

Supplementary Figure 1

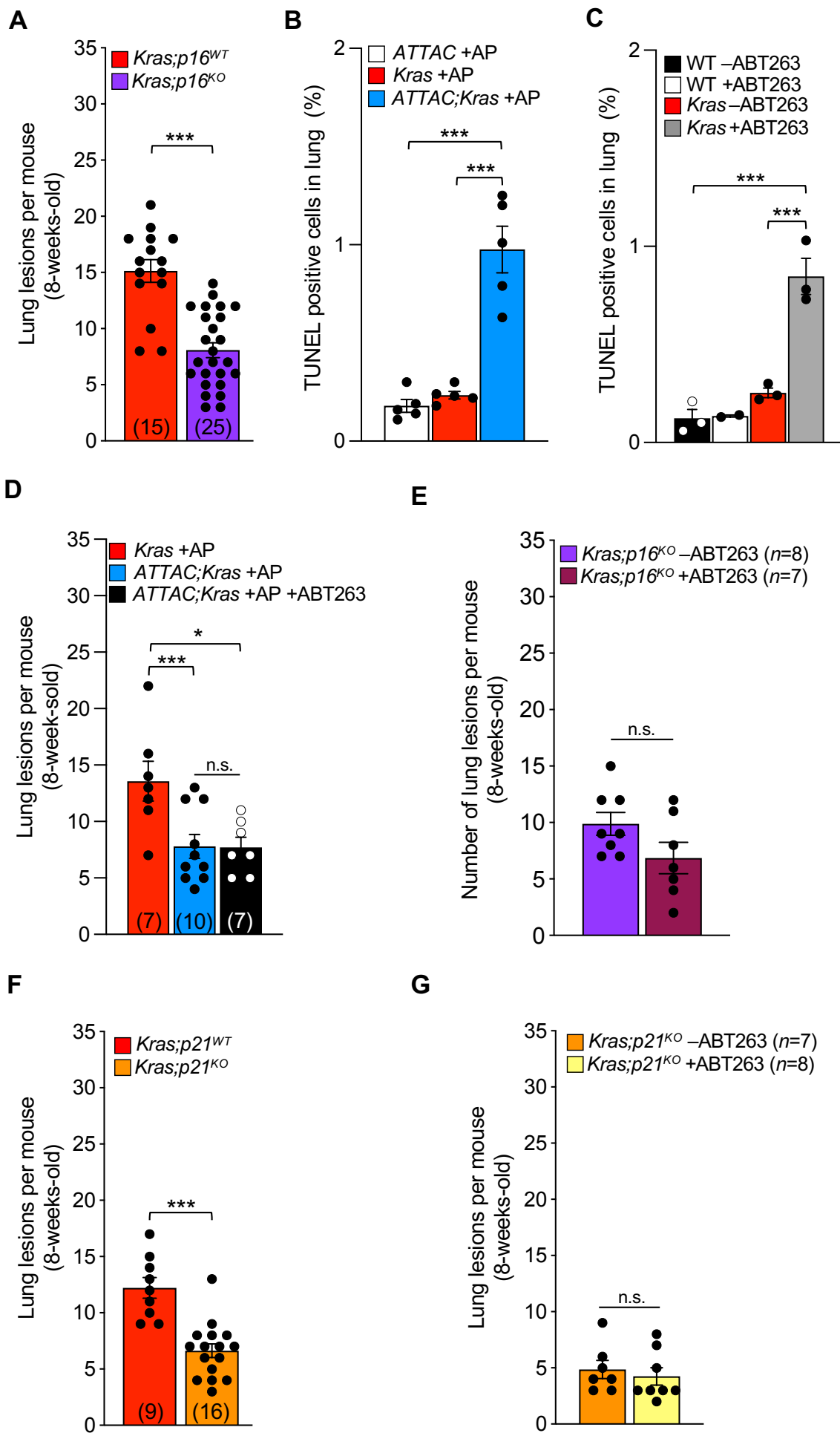


Figure S1: Senescent cells are targetable in the *Kras* lung, related to Figure 2.

(A) Number of lung lesions in *Kras* mice with and without genetic knockout of *p16*. The number of mice per group are indicated in the parenthesis.

(B–C) Immunofluorescence quantification of TUNEL⁺ cells after senescent cell clearance by AP from birth (B) or ABT263 (C) beginning at weaning age and assessment at 8 weeks in the indicated mice.

(D) Lung lesions in mice after senescent cell clearance with AP from birth or AP+ABT263 beginning at weaning age and assess at 8 weeks. The number of mice per group are indicated in the parenthesis.

(E–G) Number of lung lesions in mice with genetic knockout of *p16* or *p21* after the indicated treatment. The number of mice used per group are indicated in the parenthesis.

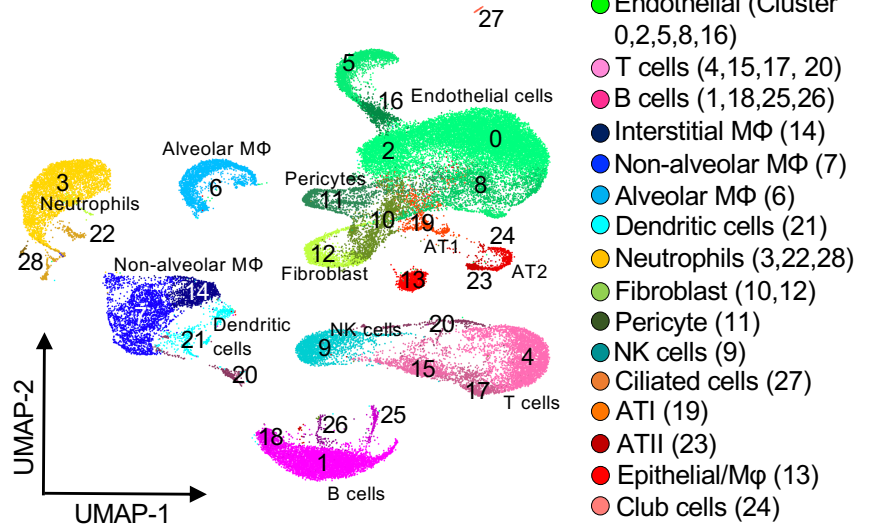
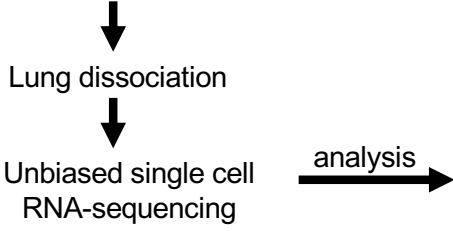
Data are means \pm SEM. $n = 3-4$ in B, C. ns, non-significant. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; (one-way ANOVA with Tukey's multiple comparison test in B, C, D. Unpaired two-tailed Student's t test in A, E, F, G).

Supplementary Figure 2

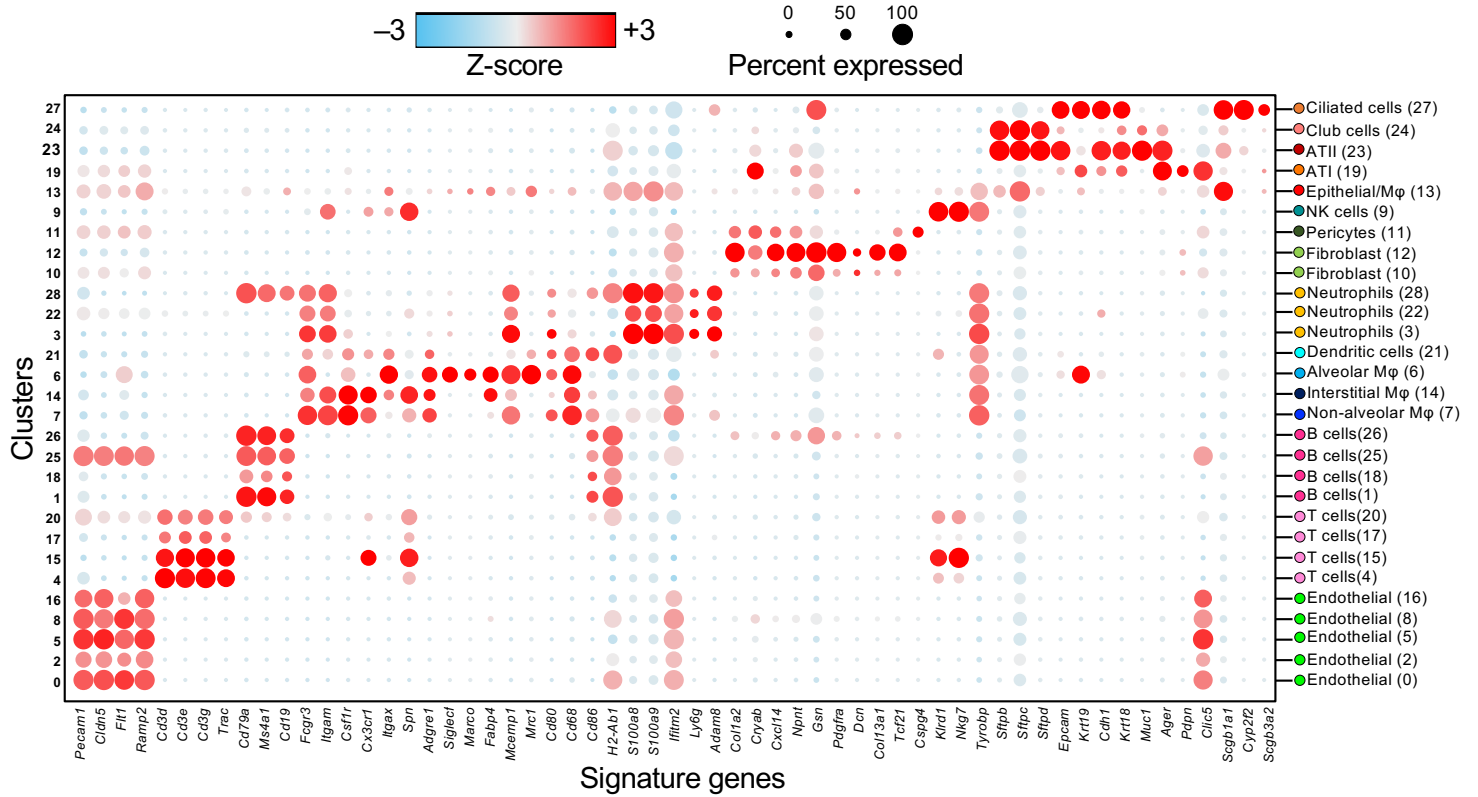
A

8-week-old mice:

1. *ATTAC* +AP (from birth)
2. *Kras* +AP (from birth)
3. *ATTAC;Kras* +AP (from birth)



B



C

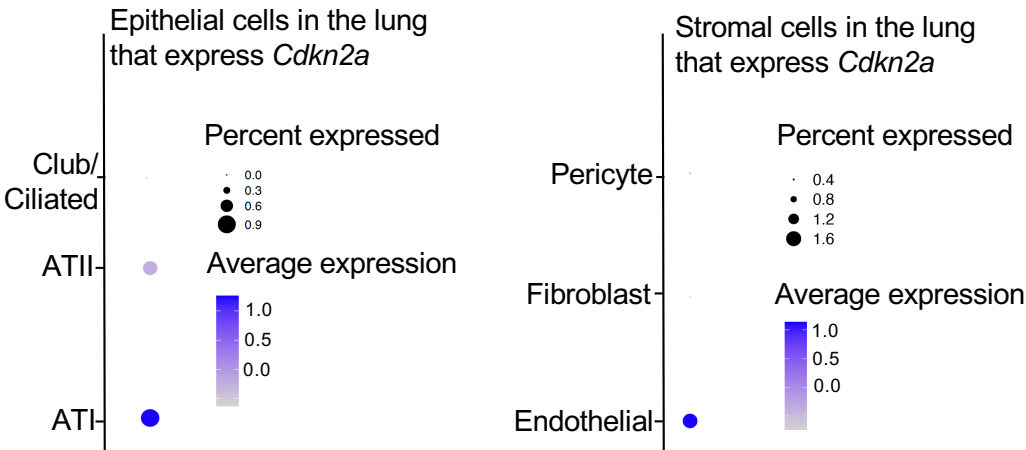


Figure S2: Unbiased single cell RNA-sequencing analysis of lungs after AP-treatment in *ATTAC*, *Kras*, and *ATTAC;Kras* mice, related to Figure 3.

(A) Study design and UMAP plot displaying all cell clusters from eight-week-old *ATTAC* +AP, *Kras* +AP, and *ATTAC;Kras* +AP mice.

(B) Bubble plot displaying the signature genes used identify cell types in each cluster.

(C) *Cdkn2a* expression in epithelial (left) and stromal (right) cells.

Supplementary Figure 3

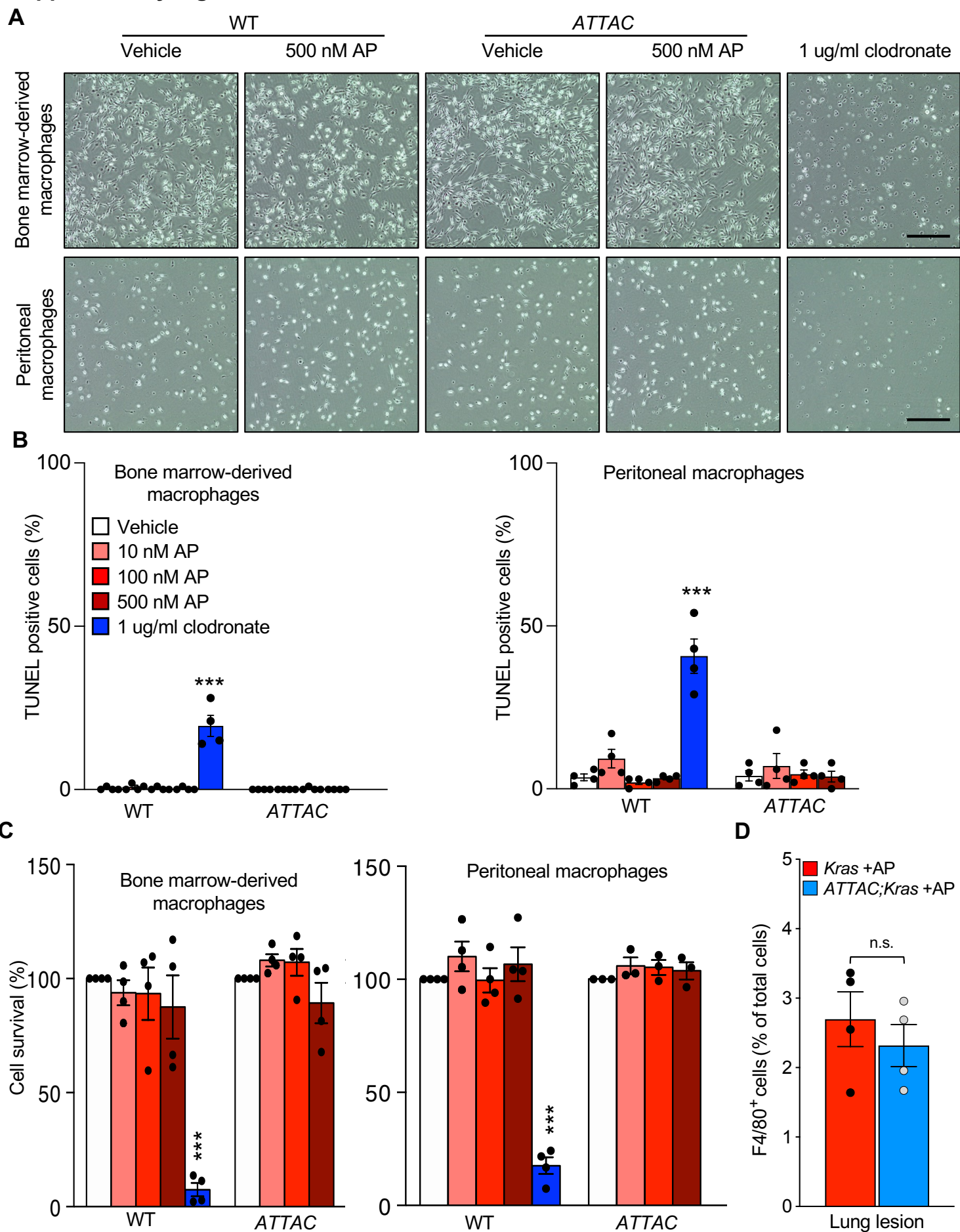


Figure S3: AP-mediated senescent cell killing does not globally target macrophages in *ATTAC;Kras* mice, related to Figure 3.

(A) Representative images of bone marrow-derived macrophages and peritoneal macrophages cultured from three-month-old wildtype (WT) and *ATTAC* mice after 48 hours of treatment with vehicle, AP, or clodronate (positive control).

(B) Quantification of TUNEL⁺ cells after indicated treatments.

(C) Cell counts of surviving cells after indicated treatments.

(D) Immunofluorescence quantification of macrophages (F4/80⁺) in lung lesions of *Kras* and *ATTAC;Kras* mice treated with AP from birth.

Scale bars: 100mm **(A)**. Data are means \pm SEM. $n=3-4$ mice in A-D. ns, non-significant. * $P<0.05$; ** $P<0.01$; *** $P<0.001$; (one-way ANOVA with Tukey's correction in **B**, one-way ANOVA with Sidak's correction in **C**, and unpaired two-tailed Student's t test in **D**).

Supplementary Figure 4

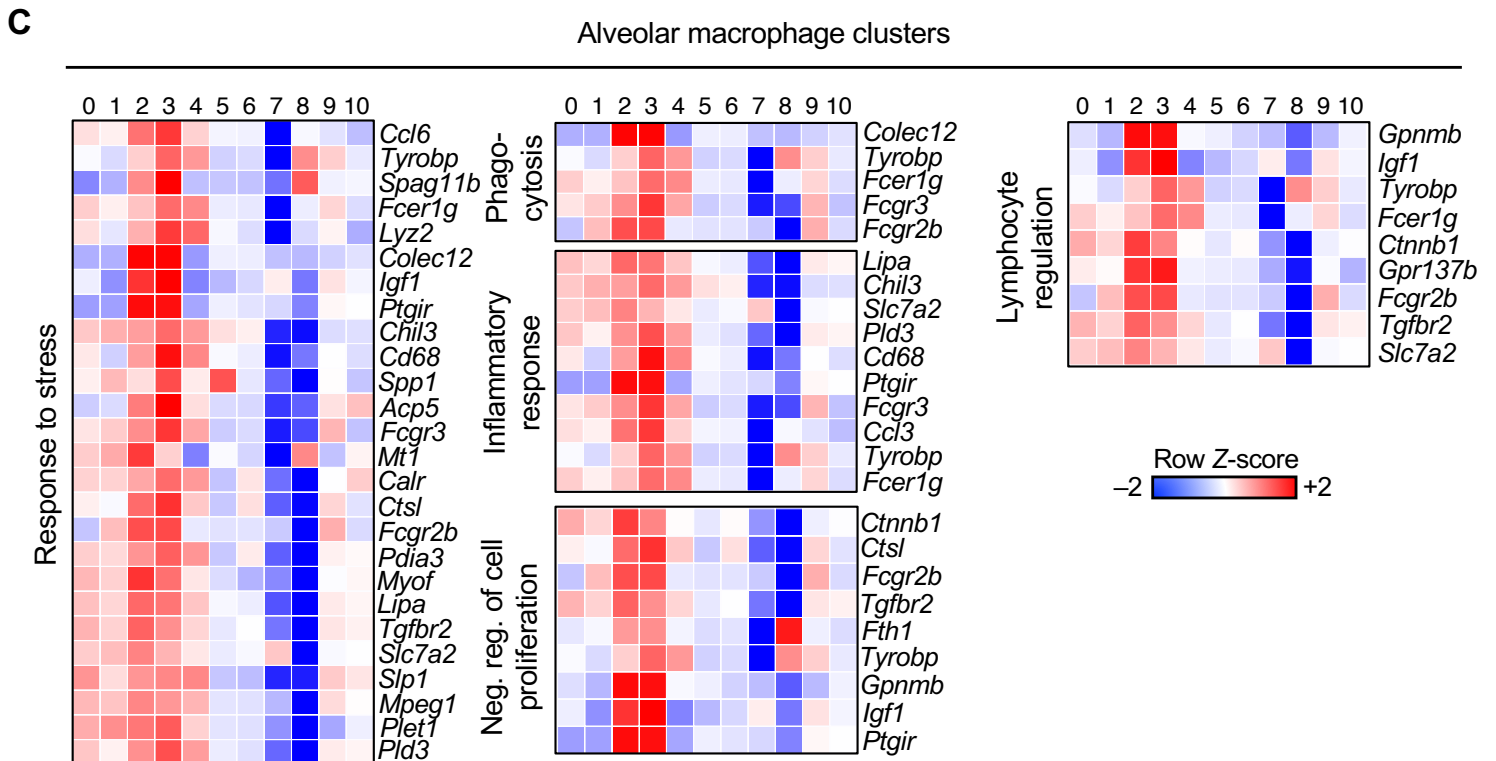
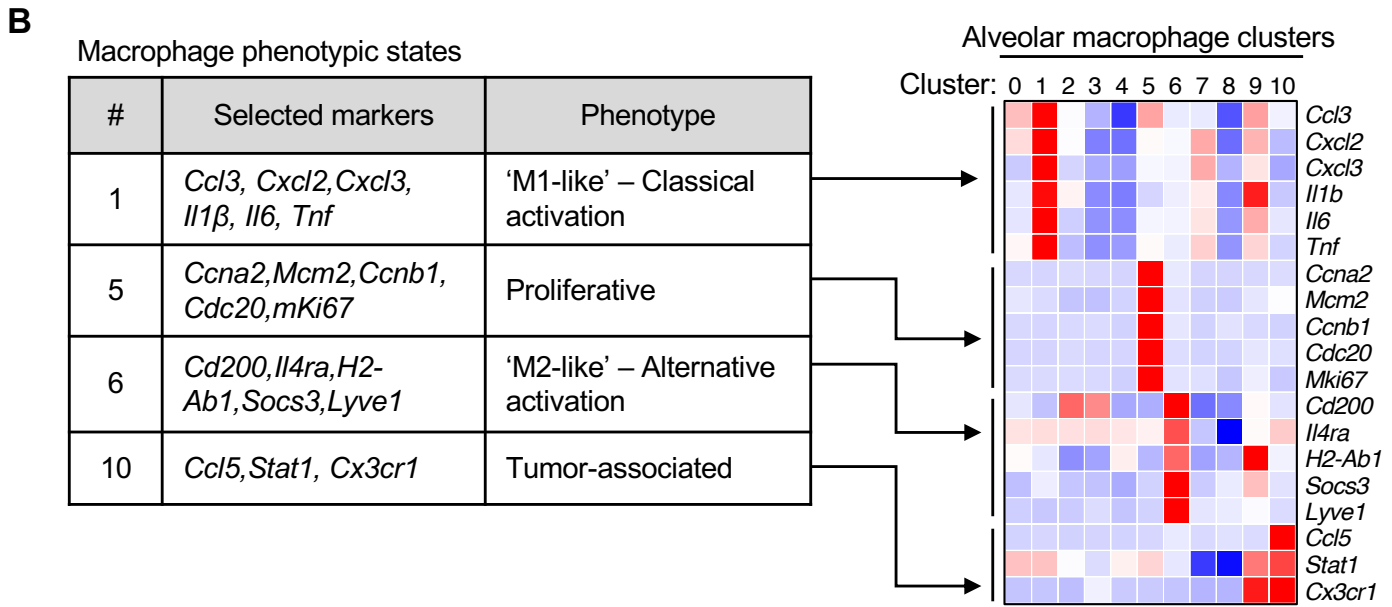
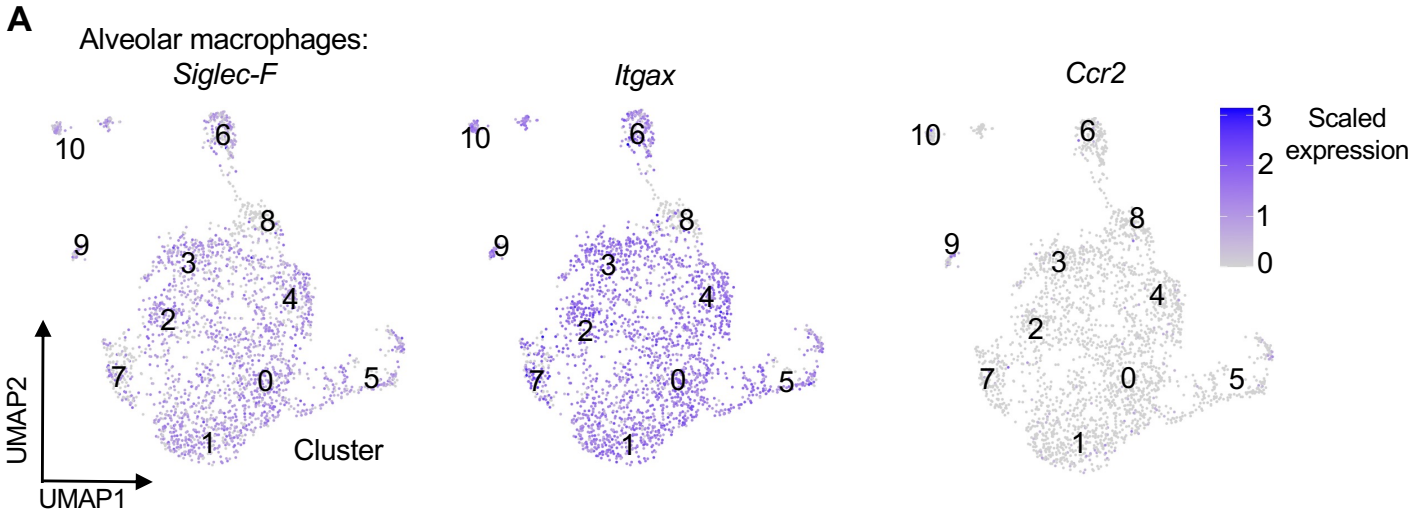


Figure S4: Characterization of alveolar macrophages using single cell RNA-sequencing analysis, related to Figure 3.

(A) UMAP feature plots for *Siglec-F*, *Itgax*, and *Ccr2* expression in alveolar macrophage clusters.

(B) Table and heatmap of gene expression marker of established macrophage phenotypes found in this single cell RNA-seq analysis.

(C) Heatmap illustrating genes in the selected functional annotations that are upregulated in alveolar macrophage cluster 2/3 (annotations depicted in **Fig 3H**).

Supplementary Figure 5

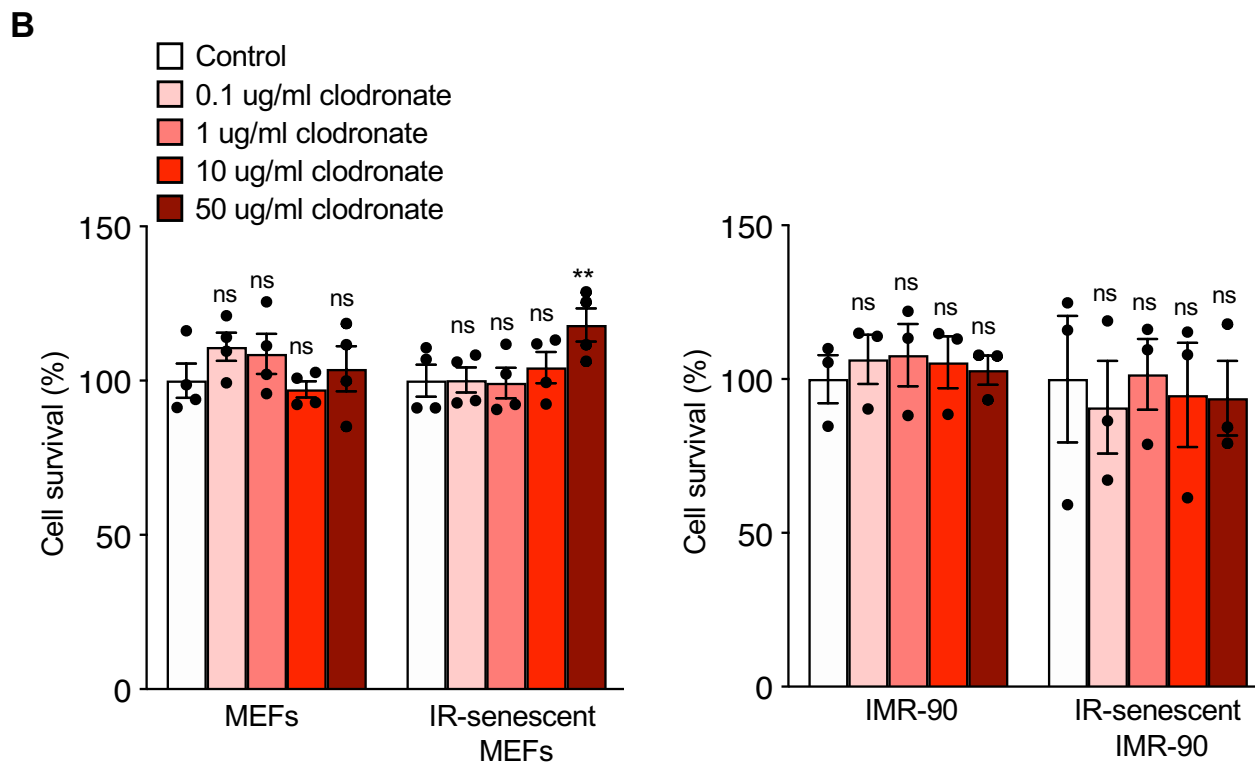
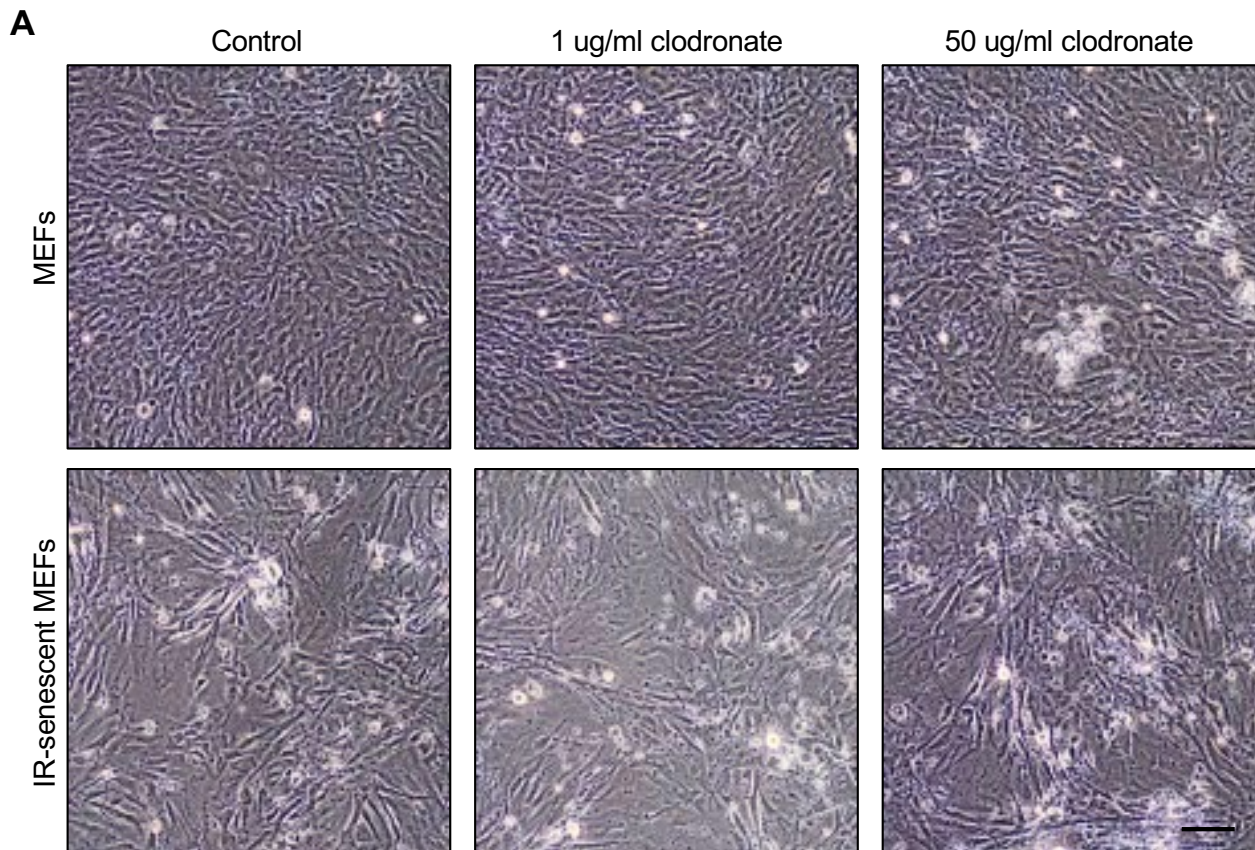


Figure S5: Senescent cells are not susceptible for elimination with liposomal clodronate *in vitro*, related to Figure 5.

(A) Representative images of control and irradiation-induced senescent mouse embryonic fibroblasts (MEFs) after 48 hours with clodronate.

(B) Cell survival as measured by MTS assay of control and irradiation-induced senescent MEFs (left) and human lung fibroblasts (IMR-90 cells, right) after 48 hours with clodronate.

Scale bars: 100mm **(A)**. Data are means \pm SEM. $n=4$ independent MEF lines, $n=3$ technical IMR-90 replicates in **B**. $*P<0.05$; $**P<0.01$; $***P<0.001$; (one-way ANOVA with Sidak's correction in **B**).

Supplementary Figure 6

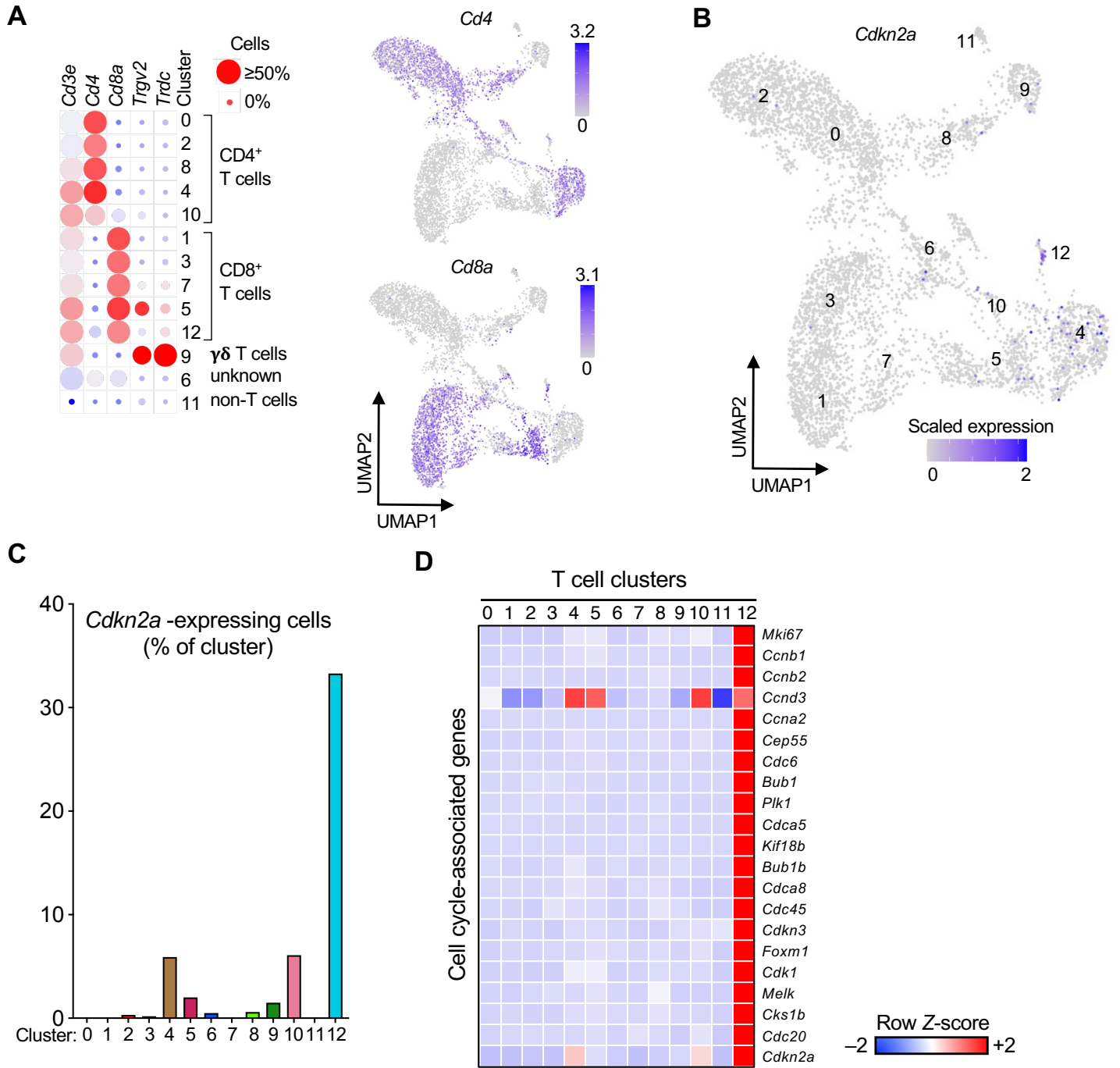


Figure S6: Single cell RNA-sequencing analysis of T-cells, related to Figure 6.

(A) Bubble (left) and UMAP (right) plots displaying signature genes used for the identification of T cell subsets.

(B) UMAP plot of *Cdkn2a* expression in T cells.

(C) Percentage of T cells expressing *Cdkn2a* in each cluster.

(D) Heatmap depicting genes involved cellular proliferation in T cell clusters.

Supplementary Figure 7

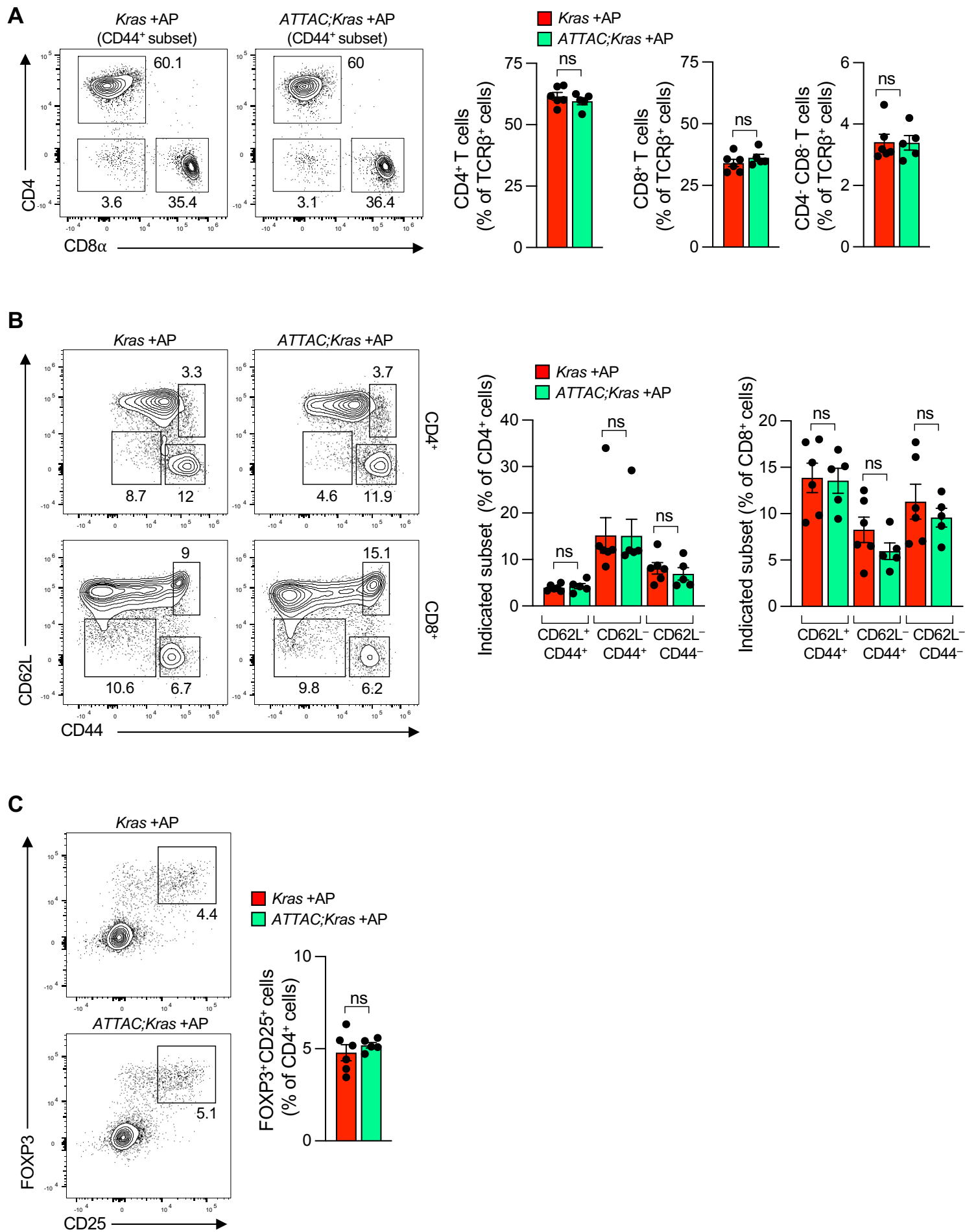


Figure S7: Flow cytometry analysis of T cells after senescent cell clearance in *Kras* mice with established lesions, related to Figure 6.

(A–C) Flow cytometry gating scheme (left) and quantification (right) of T cell subsets in 8-week-old

Kras and *ATTAC;Kras* mice treated with AP from 6-8 weeks.

Data are means \pm SEM. ns, non-significant (Unpaired two-tailed Student's t test in **A–C**).