Supplementary figure legends

SFigure 1. Examination of cellular signaling and proliferation and enlarged tumor tissues

A-B. Detection of cellular signaling (A) and proliferation (B) in parental and empty vector-transfected SKOV3 cells by western blot. **C.** Detection of ERK1/2, AKT and autophagy-associated molecules in $SKOV3^{T}$/V12 cells by western blot after silencing of ERK1/2 or AKT1/2 with specific siRNAs. **D.** Tumor tissues derived from animals subcutaneously inoculated with $SKOV3^{T}$, $SKOV3^{T}$/V12, $SKOV3^{T}$/S35, $SKOV3^{T}$/E38, or $SKOV3^{T}$/C40 cells, followed by administration of placebo, DOX, cisplatin, or DOX+cisplatin. Protein markers are properly labeled as indicated in **A** and **C**.

SFigure 2. Cellular localization of HDAC4 and HIF-1α

A-B. Selected images showing nuclear and cytoplasmic localization of HDAC4 and HIF-1α regulated by p53 induction and RAS mutant transfection. Scale bars = 10 μm.

SFigure 3. HDAC4/p-HDAC4 and HIF-1α intracellular localization regulated by p53 and RAS status.

A-C. Representative images showing cellular HDAC4 (**A**), p-HDAC4 (**B**) and HIF-1α (**C**) localization in ovarian cancer cell lines. **D.** Images showing HDAC4 (red) and HIF-1α (green) co-localization (yellow) in ovarian cancer cells HEY (KRAS mutation), SKOV3 (p53 loss) and A2780 (both p53 and RAS wild type). **E-G.** Selected images show cellular HDAC4 (**A**), p-HDAC4 (**B**) and HIF-1α (**C**) localization in lung cancer cells. **H.** Images showing HDAC4 (green) and HIF-1α (red) co-localization (yellow) in lung cancer cells A549 (RAS mutation), H1299 (p53 loss), H23 (both p53 and RAS mutations), and H358 (p53 loss and RAS mutation) cells. Scale bars = 20 μm.

SFigure 4. Interaction of HDAC4 with HIF-1α, Atg3 and Atg12

A-C. Overexpression of HDAC4 increases HDAC4 nuclear accumulation (**A**) and protein phosphorylation in cytoplasma (**B**), and stimulates HIF-1a nuclear accumulation (**C**). **D**. Knockdown of HIF-1α upregulates HDAC4 expression. **E**. No acetylation of ATG3 and ATG12 was detected by Co-IP/WB. **F**. Co-IP did not reveal a direct interaction between HDAC4 and Atg3 or Atg12 in $SKOV3^{T}$ or $SKOV3^{T}$/V12 cells. **G.** No co-localization between HDAC4 and Atg3 (upper panel) or Atg12 (lower panel) detected in $SKOV3^{T}$/V12 cells**.** Scale bars = 20 μm. **H**. Relative mRNA levels of the transcription factor CREBZF in various cell lines derived from the data of the Gene Expression arrays. Protein markers are properly labeled as indicated in **E** and **F**.

SFigure 5. HDAC4 and HIF-1α promote cisplatin resistance.

A. IC50 values of cisplatin in cells responding to HDAC4 and HIF-1α overexpression or silencing without p53 induction (DOX-). **B.** IC50 values of cisplatin in cells responding to HDAC4 or HIF-1α overexpression or silencing with p53 induction (DOX+).

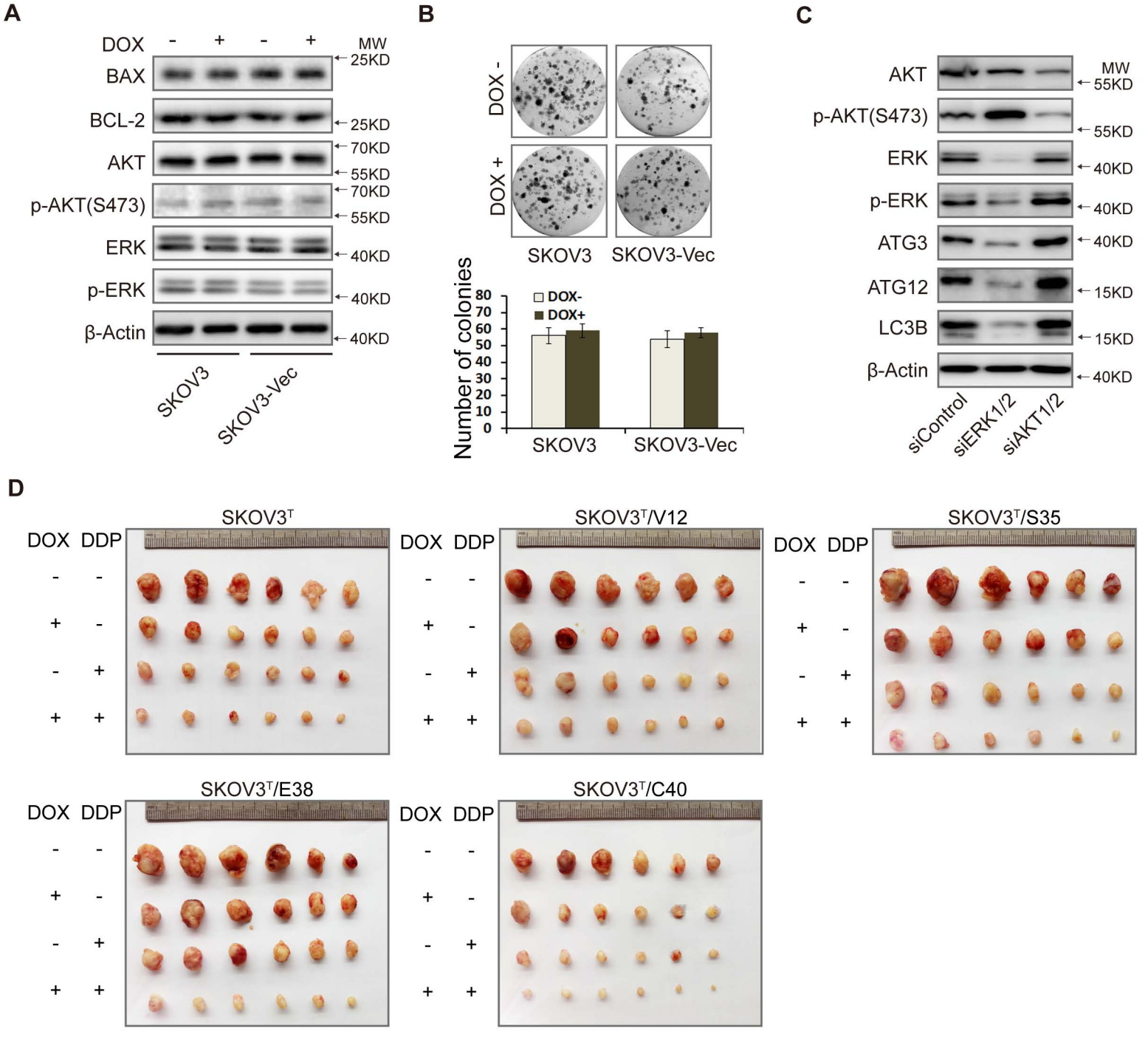
SFigure 6. Tumor tissues (enlarged)

Tumors derived from animals injected with cells overexpressing cDNA and shRNA of HDAC4 (**A**) or HIF-1α (**B**), followed by p53 induction and cisplatin treatment.

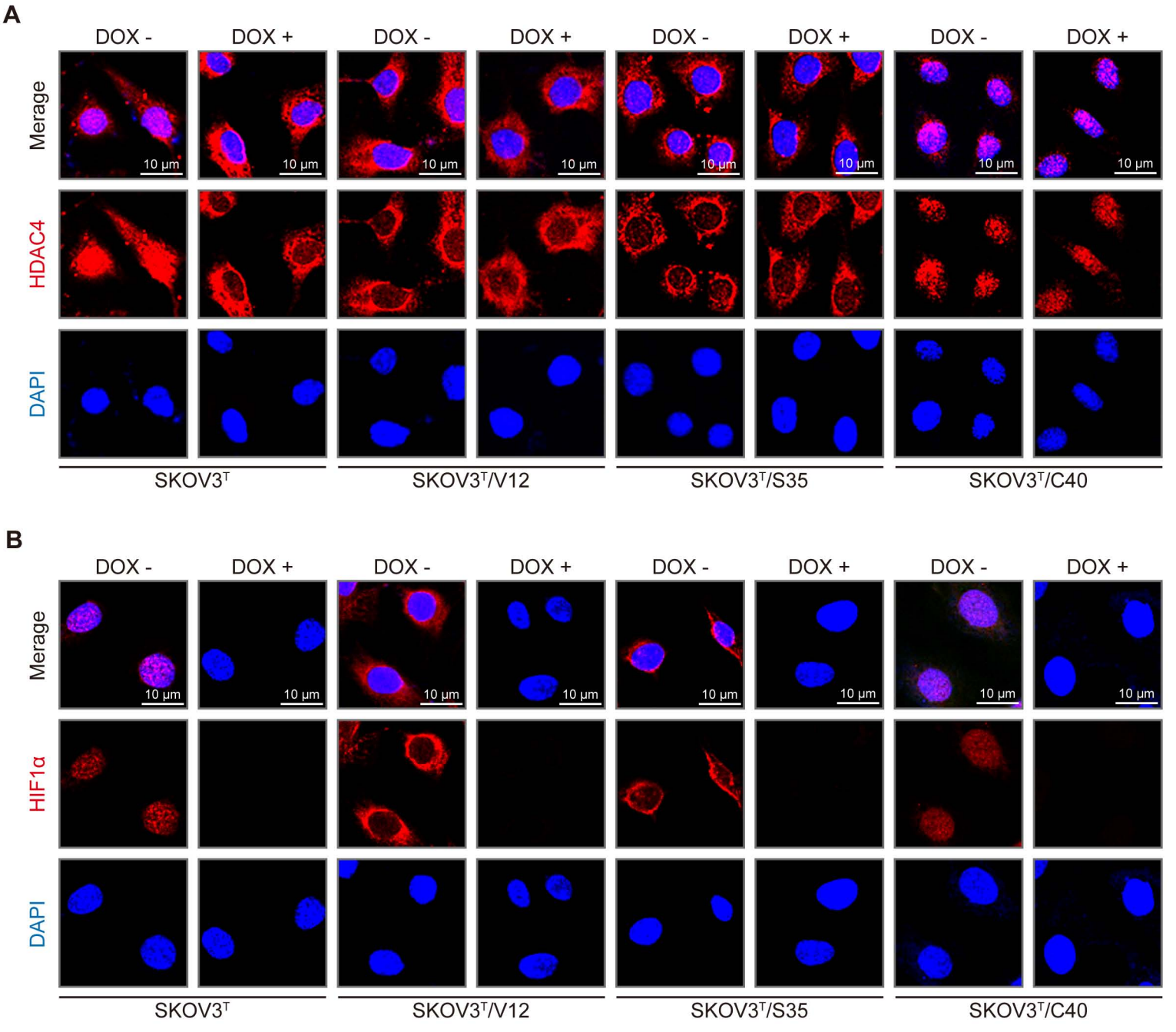
SFigure 7. High ERK mRNA expression indicates a poor prognosis in serous ovarian cancer patients.

A-C. Kaplan–Meier survival analyses were conducted to evaluate the effect of ERK on overall survival (**A**) in the presence of mutant p53 (**B**) and wild-type p53 (**C**). **D-F.** Kaplan–Meier survival analyses were conducted to evaluate the effect of ERK on progression-free survival (**D**) in the presence of mutant p53 (**E**) and wild-type p53 (**F**). **G-H.** Kaplan–Meier survival analyses to evaluate the effect of AKT on progression-free survival (**G**) in the presence of mutant p53.

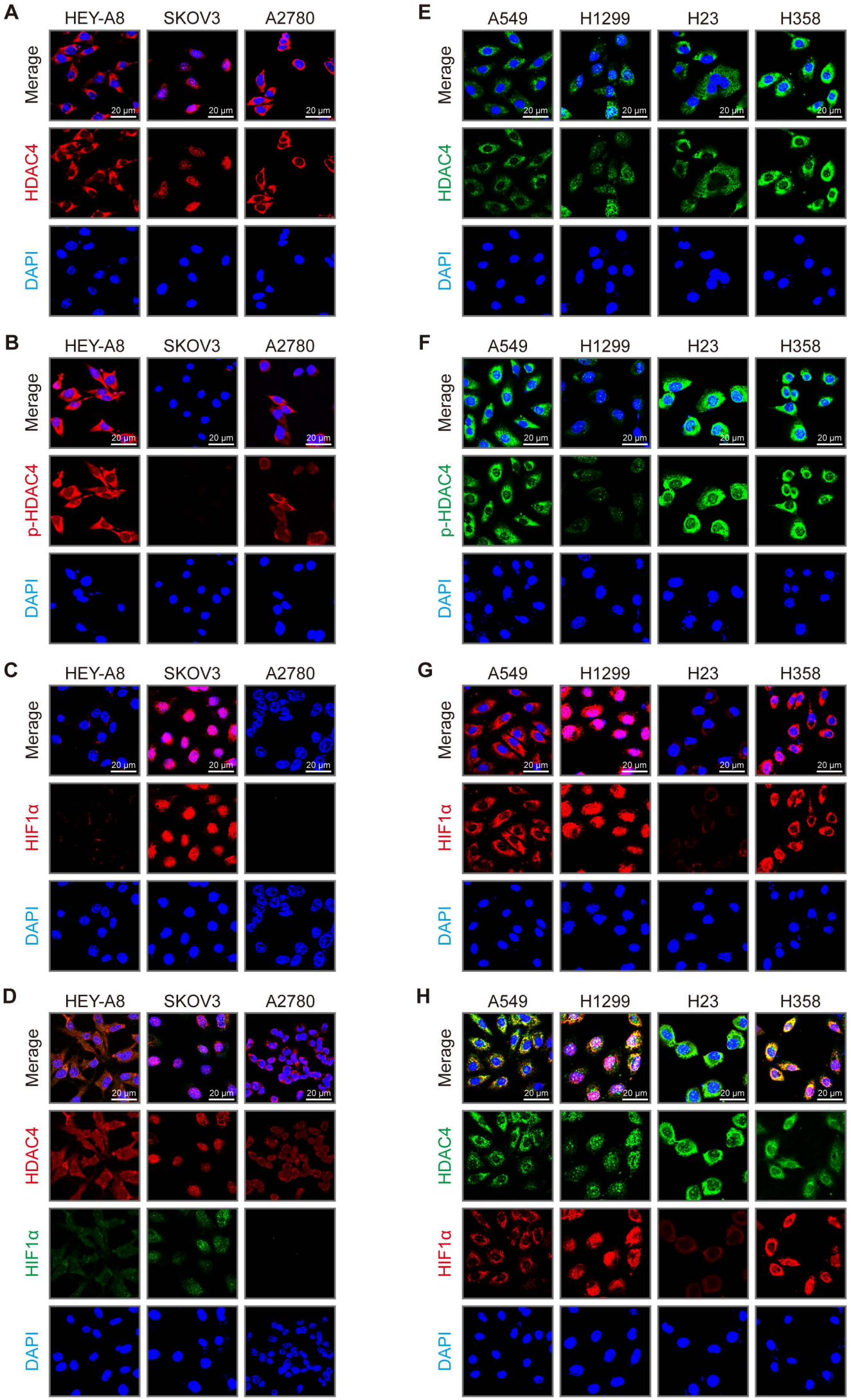
Supplementary figure 1



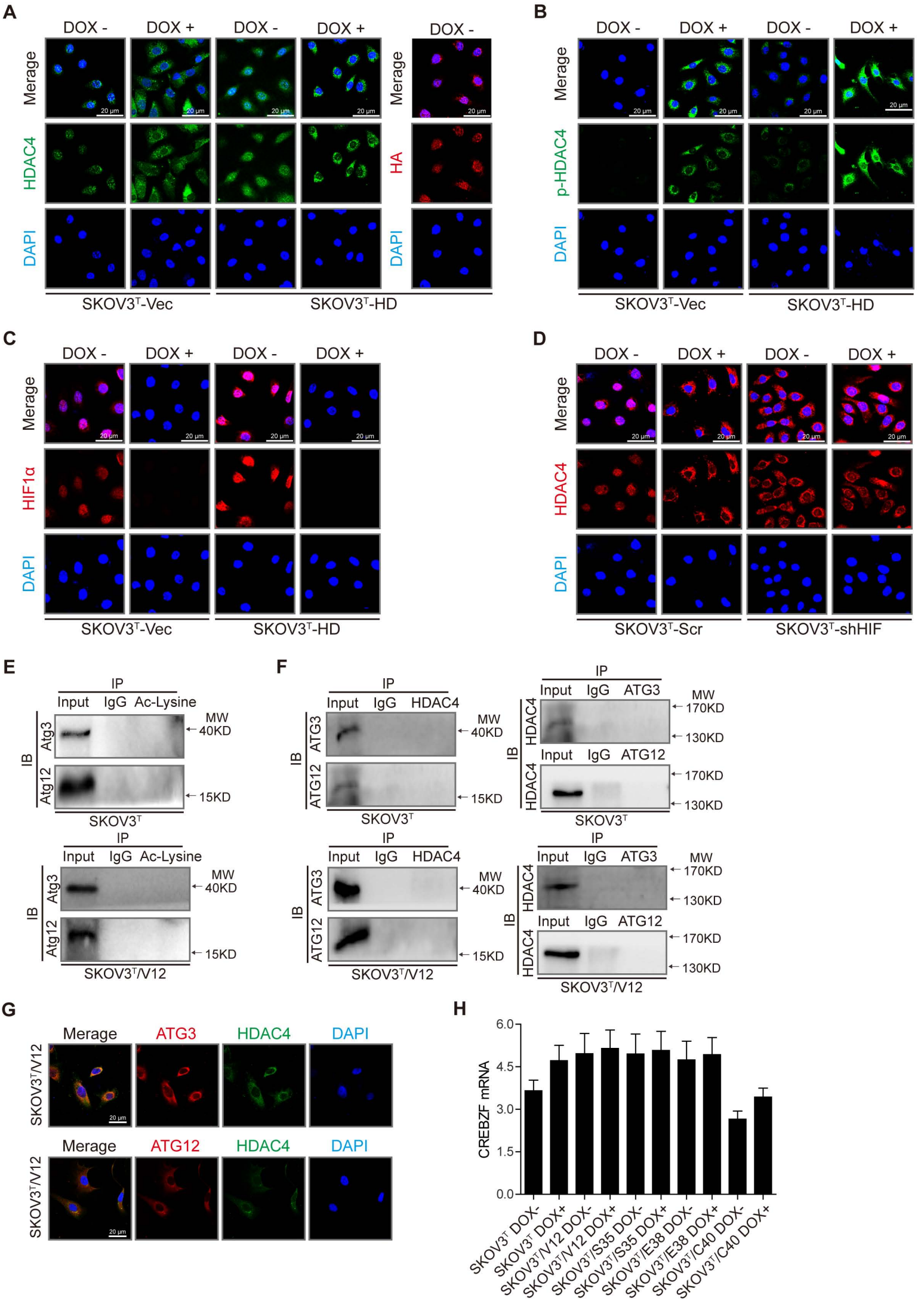
Supplementary figure 2



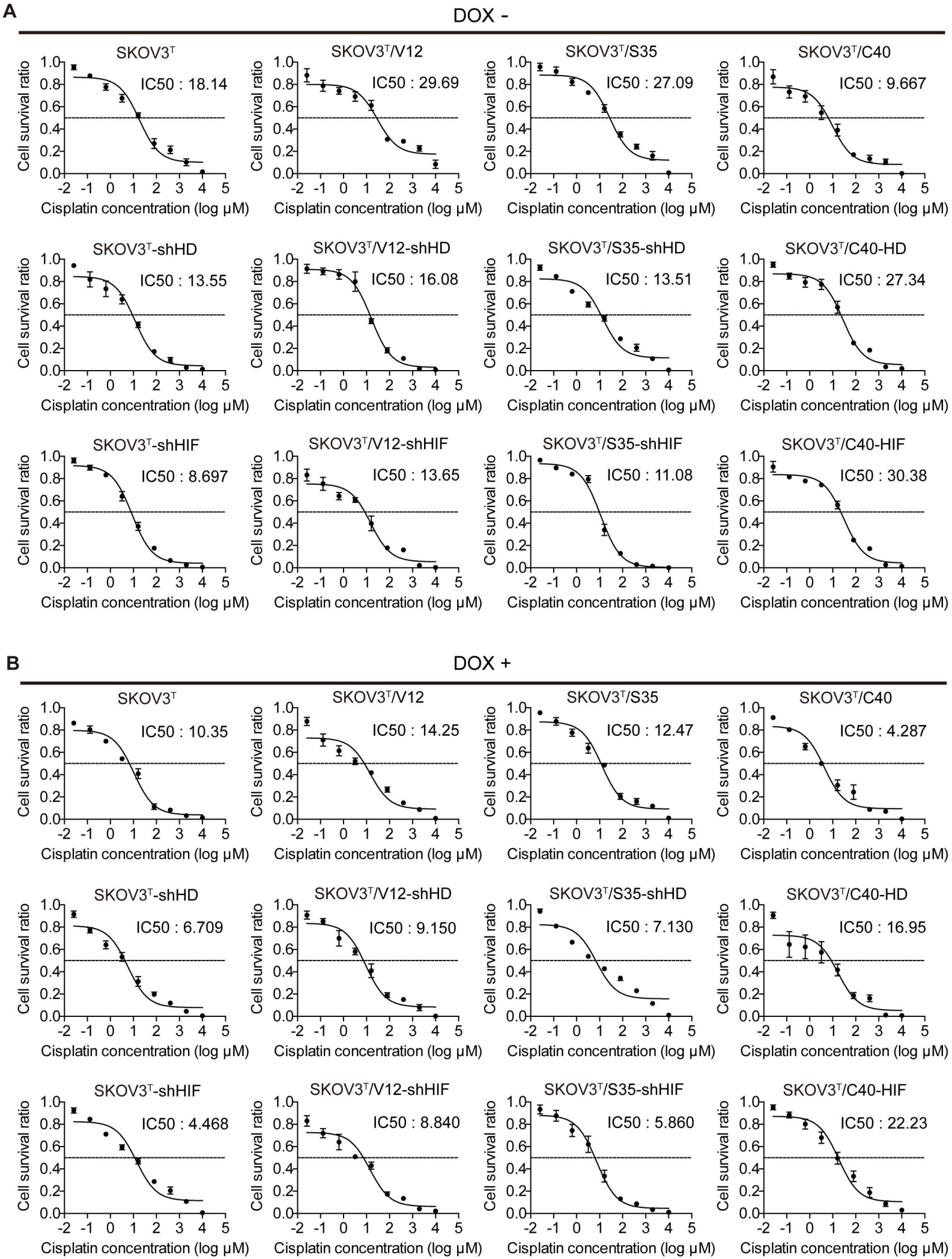
Supplementary figure 3



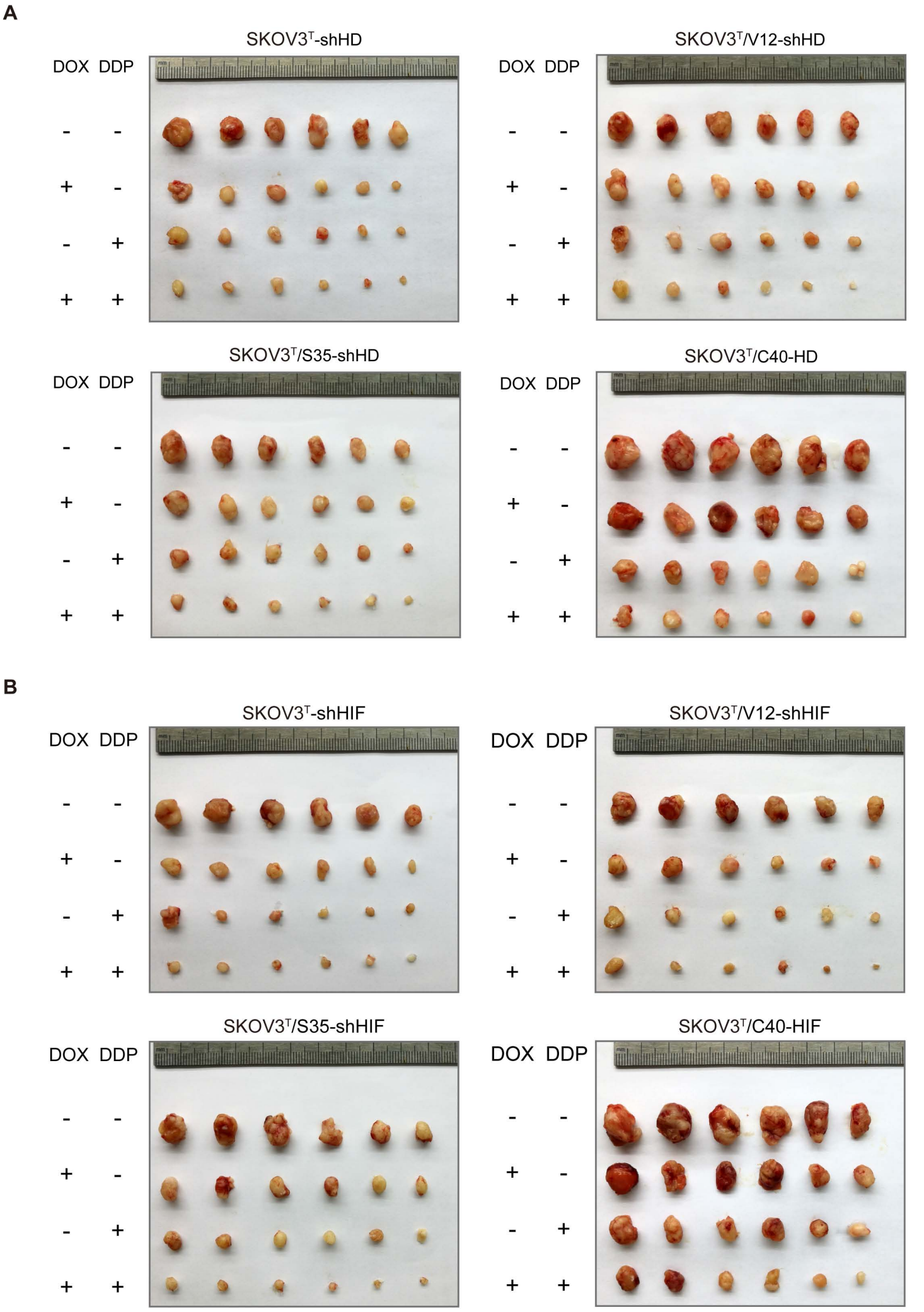
Supplementary figure 4



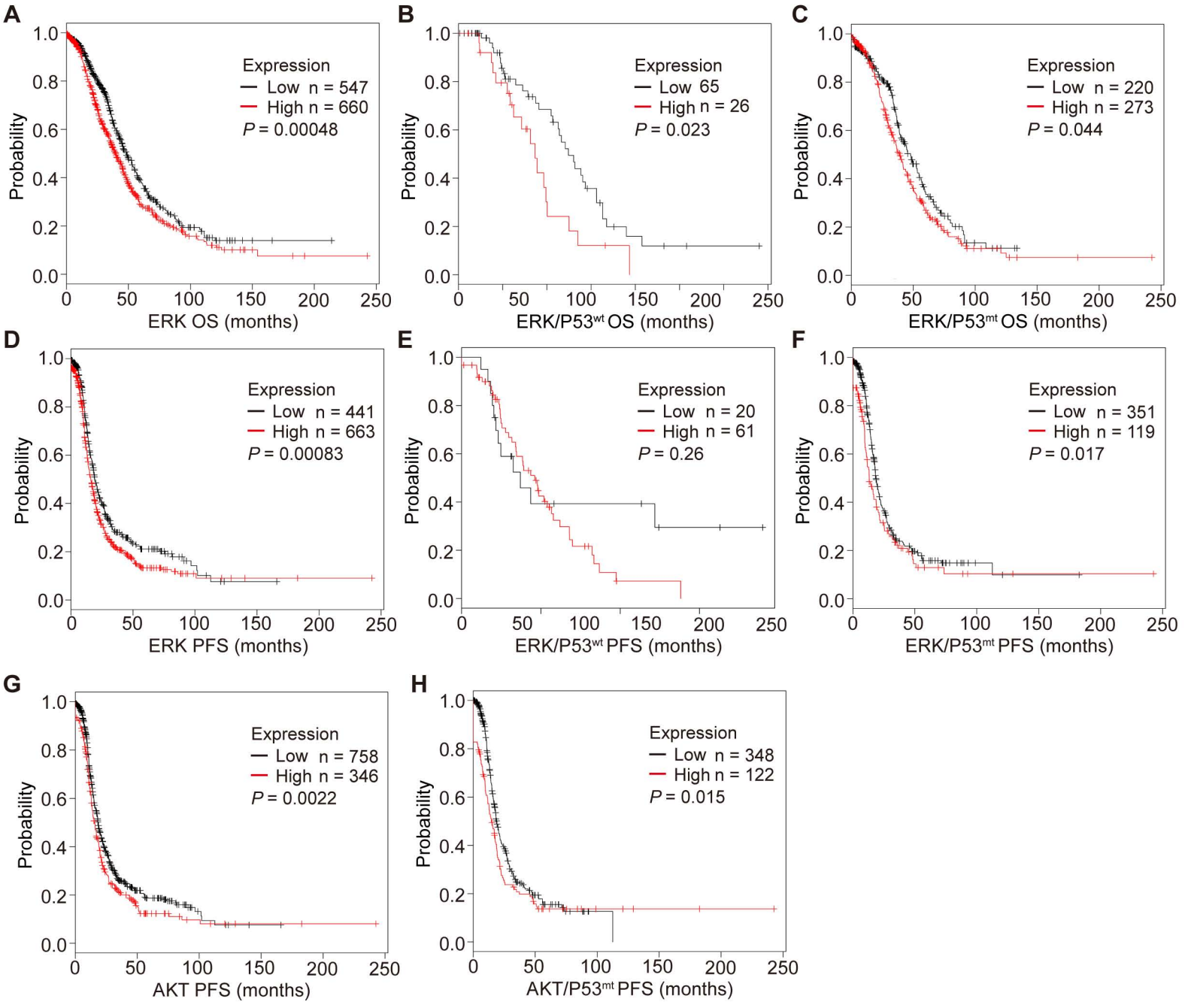
Supplementary figure 5



Supplementary figure 6



Supplementary figure 7



Supplementary table 1. Information of the primary antibodies usd in the study

Antibody	Catalog Number	Company	Dilution	Purpose
HA-Tag	cs-3724	Cell Signaling Inc.	1:3000	WB
HIS-Tag	cs-2365	Cell Signaling Inc.	1:3000	WB
E2F1	cs-3742	Cell Signaling Inc.	1:1000	WB
ERK1/2	cs-9102	Cell Signaling Inc.	1:1000	WB
p-ERK1/2	cs-9101	Cell Signaling Inc.	1:1000	WB
AKT	cs-9272	Cell Signaling Inc.	1:1000	WB
p-AKT(S473)	cs-9018	Cell Signaling Inc.	1:1000	WB
Bax	cs-5023	Cell Signaling Inc.	1:1000	WB
Bcl-2	cs-15071	Cell Signaling Inc.	1:1000	WB
Beclin-1	cs-3459	Cell Signaling Inc.	1:1000	WB
Atg3	cs-3415	Cell Signaling Inc.	1:1000	WB
Atg12	cs-4180	Cell Signaling Inc.	1:1000	WB
Atg16	cs-8089	Cell Signaling Inc.	1:1000	WB
HDAC4	cs-15164	Cell Signaling Inc.	1:1000	WB
GAPDH	cs-5174	Cell Signaling Inc.	1:5000	WB
P53	sc-126	Santa Cruz Biotech	1:1000	WB
P21	sc-271532	Santa Cruz Biotech	1:1000	WB
pan-RAS	sc-166691	Santa Cruz Biotech	1:1000	WB
SQSTM1(p62)	sc-28359	Santa Cruz Biotech	1:1000	WB
AC-Histone H3	sc-56616	Santa Cruz Biotech	1:1000	WB
LC3B	L7543	Sigma Aldrich	1:1000	WB
β-actin	A2228	Sigma Aldrich	1:5000	WB
p-HDAC4(S632)	ab39408	Abcam	1:1000	WB
HIF-1α	ab51608	Abcam	1:1000	WB
α-tubulin	11224-1-AP	Proteintech	1:5000	WB
CREBZF	19017-1-AP	Proteintech	1:1000	WB
Histone 3	17168-1-AP	Proteintech	1:3000	WB
LC3B	L7543	Sigma Aldrich	1:250	IF
HIF-1α	sc-13515	Santa Cruz Biotech	1:200	IF
Atg3	sc-393660	Santa Cruz Biotech	1:200	IF
Atg12	sc-271668	Santa Cruz Biotech	1:200	IF
β-actin	sc-1616	Santa Cruz Biotech	1:500	IF
α-tubulin	11224-1-AP	Proteintech	1:500	IF
HDAC4	ab12172	Abcam	1:200	IF
p-HDAC4(S632)	ab39408	Abcam	1:200	IF
HDAC4	cs-15164	Cell Signaling Inc.	1:100	CO-IP
Ac-Lysine	cs-9681	Cell Signaling Inc.	1:100	CO-IP
HIF-1α	ab51608	Abcam	1:100	CO-IP

Supplementary Table 2. Putative CREBZF binding sites analyzed in promoter regions of Atg3 and Atg12 genes.

Name	Sequence ID	Start	End	Predicted sequence
CREBZF	Atg3	-1770	-1762	T*TGAC**TCA*C
CREBZF	Atg3	-1046	-1038	T*TGGC**TCA*C
CREBZF	Atg12	-1106	-1098	A*TTC*T*TCA*T

Supplementary Table 3. Association of HDAC4, HIF-1α, CREBZF, ERK, AKT, and p53 mRNA expression with the prognosis of serous ovarian cancer patients.

GENES	PROBES	OS (*P*)			PFS (*P*)		
		All	mt p53	wt p53	All	mt p53	wt p53
HDAC4	204225	0.037*	0.092	-	0.45	0.36	-
	228813	0.0037**	0.27	-	0.000094***	0.011*	-
	1554322	0.054	0.1	-	0.019*	0.072	-
HIF-1α	200989	0.068	0.015*	0.018*	0.018*	0.083	0.42
CREBZF	202977	0.23	0.081	-	0.099	0.24	-
	202978	0.029*	0.052		0.033*	0.0088**	
	202979	0.038*	0.19		0.026*	0.15	
	213584	0.00046***	0.21		0.029*	0.018*	
	225594	0.039*	0.051		0.52	0.0039**	
	225595	0.25	0.13		0.0057**	0.12	
ERK	208351	0.11	0.23	0.31	0.0034**	0.04*	0.16
	209588	0.00048***	0.044*	0.023*	0.00083***	0.017*	0.26
	209589	0.0027**	0.00057***	0.15	1.7e-05***	0.00094***	0.24
	210651	0.023*	0.031*	0.42	1.2e-06***	0.0013**	0.26
	211165	0.00025***	0.19	0.073	0.26	0.082	0.25
	212271	0.17	0.1	0.1	0.061	0.12	0.21
AKT	207163	0.055	0.27	0.22	0.0022**	0.015*	0.14
p53	201746		0.061	0.31		0.011*	0.061
	211300		0.047*	0.25		0.015*	0.015

Kaplan–Meier survival analyses were conducted to evaluate the effect of HDAC4, HIF-1α, CREBZF, ERK, and AKT mRNA on the overall and progression-free survival probability in the presence of mutant and wide-type p53 expression. A red number suggests good or poor prognosis with high gene expression, respectively; * refers to $P < 0.05$; ** refers to $P < 0.01$; *** refers to $P < 0.001$.