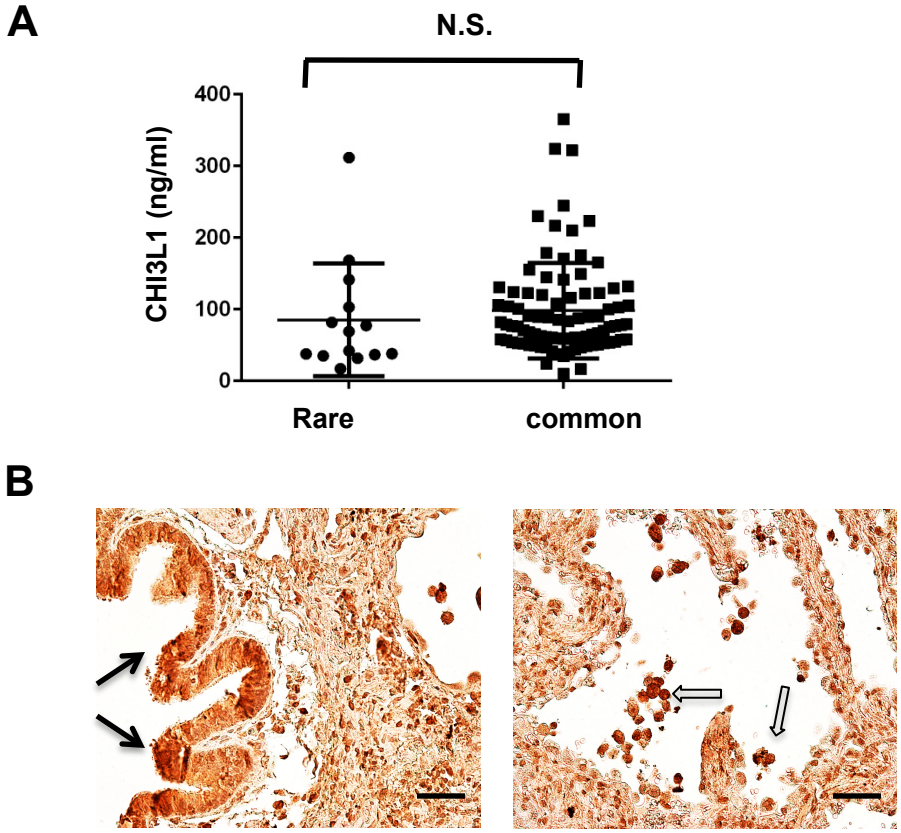
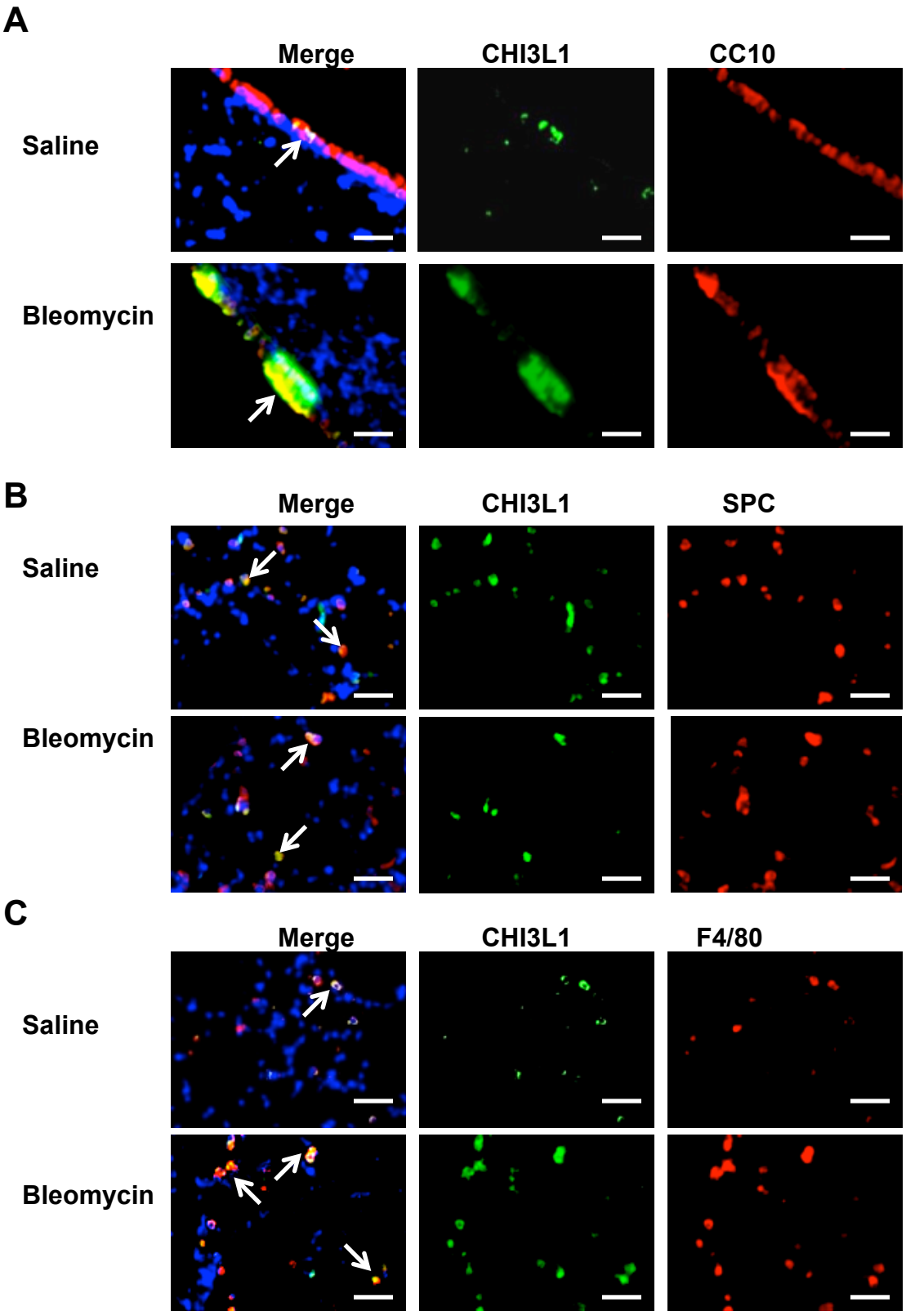
Supplementary Fig. 1



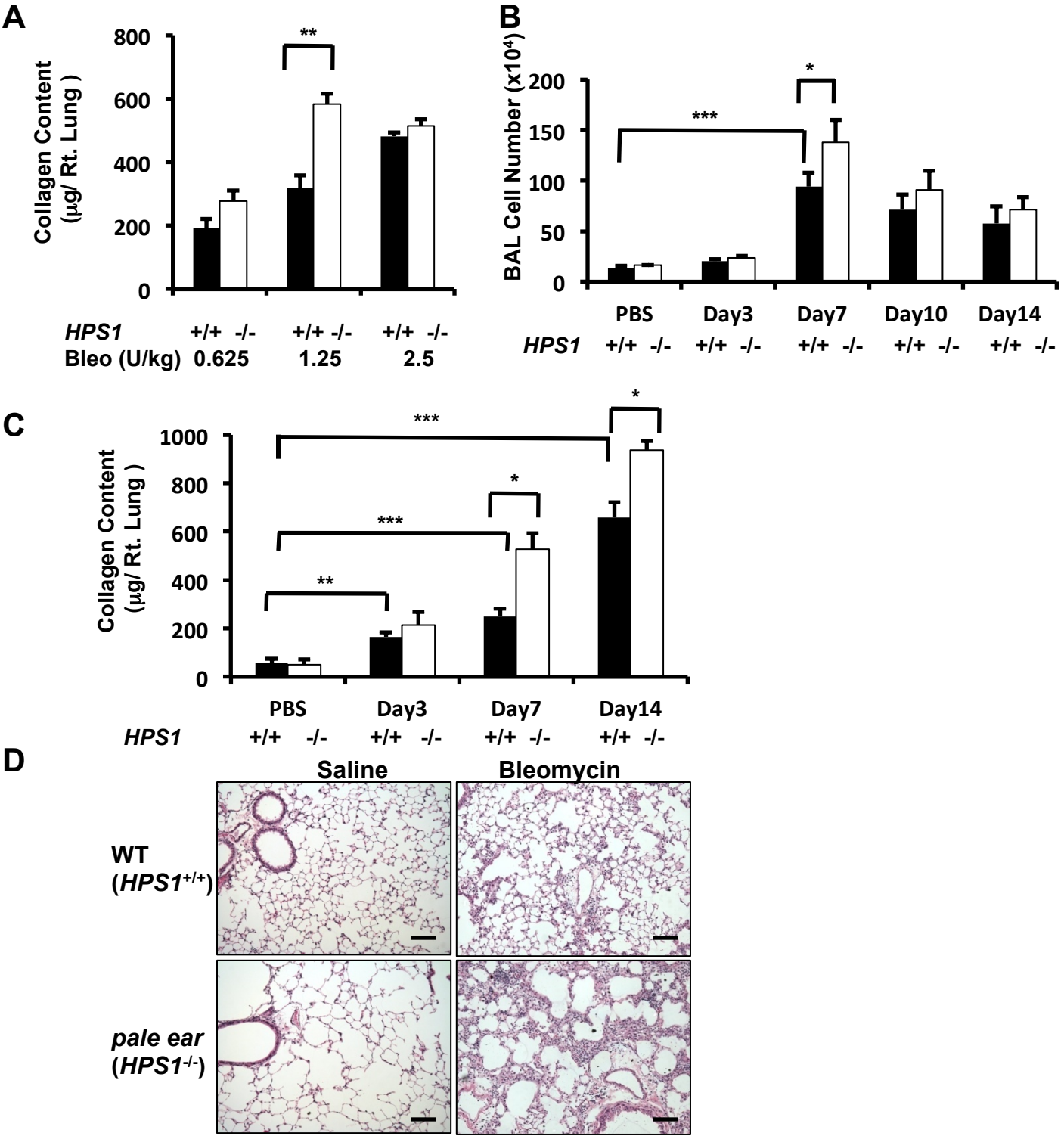
Supplementary Figure 1. CHI3L1 levels in HPS patients. (A) Plasma CHI3L1 concentrations do not differ between HPS-1 with rare (left) or common (right) mutations. The panel is presenting a different analysis of the same patient population shown in Figure 1. (B) Representative photographs of immunohistochemistry on the lung tissue from HPS1 patients. Solid and open arrows indicate airway epithelial cells and macrophages, respectively. Data are shown as median ±interquartile range. Scale bar, 100μm. Non-normally distributed data in two groups were compared using the nonparametric two-tailed Mann-Whitney test. *$p < 0.05$. N.S= not significant.

Supplementary Fig. 2



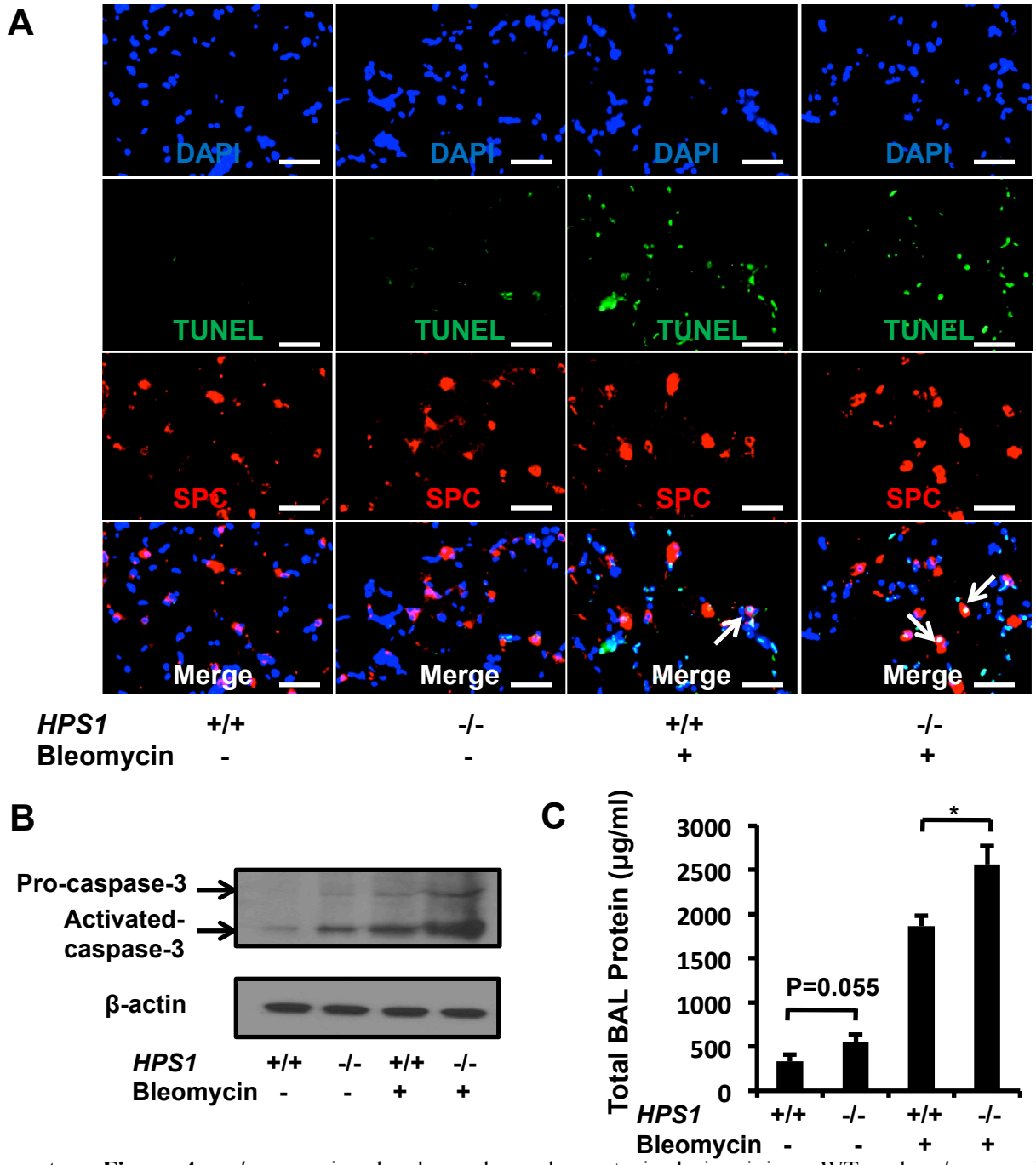
Supplementary Figure 2. Localization of CHI3L1 expression in *pale ear* mice. *Pale ear* mice were subjected to intratracheal bleomycin administration. Lungs were harvested 14 days later and lung sections were stained for CHI3L1 (green). Sections were co-stained for CC10 (A), SPC (B), or F4/80 (C). Colocalizations are indicated by arrows. Images are representative of 3 mice. Scale bar, 100μm.

Supplementary Fig. 3



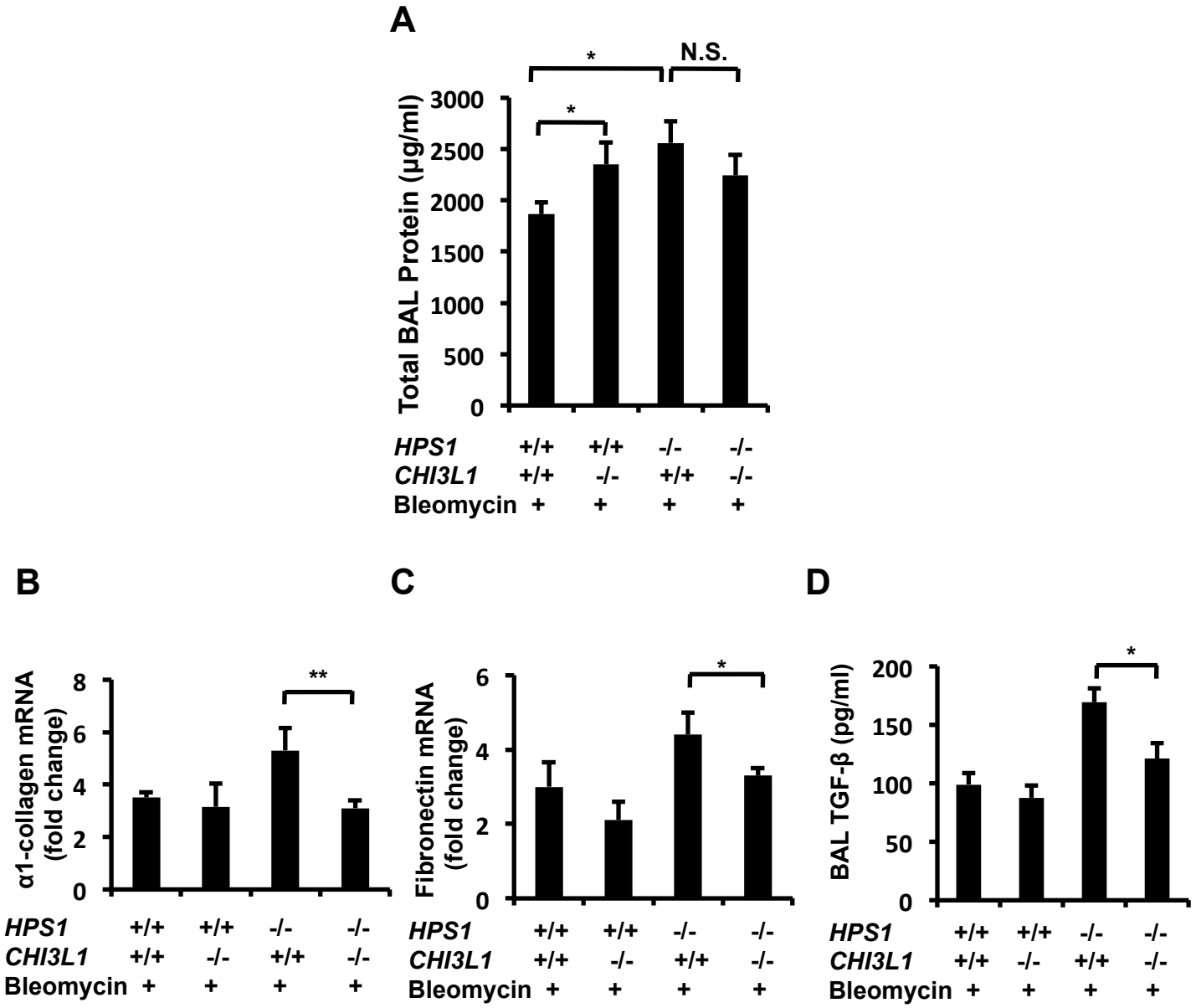
Supplementary Figure 3. Dose response and kinetics of bleomycin-induced responses. *WT* and *pale ear* mice were subjected to intratracheal bleomycin administration. (A) Total lung collagen was quantified using Sircol assay on Day 14. (B) BAL inflammation was determined on Day 3, Day 7, Day 10, and Day 14. (C) Total lung collagen was quantified using Sircol assay on Day 3, Day 7, and Day 14. Values are mean ± SEM with 6 mice in each group. *$p \leq 0.05$,**$p \leq 0.01$, ***$p \leq 0.001$. Comparisons between groups were conducted using a two-tailed Student t test. ANOVA with Bonferroni's post test was used for comparisons between groups. (D) H&E staining was performed on Day 14. Images are representative of a minimum of 4 mice in each group. Scale bar, 200µm.

Supplementary Fig. 4



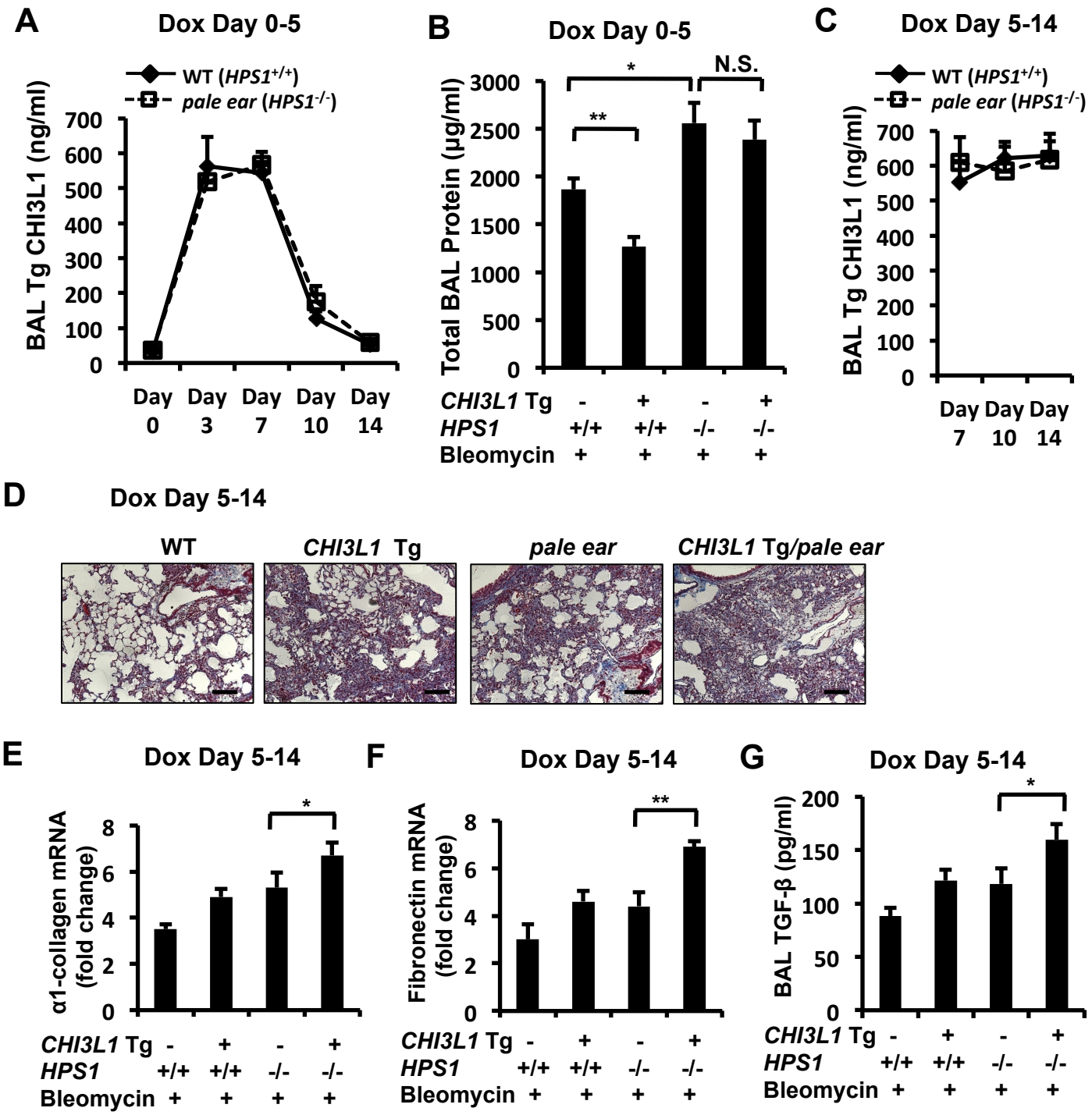
Supplementary Figure 4. *pale ear* mice develop enhanced apoptosis during injury. WT and *pale ear* mice were subjected to intratracheal bleomycin administration. (A) Type II epithelial cells were stained with an anti-SPC antibody and then labeled with red fluorescence (alexafluor 594). TUNEL staining was performed on Day 7 and TUNEL-positive cells were labeled with green fluorescence. Nuclei are stained with DAPI (blue). TUNEL-positive Type II epithelial cells show white nuclei and are indicated by arrows. Images are representative of a minimum of 4 mice in each group. Scale bar, 100µm. (B) Total protein was extracted and western blot was performed to detect Caspase-3 activation. β-actin was used as a loading controls. Images are representative of a minimum of 3 mice in each group. (C) BAL fluid was collected and total protein concentration was quantified using Bradford assay on Day 7. Values are mean ± SEM with 6 mice in each group. Comparisons were conducted using a two-tailed Student t test. ANOVA with Bonferroni's post test was used for comparisons between groups. *$p \leq 0.05$.

Supplementary Fig. 5



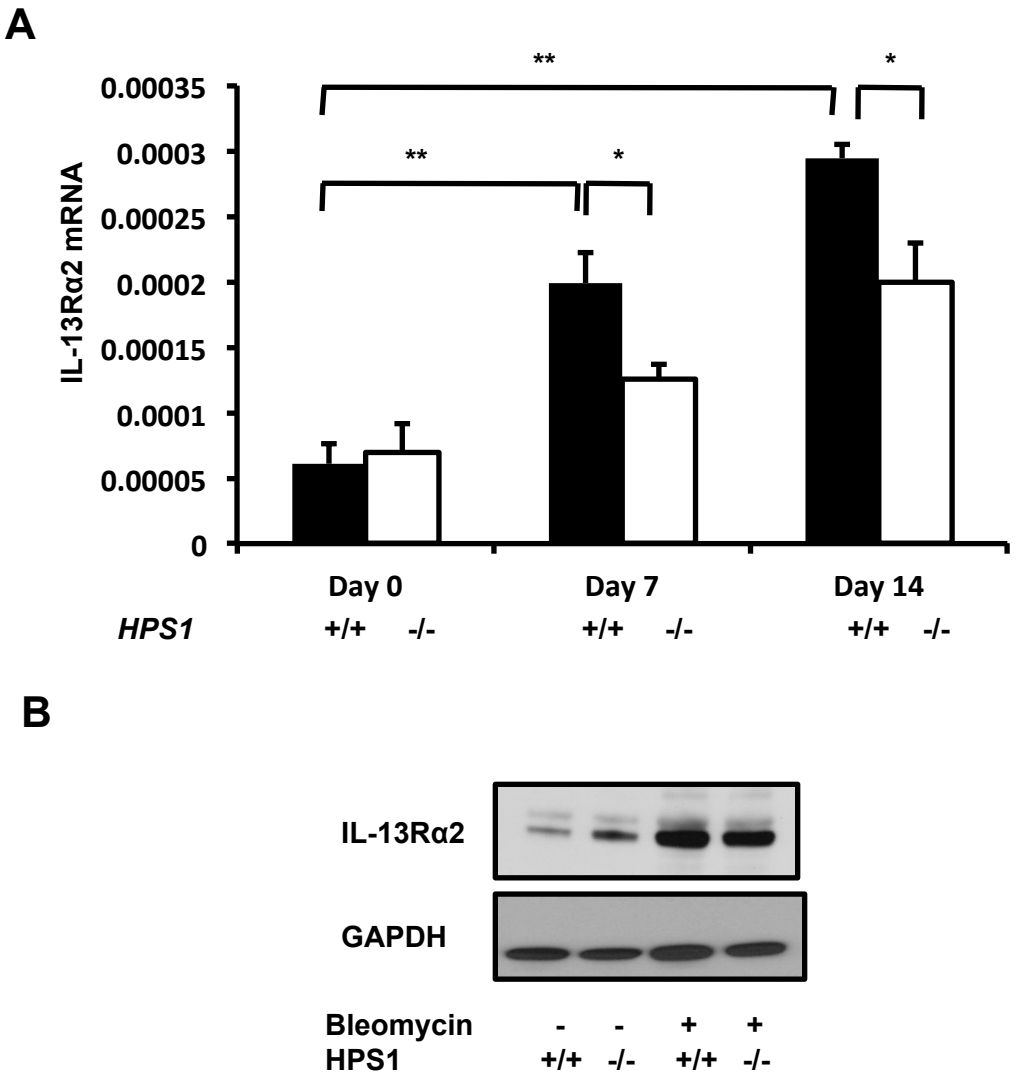
Supplementary Figure 5. WT, *CHI3L1*$^{-/-}$, *pale ear*, and *HPS1*$^{-/-}$*CHI3L1*$^{-/-}$ mice were subjected to intratracheal bleomycin administration. (A) BAL fluid was collected and total protein concentration was quantified using Bradford assay on Day 7. mRNA levels of (B) α1-procollagen (Col1-α1), (C) fibronectin were evaluated by qRT-PCR, and (D) BAL TGF-β levels were evaluated by ELISA on Day 14. Values are mean ± SEM with 6 mice in each group. Comparisons were conducted using a two-tailed Student t test. ANOVA with Bonferroni's post test was used for comparisons between groups. *$p \leq 0.05$,**$p \leq 0.01$.

Supplementary Fig. 6



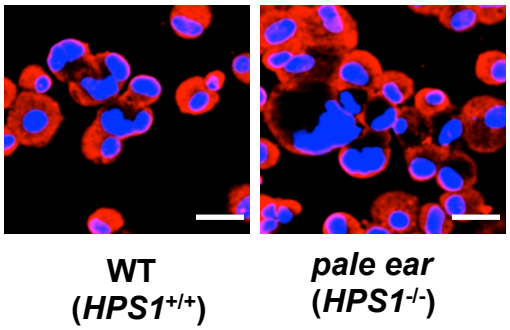
Supplementary Figure 6. CHI3L1 regulates fibroproliferative repair in *pale ear* mice. WT, *CHI3L1* Tg, *pale ear*, and *HPS1*$^{-/-}$*CHI3L1* Tg mice were subjected to intratracheal bleomycin administration. (A) Transgenic CHI3L1 production in BAL fluid was quantified using ELISA. (B) BAL fluid was collected and total protein concentration was quantified using Bradford assay on Day 7. (C) Transgenic CHI3L1 production in BAL fluid was quantified using ELISA. (D) Trichrome staining was performed to examine collagen deposition on Day 14. Scale bar, 200µm. mRNA levels of (E) α1-procollagen (Col1-α1), (F) fibronectin were evaluated by qRT-PCR, and (G) BAL TGF-β levels were evaluated by ELISA on Day 14. Values are mean ± SEM with 6 mice in each group. Comparisons were conducted using a two-tailed Student t test. ANOVA with Bonferroni's post test was used for comparisons between groups. *$p \leq 0.05$,**$p \leq 0.01$.

Supplementary Fig. 7



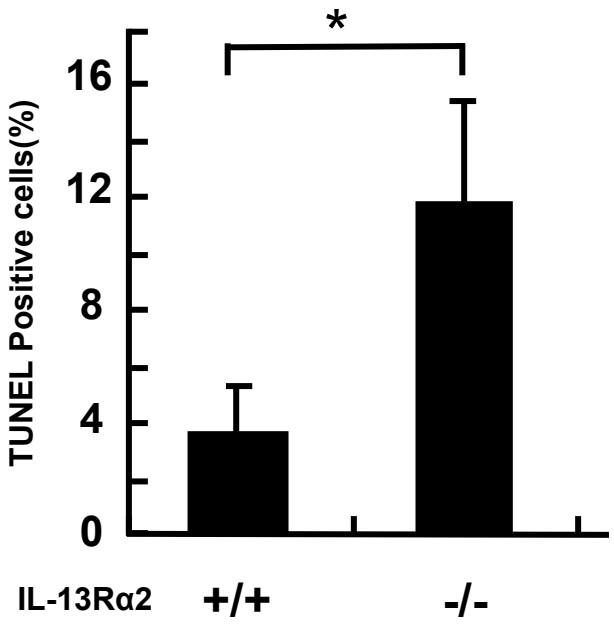
Supplementary Figure 7. WT and *pale ear* mice were subjected to intratracheal bleomycin administration. (A) mRNA levels of IL-13Rα2 were evaluated by qRT-PCR on Day 0, Day 7, and Day 14. Values are mean ± SEM with 6 mice in each group. Comparisons were conducted using a two-tailed Student t test. $*p \leq 0.05$,$**p \leq 0.01$. (B) Total protein was extracted from whole lung lysates on Day 7. Western blot analysis was performed to detect IL-13Rα2. Each experiment was undertaken at least 3 times.

Supplementary Fig. 8



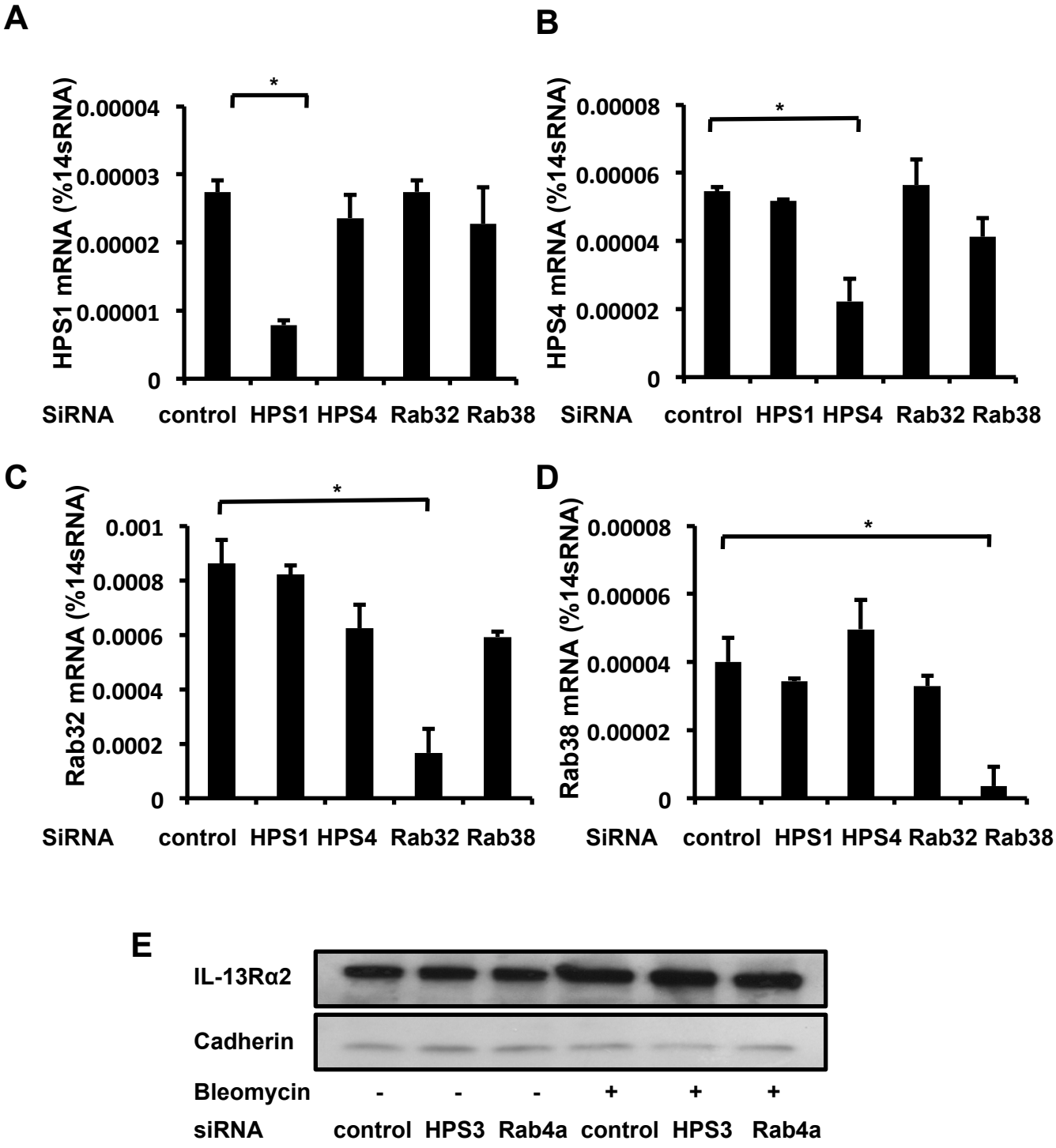
Supplementary Figure 8. IL-13Rα2 transfection. Cells are transfected with high concentrations of IL13Rα2 construct and then stained with red fluorescence (alexafluor 594). Nuclei are stained with DAPI (blue). Scale bar, 10 μm. Each experiment was undertaken at least 3 times.

Supplementary Fig. 9



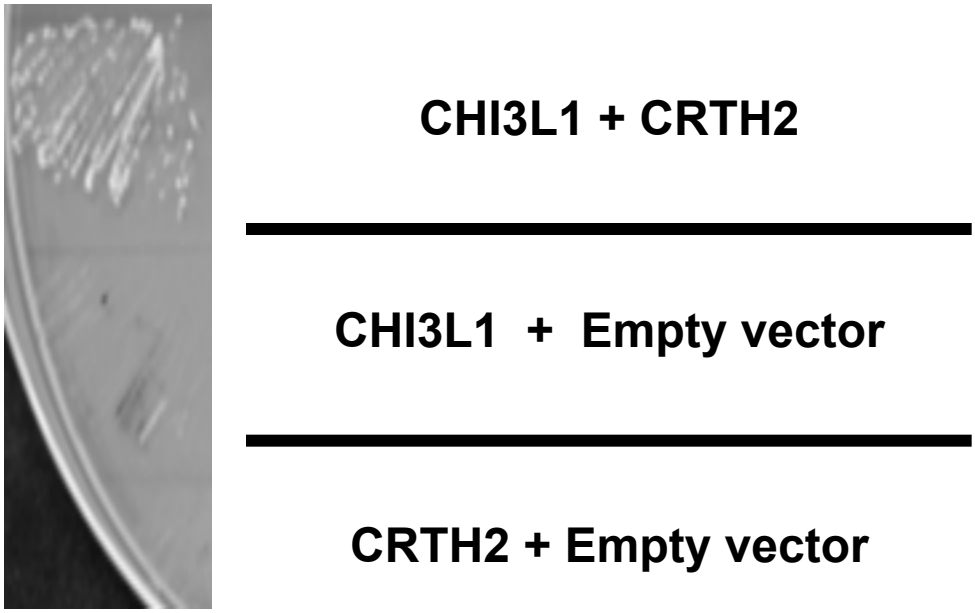
Supplementary Figure 9. IL-13Rα2$^{-/-}$ mice have increased apoptosis in the lung at baseline. TUNEL staining was performed and TUNEL-positive cells were counted. Values are mean ± SEM with 6 mice in each group. Comparisons between groups were conducted using a two-tailed Student t test. *$p \leq 0.05$.

Supplementary Fig. 10



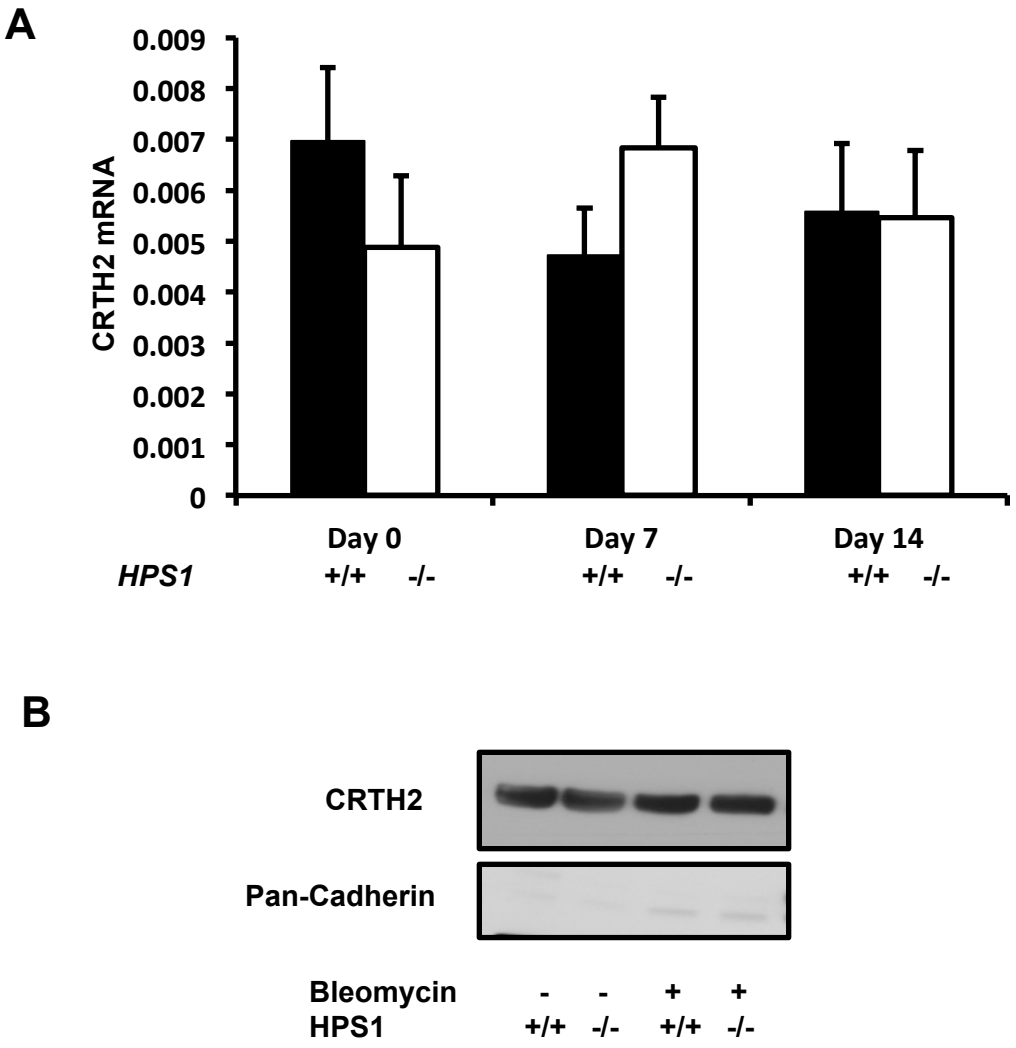
Supplementary Figure 10. (A-D) A549 cells were treated with HPS1, HPS4, Rab32, or Rab38 siRNA and the levels of mRNA encoding (A) HPS1, (B) HPS4, (C) Rab32, and (D) Rab38 were evaluated by qRT-PCR. The values represent the mean ± SEM of a minimum of 3 repeats. Comparisons between groups were conducted using a two-tailed Student t test. *$p \leq 0.05$. (E) A549 cells were treated with HPS3 or Rab4a siRNA, and bleomycin in vitro. Plasma membrane fractions were obtained and Western blot analysis was performed to detect IL-13Rα2. Pan-Cadherin was used a sa specificity and loading control. Each experiment was undertaken at least 3 times.

Supplementary Fig. 11



Supplementary Figure 11. Yeast two-hybrid characterization of CHI3L1 and CRTH2 interaction.

Supplementary Fig. 12



Supplementary Figure 12. WT and *pale ear* mice were subjected to intratracheal bleomycin administration. mRNA levels of CRTH2 were evaluated by qRT-PCR on Day 0, Day 7, and Day 14. Values are mean ± SEM with 6 mice in each group. Comparisons between groups were conducted using a two-tailed Student t test. (B) Total protein was extracted from whole lung lysates on Day 7. Western blot analysis was performed to detect CRTH2. Each experiment was undertaken at least 3 times.