

Supplementary figure legends

Supplementary figure S1. *ATM* is altered in LUAD and reduced expression correlates with poor survival

A) Genome browser view, illustrating the genomic locations for *ATMIN* and *WWOX* genes on chromosome 16, generated as a snapshot from Integrative Genomics Viewer.

B) OncoPrint plot showing distinct genetic alterations in the indicated genes across a set of LUAD cases (n=230). Percentages on the right indicate cases with the displayed alterations. Analysis performed using sequencing and copy number alterations data from TCGA in cBioPortal.

C) Kaplan-Meier plot visualising the association between *ATM* expression and survival, generated using KM Plotter.

D) Kaplan-Meier plot visualising the association between *DYNLL1* expression and survival, generated using KM Plotter.

Supplementary figure S2. *ATMIN* and *ATM* immunohistochemical staining on LUAD and adjacent normal lung tissue

A) Representative images, illustrating the scoring of *ATMIN* immunohistochemistry on LUAD and adjacent normal lung tissue.

B) Immunohistochemical staining showing *ATM* protein expression in human lung sections of tissue microarray (48 cases, 96 cores).

C) Quantification of *ATM* protein expression in human lung sections of tissue microarray (48 cases, 96 cores).

Supplementary figure S3. LUAD tumors deficient for Atmin or Atm exhibit activation of MAPK pathway and increase cell proliferation

A) Representative images illustrating histological analysis of lung lesions in KP mice, generated 10 weeks after Cre administration. H&E (Haematoxylin and eosin), pERK, TTF1, Sftpc immunohistochemistry staining at low and high (insert) magnifications. Scale bars, 100 μm .

B) Representative images of H&E sections illustrating the tumor burden in lungs isolated from mice of the indicated genotypes. Scale bar, 1000 μm .

C) Quantification of lesions detected in lungs of mice of the indicated genotypes. Each dot represents an individual mouse; mean is indicated by red horizontal line. *P* values calculated using Mann-Whitney U non-parametric test.

D) Examples of Ki67 staining in lung tumors from the indicated mouse genotypes. Scale bar, 20 μm .

E) Quantification of phospho-histone 3 (pH3) staining on lung tumors from mice of the indicated genotypes. At least 20 tumors from 3 mice per genotype were quantified. Bar chart shows mean + SEM. *P* values calculated using Mann-Whitney U non-parametric test.

F) Examples of pH3 staining in lung tumors from the indicated mouse genotypes. Scale bar, 20 μm .

Supplementary figure S4. Deletion of *Atmin* or *Atm* increases LUAD tumor burden

A) Representative images illustrating the tumor grading system. Upper and lower panels represent low and high magnification images, respectively. Scale bars, 50 μm .

B) Schematic illustration of the experimental approach used (upper panel) and a representative image of reconstructed μCT scan data illustrating a lesion in the mouse lung, 8 weeks post-intubation (lower panel). White arrow head indicates a lung lesion.

C) Dot plot illustrating the total number and volume of individual lesions in mice of the indicated genotypes, 8 weeks post-intubation. Columns represent individual mice (n=3 per genotype). Each dot represents an individual lesion, color-coded according to the respective mouse genotype.

D) Graph illustrating changes in the number of lung lesions in mice of the indicated genotypes over time.

E) Graph illustrating changes in the total volume of lesions in mice of the indicated genotypes over time. At least 3 mice per genotype were scanned and analyzed. Values are arithmetic mean + SEM.

Supplementary figure S5. *Atmin* ^{$\Delta L/+$} KP tumor cells-maintained expression of *Atmin* target gene *Dynll1*

A) Establishment of primary clonal lung tumor cell lines of the indicated genotypes.

B) Representative western blots showing ATM and p53 expression in the lung tumor cell lines.

C) Bar graph showing *Dynll1* expression in the clonal lung tumor cells.

D) Bar graph showing *Gli1* expression in the clonal lung tumor cells.

E) Bar graph showing *Ptch1* expression in the clonal lung tumor cells.

Supplementary figure S6. Homozygous and Heterozygous *Atmin* loss increases cell proliferation and tumor grafts

A) Graph showing differences in cell proliferation between genotypes.

B-C) Graph showing the volume of xenograft tumors at the indicated timepoints after subcutaneous injection of *Atmin*^{ΔL/+} KP and KP cells.

D-F) Graph showing the volume of xenograft tumors at the indicated timepoints after subcutaneous injection of *Atmin*^{ΔL/ΔL} KP and KP cells.

G) Bar graph showing the weight of xenograft tumors at the end point after subcutaneous injection of 100,000 *Atmin*^{ΔL/+} KP and KP cells (left) or 100,000 *Atmin*^{ΔL/ΔL} KP and KP cells (right).

H) Validation of *Atmin* RNA-Scope probe. Representative images of *Atmin* mRNA expression in normal lung and tumor sections of *Atmin*^{ΔL/ΔL} KP mice.

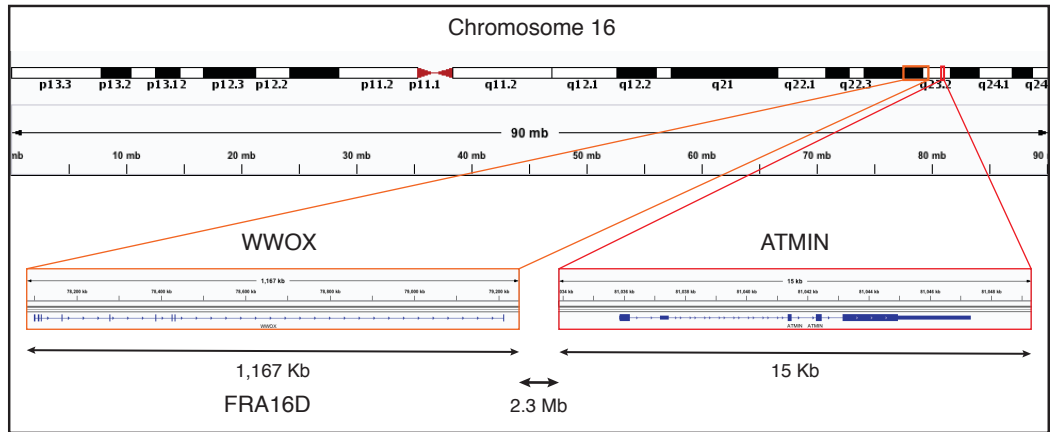
Supplementary figure S7. ATM and ATMIN deficiency confers resistance to replication stress

A) Representative images showing 53BP1 foci and γH2AX foci formation in the primary tumors of the indicated genotypes.

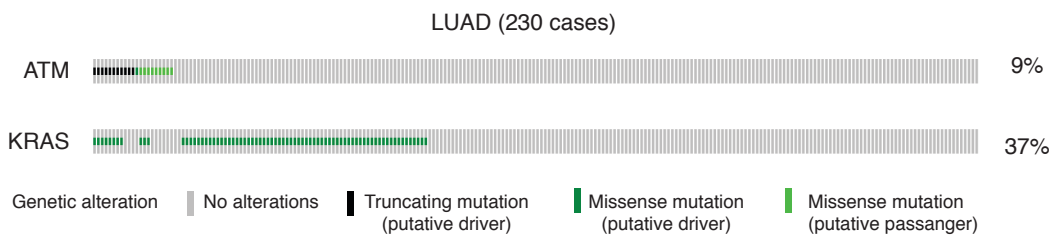
B) Representative western blots showing phosphorylation of the ATM substrate KAP1 Ser824 in unstimulated lung cancer cells and cells subjected to replication stress (0.2 μM Aphidicolin, 24 hours) and IR-induced DSBs (2 Gy IR, 30 minutes).

C) Quantification of cell viability in response to oxidative stress. Values are arithmetic mean of 3 biological replicates + SEM; significance estimated using Student's T-test.

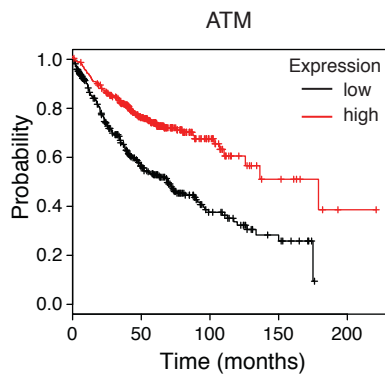
A



B



C

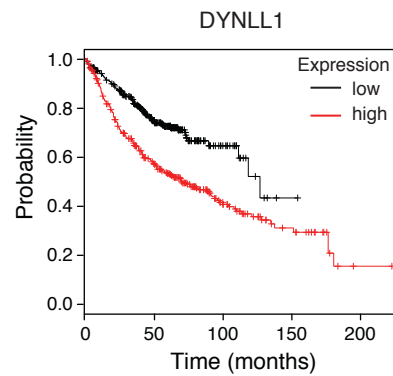


HR = 0.47 (0.37 - 0.6)

logrank P = 3.8e-10

LUAD (720 cases)

D



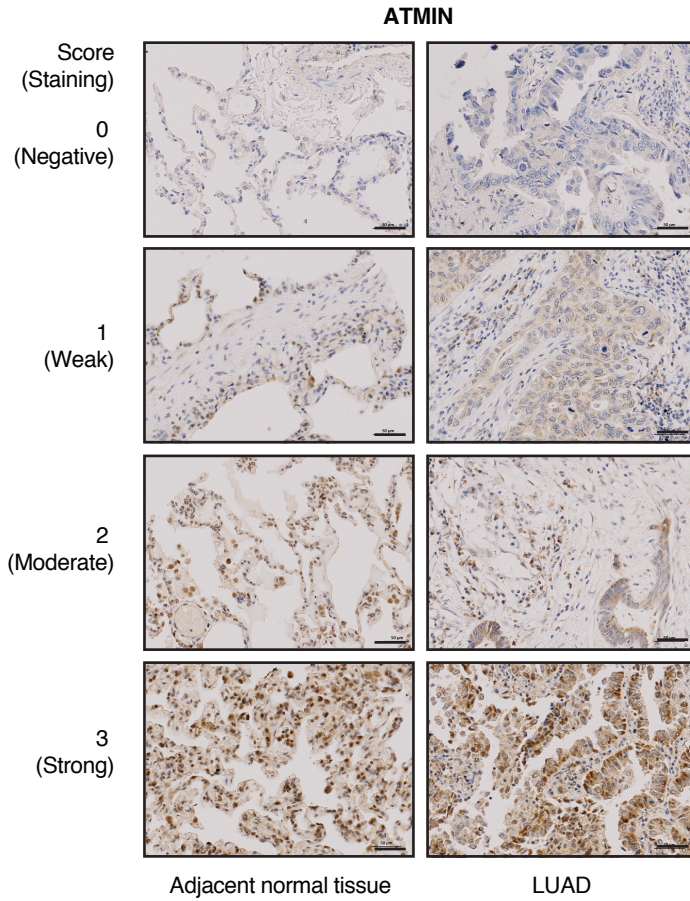
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logrank P = 1.3e-07

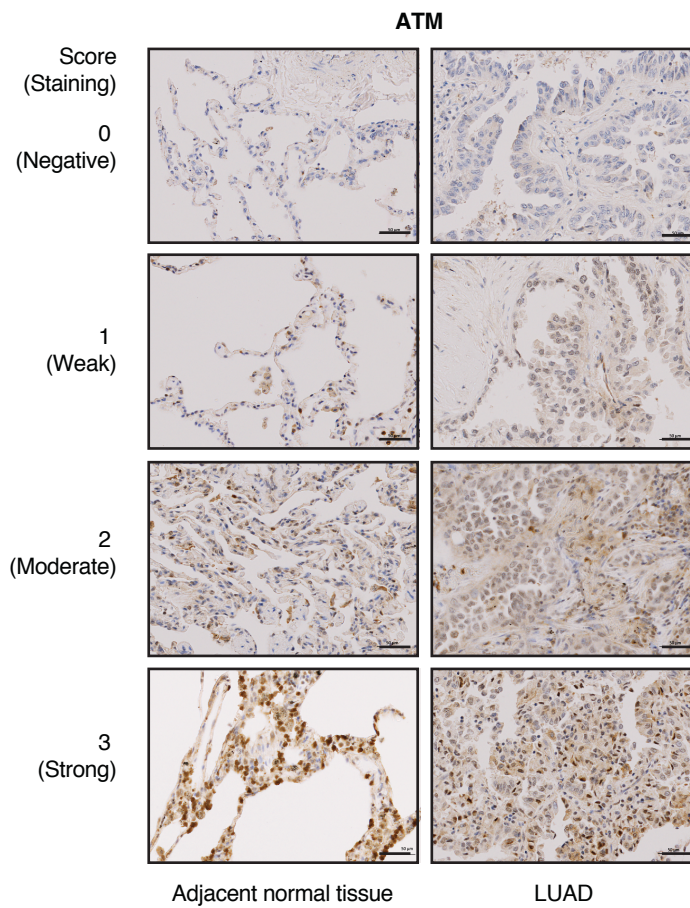
LUAD (720 cases)

Figure S1

A



B



C

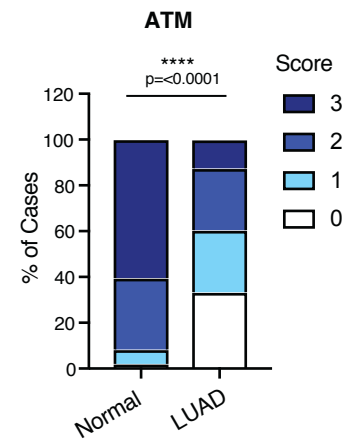


Figure S2

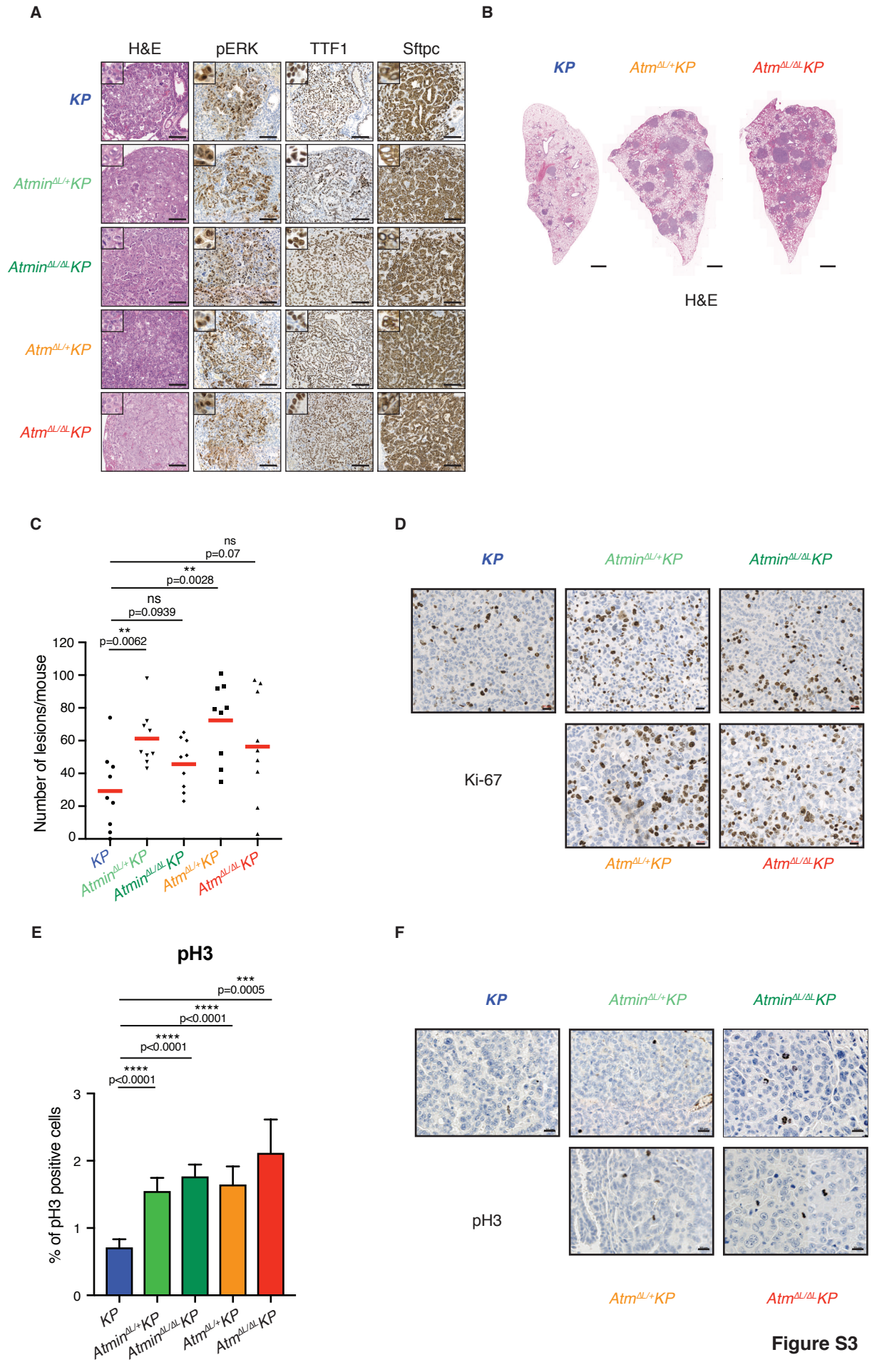
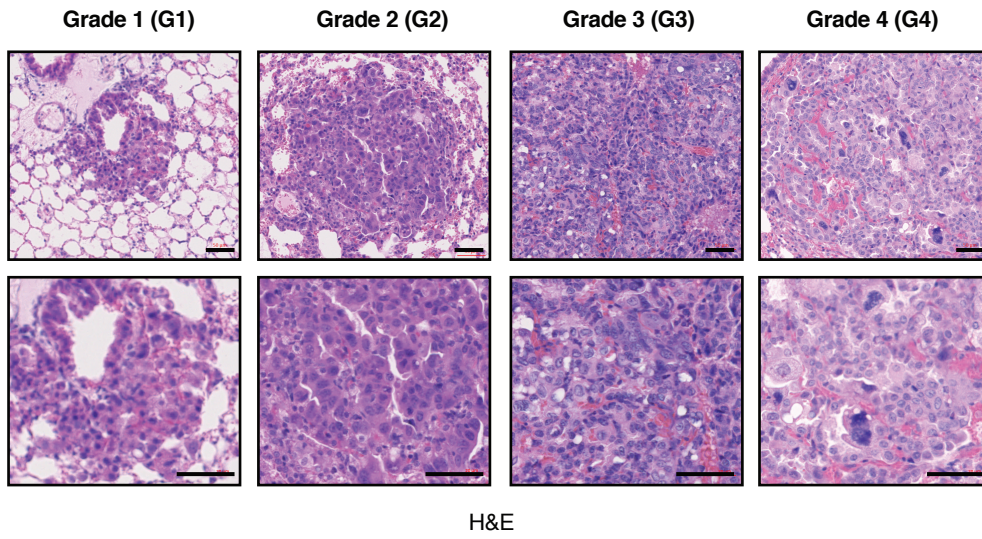
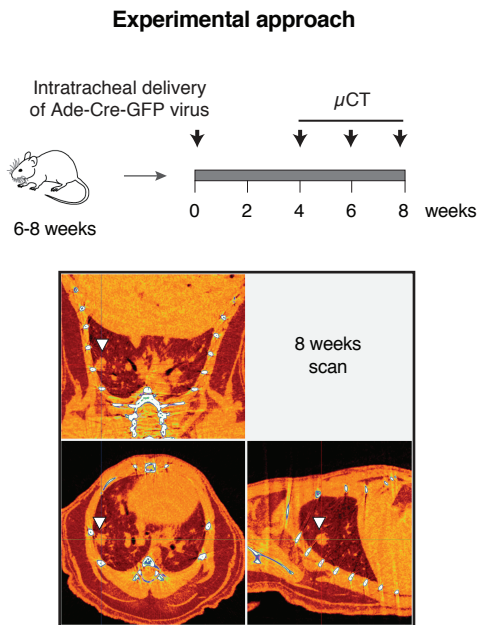
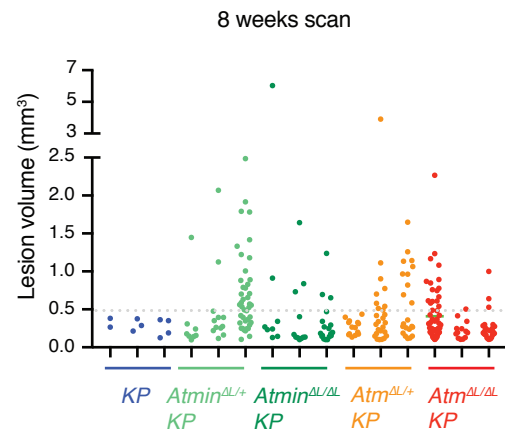
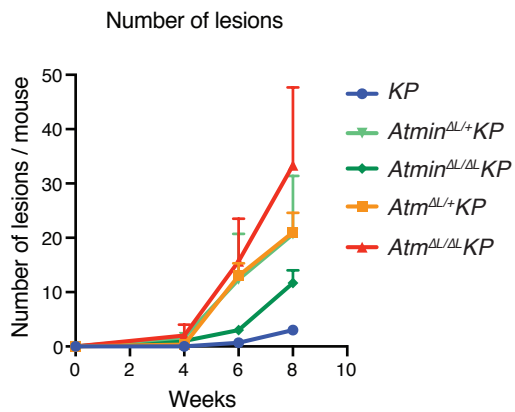
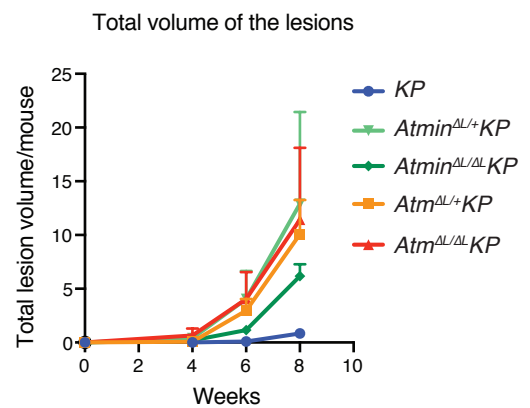
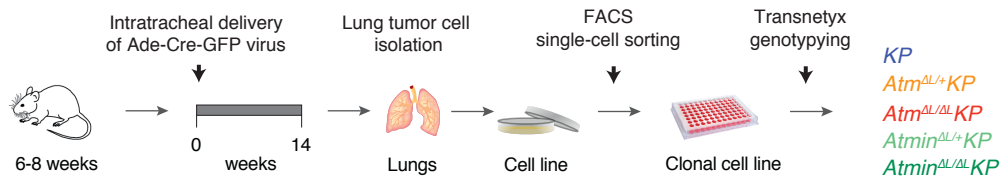


Figure S3

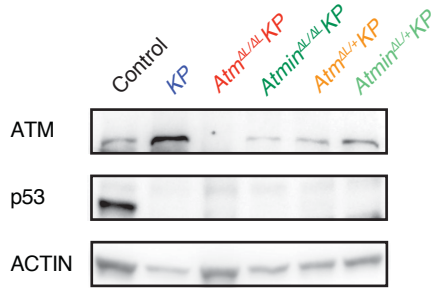
A**B****C****D****E****Figure S4**

A

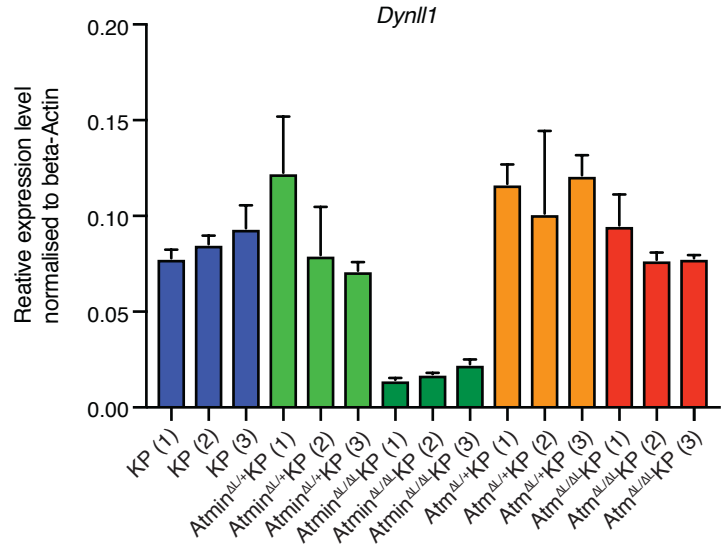
Establishment of clonal lung tumor cell lines



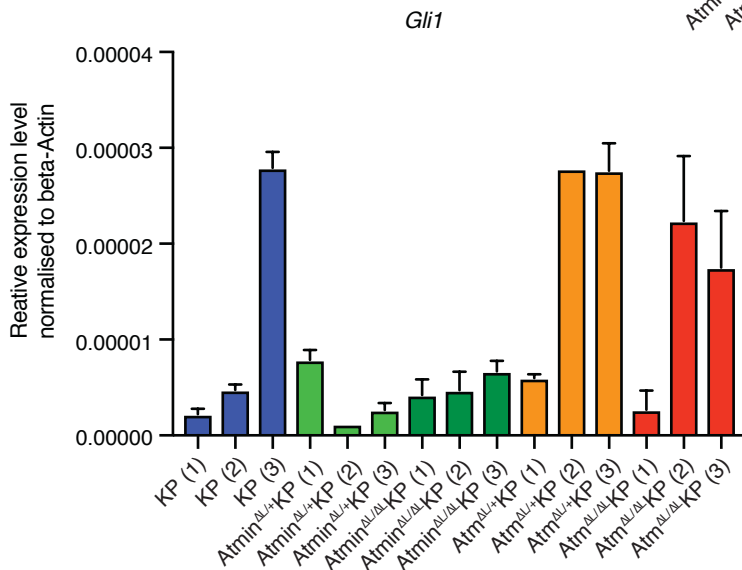
B



C



D



E

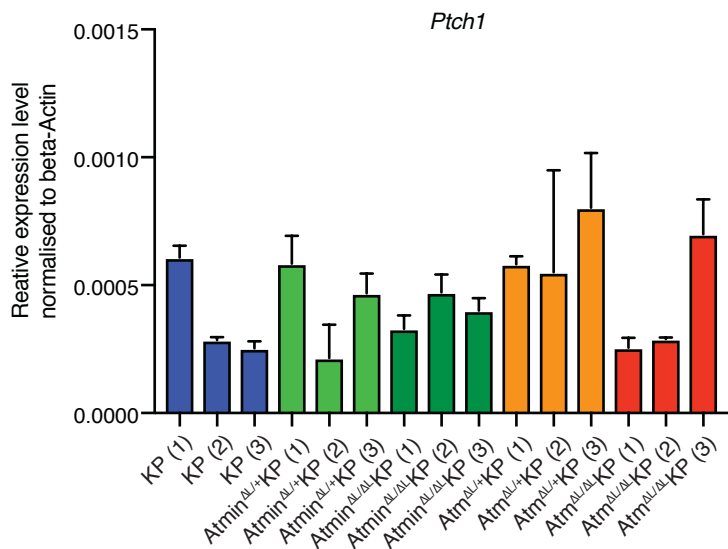


Figure S5

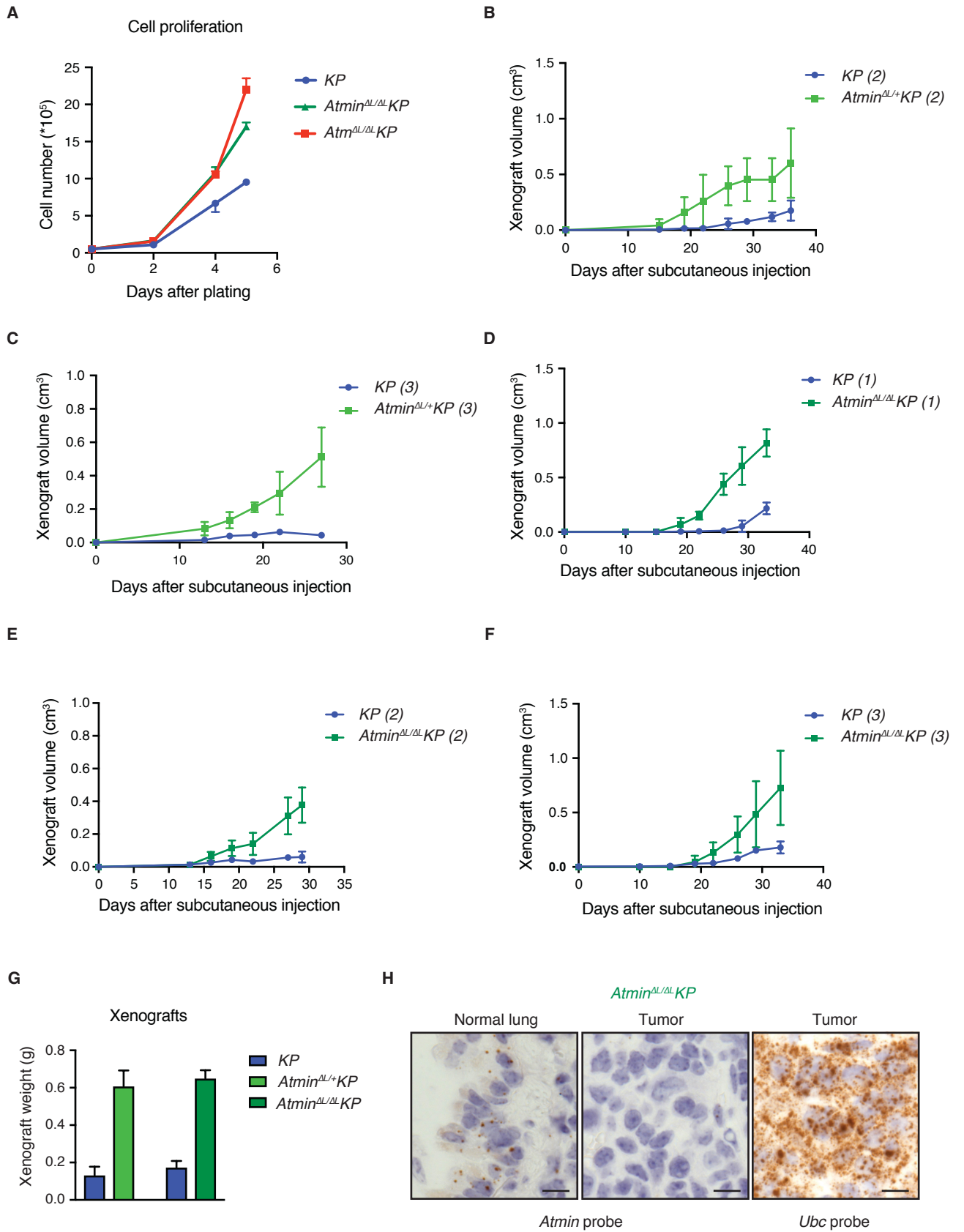
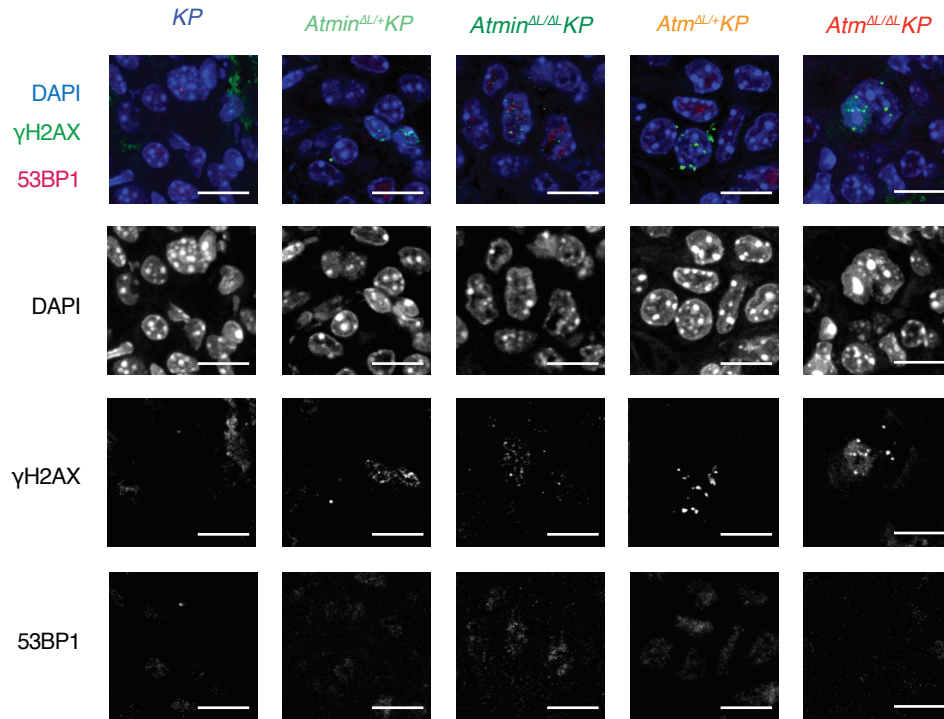
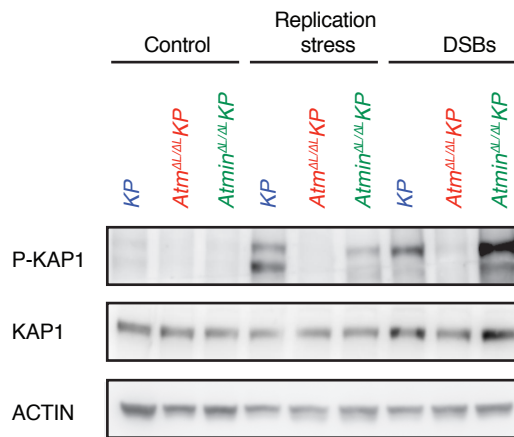
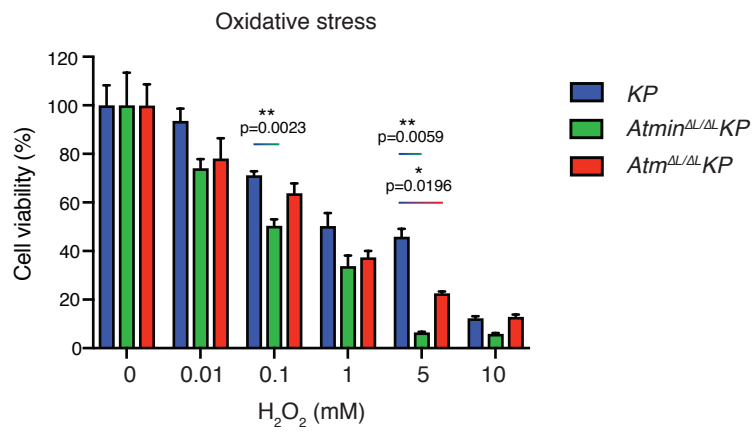


Figure S6

A**B****C****Figure S7**