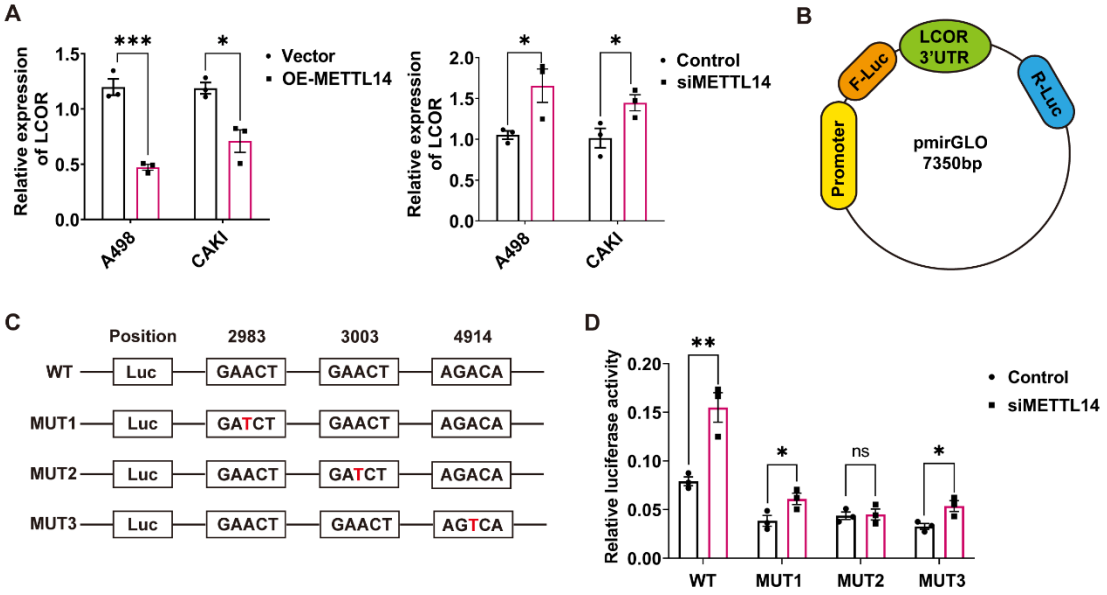
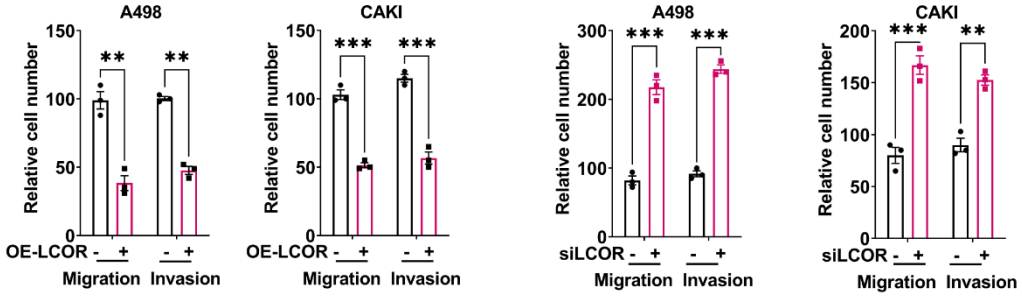
**Supplementary figure 1**



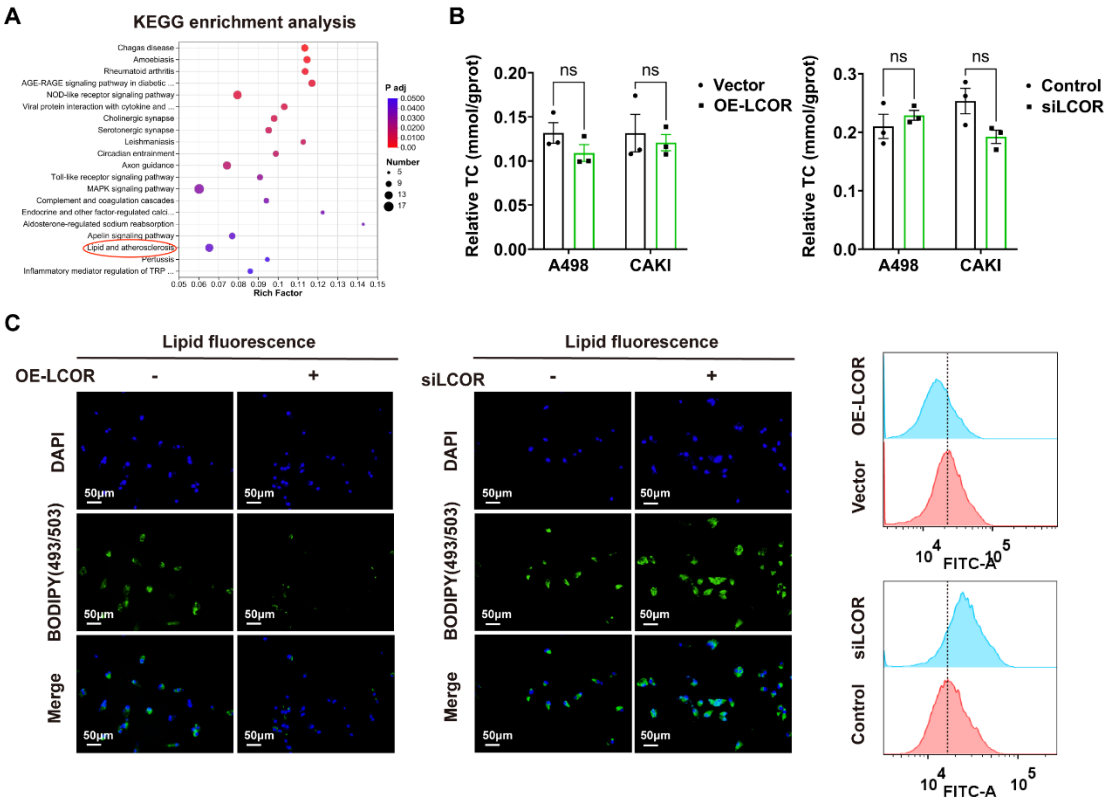

**Supplementary figure 1. METTL14-mediated m6A modification was involved in LCOR downregulation**. **(A)** The mRNA levels of LCOR in ccRCC cell lines with METTL14 overexpression and knockdown. **(B) (C)** A schematic diagram of a luciferase reporter gene that wild-type LCOR and mutant LCOR 3'-UTR at the m6A sequence sites were cloned into it. **(D)** Relative luciferase activity of the wild-type LCOR and mutant LCOR 3'-UTR reporter vectors in METTL14 knockdown HEK293T. ***p < 0.001, **p < 0.01, *p < 0.05.

**Supplementary figure 2**



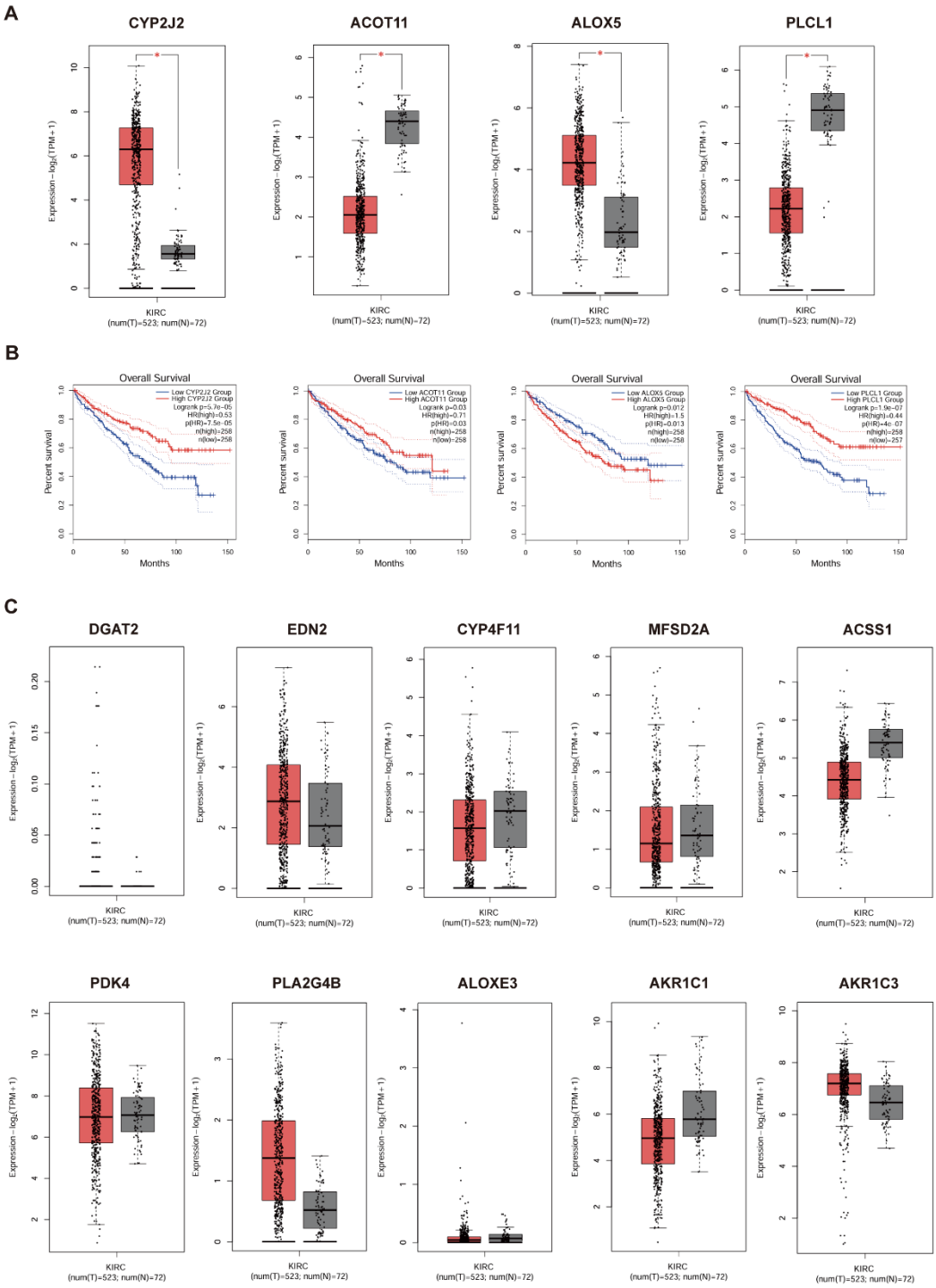

**Supplementary figure 2. LCOR repressed the progression of ccRCC in vitro.** The quantity analyses of transwell assays in ccRCC cell lines with LCOR overexpression or knockdown. ***p < 0.001, **p < 0.01.

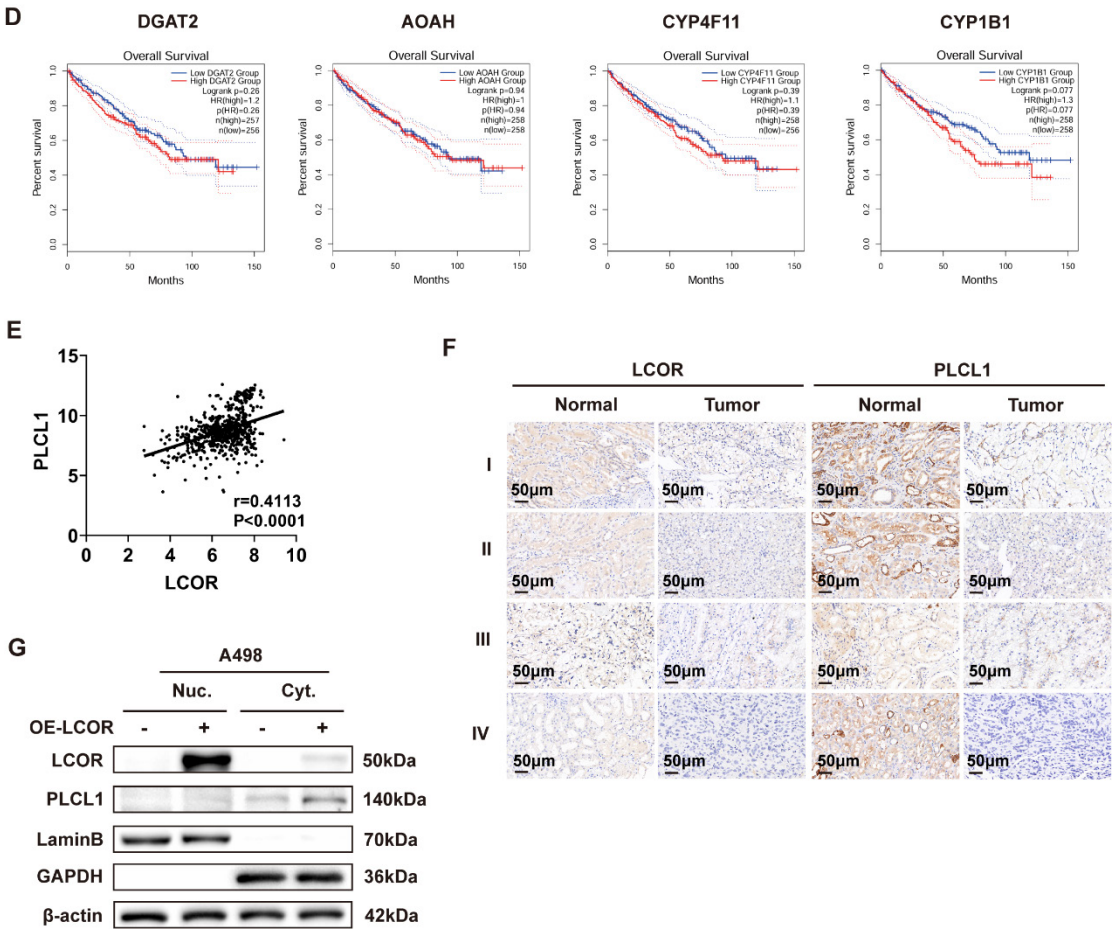
## Supplementary figure 3




**Supplementary figure 3. LCOR suppressed lipid accumulation in ccRCC. (A)** KEGG enrichment analysis of the RNA-seq. **(B)** The TC detection assays in ccRCC cell lines with LCOR overexpression and knockdown. **(C)** Lipid fluorescence staining assays and quantitative analyses (Lipid Flow Cytometry) of CAKI cells with LCOR overexpression and knockdown.

## Supplementary figure 4

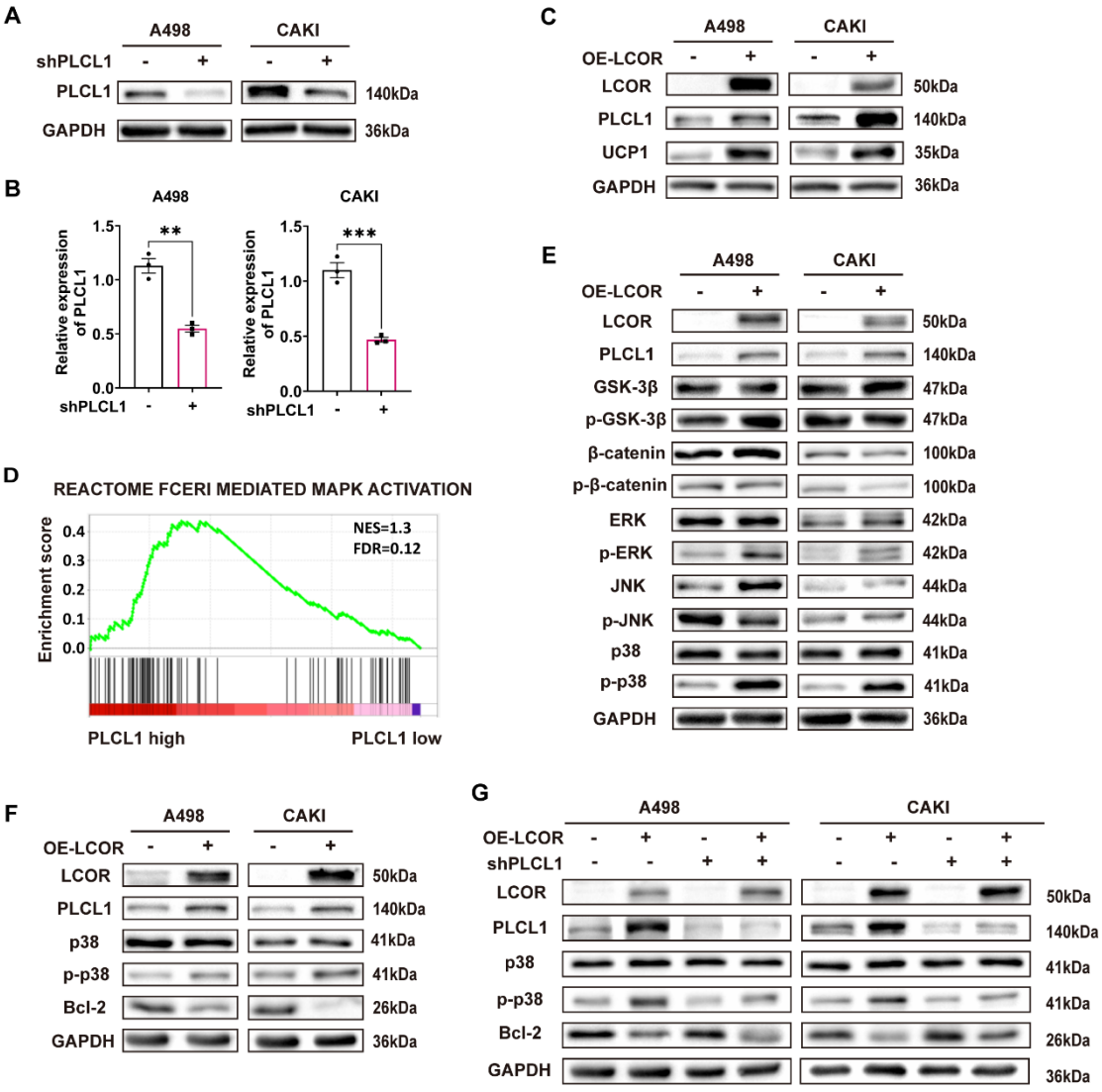





**Supplementary figure 4. LCOR positively regulated the expression of PLCL1. (A)** Analyses of significant differences between ccRCC tissue and adjacent nonmalignant tissue of CYP2J2, ACOT11, ALOX5 and PLCL1 using GEPIA2 database according to TCGA-KIRC project. **(B)** The Kaplan-Meier curves of CYP2J2, ACOT11, ALOX5 and PLCL1 based on the TCGA database for OS. **(C)** Analyses of significant differences between ccRCC tissue and adjacent nonmalignant tissue of DGAT2, EDN2, CYP4F11, MFSD2A, ACSS1, PDK4, PLA2G4B, ALOXE3, AKR1C1 and AKR1C3 using GEPIA2 database according to TCGA-KIRC project. None was statistically significant. **(D)** The Kaplan-Meier curves of DGAT2, AOAH, CYP4F11 and CYP1B1 based on the TCGA database for OS. None was statistically significant. **(E)** Pearson correlation

coefficient analysis was utilized to indicate the correlation between LCOR and PLCL1, $P < 0.05$ meant the data had statistical significance. **(F)** IHC staining for LCOR and PLCL1 in 4 patients with different clinical grades of ccRCC tissue and adjacent nonmalignant tissue. **(G)** Nucleocytoplasmic separation assay based on A498 LCOR overexpression and control cells showed the distribution of LCOR and PLCL1.

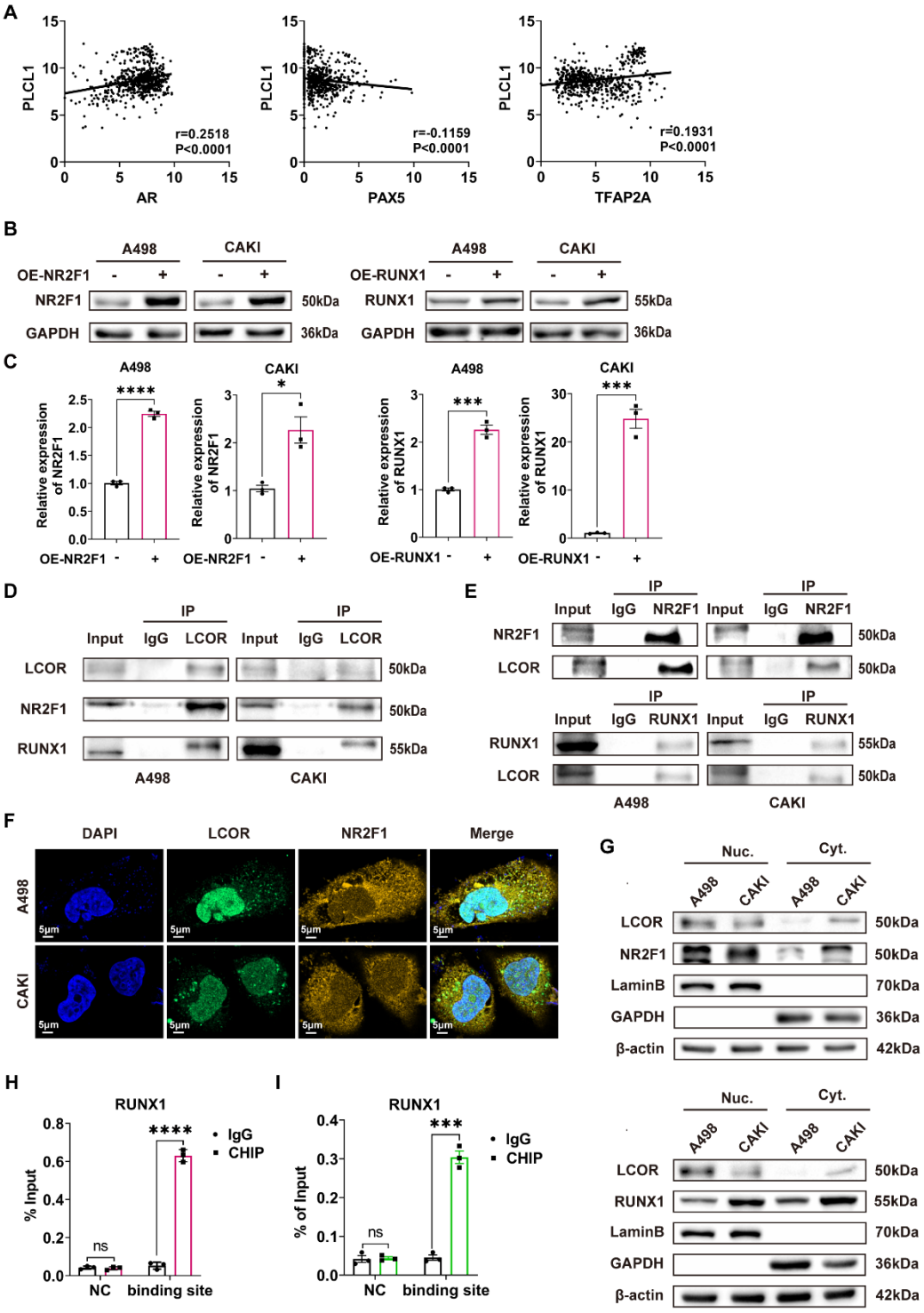
**Supplementary figure 5**

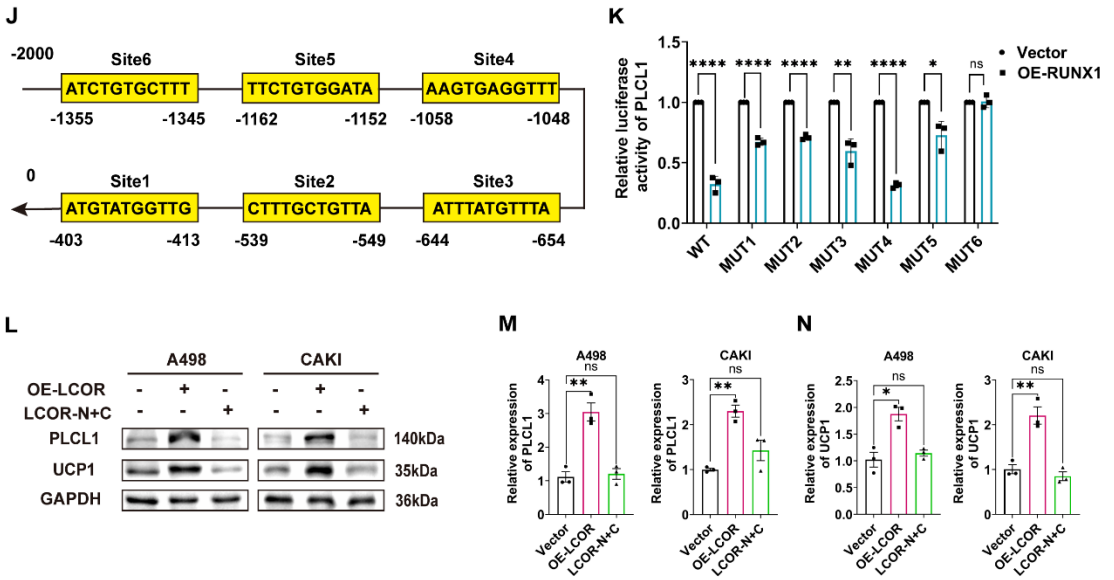



**Supplementary figure 5. LCOR repressed ccRCC progression and lipid accumulation mainly through PLCL1. (A) (B)** ccRCC cell lines with PLCL1 knockdown were established through infecting PLCL1 shRNA lentivirus. Western blot and qPCR were used to identify the knockdown of PLCL1, respectively. ***p < 0.001, **p < 0.01. **(C)** The protein expression of UCP1 in LCOR overexpressed cell lines. **(D)** The GSEA enrichment analysis of PLCL1 based on the TCGA database. FDR < 0.15 and p < 0.05 were statistically significant. **(E)** Western blot was applied in LCOR

overexpressed cell lines to detect the protein expression of key molecules in WNT and MAPK pathways. **(F)** Western blot was performed in LCOR overexpressed cell lines to detect the p38 and Bcl-2 protein expression. **(G)** Western blot was carried out in functional compensation models to detect the p38 and Bcl-2 protein expression.

## Supplementary figure 6

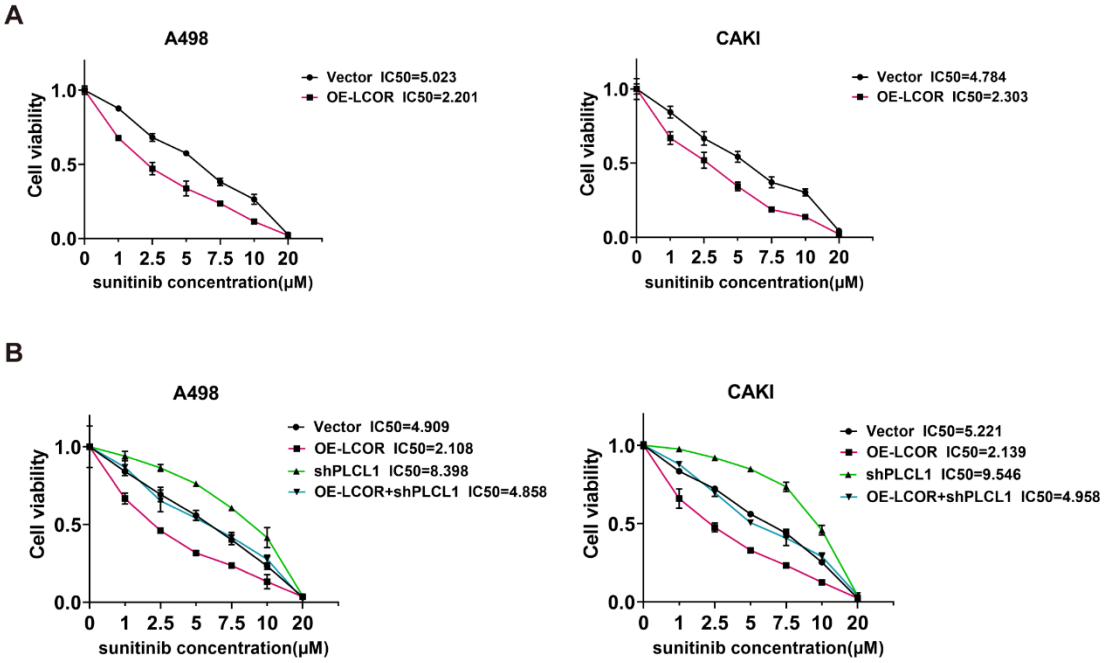





**Supplementary figure 6. LCOR regulated the expression of PLCL1 by interacting with transcriptional suppressor RUNX1.** ****p < 0.0001, ***p < 0.001, **p < 0.01, *p < 0.05. **(A)** The transcription factors (AR, PAX5, TFAP2A) of PLCL1 predicted by JASPAR database. **(B) (C)** NR2F1 overexpression or RUNX1 overexpression ccRCC cell lines was established via transfecting overexpression plasmids, respectively. Western blot and qPCR were conducted to identify the overexpression of NR2F1 or RUNX1. **(D)** The endogenous LCOR-NR2F1 or LCOR-RUNX1 interaction was detected through Co-IP assays in A498 and CAKI. **(E)** The endogenous NR2F1-LCOR or RUNX1-LCOR interaction was detected via Co-IP assays in A498 and CAKI. **(F)** Laser confocal assays were carried out to illustrate the co-localization of LCOR and NR2F1. **(G)** Nucleocytoplasmic separation assays based on A498 and CAKI cell lines showed the distribution of LCOR and NR2F1, as well as LCOR and RUNX1. **(H)** CHIP assays were applied in A498 LCOR overexpressed cell line. **(I)** CHIP assays were conducted in A498 LCOR siRNA knockdown cell line. **(J)** The diagram showed the 6 potential sites of PLCL1 promoter region binding to RUNX1 predicted by JASPAR

database. **(K)** Dual luciferase assays were applied to verify the precise site of PLCL1 promoter region binding to RUNX1. **(L) (M) (N)** Flag-P6 truncated plasmid (LCOR-N+C) was transfected into A498 and CAKI cells, western blot and qPCR were utilized to determine the expression of PLCL1 and UCP1.

**Supplementary figure 7**




**Supplementary figure 7. LCOR participated in the sensitivity of ccRCC to sunitinib. (A)** Sunitinib sensitivity curves of A498 and CAKI cells with or without LCOR overexpression. **(B)** Sunitinib sensitivity assays were performed in functional compensation models.

**Supplementary table 1**

**Sequence of primers of qPCR, siRNA**

| Gene | Forward | Reverse |
|---|---|---|
| GAPDH | GAGTCAACGGATTTGGTCGT | GACAAGCTTCCCGTTCTCAG |
| LCOR | GCTGACCAAGACTCACCTCT | CTTCCCTGGTTCCATCCTGT |
| CYP2J2 | GCTTCAAAGACATGCCAGCT | GGATTGCCTGTGTGCTTTGA |
| ACOT11 | ACCCTAGCAACCAGGTGTAC | CATGCACCACCATCTCCATG |
| ALOX5 | GATTGTCCCCATTGCCATCC | AGAAGGTGGGTGATGGTCTG |
| PLCL1 | CGAAGCGTTGAACTCGATGT | GAGCCATTACCTTCTGCTGC |
| NR2F1 | CGAGGGCTGCAAAAGTTTCT | CATTCTTCCTCGCTGAACCG |
| RUNX1 | GTGATGGCTGGCAATGATG | TGATGGCTCTGTGGTAGGTG |
| UCP1 | GCGGATGAAACTCTACAGCG | TTGATTCCGTGGAGATGGCT |
| siLCOR#1 | GCAGCGAAUGAUCCAACAATT | UUGUUGGAUCAUUCGCUGCTT |
| siLCOR#2 | GCUCGAUCCCUGCAGAUUATT | UAAUCUGCAGGGAUCGAGCTT |
| siLCOR#3 | GGAGUCUCGCACUGGUGAUTT | AUCACCAGUGCGAGACUCCTT |

**Supplementary table 2**

**Antibodies used in this study**

| Antibodies | Vendors | Cat# | Application |
|---|---|---|---|
| LCOR | Proteintech | 14476-1-AP | WB, IHC, IP |
| LCOR | Santacruz | sc-398636 | IF |
| GAPDH | ABclonal | AC002 | WB |
| CYP2J2 | ABclonal | A5805 | WB |
| ACOT11 | Sangon | D221470 | WB |
| ALOX5 | ABclonal | A2877 | WB |
| PLCL1 | Abcam | ab157200 | WB |
| Lamin B2 | ABclonal | A5001 | WB |
| β-action | ABclonal | AC026 | WB |

| | | | |
|---|---|---|---|
| **NR2F1** | **Proteintech** | **24573-1-AP** | **WB, IF, IP, CHIP** |
| **RUNX1** | **ABclonal** | **A2055** | **WB, IF** |
| **RUNX1** | **Proteintech** | **19555-1-AP** | **IP** |
| **RUNX1** | **Abcam** | **ab272456** | **CHIP** |
| **DDDDK-Tag** | **ABclonal** | **AE092** | **WB, IP, CHIP** |
| **HA** | **ABclonal** | **AE008** | **WB, IP** |
| **GSK-3β** | **ABclonal** | **A2081** | **WB** |
| **p-GSK-3β** | **ABclonal** | **AP1088** | **WB** |
| **β-catenin** | **ABclonal** | **A11512** | **WB** |
| **p-β-catenin** | **ABclonal** | **AP1315** | **WB** |
| **ERK** | **ABclonal** | **A16686** | **WB** |
| **p-ERK** | **ABclonal** | **AP0974** | **WB** |
| **JNK** | **ABclonal** | **A4867** | **WB** |
| **p-JNK** | **ABclonal** | **AP1337** | **WB** |
| **p38** | **ABclonal** | **A4771** | **WB** |
| **p-p38** | **ABclonal** | **AP1502** | **WB** |
| **Bcl-2** | **ABclonal** | **A25052** | **WB** |
| **IgG Light Chain** | **ABclonal** | **AS062** | **WB** |
| **UCP1** | **ABclonal** | **A7236** | **WB, IHC** |
| **Ki67** | **ABclonal** | **A16919** | **IHC** |