Pulmonary Stretch and Lung Mechanotransduction

Subjects: Pathology

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Interstitial lung diseases (not limited to IPF) showing a UIP pattern are subjected to acute exacerbations with dramatic gas exchange impairment requiring ventilatory assistance. Once mechanical ventilation is needed, a protective strategy is advisable in order to reduce lung stretch and consequently avoid fibrotic lung damage progression via mechanotransduction. Differently from the recommended ventilatory management of ARDS patients, an open lung approach with a high level of PEEP to prevent atelectotrauma should be rather avoided.

Keywords: mechanical ventilation ; lung fibrosis ; stress ; strain ; lung elastance ; lung compliance ; idiopathic pulmonary fibrosis ; extra-cellular matrix ; spontaneous breathing

1. Matrix Abnormalities and Mechanical Behavior in Pulmonary Fibrosis

The biomechanical features of the lung are the result of ECM composition, and they depend on a complex network of fibrous proteins, glycoproteins, proteoglycans, and associated modifying molecules (e.g., metalloproteases, matricellular proteins) that represent the non-cellular portion of lung structure, which is also called the “matrisome” [11].Matrisome,the overarching architecture of the lung, mainly consists of fibrillar collagens (types I, II, III, V, and XI) and elastic fibers, which exhibit different mechanical properties and represent the main stress-bearing constituents of lung tissue. In particular, collagen fibers, which are folded in the resting position, are stretched only at high pulmonary volumes close to total lung capacity, and they act as a blocking system determining both a limitation in lung distention and the origin of the curvilinear stress–strain behavior, whereas elastin molecules account for the lung elastic recoil [12]. The ECM in fibrotic lungs shows different mechanical properties and biochemical composition to healthy lungs. Based on these assumptions as a whole, the fibrotic lung is characterized by a highly inhomogeneous mechanical microenvironment, where lung areas with preserved elasticity are contiguous to areas of rigid lung, resulting in a peculiar mechanical behavior during inflation, especially in terms of the stress/strain relationship.

2. The Mechanotransduction Process: Biological Response to Stretch and Progression in the Fibrotic Lung

The transduction of mechanical forces is modulated through mechanosensitive focal adhesion proteins, a complex macromolecular structure consisting of scaffolding, docking, and intracellular signaling proteins that collectively serve as an interface between integrins and actin cytoskeleton [37]. Integrin receptors, once activated, can modulate the recruitment of focal adhesion proteins, promote actin polymerization, enhance adhesion stability and contractility, as well as activate mechanosensitive genes. Focal adhesion kinase (FAK) is one of the first molecules recruited in intracellular mechanotransduction; the autophosphorylation of FAK leads to its activation and a series of downstream signals within the cytoplasm. Vinculin is a multidomain cytoplasmatic protein that is able to interact with other adhesion complex proteins, and it acts as the main partner of talin in the mechanosensing process.

Observations from experimental mice models of lung fibrosis and from human subjects with IPF suggest that the activation of the Rho/ROCK pathway sustains progressive fibrotic disorders [44]. In mammalians, TEAD family transcription factors (TEAD 1–4) are the main partners of YAP in driving gene transcription, while the role of other transcriptional factors, including Smad, runt-related transcription factor1/2 YAP and TAZ are usually located in the cell cytoplasm of cells that receive low levels of mechanical signaling (cells attached to a soft ECM); conversely, they are accumulated in the nucleus of cells exposed to high mechanical stress or experiencing deformation and cytoskeletal tension. YAP/TAZ exerts its profibrotic effect through interaction with nuclear transcriptional factors and the activation of different ECM genes including plasminogen activator inhibitor-1 (PAI-1), connective tissue growth factor (CTGF), and

3. Role of Alveolar Type 2 Cells in the Progression of Lung Fibrosis

Abnormalities in the synthesis and function of surfactant, especially of its structural proteins, surfactant protein A both acquired and inherited, are associated with a higher prevalence of the development of pulmonary fibrosis compared to healthy volunteers without protein alterations [57,58]. Additionally, several studies also described the association between genetic polymorphisms for surfactant proteins and ARDS [59]. A rare mutation of the gene encoding surfactant protein A2 (SP-A2) is associated with the development of familial idiopathic pulmonary fibrosis [60].

Focusing on the role of AT2 cells apart from their contribution to the genesis of surfactant, it has recently been shown that AT2 cells also function as alveolar stem cells in the lungs, being able to self-renew and differentiate into alveolar type I (AT1) cells, which are the main epithelial component of the alveolar–capillary barrier in gas exchange—hence their key role in regeneration and repair after lung injury [63]. A prevailing concept is that AT2 cell depletion due to repeated micro-injury in the alveolar epithelium could constitute an early event in IPF pathogenesis. However, in addition to the depletion of epithelial cells, in pulmonary fibrosis, AT2 cell dysfunction could alter their ability to repair alveolar tissue after chronic micro-injury, resulting in a modification of mechanical homeostasis. Recent studies show that in AT2 cells, YAP is a key mediator in regulating mechanical tension-induced alveolar regeneration in response to lung injury through the activation of Cdc42/F-actin/mitogen-activated protein kinase (MAPK)/YAP signaling cascade [70].

Pneumonectomy is one of the main models employed to study mechanical forces driving alveolar regeneration. In an ex vivo model, mechanical tissue stretch induces the activation of TGF-β1signals through Rho/ROCK and αv integrins interactions [74]. Wu et al. suggested that an increased mechanical tension caused by defective AT2 cells alveolar renewal capacity and associated with tissue stretch occurring during spontaneous breathing could cause an aberrant TGF-β signaling loop activation resulting in fibrosis progression [73]. With this assumption, the progression of lung fibrosis could start in these regions, progressively extending in a caudal-cranial mode along the axis of distribution of mechanical forces.