Vascular permeability in the fibrotic lung

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Cite this article as: Probst CK, Montesi SB, Medoff BD, *et al*. Vascular permeability in the fibrotic lung. *Eur Respir J* 2020; 56: 1900100 [https://doi.org/10.1183/13993003.00100-2019].

ABSTRACT Idiopathic pulmonary fibrosis (IPF) is thought to result from aberrant tissue repair processes in response to chronic or repetitive lung injury. The origin and nature of the injury, as well as its cellular and molecular targets, are likely heterogeneous, which complicates accurate pre-clinical modelling of the disease and makes therapeutic targeting a challenge. Efforts are underway to identify central pathways in fibrogenesis which may allow targeting of aberrant repair processes regardless of the initial injury stimulus. Dysregulated endothelial permeability and vascular leak have long been studied for their role in acute lung injury and repair. Evidence that these processes are of importance to the pathogenesis of fibrotic lung disease is growing. Endothelial permeability is increased in non-fibrosing lung diseases, but it resolves in a self-limited fashion in conditions such as bacterial pneumonia and acute respiratory distress syndrome. In progressive fibrosing diseases such as IPF, permeability appears to persist, however, and may also predict mortality. In this hypothesis-generating review, we summarise available data on the role of endothelial permeability in IPF and focus on the deleterious consequences of sustained endothelial hyperpermeability in response to and during pulmonary inflammation and fibrosis. We propose that persistent permeability and vascular leak in the lung have the potential to establish and amplify the pro-fibrotic environment. Therapeutic interventions aimed at recognising and "plugging" the leak may therefore be of significant benefit for preventing the transition from lung injury to fibrosis and should be areas for future research.