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Title: Epithelial Pten controls acute lung injury and fibrosis by regulating intercellular junctional integrity and EMT

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Body: Injury to alveolar epithelial cells (AECs) and its repair process are integral to the pathogenesis of acute lung injury (ALI) and idiopathic pulmonary fibrosis (IPF). Disruption of AECs integrity and its reconstitution are crucial for ALI progression. In addition, myofibroblasts, key effector cells in IPF, partially originate from AECs through epithelial-mesenchymal transition (EMT). However, the regulation mechanisms of AECs integrity remains unclear. We explored the role of epithelial Pten in lung injury by generating a postnatally, and lung epithelium-specifically Pten-null (SO^{Pten}) mouse strain. Sixty percent of SO^{Pten} mice died of hypoxia, whereas all control mice survived after bleomycin insult. SO^{Pten} mice demonstrated aggravated ALI and lung fibrosis with enhanced disruptions of intercellular junctional complexes of AECs and degradation of basement membranes. Epithelial-derived myofibroblasts were increased in epithelium-specific Pten-deficient mice. Lungs of bleomycin-treated SO^{Pten} mice showed increased pAkt, pS6K, Snail and MMP expressions, and decreased claudin-4, E-cadherin, and laminin-beta1 expressions. Systemic Akt inactivation definitively saved SO^{Pten} mice through amelioration of ALI and aberrant EMT. Finally, we detected reduction of PTEN expression and hyperactivation of AKT in the AECs of human IPF lung. Our results indicate the pivotal role of EMT process for the progression of ALI and lung fibrosis. They also highlight epithelial Pten as an essential gatekeeper controlling ALI and lung fibrosis by modulating intercellular junctional integrity and EMT, and the Pten/PI3K/Akt pathway as a potential therapeutic target in these intractable diseases.