Supplementary Figure S1

A) The blots shown in Figure 1B were qualified by using Gel-Pro analyzer software (Rockville, MD, USA). The ratio of LC3II/LC3I to actin was then calculated. The data are represented as mean±SD from three independent experiments.

B) The blots in Figure 1E were qualified and the ratio of LC3II/LC3I to actin was then calculated. The data are represented as mean±SD from three independent experiments.

C) HCT116 cells with stable expression of GFP-LC3 were treated with Embelin as indicated. GFP-LC3 puncta accumulation was observed by a microscope. Quantification of LC3 punctate cells was shown on the right. The data are represented as means±SD of three independent experiments.

D-G) The blots in Figures 1G, 1H, 1I and 1J were qualified and the ratio of LC3II/LC3I to actin was then calculated and shown in D, E, F and G, respectively. The data are represented as mean±SD from three independent experiments.

Supplementary Figure S2

A) The blots in Figure 2A were qualified and the ratio of LC3II/LC3I to actin was then calculated. The data are represented as mean±SD from three independent experiments.

B) MCF7, MCF10A, HepG2 and LO2 cells were individually treated with XIAP specific or control siRNAs. 48 h after transfection, cell lysates were analyzed by Western blotting with the indicated antibodies. The data are representative of two biological replicates.

C) HCT116 cells were infected with lentiviruses expressing control shRNA or 3 different sets of XIAP specific shRNAs. 48 h after infection, cell lysates were subjected to Western blot analysis with the indicated antibodies. The data are representative of three biological replicates.

D-F) The blots in Figures 2B, 2D and 2E were qualified and the ratio of LC3II/LC3I to actin was then calculated and shown in D, E and F, respectively. The data are represented as mean±SD from three independent experiments.

G) HCT116 XIAP KO cells were transfected with Flag-p53-WT (wild type) or the indicated p53 mutants. 24 h after transfection, cell lysates were analyzed by Western blotting with the indicated antibodies. The data are representative of two biological replicates.

H) The blots in Figure 2F were qualified and the ratio of LC3II/LC3I to actin was then calculated. The data are represented as mean±SD from three independent experiments.

Supplementary Figure S3

A) Lysates from HCT116 cells were immunoprecipitated with anti-Mdm2 antibody or an isotope-matched control antibody. Immunoprecipitates and cell lysates were analyzed by Western blotting. The data are representative of two biological replicates.

B) The blots in Figure 3C were qualified and the ratio of Mdm2 to actin was then calculated. The data are represented as mean±SD from three independent experiments.

C and D) HCT116 XIAP WT and XIAP KO cells were treated with 50μg ml^{-1} cycloheximide for the indicated periods of time. The half-life of Mdm2 was measured by Western blot analysis (C). We should mention that amounts of cell lysates were adjusted to achieve similar expression levels of Mdm2 at time 0. The blots were qualified and the ratio of Mdm2 to actin was then calculated. The data are represented as mean±SD from three independent experiments (D).

E) HCT116 XIAP KO cells were transfected with Mdm2 and XIAP constructs as indicated. 24 h after transfection, cells were treated with 50μg ml^{-1} cycloheximide for the indicated periods of time followed by western blot analysis with the indicated antibodies. The data are representative of three biological replicates.

Supplementary Figure S4

A) Lysates from HEK 293T cells expressing HA-Mdm2 alone or HA-Mdm2 plus Flag-XIAP were immunoprecipitated with anti-Flag antibody. Immunoprecipitates were then analyzed by Western blotting. The data are representative of two biological

replicates.

B) HCT116 XIAP KO cells were transfected with HA-Mdm2 alone or HA-Mdm2 plus Flag-XIAP D148A/W310A. 24 h after transfection, cells were treated with CHX for the indicated periods of time. Cell lysates were then analyzed by Western blotting. The blots were qualified and the ratio of HA-Mdm2 to Actin was then calculated. The data are represented as mean±SD from three independent experiments

C) Lysates from HEK 293T cells expressing HA-Mdm2 alone or HA-Mdm2 plus Flag-XIAP H467A were immunoprecipitated with anti-Flag antibody followed by Western blot analysis. The data are representative of two biological replicates.

Supplementary Figure S5

A) Purified Flag-Mdm2 C464A was incubated with increasing amounts of His-XIAP recombinant protein in a total of 20 μl *in vitro* ubiquitination reaction buffer at 37°C for 2h. The reaction mixtures were analyzed by Western blotting with anti-Mdm2 antibody. The data are representative of three biological replicates.

B) HCT116 cells expressing XIAP specific or control siRNAs were treated with 20μM MG-132 for 4h. Cell lysates were denatured before immunoprecipitation with anti-Mdm2 and anti-p53 antibodies. Immunoprecipitates were analyzed by Western blotting with anti-ubiquitin antibody. The data are representative of three biological replicates.

C) $p53^{-/-}Mdm2^{-/-}$ MEF cells were transfected with the indicated plasmids. 24 h after transfection, cell lysates were immunoprecipitated with anti-HA antibody. The input and immunoprecipitates were analyzed by Western blotting. The data are representative of two biological replicates.

Supplementary Figure S6

A) HCT116 XIAP WT and XIAP KO cells were treated with EBSS for the indicated periods of time. Cell lysates were subjected to Western blot analysis with the indicated antibodies. The data are representative of three biological replicates.

B-D) The blots in Figures 4B, 4C and 4F were qualified and the ratio of LC3II/LC3I

to actin was then calculated and shown in B, C and D, respectively. The data are represented as mean±SD from three independent experiments.

Supplementary Figure S7

Expression levels of Mdm2, p53, XIAP and LC3 conversion in the tumors excised from 4 indicated different groups of mice (Figure 5A) were evaluated by Western blot analysis. Left and Right indicate tumors grown in the left and right flanks of mice, respectively. The data are representative of two biological replicates.

Supplementary Figure S8

Histological sections of the indicated xenograft tumors were stained with the indicated antibodies.

Supplementary Figure S9

A and B) The blots in Figures 5G and 5H were qualified and the ratio of LC3II/LC3I to actin was then calculated and shown in A and B, respectively. The data are represented as mean±SD from three independent experiments.

Supplementary Figure S10

The tumor tissues (T) from human Breast, Lung and Stomach and their adjacent normal tissues (N) were homogenized for protein extraction. Protein extracts were analyzed by Western blotting with the indicated antibodies. As shown in the table, 5 of 31 esophagus cancers (31%), 3 of 5 intestine cancers (60%), 1 of 3 breast cancers (33%), 2 of 8 lung cancers (25%), and 3 of 10 stomach cancers (30%) exhibited the great autophagy inhibition along with the elevated expression of p-XIAP, XIAP, and p53 and the decreased expression of Mdm2 compared to those from their matched adjacent normal tissues. The data are representative of three biological replicates.

Supplementary Figure S11

Histological sections of the tumor tissues from human Breast, Colon, Esophagus,

Stomach, and Lung and their adjacent normal tissues were stained with the indicated antibodies.

Figure S1

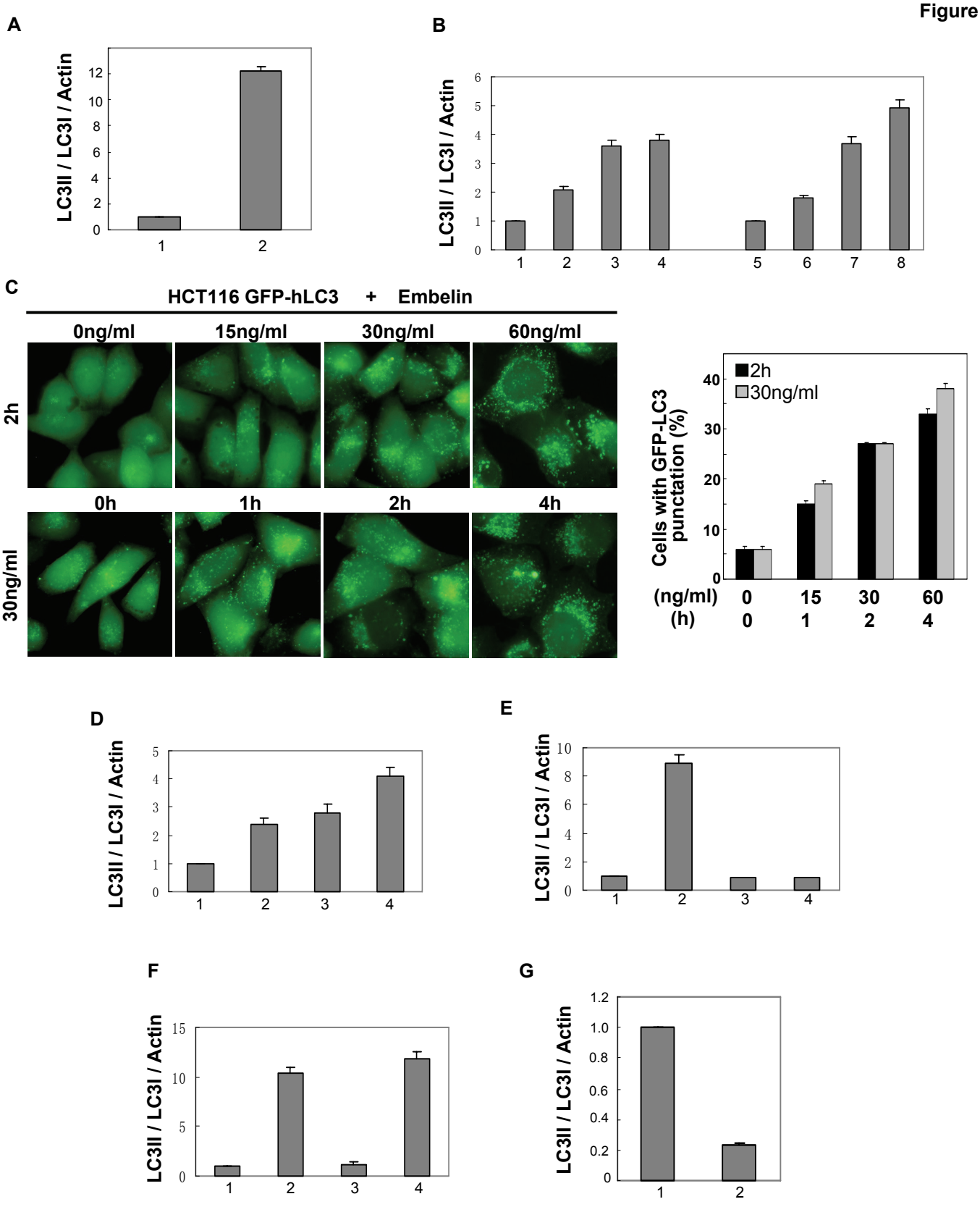

A
LC3II / LC3I / Actin
B
LC3II / LC3I / Actin
C
HCT116 GFP-hLC3 + Embelin
0ng/ml
15ng/ml
30ng/ml
60ng/ml
2h
30ng/ml
0h
1h
2h
4h
Cells with GFP-LC3 punctation (%)
2h
30ng/ml
(ng/ml) 0 15 30 60
(h) 0 1 2 4
D
LC3II / LC3I / Actin
E
LC3II / LC3I / Actin
F
LC3II / LC3I / Actin
G
LC3II / LC3I / Actin

Figure S2

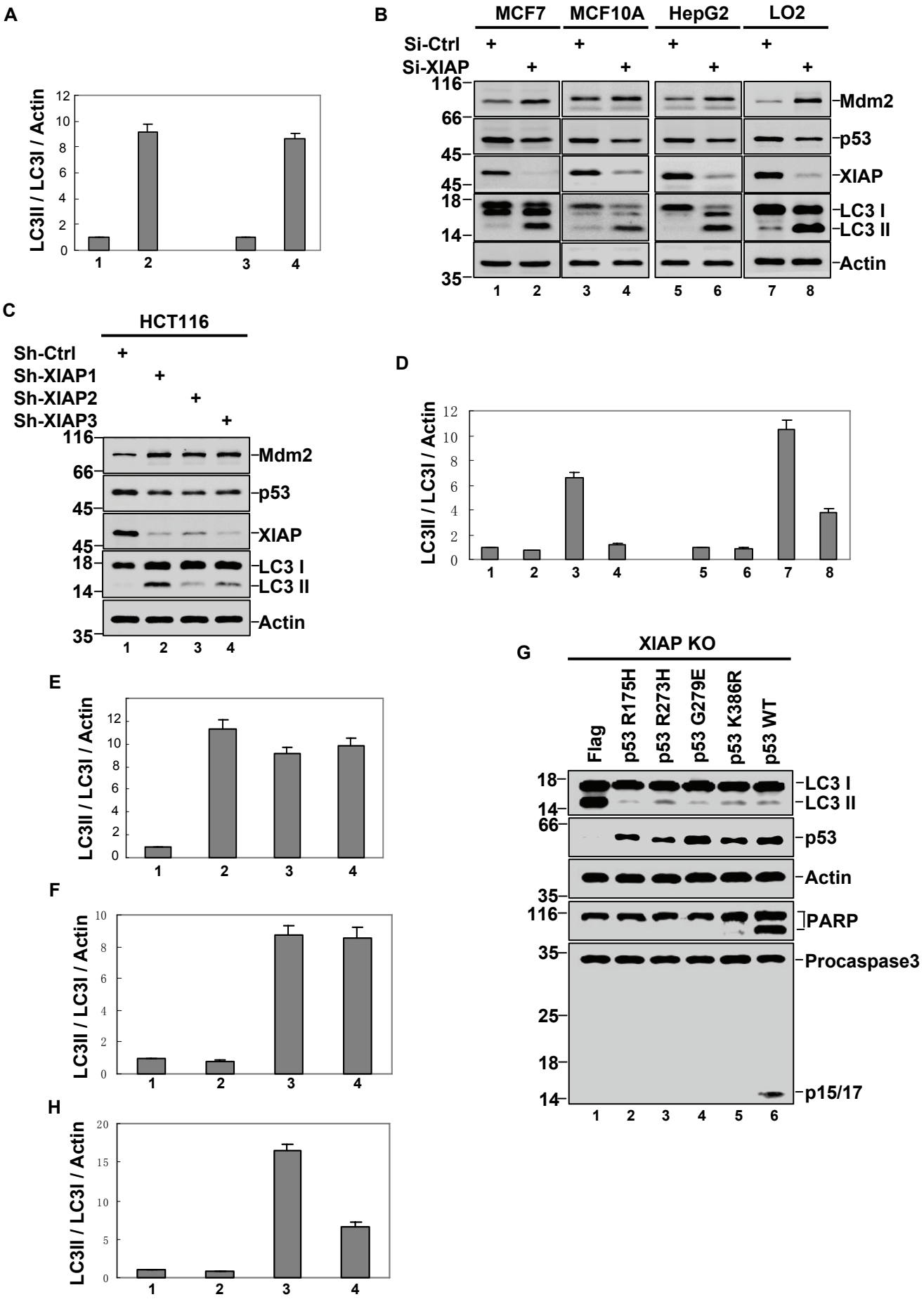

A
LC3II / LC3I / Actin
B
MCF7
MCF10A
HepG2
LO2
Si-Ctrl
Si-XIAP
Mdm2
p53
XIAP
LC3 I
LC3 II
Actin
C
HCT116
Sh-Ctrl
Sh-XIAP1
Sh-XIAP2
Sh-XIAP3
D
E
F
G
XIAP KO
Flag
p53 R175H
p53 R273H
p53 G279E
p53 K386R
p53 WT
PARP
Procaspase3
p15/17
H

Figure S3

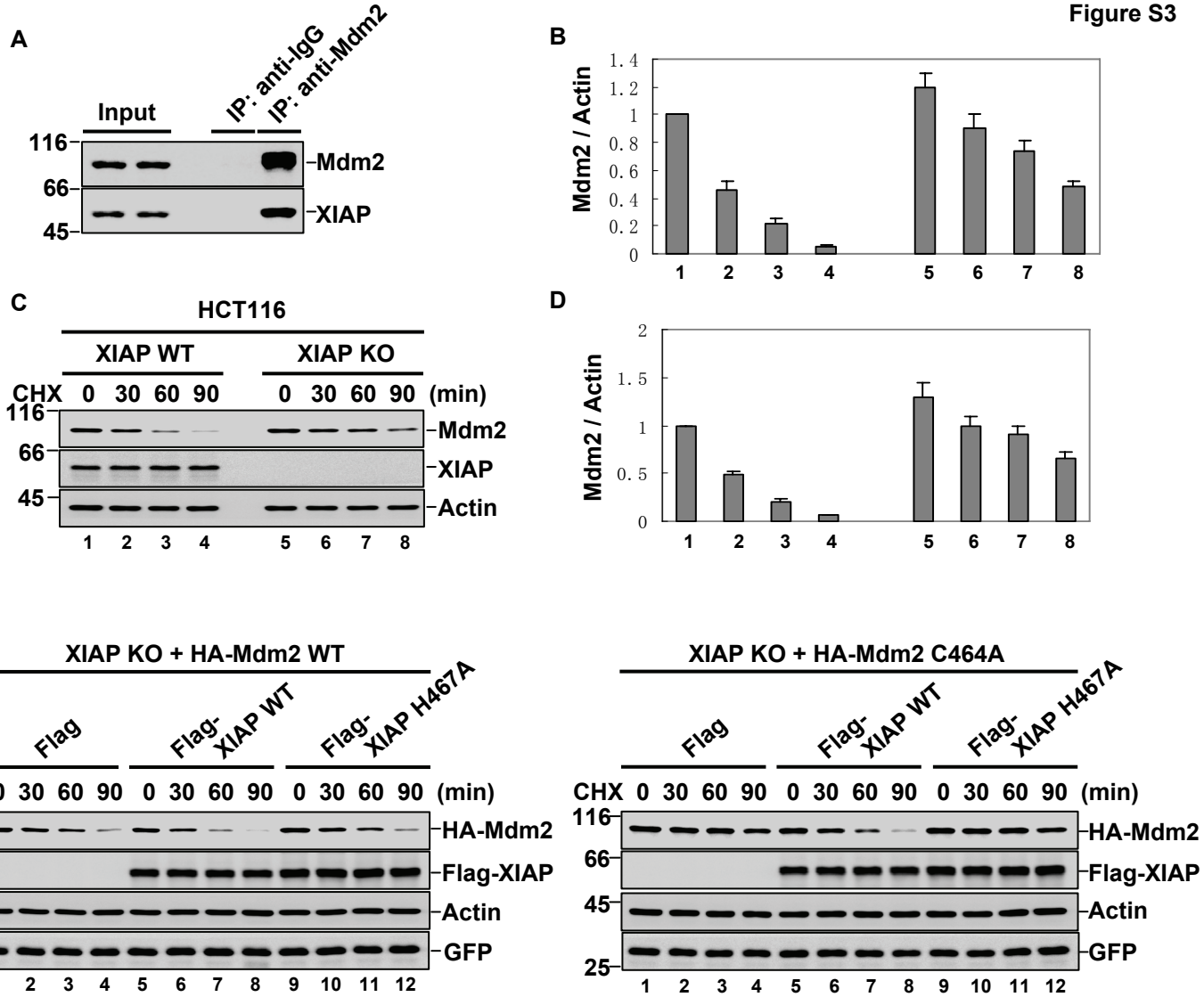

A
Input
IP: anti-IgG
IP: anti-Mdm2
116
66
45
Mdm2
XIAP
B
Mdm2 / Actin
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1 2 3 4 5 6 7 8
C
HCT116
XIAP WT
XIAP KO
CHX 0 30 60 90 0 30 60 90 (min)
116
66
45
Mdm2
XIAP
Actin
1 2 3 4 5 6 7 8
D
Mdm2 / Actin
2
1.5
1
0.5
0
1 2 3 4 5 6 7 8
E
XIAP KO + HA-Mdm2 WT
XIAP KO + HA-Mdm2 C464A
Flag
Flag-XIAP WT
Flag-XIAP H467A
CHX 0 30 60 90 0 30 60 90 0 30 60 90 (min)
116
66
45
25
HA-Mdm2
Flag-XIAP
Actin
GFP
1 2 3 4 5 6 7 8 9 10 11 12

Figure S4

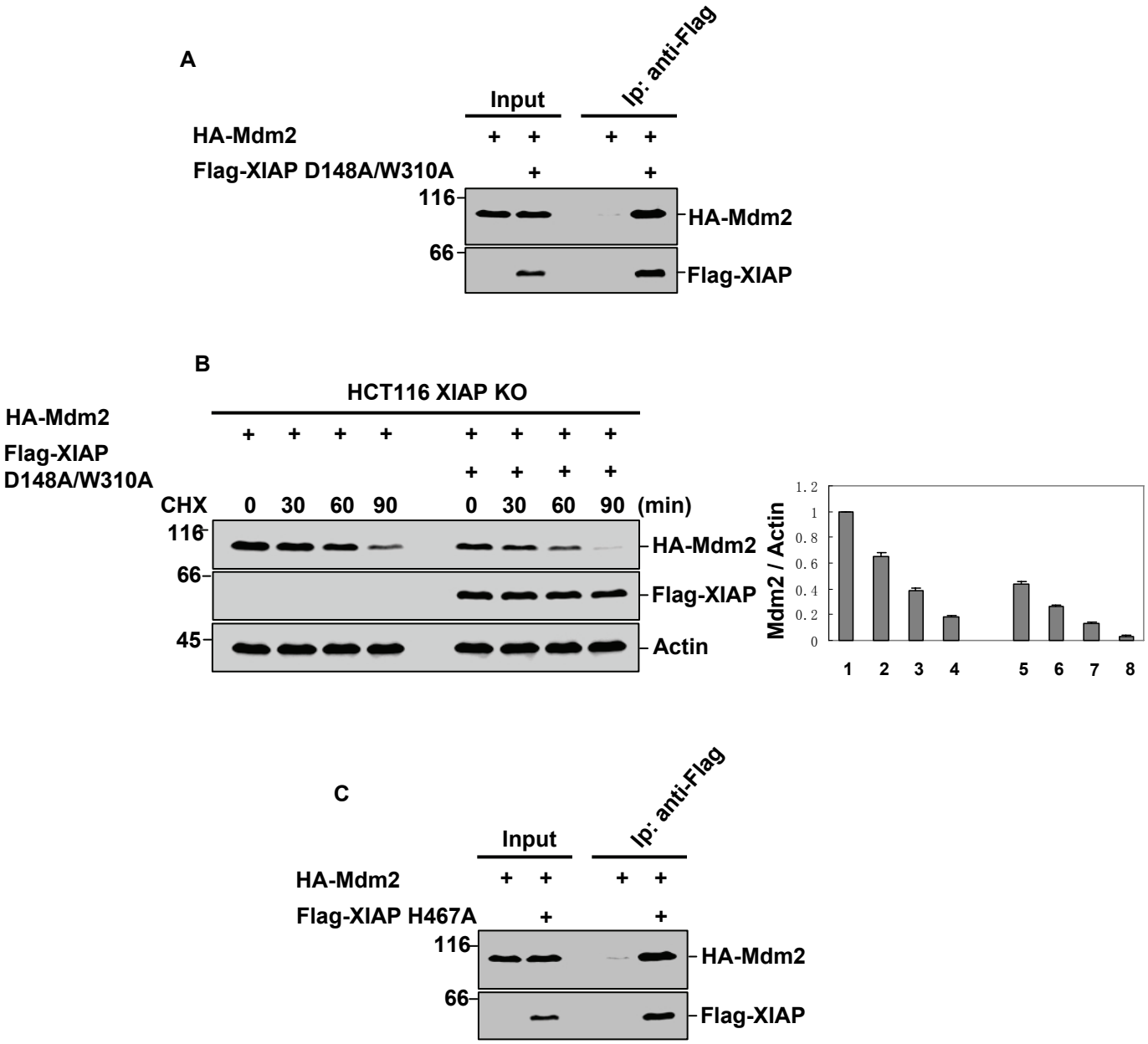

A
Input
Ip: anti-Flag
HA-Mdm2
Flag-XIAP D148A/W310A
116
66
HA-Mdm2
Flag-XIAP
B
HCT116 XIAP KO
HA-Mdm2
Flag-XIAP
D148A/W310A
CHX 0 30 60 90 0 30 60 90 (min)
116
66
45
HA-Mdm2
Flag-XIAP
Actin
Mdm2 / Actin
1.2
1
0.8
0.6
0.4
0.2
0
1 2 3 4 5 6 7 8
C
Input
Ip: anti-Flag
HA-Mdm2
Flag-XIAP H467A
116
66
HA-Mdm2
Flag-XIAP

Figure S5

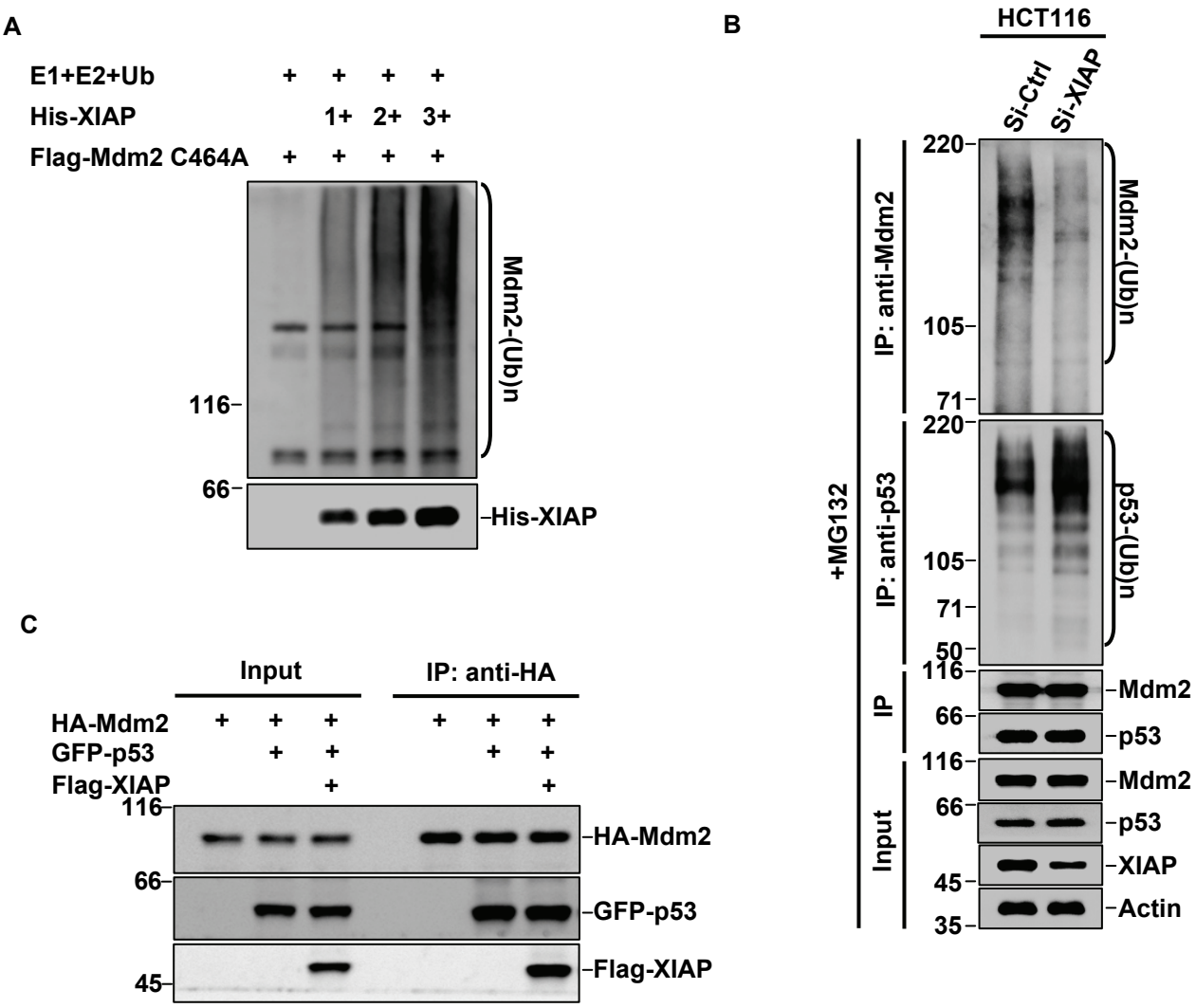

A
E1+E2+Ub + + + +
His-XIAP 1+ 2+ 3+
Flag-Mdm2 C464A + + + +
116
66
Mdm2-(Ub)n
His-XIAP
B
HCT116
Si-Ctrl
Si-XIAP
+MG132
IP: anti-Mdm2
IP: anti-p53
IP
Input
220
105
71
50
116
66
45
35
Mdm2-(Ub)n
p53-(Ub)n
Mdm2
p53
XIAP
Actin
C
Input
IP: anti-HA
HA-Mdm2 + + + + + +
GFP-p53 + + + +
Flag-XIAP + +
116
66
45
HA-Mdm2
GFP-p53
Flag-XIAP

Figure S6

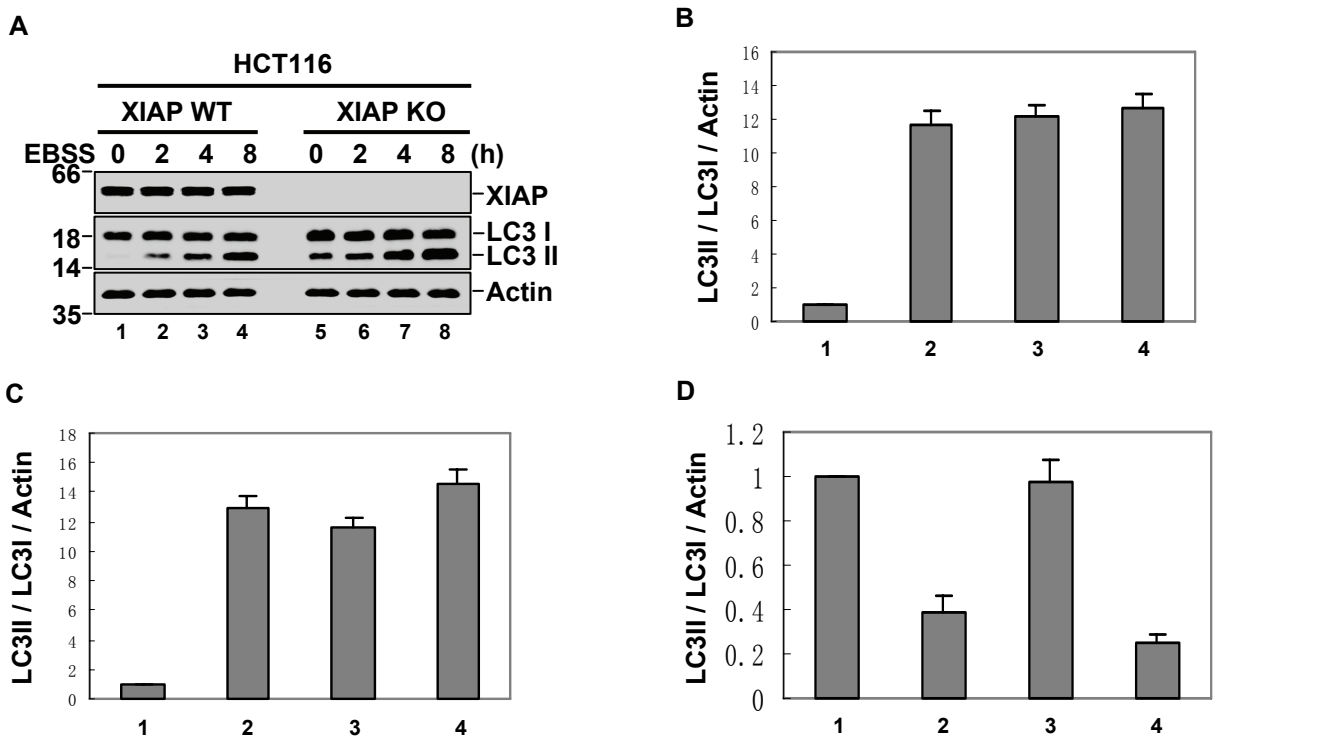

A
HCT116
XIAP WT
XIAP KO
EBSS 0 2 4 8 0 2 4 8 (h)
66
18
14
35
XIAP
LC3 I
LC3 II
Actin
1 2 3 4 5 6 7 8
B
LC3II / LC3I / Actin
C
LC3II / LC3I / Actin
D
LC3II / LC3I / Actin

Figure S7

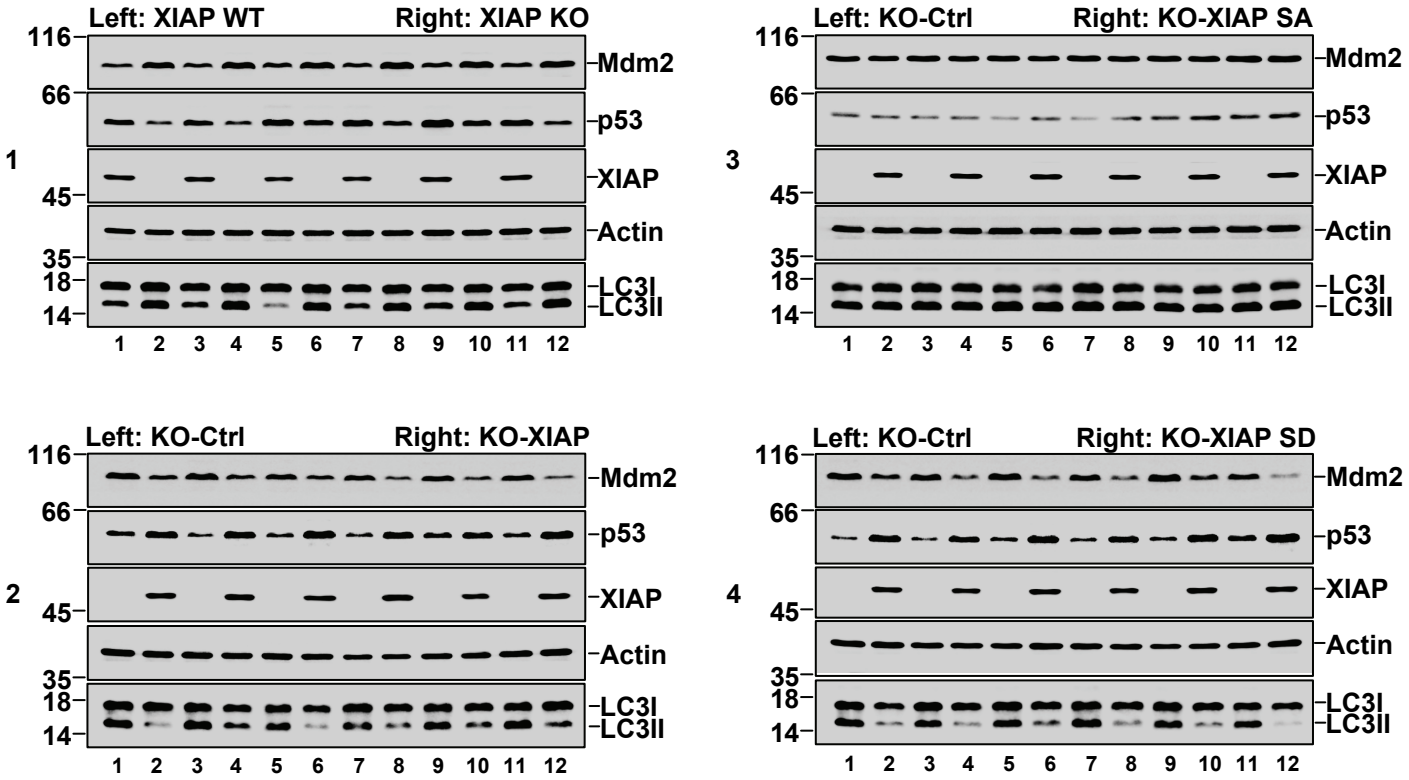

1
Left: XIAP WT
Right: XIAP KO
116
66
45
35
18
14
Mdm2
p53
XIAP
Actin
LC3I
LC3II
1 2 3 4 5 6 7 8 9 10 11 12
3
Left: KO-Ctrl
Right: KO-XIAP SA
2
Left: KO-Ctrl
Right: KO-XIAP
4
Left: KO-Ctrl
Right: KO-XIAP SD

Figure S8

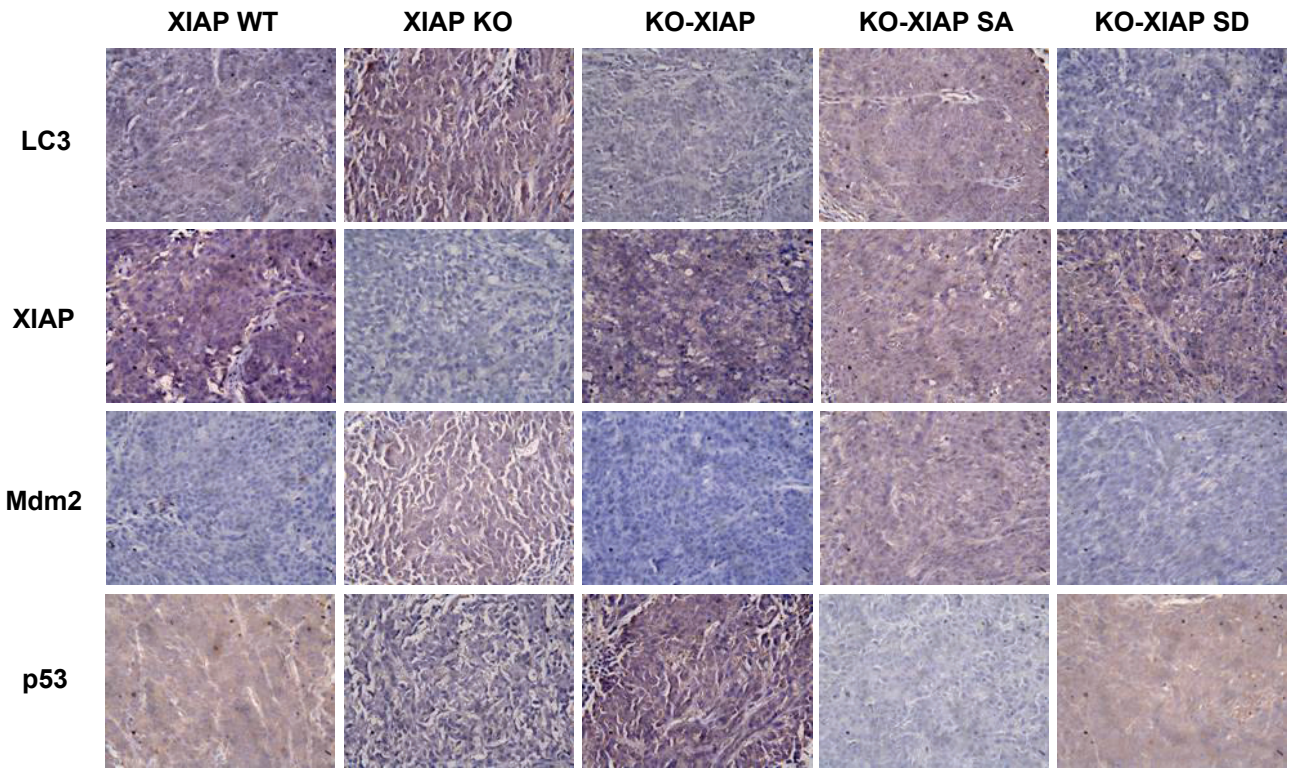


Figure S9

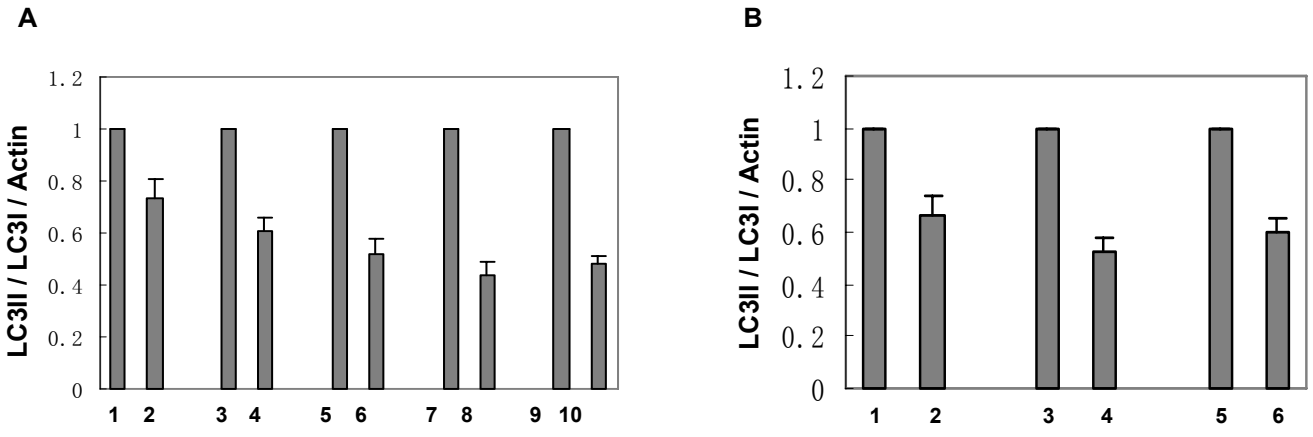
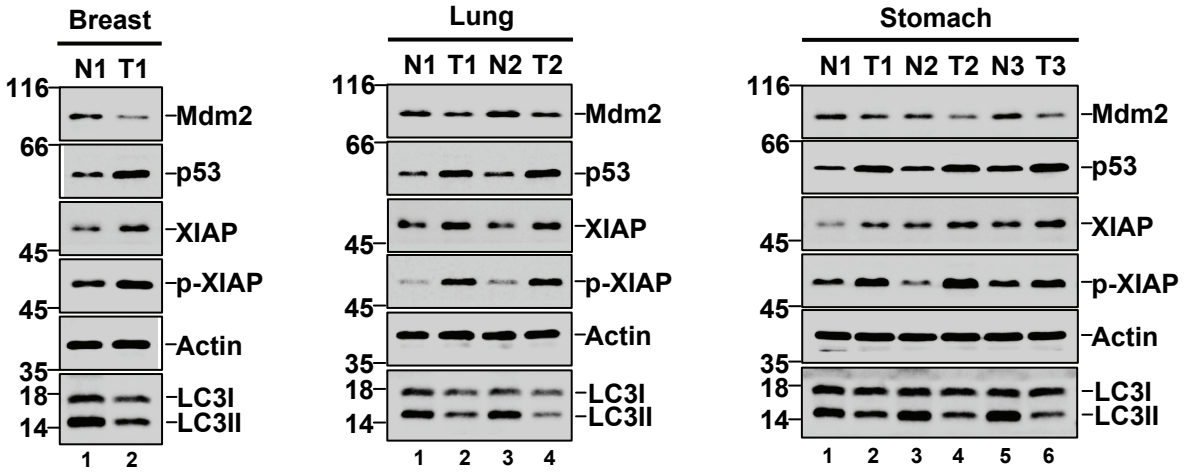
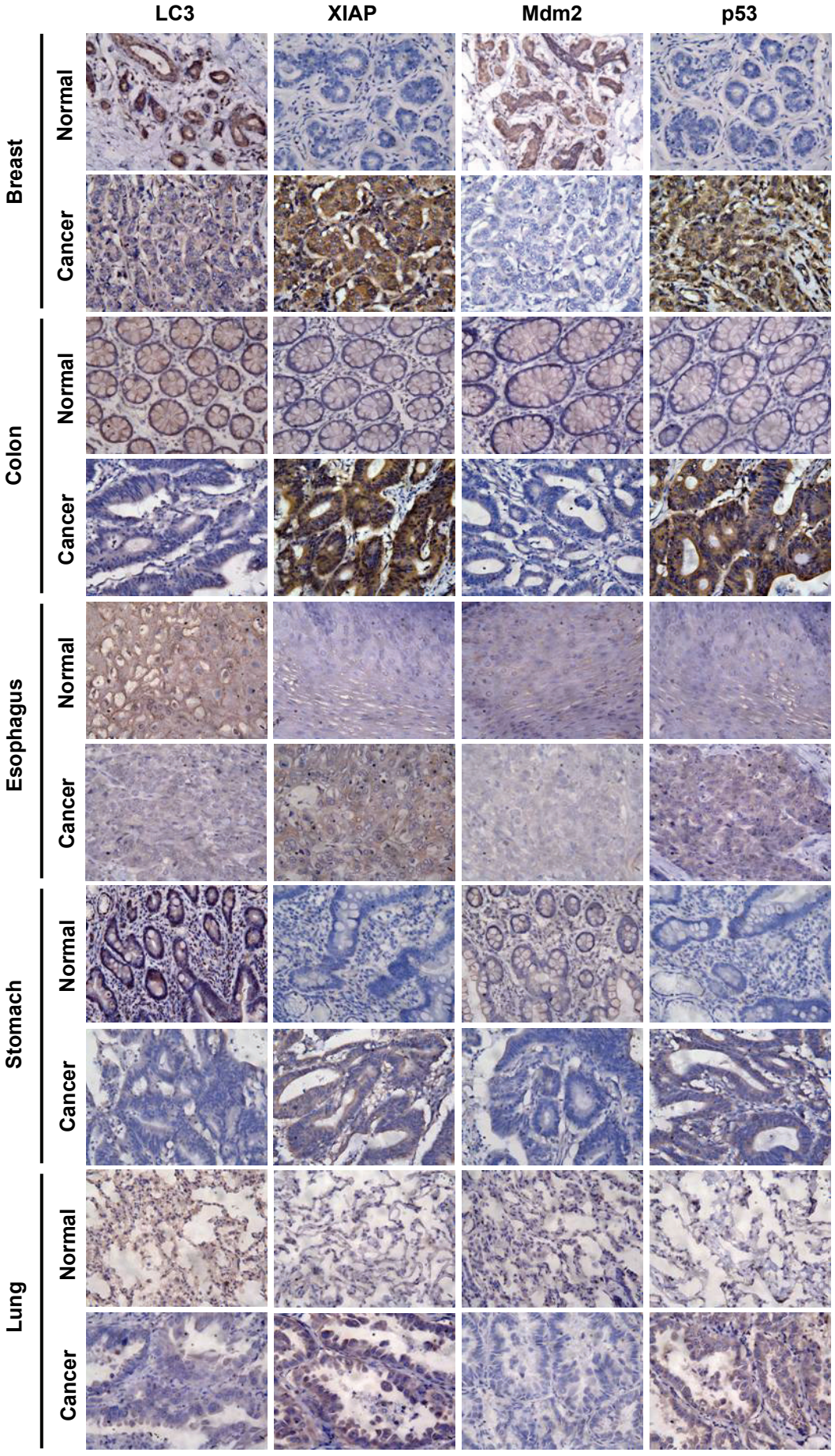

A
LC3II / LC3I / Actin
1.2
1
0.8
0.6
0.4
0.2
0
1 2 3 4 5 6 7 8 9 10
B
LC3II / LC3I / Actin
1.2
1
0.8
0.6
0.4
0.2
0
1 2 3 4 5 6

Figure S10



Esophagus	31% (5 / 16)
Intestine	60% (3 / 5)
Breast	33% (1 / 3)
Lung	25% (2 / 8)
Stomach	30% (3 / 10)

Figure S11


LC3
XIAP
Mdm2
p53
Breast
Normal
Cancer
Colon
Normal
Cancer
Esophagus
Normal
Cancer
Stomach
Normal
Cancer
Lung
Normal
Cancer