A

Genotypes	Pdx1-Cre;Kras^{G12D};Sag$^{+/+}$	Pdx1-Cre;Kras^{G12D};Sag$^{fl/+}$	Pdx1-Cre;Kras^{G12D}; Sag$^{fl/fl}$
# Mice with tumor/total mice	2/14 (14.3%)	5/11 (45.5%)	24/29 (82.8%)
Median latent periods (weeks)	> 38.5	> 38.5	10.0
Sex of mice with tumors	1 male /3 females	1 males /4 females	9 males /15 females
Locations of tumors	On face only: 1 female On anus only: 1 female	On face only: 1 male On anus only: 4 females	On face only: 9 males and 3 females On anus only: 7 female On both sites: 5 female

B

Pdx1-Cre; Kras^{G12D}

Pdx1-Cre; Sag$^{fl/fl}$
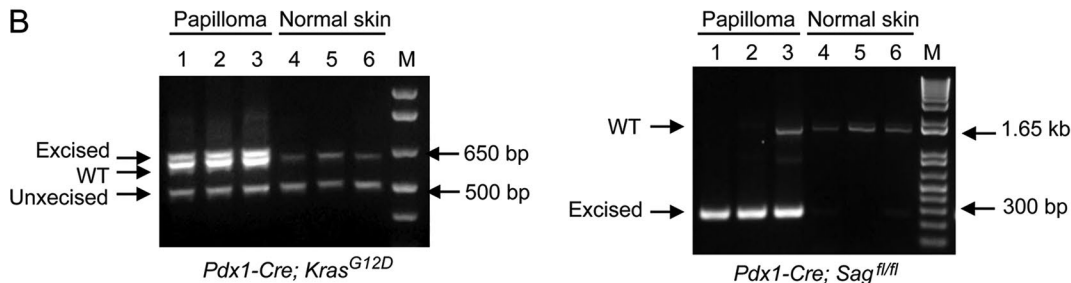
C

| Genotypes	K5-Cre;Kras^{G12D};Sag$^{+/+}$	K5-Cre; Kras^{G12D};Sag$^{fl/+}$	K5-Cre; Kras^{G12D};Sag$^{fl/fl}$
# mice with tumor/total mice	10/18 (55.6%)	14/16 (87.6%)	20/22 (90.9%)
Median latent periods (weeks)	16.7	14.2	9.1
Sex of mice with tumors	7 males/11 females	4 males/12 females	6 males/16 females
Locations of tumors	On face only: 3 males and 5 females On anus only: 1 female On both sites: 1 female	On face only: 3 males and 7 females On anus only: 1 female On both sites: 3 females	On face only: 5 males and 8 females On anus only: 1 female On both sites: 6 females

D

Kras^{G12D}

Sag
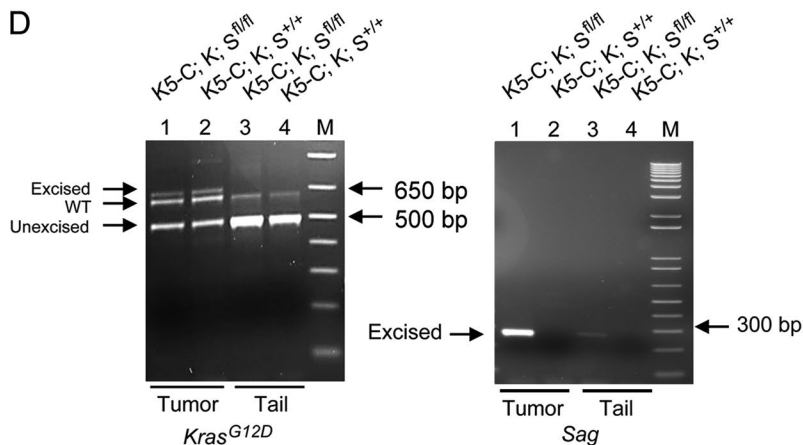
Figure S1. **Sag deletion promotes Kras^{G12D}-induced skin tumor formation.** (A) Development of Kras^{G12D}-induced papillomas in mice with three different Sag genotypes. The Sag deletion was mediated by Pdx1-Cre. Percentage of mice with tumor development, latent time period for tumor formation, and tumor location were recorded for up to 40 wk of age. Pdx1-C;K;S$^{fl/fl}$ mice have significantly shorter time-to-tumor initiation compared with Pdx1-C;K;S$^{+/+}$ and Pdx1-C;K;S$^{fl/+}$ mice (P < 0.001 for both comparisons). Pdx1-C;K;S$^{+/+}$ appears to have longer time-to-tumor initiation compared with Pdx1-C;K;S$^{fl/+}$, but it did not reach statistical significance (P = 0.11), which is likely because of a small number of events (mice with tumors) observed in the Pdx1-C;K;S$^{+/+}$ group. (B) Kras activation and Sag deletion were measured by PCR. DNA was isolated from three independent skin papillomas, along with normal skin tissue from the same mouse with the indicated genotype and subjected to PCR genotyping for Kras activation (left) and Sag deletion (right). (C) Development of Kras^{G12D}-induced papillomas in mice with three different Sag genotypes. The Sag deletion was mediated by K5-Cre. Percentage of mice with tumor development, latent time period for tumor formation, and tumor location were recorded for up to 17 wk of age. (D) DNA was isolated from two skin papillomas, along with tail skin tissues with the indicated genotype, and subjected to PCR genotyping for Kras activation (left) and Sag deletion (right).
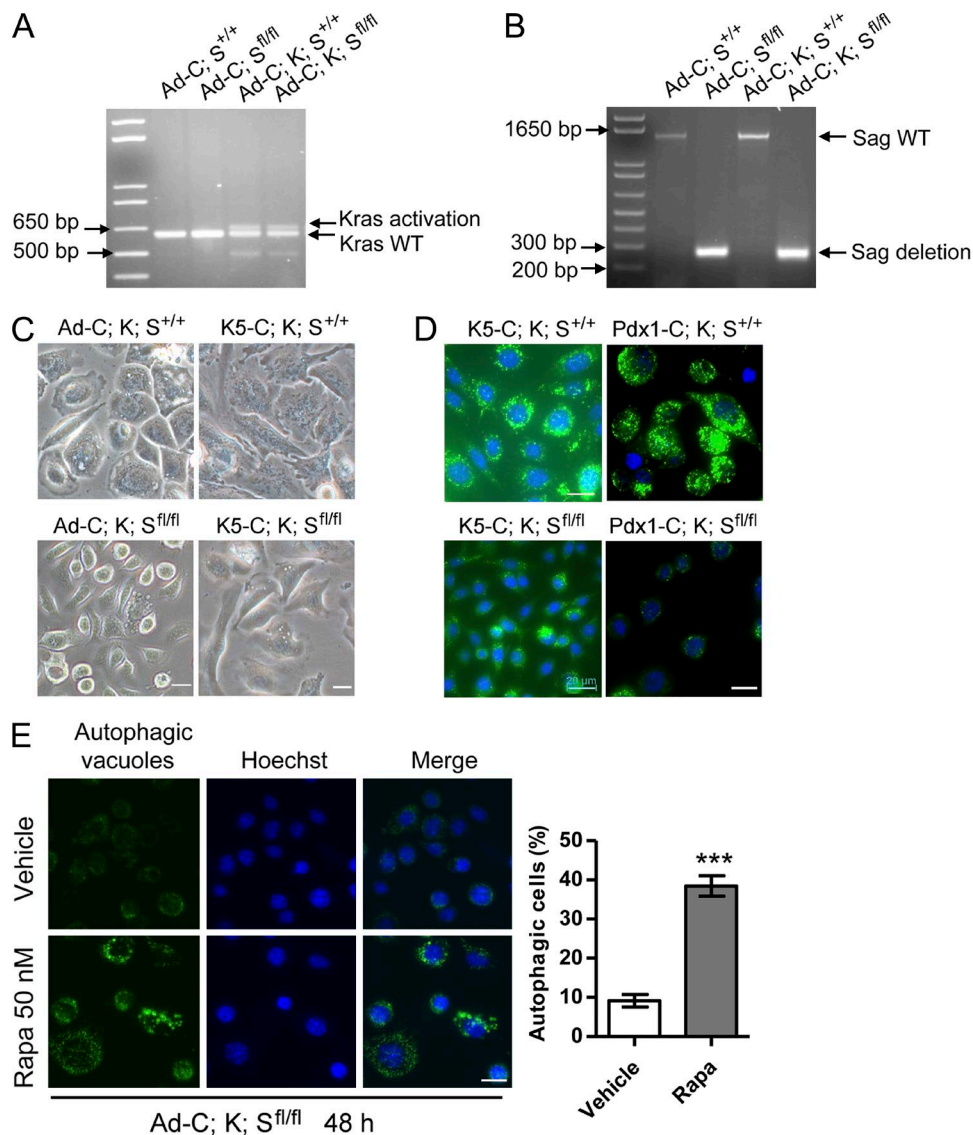
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Figure S2.   ***Sag* deletion inhibits autophagy in both keratinocytes and skin tumors.** (A and B) *Kras* activation (A) and *Sag* deletion (B) measured by PCR. Primary keratinocytes with the indicated genotypes were isolated from p1 pups and infected with Ad-Cre, followed by DNA isolation and PCR genotyping. (C) Morphological appearance. Keratinocytes with the indicated genotypes were infected with Ad-Cre to activate *Kras* and delete *Sag*. Cells at passage 3 were imaged by a microscope. (D) Autophagy measurement by staining. Keratinocytes (left) and skin tumor cells, established from papilloma tissues (right) with the indicated genotypes, were stained with a Cyto-ID autophagy detection kit. Cells were imaged by fluorescence microscopy. (E) Autophagy induction by rapamycin. *Ad-C;K;S^fl/fl* keratinocytes were treated with vehicle (0.1% DMSO) or rapamycin (Rapa) for 48 h and subjected to autophagy staining using a Cyto-ID autophagy detection kit. Cells with >10 autophagic vacuoles were counted as autophagic cells. The data shown are from a single representative experiment out of three repeats. A total of 400 cells were counted in each group. Error bars indicate the SEM. ***, P < 0.001. Bars, 20 µm.
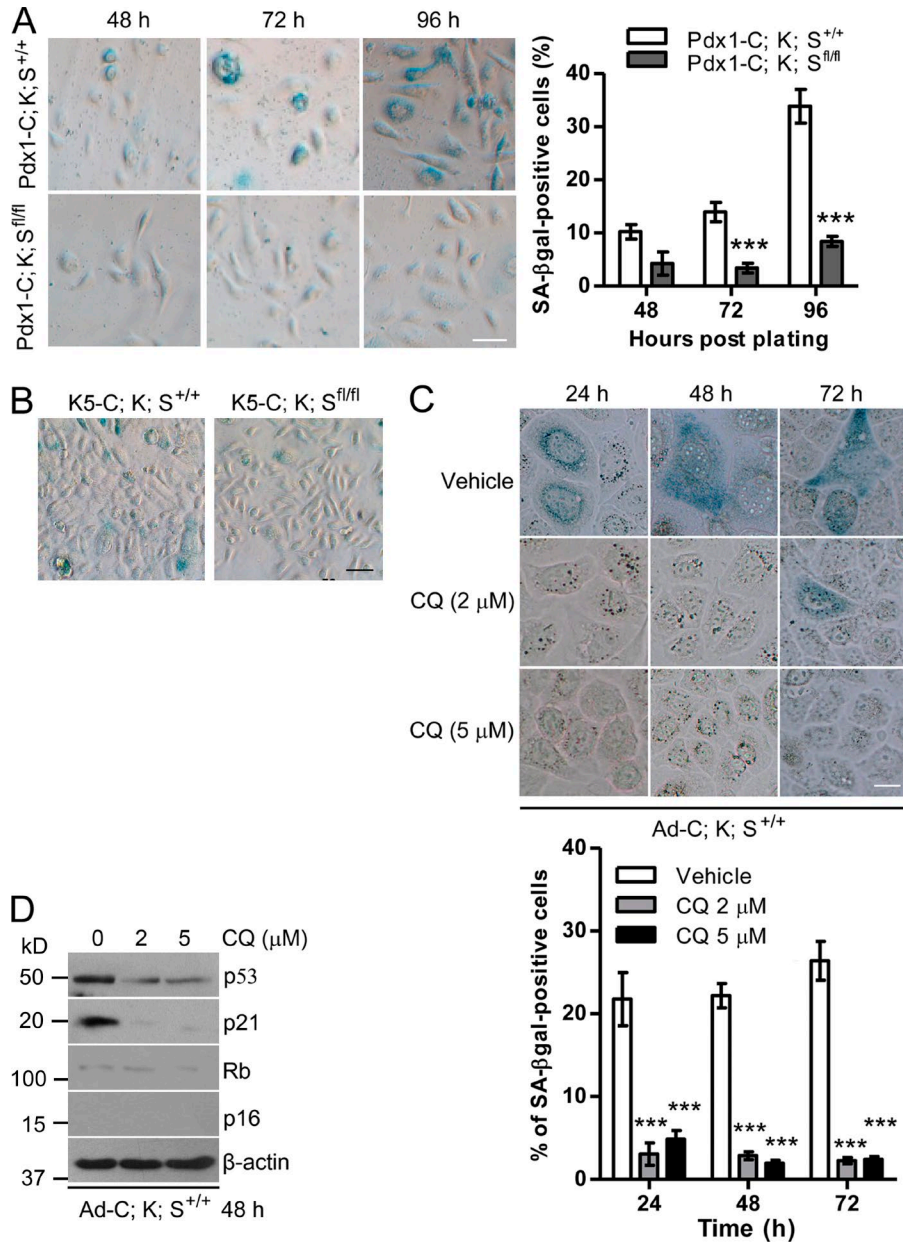
Figure S3. ***Sag*** **deletion inhibits senescence in both keratinocytes and skin tumor cells.** (A) Senescence measurement by staining. Skin tumor cells with the indicated genotypes were stained at various time points with X-gal and photographed. (B and C) Senescence measurement by staining. Keratinocytes with the indicated genotypes were left untreated (B) or were treated with CQ (C), followed by staining with X-gal, and photographed. The data shown are from a single representative experiment out of three repeats. A total of 200 cells were counted in each group (bottom). Error bars indicate the SEM. ***, P < 0.001. Bars, 20 µm. (D) The *Ad-C;K;S*[+/+] keratinocytes were treated with the autophagy inhibitor CQ and subjected to IB.
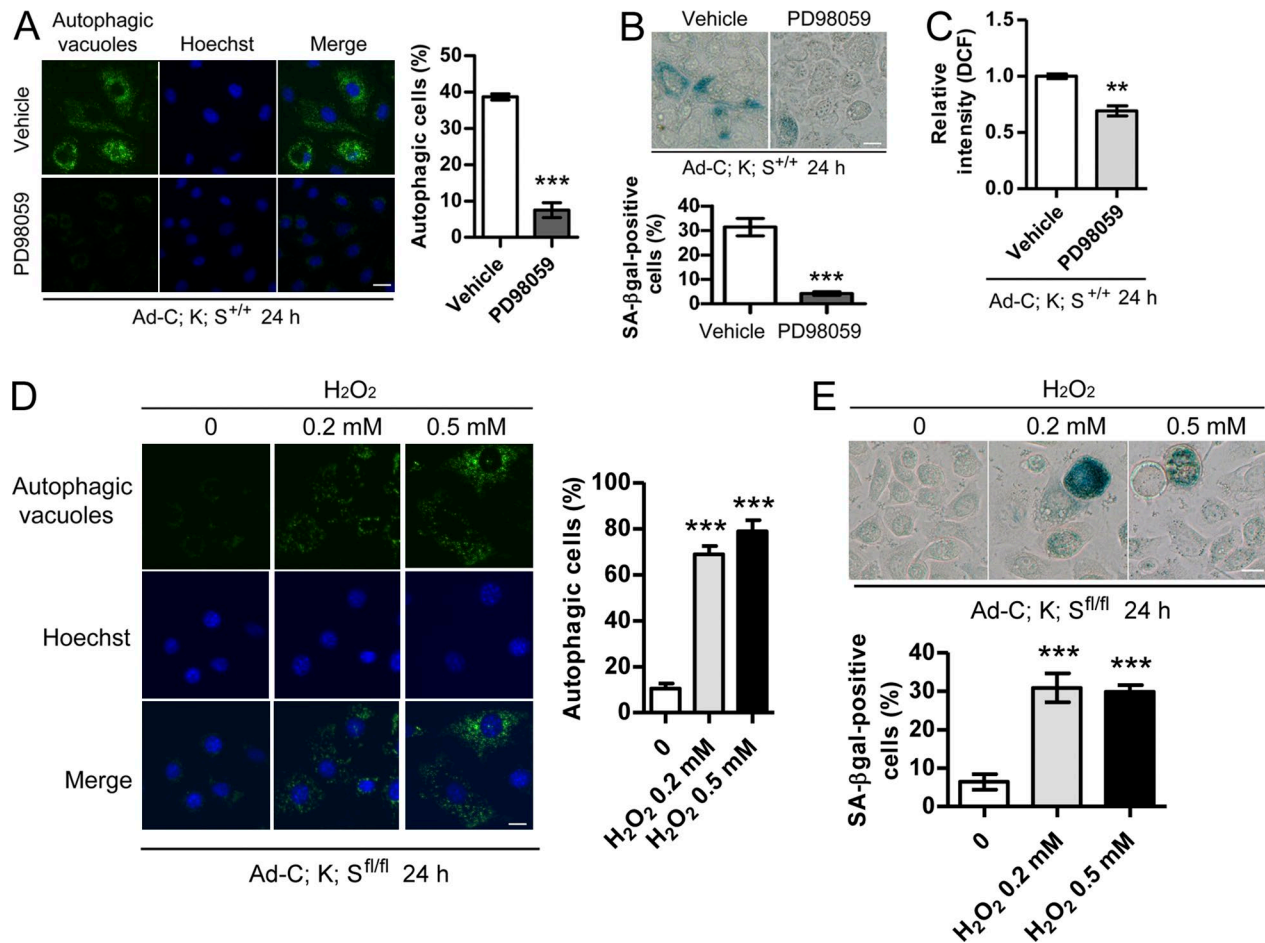
Figure S4. **Mek inhibitor blocks, whereas H_2O_2 promotes, autophagy and senescence in keratinocytes.** (A–E) Keratinocytes with the indicated genotypes were left untreated or were treated with 0.3 µM PD98059 (A–C) or were left untreated or were treated with H_2O_2 (D and E) and subjected to ROS measurement using DCFHDA staining (C; $n = 2$), autophagy staining using Cyto-ID autophagy detection kit (A and D), or senescence staining using X-gal (B and E). The data shown are from a single representative experiment out of three repeats. A total of 150 cells were counted in each group (for A, B, D, and E). Error bars indicate the SEM. **, $P < 0.01$; ***, $P < 0.001$. Bars, 20 µm.
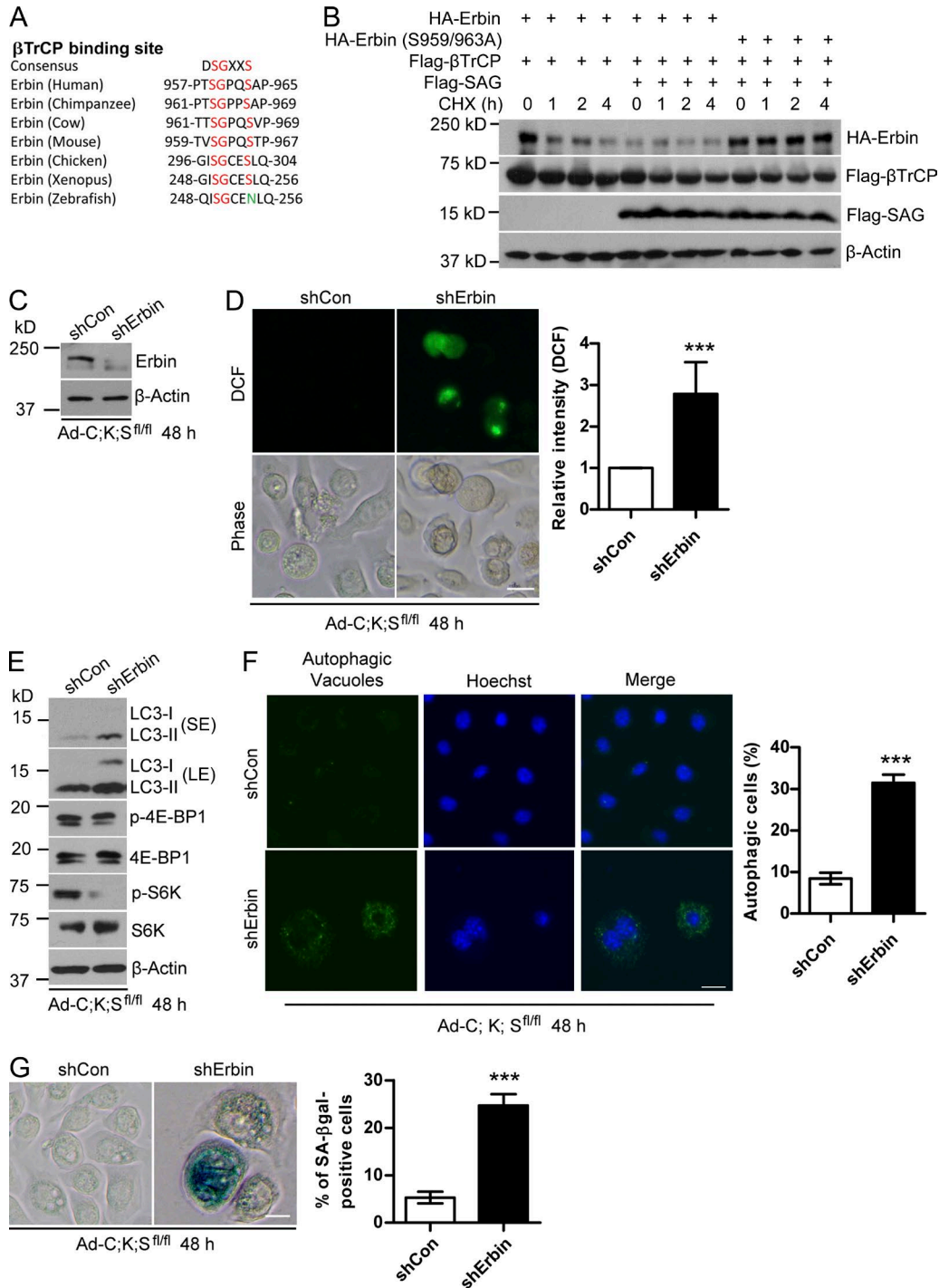
Figure S5. **Erbin is a novel substrate of SAG-βTrCP E3 ubiquitin ligase.** (A) Evolutionary conservation of the βTrCP-binding site on Erbin. Consensus βTrCP-binding motif found in Erbin from seven different species. (B) SAG promotes βTrCP-mediated degradation of Erbin but not its binding site mutant. HEK293 cells were transfected with the indicated plasmids. 48 h later, cells were treated with CHX for the indicated time periods and harvested for IB. (C–G) *Ad-C;K;S$^{fl/fl}$* keratinocytes were transfected with shErbin or shCon, followed by IB (C and E) or staining for ROS (D; *n* = 2), autophagy (F), or senescence (G). The data shown are from a single representative experiment out of three repeats. A total of 100 cells were counted in each group (F and G). Error bars indicate the SEM. LE, long exposure; SE, short exposure. ***, P < 0.001. Bars, 20 µm.