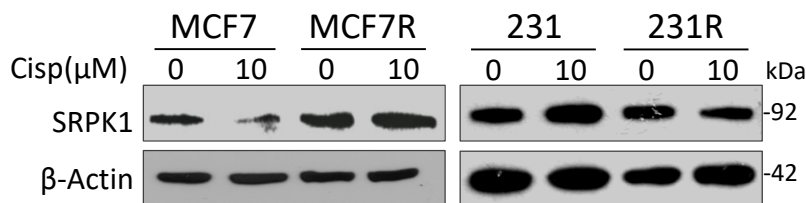
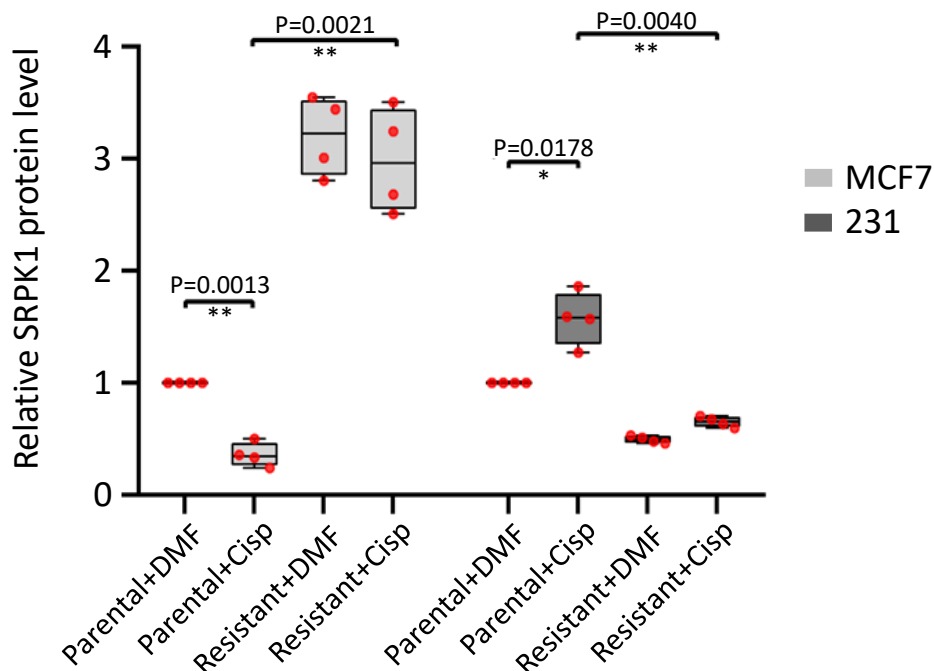
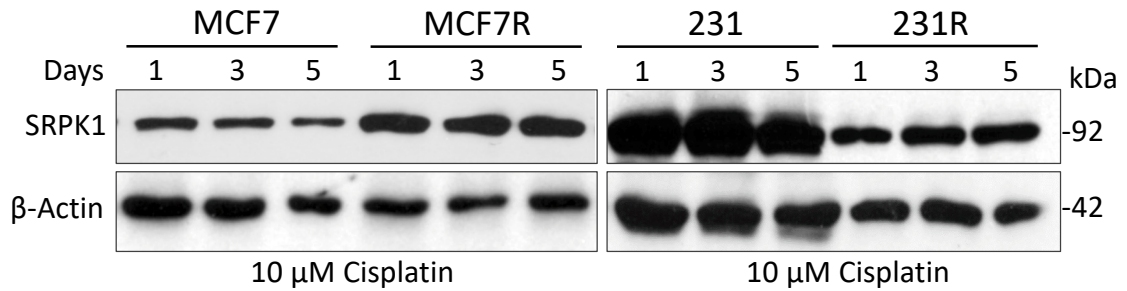
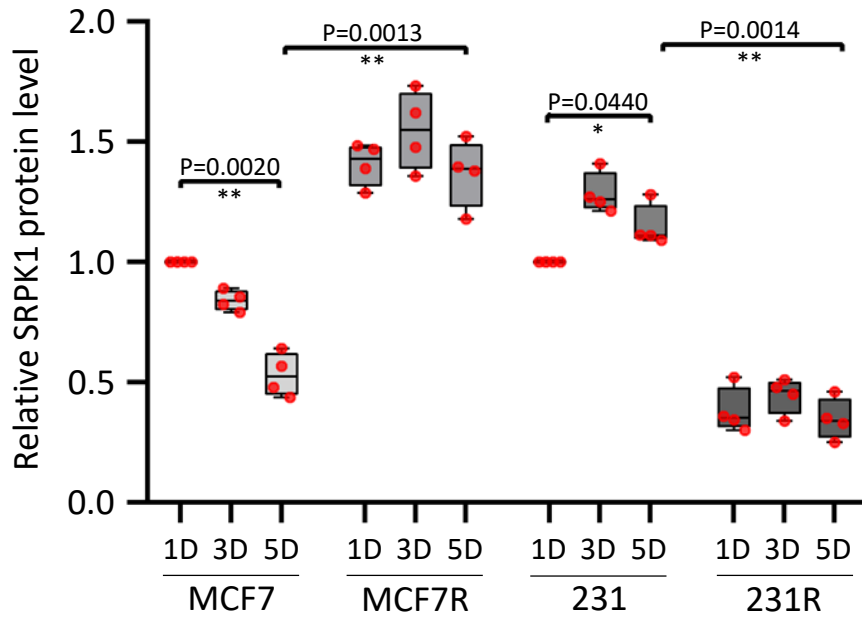


**Supplementary Figure 1. Verification of cisplatin-resistant breast cancer cells.** MCF7/MCF7R (**a**) and 231/231R cells (**b**) were treated with DMF or 10  $\mu$ M cisplatin for 5 days. The extent of DNA damage was assessed by immunostaining for pH2AX. The nuclei were counterstained with Hoechst 33342, and pH2AX-positive cells were counted (**c**). Scale bar: 100  $\mu$ m. Boxplot: n=5; \*\* $p$ <0.01, \*\*\* $p$ <0.001 by Student's *t*-test. NS: no significance.

**a****b**

**Supplementary Figure 2. The effect of cisplatin on SRPK1 expression.** (a) The indicated cells were treated with DMF or 10  $\mu$ M cisplatin for 5 days. Immunoblotting was then performed with the SRPK1 antibody. The blots are representative of four experiments with similar results. (b) Quantification of SRPK1 expression in relative to  $\beta$ -Actin. Boxplot:  $n=4$ ; \* $p<0.05$ , \*\* $p<0.01$  by Student's *t*-test.

**a****b**

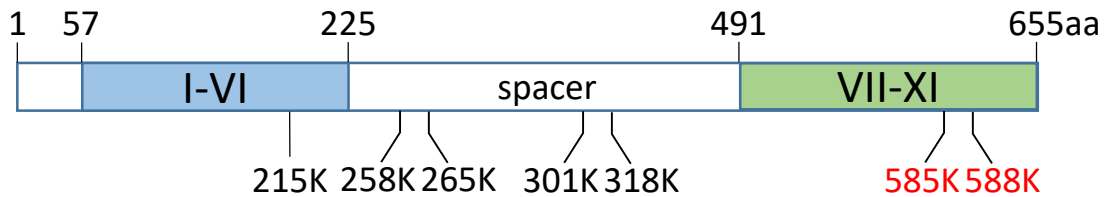
**Supplementary Figure 3. The time-course effect of cisplatin on SRPK1 expression.** (a) The indicated cells were treated with 10 μM cisplatin for 1 day, 3 days and 5 days. The SRPK1 protein level was determined by immunoblotting. The blots are representative of four experiments with similar results. (b) Quantification of SRPK1 expression in relative to β-Actin. Boxplot: n=4; \* $p < 0.05$ , \*\* $p < 0.01$  by Student's *t*-test.



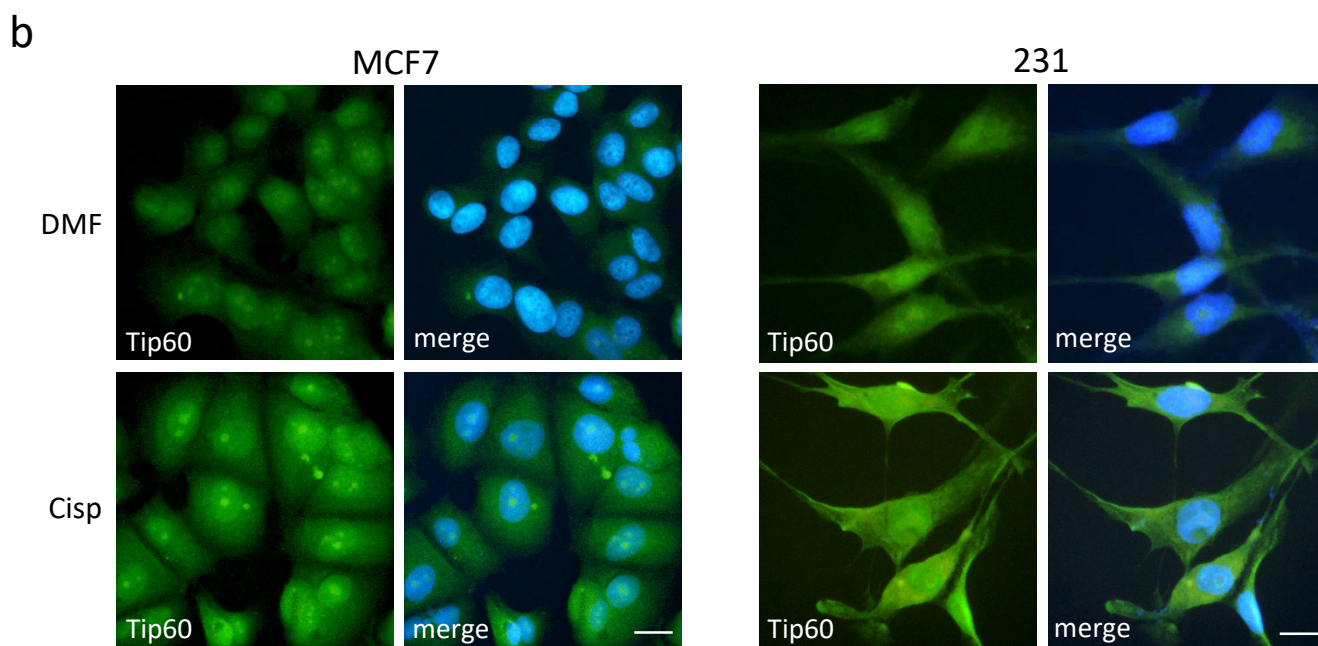
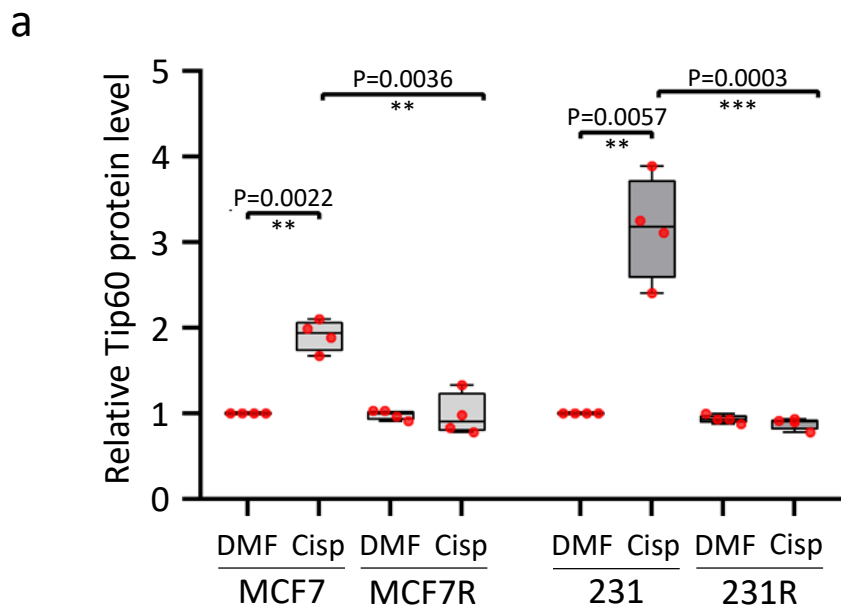
a

Acetylation site	Sequence	SRPK1 +Tip60	SRPK1 +Tip60-mut
215K	IIHTDI <u><b>K</b></u> PE	+	-
258K	SGAPPPSGSAVSTAPQ <u><b>P</b></u> KPADKMSK	+	-
265K	SGAPPPSGSAVSTAPQ <u><b>P</b></u> KPADKMS <u><b>K</b></u>	+	-
301K	MQEIEEMEKESGPG <u><b>K</b></u>	+	-
318K	QEESESPVERPL <u><b>K</b></u> ENPPNK	+	-

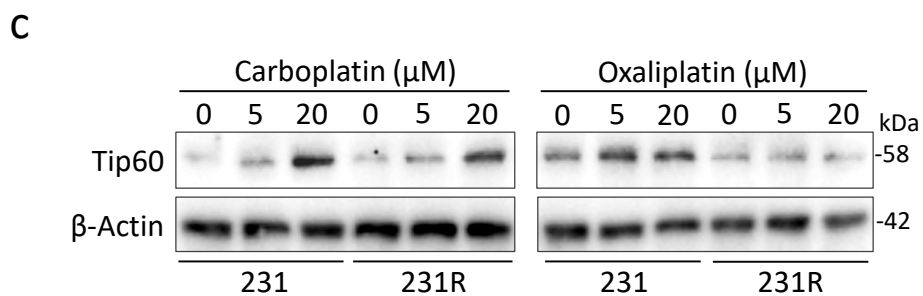
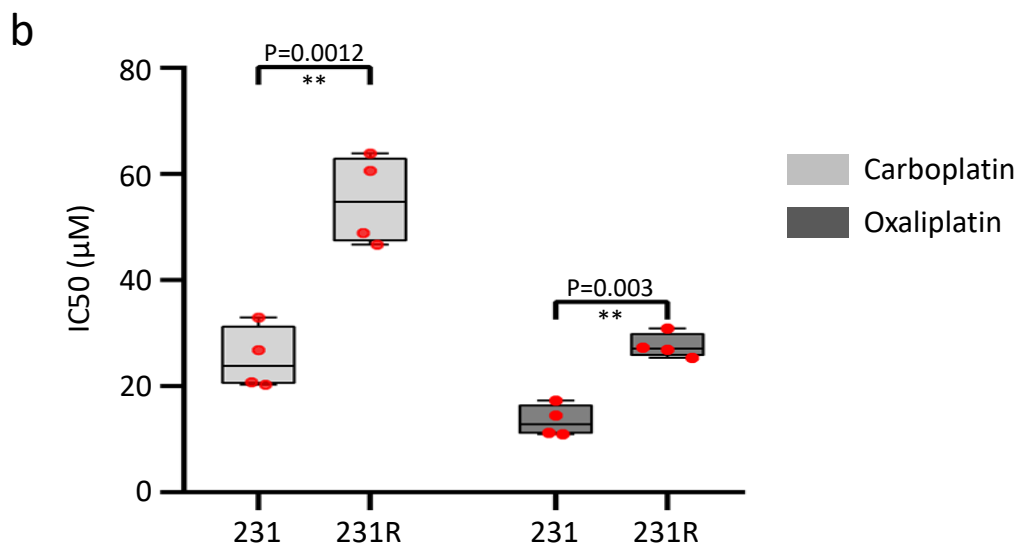
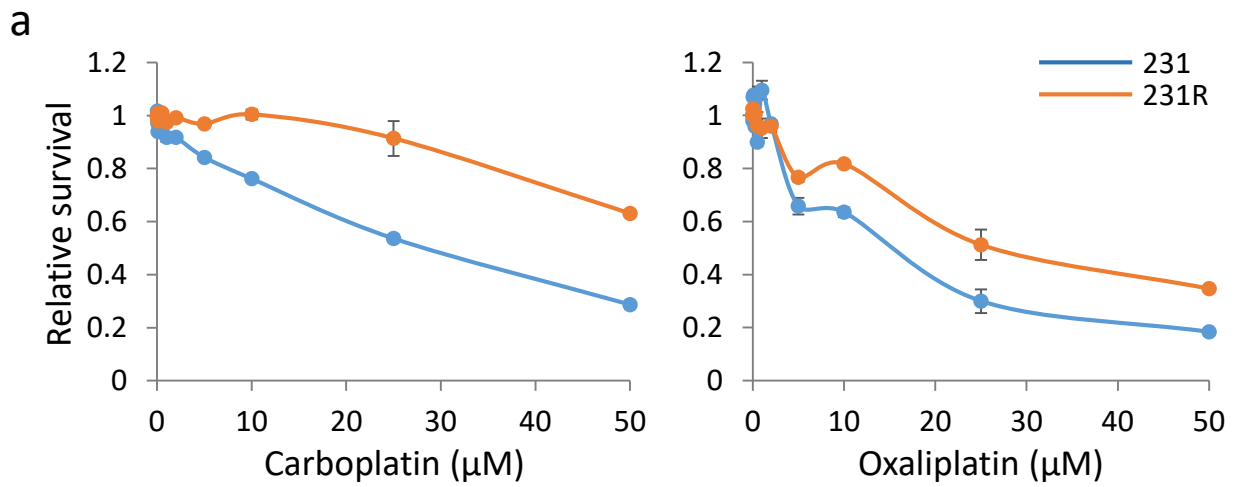
b



**Supplementary Figure 4. Potential sites of acetylation in SRPK1.** (a) SRPK1 was co-expressed with Tip60 or the HAT-deficient mutant, Q377E/G380E, in 293T cells. The acetylation of SRPK1 was analysed by mass spectrometry. The acetylated residues are in bold and underlined. (b) The positions of potential acetylated lysine residues in SRPK1. The sites in red are reported by Choudhary et al. 2009 [27].

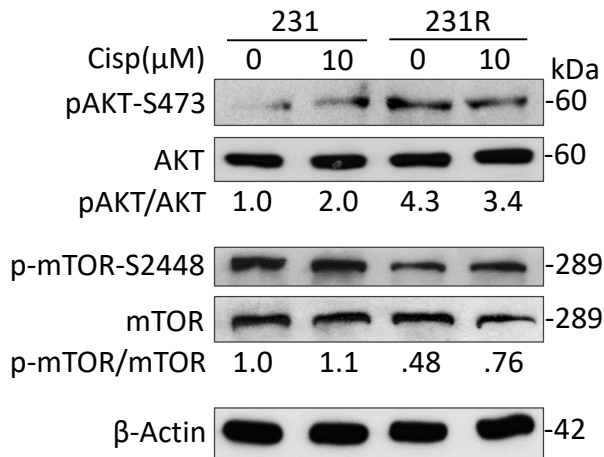


**Supplementary Figure 5. Tip60 was increased by cisplatin treatment in the parental cells. (a)** Quantification of Tip60 protein level in relative to  $\beta$ -Actin in the indicated cells. Boxplot:  $n=4$ ; \*\* $p<0.01$ , \*\*\* $p<0.001$  by Student's  $t$ -test. **(b)** MCF7 and 231 cells were treated with DMF or 10  $\mu$ M cisplatin for 5 days. Immunofluorescence was then performed to detect the expression and subcellular localization of Tip60. The nuclei were counterstained with Hoechst 33342. Scale bar: 20  $\mu$ m. The images are representative of three experiments with similar results.



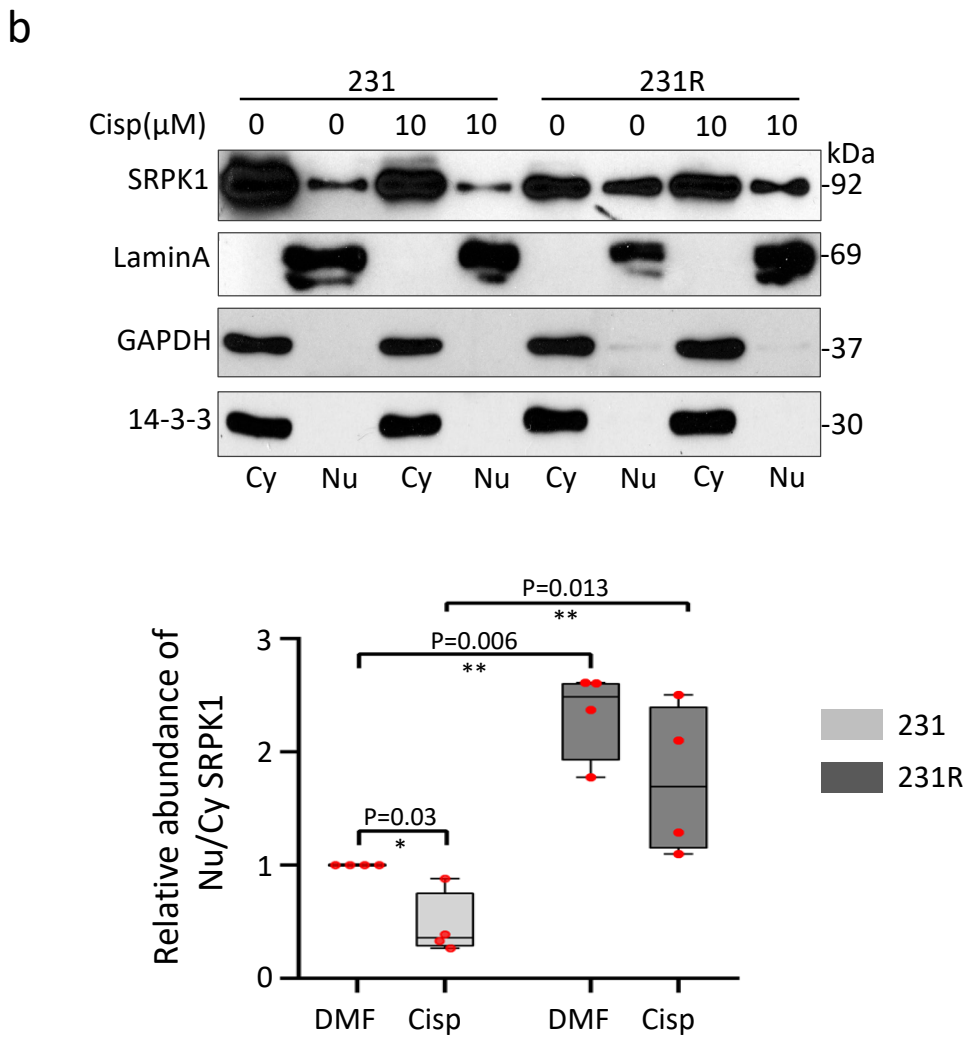
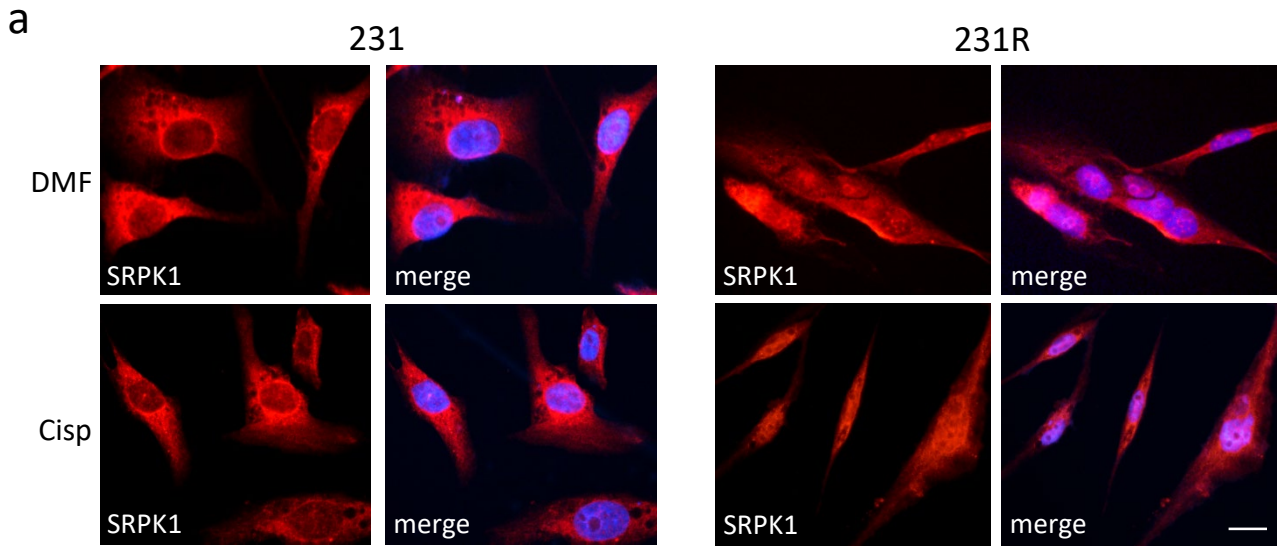
**Supplementary Figure 6. The effect of carboplatin and oxaliplatin on Tip60 expression.**

(a) 231 and 231R cells were treated with carboplatin or oxaliplatin. The cell survival was then assessed by the MTS viability assay. The reading was normalized to DMSO-treated cells. Data points: mean  $\pm$  SD; n=3. (b) The IC<sub>50</sub> of carboplatin and oxaliplatin for the indicated cell lines was calculated using the Hill equation. Boxplot: n=4; \*\* $p$ <0.01 by Student's *t*-test. (c) The cells were treated with the indicated doses of carboplatin and oxaliplatin for 2 days and the protein level of Tip60 was checked by immunoblotting. The blots are representative of three experiments with similar results.

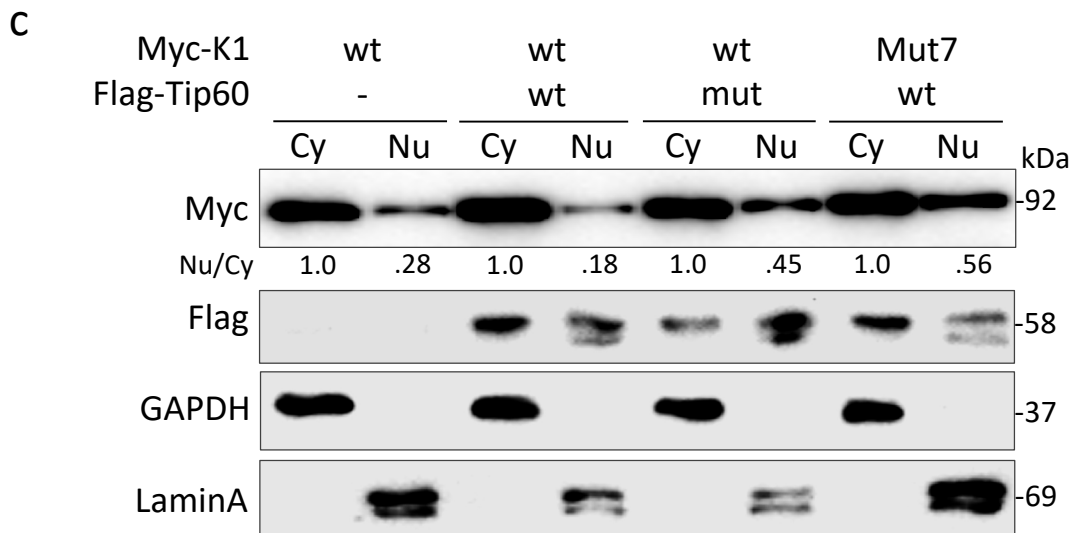
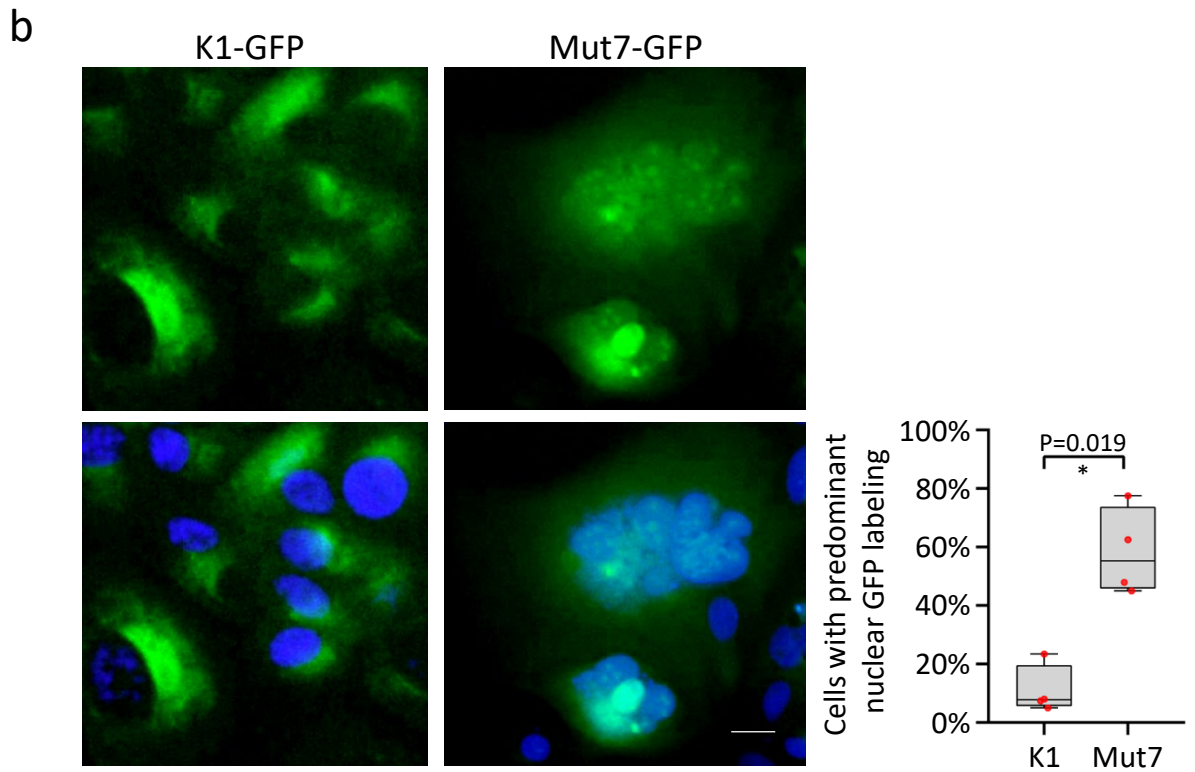
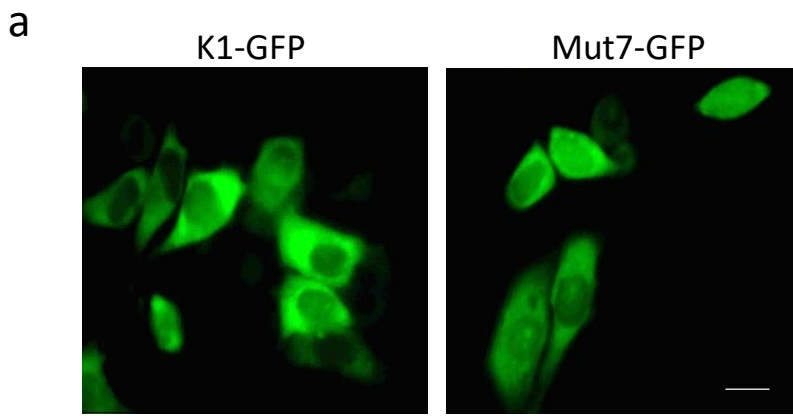


**Supplementary Figure 7. The activation status of AKT/mTOR in 231 and 231R cells.**

The indicated cells were treated with DMF or 10 μM cisplatin for 5 days. Then the cells were subject to immunoblotting to detect the activation of AKT and mTOR with indicated antibodies. The decimals below the gel strips denote the relative abundance of phosphorylated AKT (pAKT) or phosphorylated mTOR (p-mTOR) against the respective total protein. The blots are representative of three experiments with similar results.

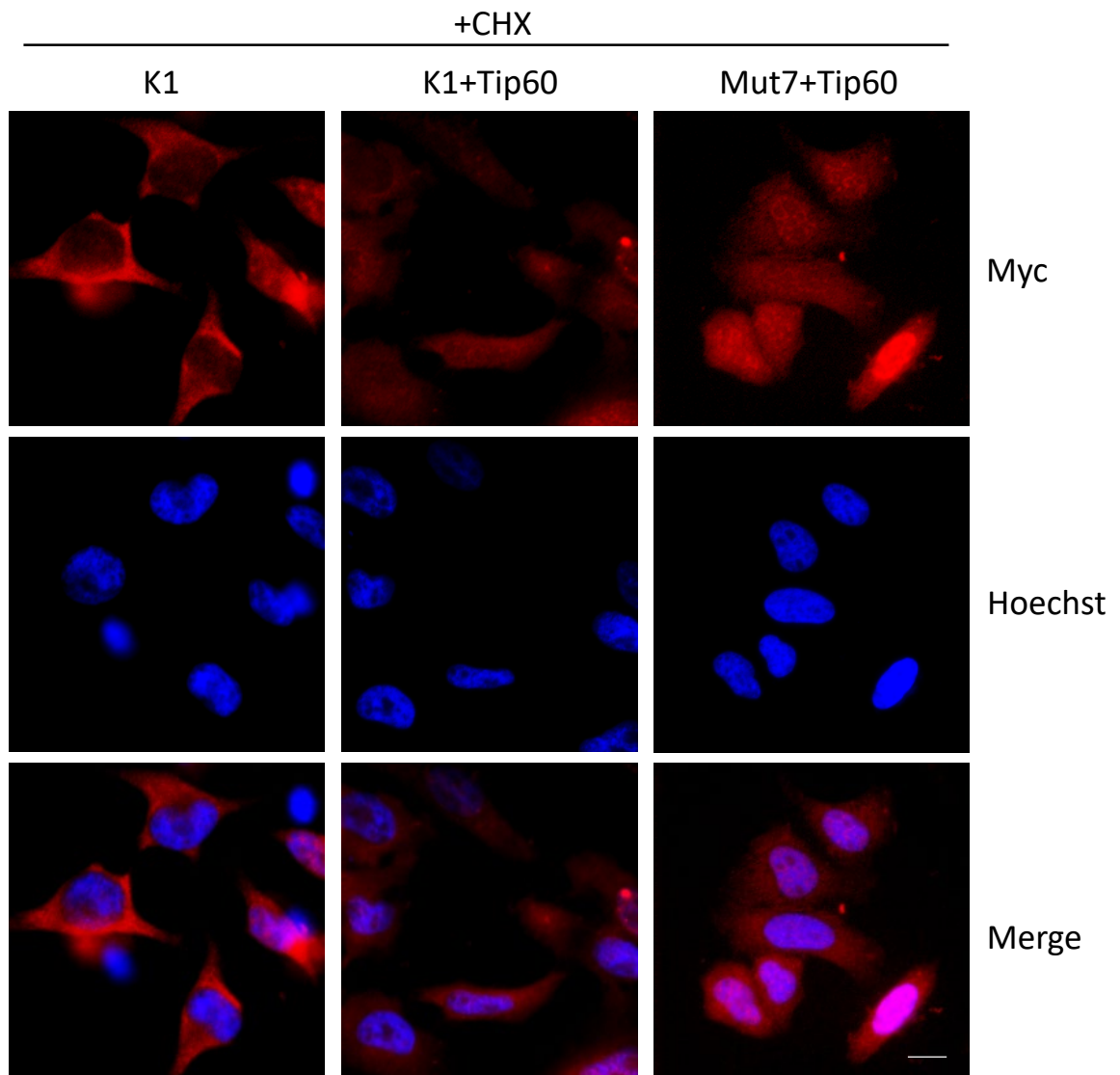


**Supplementary Figure 8. Acetylation could affect the subcellular localization of SRPK1.** (a) 231 and 231R cells were treated with cisplatin for 5 days and immunostained for SRPK1. The nuclei were counterstained with Hoechst 33342. Scale bar: 20  $\mu\text{m}$ . The images are representative of three experiments with similar results. (b) Cisplatin-treated 231 and 231R cells were fractionated into cytoplasmic (Cy) and nuclear (Nu) portions. The relative abundance of SRPK1 in each fraction was assessed by immunoblotting. LaminA was used as the marker for the nuclear fraction; GAPDH and 14-3-3 $\beta$  for the cytoplasmic fraction. The blots are representative of four experiments with similar results. The Nu/Cy ratio was normalized against the “231+DMF” group. Boxplot: n=4; \* $p$ <0.05, \*\* $p$ <0.01 by Student’s *t*-test.

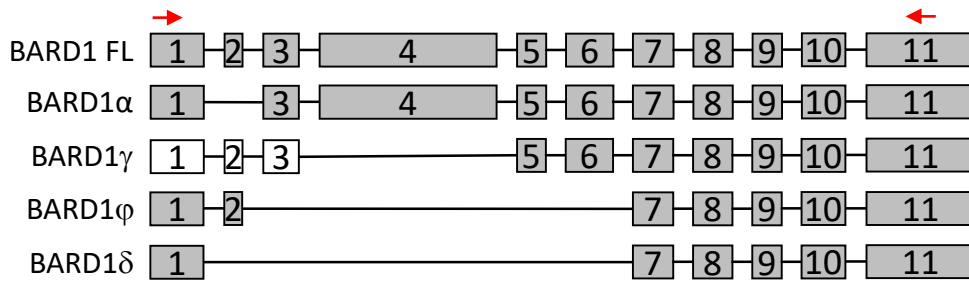
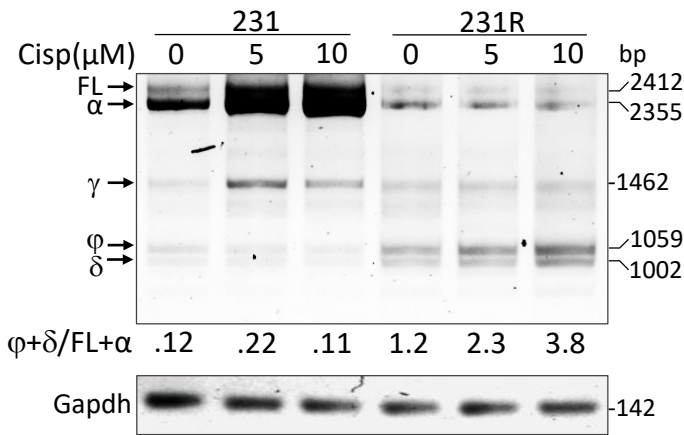
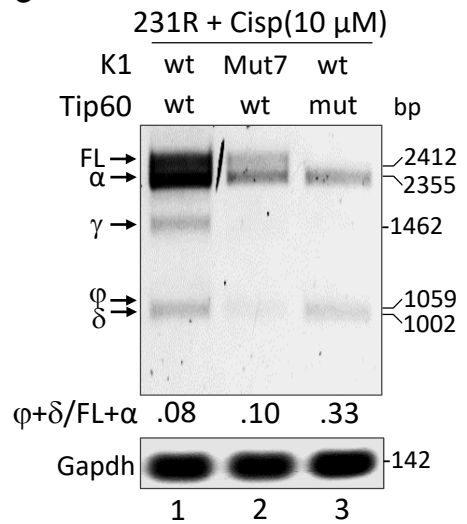
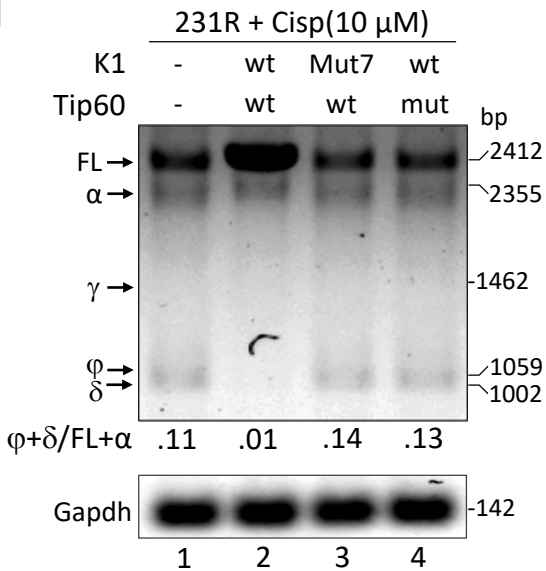




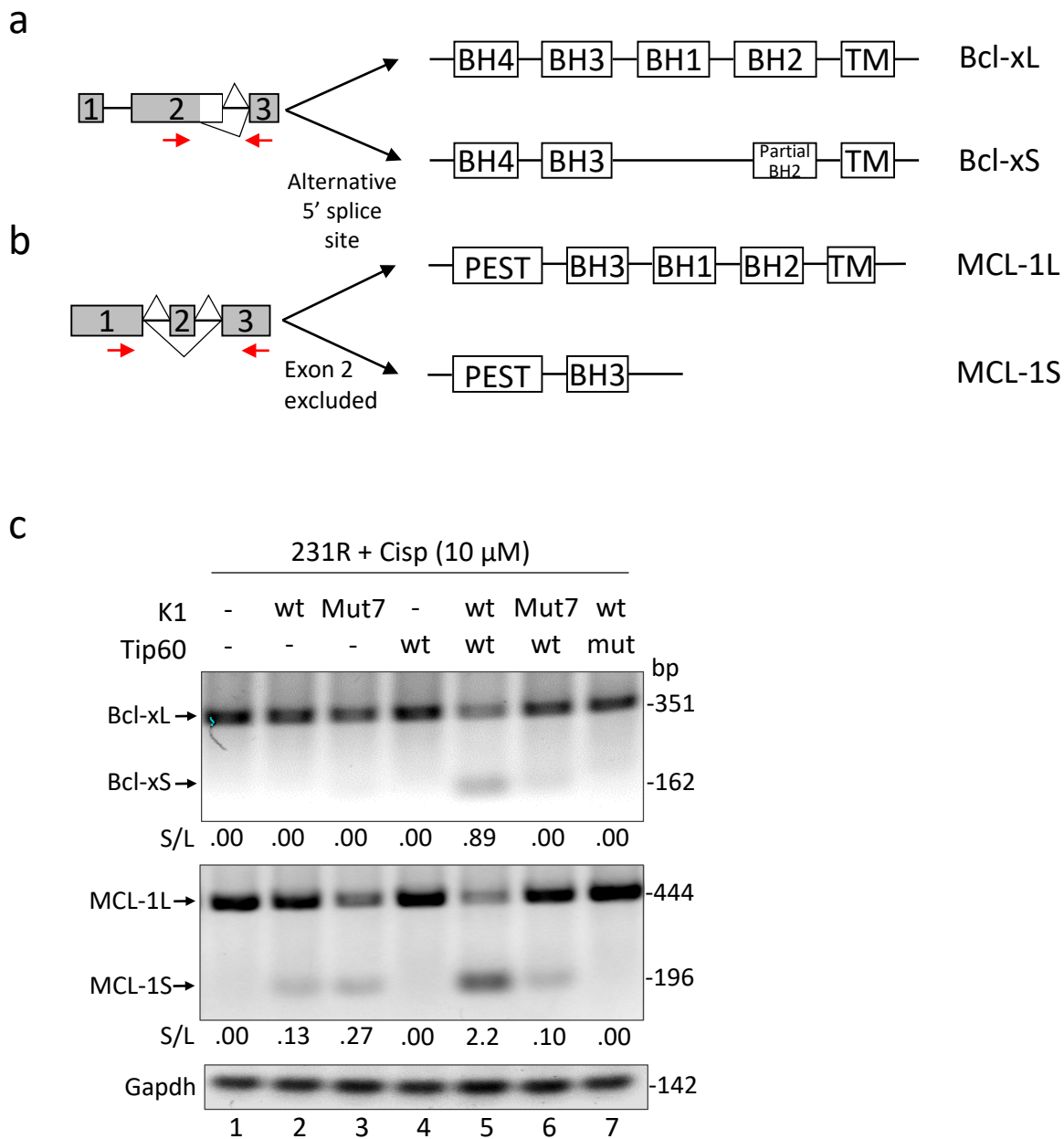
**Supplementary Figure 9. Acetylation could affect the subcellular localization of SRPK1.** (a) HeLa were transfected with GFP-tagged SRPK1 (K1-GFP) or Mut7 (Mut7-GFP). The subcellular localization of GFP signals was examined by the live cell imaging. (b) MCF-7 cells were similarly transfected as HeLa in (a). The cells were then fixed and the nuclei counterstained with Hoechst 33342. Scale bar: 20  $\mu$ m. Boxplot: n=4; \* $p$ <0.05 by Student's  $t$ -test. (c) HeLa cells were transfected with the indicated constructs and subjected to cytoplasmic (Cy) and nuclear (Nu) fractionation. The lysates were then analysed by immunoblotting to study the subcellular localization of overexpressed Myc-tagged SRPK1 (Myc-K1). GAPDH and LaminA were used as markers for the cytoplasmic and nuclear fractions, respectively. The decimals below the gel strip of anti-Myc denote the relative abundance of nuclear vs. cytoplasmic SRPK1. wt: wild-type; mut: HAT-deficient Tip60; Mut7: acetylation-deficient SRPK1. For immunofluorescence images in panels (a, b) and Western blots in (c), they are representative of four and three experiments with similar results, respectively.



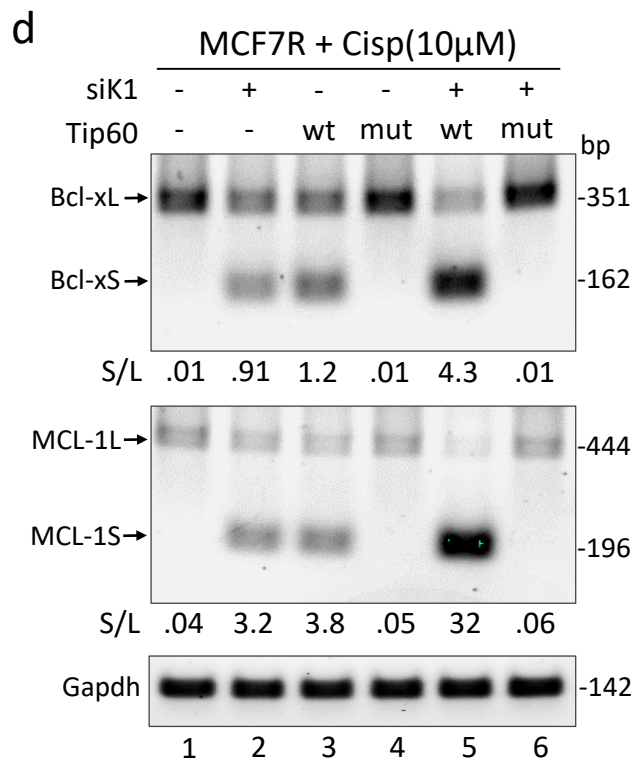
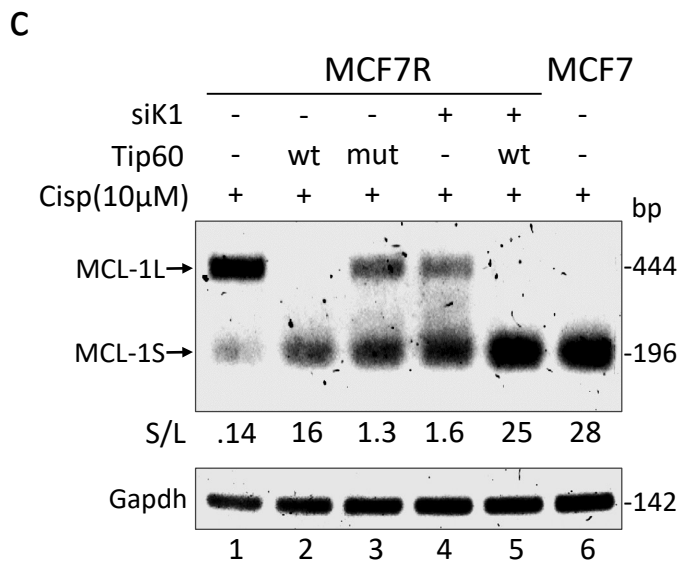
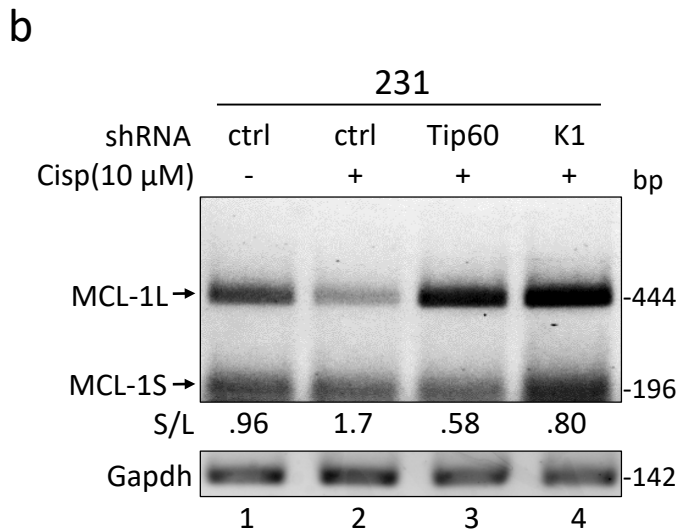
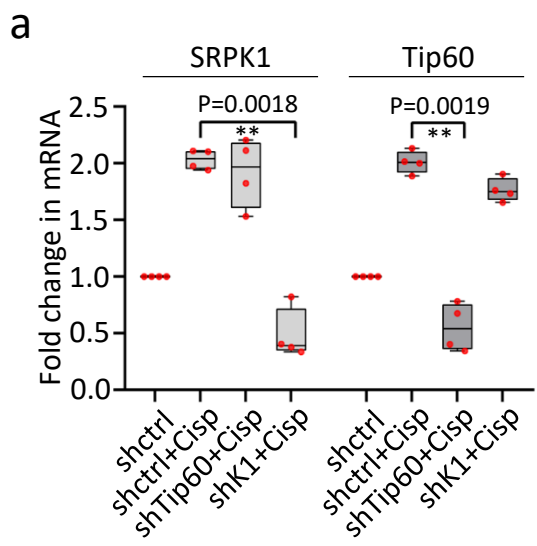
**Supplementary Figure 10. The protein stability of SRPK1 was affected by acetylation.** 293T cells were transfected with Myc-tagged SRPK1 (K1) or Mut7 and Tip60 as indicated. The cells were then immunostained with the c-Myc antibody. The nuclei were counterstained with Hoechst 33342. Scale bar: 5  $\mu$ m. The images are representative of three experiments with similar results.

**a****b****c****d**

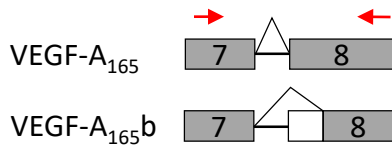
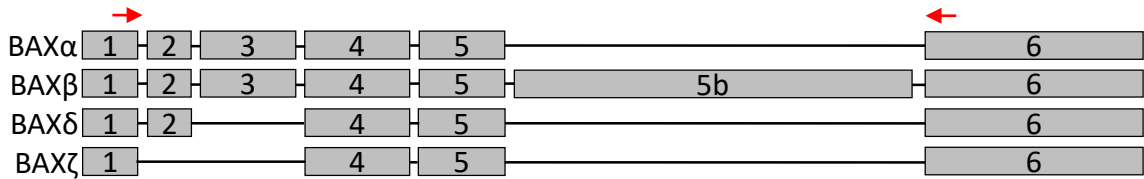
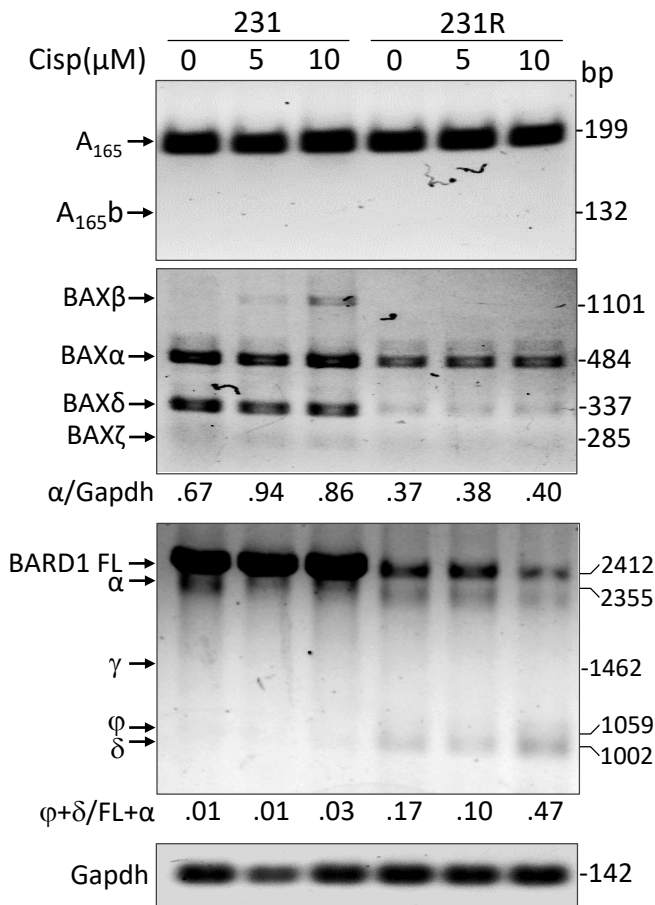
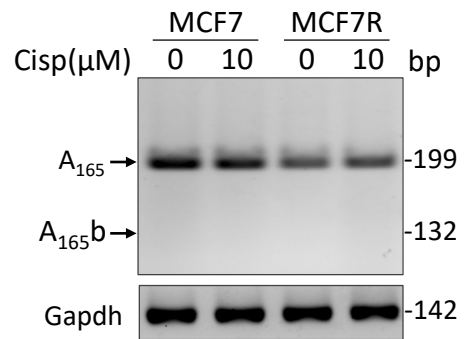
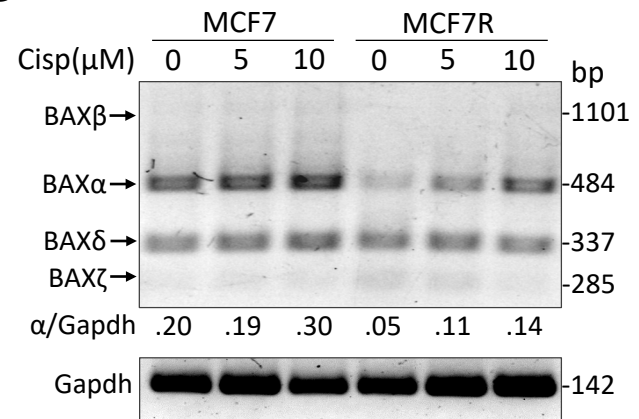
**Supplementary Figure 11. Alternative splicing of *BARD1* in the parental and cisplatin-resistant cells.** (a) Schematic structures of *BARD1* and its splice variants. The red arrows indicate the primers used for PCR. The grey boxes indicate coding exons and white boxes noncoding exons. (b) 231 and 231R cells were treated with cisplatin of indicated concentrations for 5 days. The transcript levels of *BARD1* splice variants were checked by RT-PCR. (c, d) 231R cells were transfected with SRPK1 and Tip60 constructs as indicated and treated with cisplatin. The splicing of *BARD1* was then examined by RT-PCR. wt: wild-type; Mut7: acetylation-deficient SRPK1; mut: HAT-deficient Tip60. The decimals below the gel strips (b-d) denote the relative abundance of oncogenic variants versus tumour suppressive variants. The RT-PCR gel images in (b-d) are representative of three experiments with similar results.



**Supplementary Figure 12. Alternative splicing of *BCL2L1* and *MCL-1* could be affected by SRPK1 acetylation.** (a, b) Schematic structures of *BCL2L1*, *MCL-1* and their splice variants. The red arrows indicate the primers used for PCR. (c) 231R cells were transfected with SRPK1 and Tip60 constructs as indicated, and treated with cisplatin for 5 days. The levels of alternatively spliced variants of *BCL2L1*, *MCL-1* and *BARD1* were checked by RT-PCR. The decimals below the gel strips denote the relative abundance of pro-apoptotic versus anti-apoptotic variants. The RT-PCR gel images in (c) are representative of three experiments with similar results.

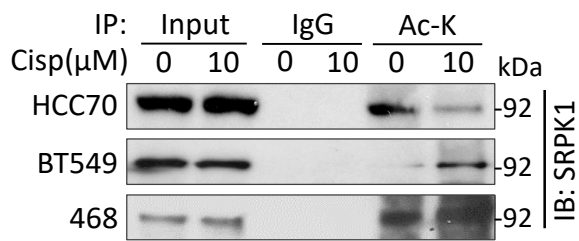
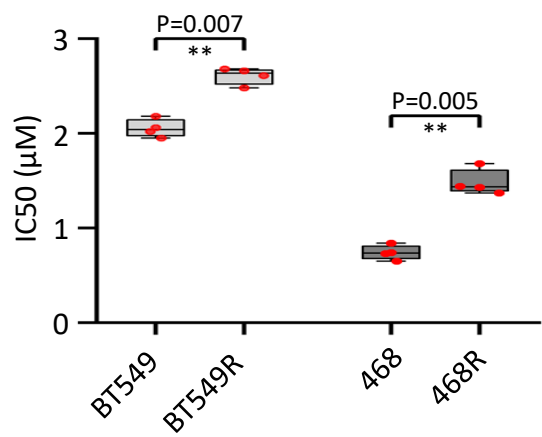
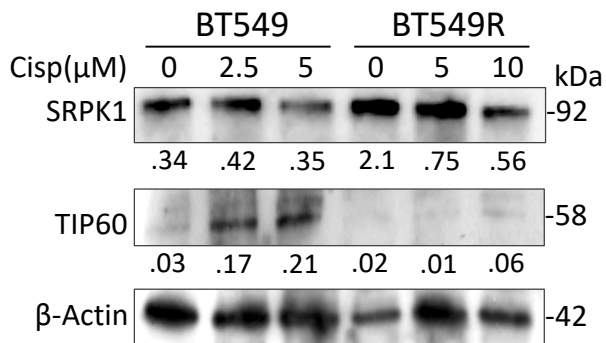
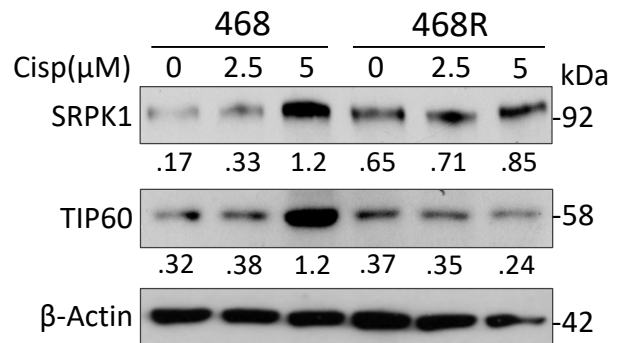
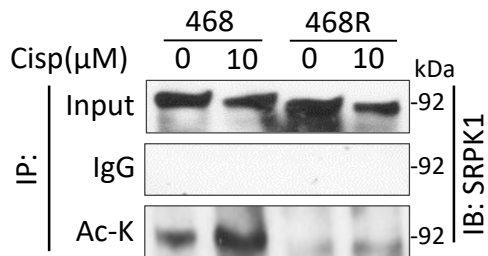
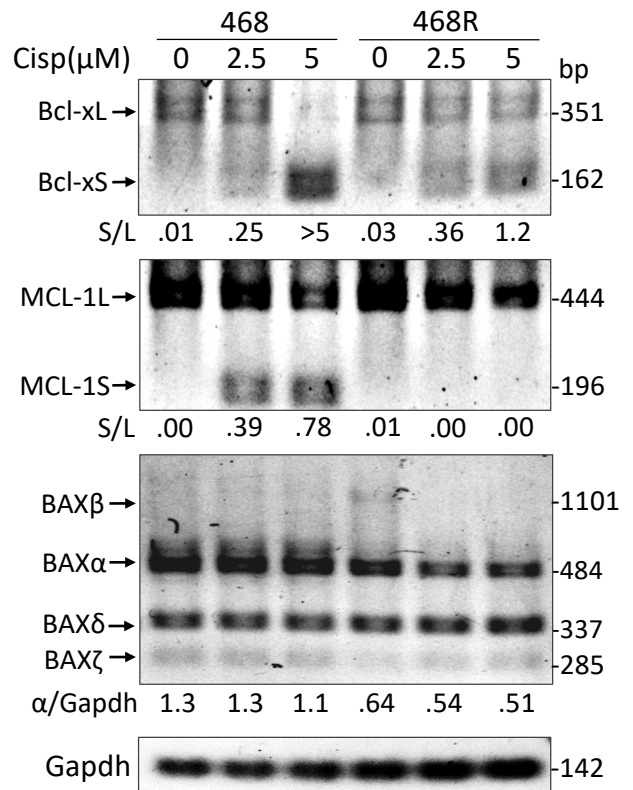


**Supplementary Figure 13. Alternative splicing of *BCL2L1* and *MCL-1* could be affected by SRPK1 acetylation.** (a) 231 cells were transfected with the shRNAs targeting Tip60 or SRPK1 and treated with cisplatin. The knockdown efficiency was then determined by qPCR. Boxplot: n=4; \*\* $p < 0.01$  as determined by Student's *t*-test. (b) 231 cells were transfected with shRNAs targeting Tip60 or SRPK1 and treated with cisplatin. The splicing of *MCL-1* was checked by RT-PCR. (c, d) MCF7R cell were transfected with the siRNA pool targeting SRPK1 (siK1) and Tip60 constructs as indicated, and then treated with cisplatin. The splicing of *MCL-1* and *BCL2L1* was evaluated by RT-PCR. MCF7 was included as a negative control. The decimals below the gel strips in (c, d) denote the relative abundance of short (S) versus long (L) variants. wt: wild-type Tip60; mut: HAT-deficient Tip60. The RT-PCR gel images in (b-d) are representative of three experiments with similar results.

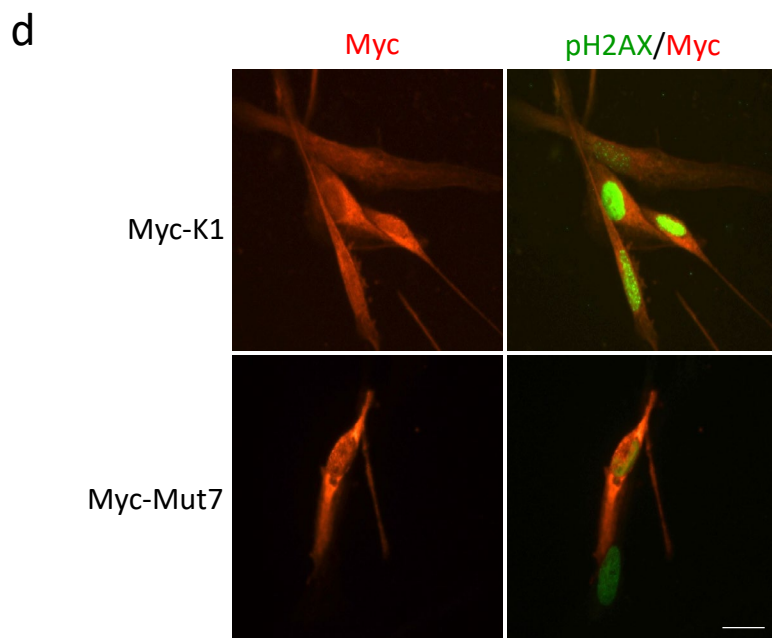
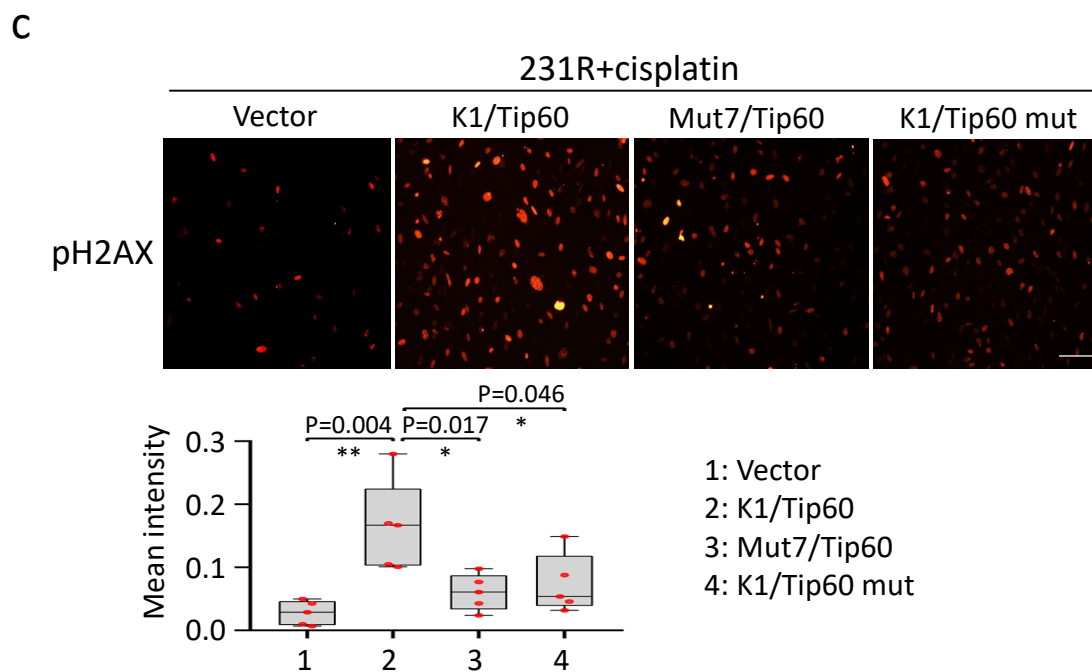
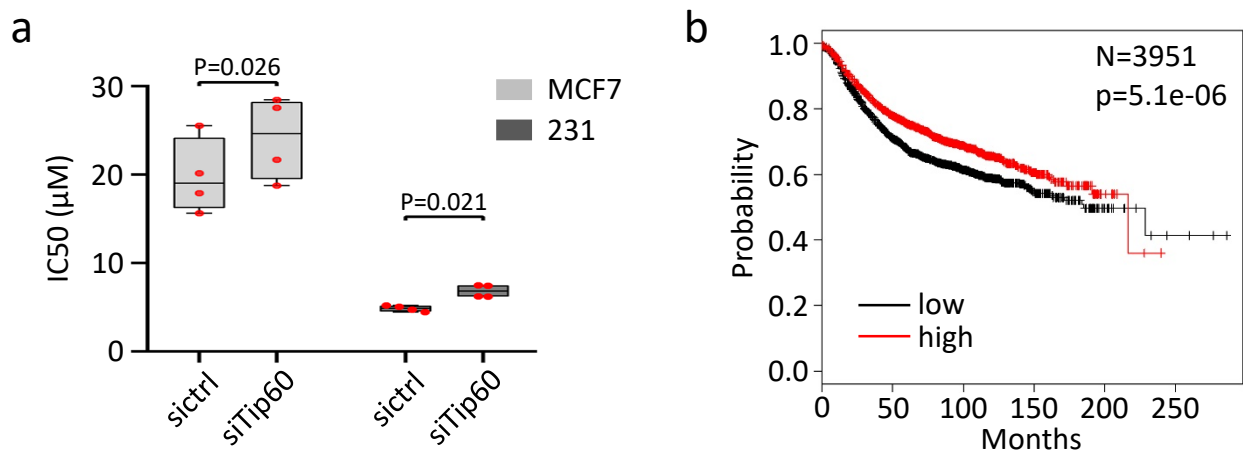
**a****b****c****d****e**



**Supplementary Figure 14. Alternative splicing of *VEGF-A<sub>165</sub>* and *BAX* in the parental and cisplatin-resistant cells.** (a, b) Schematic structures of *VEGF-A<sub>165</sub>* and *BAX*, and the respective splice variants. The red arrows indicate the primers used for PCR. The grey boxes indicate coding exons and white boxes noncoding stretch. (c) 231 and 231R cells were treated with cisplatin of indicated concentrations. The alternative splicing of *VEGF-A<sub>165</sub>* and *BAX*, as well as *BARD1* was examined by RT-PCR. (d, e) MCF7 and MCF7R cells were treated with cisplatin of indicated concentrations. The alternative splicing of *VEGF-A<sub>165</sub>* (d) and *BAX* (e) was examined by RT-PCR. The decimals below the gel strips in (c, e) denote the relative abundance of indicated variants. The RT-PCR gel images in (c-e) are representative of three experiments with similar results.

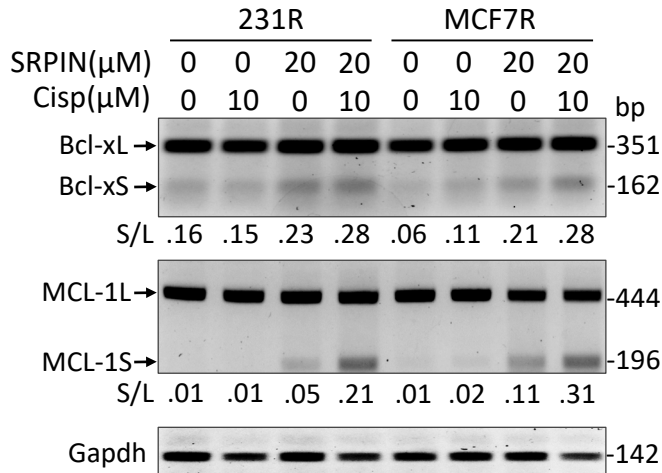
**a****b****c****d****e****f**

**Supplementary Figure 15. Acetylation of SRPK1 could be observed in multiple TNBC cells.** (a) HCC70, BT549 and 468 cells were treated with DMF or cisplatin for 2 days, then the acetylation of SRPK1 was assessed by immunoprecipitation with the Ac-K antibody. (b) The cell survival of parental and resistant BT549 or 468 cells was assessed by the MTS viability assay. Boxplot: n=4; \*\* $p < 0.01$  by Student's *t*-test. (c, d) BT549/BT549R (c) and 468/468R cells (d) were treated with DMF or cisplatin for 5 days. The protein levels of Tip60 and SRPK1 were determined by immunoblotting. The decimals below the gel strips denote the protein abundance in relative to  $\beta$ -Actin. (e) 468 and 468R cells were treated with DMF or cisplatin for 2 days. SRPK1 acetylation was then determined by using the Ac-K antibody in immunoprecipitation. (f) The splicing of *BCL2L1*, *MCL-1* and *BAX* in cisplatin-treated 468 and 468R cells was assessed by RT-PCR. The decimals below the gel strips denote the relative abundance of indicated variants. For Western blots in (a, c-e) and RT-PCR gel images in (f), they are representative of three experiments with similar results.

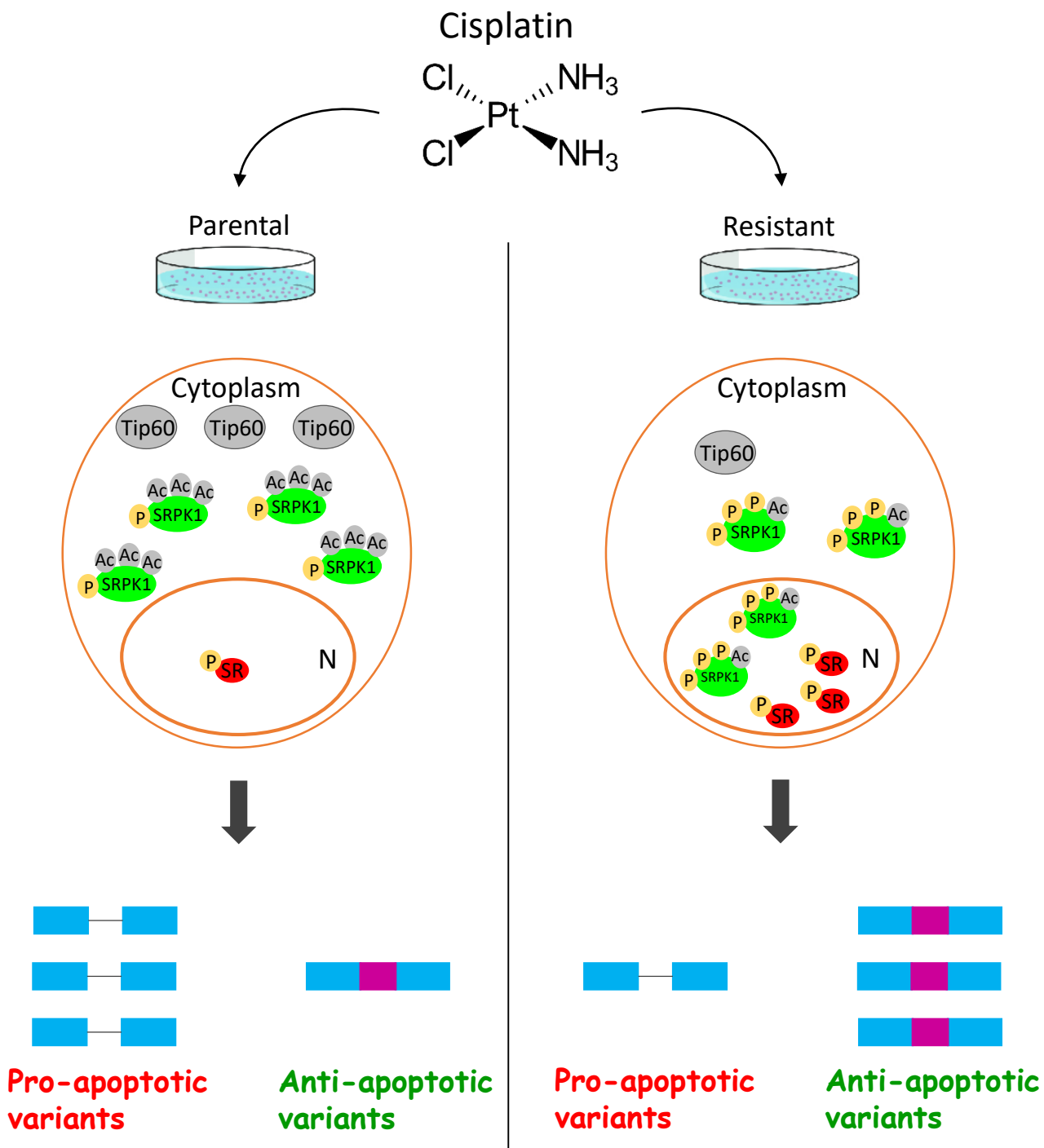


**Supplementary Figure 16. SRPK1 acetylation affected cellular response to cisplatin. (a)**

After Tip60 was knocked down in MCF7 and 231 cells, the IC50 of cisplatin was determined by MTS viability assays. Bars: mean  $\pm$  SD; n=3; \* $p$ <0.05 by Student's *t*-test. **(b)** Kaplan-Meier analyses of the survival probability of 3,951 breast cancer patients grouped by the high or low expression of Tip60. **(c)** 231R cells were transfected with SRPK1 and Tip60 constructs as indicated, and treated with cisplatin. The cells were then immunostained for pH2AX. Scale bar: 100  $\mu$ m. The mean fluorescence intensity was quantified from five random fields using Image J. Boxplot: n=5; \* $p$ <0.05, \*\* $p$ <0.01 by Student's *t*-test. **(d)** 231R cells were transfected with Myc-tagged SRPK1 or acetylation-deficient Mut7 and treated with cisplatin. The cells were double-stained for Myc and pH2AX. Scale bar: 20  $\mu$ m. The images are representative of three experiments with similar results.



**Supplementary Figure 17. Inhibition of SRPK1 activity could favor pro-apoptotic splicing.** 231R and MCF7R were co-treated with cisplatin and SRPIN340 as indicated. The alternative splicing of *BCL2L1* and *MCL-1* was assessed by RT-PCR. The decimals below the gel strips denote the relative abundance of short (S) versus long (L) variants. The RT-PCR gel images are representative of three experiments with similar results.



**Supplementary Figure 18.** The putative model. N: nucleus. P: phosphorylation. Ac: acetylation.

**Supplementary Table 1:** Primers used in RT-PCR and cloning of shRNA targeting SRPK1

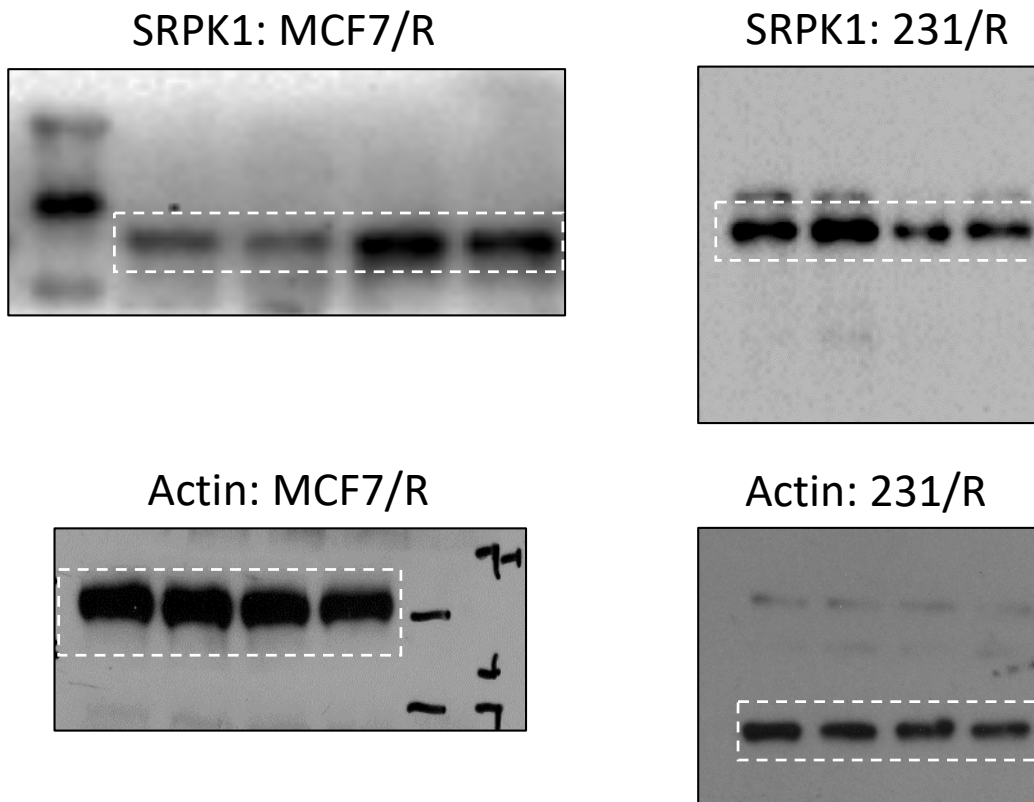
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BCL2L1-R	gcattgtcccatagagtcc
BARD1-F	gaggagcctttcatccgaaggc
BARD1-R	gctctcacaaccgtgcaaa
SRPK1-F	gtgtgccagtcttctcaactg
SRPK1-R	ggtcagcaatcttcacctgag
KAT5-F	gtttcaccagcaactccagtgc
KAT5-R	acggtattccatcagagctctcc
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VEGF-R	tcgttctgtatcagtctttctgg
BAX-F	cggggagcagcccaga
BAX-R	aaagtaggagaggaggccgt
GAPDH-F	aacatcatccctgccttactgg
GAPDH-R	gttttctagacggcaggtcagg
shSRPK1 sense	ccggcccattaggacatcctttaaactgcagtttaaaggatgtcctaattgggtttt
shSRPK1 antisense	aattaaaaaccattaggacatcctttaaactgcagtttaaaggatgtcctaattggg

F: forward primer; R: reverse primer

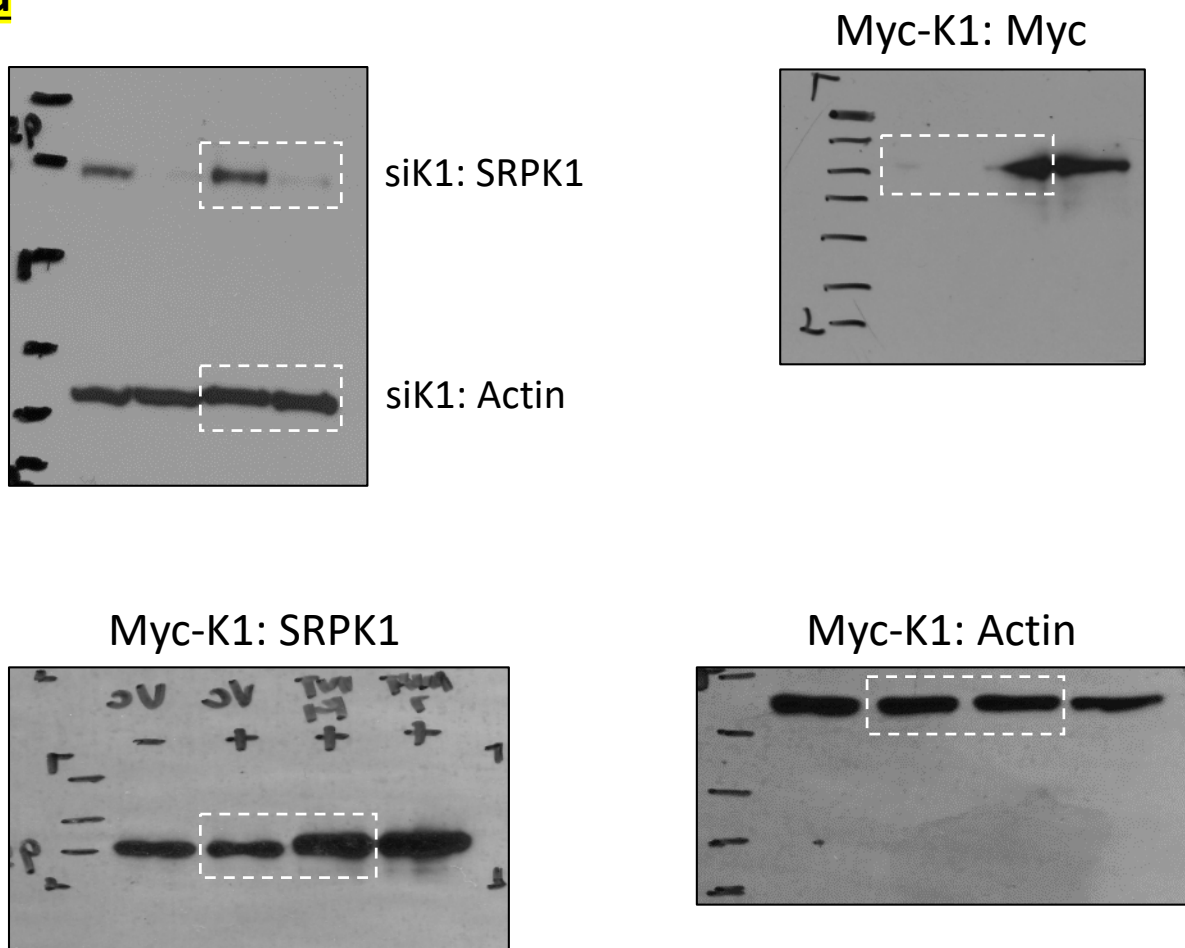


Uncropped blot and gel images

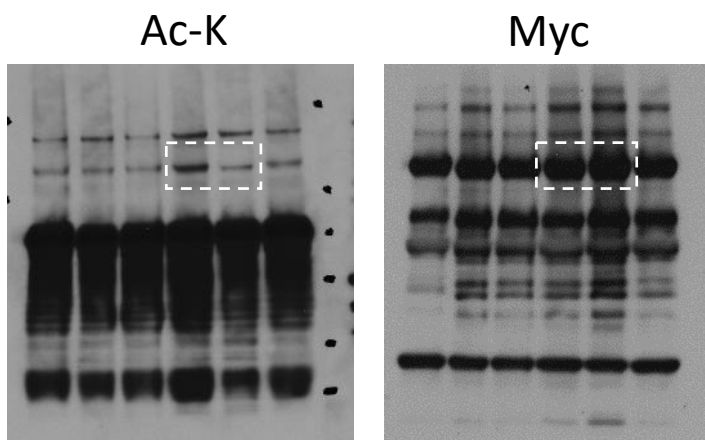
**Fig 1c**



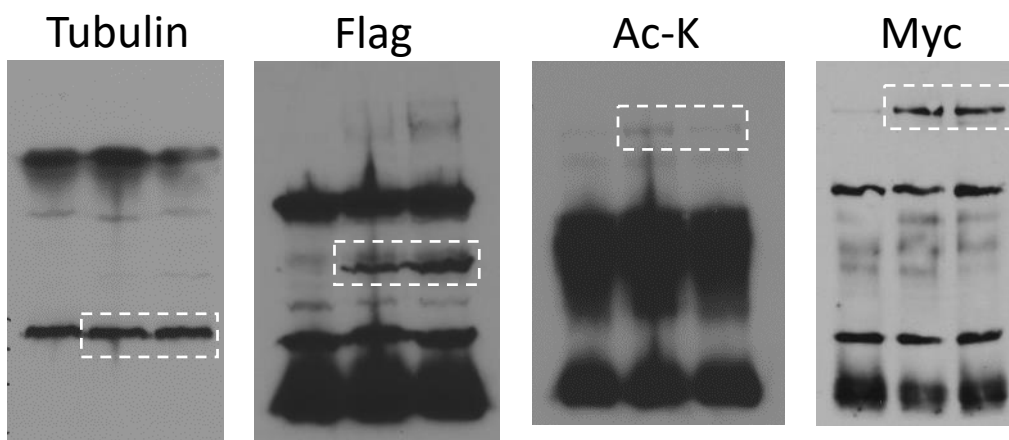
**Fig 1d**



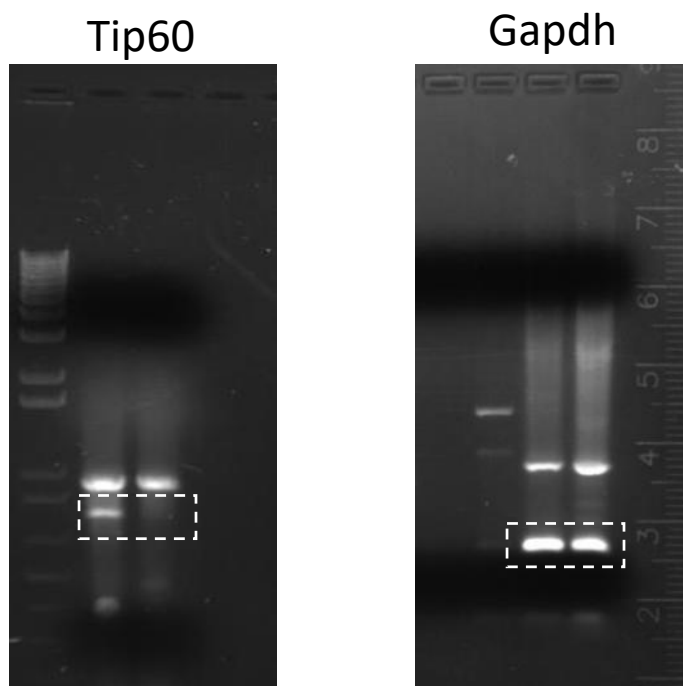
**Fig 2a**



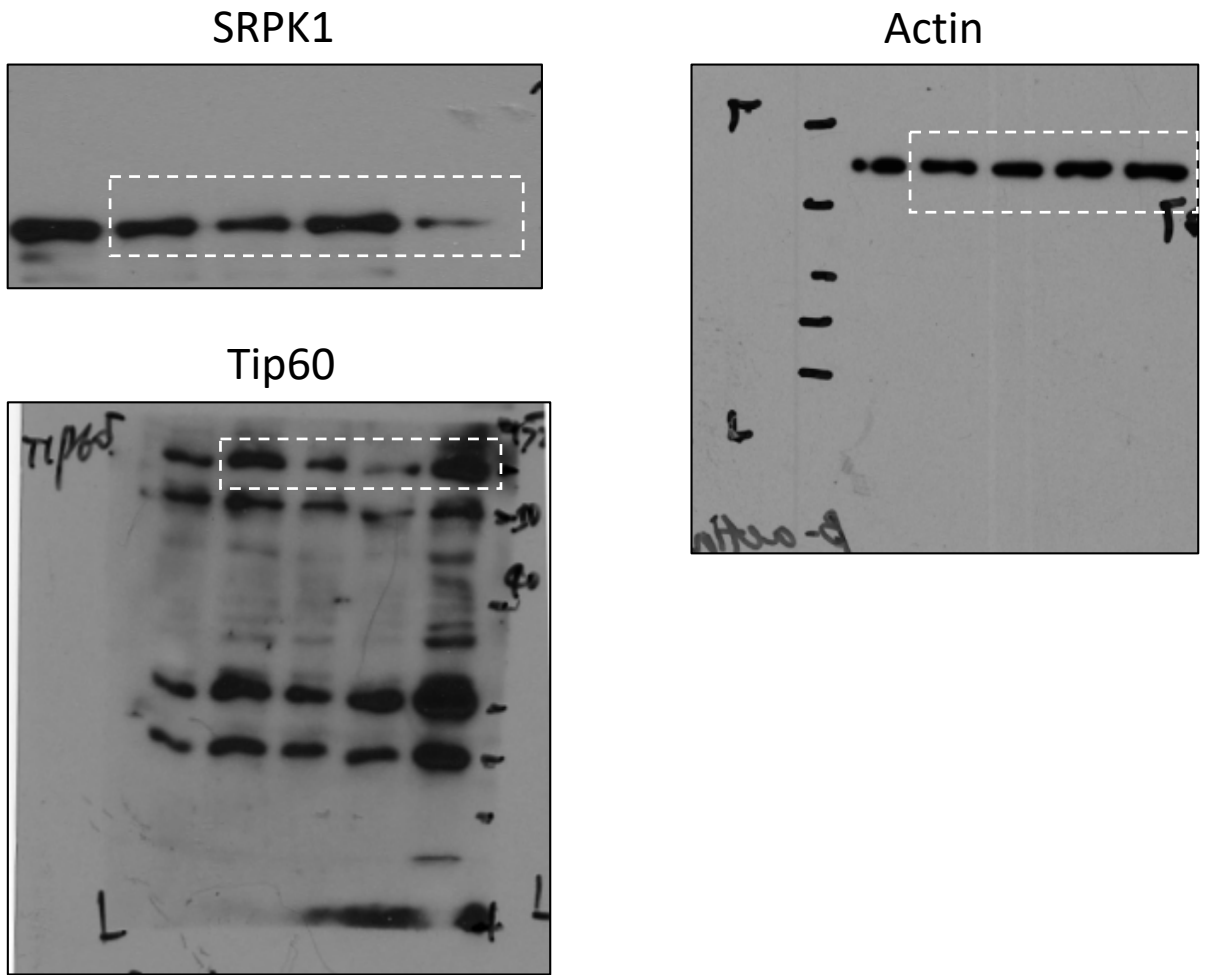
**Fig 2b**



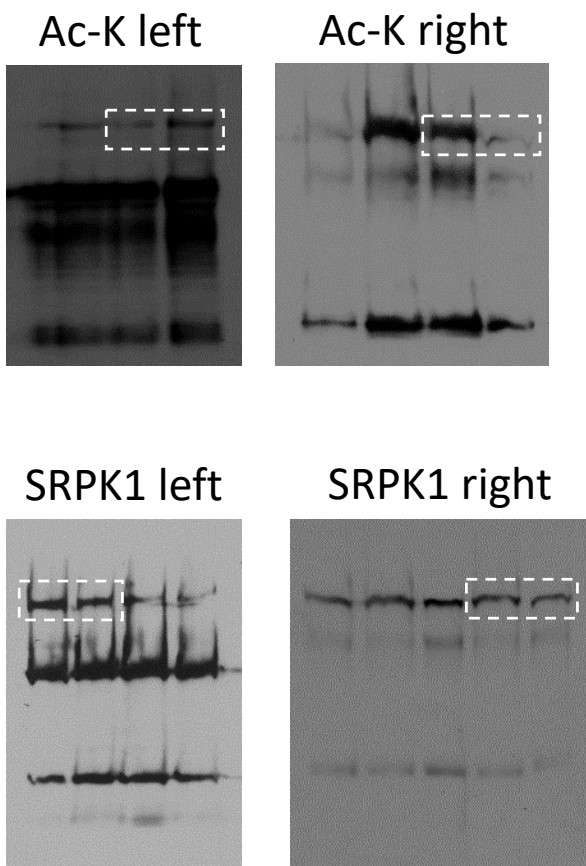
**Fig 2c**



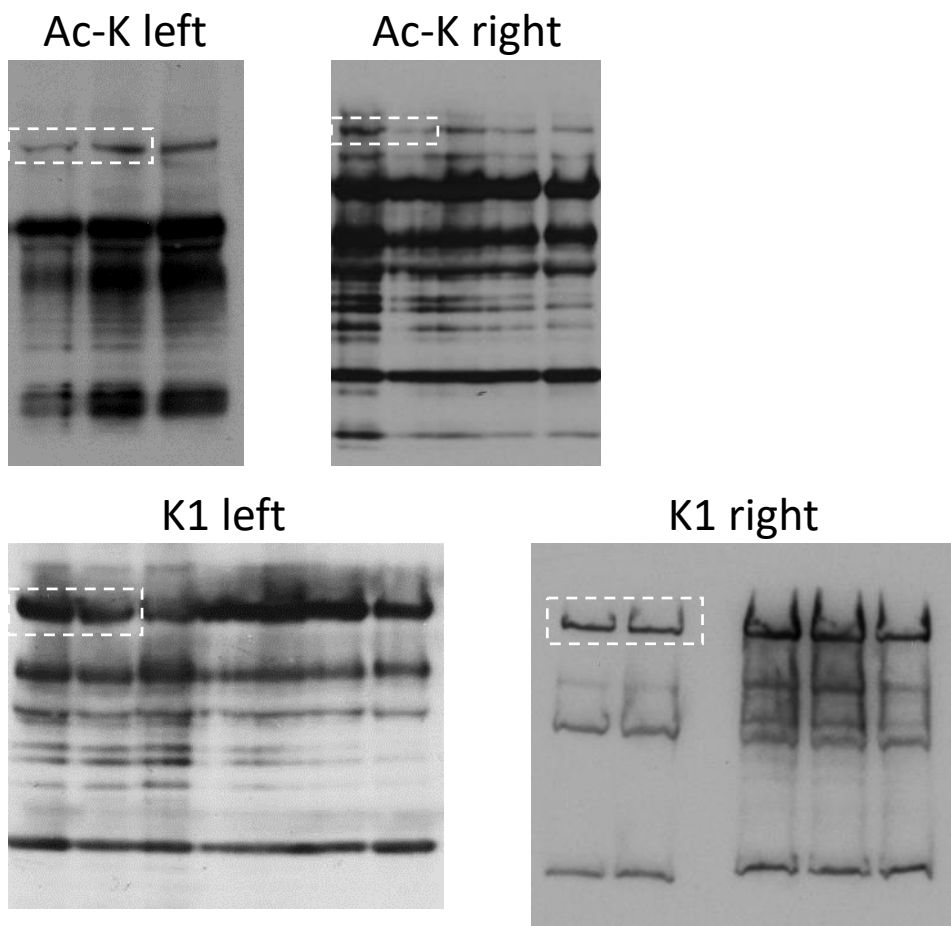
**Fig 2e**



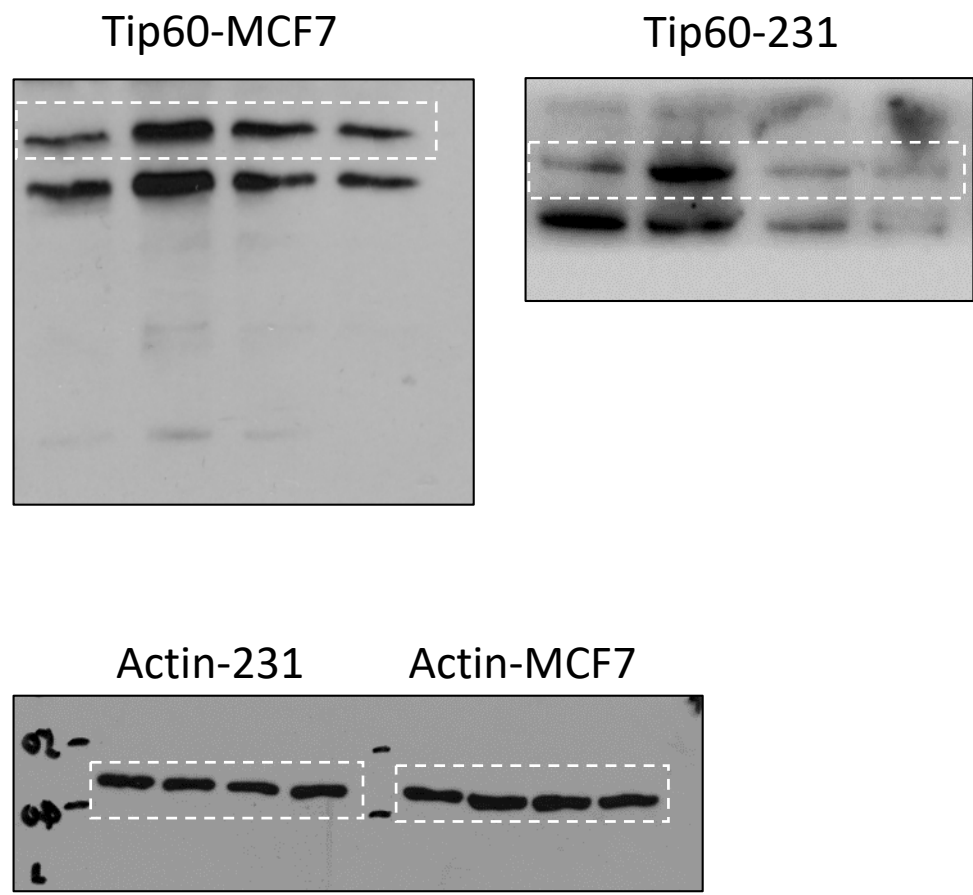
**Fig 2f**



**Fig 2g**

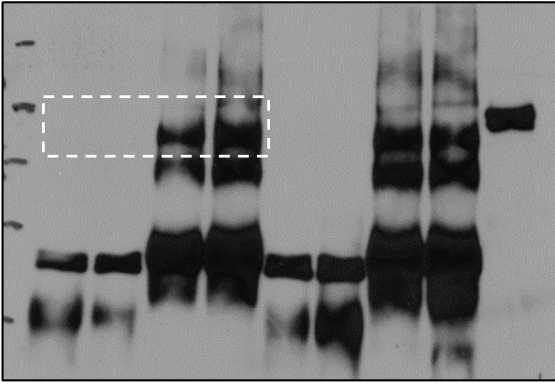


**Fig 2h**

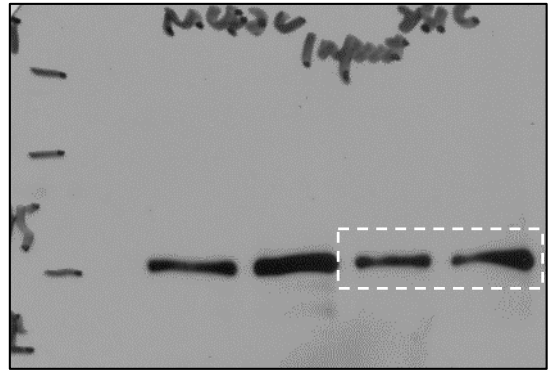


**Fig 2i**

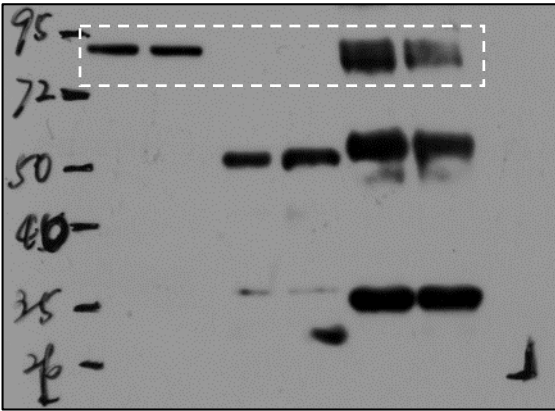
231 IP



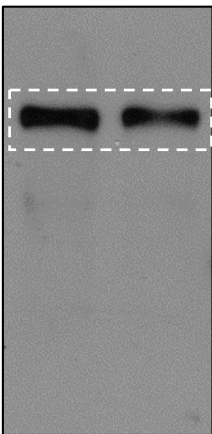
231 Input



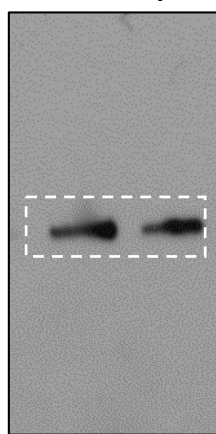
MCF7R



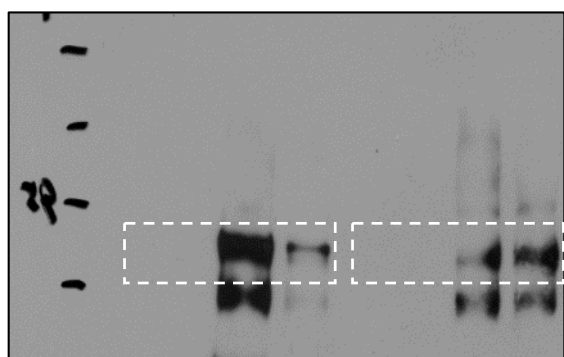
MCF7 Input



231R Input



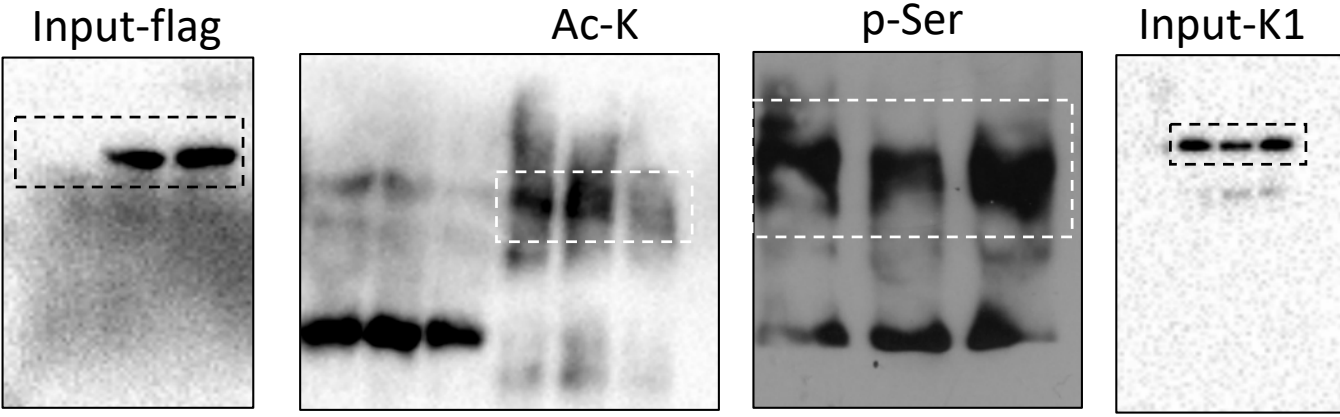
231R IP



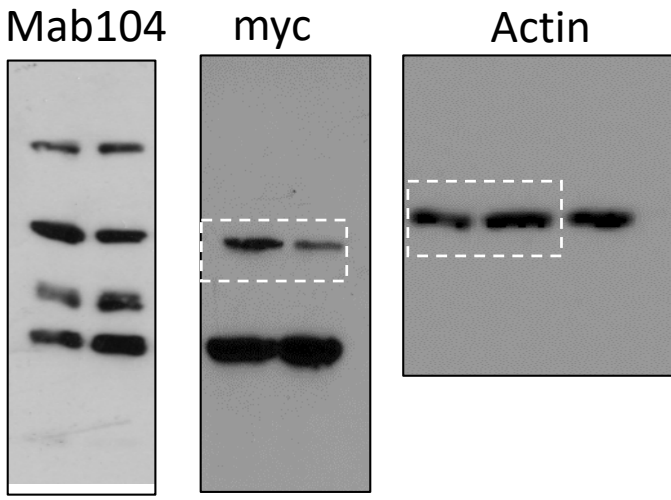
MCF7 IP



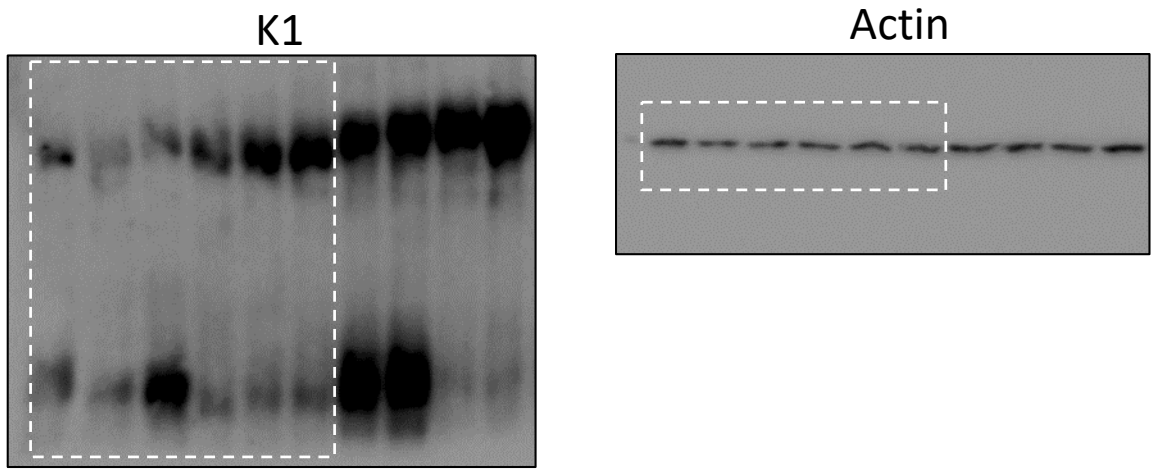
**Fig 3a**



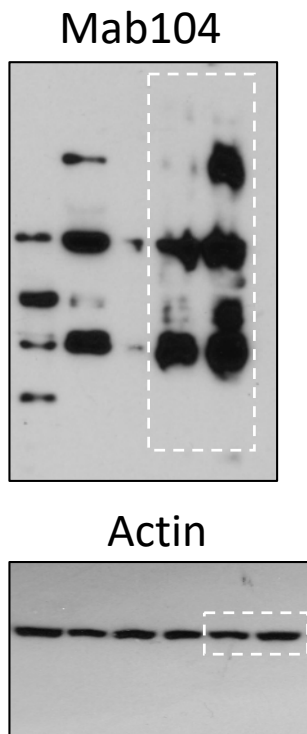
**Fig 3b**



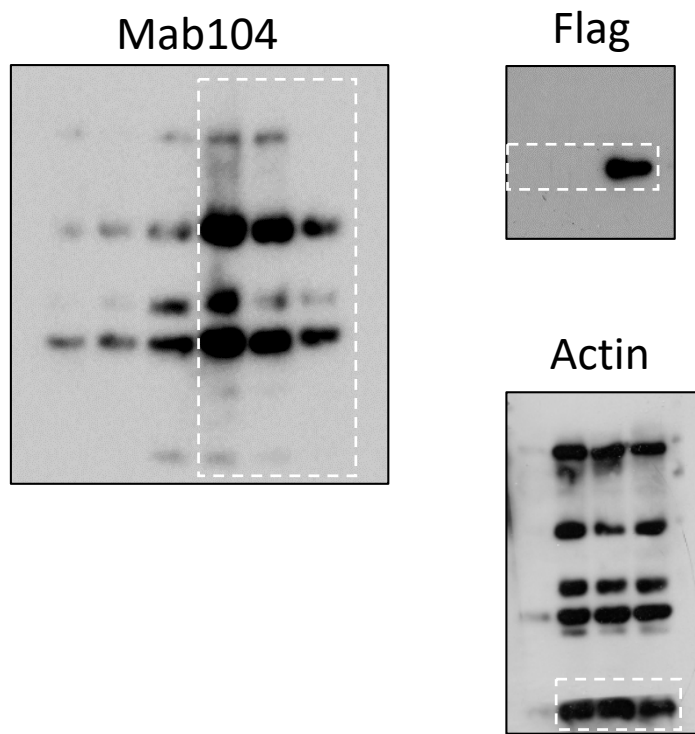
**Fig 3c**



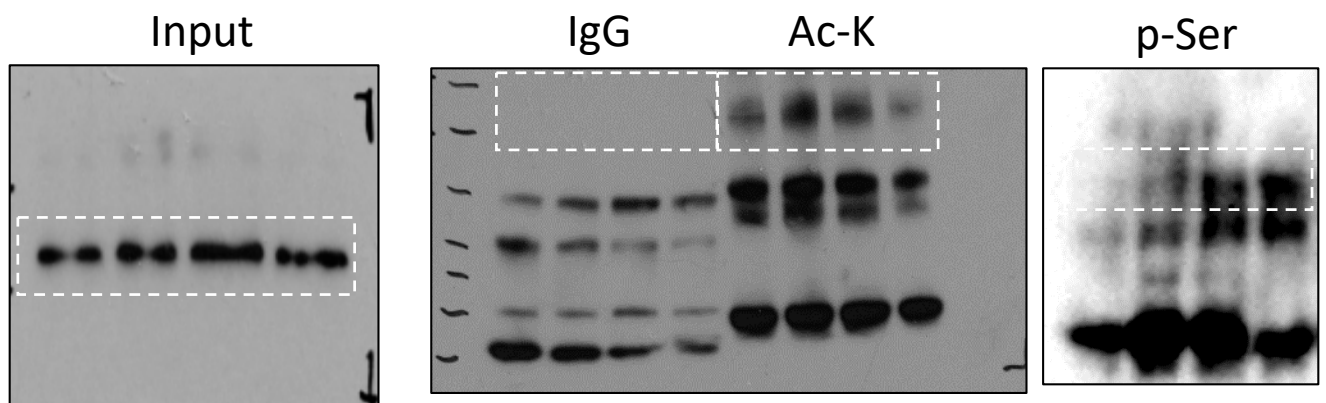
**Fig 3d**



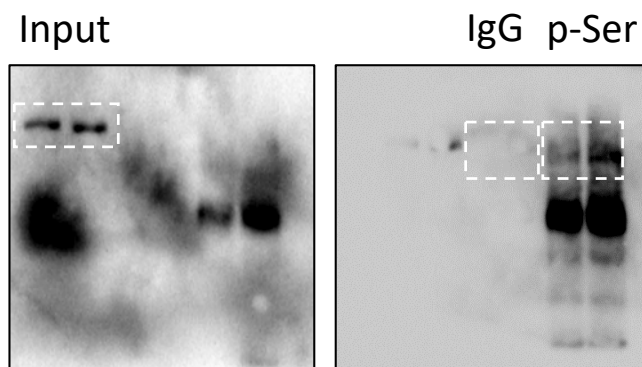
**Fig 3e**



**Fig 3f**

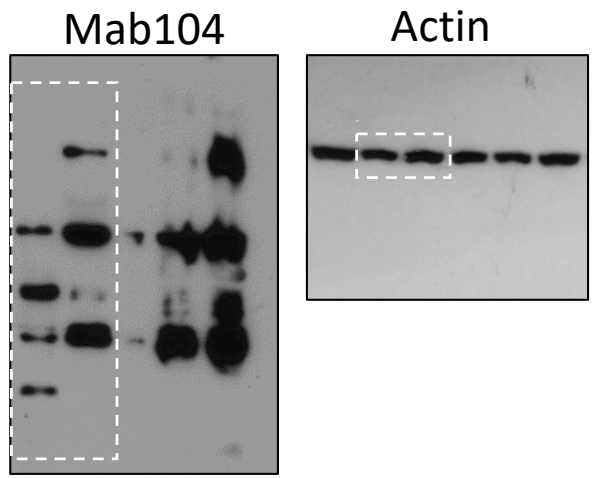


**Fig 3g**

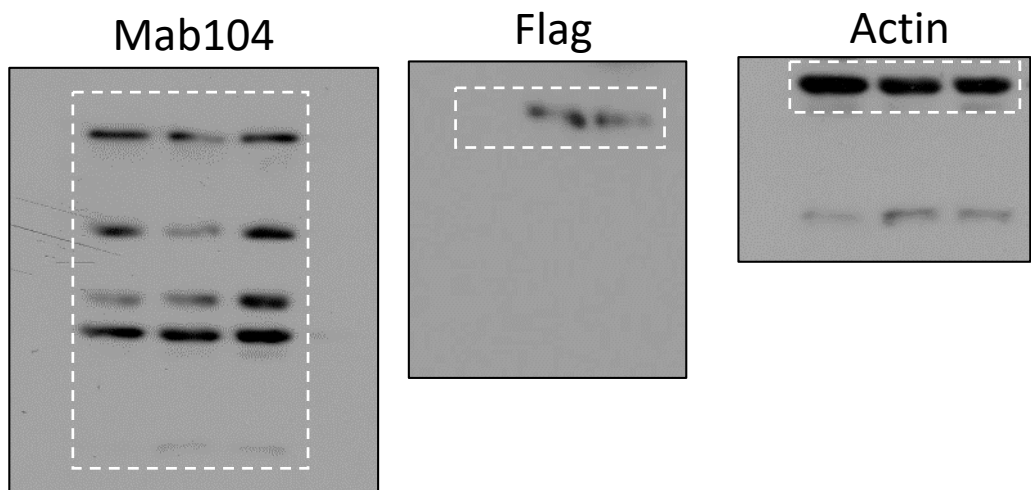




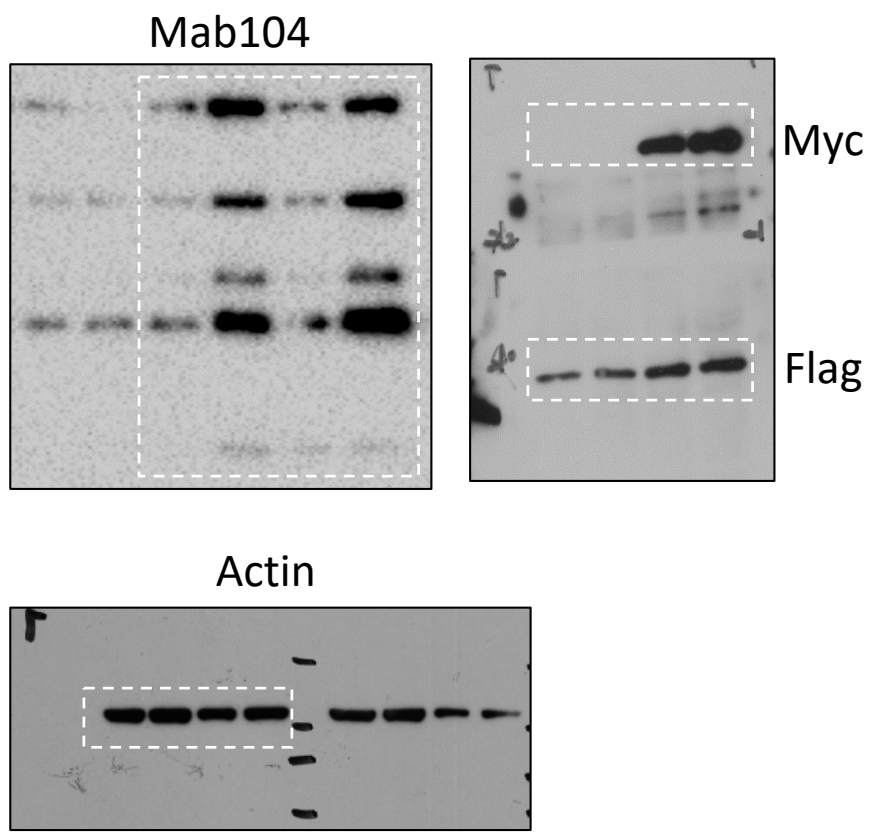
**Fig 3h**



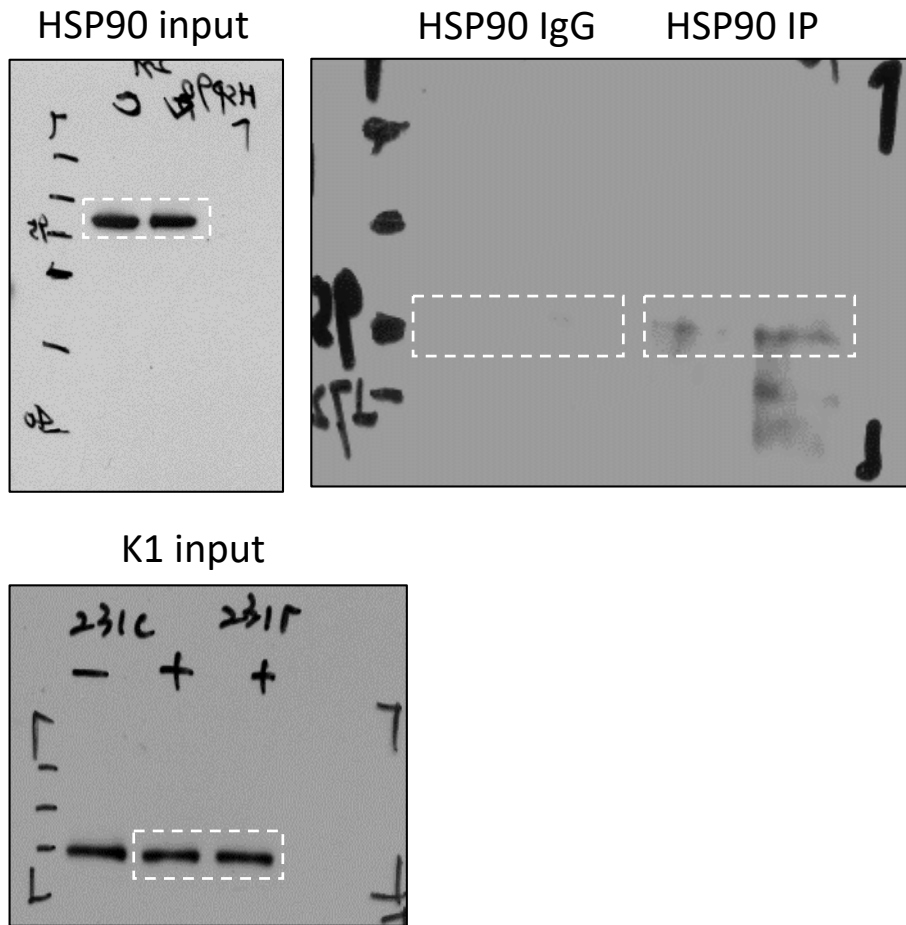
**Fig 3i**



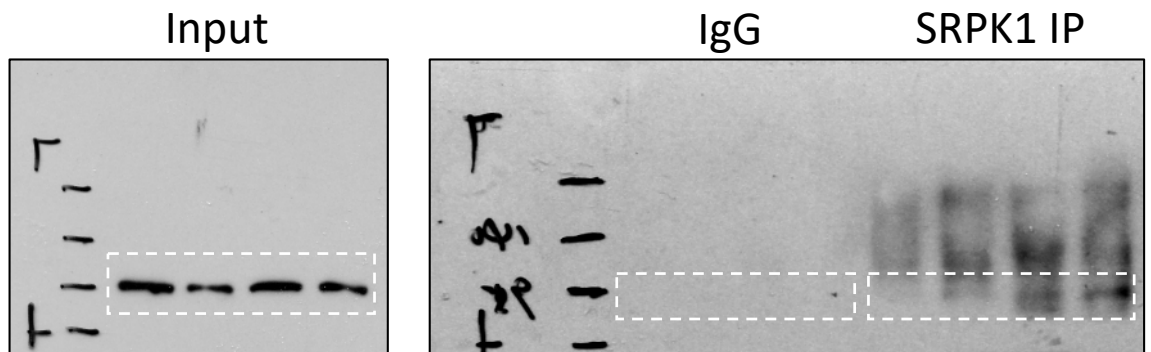
**Fig 3j**



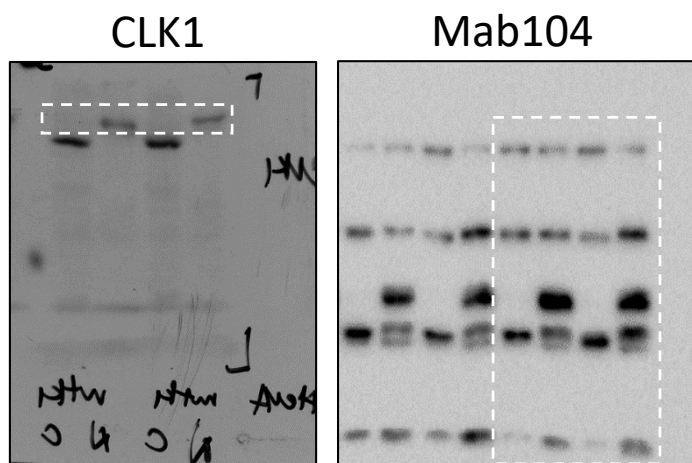
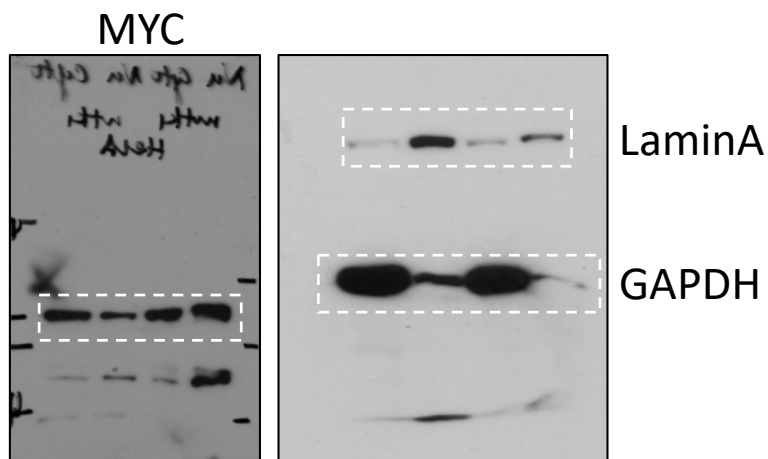
**Fig 4b**



**Fig 4c**

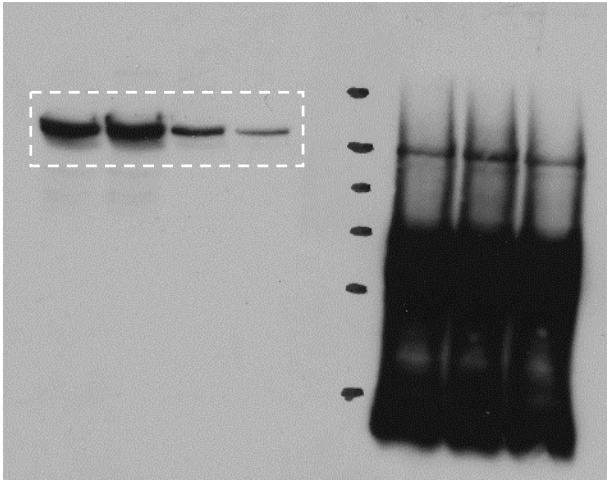


**Fig 4e**

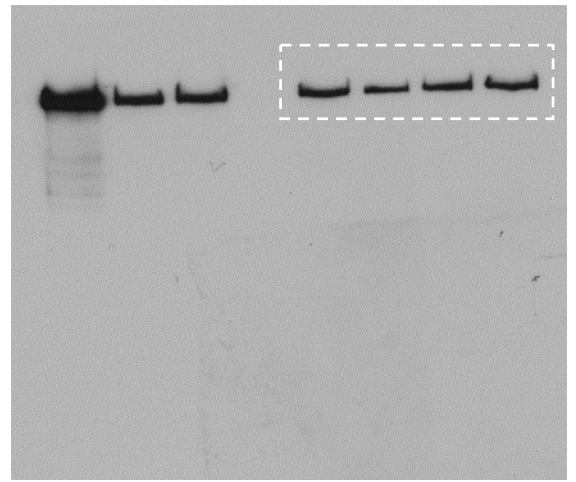


**Fig 5a**

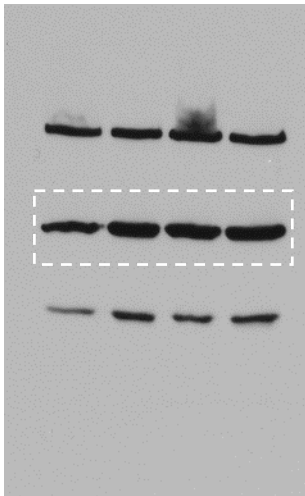
Myc left



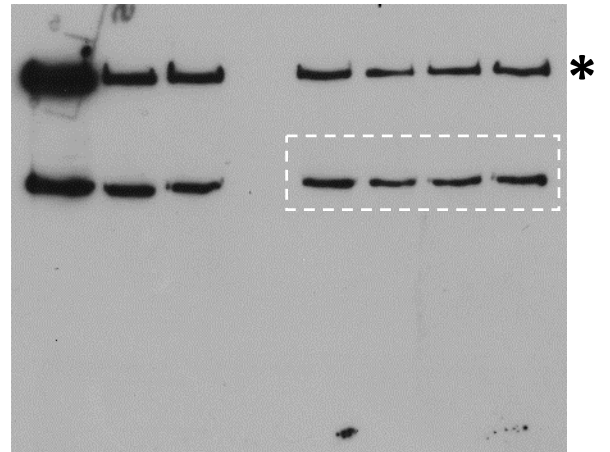
Myc right



Actin left

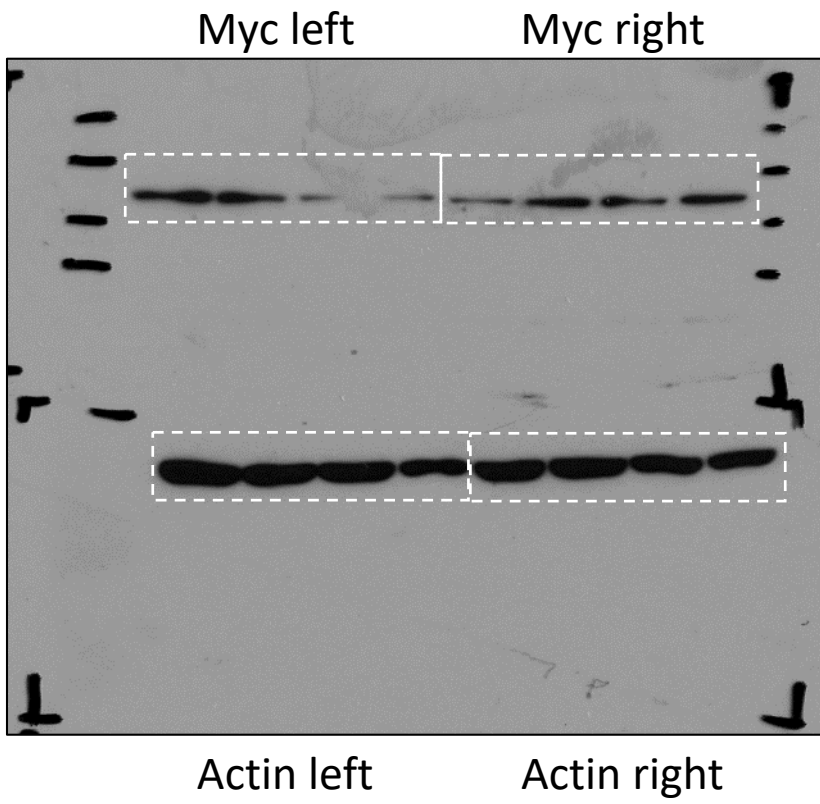


Actin right

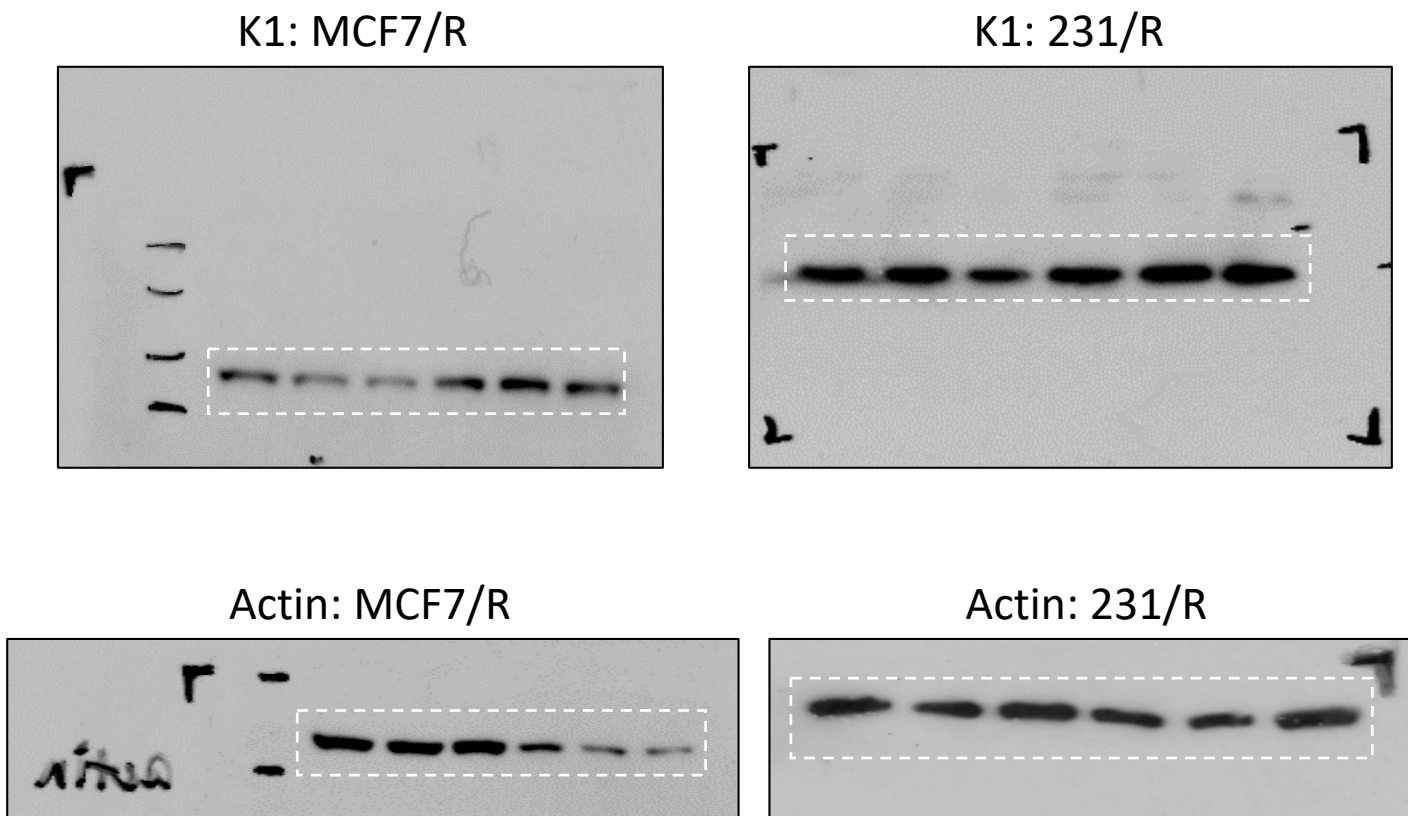


\* Incomplete stripping of anti-Myc signals carried over from the blot above

**Fig 5b**

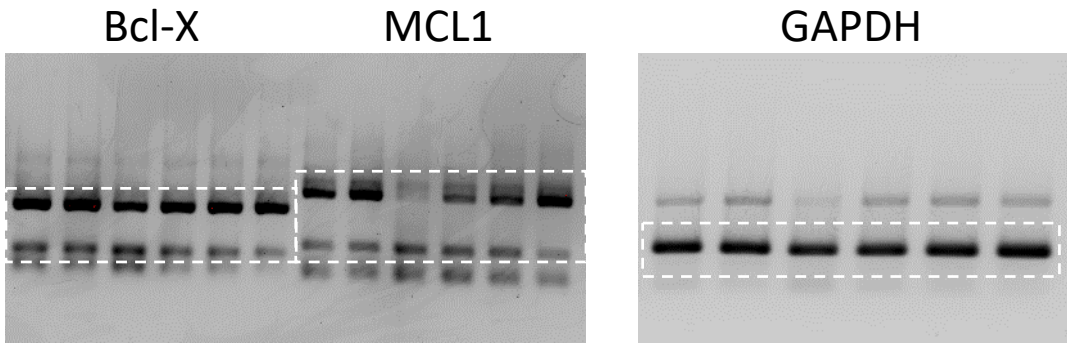


**Fig 5d**

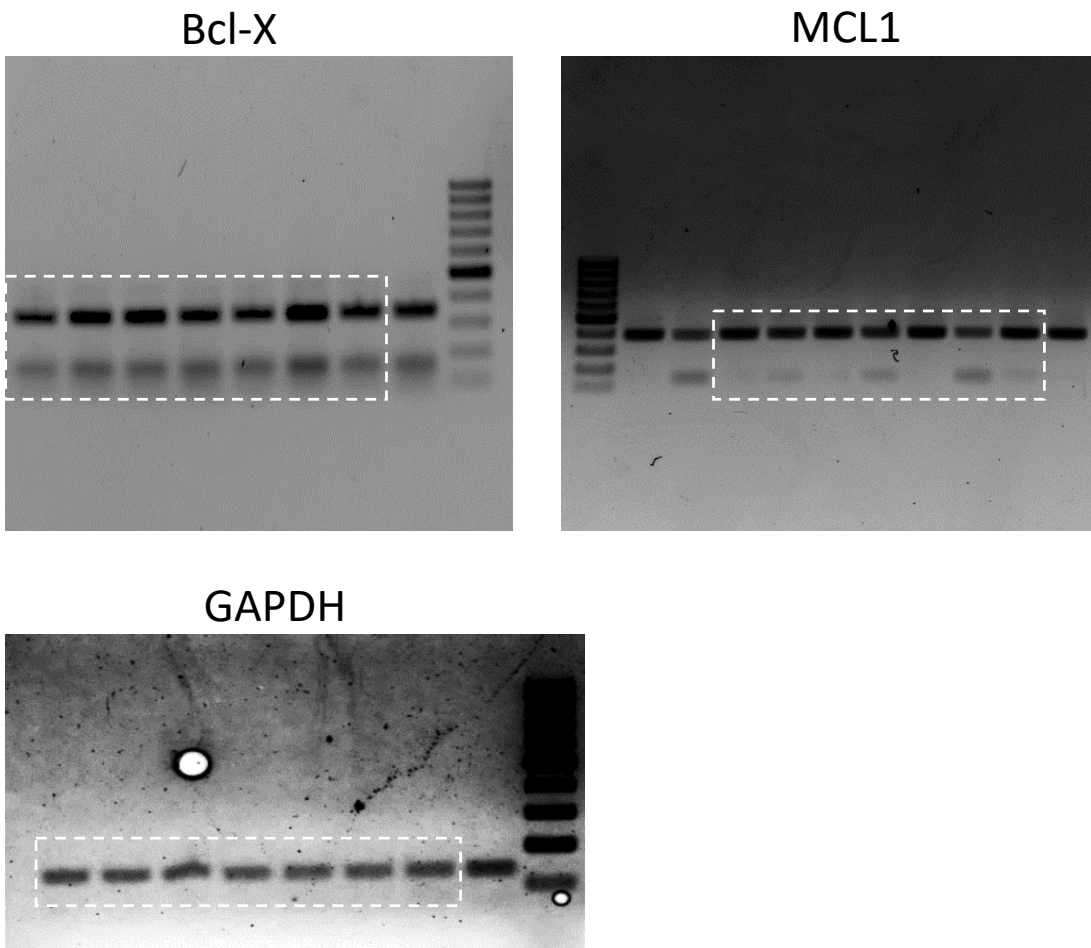




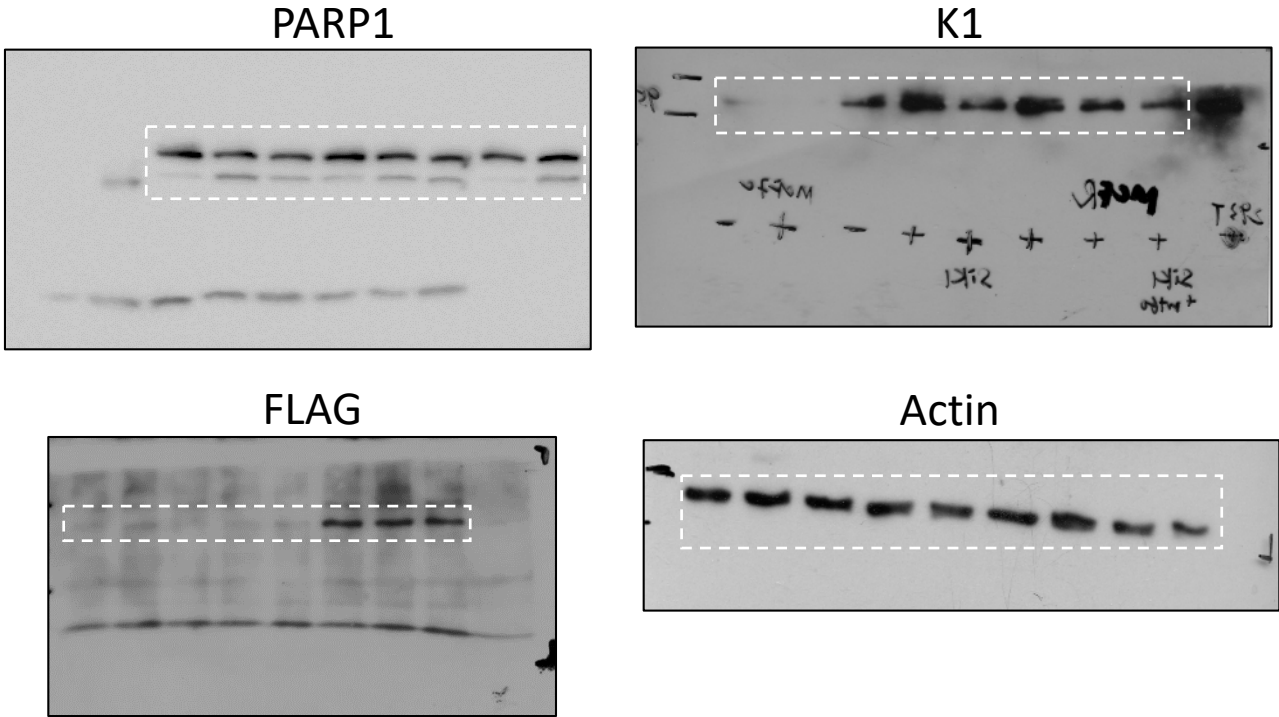
**Fig 6a**



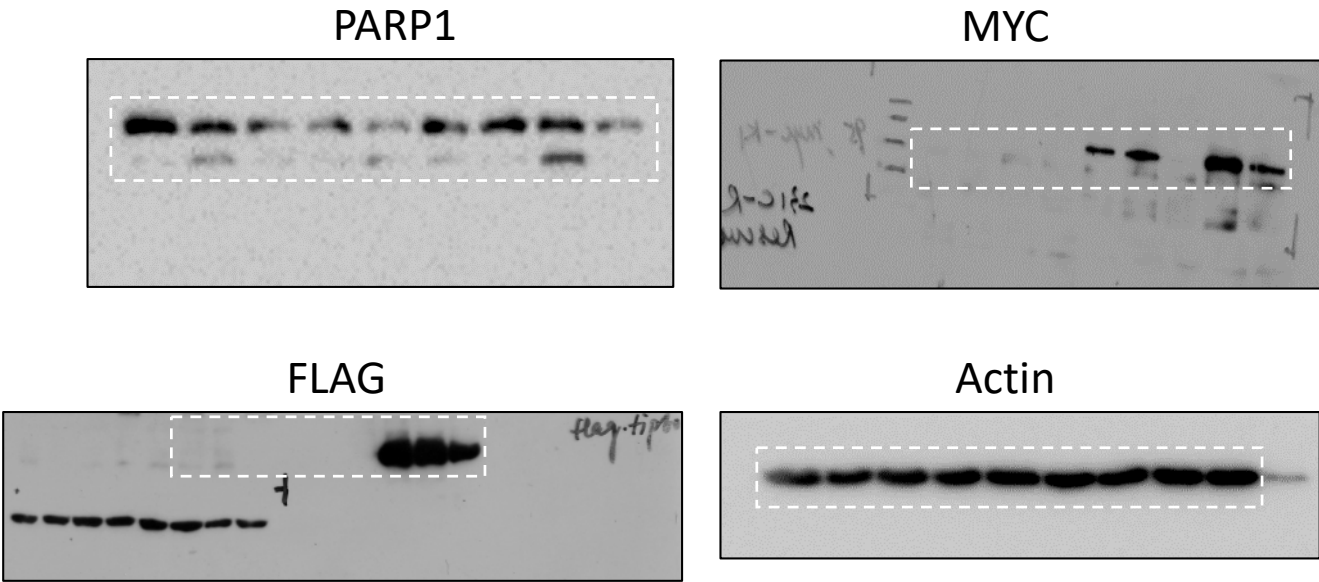
**Fig 6b**



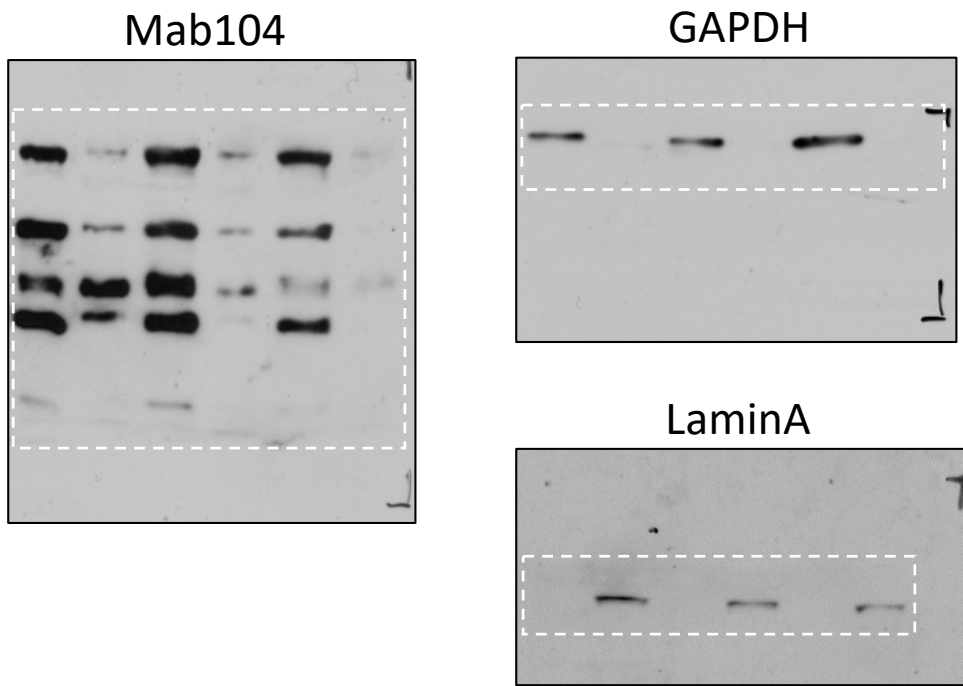
**Fig 7c**



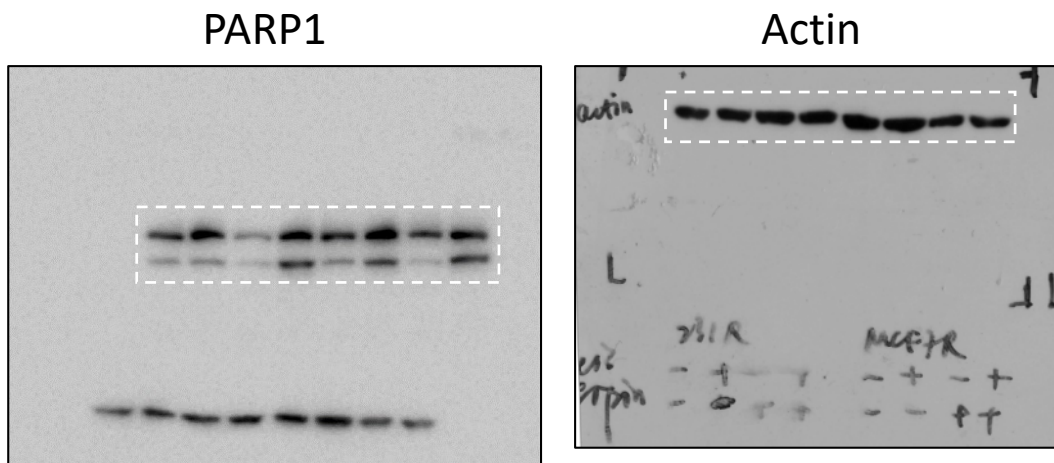
**Fig 7d**



**Fig 8a**



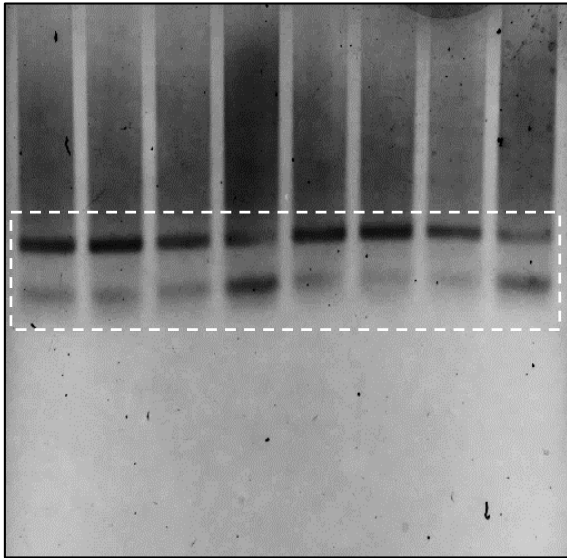
**Fig 8c**



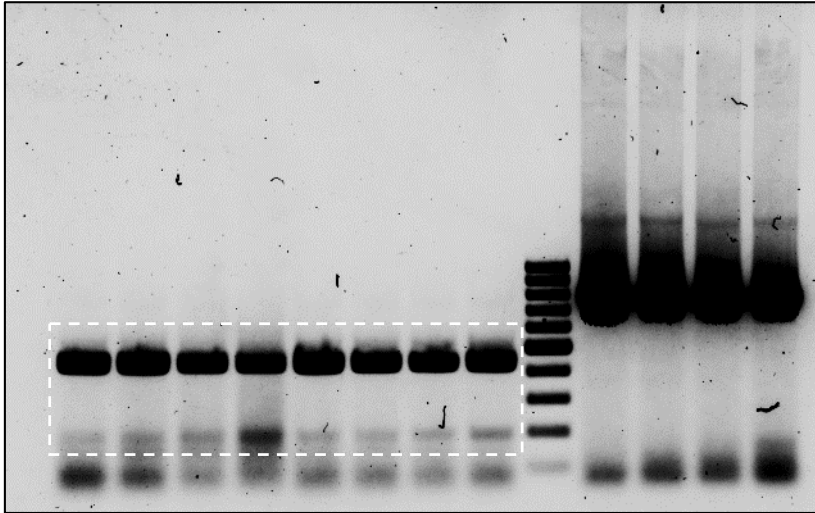


**Fig 8d**

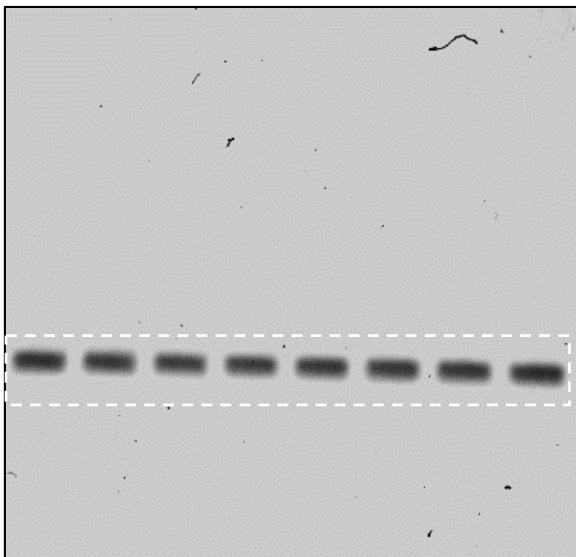
Bcl-X



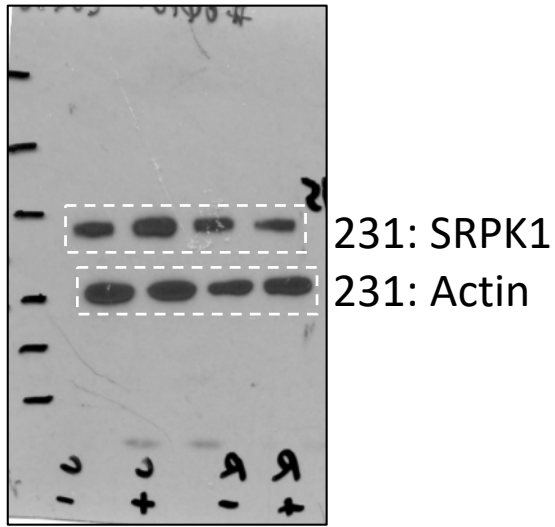
MCL-1



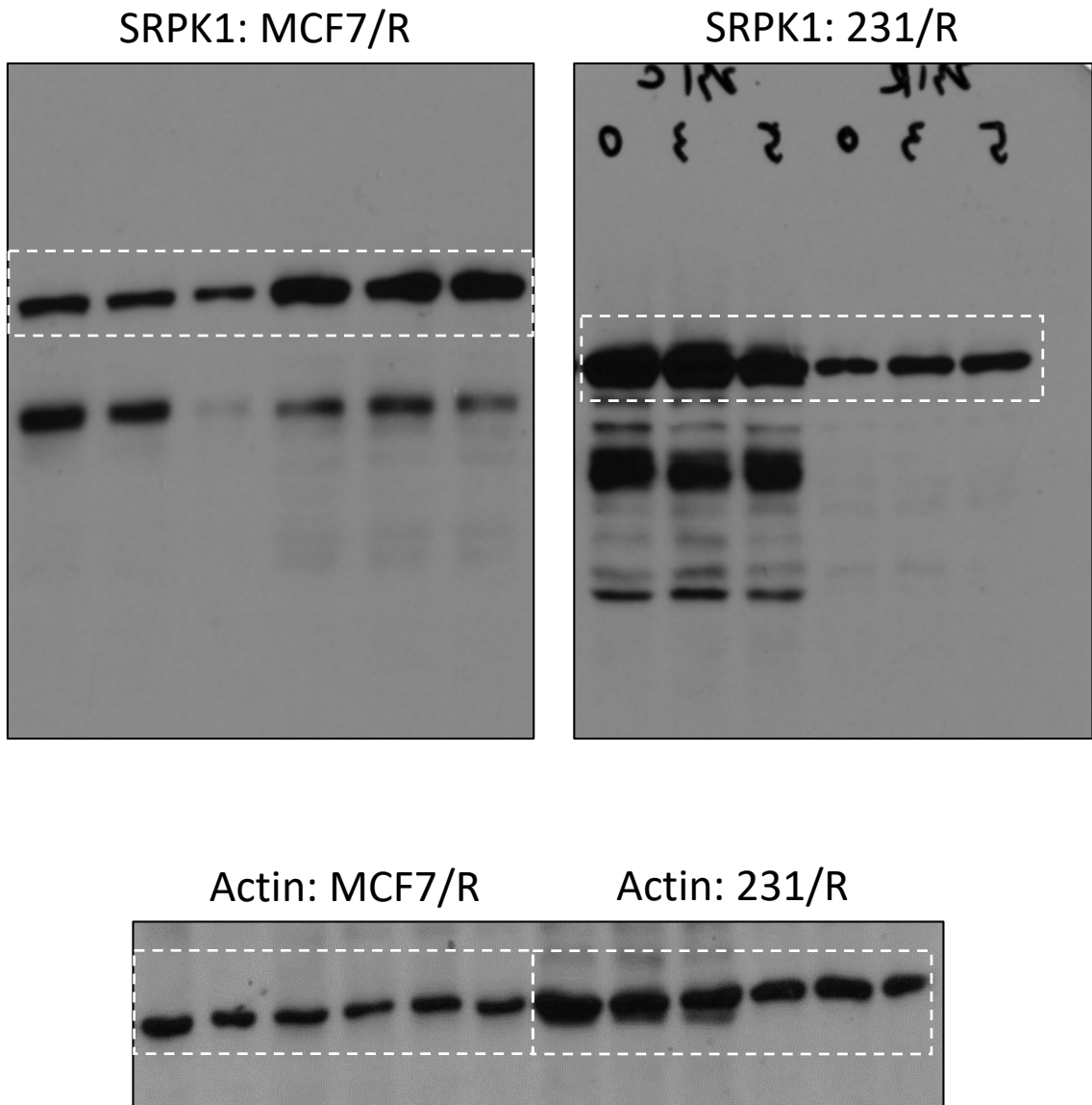
GAPDH



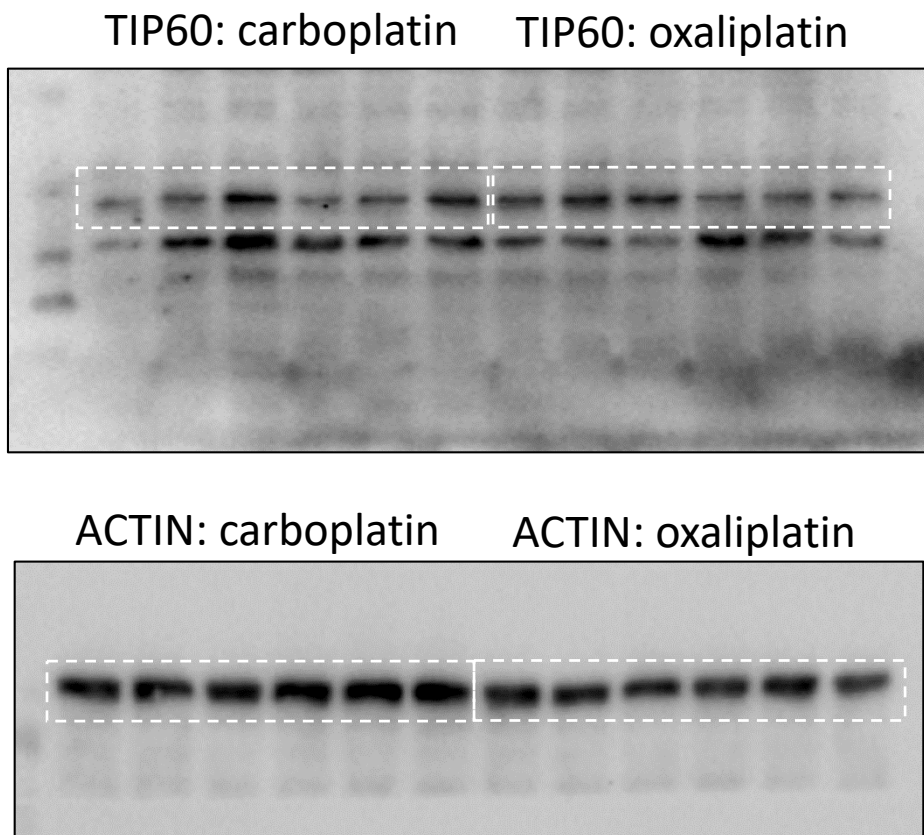
**Sup Fig 2**



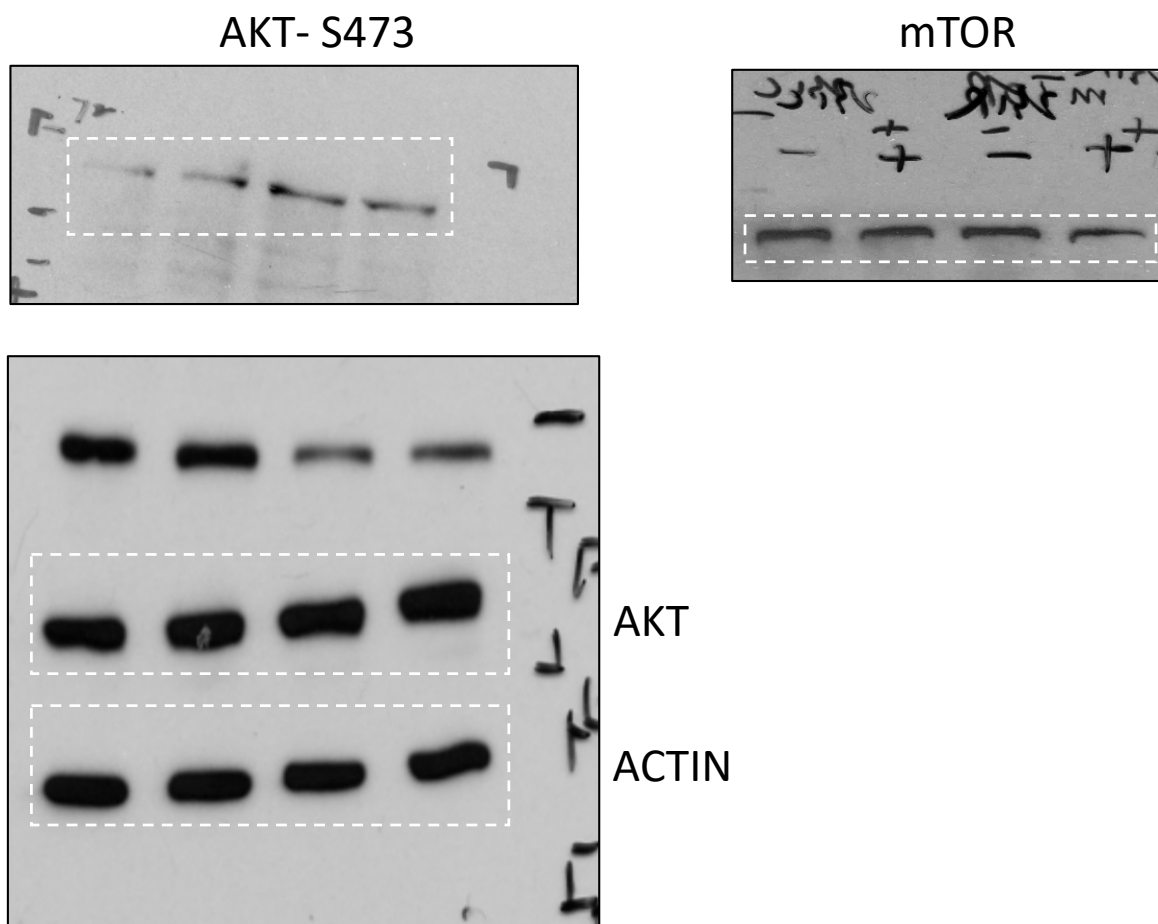
**Sup Fig 3a**



**Sup Fig 6c**

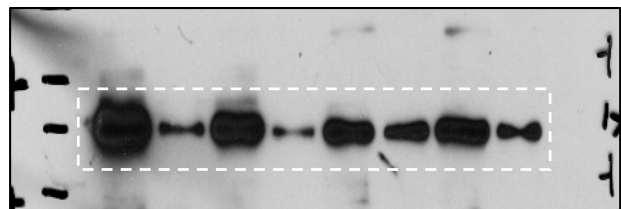


**Sup Fig 7**

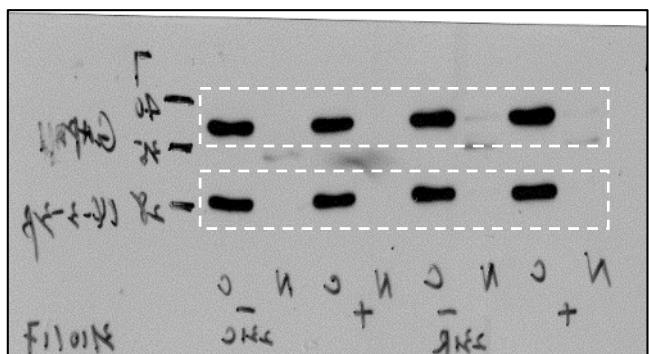
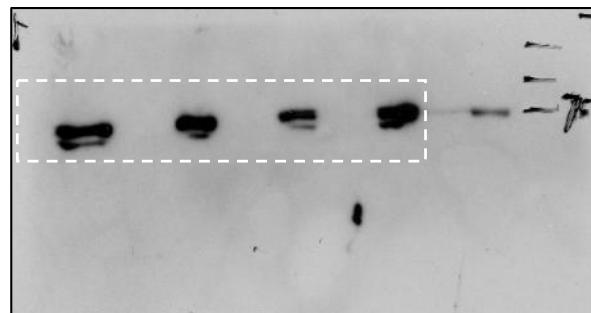


**Sup Fig 8b**

SRPK1



Lamin A

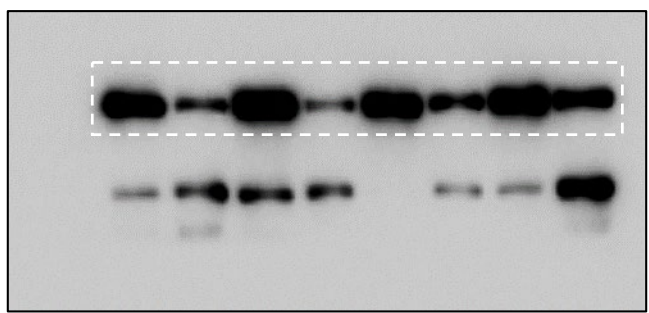


GAPDH

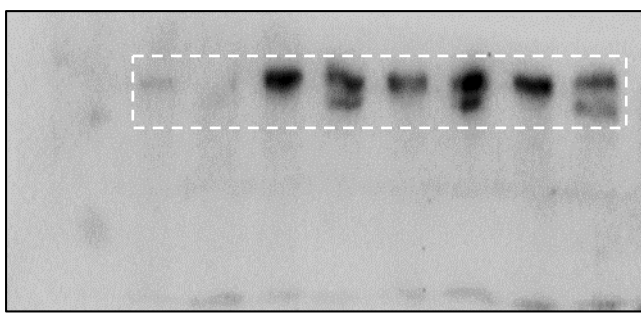
14-3-3

**Sup Fig 9c**

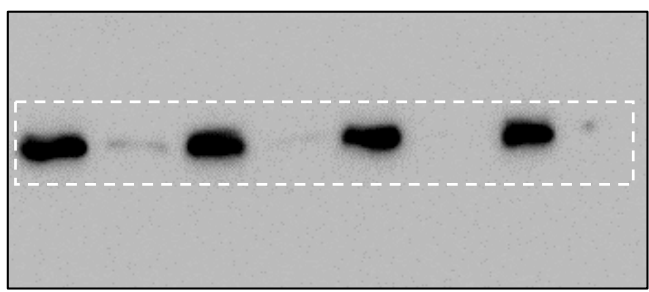
MYC



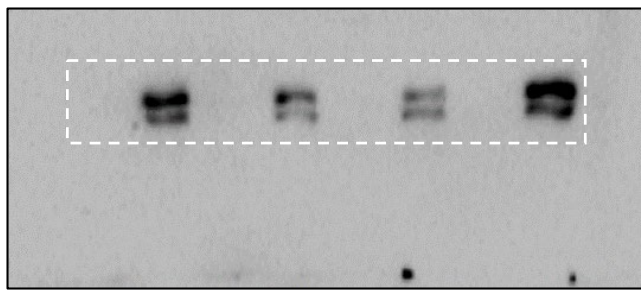
FLAG



GAPDH



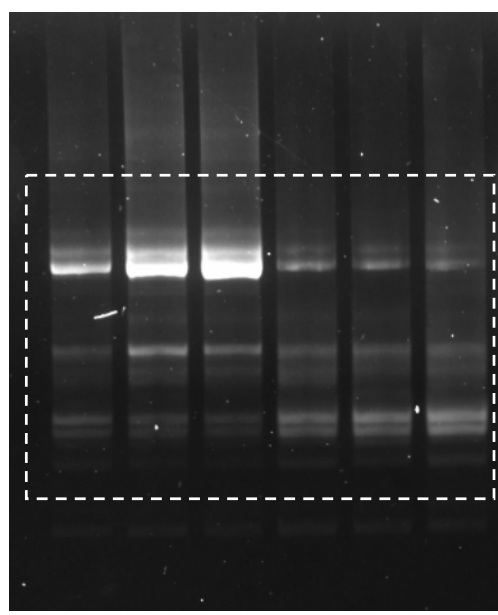
LaminA



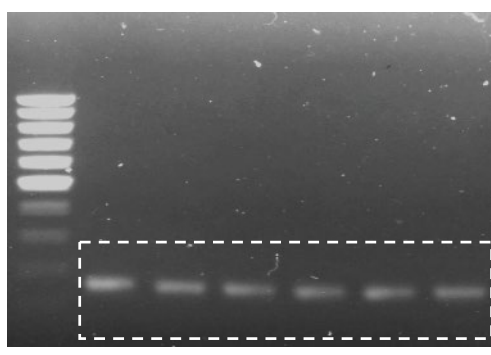


**Sup Fig 11b**

BARD1

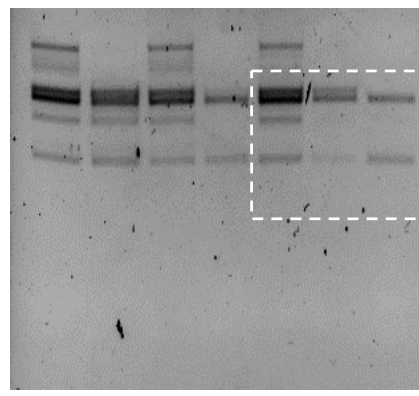


GAPDH

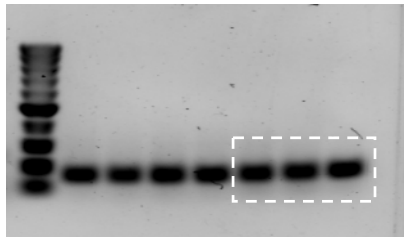


**Sup Fig 11c**

BARD1

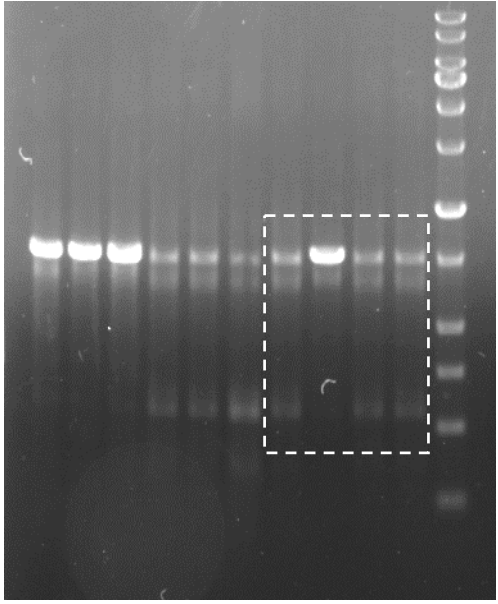


GAPDH

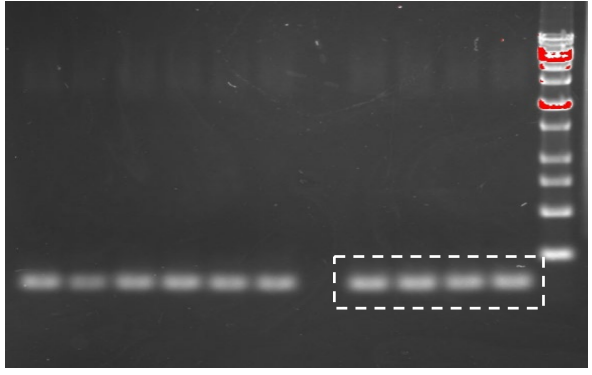


**Sup Fig 11d**

BARD1

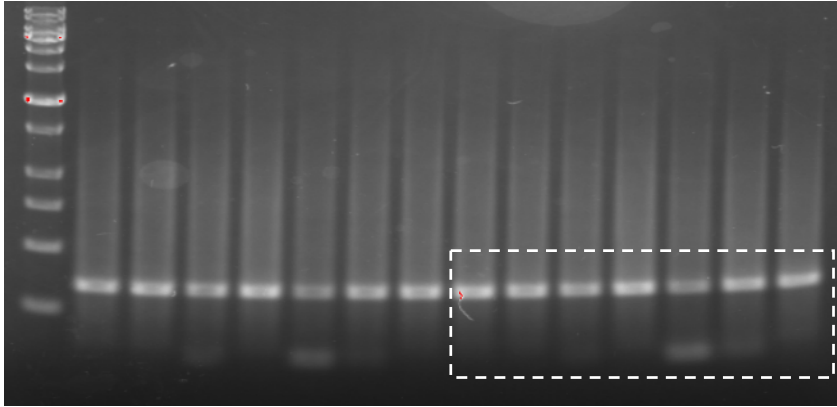


GAPDH

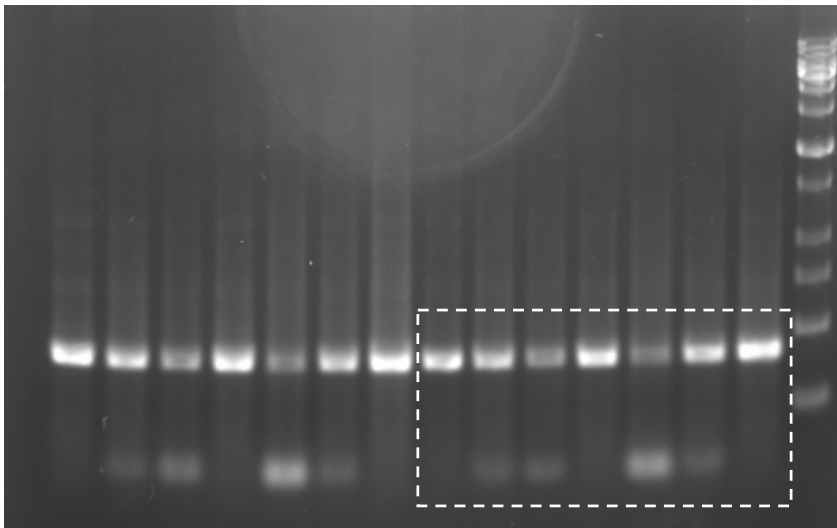


**Sup Fig 12c**

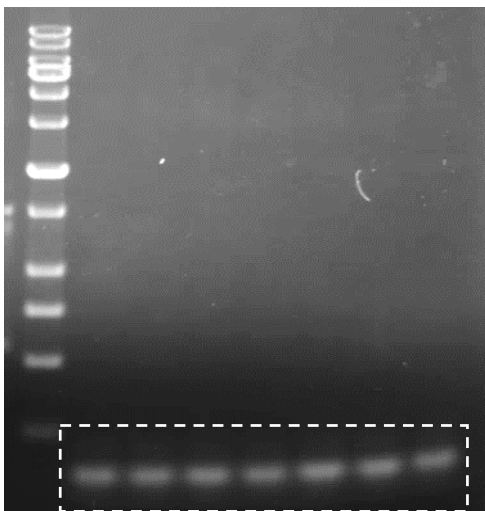
Bcl-X



MCL-1

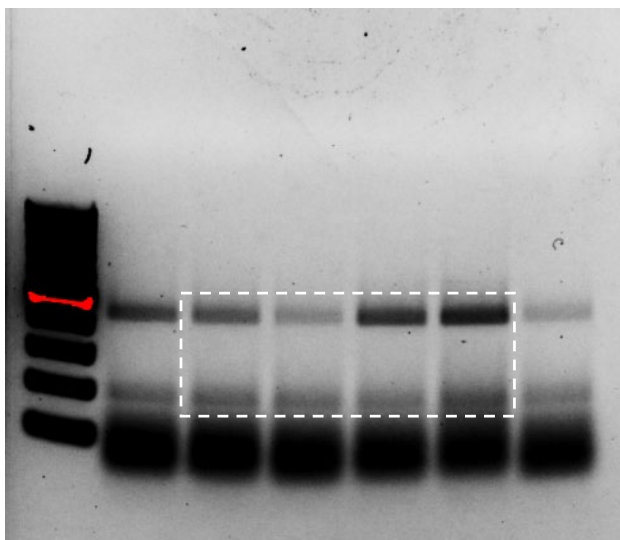


GAPDH

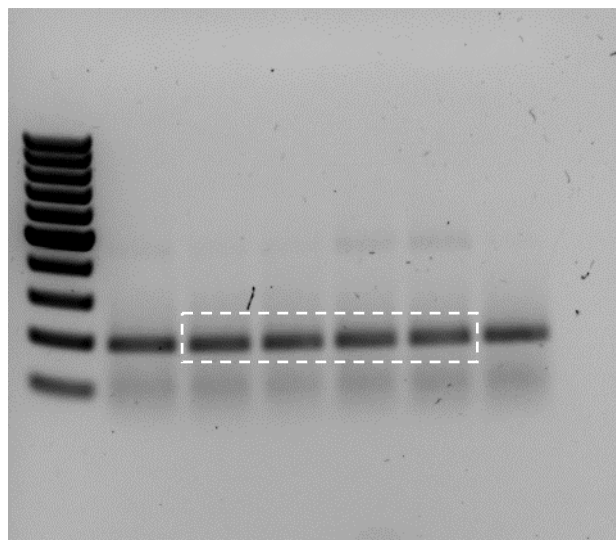


**Sup Fig 13b**

MCL-1

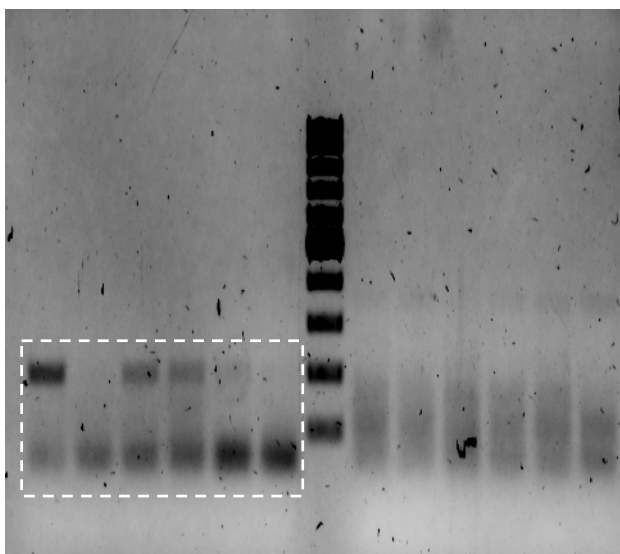


GAPDH

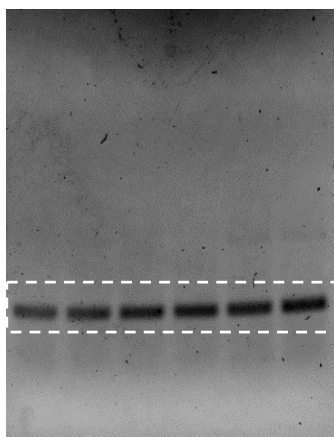


**Sup Fig 13c**

MCL-1



GAPDH

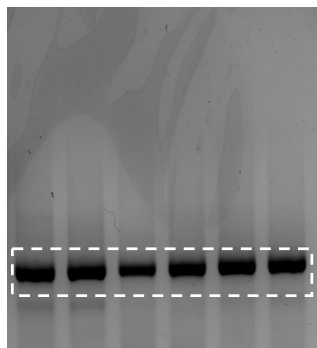
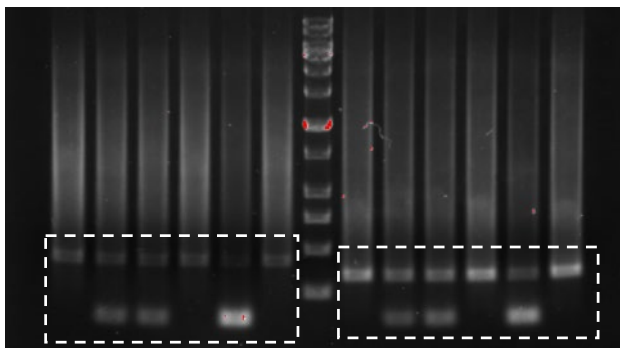


**Sup Fig 13d**

MCL-1

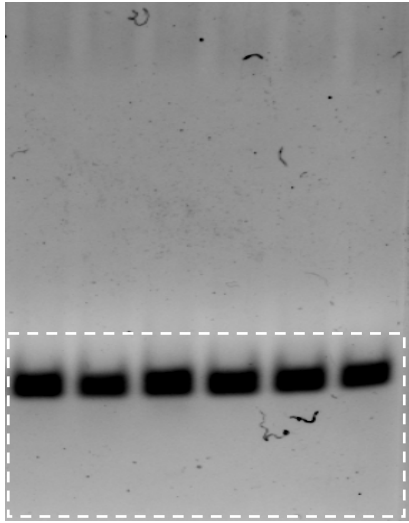
Bcl-X

GAPDH

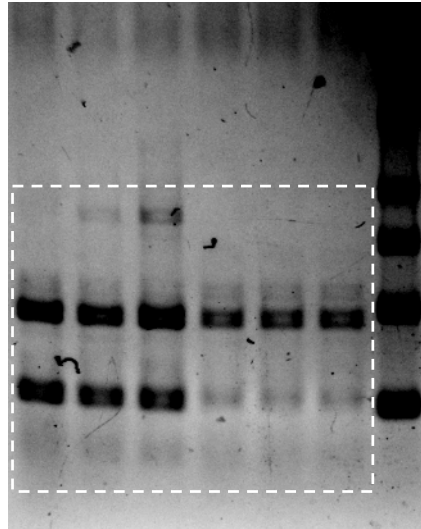


**Sup Fig 14c**

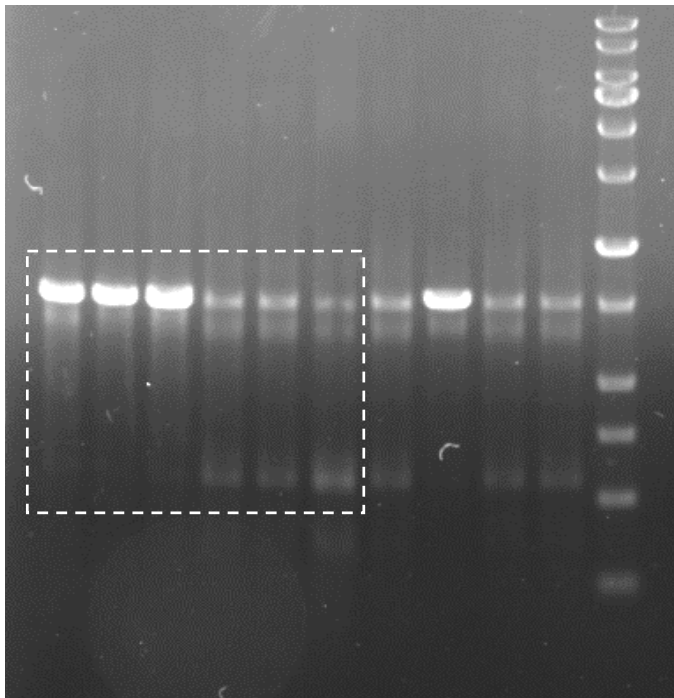
VEGF



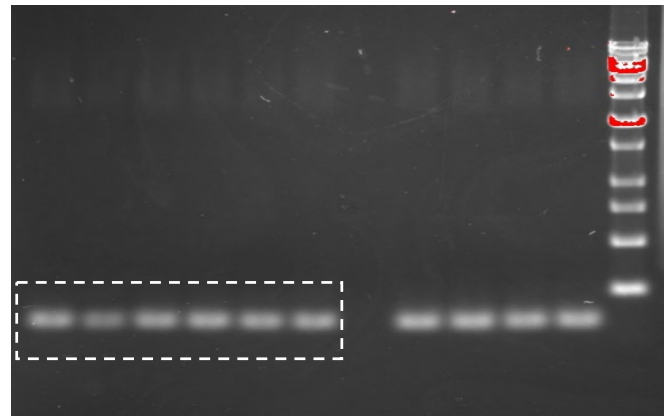
BAX



BARD1



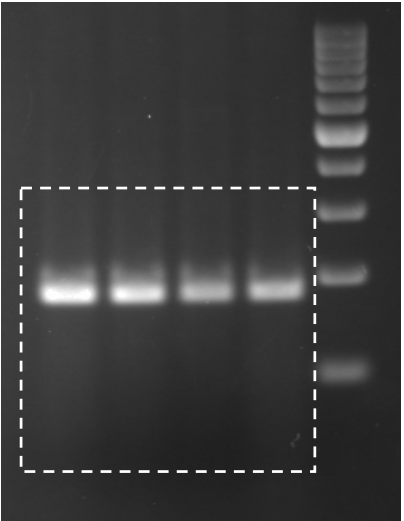
GAPDH



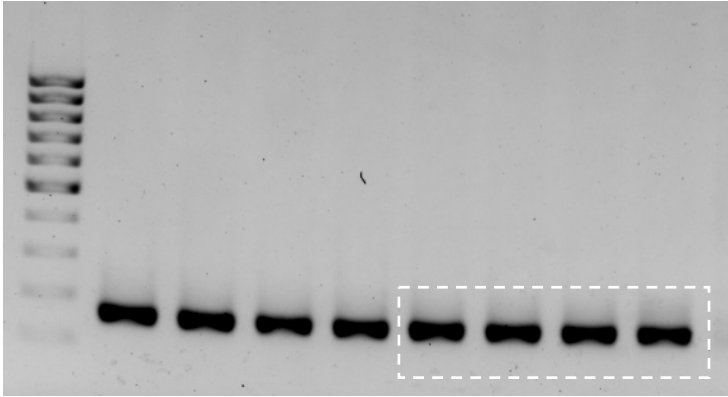


**Sup Fig 14d**

VEGF

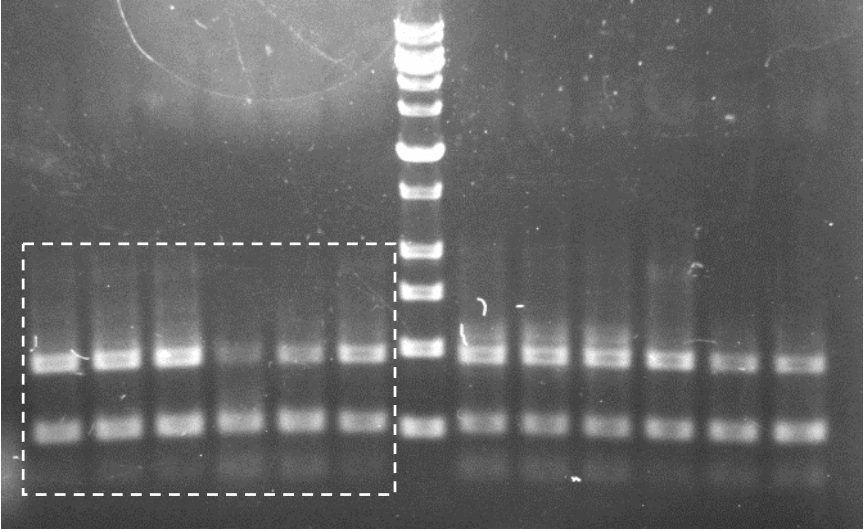


GAPDH

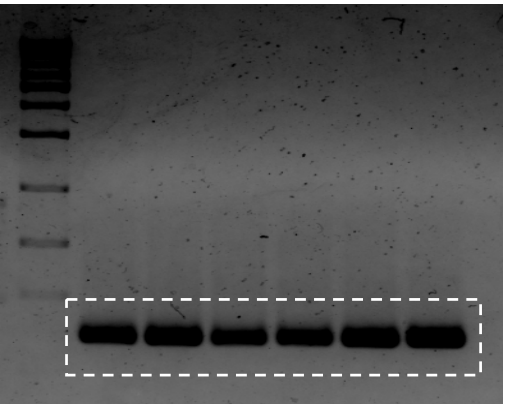


**Sup Fig 14e**

BAX

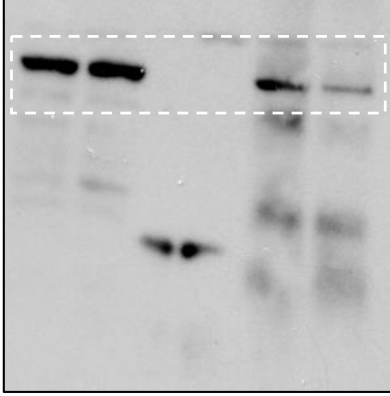


GAPDH

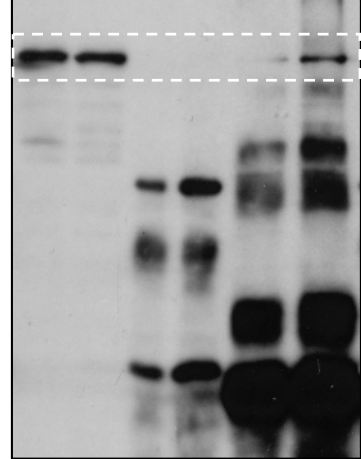


**Sup Fig 15a**

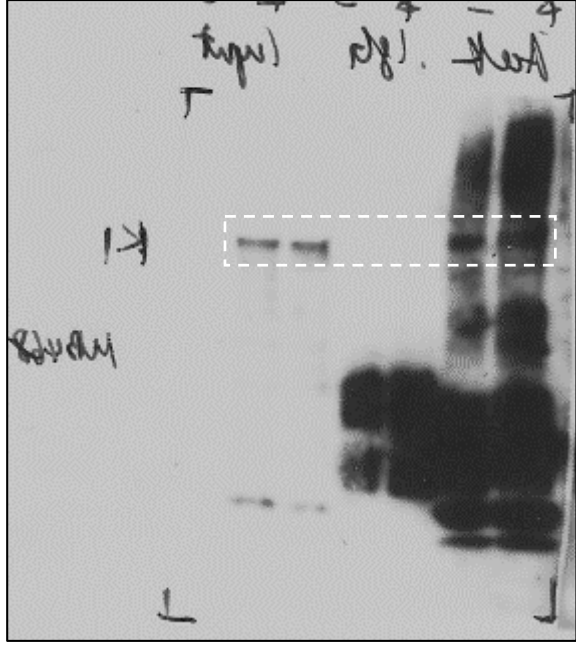
HCC70



BT549

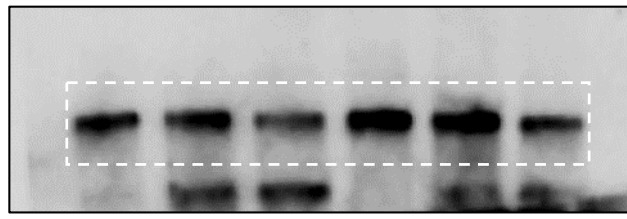


468

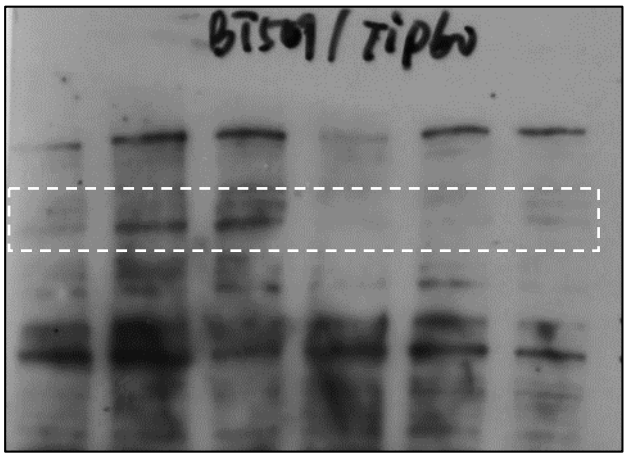


**Sup Fig 15c**

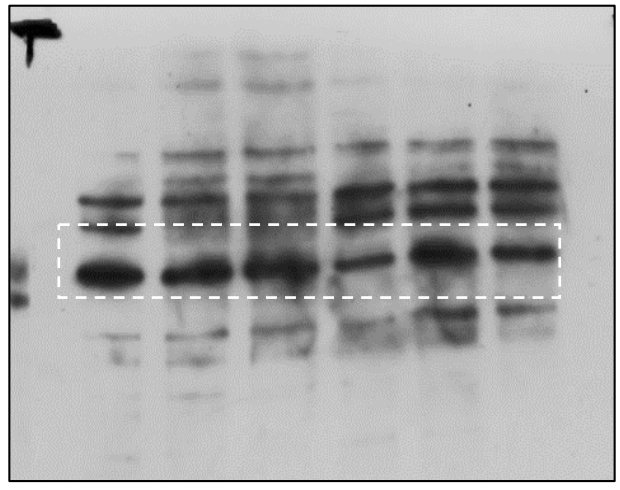
SRPK1



TIP60

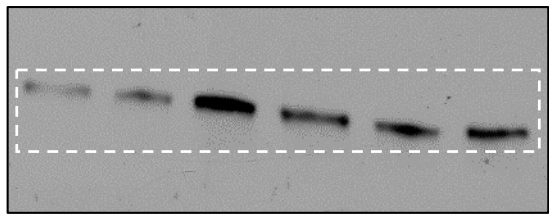


Actin

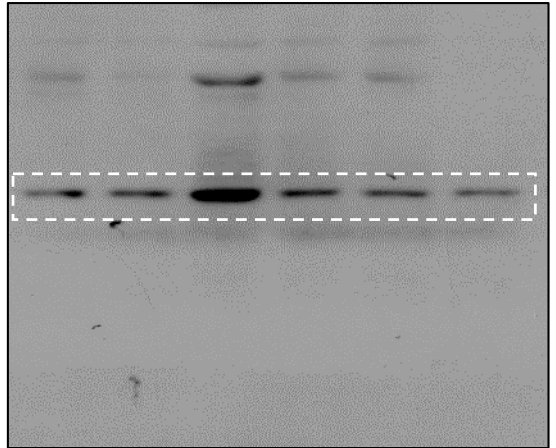


**Sup Fig 15d**

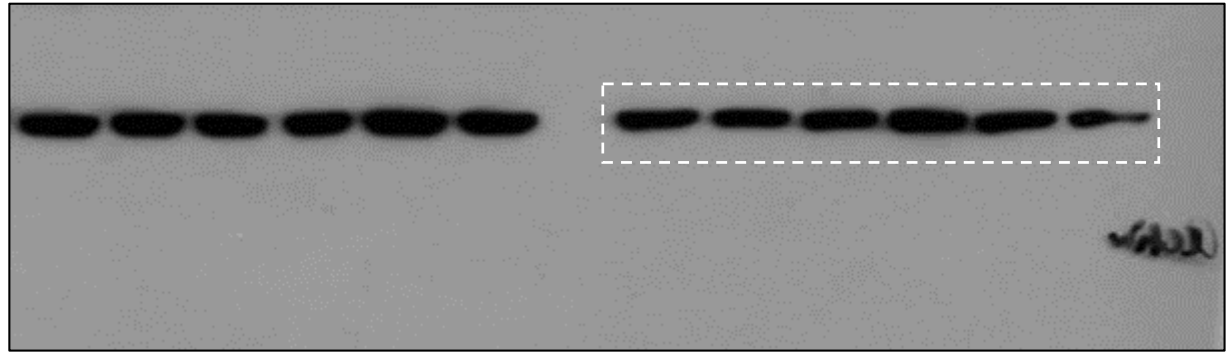
SRPK1



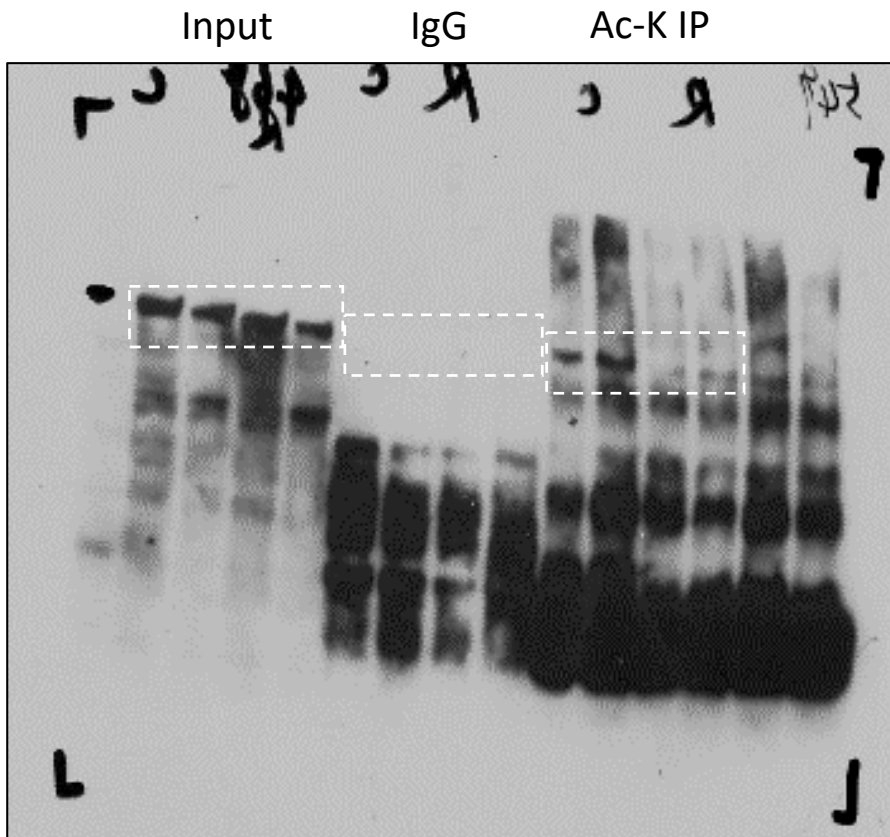
TIP60



Actin



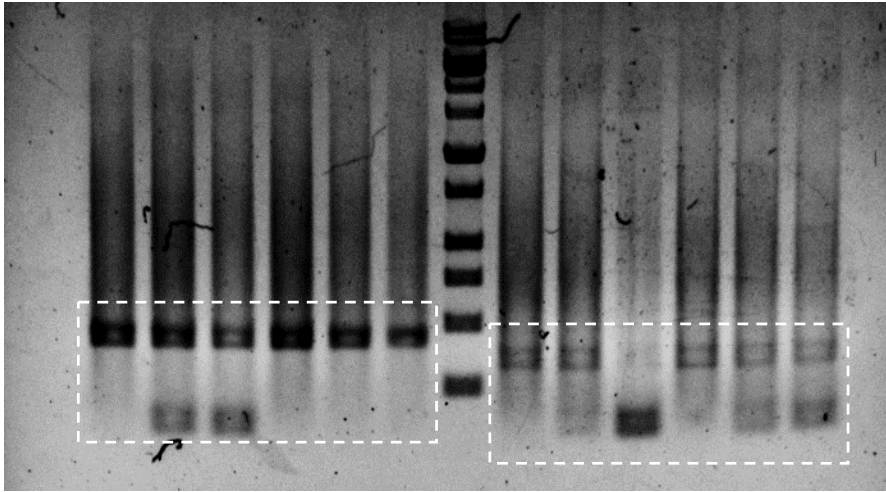
**Sup Fig 15e**



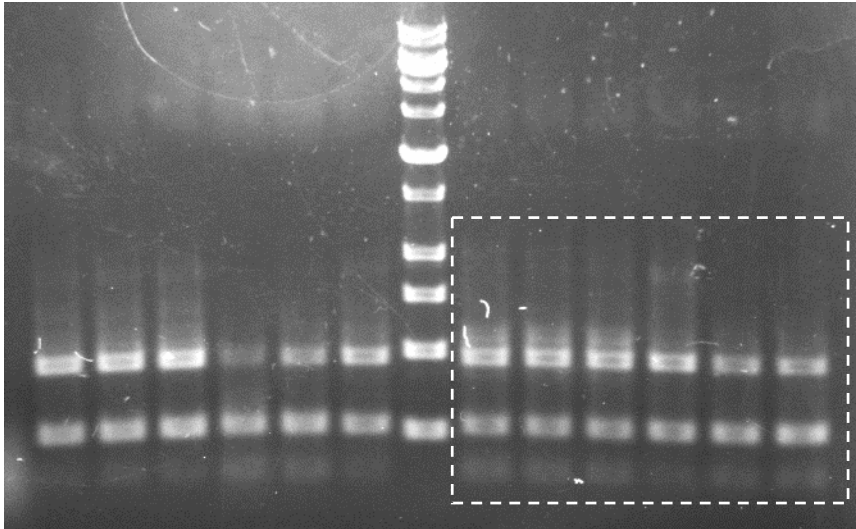
**Sup Fig 15f**

MCL-1

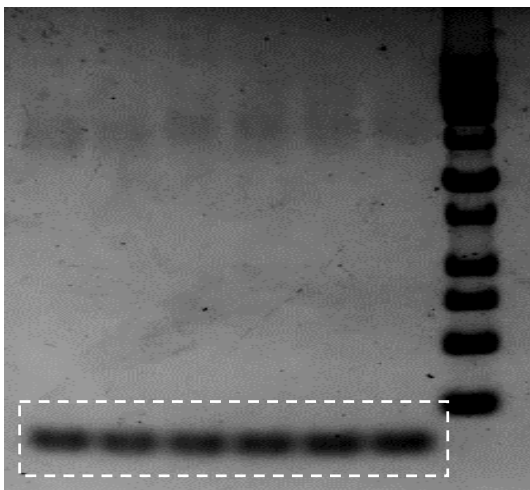
Bcl-X



BAX



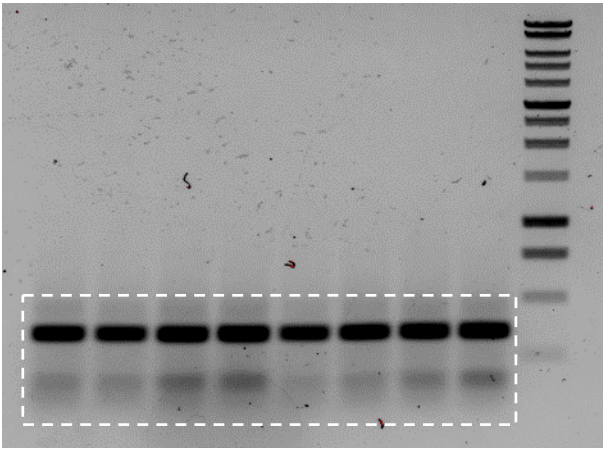
GAPDH



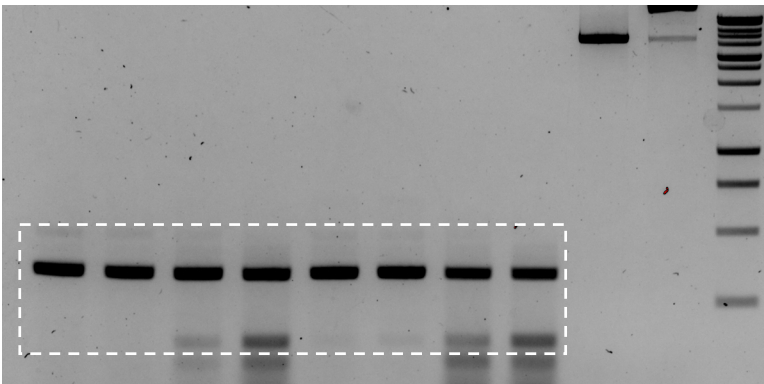


**Sup Fig 17**

Bcl-X



MCL-1



GAPDH

