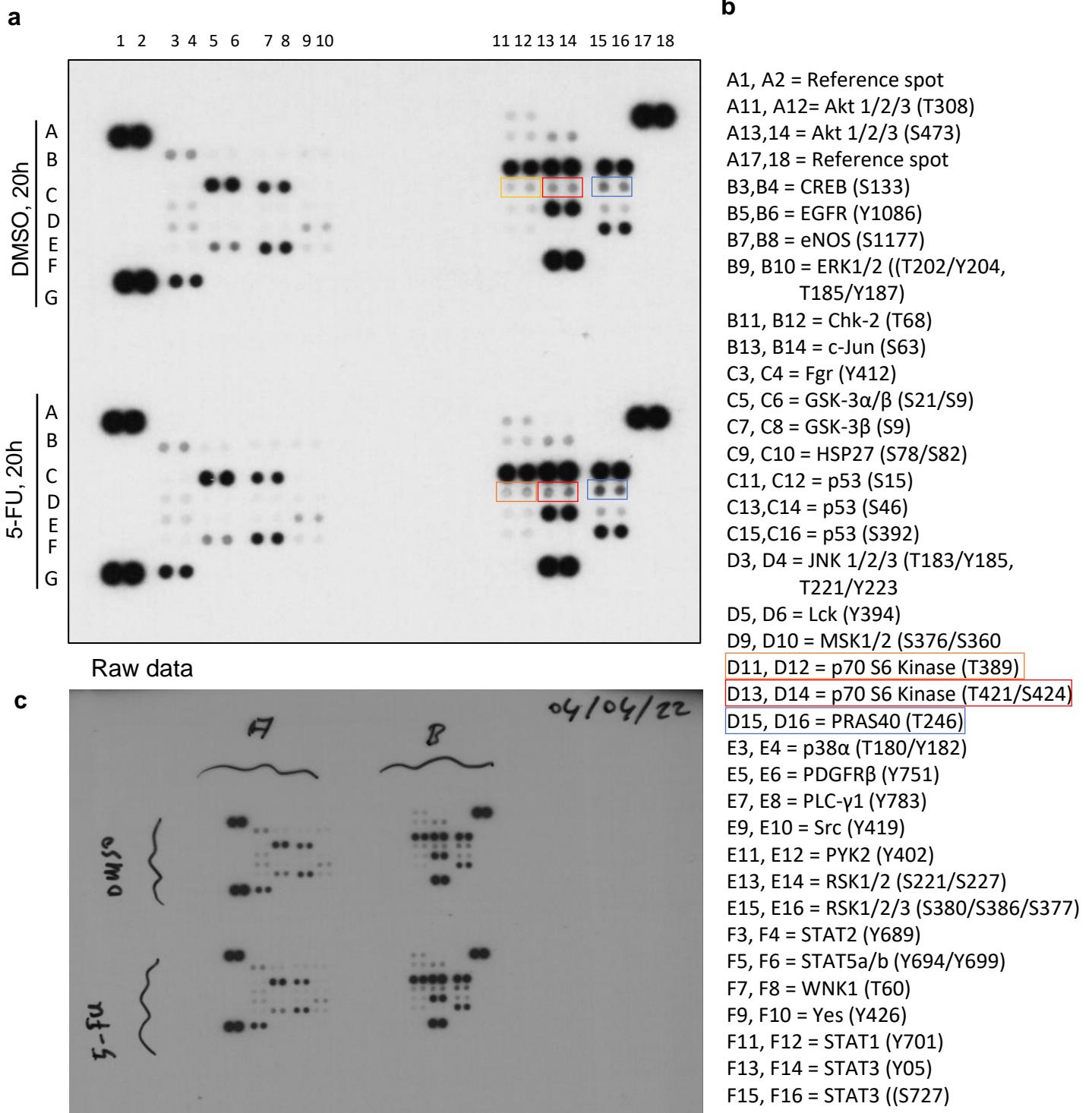


SI Figure 1

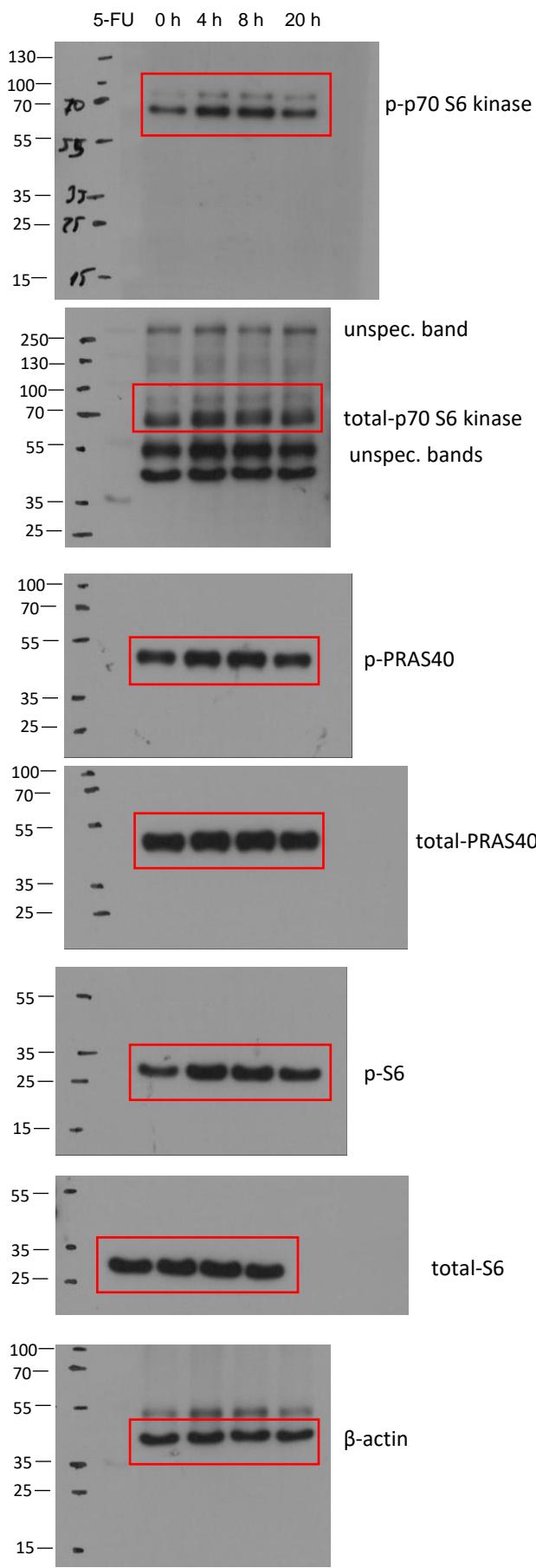
Processed and raw data of phospho-kinase array used for the quantification of Figure 1c

Processed results



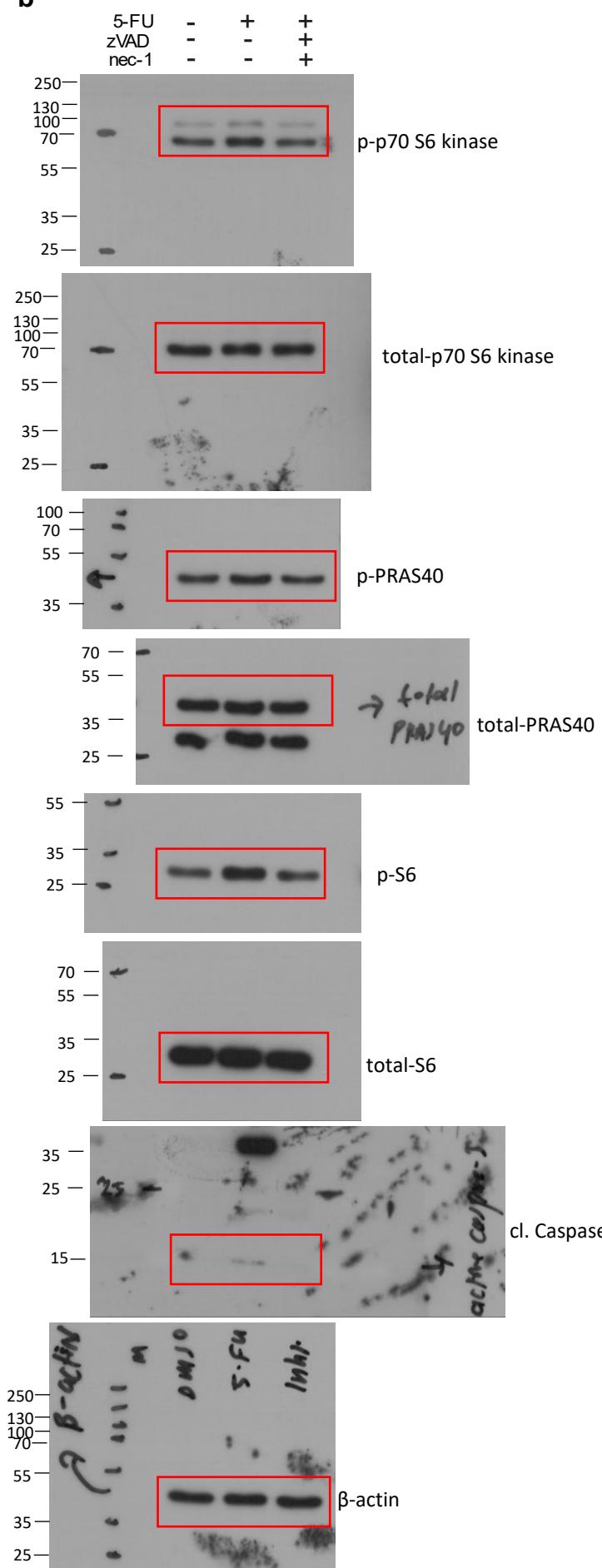
SI Figure 2

a



Immunoblot scans for Figure 1d

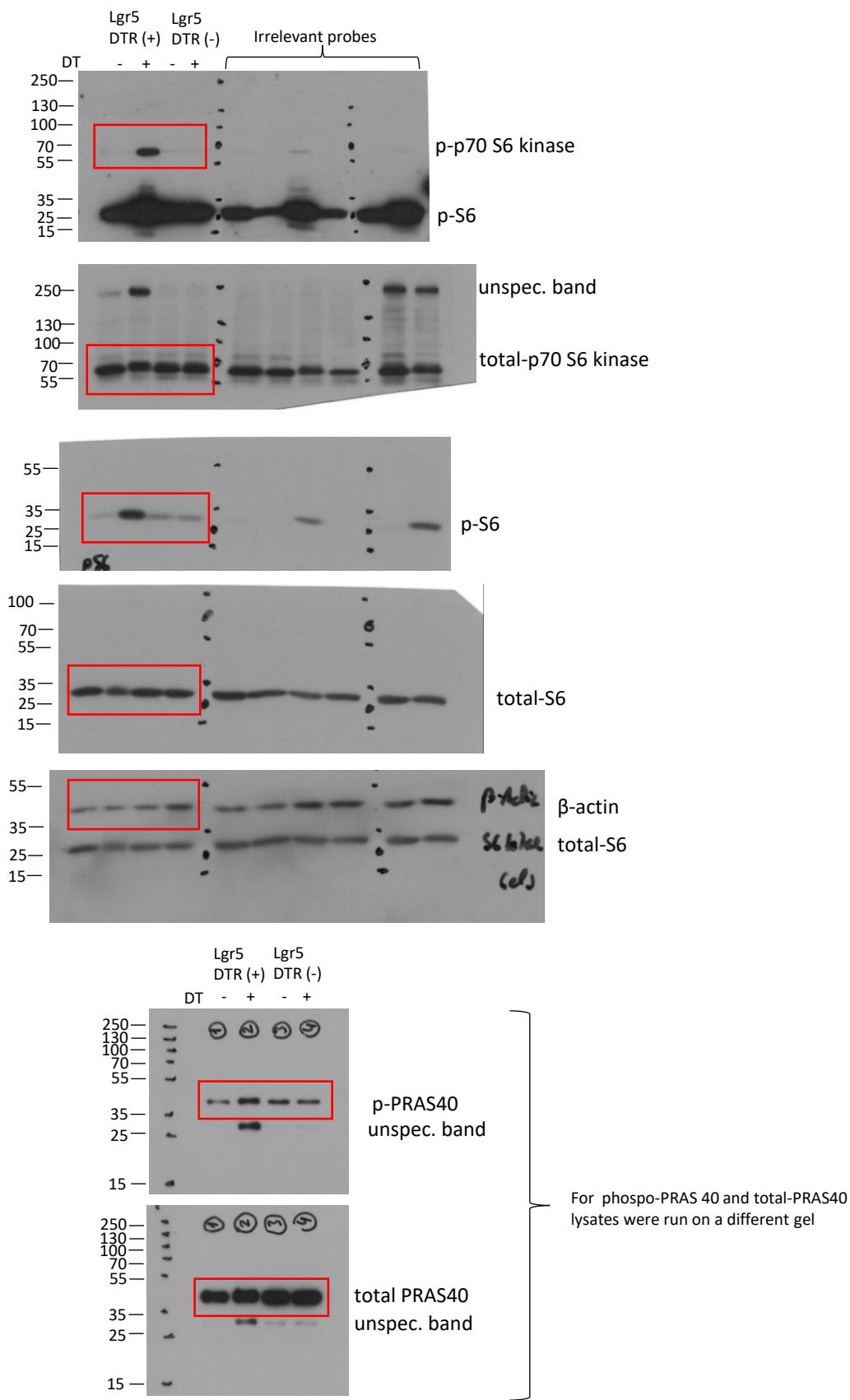
b



Immunoblot scans for Figure 1e

SI Figure 3

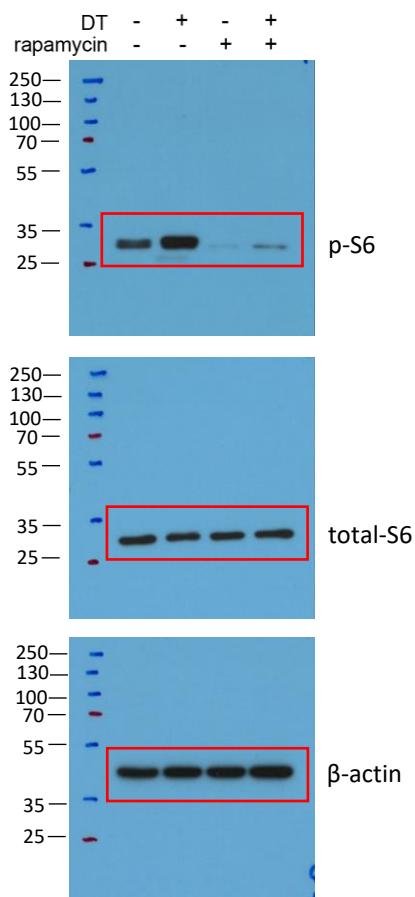
a



Immunoblot scans for Figure 2a

SI Figure 4

a



Immunoblot scans for Figure 2g

SI Figure 5

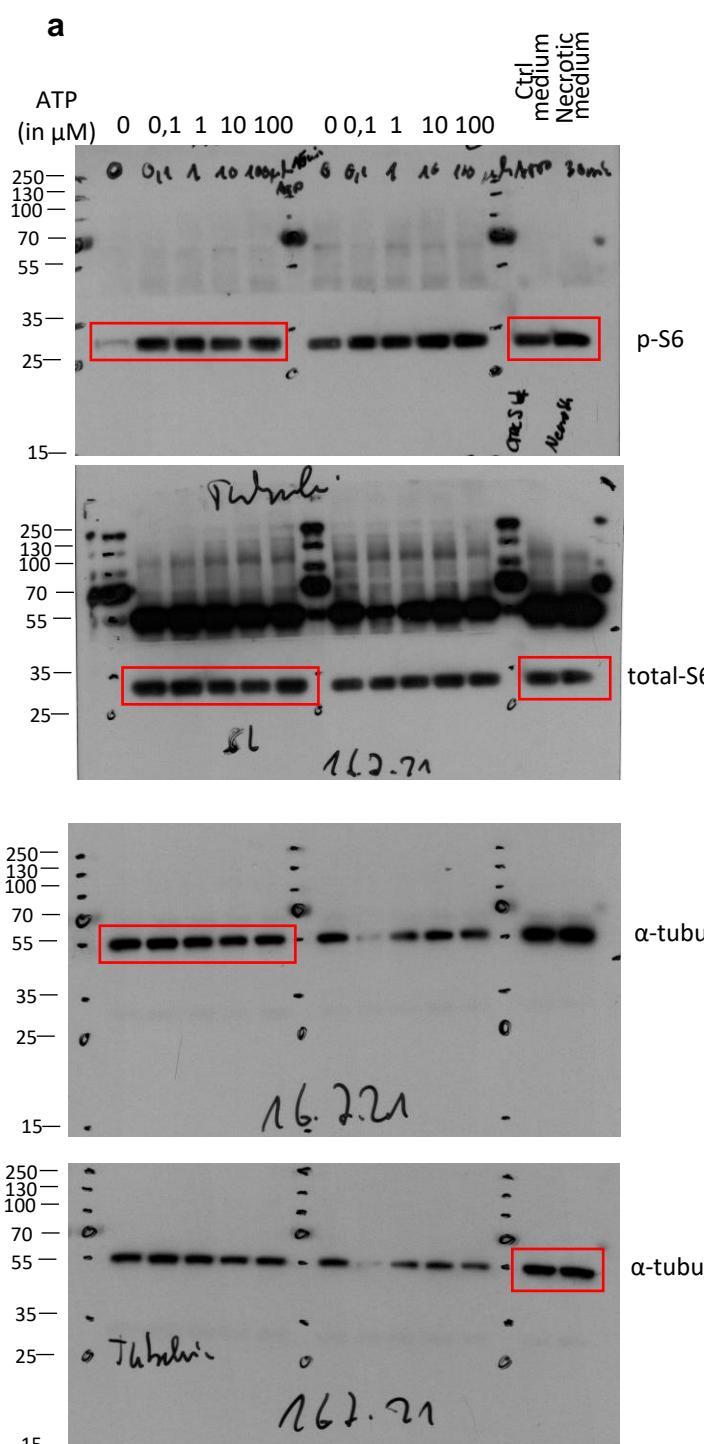
a

Western blot analysis showing protein levels in Lgr5 DTR (+) and (-) cells. The blot includes three panels: p-S6, total-S6, and β -actin. Molecular weight markers (kDa) are indicated on the left.

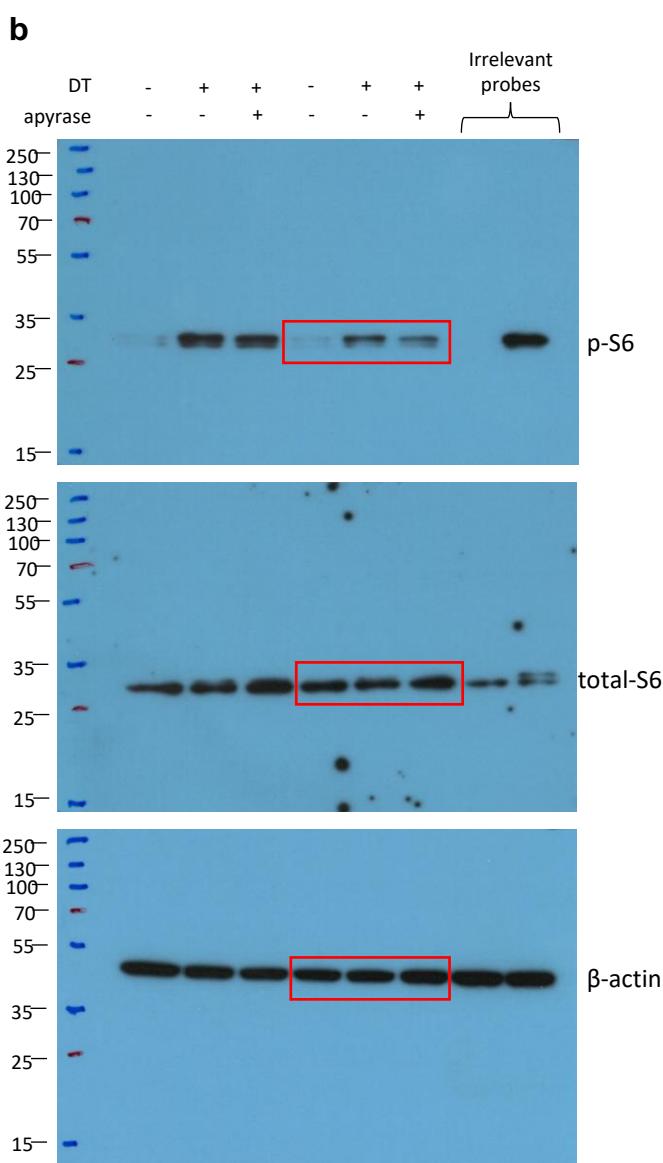
	DT	Lgr5 DTR (+)	Lgr5 DTR (-)	Irrelevant probes
DT supernat.	-	+	-	-
p-S6	~35 kDa	~35 kDa (boxed)	~35 kDa (boxed)	~35 kDa
total-S6	~35 kDa	~35 kDa (boxed)	~35 kDa (boxed)	~35 kDa
β -actin	~35 kDa	~35 kDa (boxed)	~35 kDa (boxed)	~35 kDa

Immunoblot scans for Figure 3a

SI Figure 6



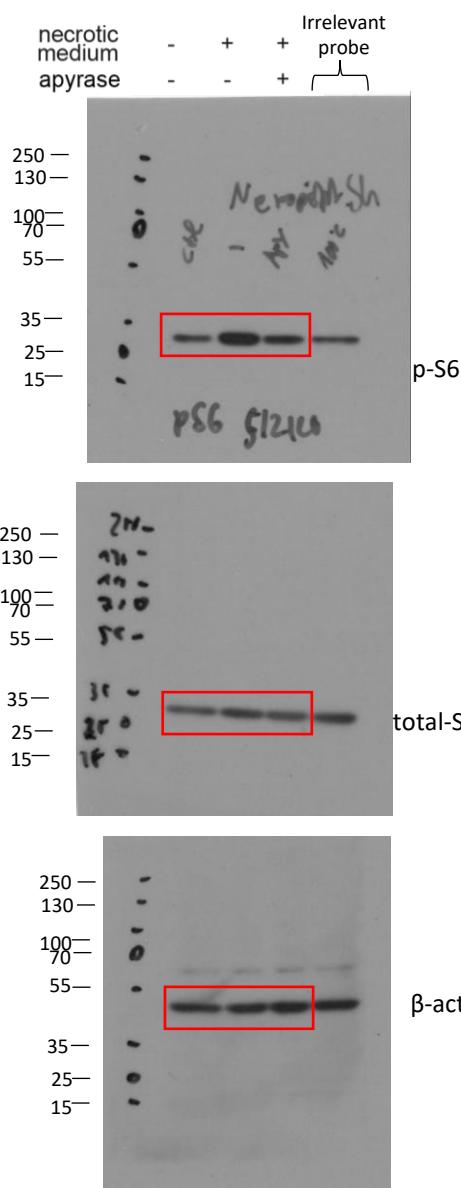
Immunoblot scans for Figure 3c and e



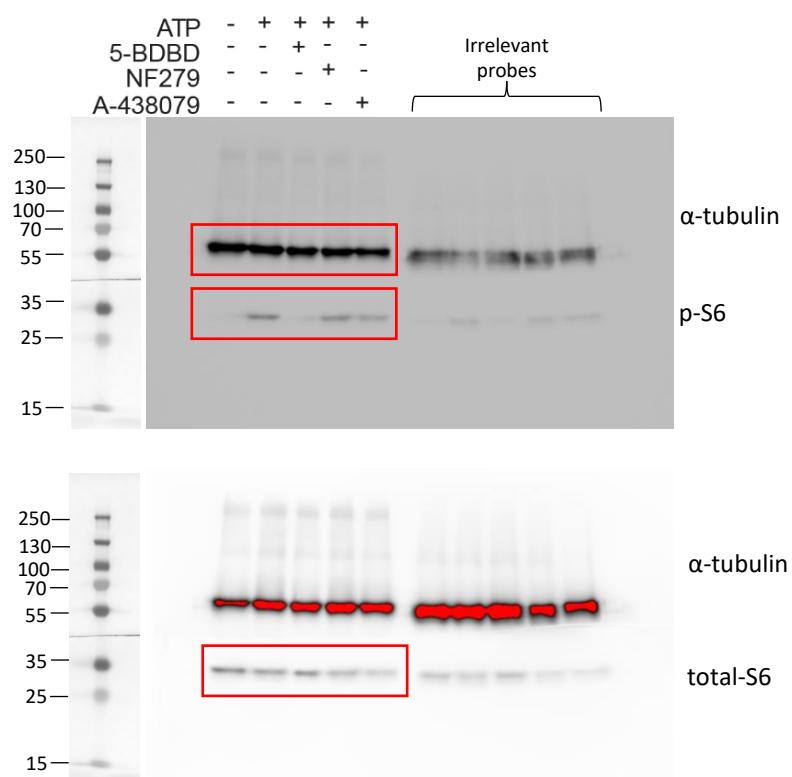
Immunoblot scans for Figure 3f

SI Figure 7

a



b

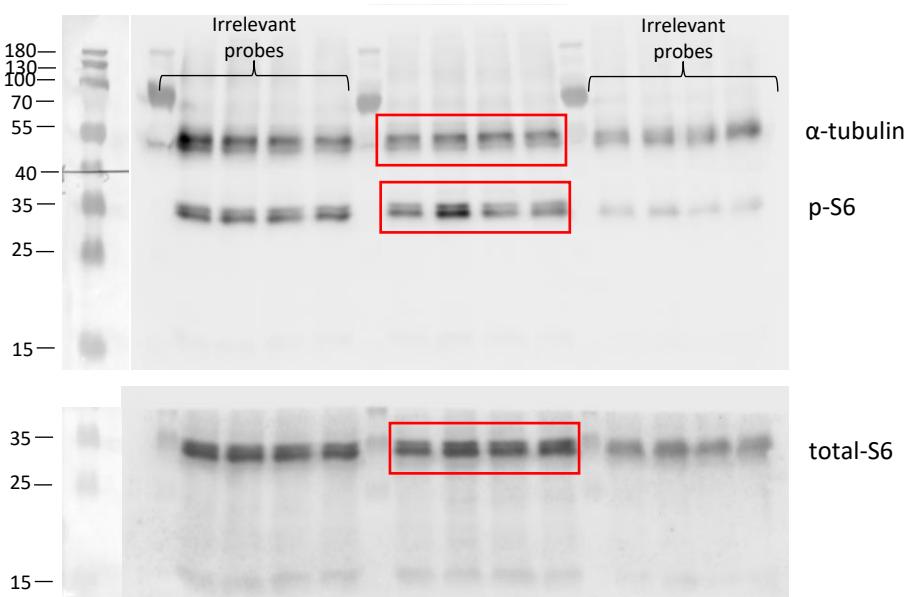


Immunoblot scans for Figure 3j

Immunoblot scans for Figure 3g

c

Dox	-	-	+	+
necrotic medium	-	+	-	+

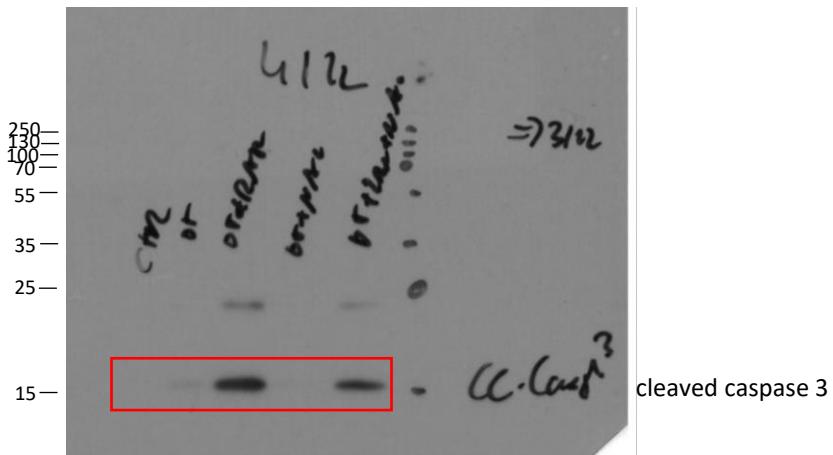
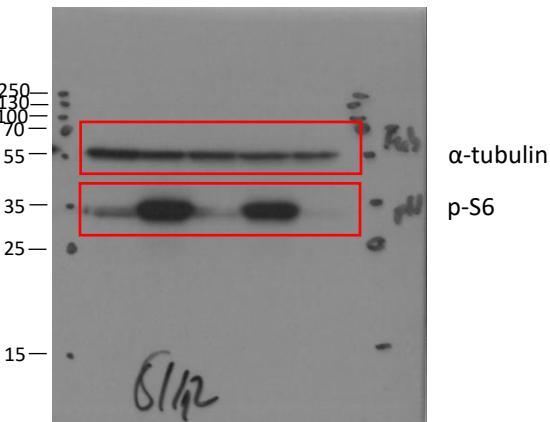


Immunoblot scans for Figure 3l

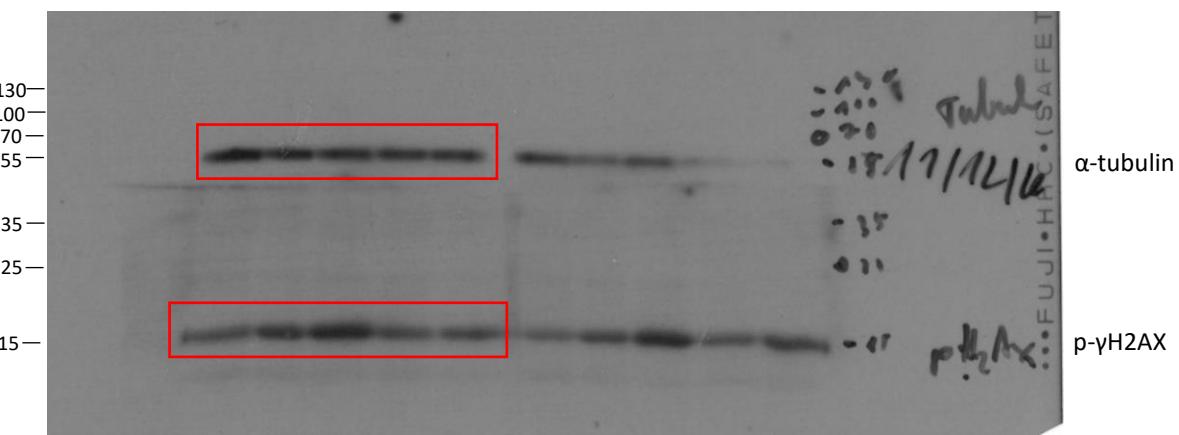
SI Figure 8

a

DT	-	+	+	+	+
rapamycin	-	-	+	-	+
NAC	-	-	-	+	+



DT	-	+	+	+	+	-	+	+	+	+
rapamycin	-	-	+	-	+	-	-	+	-	+
NAC	-	-	-	+	+	-	-	-	+	+

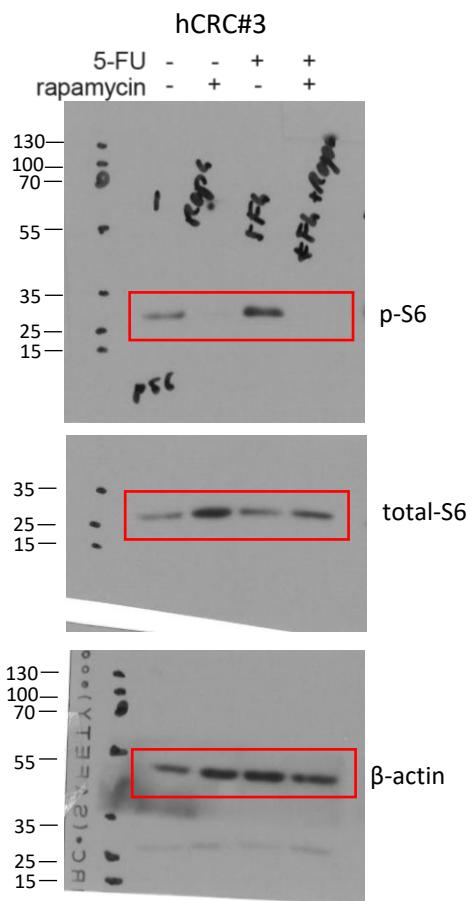
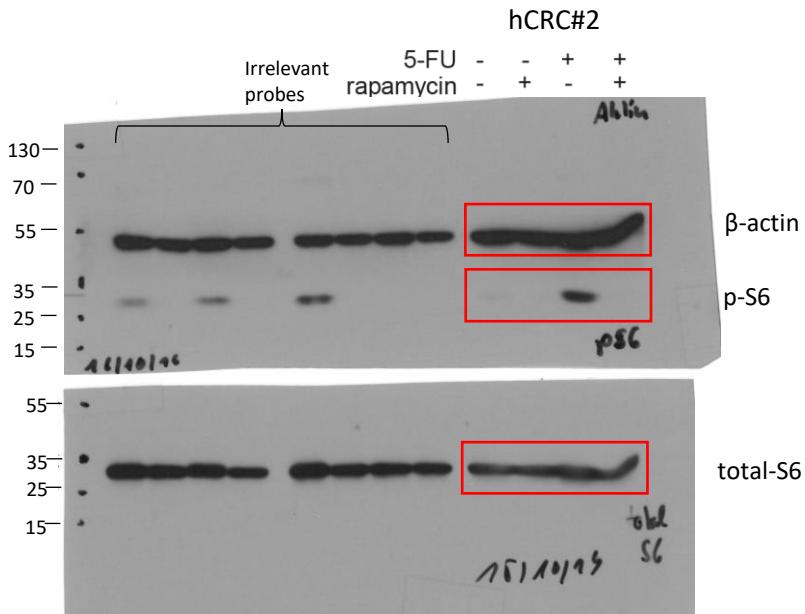


For pyH2AX detection samples had to be reloaded on a separate gel

Immunoblot scans for Figure 4f

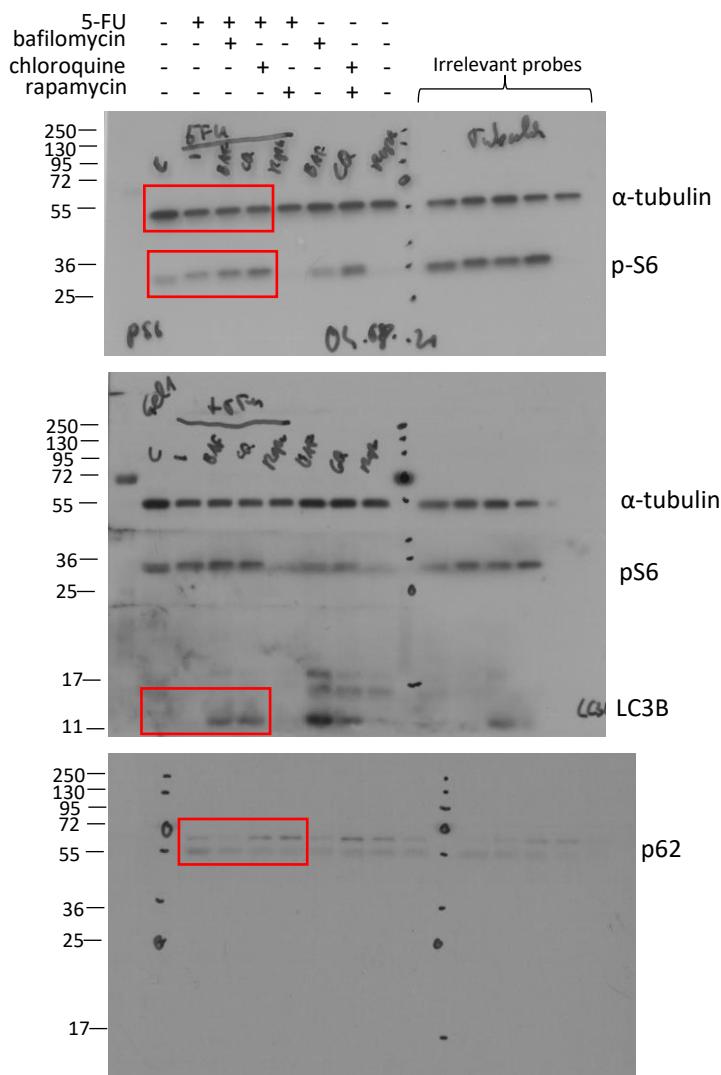
SI Figure 9

a



Immunoblot scans for Extended data Figure 1a

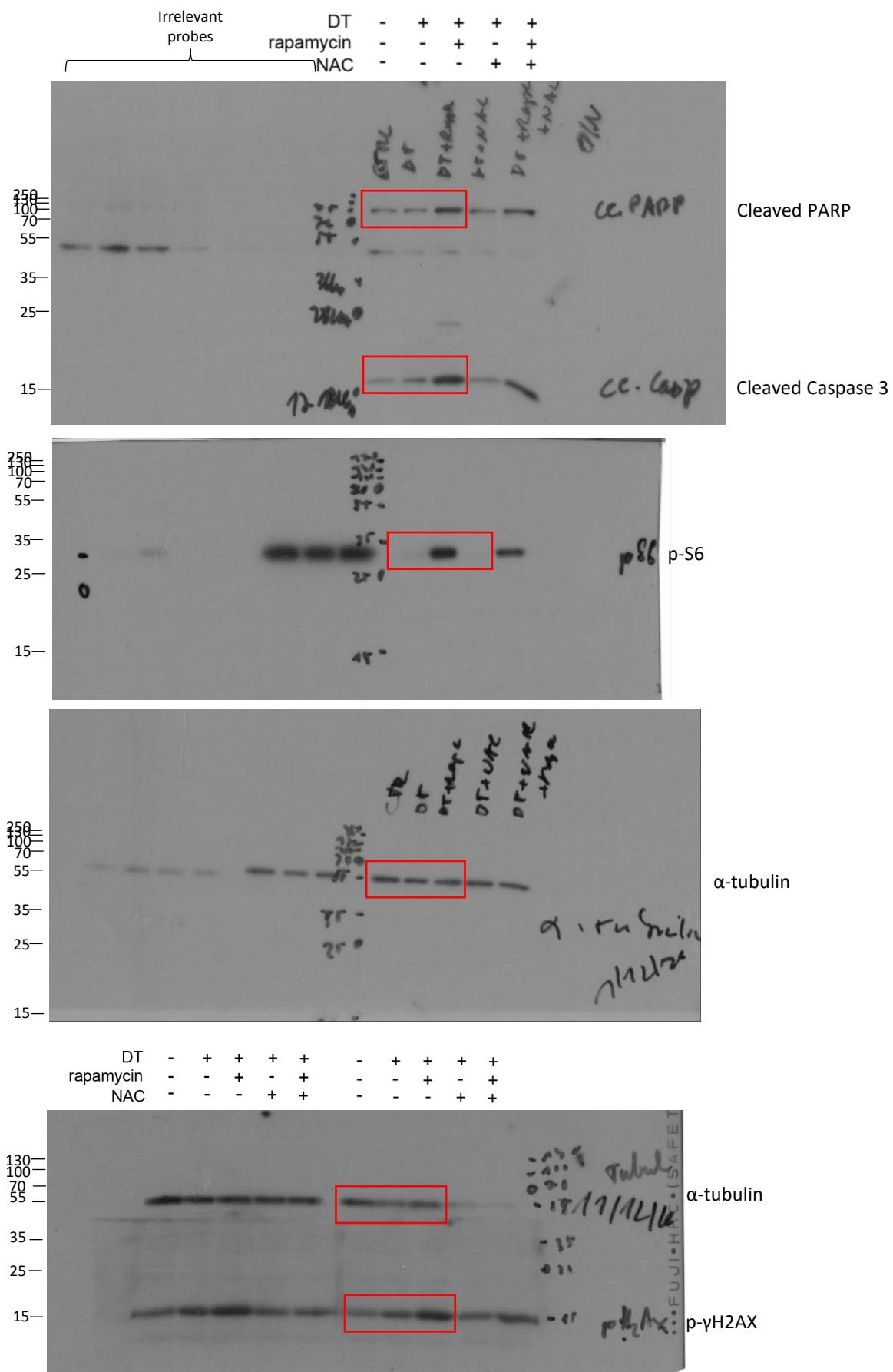
b



Immunoblot scans for Extended data Figure 1i

SI Figure 10

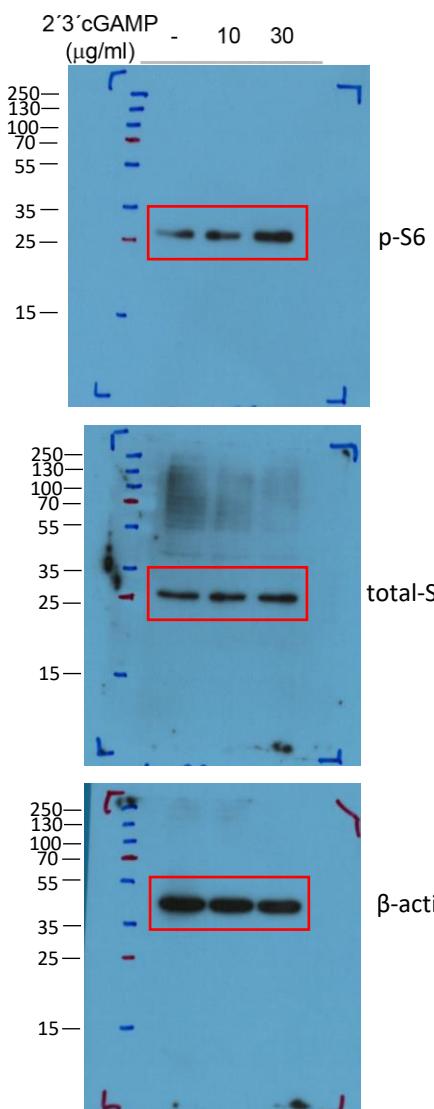
a



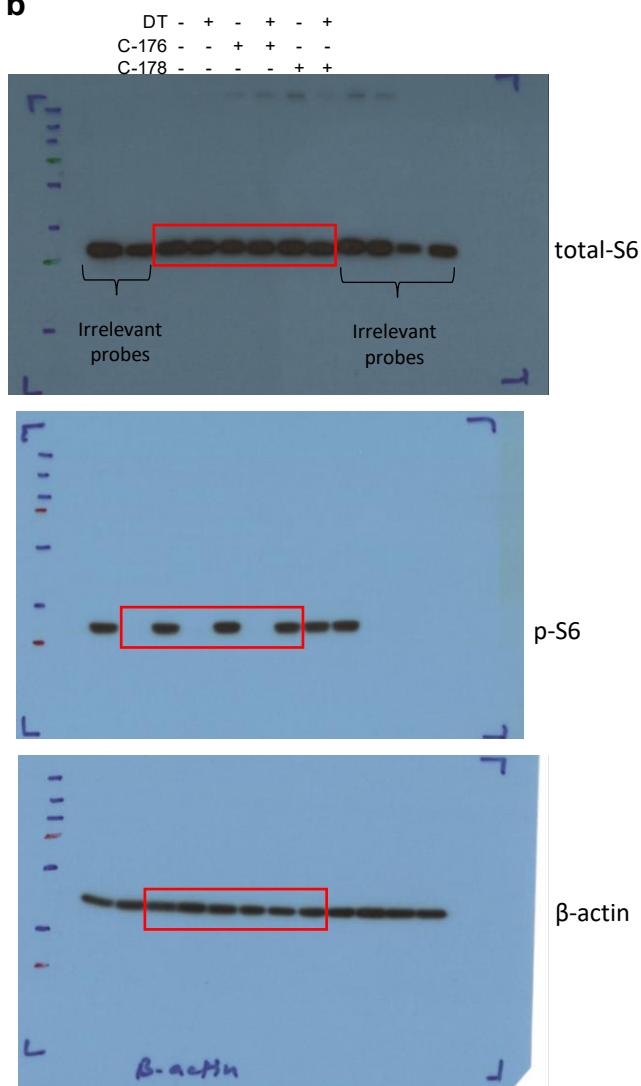
For p γ H2AX detection samples had to be reloaded on a separate gel (separated by grid lines in the Figure)

Immunoblot scans for Extended data Figure 2b

SI Figure 11

a

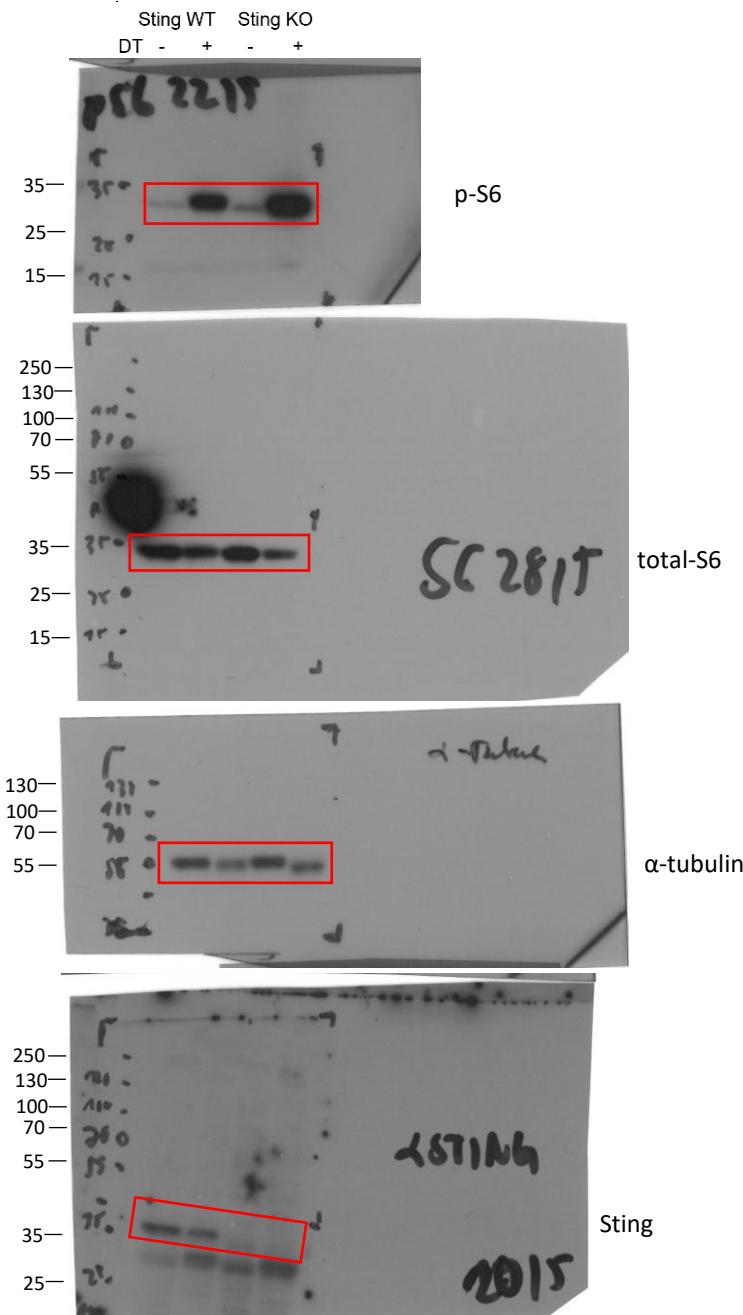
Immunoblot scans for
Extended data Figure 3c

b

Immunoblot scans for
Extended data Figure 3d

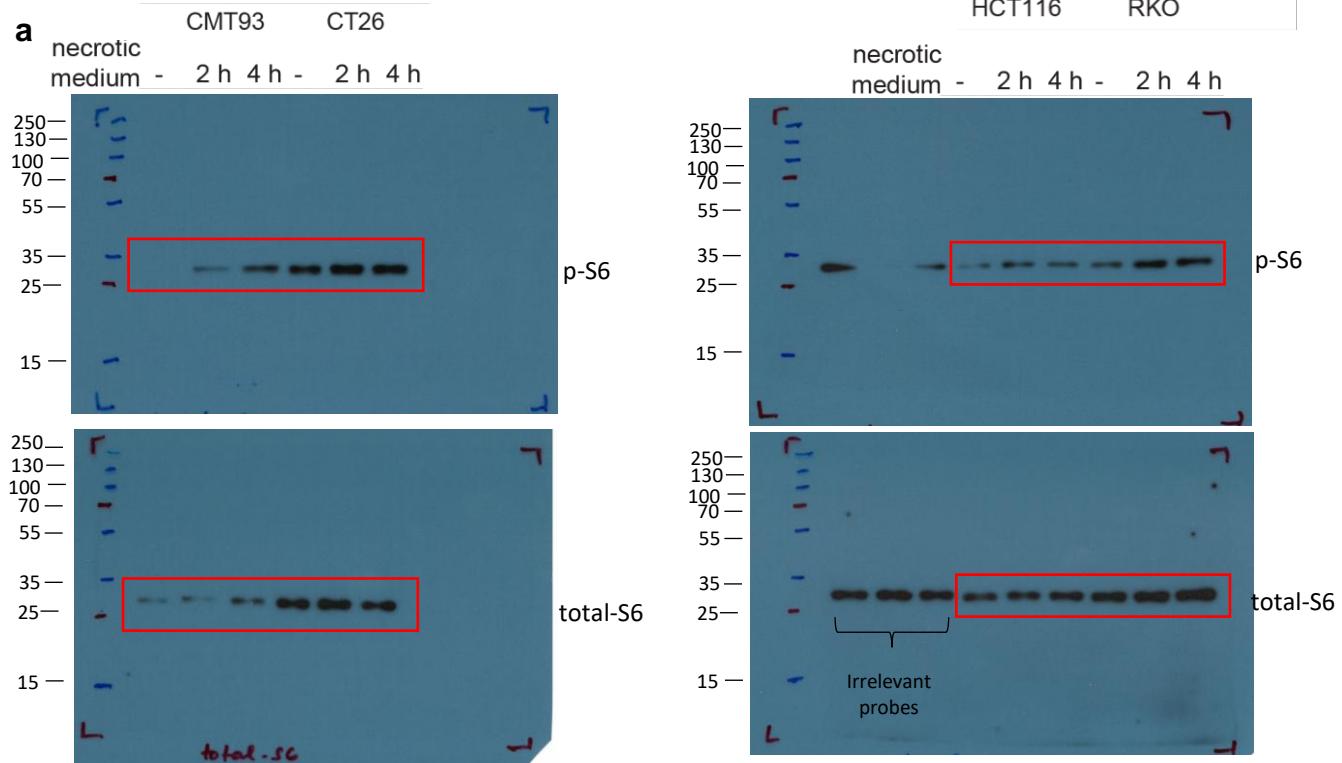
SI Figure 12

a



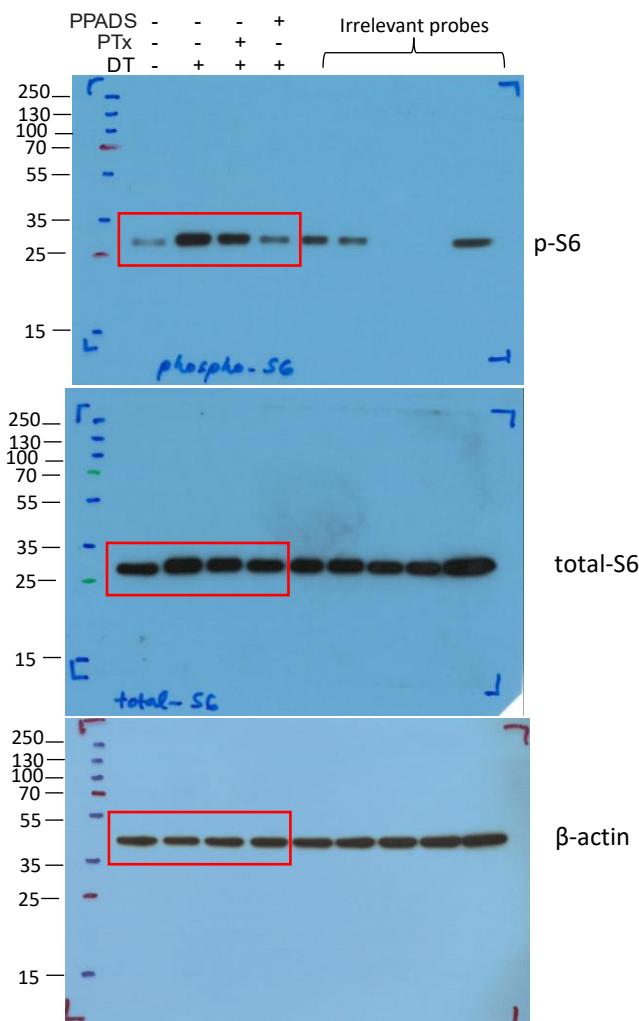
Immunoblot scans for Extended data Figure 3e

SI Figure 13



Immunoblot scans for Extended data Figure 3f

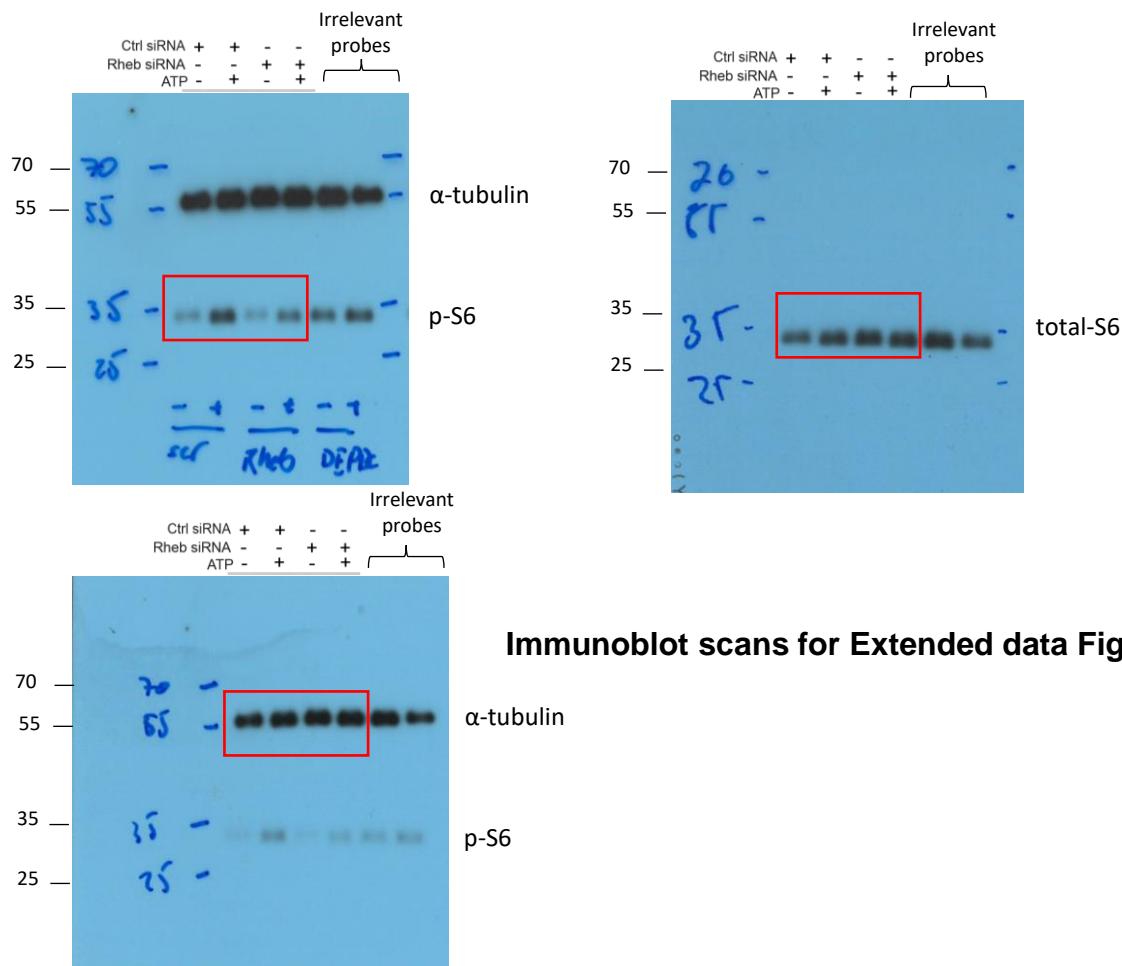
b



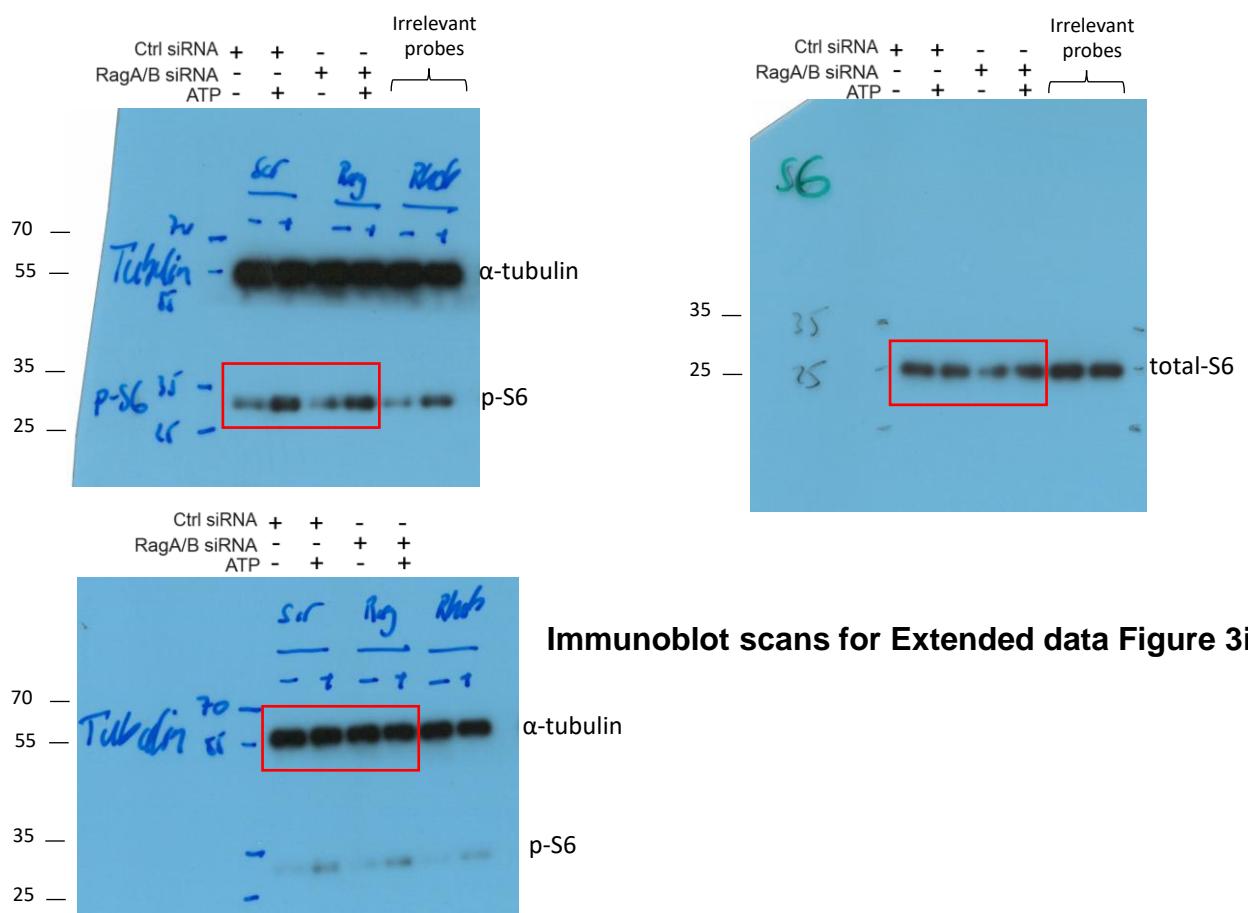
Immunoblot scans for Extended data Figure 3g

SI Figure 14

a

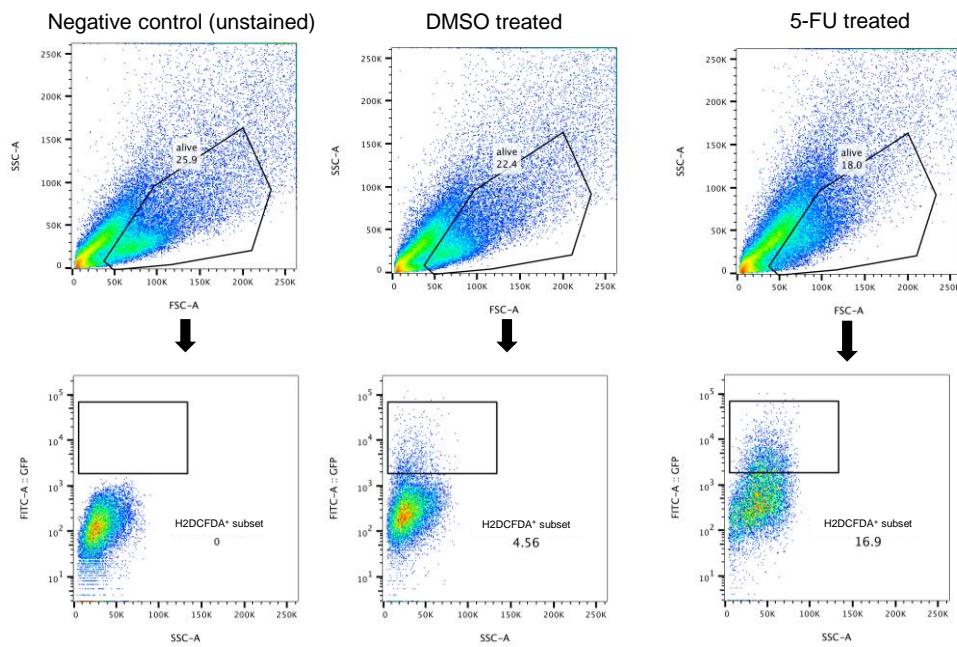


b



SI Figure 15

a



Representation of flow cytometry gating strategy for assessment of H2DCFDA⁺ cells from Figure 4e

SI Table 1

Oligo sequences used in this study

Target	Forward primer	Reverse primer
Isg15	ACCCTTCAGTCTGGTCT	TCGCTGCAGTTCTGTACAC
Infar1	CACGGTCGCTGAGAAGTAAAG	TCTCCTCCTTCGTTGGAATA
Mx1	ATGTCAGCTCCCCAAATGTCC	TGCCTACAGCCACCCCTGG
Ifit1	GCTTGCGAAGGCTCTGAAA	TGGCGATAGGCTACGACTGC
Ifit2	CACCTCTGGACTGGCAATAGC	AGAGGGTCAATGGCGTTCTG
Ifitm1	TCTTCACCATCCTCACGGC	TGTTGCAAGACATCTCACATCATC
C2ta	GACAGAGGCCAGCTAGCC	CTCTCCTGGTCGCCTGCA
Irf1	GCTACCTGGGTAGGACTTG	CAGAGAGACTGCTGCTGACG
Oas	CAAGGTGGTGAAGGGTGGC	TCAAAGCTGGTGAGATTGTTAAGG
Cyclophilin	ATGGTCAACCCCACCGTGT	TTCTGCTGTCTTGGAACTTGTC
RagA	GAACCTGGTGCTGAACCTGT	GATGGCTTCAGACACGATT
RagB	TTCGATTTCTGGGAAACCTG	AGTCACGGCTCTCCACATC
Rheb	GGCAAGTTGTTGGATATGGTGGG	CCAAGATTCTGCCAAAGCCTTC
hRaptor	GGACCTGGCTGTTGACATCT	TGCACTTGGCTTAACAGCAC
hRictor	CGGTTGTAGGTTGCCAGTT	CATGAGGGTGGCAAGAAAGT
hP2RX1	GCTACGTGGTGCAAGAGTC	GTAGTTGGTCCCCTCTCCA
hP2RX2	GCTCCTTCCATCTCACTGG	GGAAAGTGAGCAGCCCTGTAG
hP2RX3	ACAGCCAGGGACATGAAGAC	AGCCGGGTGAAGGAGTATT
hP2RX4	GAGATTCAGATGCGACC	GACTTGAGGTAAGTAGTGG
hP2RX5	CTGGTCGTATGGGTGTTCC	CTGGGCTGGAATGACGTAGT
hP2RX6	ACTCTGTGGAGGGAGCTG	GGCAAGTGGGTGTCAGAACT
hP2RX7	AAGCTGTACCAGCGGAAAGA	GCTCTGGCCTCTGTTTG
hP2RY1	AAAATAGCCCCCTGCAACT	GATCTGATGCCGGATGAACT
hP2RY2	CCACCTGCCTCTCACTAGC	TGGGAAATCTCAAGGACTGG
hP2RY4	CGTCTTCTGCCTCCGCTCT	GCCCTGCACTCATCCCCTTTCT
hP2RY6	AGCTGGGCATGGAGTTAAGA	GCTGACTGGGACCTCTCAAG
hP2RY11	CCTCTACGCCAGCTCTATG	CACTGCCGATGTAGAGTA
hP2RY12	TTTGGCCGAATTCTTACAC	ATTGGGGCACTTCAGCATAAC
hP2RY13	CCCCTGGTACACTTGGAAAGA	TACAGAGGAGGGGGTGATTG
hP2RY14	TCTTGGGCTCATCAGCTT	TCCGTCCCAGTTCACTTTTC
mp2RX1	CATGGGGACAGCTCTTGT	GAGTGCAGCCACTGTCACT
mp2RX2	CCAAGGCACCCCTCAAGTAG	CTCTGCCCTTCTCCAAAG
mp2RX3	TGCTTCAACCAACCCAGTGT	TAAGAGCCCCCTCTCTCCCC
mp2RX4	CCTGGCTACGTCATTGGGT	AAGTGTGGTCACAGCCACA
mp2RX5	TCTACTGCCCATCTTCCGA	ATAGTGTGGGTTGCAGTGGG
mp2RX6	GCTGCACCATGGACCTACTT	GCTTCAGGTGAGCTGTTCT
mp2RX7	GCACGAATTATGGCACCGTC	CCCCACCCCTGTGACATT
mp2RY1	TTATGTCAGCGTGCTGGTGT	ACGTGGTGTACAGCAGGTG
mp2RY2	TCAAACCGGCTTATGGGACC	GGCAGCTGAGGTCAAGTGT
mp2RY4	GCTCTATCTGTTACGGGGG	AGGGAGGAAGCAGTTGTTG
mp2RY6	GGGTAGTGTGGAGTCGTG	AGCGAGTAGACAGGATGGGT
mp2RY12	TGCTGTACACCGCCTGTT	CGGCTCCCAGTTAGCATCA
mp2RY13	GCATCAGGTGGTCAGTCACA	GTGGGGCAAAGCAGACAAAG
mp2RY14	CCACATTGCCAGAACCCCT	AGCCGAGAGTAGCAGAGTGA

SI Table 2

shRNA guide sequences used in the study

Target	Guide sequence
P2x4_sh849	TCTCATAGGTGAAGAAGTCGGA
P2x4_sh877	TTCCATTTGTAGTACTTGGCA
Rictor_sh4860	TAATCTTAGAACATTCTTGCAGA
Rictor_sh5055	TTGTAGAAACTGTACATCTTGA
Raptor_sh973	TAAGGCAACACTGACTGTCTTC
Raptor_sh4182	TTGTTGATGAGCTCTCCGCTGC
Tgfr2	GGCCGCTGCATATCGTCCTG

SI Table 3

Sequences of siRNAs used in this study

Name	Target sequence
ON-TARGET plus SMARTpool siRNA J-057667-09, Rraga	GAAUUCACCUGACGCCAAA
ON-TARGET plus SMARTpool siRNA J-057667-10, Rraga	UCUUAGUAUUGGACGCUAU
ON-TARGET plus SMARTpool siRNA J-057667-11, Rraga	GGGACAACAUUUCCGUAA
ON-TARGET plus SMARTpool siRNA J-057667-12, Rraga	GAAAGAGCGGGUCGGGGAA
ON-TARGET plus SMARTpool siRNA J-066440-05, Rragb	GCGUUUAUCGCGUCCGCUA
ON-TARGET plus SMARTpool siRNA J-066440-06, Rragb	AUGUAUACGUAGGCGAUAU
ON-TARGET plus SMARTpool siRNA J-066440-07, Rragb	GGAAAUGAACCUUGCGGAAU
ON-TARGET plus SMARTpool siRNA J-066440-08, Rragb	GCGAGAUGCCCACCGAUUU
ON-TARGETplus SMARTpool siRNA J-057044-05, Rheb	GCCAAUUUGUUGAUUCCUA
ON-TARGETplus SMARTpool siRNA J-057044-06, Rheb	GCUCGGUGAUGUGACAAUU
ON-TARGETplus SMARTpool siRNA J-057044-07, Rheb	UUAAAGUUUAUCCAUGGCAA
ON-TARGETplus SMARTpool siRNA J-057044-08, Rheb	CCAAGUUGAUCACGGUAAA
ON-TARGETplus Non-targeting Pool	UGGUUUACAUGUCGACUAA, UGGUUUACAUGUUGUGUGA, UGGUUUACAUGUUUUCUGA, UGGUUUACAUGUUUUCUA