# Unexpected role of dendritic cells in pulmonary fibrosis

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Pulmonary fibrosis is one of the most devastating diseases in which scars are formed in the lungs in a progressive and non-reversible fashion resulting in breathlessness and respiratory failure. Some treatments may improve symptoms or slow progression of the disease, but the benefits are temporary. Lung transplantation can be an option for treatment but involves serious complications, such as rejection and infection. Therefore, the development of a new treatment is in urgent need.

Past studies have shown that idiopathic pulmonary fibrosis (IPF) is associated with infiltration of lungs by dendritic cells (DCs). DCs are best known for their role in bridging innate and adaptive immunity. They reside in peripheral tissues, capture foreign antigens, produce inflammatory cytokines and present antigens to antigen-specific T lymphocytes inducing antigen-specific immune responses.[1] Interestingly, an immunohistochemical analysis has shown that lungs of patients with IPF were associated with lymphoid aggregates and that these aggregates were enriched with DCs.[2] Some other studies using flow cytometry have reported a significant increase in the frequency of DCs in the lungs and the bronchial lavage fluid in patients with IPF.[3 4] These findings have raised a possibility that DC's immune-stimulatory activity may play a significant role in the progression of pulmonary fibrosis.

The association of DCs with pulmonary fibrosis has been also observed in animal models. Intratracheal challenge of mice with bleomycin induced severe fibrosis in the lungs and the fibrosis was accompanied by a significant increase in the number of DCs.[5] Interestingly, treatment of these mice with VAG539, an agent capable of inhibiting immune-stimulatory activity of DCs, attenuated fibrosis.[5] Others have shown that injection of diphtheria toxin (DT) to CD11c-DT receptor (DTR)-transgenic mice resulted in depletion of DCs from the mice and attenuated fibrosis on exposure to bleomycin.[6] These studies have been frequently referred to as the evidence that supports the contribution of DCs to pulmonary fibrosis. There is, however, limitation in both studies. It is unclear whether the inhibitory effect of VAG539 in pulmonary fibrosis was through its effect on DCs because VAG539 modulates cell physiology by binding the transcription factor aryl hydrocarbon receptor expressed in many cell types other than DCs.[7] It is unclear whether the inhibitory effect of DT in pulmonary fibrosis observed in CD11c-DTR mice was attributed to the depletion of DCs or macrophages. Injection of DT to CD11c-DTR mice not only depletes DCs but also pulmonary macrophages as CD11c is highly expressed in both.[8] Pulmonary macrophages secrete numerous pro-fibrotic soluble mediators, chemokines and enzymes playing a crucial role in promoting and maintaining fibrosis.[9] Lastly, the relevance of bleomycin-induced mouse model to human disease has not been firmly established. The bleomycin-induced fibrosis is preceded by massive inflammation in the lungs, whereas IPF is mostly non-inflammatory and resistant to immune-suppressive drugs.[10]

Tarrés *et al*, published in *Thorax*,[11] revisited the role of DCs in pulmonary fibrosis using a reagent that targets DCs specifically and a mouse model devoid of inflammation. The authors first noticed that the concentration of fms-like tyrosine kinase-3 ligand (Flt3L), a cytokine that promotes differentiation and proliferation of DCs,[12] was significantly elevated in the serum and the lungs of patients with IPF. This elevation was also observed in the mouse model of pulmonary fibrosis with limited inflammation induced by the adenovirus encoding transforming growth factor-β (TGF-β). The TGF-β-induced fibrosis also accompanied a significant increase in the number of DCs in the lungs. To determine the relevance in the increase in Flt3L and DCs to fibrosis, the authors altered the expression of Flt3L in mice and examined how the alteration affects DCs, lung fibrosis and lung function. The authors found that mice depleted of Flt3L, and thus deficient in DCs, developed more severe fibrosis than control animals and that the lung functions of these animals were more severely impaired. In contrast, mice supplemented with recombinant Flt3L, and thus equipped with an increasing number of DCs, developed milder fibrosis and their lung functions were less impaired. These findings suggested that DCs might play a regulatory role in pulmonary fibrosis. To confirm this possibility, the authors used a mouse strain that expresses DTR under the control of the promoter of zinc finger and BTB domain containing 46 (Zbtb46), the transcription factor recently identified to be specifically expressed in DCs.[13 14] When treated with DT, and thus depleted of DCs, these mice developed more severe fibrosis, and the lung functions were more severely impaired. These data confirm that DCs indeed play a negative regulatory role in the TGF-β-induced mouse model of pulmonary fibrosis.

While the study presented by Tarrés *et al*[11] implicates a novel role for Flt3L and DCs in negative regulation of pulmonary fibrosis (figure 1), many questions remain to be answered. For example, what is the mechanism underlying the increase in Flt3L in fibrotic lungs? NK and T cells have been shown to be the major source of Flt3L in haematopoietic organs, such as spleen and bone marrow, while epithelial and other stromal cells can also produce Flt3L in peripheral tissues, including lungs.[15 16] Identifying the cellular source of Flt3L would help to understand the self-regulatory mechanism that may be activated during the progression of pulmonary fibrosis.

The mechanism by which DCs exert the anti-fibrotic effect also remains unclear. The authors showed that $CD103^+$ DCs are dispensable for the anti-fibrotic role of DCs, while $CD11b^+$ DCs upregulate the expression of some matrix metalloproteinases (MMPs) in fibrotic lungs. MMPs are the major group of enzymes responsible for the collagen and other protein degradation in the extracellular matrix. Whether upregulation of these MMPs is involved in the anti-fibrotic effects, and if so, which specific MMPs play a major role will need to be defined. It is also possible that DCs exert the anti-fibrotic effect through an indirect mechanism, such as by modulating the activity of other pro-fibrotic immune cells, such as macrophages or type 2 innate lymphocytes.[9 17]

Lastly, the regulatory role of DCs in human pulmonary fibrosis remains to be determined. Apparently, DCs that infiltrate the lungs of patients with IPF are not sufficient to control the disease. Nevertheless, whether these DCs possess the ability to exert anti-fibrotic effects are worthy of

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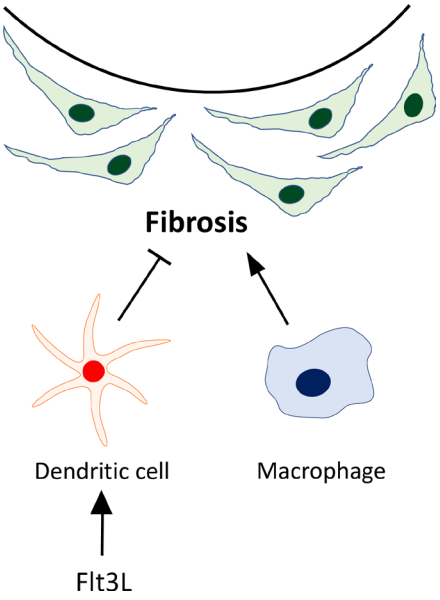


**Figure 1** A model illustrating the role of Flt3L, dendritic cells and macrophages in pulmonary fibrosis. Flt3L, fms-like tyrosine kinase-3 ligand.

examining. A gene expression analysis of DCs associated with the lungs of patients with IPF may help in predicting anti-fibrotic ability and designing in-vitro experiments to test that prediction. If the DCs indeed have the ability to decrease fibrosis, one can inject patients with Flt3L, which has been shown to be safe and effectively increase the number of DCs in humans.[18] The detailed mechanistic understanding of the anti-fibrotic effect of DCs may also help in developing new options of treatment for this devastating disease.

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