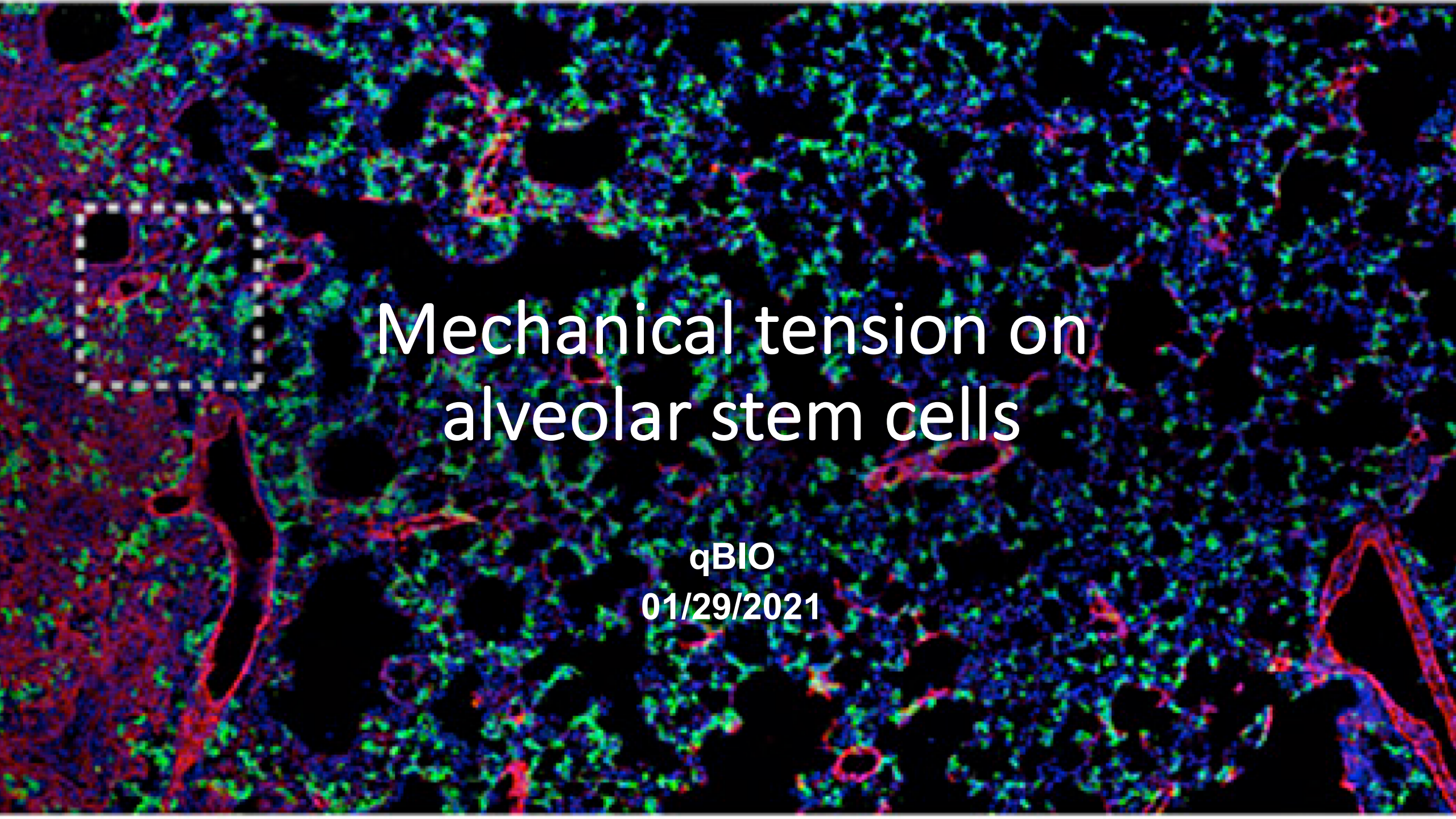


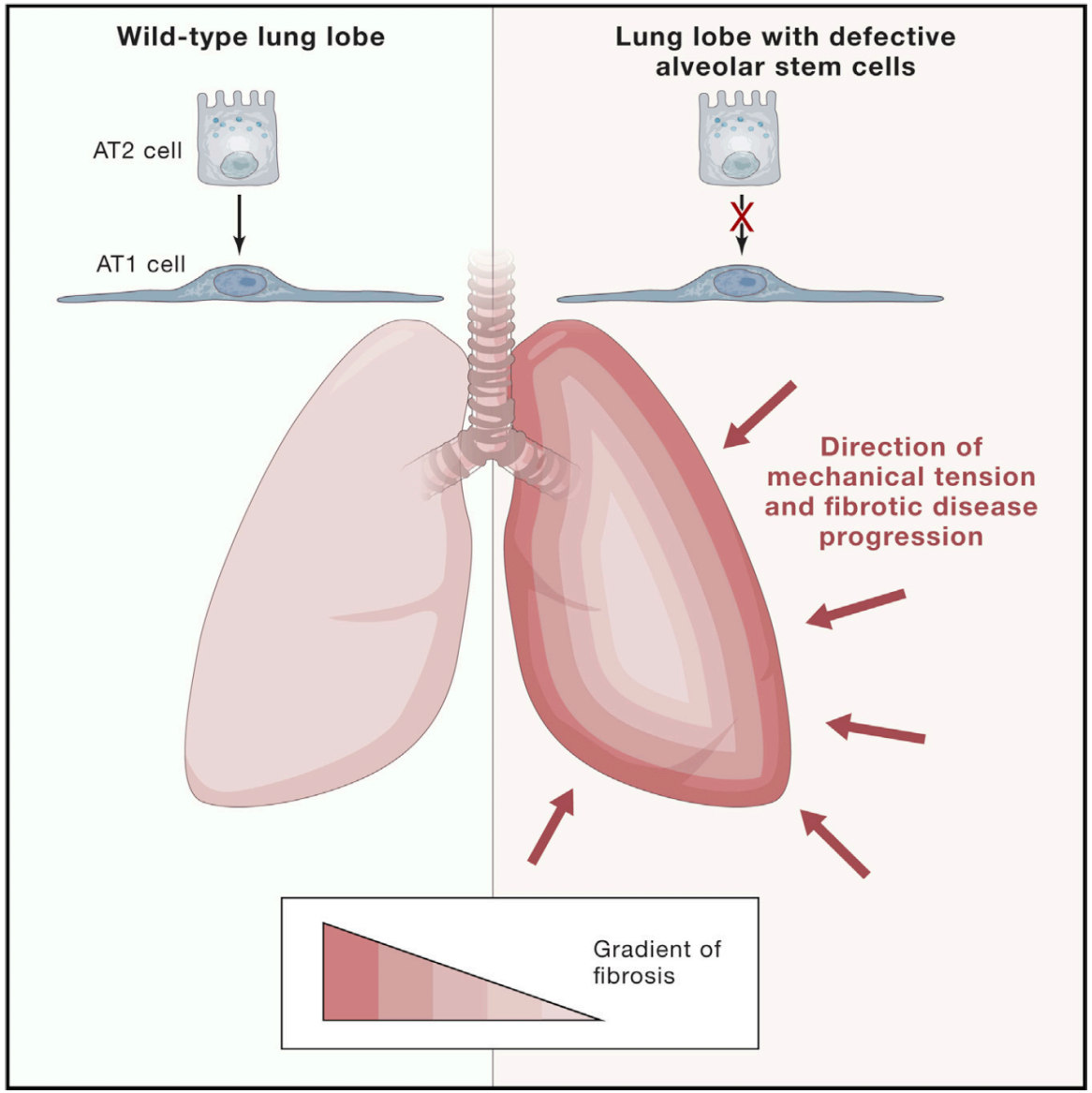
Mechanical tension on alveolar stem cells

qBIO

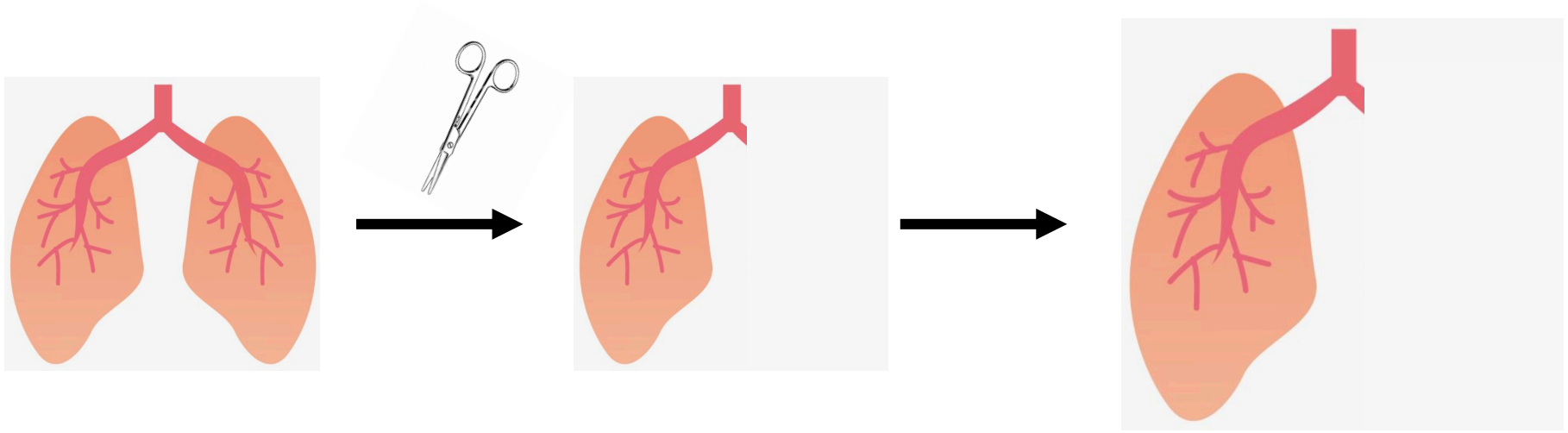
01/29/2021

Mechanosensing in the lung

Defective alveolar stem cells and mechanical tension lead to spatially specific fibrosis



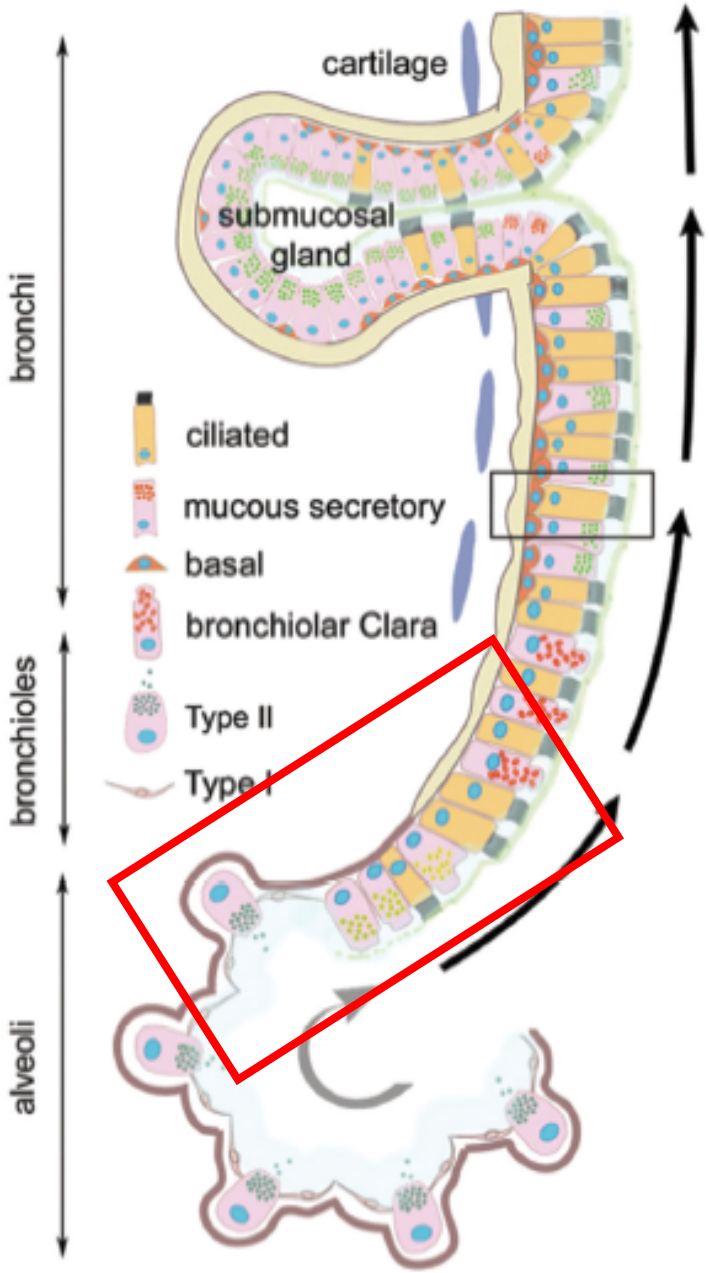
Lung regeneration*: Pneumonectomy (PNX) as a model of compensatory growth

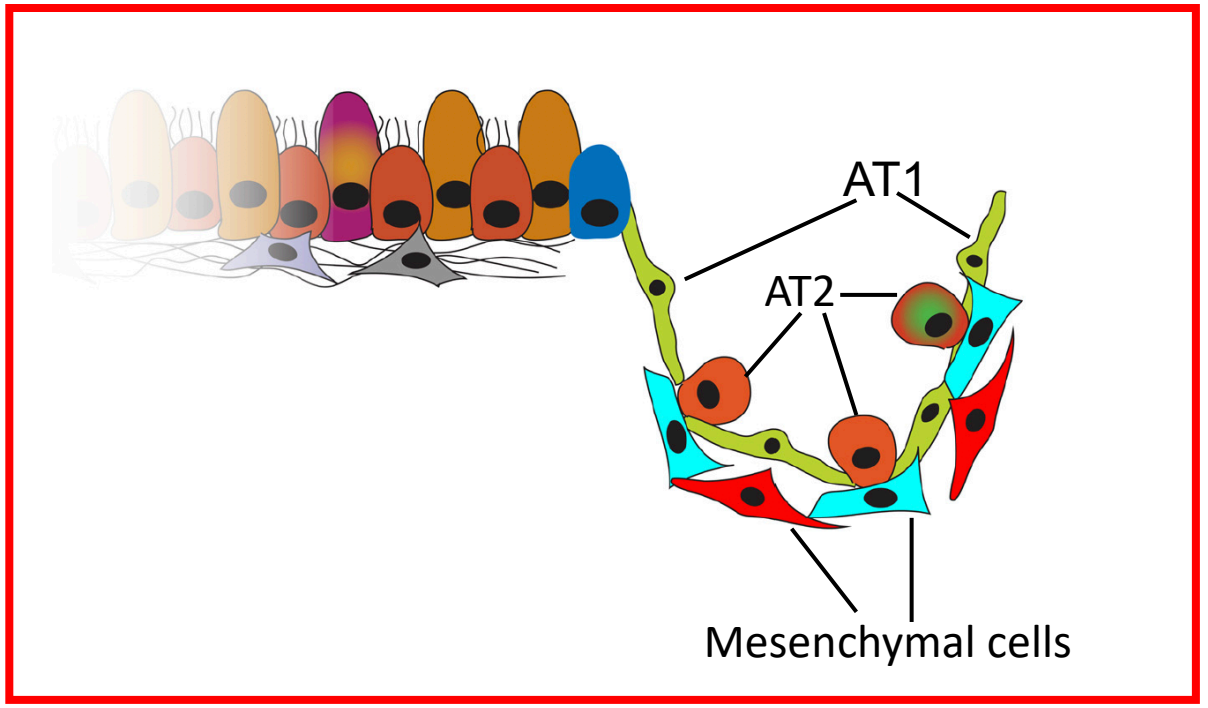


1) Unilateral removal of 1 lobe
2) Growth of remaining lobe

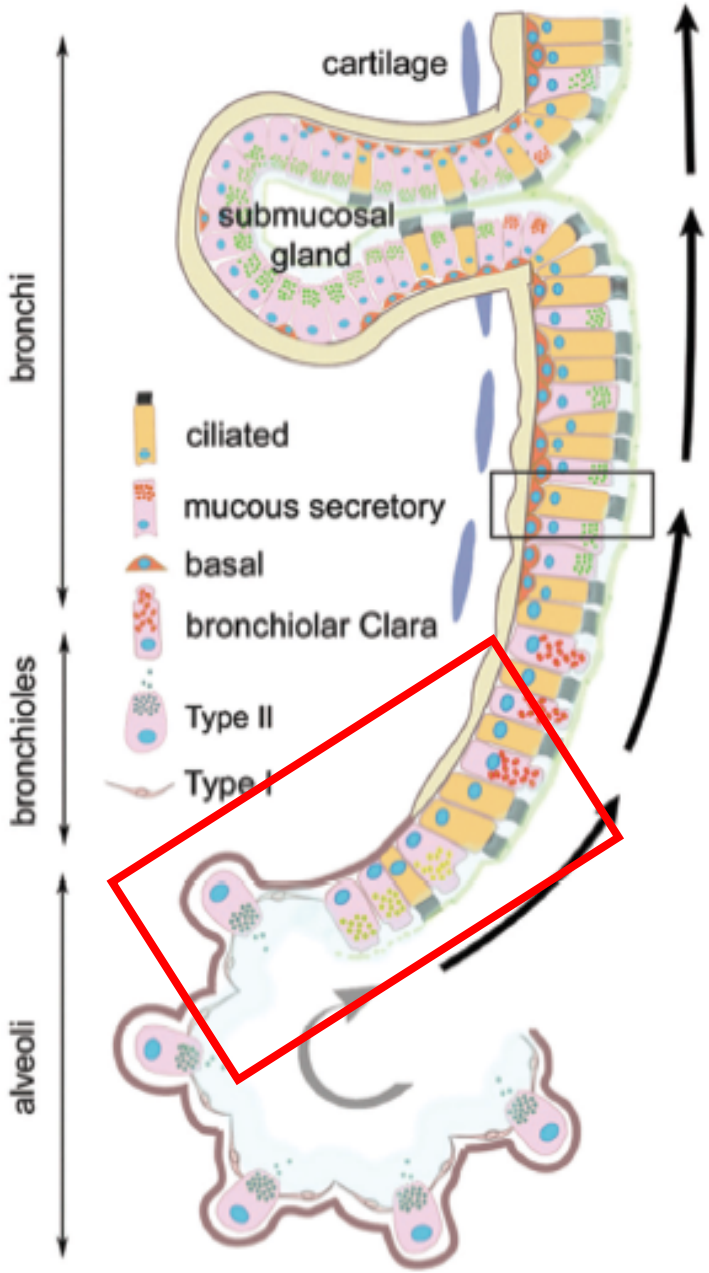
Which cells act as progenitor cells?
What signals are important to activate progenitors?

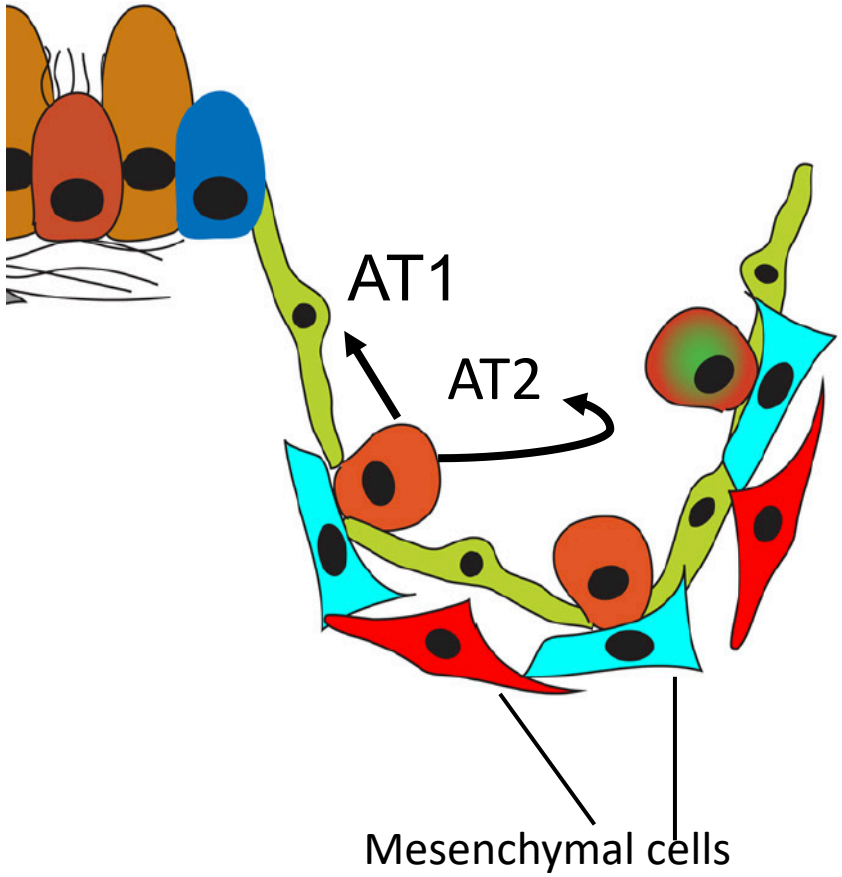
Alveolar Epithelial Cells: AT1 and AT2



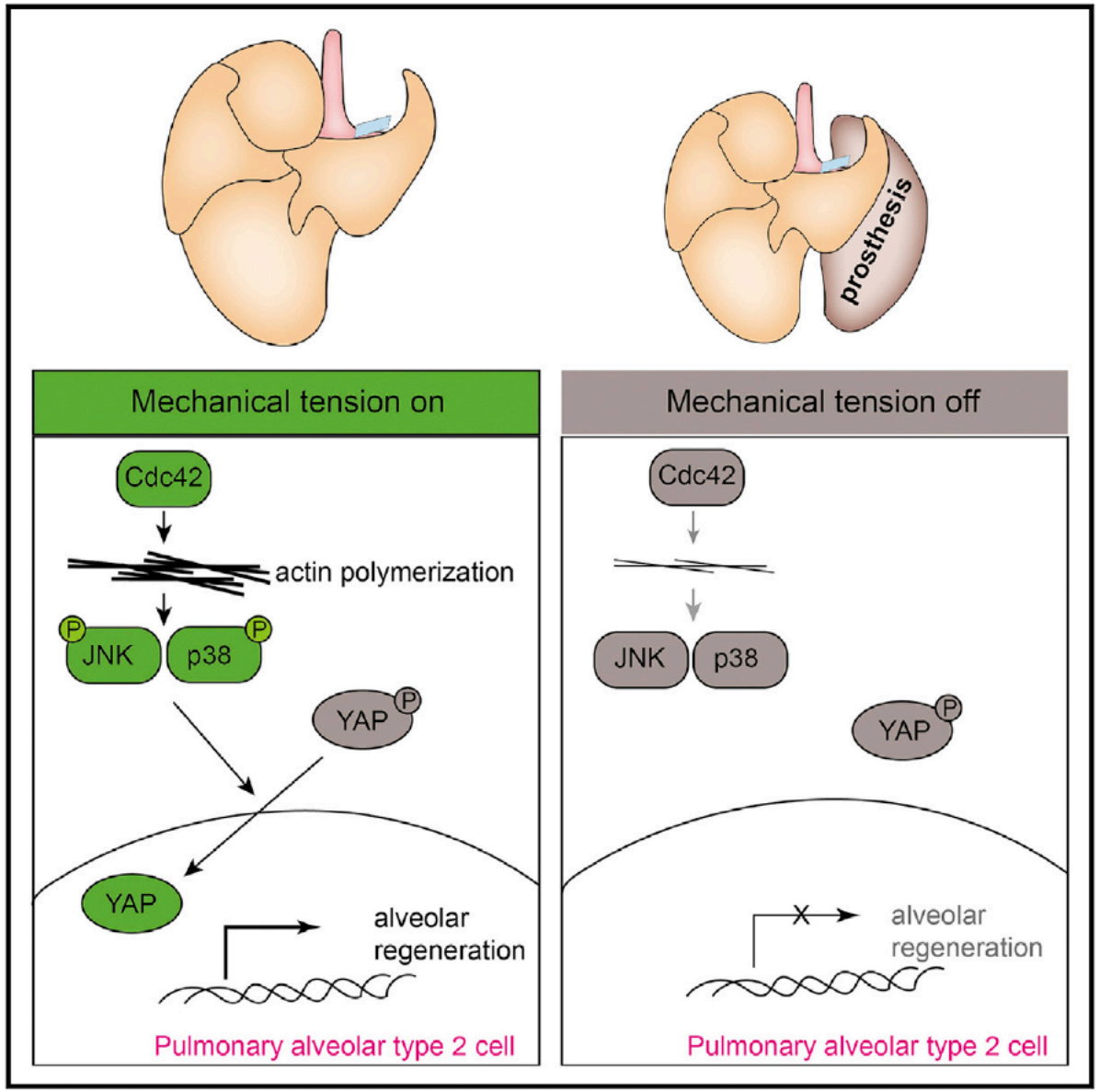


Alveolar Epithelial Cells: AT2 Progenitor Function



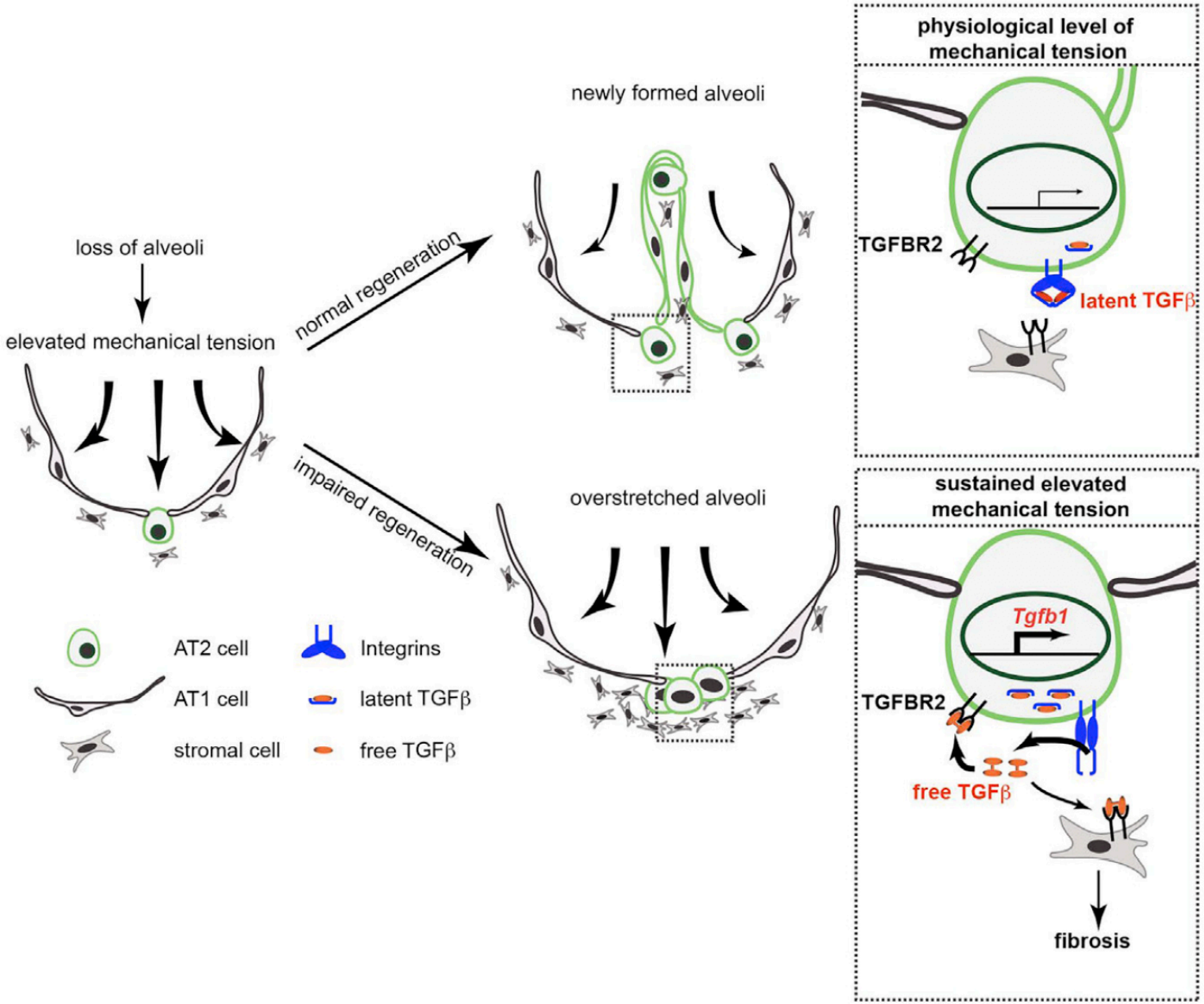


Cdc42 signaling cascade is required for AT2 regenerative response to mechanical tension



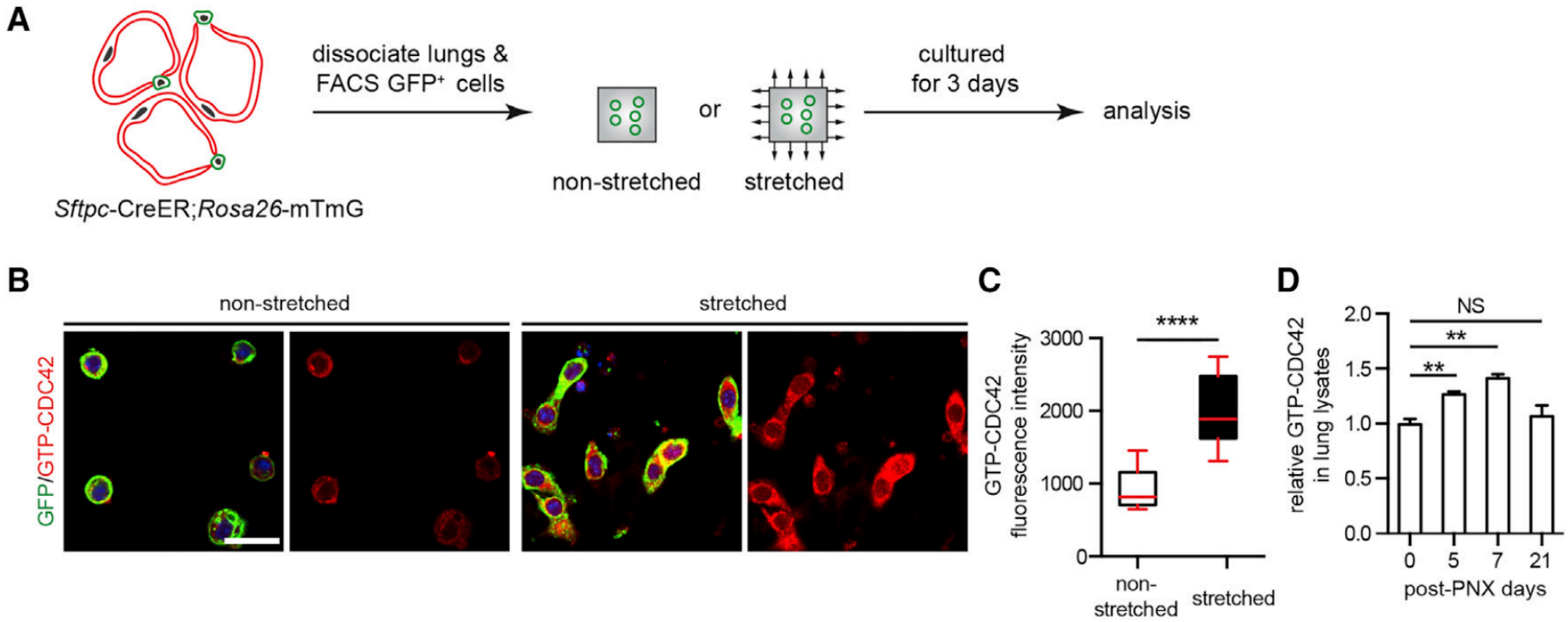
MAPK-Mediated YAP Activation Controls Mechanical-Tension-Induced Pulmonary Alveolar Regeneration
Cell Reports, 2016

Mechanical tension induced AT2 signaling can lead to regeneration or progressive pulmonary fibrosis



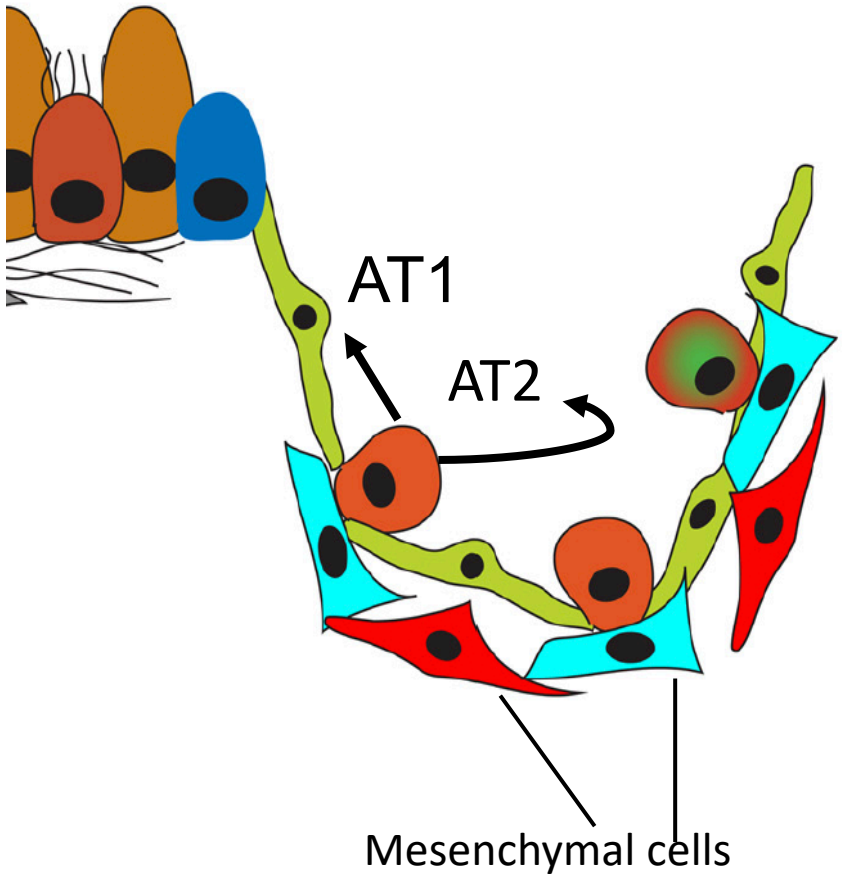
Is Cdc42 required for AT2 cell mechanosensing?

Figure 1

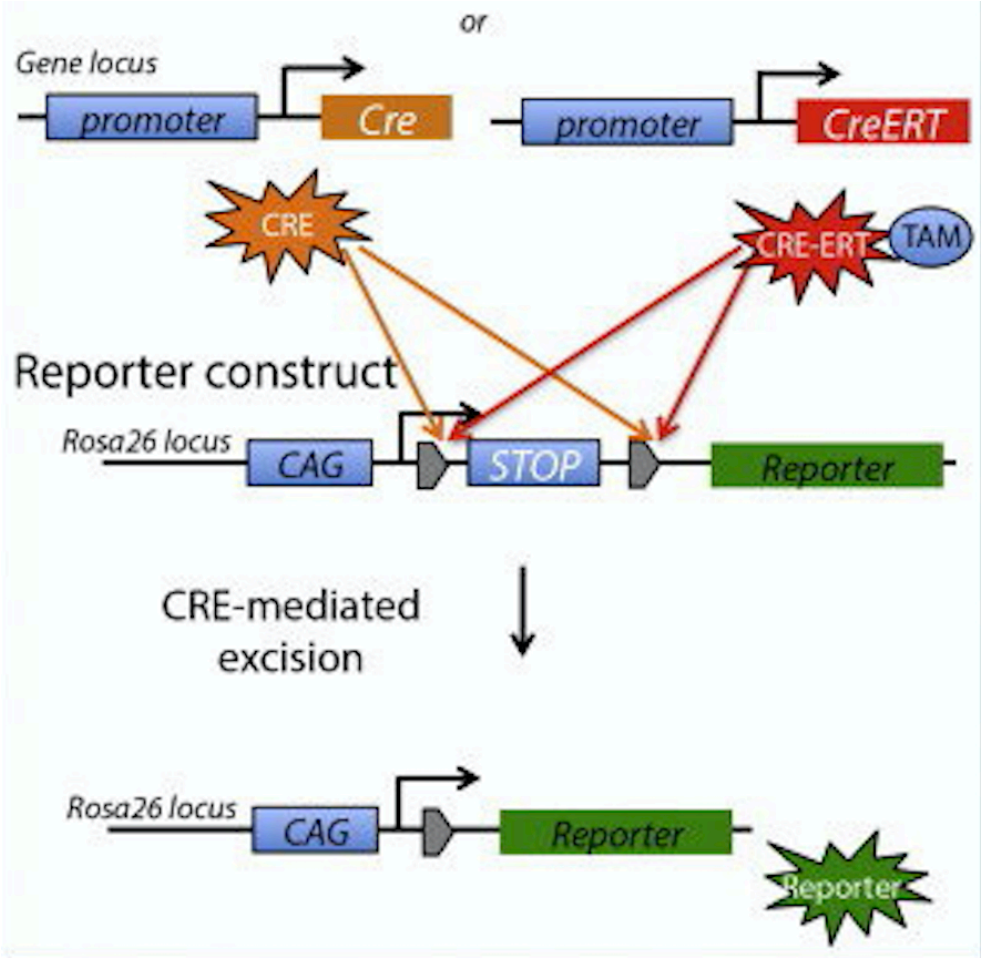


Activation of Cdc42 in stretched AT2 cells and after PNX

Is Cdc42 required for AT2 cell differentiation to AT1 cell?

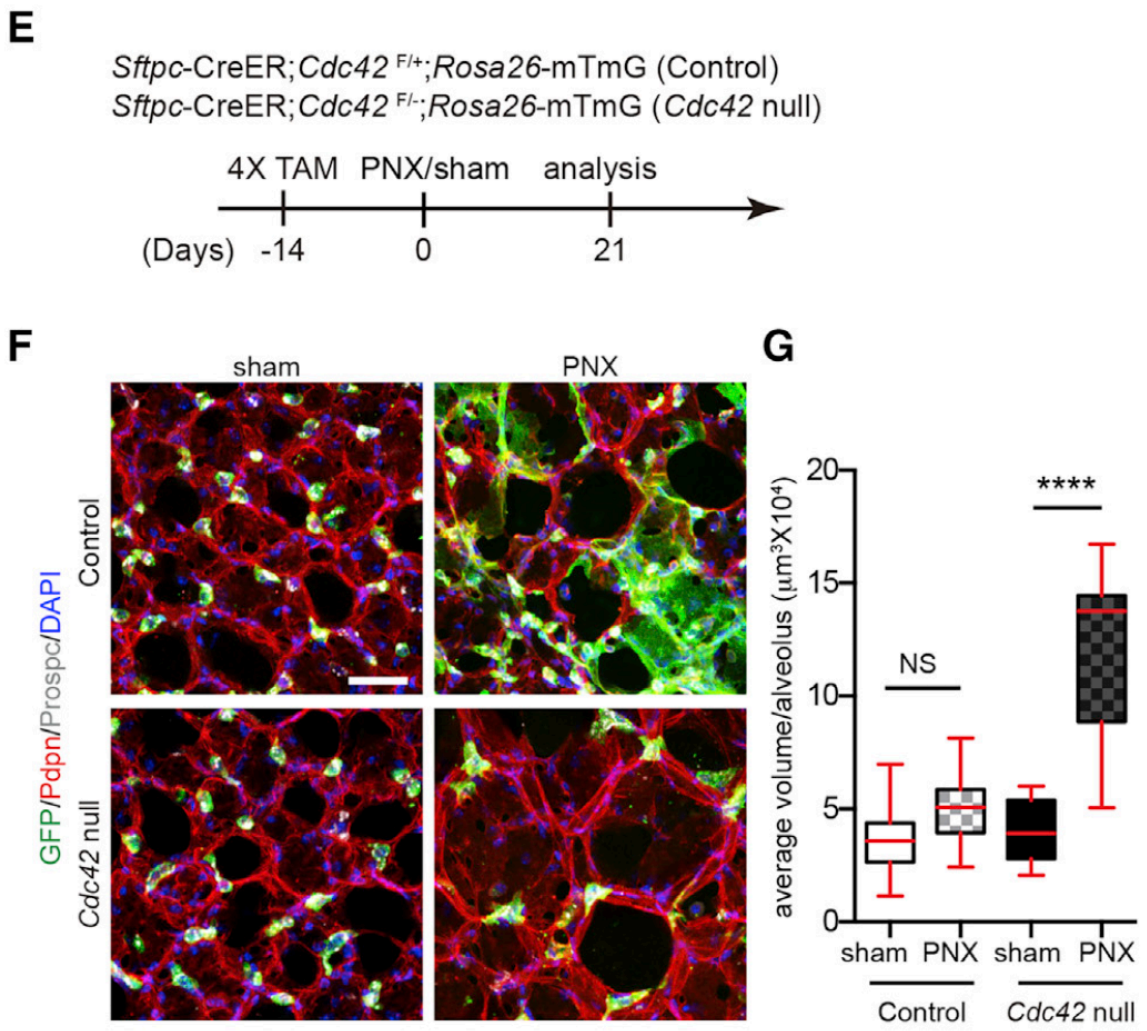


Lineage tracing strategy



Is Cdc42 required for AT2 cell differentiation to AT1 cell?

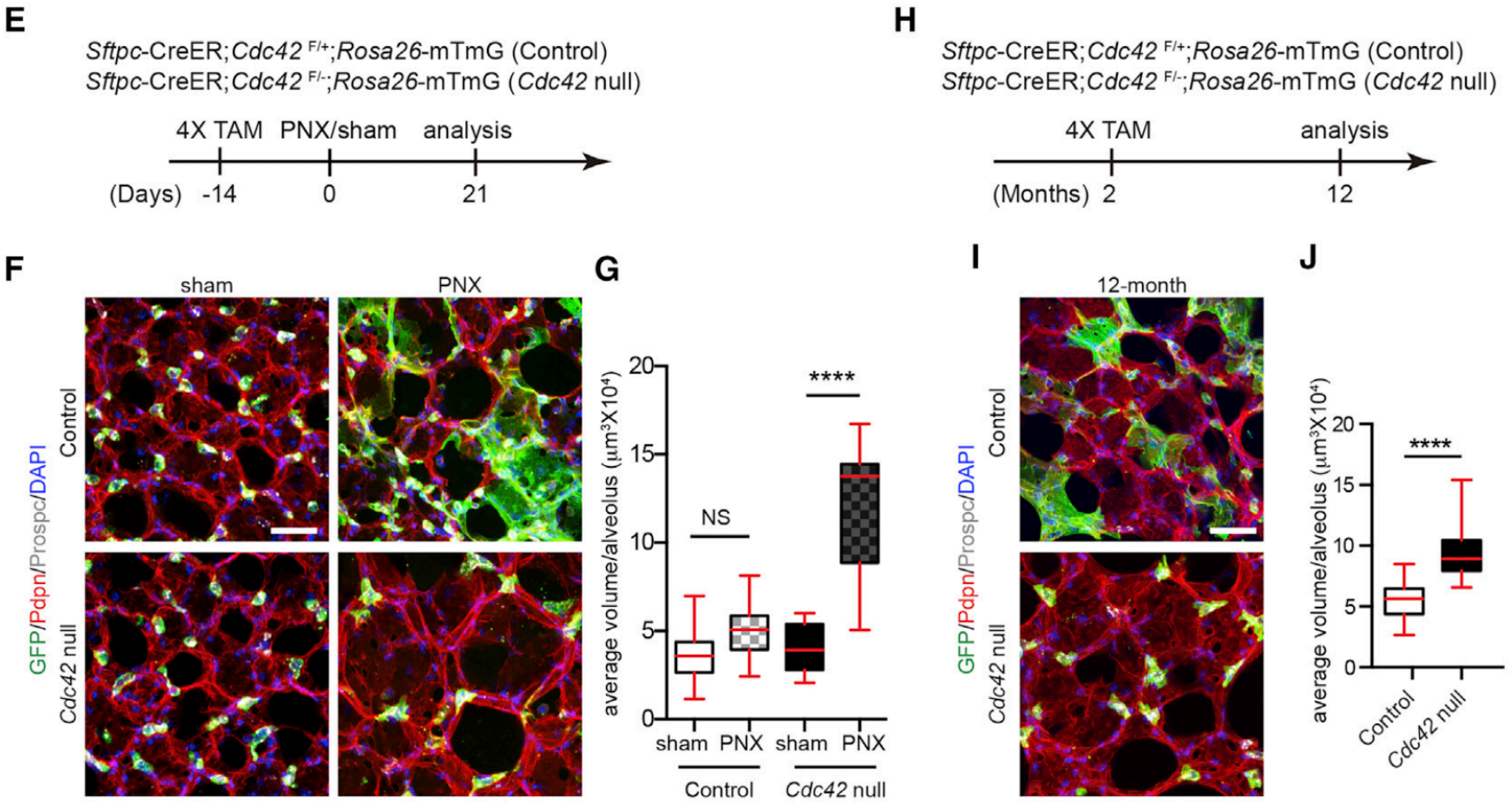
Figure 1



Cdc42 required for AT2 regeneration of alveolar compartment after PNX

Is Cdc42 required for AT2 cell differentiation to AT1 cell?

Figure 1

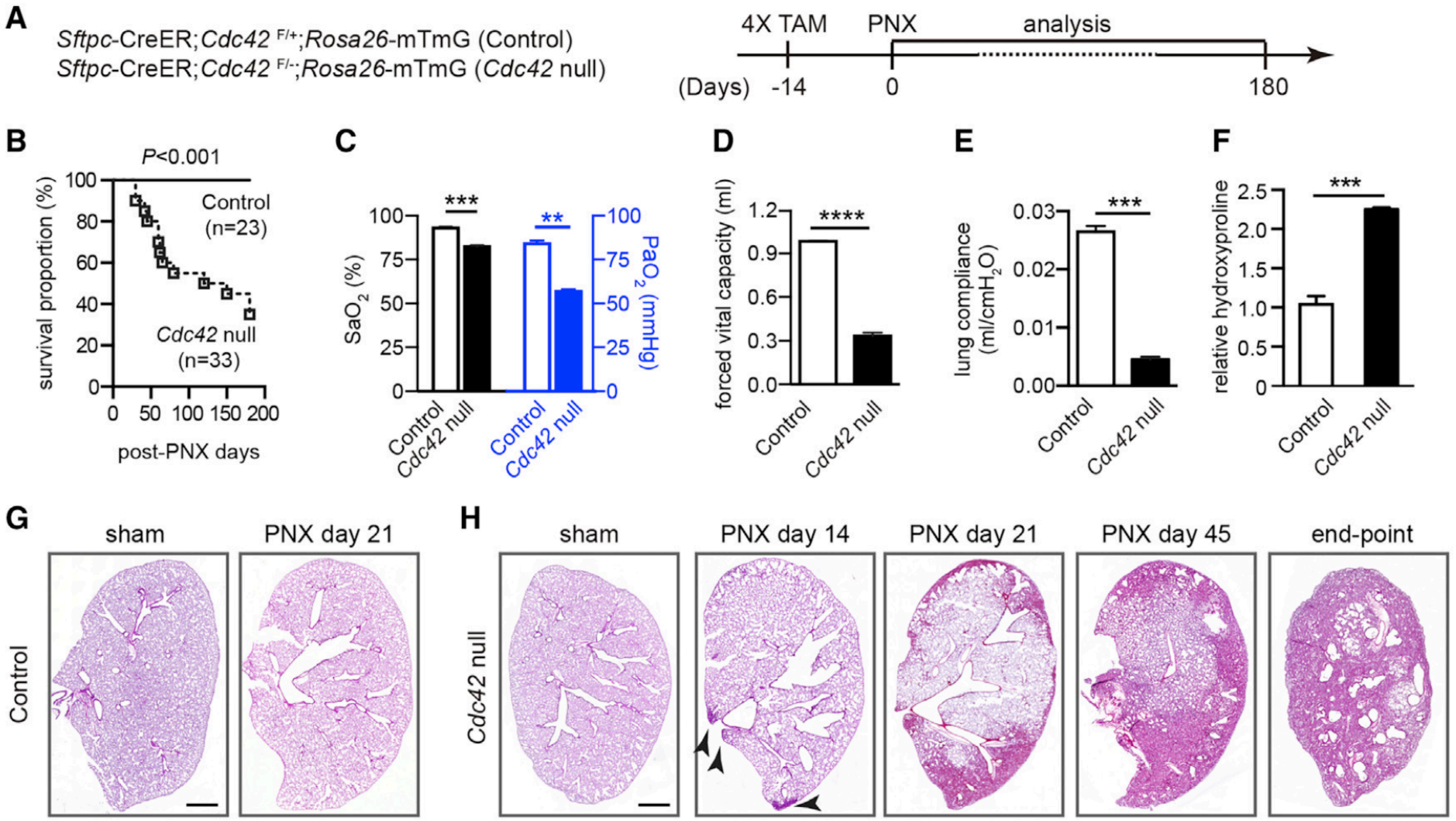


Cdc42 required for AT2 regeneration of alveolar compartment after PNX

AT2 progenitor function prevents alveolar simplification after PNX or with aging

What are the long-term consequences of failed AT2 regeneration following PNX?

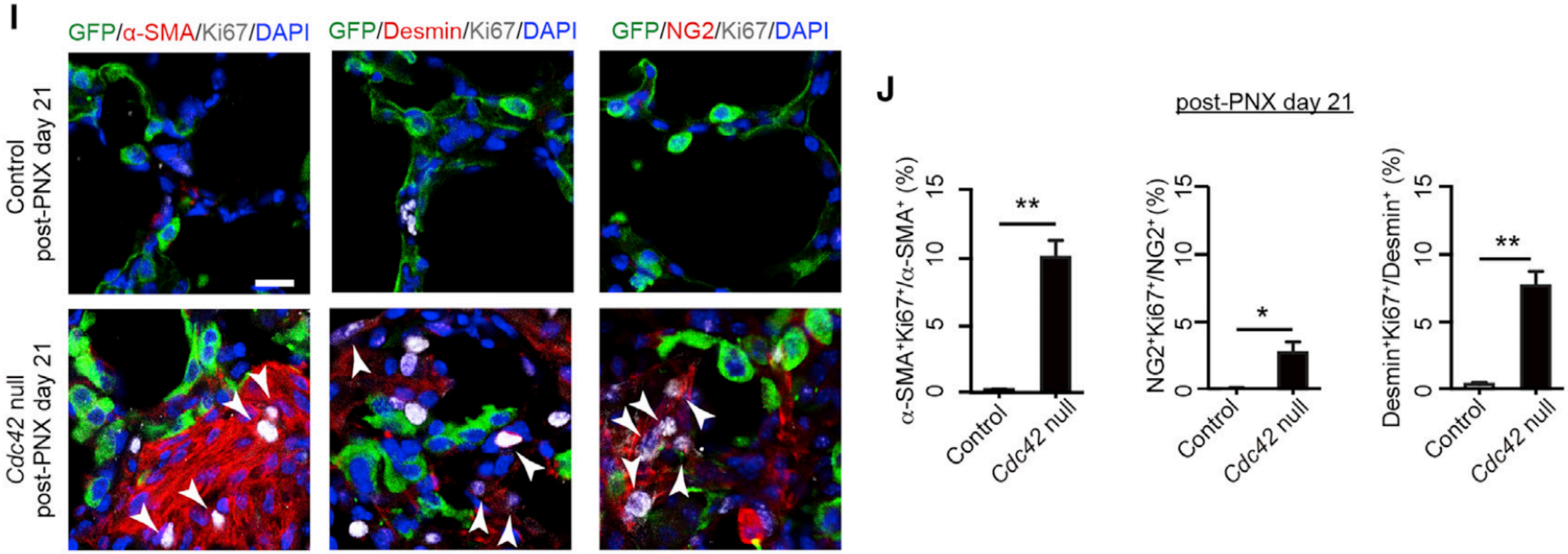
Figure 2



Decreased lung function and progression of outside-in fibrosis

What cell types in the lung mediate fibrosis following PNX when AT2 cell regeneration is compromised?

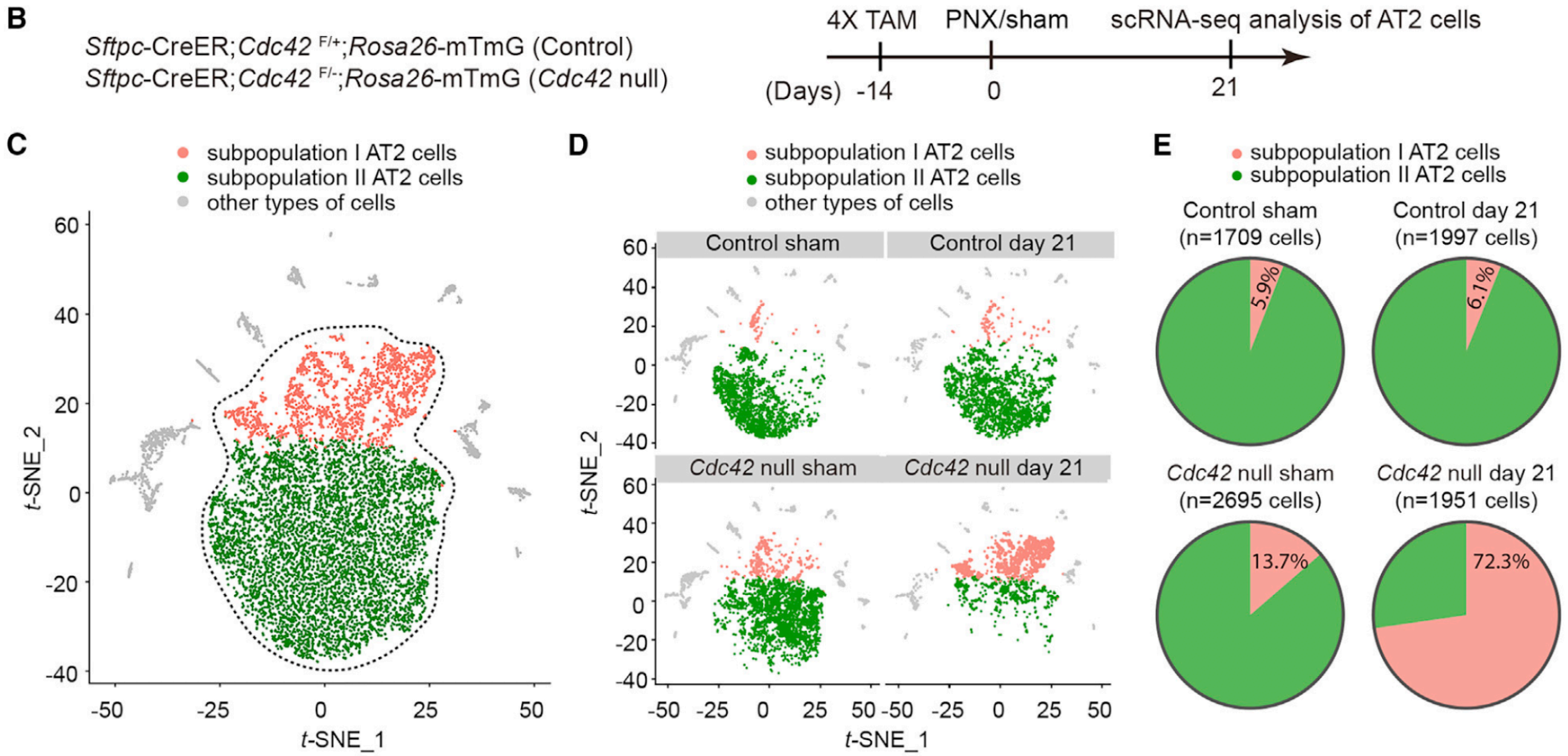
Figure 2



Mesenchymal myofibrolast proliferation contributes to fibrotic phenotype

What molecular changes are observed in AT2 cells that fail to differentiate into AT1 cells after PNX?

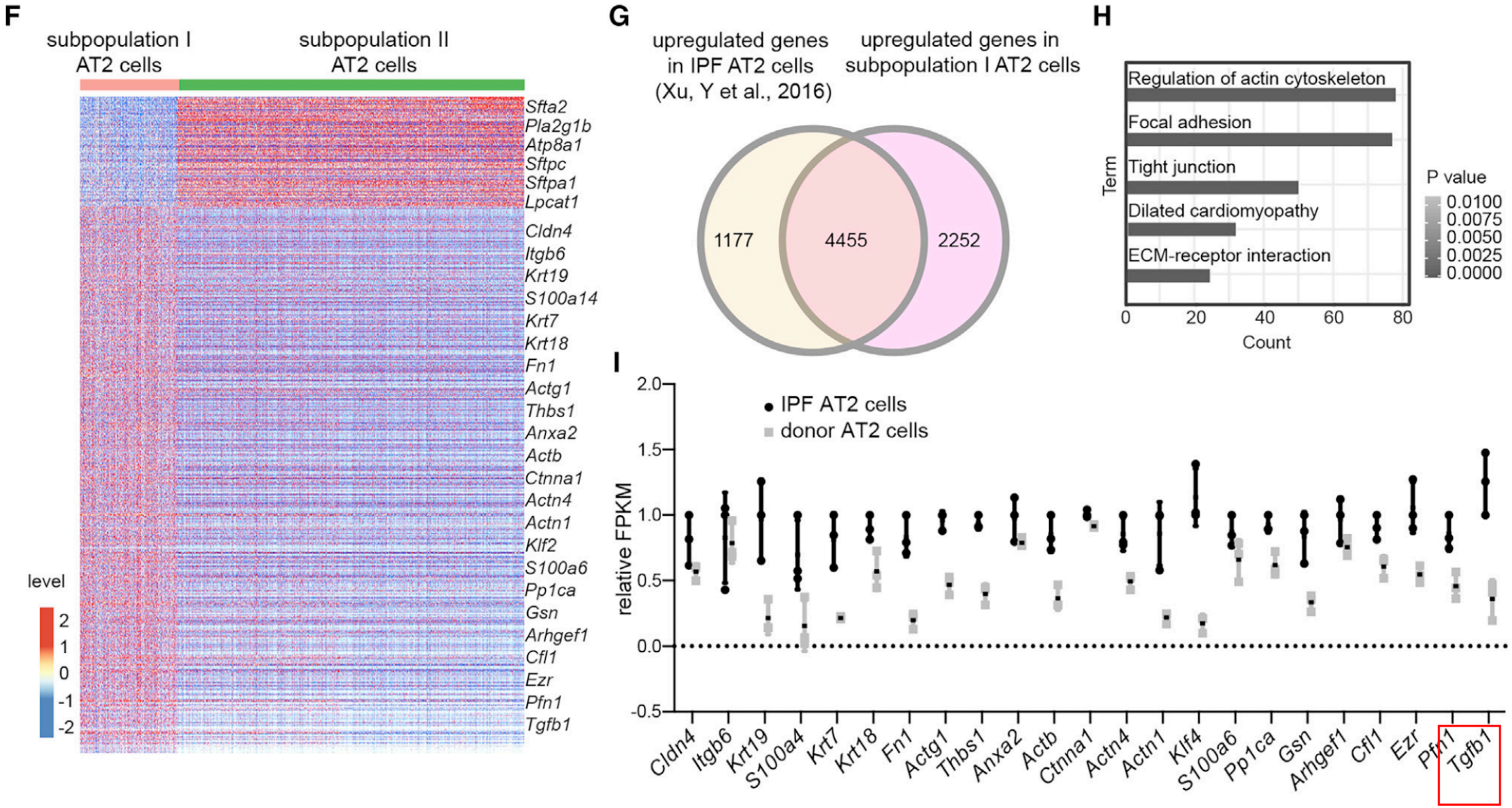
Figure 3



There are 2 populations of AT2 cells; subpopulation I is increased in the mutant following PNX

What are the molecular characteristics of subpopulation I AT2 cells?

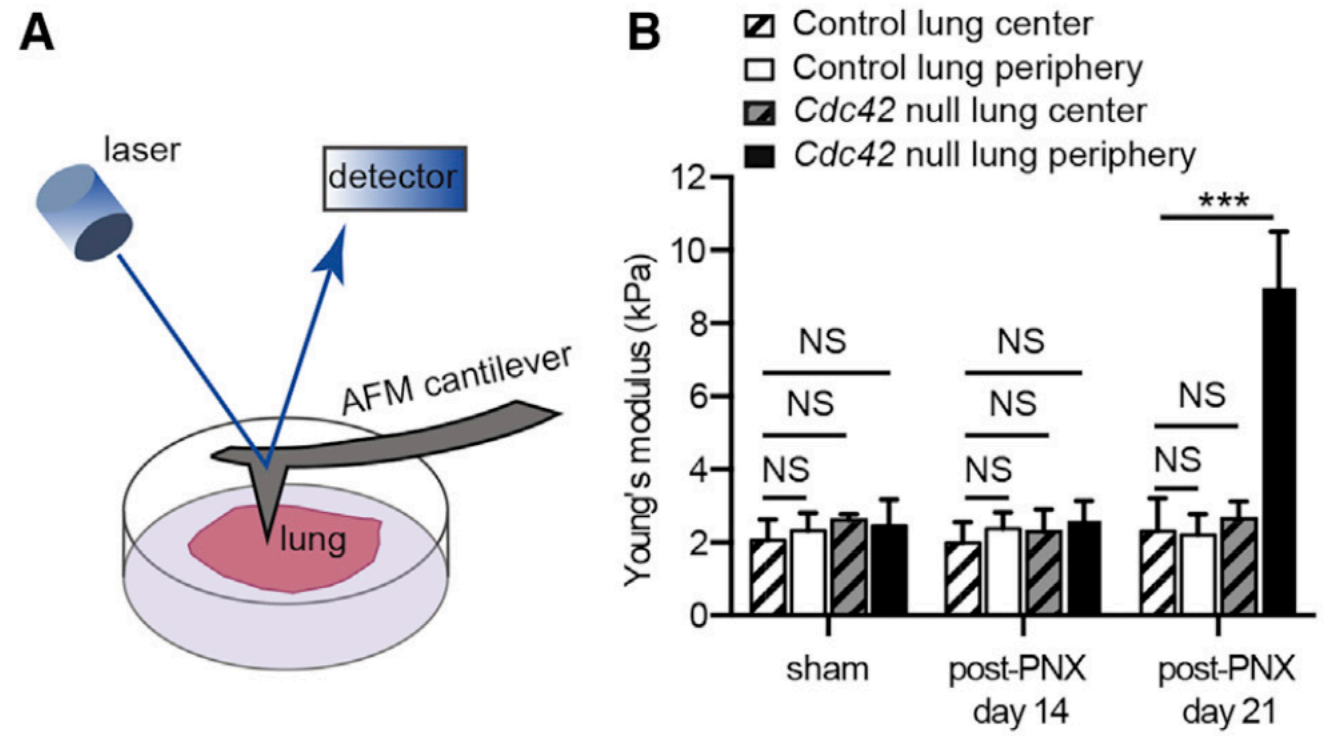
Figure 3



> 2/3 of upregulated genes in subpopulation I are also upregulated in IPF

Is increased mechanical tension responsible for the progression of lung fibrosis?

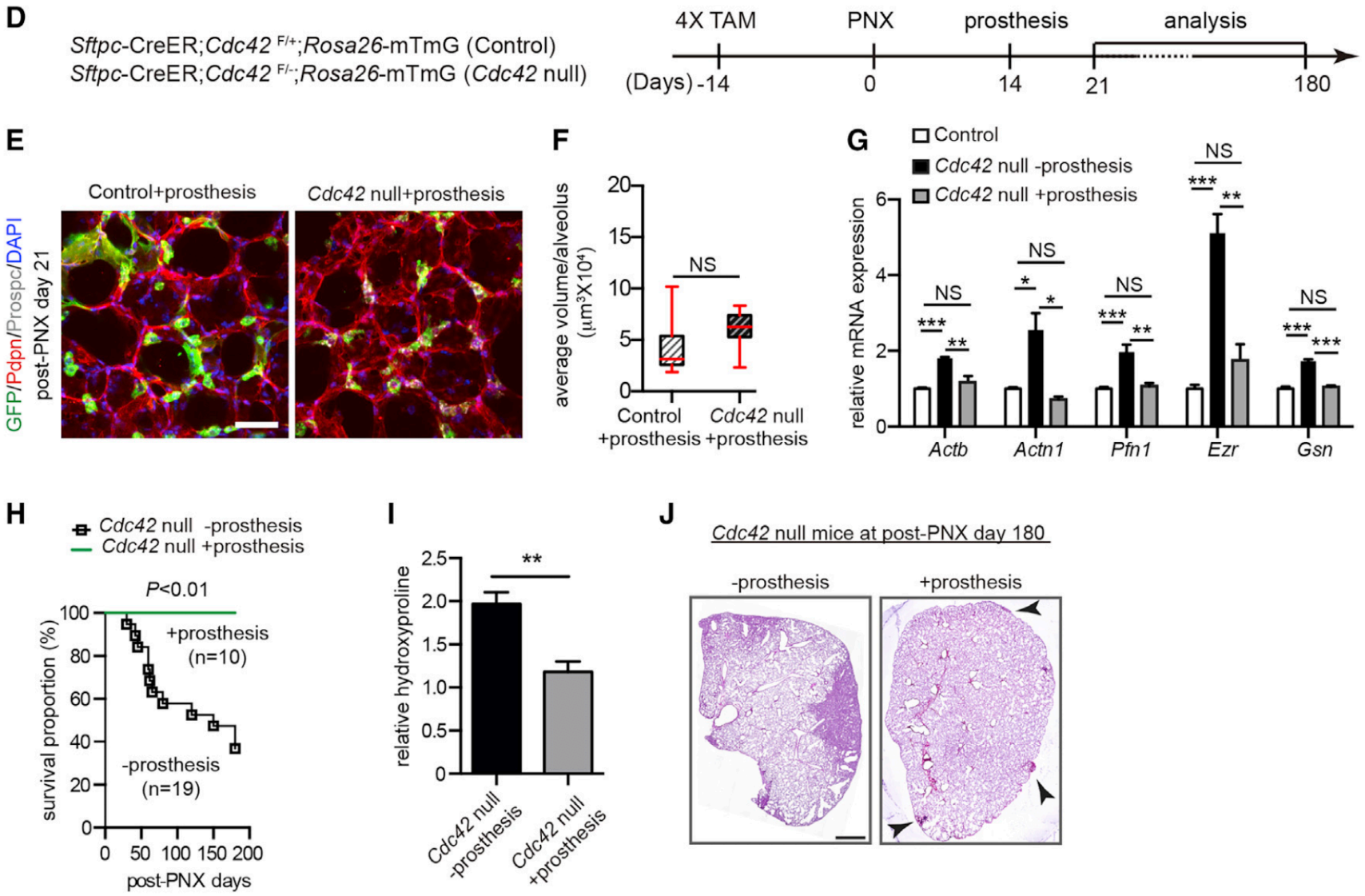
Figure 4



Increased tissue stiffness at the periphery during outside-in lung fibrosis

Is increased mechanical tension responsible for the progression of lung fibrosis?

Figure 4



Reducing mechanical tension leads to rescue of fibrotic phenotype

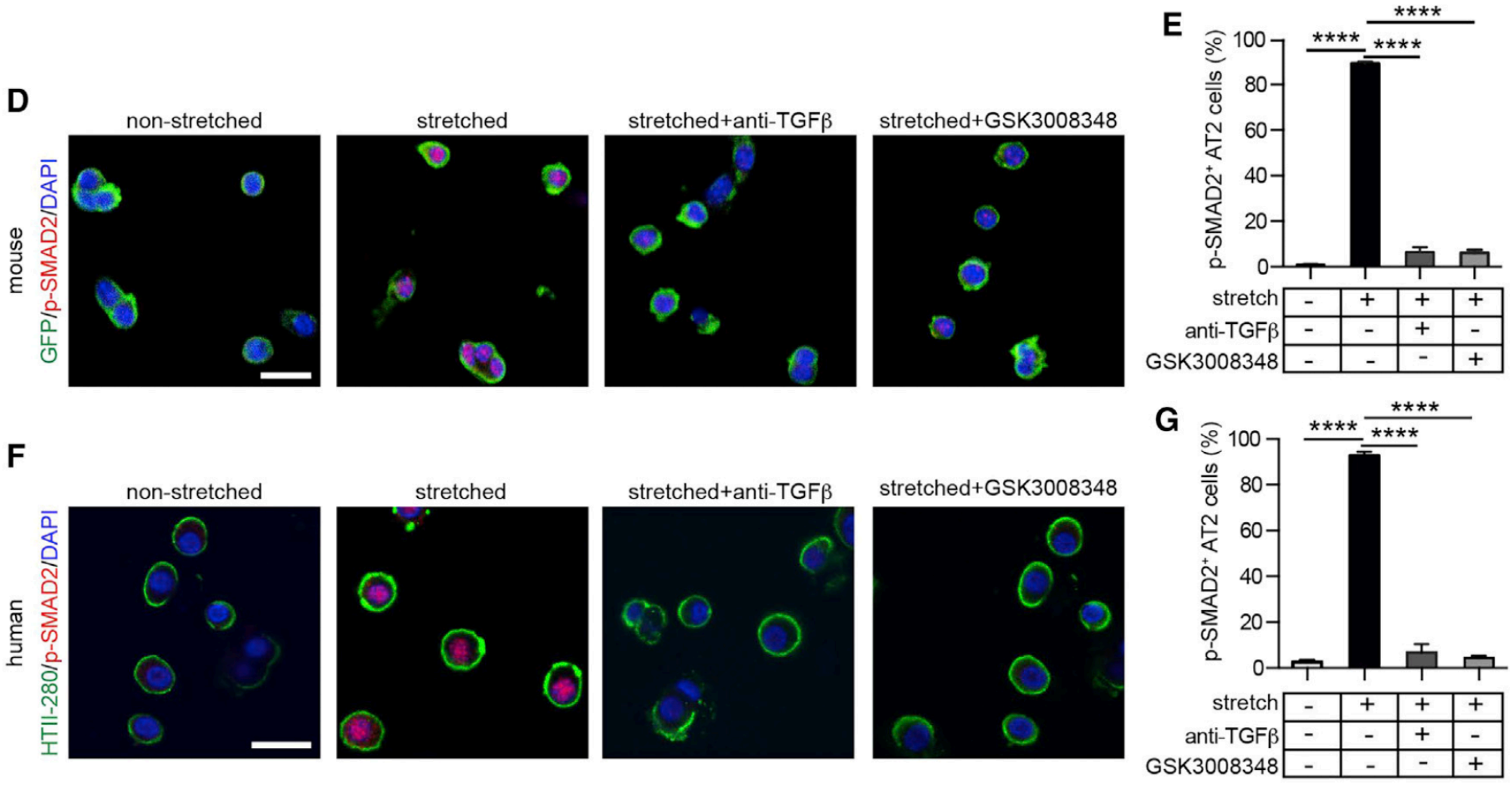
What signaling pathways mediate mechanical tension induced fibrosis?

Figure 5

Stretched AT2 cells express Tgf-B locally

What signaling pathways mediate mechanical tension induced fibrosis?

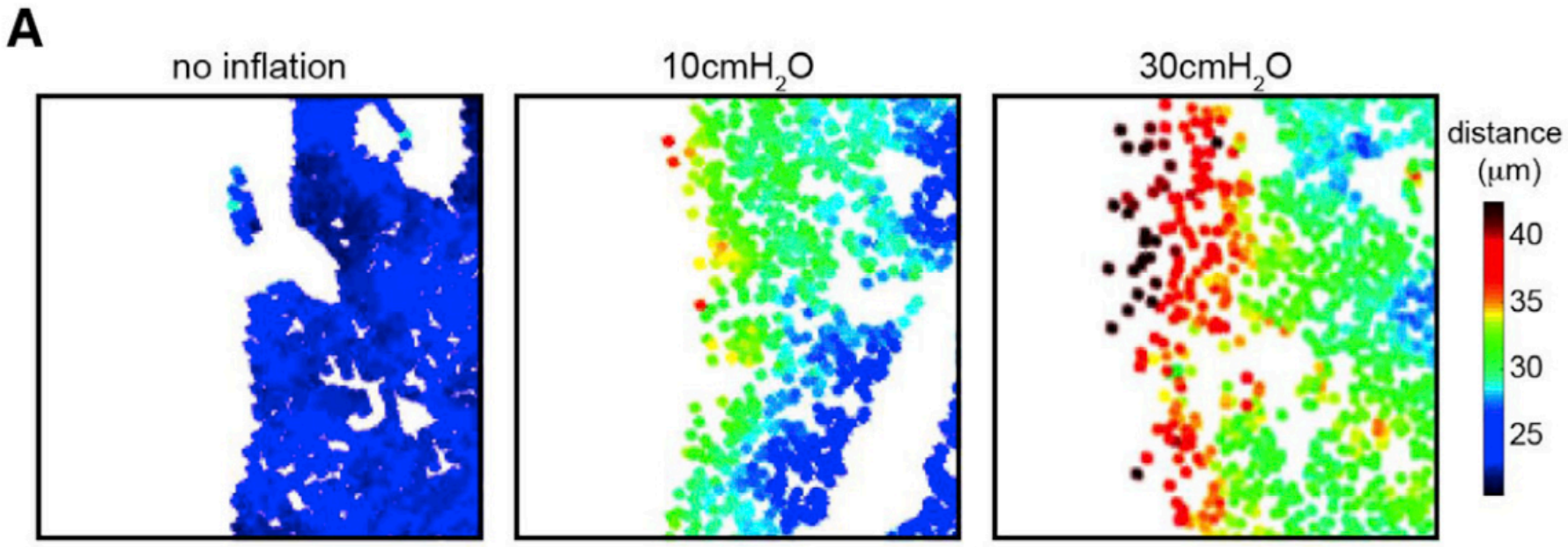
Figure 5



Downstream target of Tgf-B signaling upregulated in AT2 cells

Is mechanical tension spatially regulated within the lung?

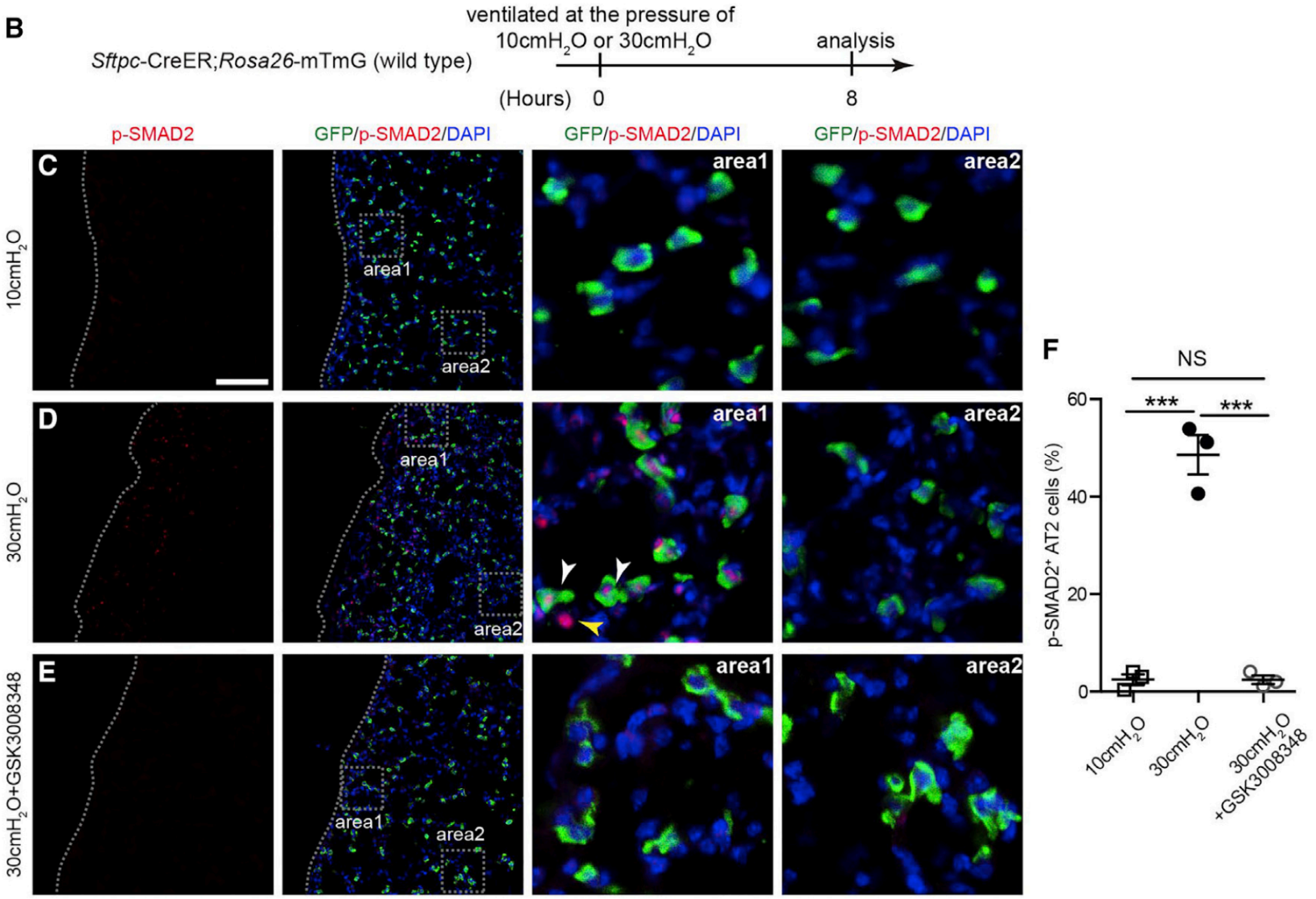
Figure 6



Peripheral alveoli are more stretched at high inflation pressure

What signaling pathways mediate mechanical tension induced fibrosis?

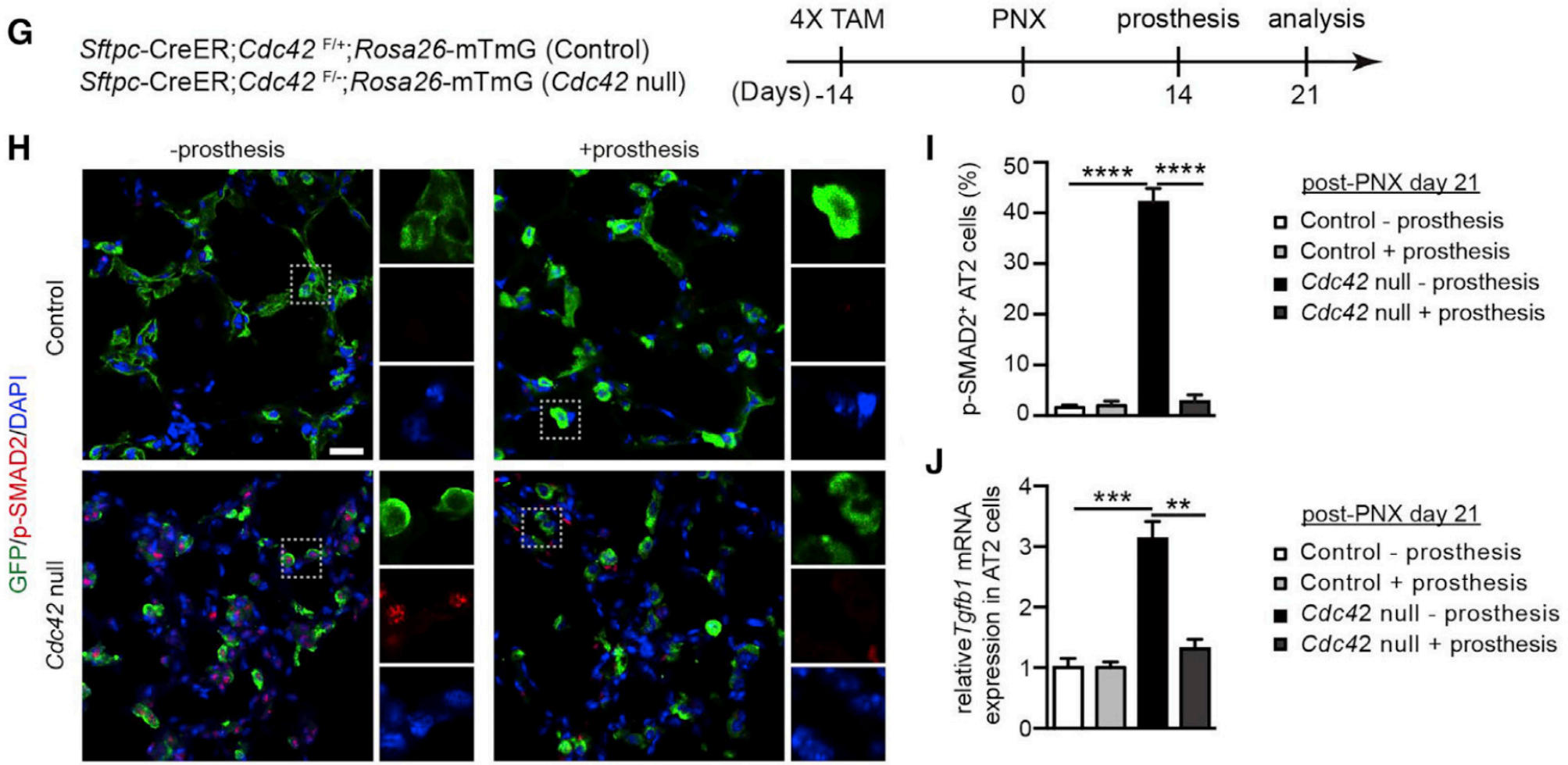
Figure 6



Tgf-B signaling is activated at the periphery at high inflation pressure

What signaling pathways mediate mechanical tension induced fibrosis?

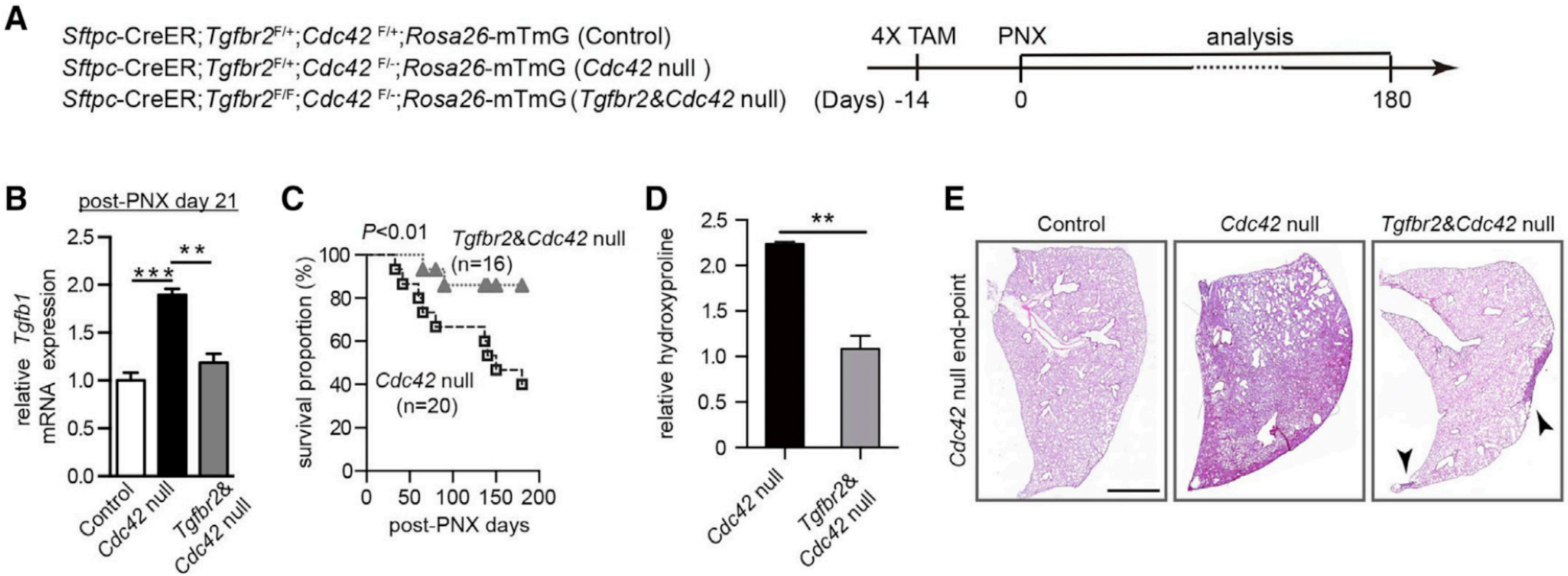
Figure 6



Tgf-B signaling in AT2 cells is activated in fibrosis model

Is Tgf-B signaling required for progression of lung fibrosis?

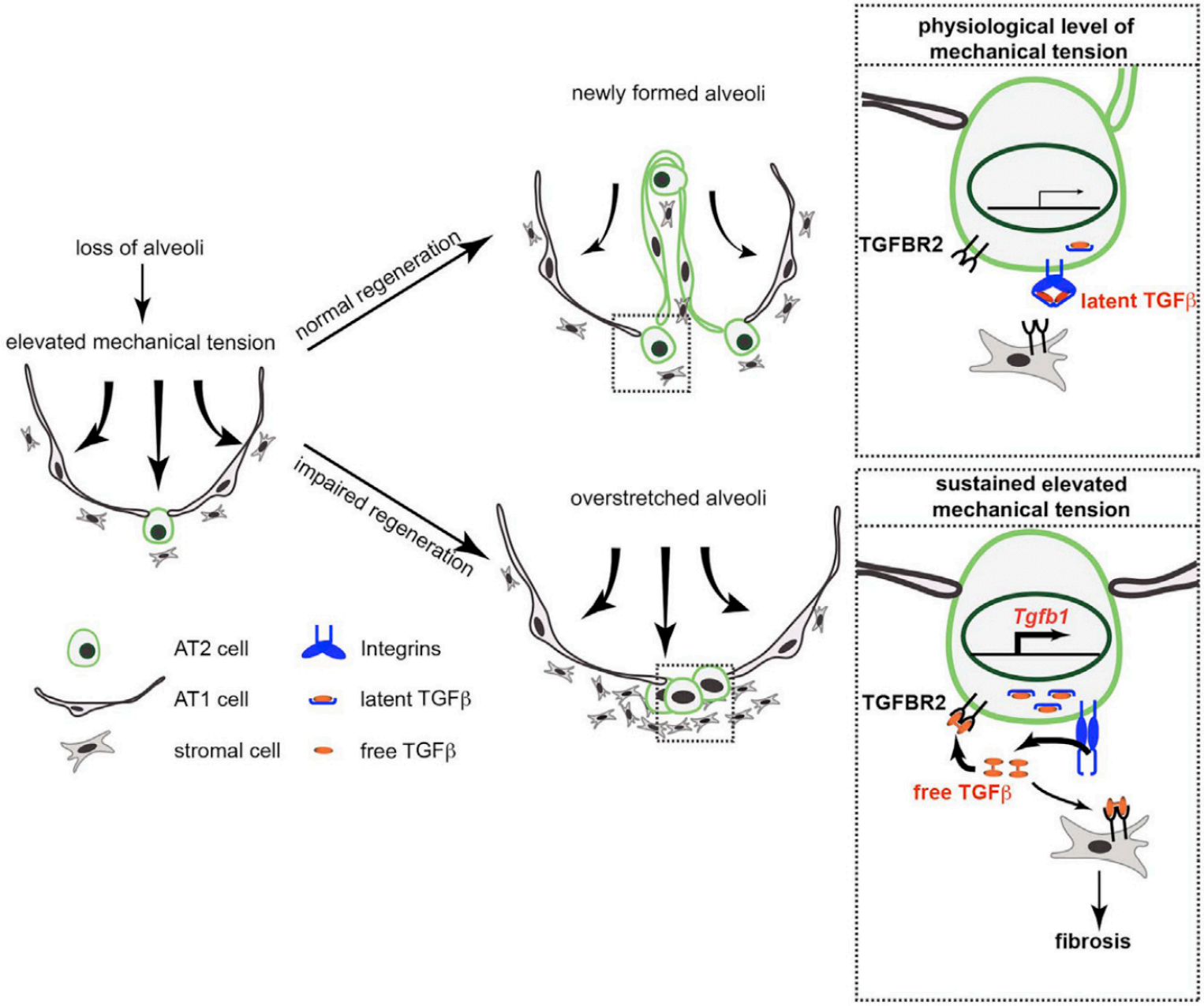
Figure 7



Loss of Tgf-B signaling rescues fibrotic phenotype due to failed alveolar regeneration following PNX

Mechanical tension induces AT2 signaling can lead to regeneration or progressive pulmonary fibrosis

Figure 7



Discussion Questions

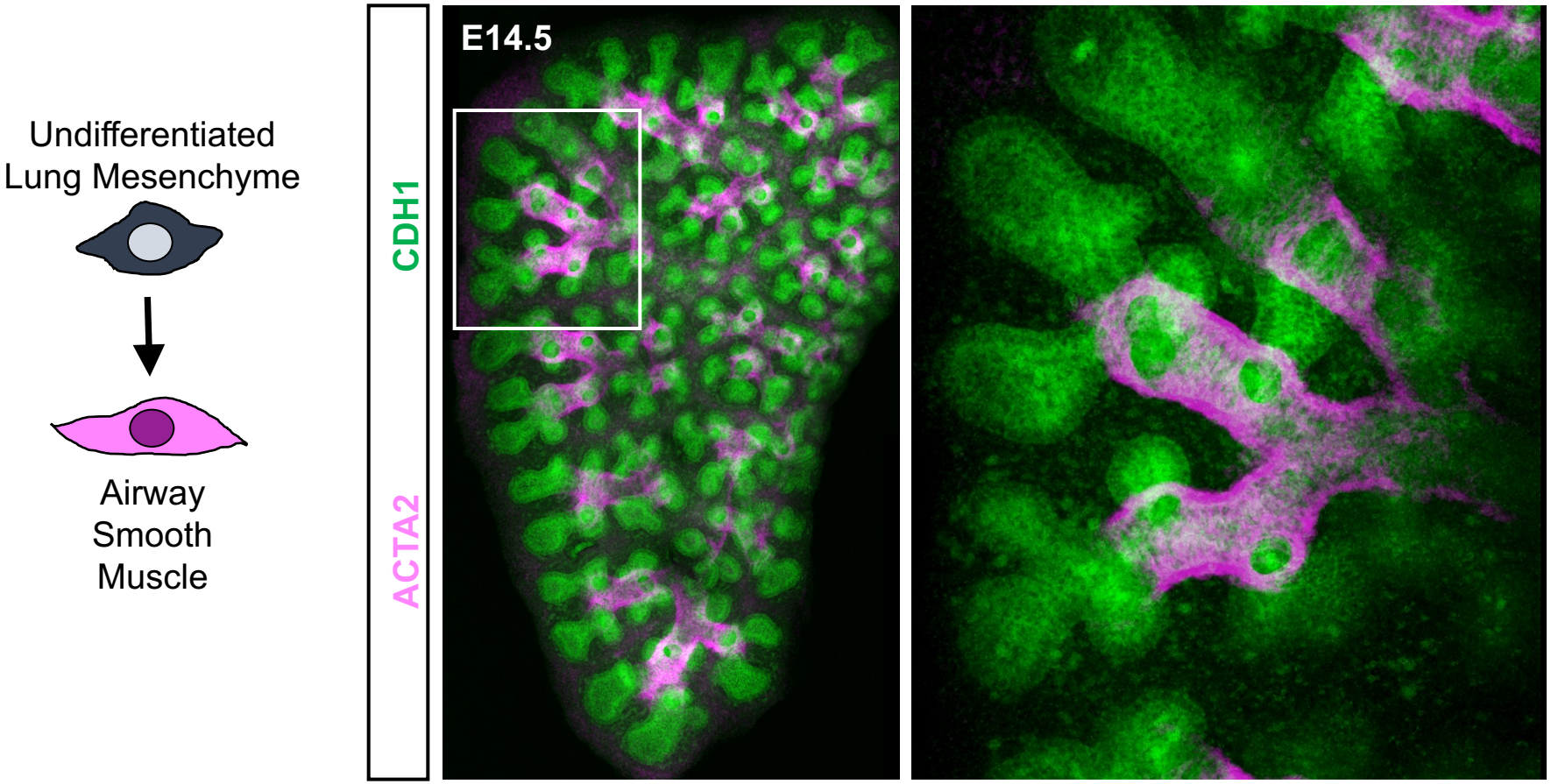
- What niche signals are important for AT2 stem cell response to mechanical tension?
- What's the signal from AT2 cells to fibrotic cells?
- What regenerative pathways are important to protect the lung from fibrosis during aging?
- Why does AT2 regenerative ability decrease with age?
- Are there treatments that can reduce mechanical stress and prevent fibrosis?

Questions about lung regeneration/repair?

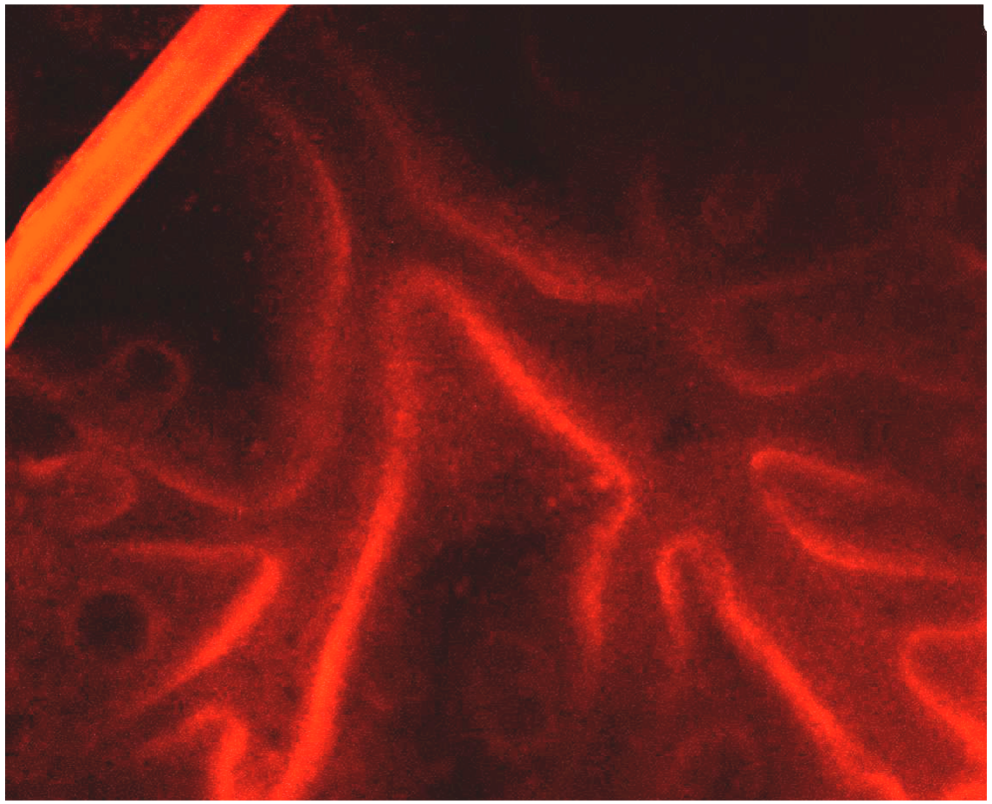
j1barr@health.ucsd.edu
Sun lab postdoc

Airway Smooth Muscle Cells in Lung Branching

Airway smooth muscle surrounds the airway epithelium



Prevailing hypothesis: Airway smooth muscle promotes lung branching



Airway Smooth Muscle

↓

Airway Smooth Muscle Contraction

↓

Airway Peristalsis

↓

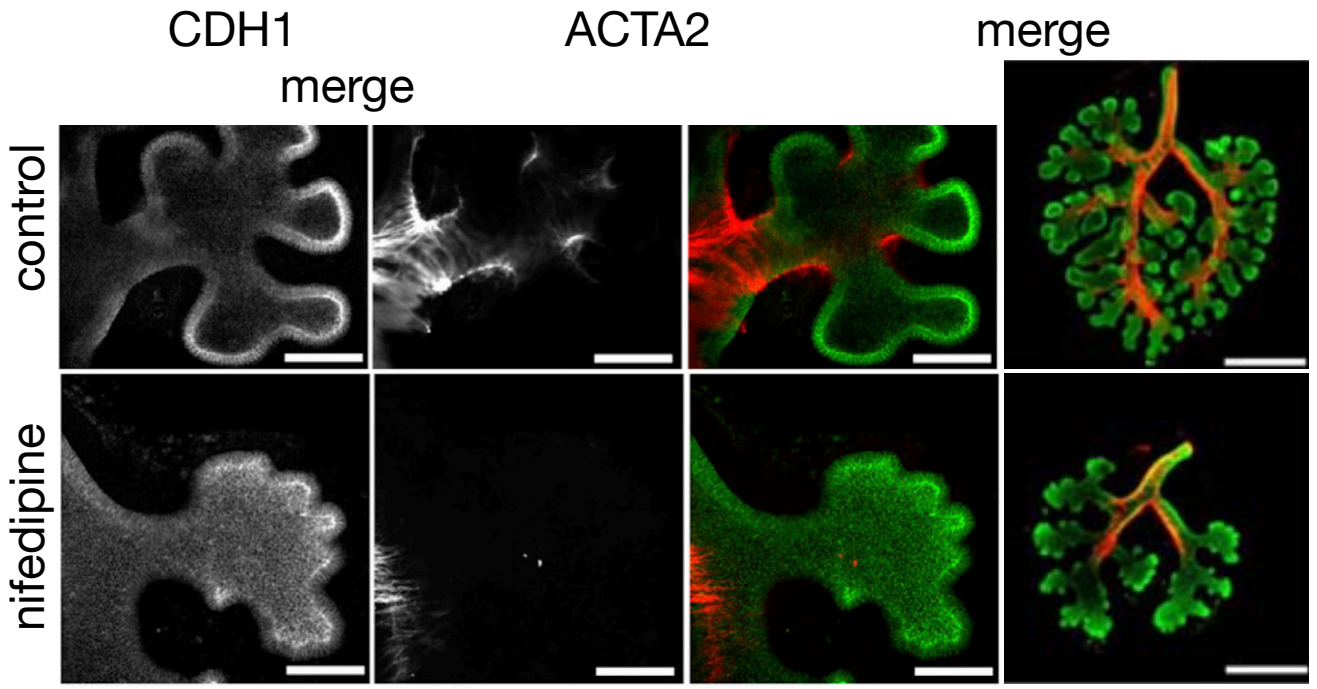
Airway Pressure

↓

Lung Branching

Brennan et al. *PLOS One* 2013

Chemical inhibition of smooth muscle contraction disrupts epithelial branching *ex vivo*



Kim and Nelson et. al. *Developmental Cell,* 2015
Goodwin and Nelson et al. *Development* 2019

Airway Smooth Muscle

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Airway Smooth Muscle Contraction

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Airway Peristalsis

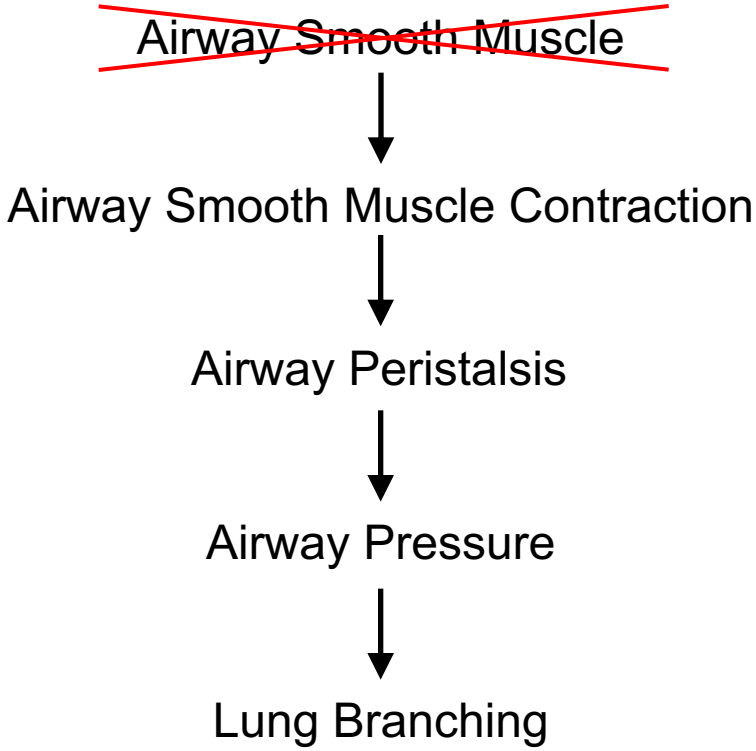
↓

Airway Pressure

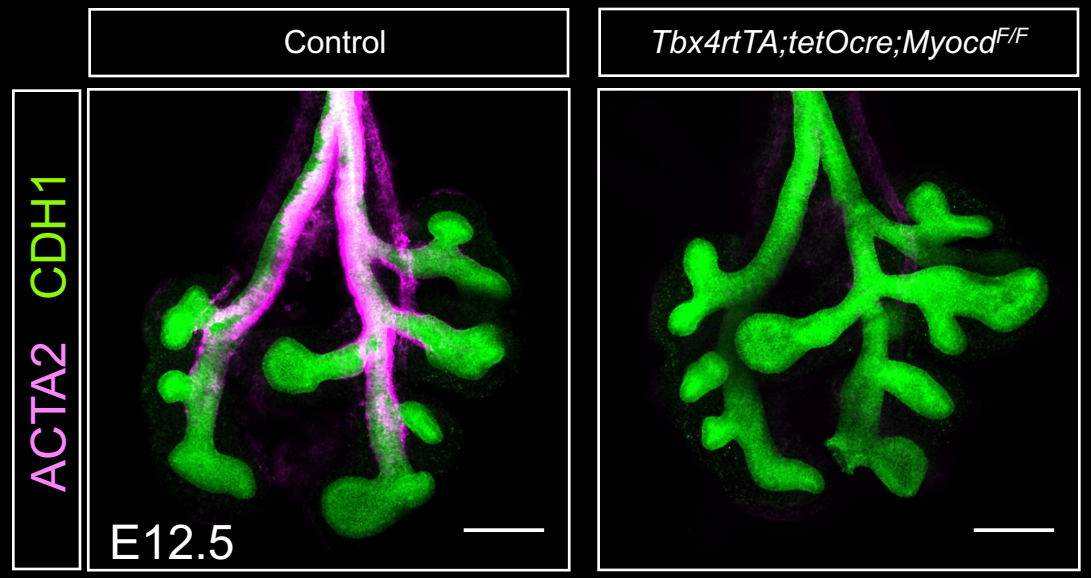
↓

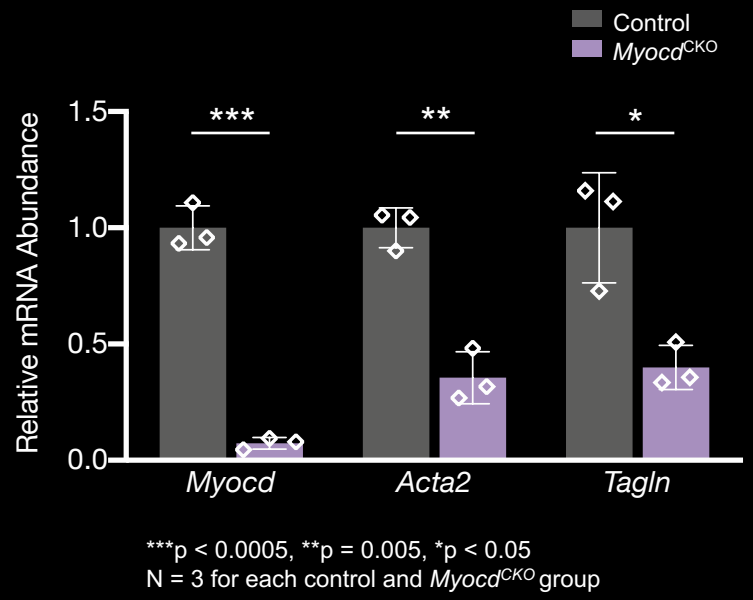
Lung Branching

In vivo testing of the prevailing hypothesis



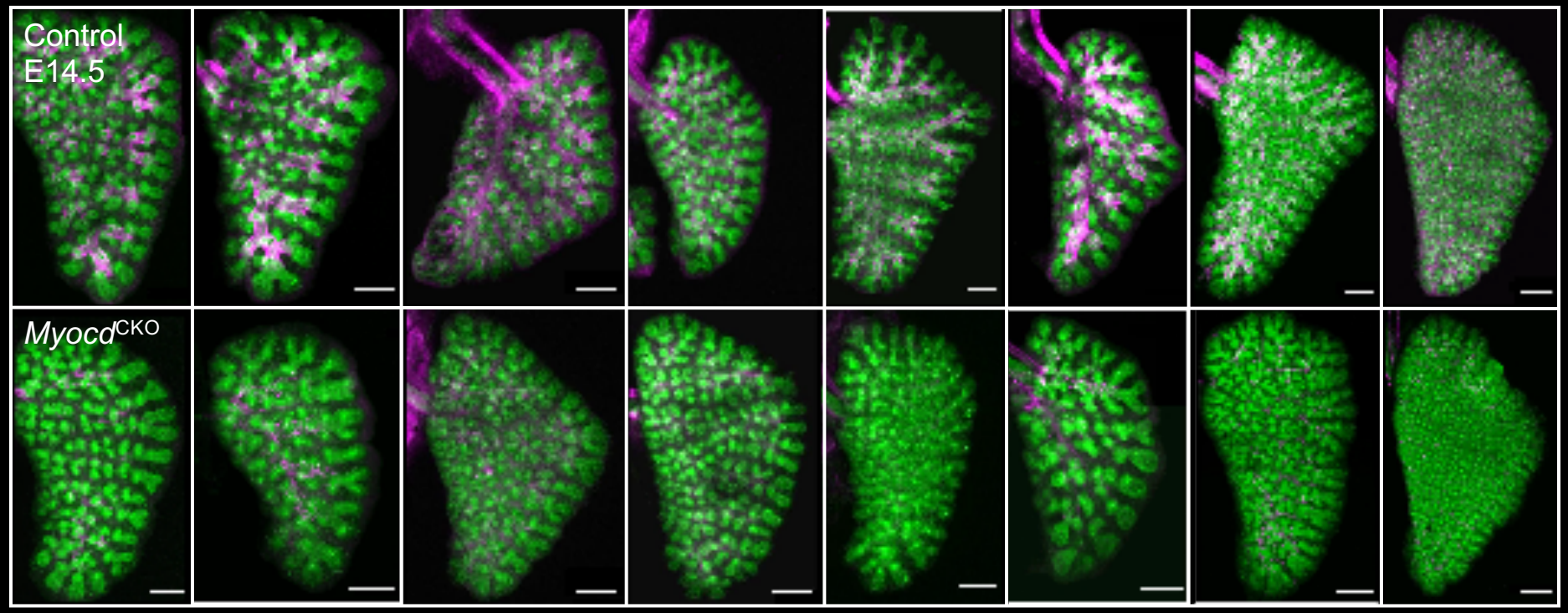
Myocd^{CKO} inactivation led to loss of airway smooth muscle



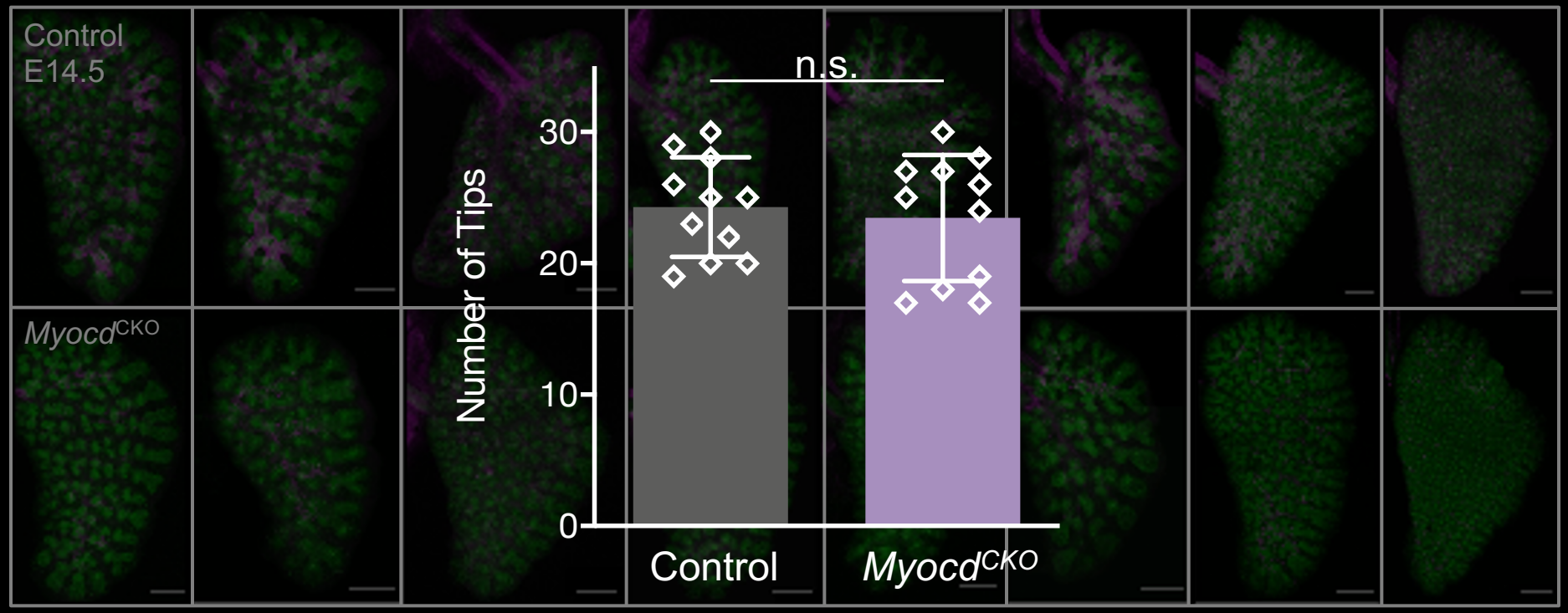


***p < 0.0005, **p = 0.005, *p < 0.05
N = 3 for each control and *Myocd*^{CKO} group

Inhibiting airway smooth muscle differentiation does not disrupt lung epithelial branching



Inhibiting airway smooth muscle differentiation does not disrupt lung epithelial branching



Airway smooth muscle is dispensable for lung branching morphogenesis in vivo