ORIGINAL ARTICLE
INTERSTITIAL LUNG DISEASE AND BASIC SCIENCE

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A spatially restricted fibrotic niche in pulmonary fibrosis is sustained by M-CSF/M-CSFR signalling in monocyte-derived alveolar macrophages

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Cite this article as: Joshi N, Watanabe S, Verma R, *et al*. A spatially restricted fibrotic niche in pulmonary fibrosis is sustained by M-CSF/M-CSFR signalling in monocyte-derived alveolar macrophages. *Eur Respir J* 2020; 55: 1900646 [https://doi.org/10.1183/13993003.00646-2019].

ABSTRACT Ontologically distinct populations of macrophages differentially contribute to organ fibrosis through unknown mechanisms.

We applied lineage tracing, single-cell RNA sequencing and single-molecule fluorescence *in situ* hybridisation to a spatially restricted model of asbestos-induced pulmonary fibrosis.

We demonstrate that tissue-resident alveolar macrophages, tissue-resident peribronchial and perivascular interstitial macrophages, and monocyte-derived alveolar macrophages are present in the fibrotic niche. Deletion of monocyte-derived alveolar macrophages but not tissue-resident alveolar macrophages ameliorated asbestos-induced lung fibrosis. Monocyte-derived alveolar macrophages were specifically localised to fibrotic regions in the proximity of fibroblasts where they expressed molecules known to drive fibroblast proliferation, including platelet-derived growth factor subunit A. Using single-cell RNA sequencing and spatial transcriptomics in both humans and mice, we identified macrophage colony-stimulating factor receptor (M-CSFR) signalling as one of the novel druggable targets controlling self-maintenance and persistence of these pathogenic monocyte-derived alveolar macrophages. Pharmacological blockade of M-CSFR signalling led to the disappearance of monocyte-derived alveolar macrophages and ameliorated fibrosis.

Our findings suggest that inhibition of M-CSFR signalling during fibrosis disrupts an essential fibrotic niche that includes monocyte-derived alveolar macrophages and fibroblasts during asbestos-induced fibrosis.