR-1 for 1 and 3 hours. The nuclei and endosomes were stained with Hoechst 33342 and Lysotracker green,
respectively. (D) Fluorescence images of NCI-H1299 cells incubated with the control NPs and NT-NPs si-LCDR-1 for 6 hours. Scale bars, 30µm. (E) Fluorescence intensity of Cy5-si-LCDR-1 in the nuclei of NCI-H1299 cells incubated with control NPs and the NT-NPs si-LCDR-1. These data are presented as mean ± SD from three independent experiments. *p < 0.05 and ***p < 0.001, Student's t test.
Figure S17. NPs-mediated LCDR silencing induces lysosome cell death in NCI-H1299 cells. (A) The KD efficiency of LCDR was verified by qRT-PCR analysis of NCI-H1299 cells transfected with PBS, control NPs and NT-NPs si-LCDR-1. (B) The CTG assay for the cell proliferation in NCI-H1299 cells transfected with PBS, control NPs and NT-NPs si-LCDR-1. (C) The quantification data (top) and representative images of colony formation assay (down) in NCI-H1299 cells transfected with PBS, control NPs and NT-NPs si-LCDR-1. (D-E) Microscopic images of NCI-H1299 cells transfected with PBS, control NPs and NT-NPs si-LCDR-1. (E-F) Representative flow cytometry plots (E) and quantifications (F) of the cell death of NCI-H1299 cells transfected with PBS, control NPs and NT-NPs si-LCDR-1 for 48 hours. (G) Representative cytochrome c confocal images of NCI-H1299 cells transfected with PBS, control NPs and NT-NPs si-LCDR-1. Scale bars, 25 µm. (H-I) Immunoblot analysis of the indicated proteins of NCI-H1299 cells transfected with PBS, control NPs and NT-NPs si-LCDR-1. (J-K) Representative confocal images showing LAPT5 expression (J) and localization or colocalization between LAMP1 and CTSB (K) in NCI-H1299 cells transfected with PBS, control NPs and NT-NPs si-LCDR-1. Scale bars, 10 µm. These data are presented as mean ± SD from three independent experiments. *p < 0.05 and ***p < 0.001, Student’s t test.
Figure S18. The toxicity assessment of NT-NPs. (A) Overlaid fluorescence image of tumors and main organs of PDX tumor-bearing mice at 24 h post injection of naked si-LCDR or NT-NPs si-LCDR-1. (B-C) Mice weight curves (B)
and mice weight (C) of the PDXs after treatment with PBS, control NP, and NT-NPs-si-LCDR-1 (n = 5). (D-G) Serum levels of TNF-α (D), IFN-γ (E), IL-6 (F) and IL-12 (G) after three consecutive injections of PBS, control NPs, and NT-NPs si-LCDR-1. (H-M) Serum levels of AST (H), ALT (I), ALB (J), BUN (K), creatinine (L), and total proteins (M) after three consecutive injections of PBS, control NPs, and NT-NPs si-LCDR-1. (N) Histological section of the major organs using Hematoxylin-eosin staining of healthy mice after receiving three consecutive injections of PBS, control NPs, and NT-NPs si-LCDR-1. Scale bars, 100 µm. These data are presented as mean ± SD from three independent experiments. *p < 0.05 and ***p < 0.001. ns, not significant, Student's t test.
### Supplementary Tables

#### Table S1 Nucleotide sequences of LCDR (5’-3’)

| Sequence                                                                 |
|-------------------------------------------------------------------------|
| GTCGTCTCGTAGGCTTGAAAGGTAGGTGCCCGACATTAGGAGACTGTGCAGCCAGGGGAATTGTCCCCATCTGCTGGCTTACCTTGTGGGCGTGGATCCCCTCTAACTTTCCTATGTCCTCTCTGTGGTGCAGGACGACAGCAACAGCAGCACTAGTTGCTGGATGATGTCACATTTACCAGACAGAGGATGTGCAGCGTTTACTGTTGATTTCTCTCTTTTCCTCCCTATCACCTCAGTTAGTTCCAGGATCCAACGCTGCTGCCTTGCCTCCCTGACAGACACTGGCCTTAGGATGACATGCGGCAGGAAGGAACGGATCTGGGGT |
| TGTTAATCTAGTTGATGACATTGATGACTGAACATGGATCTGGGATGAGATCTGAGTTCTAGTCTAGTCTAGGAGAAGCAGGTGGATTTATGCTAGGTGGAGAGGTAGGATAAACGCACTGGGCTTACATATGAAGAATATCCAAAAGCGGATGACCTGTGTTCACTGGGGTGAAGATTTAACATTTAAATGTATTATAATTAGGCTGTAAATGCAAAAAGGTGAAACATAGGGCACAAGTTCACGATCTGTGCAATCTCCAGAGACCAGTCTGATCTAGCCGTCAGCTGGCAGTCATCTGTCAAGAAGGGGCTCTTTGTAGCCCAGAGTAGCTGTCAGGTTGGAAACCCCTGAATACTTATCATAGCAGAAGTTCAGCCACTGTAGCCCTACCTCAGGACCGCTTTTATGGGAAAGAATATTCCTTTAACTGCTTGAGCCATTTGAGTTGTGGCTGCTTTTGGTACTTGTAATAAATTGAAAGCATCTTGAATGTTCTGGGACAGTAAAAGAATGTGCCTTTGTTTCTGACAGCAATATAAAATCAATTATGTTTATATTCTAAAAAATGTTTTGAGTAATGCTGACATCATTGAAGAAAAGTGCATCACTTAGAAAATGTATCTGTGTGTCAATTTTGTTTGTTCAAAATCAGTTTCATTAATTTGTGGGAAGATACACCTTGTACATTTTACCTAATTAAAAAAAATATTGCCAGTTGAGTATACTTGTGATATATTCAAAGATAAATAAACTTTTTCAATTTTAGATATTCATAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
| Targets     | RNA-Forward (5'-3')          | RNA-Reverse (5'-3')          |
|------------|-----------------------------|-----------------------------|
| sh-c-Jun-1 | GATCCGCAAACCTCAGCAACTT     | AATTCAAAAAACGCAAACTCAG      |
|            | CAACTCGAGTTGAAGTTGCTGA     | CAACTTCAACTCGAGTTGAAAGT     |
|            | GGTTCGCTTCTTTTCTTTG        | TGCTGAGGTTTGCG              |
| sh-c-Jun-2 | GATCCCTATCGACATGGAGTTG     | AATTCAAAAACCTATCGACATGG     |
|            | CAGCTCGAGCTGAGACTCCATG     | AGTCTCAGCTCAGCTGAGACT       |
|            | TCGATAGGTGTCTTTTTT         | CCATGTCGATAGG               |
| sh-LCDR-1  | GATCCGCCGTTCTCTGTCTCTGT    | AATTCAAAAAACGTTCTCTGT       |
|            | CACAGTTCAAGAGACTGTGACA     | CTGTCACAGTCTCTTGAAACTGT     |
|            | GGACAGAGAACCCTTTTTT        | GACAGGACAGAGAACCCTTT       |
| sh-LCDR-2  | GATCCGCCTTTGTTTCTGACAG     | AATTCAAAAAACCTTTTGTTTCTG    |
|            | CAATTTTCAAGAAGATTTGCTGT    | ACCAGAATTTCTCTTGAAATTTG     |
|            | CAGAAAAGAGGTGTTTTT         | CTGTCAGAAAAACAGGCG          |
| si-NC      | UUCUCGAGAAGUCUGACGUTT      | ACGUGCACAGUGUCAGGAGATT      |
| si-LCDR-1  | GGUAGGAUAUAACGUAUUCUTT     | AGAAAUACGUAUACCUACCTT       |
| si-LCDR-2  | GUGGGAAGUAACACCUUGUTT      | ACAAGGUGUACUUCCACCTT        |
| si-hnRNP K-1 | GGGUUGUAGAGUGCAUAAATT     | UUUUGACUCUCUAAACCTT        |
| si-hnRNP K-2 | GCCUCAUCUAAGAGAGAUTT     | AUCUCUUCUAAGUGGAGGCTT       |
| si-LAPTM5-1 | CCUGCAAAUCAUGGACAUATT    | AUAGUCCAUGAUUUGCAGGTT       |
| si-LAPTM5-2 | CCAGGAGGAUAUGCCUACUTT     | AUGAGGCAUAUCCUCUGGTT        |
| si-ACP2-1  | GGUUUGUGUCAGUUAACCAATT    | UUGGGUAACUGACAAACCTT        |
| si-ACP2-2  | GCGCUAUCACCGCUUCCUATT     | UAGGAAGCGCUGUAAGCGCCTT      |
| si-ARSB-1  | GGUUUGACGACCAAUAATT       | UUAUUUGUGCGUAAACCTT        |
| si-ARSB-2  | GCUUAGCCUCUAUACCUATT      | UAGUUAUGAGGCGUAAAGCTT       |
| si-ASAH1-1 | GGCACCAGUGCUAAAGGUUTT     | AACCUUUAGCAGUCUGUGCCTT      |
| si-ASAH1-2 | GGCUAUGUGGGCAUGUAUATT     | UUAACAGGCCCACUAAGCCTT       |
| si-HGSNAT-1 | GCUUUGCUACUAUCCAUATT     | UAGGAUGAUGAAGCAAGCCTT       |
| si-HGSNAT-2 | GCCAUAGUUCUGAGAAATT      | UUCUCGAGAACUUAGGCTT        |
### Table S3 List of primary antibodies

| Antibodies   | Manufacturer          | Application                          |
|--------------|-----------------------|--------------------------------------|
| Mcl1         | Proteintech, #16225-1-AP | 1:1000 for IB                         |
| GAPDH        | Proteintech, #60004-1-lg | 1:5000 for IB                         |
| Tubulin      | Proteintech, #66031-1-lg | 1:5000 for IB                         |
| Bcl2         | Proteintech, #12789-1-AP | 1:3000 for IB                         |
| Bax          | Proteintech, #50599-2-lg | 1:2000 for IB                         |
| H3K27ac      | Abacam, #ab4729        | 1:1000 for IB                         |
| Flag         | Cell Signaling Technology, #14793 | 1:2000 for IB, 5 μg for RIP, 5 μg for CHIP |
| hnRNP K      | Abacam, #ab39975       | 1:2000 for WB, 5 μg for RIP, 1:250 for IHC and IF |
| cytochrome c | Abacam, #ab133504      | 1:300 for IF                          |
| H4K16ac      | Abacam, #ab109463      | 1:1000 for IB                         |
| Bak          | Abacam, #ab32371       | 1:1000 for IB                         |
| LAMP1        | Abacam, #ab24170       | 1:300 for IF                          |
| c-Jun        | Cell Signaling Technology, #9615 | 1:1000 for IB                         |
| PARP         | Cell Signaling Technology, #9532 | 1:1000 for IB                         |
| Cleaved caspase 3 | Cell Signaling Technology, #9661 | 1:1000 for IB, 1:250 for IF           |
| Bcl-xl       | Cell Signaling Technology, #2764 | 1:1000 for IB                         |
| Bid          | Cell Signaling Technology, #8762 | 1:1000 for IB                         |
| Cathepsin B  | Cell Signaling Technology, #31718 | 1:250 for IF                          |
| LAPTM5       | Invitrogen#PA5-23582   | 1:500 for IB, 1:200 for IF, 1:100 for IHC |
| Histone H3   | Beyotime#AF0009        | 1:1000 for IB                         |
### Table S4 List of qRT-PCR primers

| Regions       | Forwards (5’-3’)                          | Reverses (5’-3’)                           |
|---------------|-------------------------------------------|--------------------------------------------|
| **LCDR**      | AAATCAAAAGCCACACTTAGCG                    | CGCCCCGGGAATTAGGAAAGT                     |
| **Promoter**  |                                           |                                            |
| **LCDR**      | TTCAGCCATGAGGCTGCTG                       | AAGCAGCCACAATCAAATGGG                     |
| **hnRNP K**   | ATCTTCTCTTCTCCACCA                        | CATCAGCAGCTGAAAACCAACC                    |
| **c-Jun**     | TCCAAGTGCCCCAAAAAGGAAG                    | CGAGTTCTGAGCTTTCAAGGT                     |
| **MCL1**      | GAGTTGGTCGGGGAATCTG                        | ATTAATCCAGCGACTGC                        |
| **BCL-XL**    | GCCATCAATGGCAACCCATC                      | CTTTACTGCTGCCATGGGGG                     |
| **BCL2**      | GAACTGGGGGAGGATTTG                        | GCCGGGTTTGCTAGCTAC                      |
| **Bak**       | CCACGCGAGAATGCGCTAT                      | ATGCAGCATGGAAGCTGAAACA                   |
| **Bax**       | TCATGGGCTGGACATTGGAC                      | GCGTCGCAAGTAGGAGG                      |
| **Bid**       | CTGCAGGCTACCTAGAGA                       | CGTAGGTGCAGTTCTGG                        |
| **GAPDH**     | GGAGCGGAGATCCCTCCAAAT                     | GGCTGTGTCTACTTTCTCATGG                   |
| **U1**        | GGGAGATACCGATCTGCAAGA                     | CCACAATAATTCAGCTCAGTCTGTTTT             |
| **LAPTM5-3’UTR** | ATGCCAACCTCGGGAATGGT                    | ATGGACTGGCAGCTCATCAGC                    |
| **LAPTM5**    | CTCTCCAGCATGGGCTACCT                     | GACTACGCCGATCAGTAGGC                    |
| **ARSB**      | GAACTCTCCTACGGGCTACC                     | TGGTAGAAGCTGTAGGCGG                      |
| **ASAH1**     | ATTCTGGATTTTGGCATTTTG                    | ACCTTTAGCAGCTGGCTTGG                    |
| **HNSGAT**    | CAAGGCTCGGACAAAGACA                      | ACCAGCAGGATGAAAGAAGGC                    |
| **ACP2**      | GAGTCTCGGCTCTCGTTACCT                    | CCCAGTCCCAGTGGCTGTAG                     |
| **GLB1**      | GCTCCTCCGACCAGATTAC                      | AACAGAACACATCATCC                      |
| Probe | Sequences (5’-3’) |
|-------|------------------|
| *LCDR* | ACCAGACACGGCAGCAACAGCTGTCTAAGTTTCAACTCGCTCCTTCC |
|       | CGCAAAATGTAGAAGCTCAATCCCTATAGCAAATCCCATATATTCTATTCATTTC |
|       | TTAATGTCTCCGTCTCTCAGTTGAATCTAGATGGGATACAACTCATG |
| Probes         | Sequences (5’-3’)                                      |
|---------------|-------------------------------------------------------|
| **LCDR EMSA probe** | TCAGTTTCTTTCCACTTCTGGGGCAGGCTGCTTGTCCTGCCACT          |
|               | CTCAGGCCCCCCACCAGACACGGCAGCAACAGCTGTTCTAA             |
|               | GTGTTCAACTCGCTC                                      |
| **Mut-LCDR EMSA probe** | TCAGTTTCTTTCCACTTCTGGGGCAGGCTGCTTGTCCTGCCACT          |
|               | CTCAGGAAAAAACAAAGACACGGCAGCAACAGCTGTTCTAAAGT         |
|               | GTTCAACTCGCTC                                      |
| **LAPTM5 3’UTR EMSA probe** | CTGCCTCATAATCTGGTTTTTTTGCTTTTGTTGTCGCCCTGTCGCT      |
|               | GGTTGGGCCCTTCCGCCCCTCCCTGCGCAGGACAATCTGCTTG         |
|               | TGTCTCCCTCGCTG                                      |
| **Mut-LAPTM5 3’UTR EMSA probe** | CTGCCTCATAATCTGCTTTTTTGCTTTGTGGGCCCCTGTCGCCT      |
|               | GGTTGGGAAAGAATAAAAAGAATGGCAGGACAATCTGCTTG           |
|               | GTCTCCCTCGCTG                                      |
References

1. Clough, E. and T.J.M.i.m.b. Barrett, The Gene Expression Omnibus Database. 2016. 1418: p. 93-110.

2. Love, M., W. Huber, and S.J.G.b. Anders, Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. 2014. 15(12): p. 550.

3. Livak, K. and T.J.M. Schmittgen, Analysis of relative gene expression data using real-time quantitative PCR and the 2(−Delta Delta C(T)) Method. 2001. 25(4): p. 402-8.

4. Qu, L., et al., Exosome-Transmitted IncARSR Promotes Sunitinib Resistance in Renal Cancer by Acting as a Competing Endogenous RNA. 2016. 29(5): p. 653-668.

5. Wang, J., et al., Long non-coding RNA MYU promotes prostate cancer proliferation by mediating the miR-184/c-Myc axis. 2018. 40(5): p. 2814-2825.

6. Wang, X., et al., Tumor cell-intrinsic PD-1 receptor is a tumor suppressor and mediates resistance to PD-1 blockade therapy. 2020. 117(12): p. 6640-6650.

7. Xu, X., et al., Ultra-pH-Responsive and Tumor-Penetrating Nanoplatform for Targeted siRNA Delivery with Robust Anti-Cancer Efficacy. 2016. 55(25): p. 7091-7094.