Supplemental Figure 1: Clara cell , squamous differentiation, and pulmonary stem cell markers in normal bronchioles and alveoli in Acetone-treated mice and in squamous dysplasia and SCC in NTCU-treated mice.

Normal bronchioles and alveoli in acetone-treated mice (**A1-D1**) and squamous dysplasia (**A2-D2**) and pLSCCs (**A3-D3**) in NTCU-treated mice. CC10 was expressed in normal bronchiolar cells but was rarely detected in squamous dysplasias or pLSCCs (A1-A3). Cells positive for CK5/6 and deltaNp63 were not observed in bronchioles or alveoli in the control mice, but were diffusely present in squamous dysplasias and pLSCCs in NTCU-treated mice (B1-3 and C1-3). A few normal bronchiolar epitheliums were positive for CD44v (D1). In contrast, a number of CD44v-postive cells were observed in the basal cell layers of squamous dysplasias and pLSCCs (D2 and D3).Bar=100 μm.

Supplemental Figure 2: Co-localization of CC10, deltaNp63, and CD44v or CK5/6 proteins in acetone-treated mouse lung bronchi, bronchioles, and alveoli.

A, B: deltaNp63^{pos}CD44v^{pos} basal cells were only detected in the bronchus, but these cells were negative for CK5/6. **C, D**: Neither deltaNp63^{pos}CD44v^{pos}CC10^{pos} nor deltaNp63^{pos}CK5/6^{pos}CC10^{pos} cells were detected in bronchioles or alveoli. Bar=100 μm.

Supplemental Figure 3: Co-localization of ki-67 and CD44v or deltaNp63 in precancerous lesions, normal alveoli and bronchi, and esophagus in NTCU-treated mouse lung.

A: Double staining of Ki-67 and CD44v or deltaNp63 in precancerous lesions containing atypical bronchiolar hyperplasia, squamous metaplasia, and squamous dysplasia. White arrows indicate double positive Ki-67 and CD44v or deltaNp63 cells. **B**: Double staining of Ki-67 and CD44v or deltaNp63 in NTCU-treated mouse lung (right panels) and esophagus (left panels); the esophagus is used as a positive control. Yellow arrows indicate Karyomegalic alveolar cells. White arrows indicate double positive Ki-67 and CD44v or deltaNp63 cells. Bar=100 μm.

Supplemental Figure 4: p38α and phospho-p38α expression in CD44v positive cancer cells, and LSH and Trim29 expression in deltaNp63 positive cancer cells.

A, B: Expression of the CD44v downstream molecules p38α (**green**) and phospho-p38α (**green**) in CD44v (**red**) positive cancer cells. **C, D**: Expression of the deltaNp63 downstream markers LSH (**red**) and Trim29 (**red**) in deltaNp63 (**green**) positive cancer cells. CD44v downstream molecules p38α and phospho-p38α were observed in CD44v^{pos} cancer cells (A and B), and deltaNp63 downstream molecules LSH and Trim29 were observed in deltaNp63^{pos} cancer cells (C and D). Bar=100 μm.

Supplemental Figure 5: Expression of human lung squamous cell carcinoma progression markers in deltaNp63 positive cancer cells.

Expression of PI3K/AKT signaling pathway related molecules PI3K (**A**), phospho-PDK1 (**B**), phospho-mTOR (**C**), phospho-4EBP1 (**D**), and phospho-p70S6K (**E**) and its target protein HIF1α (**F**); expression of the NFE2F2/KEAP1/CUL3 signaling pathway related molecule Nrf2 (**G**); and expression of the CDKN2A/RB1 signaling pathway molecule CDKN2A/p16 INK4A (**H**) in deltaNp63 positive cancer cells in pLSCCs. Proteins of interest (**red**) are co-stained with deltaNp63 (**green**) and nuclei (**blue**). Yellow in merged images represents co-expression of the protein of interest and deltaNp63. While all the molecules were overexpressed in lung pLSCCs, the overexpression was not deltaNp63^{pos}CD44v^{pos} cancer cell-specific or area-specific. Bar=100 μm.

Supplemental Figure 6: Examination of TAMs, phospho-EGFR, and phospho-STAT3 expression in precancerous lesions in NTCU-treated mice lung.

Examination of TAM markers CD163L1 (**A1-3**), CD68 (**B1-3**), CD204 (**C1-3**), phospho-EGFR (pY1068) (**D1-3**), and phospho-STAT3 (Tyr705) (**E1-3**) in precancerous lesions containing atypical bronchiolar hyperplasia, squamous metaplasia, and squamous dysplasia. TAM marker positive macrophages and phospho-EGFR were seldom detected in these lesions and phospho-STAT3 was not detected in these lesions. Bar=100 μm.

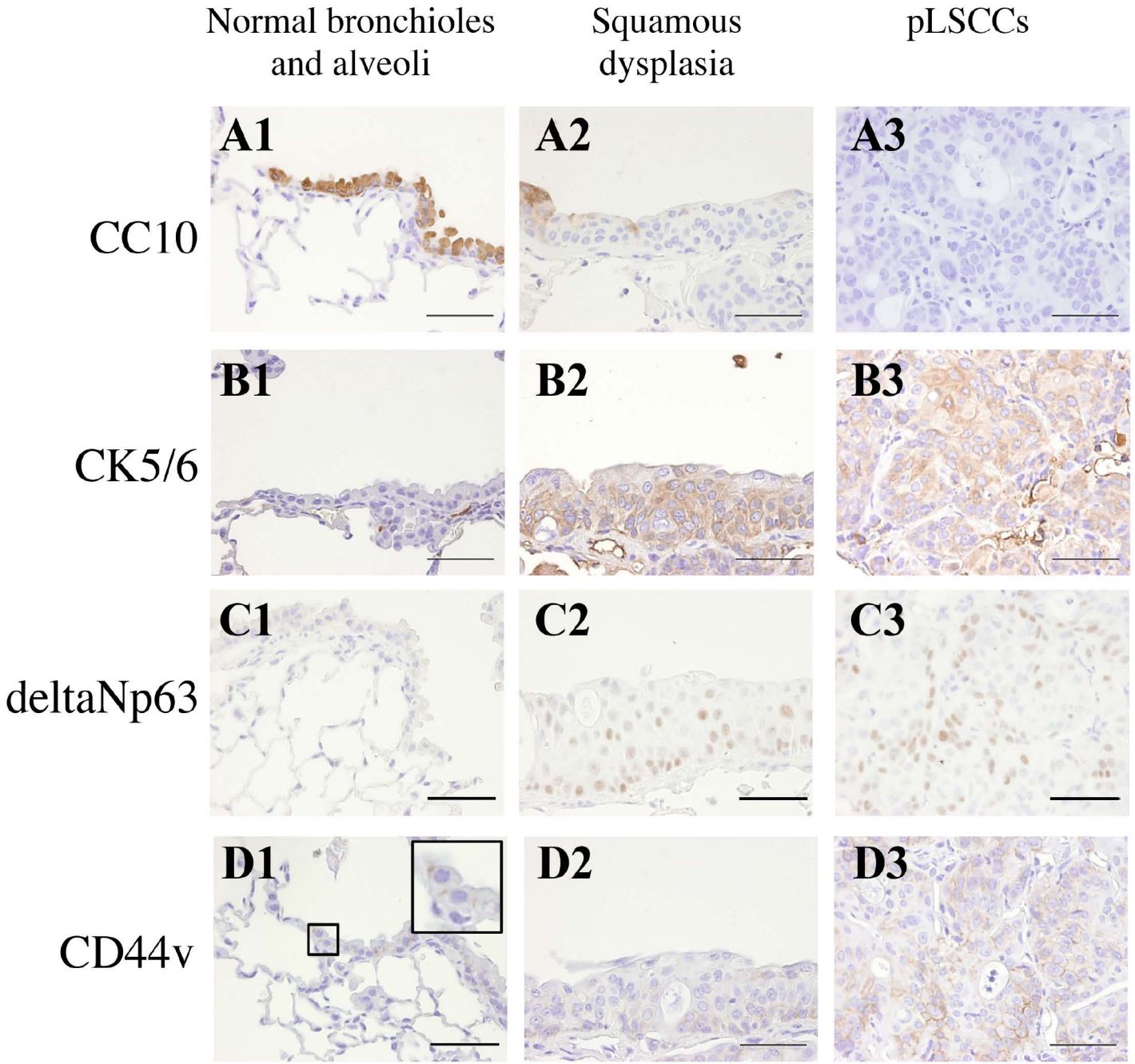

Fig. S1: Clara cell, Squamous differentiation, and pulmonary stem cell markers in normal bronchioles and alveoli in Acetone-treated mice and in squamous dysplasia and SCC in NTCU-treated mice.

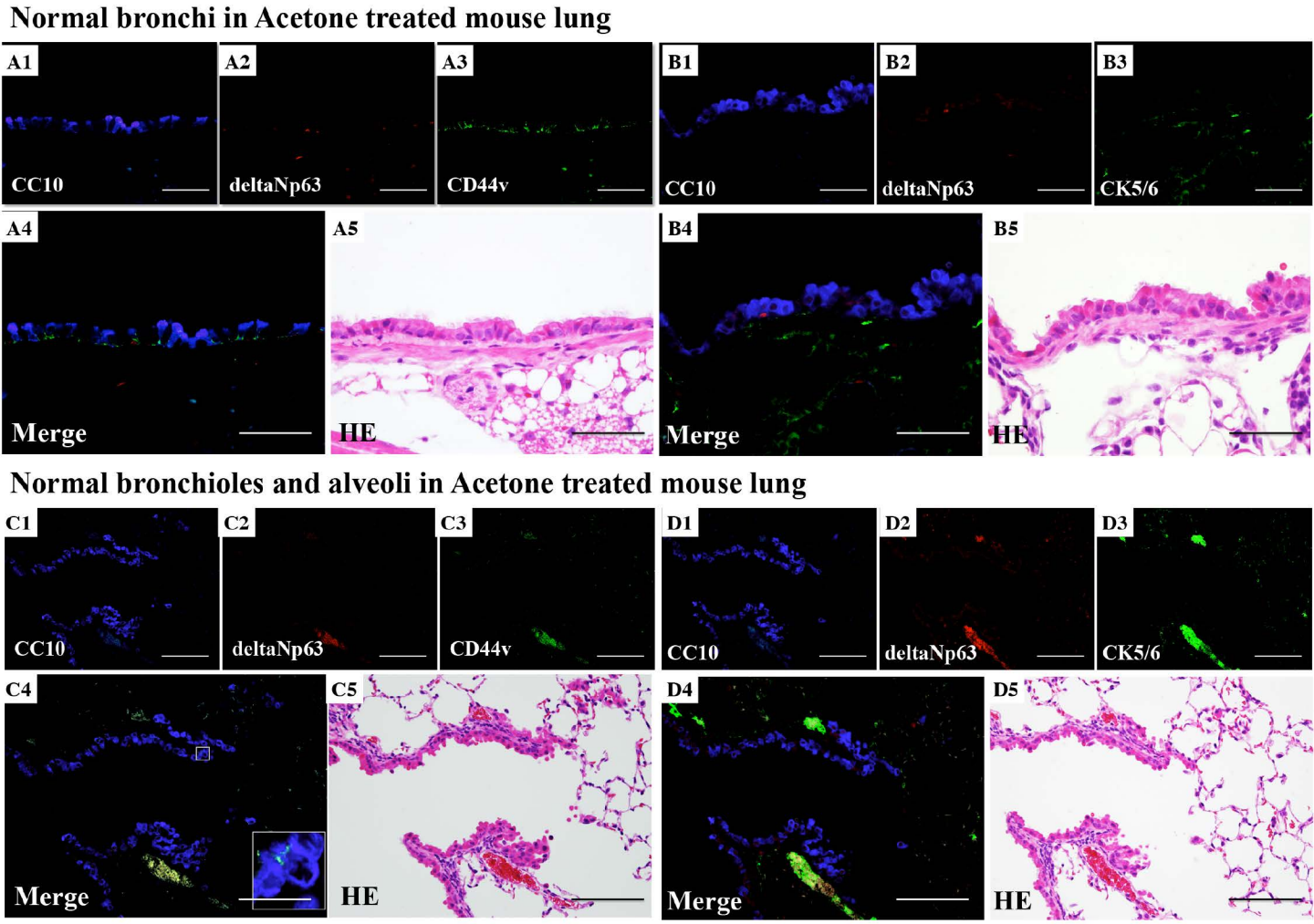

Fig. S2: Co-localization of CC10, deltaNp63, and CD44v or CK5/6 proteins in acetone-treated mouse lung bronchi, bronchioles, and alveoli.

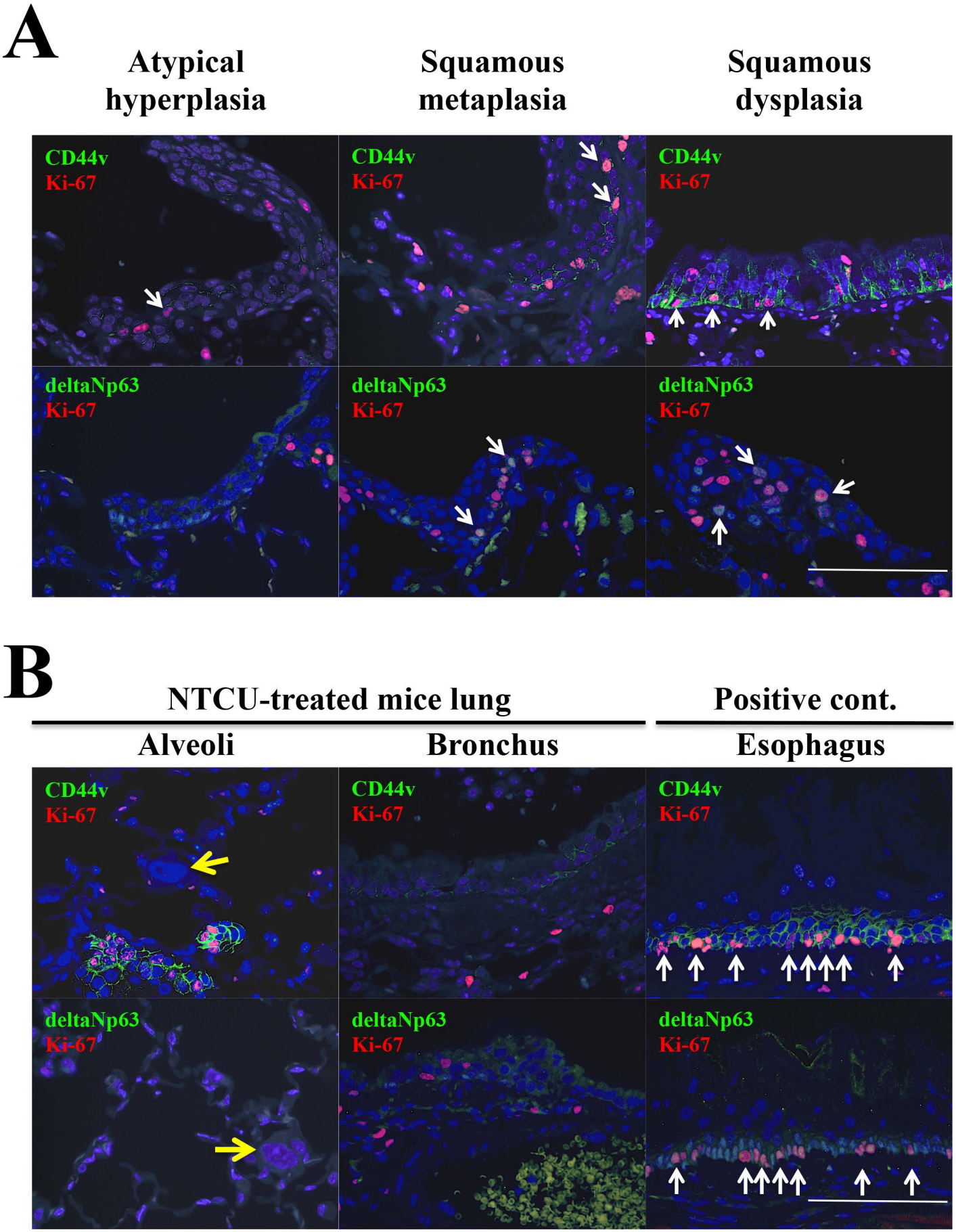

Fig. S3: Co-localization of ki-67 and CD44v or deltaNp63 in precancerous lesions, normal alveoli and bronchi, and esophagus in NTCU-treated mouse lung.

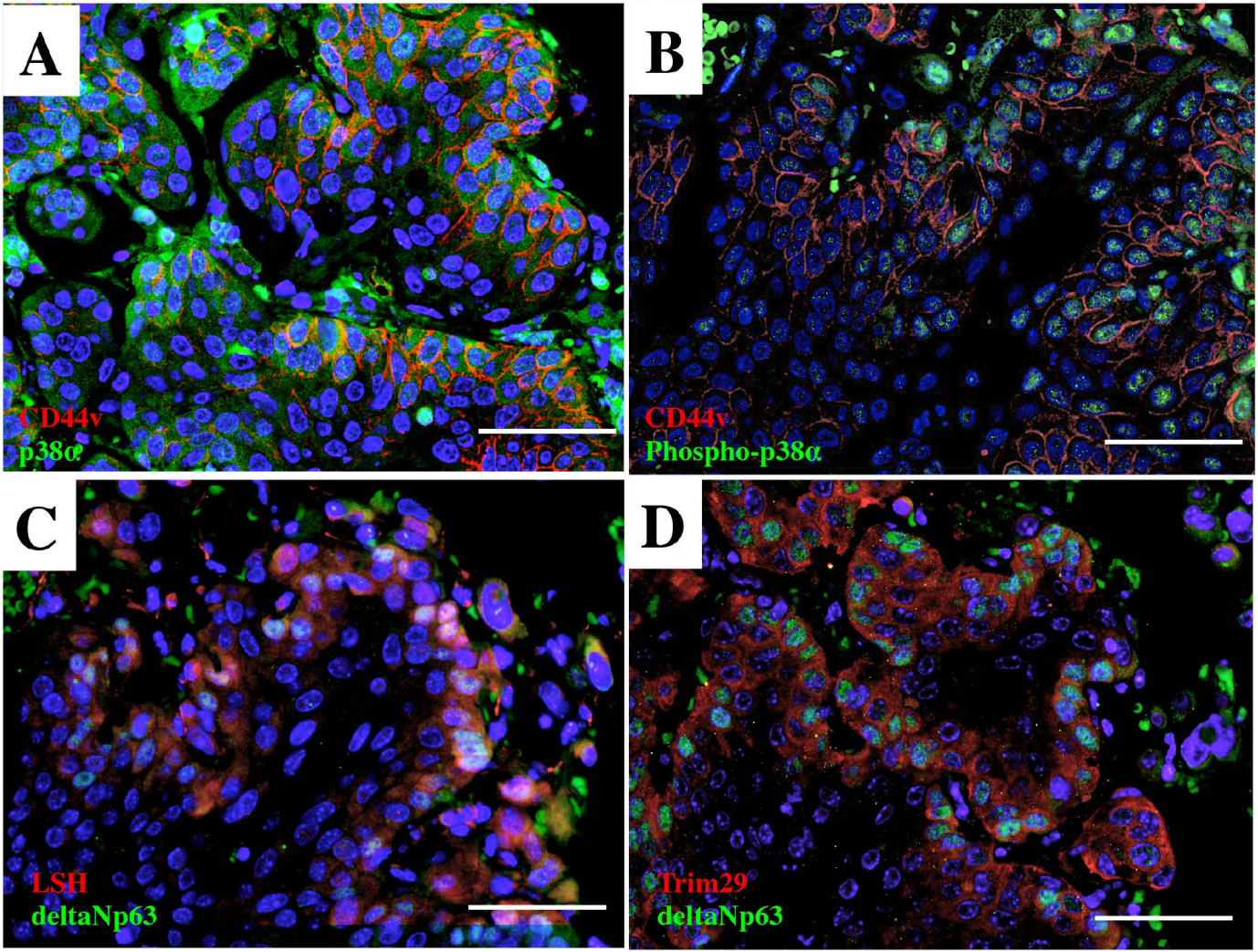

Fig. S4: p38α and phospho-p38α expression in CD44v positive cancer cells, and LSH and Trim29 expression in deltaNp63 positive cancer cells.

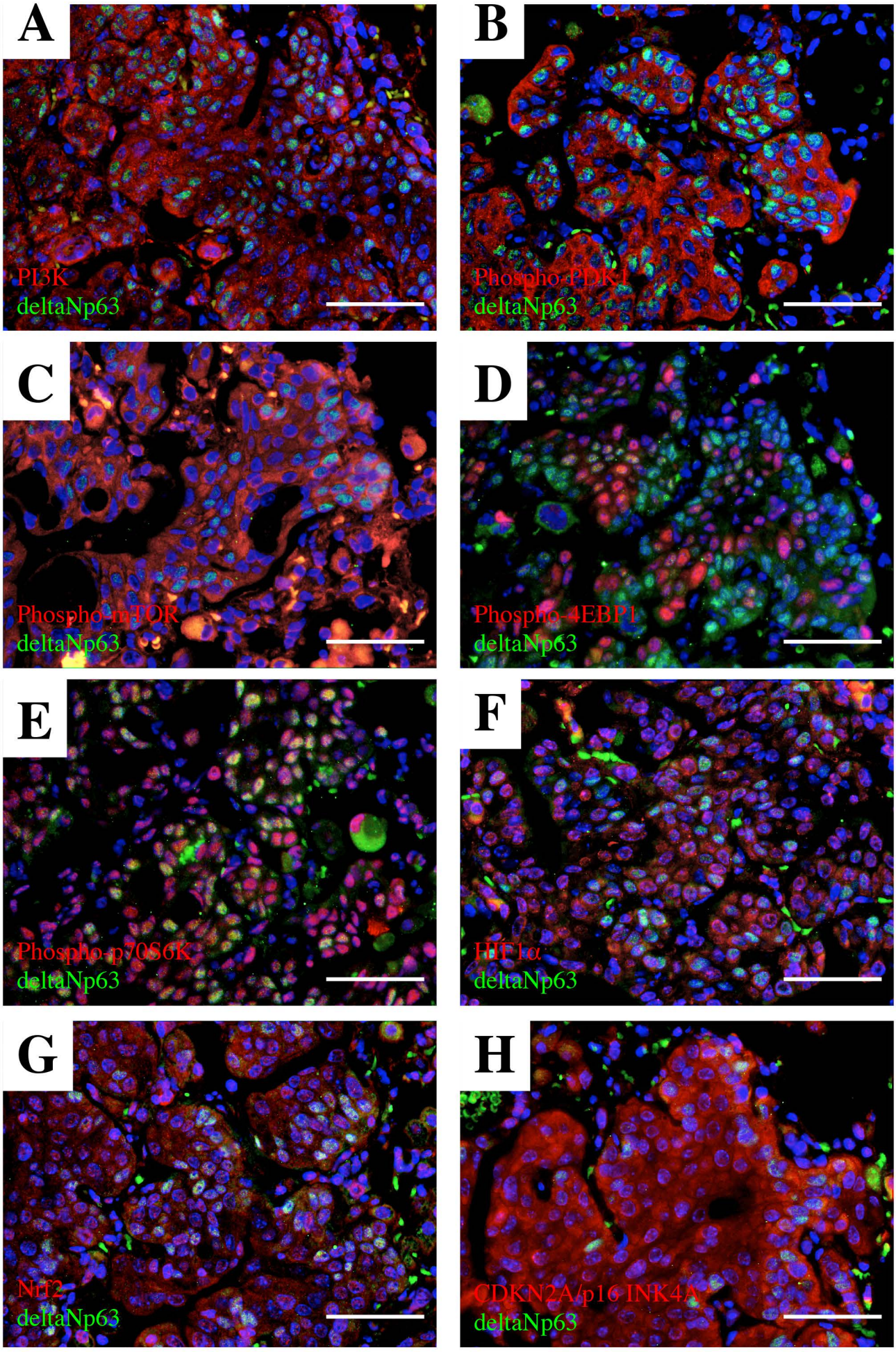

Fig. S5: Expression of human lung squamous cell carcinoma progression markers in deltaNp63 positive cancer cells.

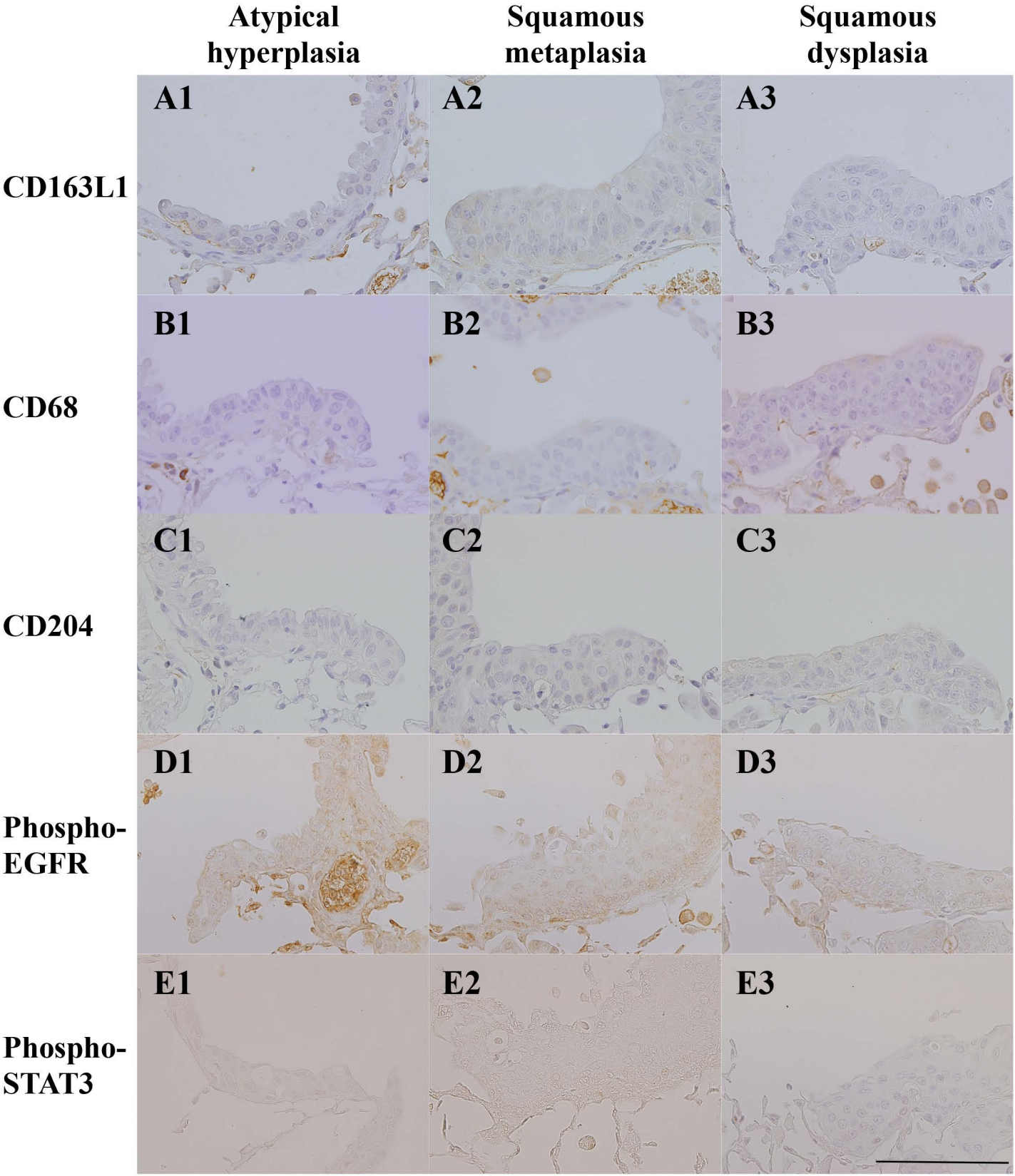

Fig. S6: Examination of TAMs, phospho-EGFR, and phospho-STAT3 expression in precancerous lesions in NTCU-treated mice lung.