Supplemental information

Figure S1 Suppression of miR-765 level accelerates the proliferation and EMT of UCEC.

A Level of miR-765 after treated with miR-765 mimics in KLE by RT-qPCR. **B** KLE cell viability was measured by CCK-8 at 12 h, 24 h, 36 h, 48 h after treated with miR-765 mimics. **C** After treated with miR-765 mimics, KLE cell proliferation was determined with Ki67 by flow cytometry. **D** Tumor volume growth and of NC and LV-miR-765 KLE cells xenografts in mice were measured every day. **E** Survival curves of NC and LV-miR-765 KLE cells xenografts-bearing mice. **F** mRNA levels of EMT related markers (*COL1A, COL3, FN1, CDH1, CDH2, S100A, MMP2, MMP9, SNAIL, VIMENTIN, ZEB1, TJP1*) in NC and miR-765 mimics treated KLE cells by RT-qPCR. Data were presented as mean ± SEM and analyzed by t test or ANOVA. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$, NS: no significance.

Figure S2 MiR-765 negatively regulates PLP2 expression of UCEC in a miRNAs cluster regulatory manner.

A The ratio of PLP2 to GAPDH was quantified after Ishikawa and KLE cells were treated with miR-765 mimics according to the images of western blotting in Figure 2D. **B** Potential transcription factors downstream miR-765 predicted by bioinformatics analysis. **C** Levels of target miRNAs (miR-3584-5p, miR-7-5p, miR-150-5p and miR-124-3p) after treated with miR-765 mimics in KLE cells by RT-qPCR. **D** Levels of PLP2 after treated with miR-3584-5p, miR-7-5p, miR-150-5p and miR-124-3p mimics in KLE cells by RT-qPCR. **E** Levels of target miRNAs (miR-3584-5p, miR-7-5p, miR-150-5p and miR-124-3p) were

assessed to evaluated the efficiency of miRNA inhibitors in KLE cell by RT-qPCR. **F** Levels of PLP2 after treated with miR-765 mimics and/or miRNA inhibitors in KLE cell by RT-qPCR. Data were presented as mean ± SEM and analyzed by t test or ANOVA. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$, NS: no significance.

Figure S3 PLP2 promotes the EMT process and invasion of UCEC.

A-B RT-qPCR and western blotting were performed to evaluate the efficiency of siPLP2 respectively in Ishikawa and KLE. The ratio of PLP2 to GAPDH was quantified in (**C**). **D-E** The ratios of EMT related markers (Vimentin and E-cadherin) to GAPDH in NC or siPLP2 Ishikawa and KLE cells were quantified according to the images of western blotting in Figure.3C. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$, NS: no significance.

Figure S4 PLP2 enhances the EMT process of UCEC by activation of Notch signaling.

A-B mRNA and protein levels of Notch-related molecules (Notch1, NID, Hes1) in NC and OE-PLP2 KLE cells by RT-qPCR. After NC or PLP2-OE KLE cells after treated with DART or not, levels of EMT related markers (E-cadherin and Vimentin) (**C),** cell invasion **(D)** and cell viability (**E)** was detected. Data were presented as mean ± SEM and analyzed by t test or ANOVA. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$, NS: no significance.

Figure S5 Estrogen regulates the miR-765/PLP2 level in UCEC through the ERβ.

A The ratio of PLP2 to GAPDH was quantified according to the images of western blotting in Figure. 5G. **B-C** The ratio of PLP2 to GAPDH was quantified according to the images of

western blotting in Figure. 5H-I. **D-E** The ratio of PLP2 to GAPDH was quantified according to the western blotting images of Figure. 5L-M. **F** Levels of ESR2 were assessed after Ishikawa and KLE cells were treated with Fulvestrant by RT-qPCR. **G** Levels of ESR1 were assessed after Ishikawa and KLE cells were treated with Fulvestrant by RT-qPCR. **H** Levels of miR-765 were assessed after Ishikawa and KLE cells were treated with Fulvestrant by RT-qPCR. **I-J** Levels of PLP2 were assessed after Ishikawa and KLE cells were treated with Fulvestrant by RT-qPCR and western blotting. The ratio of PLP2 to GAPDH was quantified in (**K**). **L** Levels of miR-765 were measured after NC or si-ERβ transfected Ishikawa and KLE cells were treated with Fulvestrant or not by RT-qPCR **M** Levels of PLP2 were assessed after NC or si-ERβ transfected Ishikawa ~~and KLE~~ cells were treated with Fulvestrant or not by immunofluorescence. Data were presented as mean ± SEM and analyzed by t test or ANOVA. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$, NS: no significance.

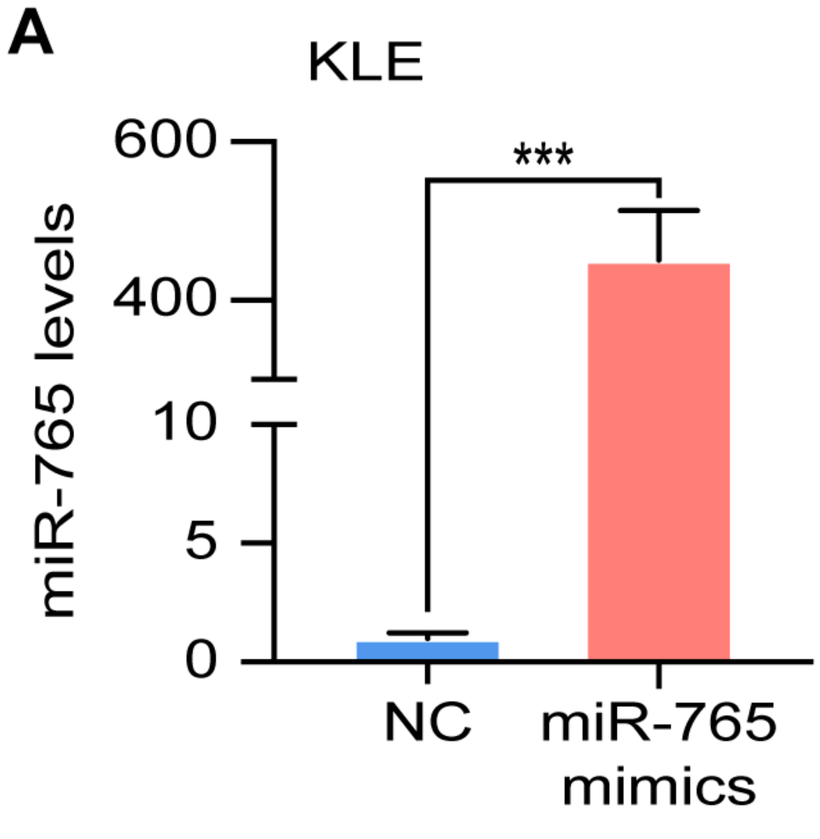
Figure S6 $CD45RO^{-}CD8^{+}$ T cell-derived exosomal miR-765 partly suppressed PLP2 in UCEC cells.

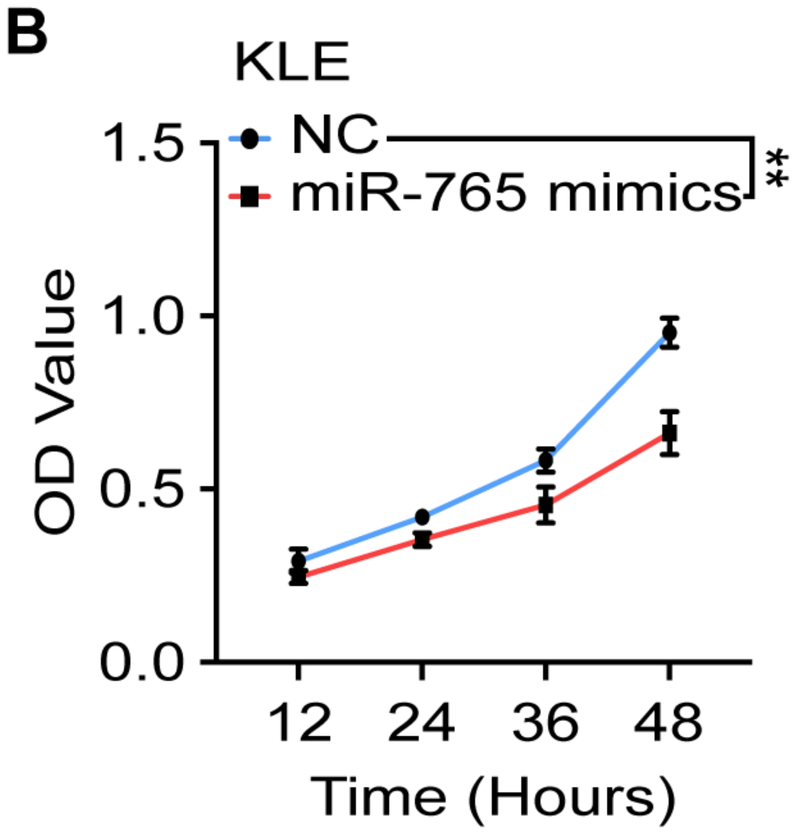
A Sorting strategy of $CD45RO^{+}CD8^{+}$ and $CD45RO^{-}CD8^{+}$ T cells by flow cytometry. **B** Histogram showing the particle diameter (nm) of the exosomes. **C** Exosome markers, CD63, TSG101, and GRP78, were assayed in exosomes and lysate using western blotting. The ratio of CD63/TSG101/GRP78 to PSMA was quantified in **(D-F)**. **G** Levels of miR-765 in KLE were tested after treated with $CD45RO^{-}CD8^{+}$T cells exosomes by RT-qPCR. **H** Levels of PLP2 in KLE were tested after treated with $CD45RO^{-}CD8^{+}$ T cell-derived exosomes by RT-qPCR. **I** The ratio of PLP2 to GAPDH was quantified according to images of western

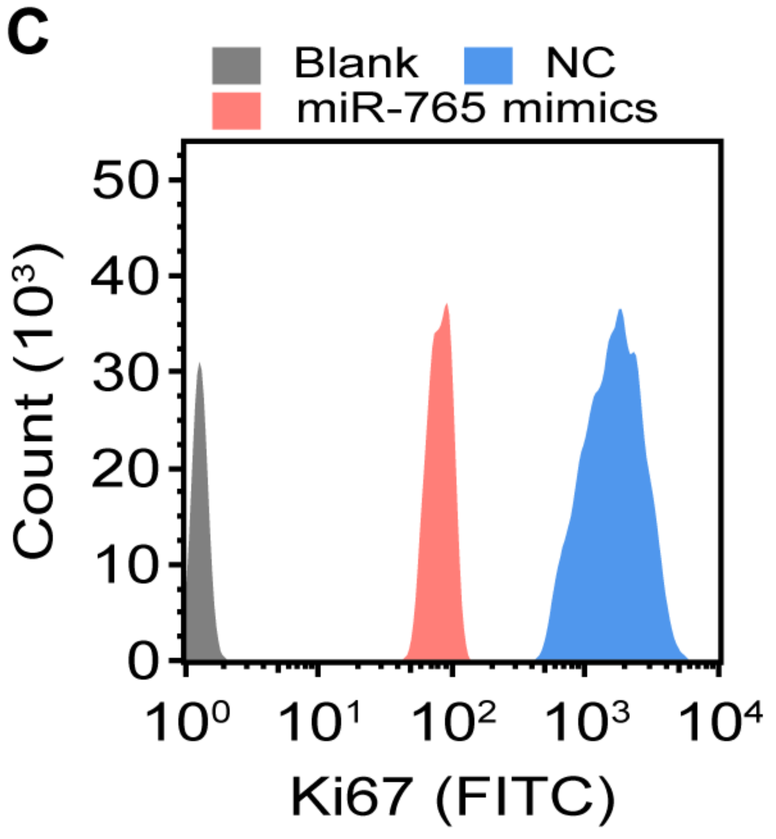
blotting in Figure. 6G. **J-K** mRNA and protein levels of PLP2 in KLE were tested after treated with $CD45RO^{-}CD8^{+}$ T cell-derived exosomes and/or GW4869 by RT-qPCR and western blotting. Data were presented as mean ± SEM and analyzed by t test or ANOVA. * P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001, NS: no significance.

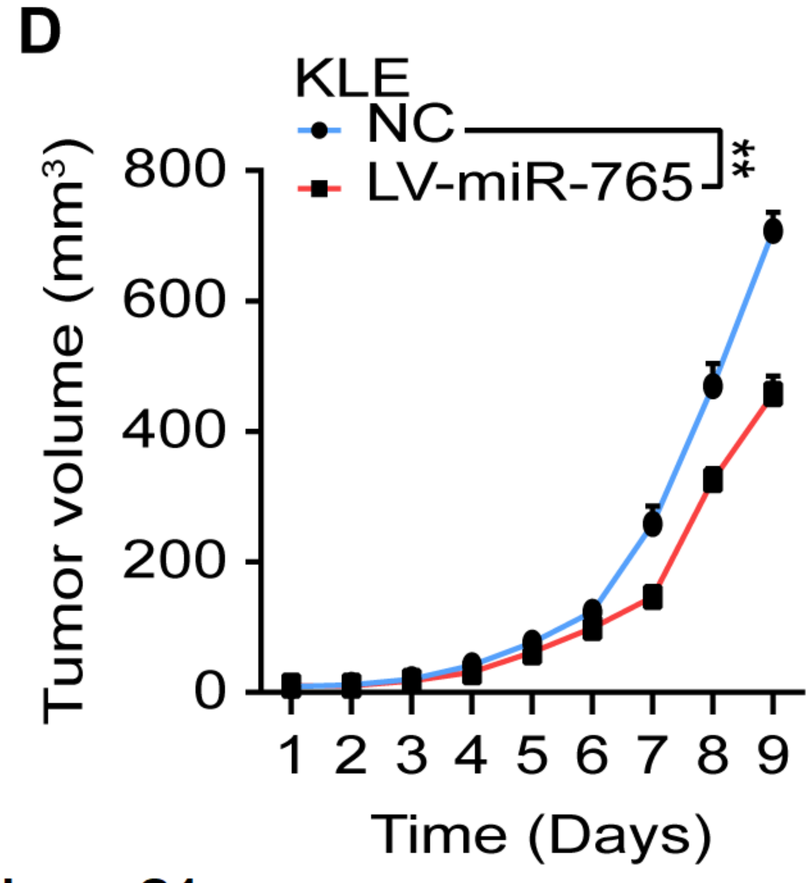
Figure S7 Exosomes originated from $CD45RO^{-}CD8^{+}$ T cell partly suppress UCEC development in a miR-765/PLP2-dependent manner.

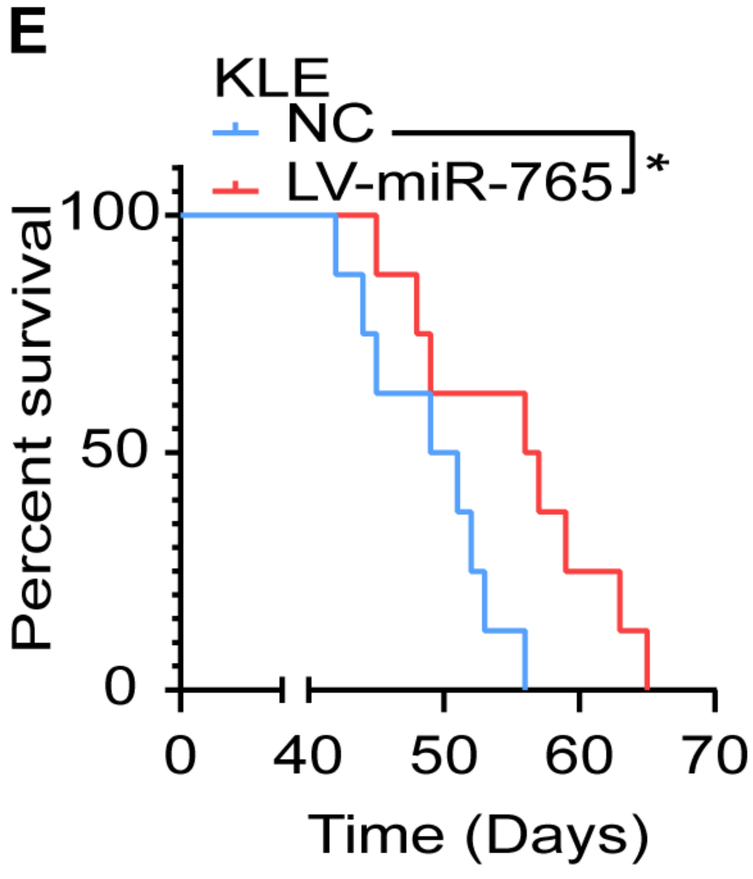
After KLE cells were treated with estrogen and/or $CD45RO^{-}CD8^{+}$T cell-derived exosomes for 24h, **A** Levels of miR-765 were tested by RT-qPCR. **B-C** Levels of PLP2 were tested by RT-qPCR and western blotting. **D** Cell viability was measured by CCK-8 at 12 h, 24 h, 36 h, 48 h. **E** Cell proliferation was determined with Ki67 by flow cytometry. **F** Levels of EMT related markers (Vimentin and E-cadherin) were measured by western blotting and were quantified in **(G-H),** respectively. **I** Cell invasion was detected by transwell assays. Scale bars: 100 μm. **J** Ultimate tumor volume of ~~Ishikawa~~ cells xenografts in mice were measured. **K** Survival curves of KLE cells xenografts-bearing mice was plotted. Data were presented as mean ± SEM and analyzed by t test or ANOVA. * P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001, NS: no significance.


A
KLE
600
400
10
5
0
miR-765 levels
***
NC
miR-765
mimics


B
KLE
NC
miR-765 mimics
**
1.5
1.0
0.5
0.0
OD Value
12
24
36
48
Time (Hours)


C
Blank
NC
miR-765 mimics
50
40
30
20
10
0
Count (10³)
10⁰
10¹
10²
10³
10⁴
Ki67 (FITC)


D
KLE
NC
LV-miR-765
**
800
600
400
200
0
Tumor volume (mm³)
1 2 3 4 5 6 7 8 9
Time (Days)


E
KLE
NC
LV-miR-765
*
100
50
0
Percent survival
0
40
50
60
70
Time (Days)

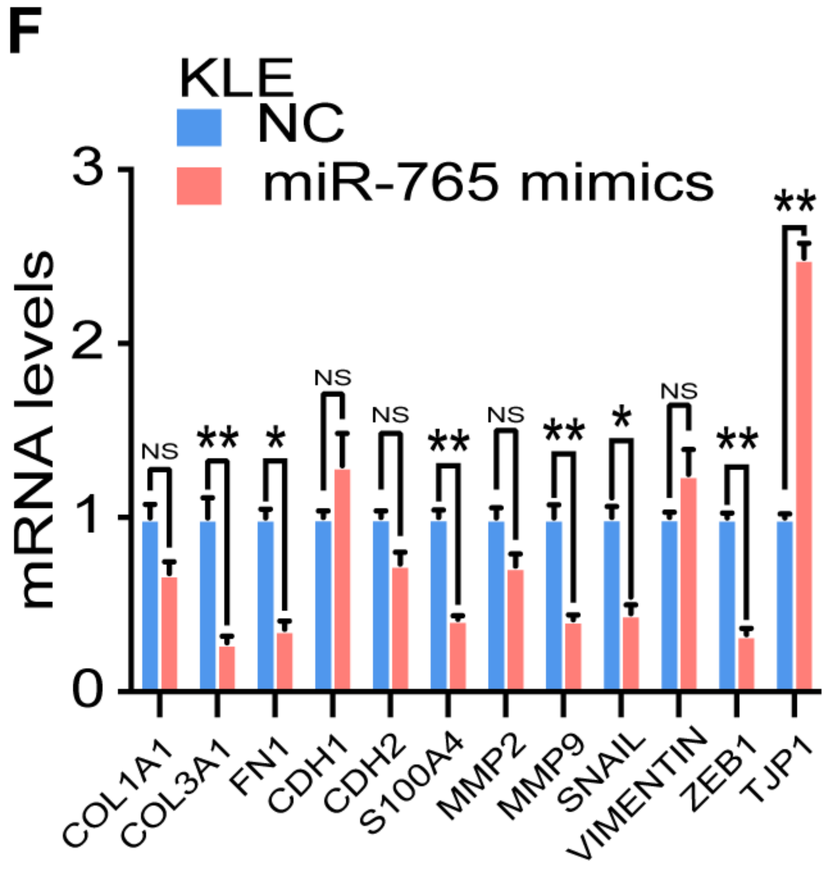

F
KLE
NC
miR-765 mimics
3
2
1
0
mRNA levels
NS
**
*
NS
NS
**
NS
**
*
NS
**
**
COL1A1
COL3A1
FN1
CDH1
CDH2
S100A4
MMP2
MMP9
SNAIL
VIMENTIN
ZEB1
TJP1

Figure S1

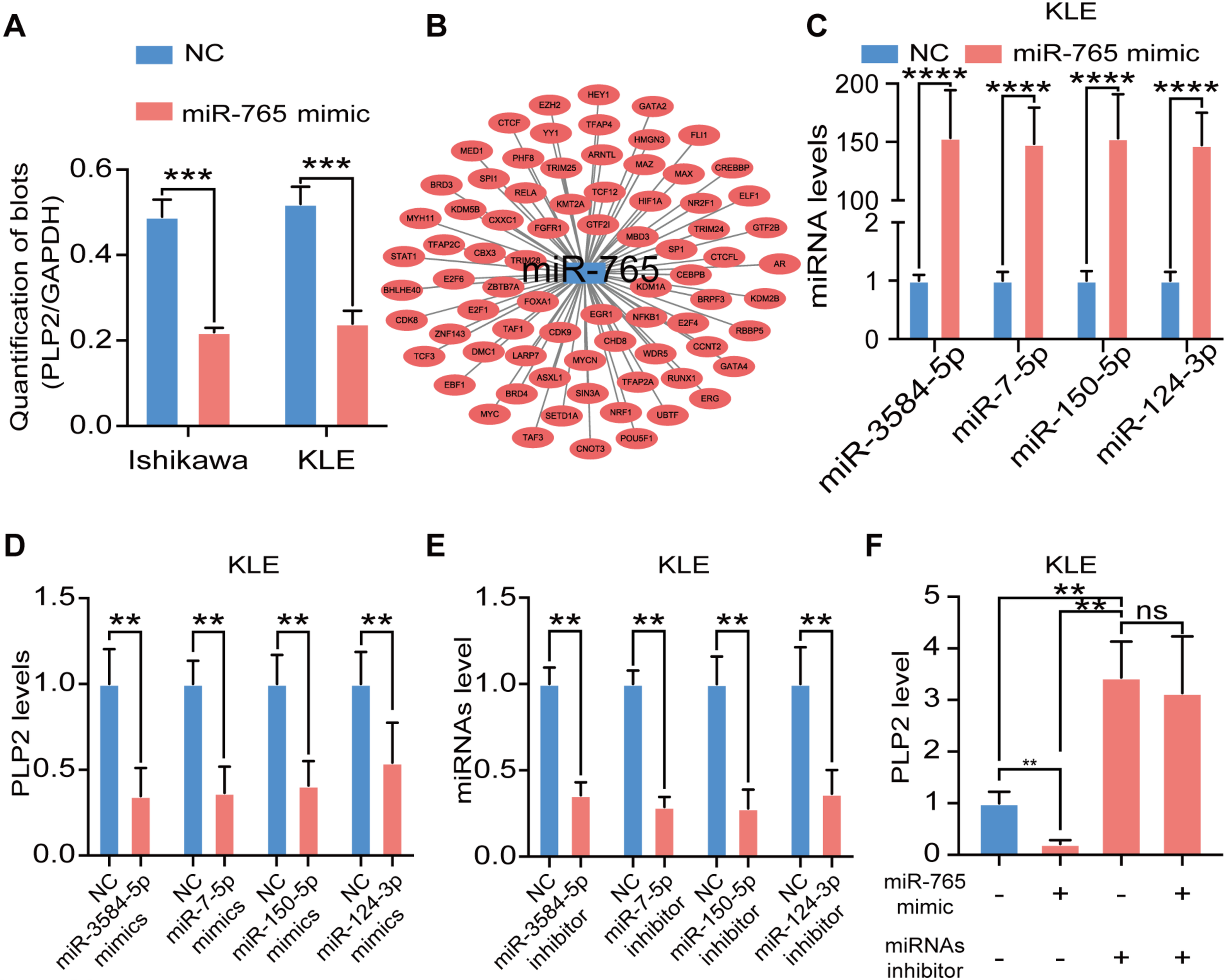

A
NC
miR-765 mimic
Quantification of blots (PLP2/GAPDH)
0.6
0.4
0.2
0.0
***
***
Ishikawa
KLE
B
miR-765
HEY1
EZH2
GATA2
CTCF
TFAP4
YY1
HMGN3
FLI1
MED1
PHF8
ARNTL
MAZ
TRIM25
MAX
CREBBP
BRD3
SPI1
RELA
TCF12
HIF1A
NR2F1
ELF1
KDM5B
KMT2A
MYH11
CXXC1
FGFR1
GTF2I
TRIM24
GTF2B
MBD3
TFAP2C
SP1
CBX3
CTCFL
STAT1
TRIM28
AR
E2F6
CEBPB
BHLHE40
ZBTB7A
KDM1A
FOXA1
BRPF3
KDM2B
E2F1
EGR1
NFKB1
CDK8
E2F4
TAF1
RBBP5
ZNF143
CDK9
CHD8
CCNT2
TCF3
DMC1
LARP7
MYCN
WDR5
GATA4
ASXL1
TFAP2A
RUNX1
EBF1
BRD4
SIN3A
ERG
MYC
SETD1A
NRF1
UBTF
TAF3
POU5F1
CNOT3
C
KLE
NC
miR-765 mimic
miRNA levels
200
150
100
2
1
0
****
****
****
****
miR-3584-5p
miR-7-5p
miR-150-5p
miR-124-3p
D
KLE
PLP2 levels
1.5
1.0
0.5
0.0
**
**
**
**
NC
miR-3584-5p mimics
NC
miR-7-5p mimics
NC
miR-150-5p mimics
NC
miR-124-3p mimics
E
KLE
miRNAs level
1.5
1.0
0.5
0.0
**
**
**
**
NC
miR-3584-5p inhibitor
NC
miR-7-5p inhibitor
NC
miR-150-5p inhibitor
NC
miR-124-3p inhibitor
F
KLE
PLP2 level
5
4
3
2
1
0
**
**
ns
**
miR-765 mimic
- + - +
miRNAs inhibitor
- - + +

Figure S2

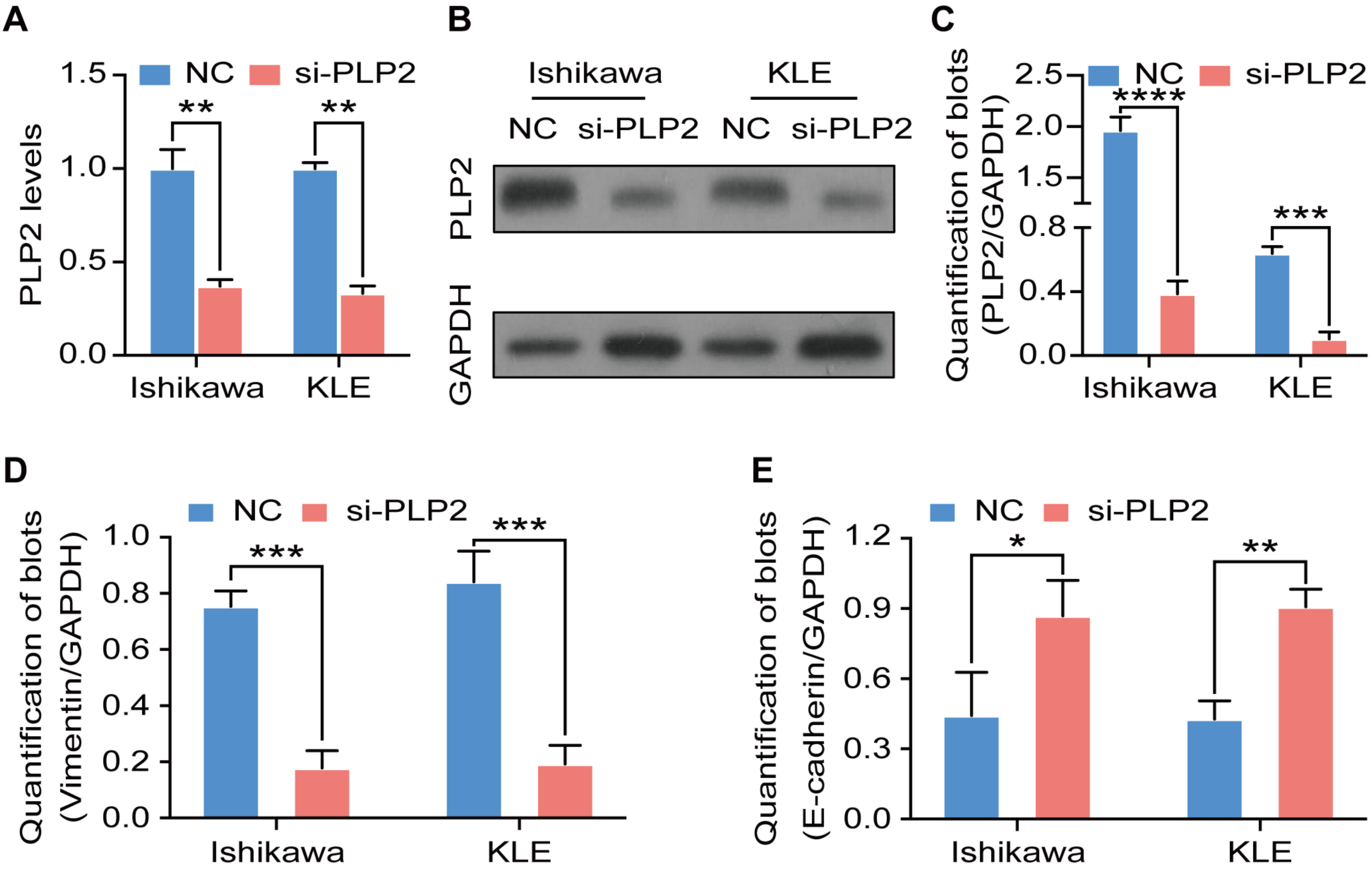
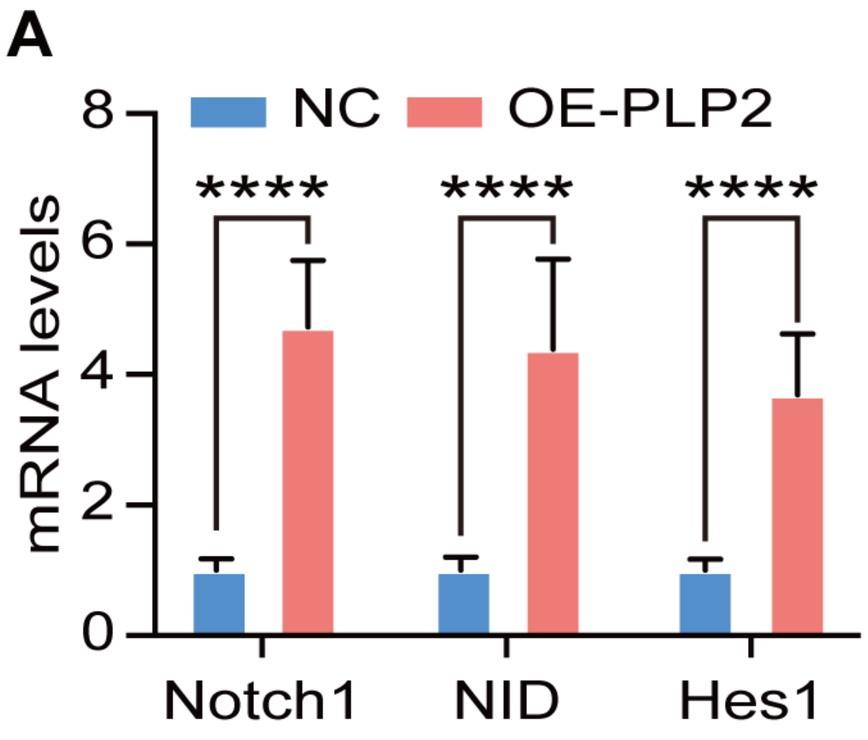
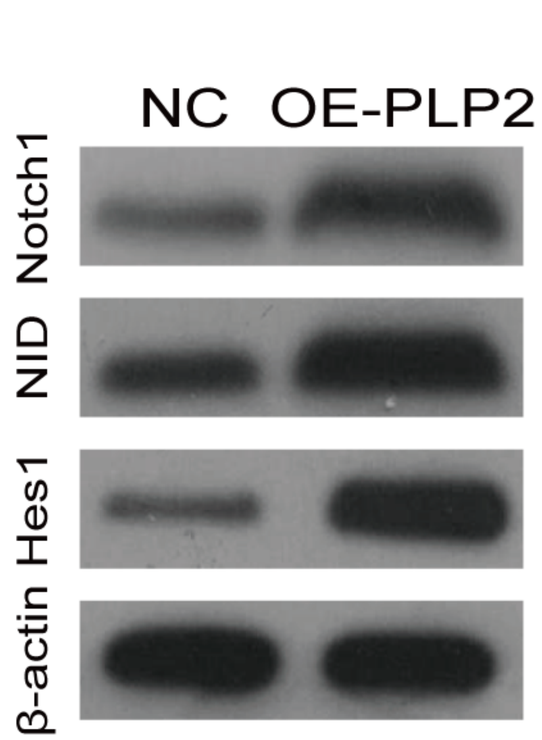
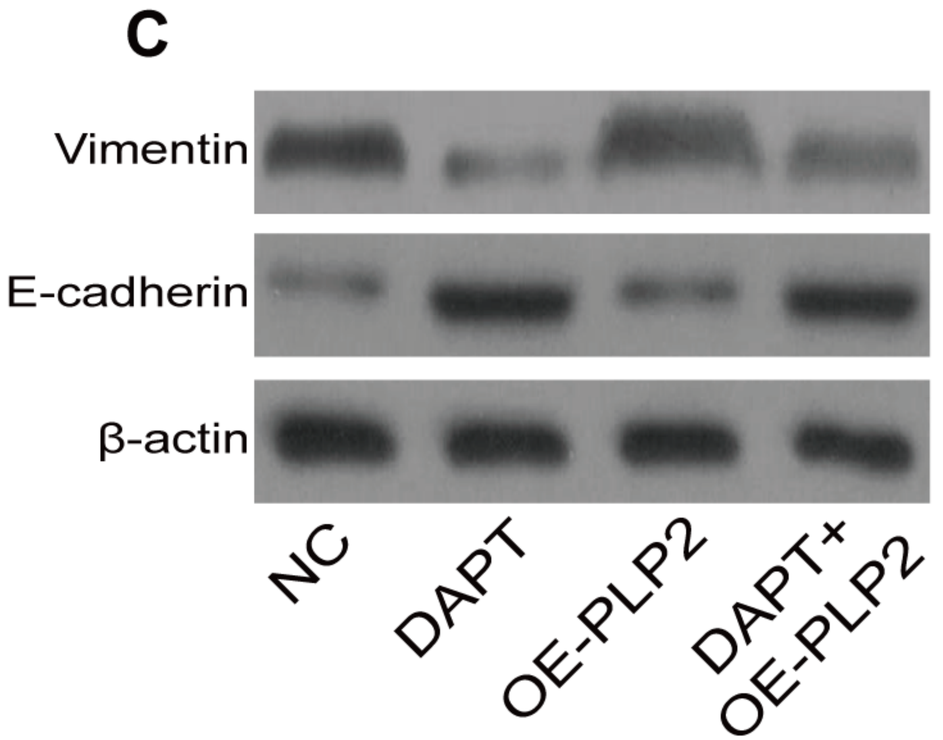
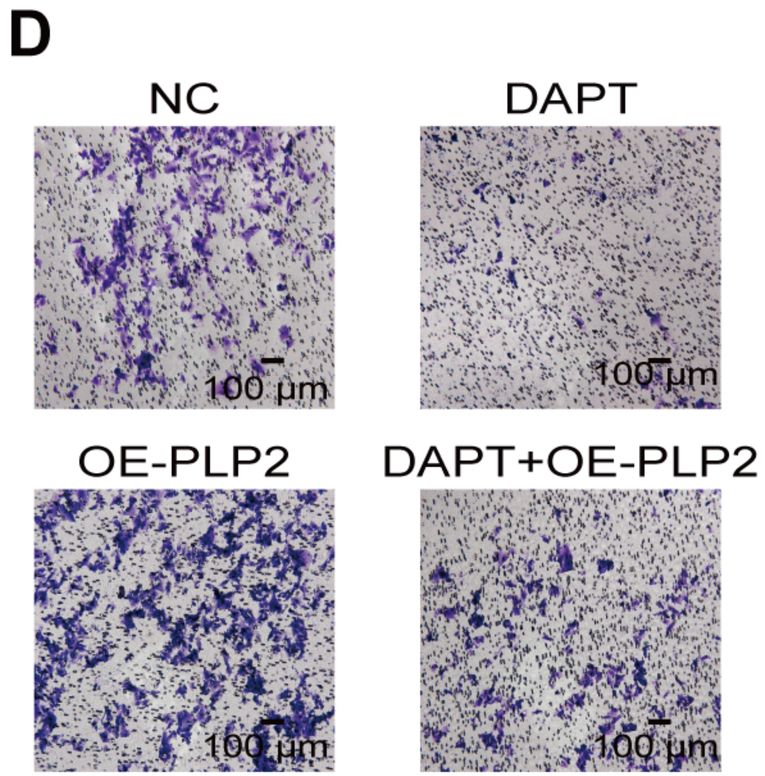

A
PLP2 levels
1.5
1.0
0.5
0.0
NC
si-PLP2
**
**
Ishikawa
KLE
B
Ishikawa
KLE
NC
si-PLP2
NC
si-PLP2
PLP2
GAPDH
C
Quantification of blots
(PLP2/GAPDH)
2.5
2.0
1.5
0.8
0.4
0.0
NC
si-PLP2
****
***
Ishikawa
KLE
D
Quantification of blots
(Vimentin/GAPDH)
1.0
0.8
0.6
0.4
0.2
0.0
NC
si-PLP2
***
***
Ishikawa
KLE
E
Quantification of blots
(E-cadherin/GAPDH)
1.2
0.9
0.6
0.3
0.0
NC
si-PLP2
*
**
Ishikawa
KLE

Figure S3


A
NC
OE-PLP2
mRNA levels
8
6
4
2
0
****
****
****
Notch1
NID
Hes1


B
NC
OE-PLP2
Notch1
NID
Hes1
β-actin


C
Vimentin
E-cadherin
β-actin
NC
DAPT
OE-PLP2
DAPT+
OE-PLP2


D
NC
DAPT
OE-PLP2
DAPT+OE-PLP2
100 μm
100 μm
100 μm
100 μm

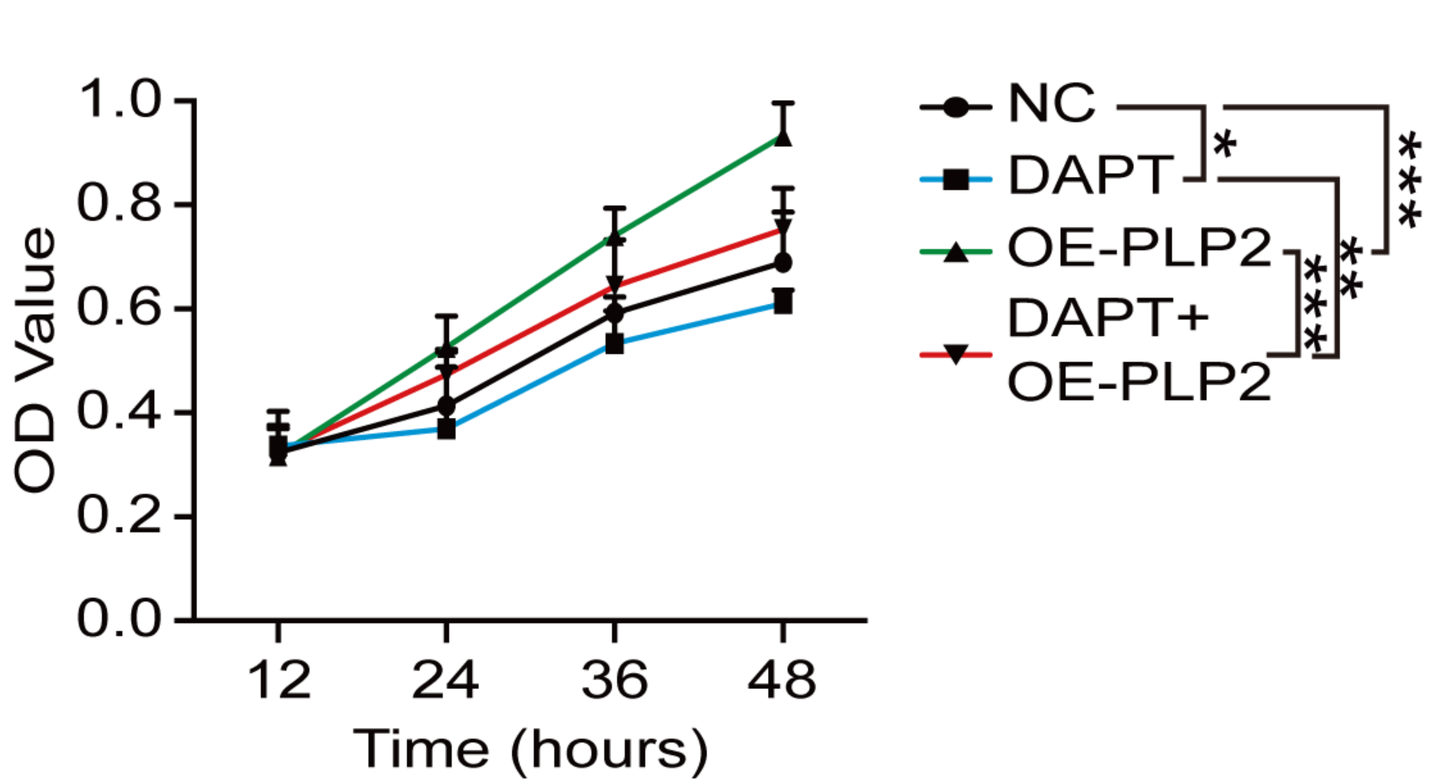

E
OD Value
1.0
0.8
0.6
0.4
0.2
0.0
12
24
36
48
Time (hours)
NC
DAPT
OE-PLP2
DAPT+
OE-PLP2
*
****
**
***

Figure S4

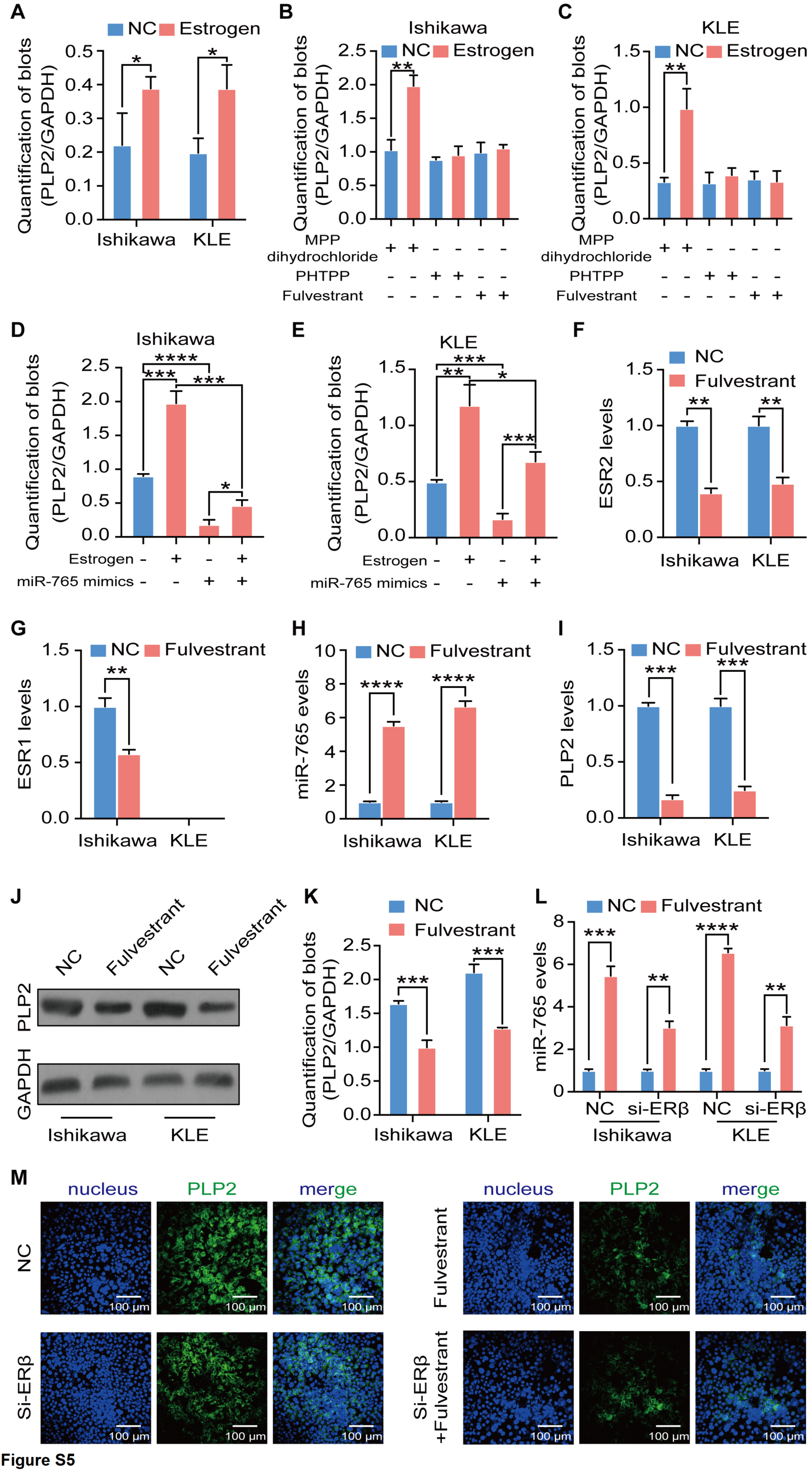

A
NC
Estrogen
Quantification of blots (PLP2/GAPDH)
Ishikawa
KLE
B
Ishikawa
MPP dihydrochloride
PHTPP
Fulvestrant
C
KLE
D
Ishikawa
Estrogen
miR-765 mimics
E
KLE
F
ESR2 levels
Fulvestrant
G
ESR1 levels
H
miR-765 evels
I
PLP2 levels
J
PLP2
GAPDH
K
L
si-ERβ
M
nucleus
PLP2
merge
100 μm
Si-ERβ
Si-ERβ +Fulvestrant

Figure S5

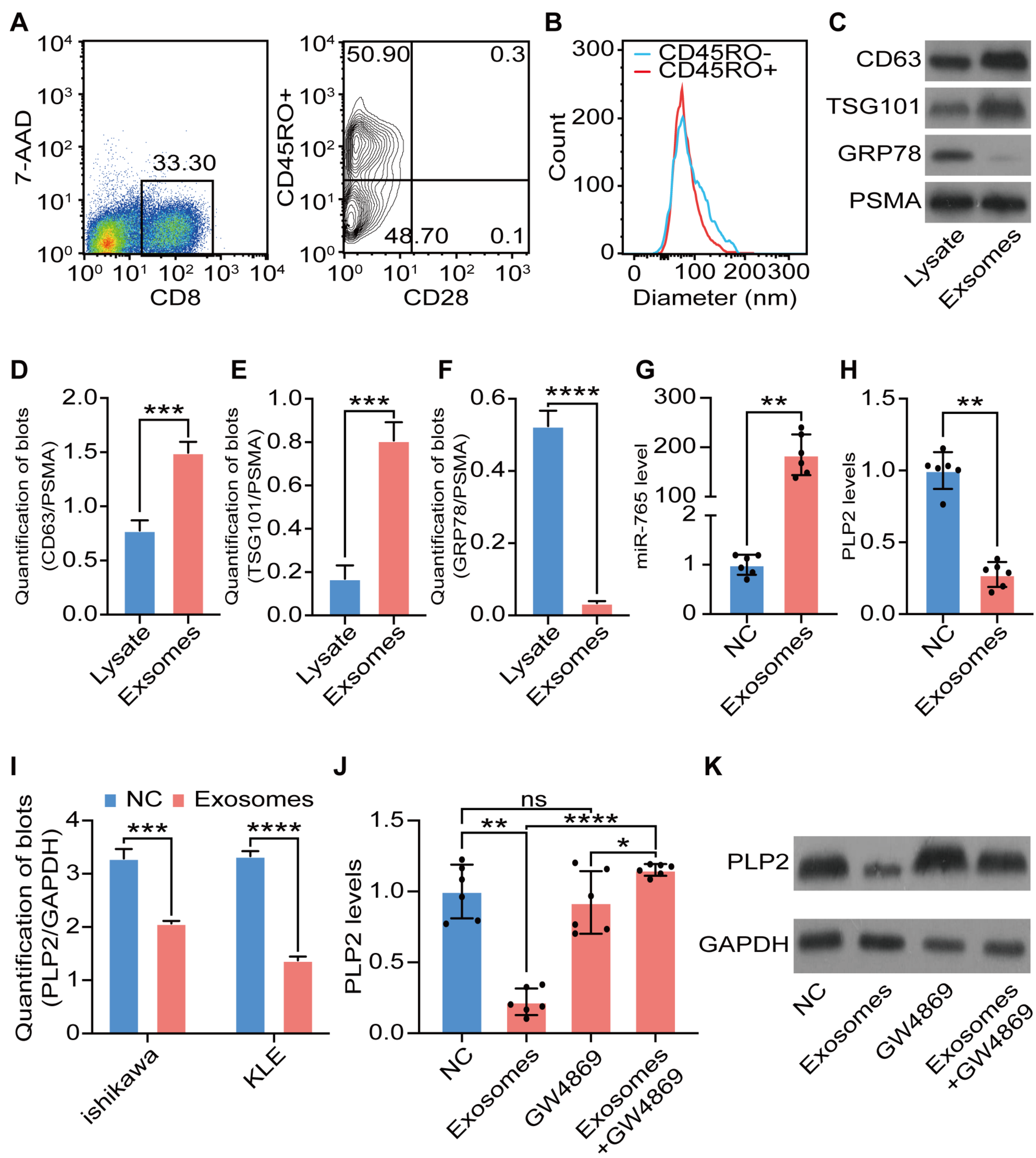

A
7-AAD
CD8
33.30
CD45RO+
CD28
50.90
0.3
48.70
0.1
B
Count
Diameter (nm)
CD45RO-
CD45RO+
C
CD63
TSG101
GRP78
PSMA
Lysate
Exsomes
D
Quantification of blots (CD63/PSMA)
E
Quantification of blots (TSG101/PSMA)
F
Quantification of blots (GRP78/PSMA)
G
miR-765 level
NC
Exosomes
H
PLP2 levels
I
Quantification of blots (PLP2/GAPDH)
ishikawa
KLE
J
PLP2 levels
ns
NC
Exosomes
GW4869
Exosomes +GW4869
K
PLP2
GAPDH

Figure S6

A
B
C
D
E
F
G
H
I
J
K
miR-765 levels
PLP2 levels
PLP2
GAPDH
Estrogen
Exosomes
NC
Estrogen
Exosomes
Estrogen+ Exosomes
OD Value
Time (hours)
Blank
Count (10^3)
Ki67 (FITC)
Vimentin
E-cadherin
Quantification of blots (Vimentin/GAPDH)
Quantification of blots (E-cadherin/GAPDH)
100 μm
Tumor volume (mm^3)
Percent survival
Time (Days)
ns

Figure S7