



SHAREABLE PDF

The self-fulfilling prophecy of pulmonary fibrosis: a selective inspection of pathological signalling loops

Ashley R. Rackow ^{1,7}, David J. Nagel ^{2,7}, Claire McCarthy³, Jennifer Judge⁴, Shannon Lacy⁵, Margaret A.T. Freeberg ⁶, Thomas H. Thatcher ⁶, R. Matthew Kottmann² and Patricia J. Sime^{2,6}

Affiliations: ¹Dept of Environmental Medicine, University of Rochester Medical Center, Rochester, NY, USA. ²Division of Pulmonary Diseases and Critical Care, University of Rochester Medical Center, Rochester, NY, USA. ³National Cancer Institute, Bethesda, MD, USA. ⁴Cook MyoSite, Pittsburgh, PA, USA. ⁵US Army of Veterinary Corps, Fort Campbell, KY, USA. ⁶Department of Medicine, Virginia Commonwealth University, Richmond, VA, USA. ⁷Authors contributed equally to this work.



@ERSpublications

There are several signalling cascades involved in the progression of pulmonary fibrosis. Studying the complexity of these loops allows an examination of the ways in which fibrosis begets more fibrosis.
<https://bit.ly/3fcGifR>

Cite this article as: Rackow AR, Nagel DJ, McCarthy C, *et al.* The self-fulfilling prophecy of pulmonary fibrosis: a selective inspection of pathological signalling loops. *Eur Respir J* 2020; 56: 2000075 [<https://doi.org/10.1183/13993003.00075-2020>].

This single-page version can be shared freely online.

ABSTRACT Pulmonary fibrosis is a devastating, progressive disease and carries a prognosis worse than most cancers. Despite ongoing research, the mechanisms that underlie disease pathogenesis remain only partially understood. However, the self-perpetuating nature of pulmonary fibrosis has led several researchers to propose the existence of pathological signalling loops. According to this hypothesis, the normal wound-healing process becomes corrupted and results in the progressive accumulation of scar tissue in the lung. In addition, several negative regulators of pulmonary fibrosis are downregulated and, therefore, are no longer capable of inhibiting these feed-forward loops. The combination of pathological signalling loops and loss of a checks and balances system ultimately culminates in a process of unregulated scar formation. This review details specific signalling pathways demonstrated to play a role in the pathogenesis of pulmonary fibrosis. The evidence of detrimental signalling loops is elucidated with regard to epithelial cell injury, cellular senescence and the activation of developmental and ageing pathways. We demonstrate where these loops intersect each other, as well as common mediators that may drive these responses and how the loss of pro-resolving mediators may contribute to the propagation of disease. By focusing on the overlapping signalling mediators among the many pro-fibrotic pathways, it is our hope that the pulmonary fibrosis community will be better equipped to design future trials that incorporate the redundant nature of these pathways as we move towards finding a cure for this unrelenting disease.