

Chronic disease results from the failure of tissues to maintain homeostasis. In the lung, coordinated repair of the epithelium is essential for preserving homeostasis. In animal models and human lung disease, airway epithelial cells mobilize in response to lung injury in an attempt to maintain gas exchange and tissue integrity. This remodeling of the distal airspace can result in airway-like honeycomb cysts with persistent loss of functional cell types and parenchymal architecture. However, the dynamic mechanisms and signaling modalities directing the reorganization of injured epithelia remain unclear. Utilizing live-cell imaging, we demonstrate that airway-centric lung remodeling occurs through fluidization of the epithelium and is conserved across multiple models of lung repair and fibrosis. The phase dynamics of epithelial fluidization are regulated through active interleukin-6 family signaling, and dysregulation of this signaling cascade along the proximal-distal lung axis drives persistent biophysical dysfunction. Furthermore, we demonstrate that this mechanism for airway fluidization operates through non-canonical SFK/YAP-dependent signaling. Specific targeting of IL-6 signaling in mouse models of injury is sufficient to attenuate lung remodeling including honeycombing and fibrosis. Together our findings illustrate the critical role of cytokine-driven epithelial fluidization in coordinating the balance between homeostatic lung repair and fibrotic airspace remodeling.