News Release

Title

Fibroblasts positive for meflin have anti-fibrotic property in pulmonary fibrosis.

Key Points

- Single-cell RNA sequencing combined with in situ RNA hybridization identified proliferating fibroblasts positive for meflin in fibroblastic foci, not dense fibrosis, of fibrotic lungs in patients with idiopathic pulmonary fibrosis.
- A bleomycin-induced lung fibrosis model for meflin-deficient mice showed that fibroblasts positive for meflin had anti-fibrotic property to prevent pulmonary fibrosis.
- An increase in soluble meflin could be observed in bronchoalvaolar lavage (BAL) supernatants from BLM-treated lungs. compared with those from saline-treated lungs.

Summary

The prognosis of elderly individuals with idiopathic pulmonary fibrosis remains poor with a 5-year survival rate worse than several types of cancer. The pathological hallmark lesions in IPF comprise fibroblastic foci in fibrotic lesions that may progress to dense fibrosis. Fibroblastic foci have been assumed to represent focal areas of active fibrogenesis, in which aggregates of proliferating fibroblasts and myofibroblasts are involved. As fibroblasts isolated from IPF lungs have heterogenous phenotypes and properties different from those of normal lung fibroblasts, their diversity makes it difficult to understand the pathogenesis of pulmonary fibrosis. Therefore, to determine of the pathogenesis of IPF, identification of functional fibroblasts is warranted. A new therapeutic strategy for pulmonary fibrosis might be warranted according to the data showing repressive effect of meflin reconstitution into fibroblasts against TGF-β-induced fibrogenesis.

Research Background

The prognosis of elderly individuals with idiopathic pulmonary fibrosis (IPF) remains poor. Fibroblastic foci, in which aggregates of proliferating fibroblasts and myofibroblasts are involved, are the pathological hallmark lesions in IPF to represent focal areas of active fibrogenesis. Fibroblast heterogeneity in fibrotic lesions hampers the discovery of the pathogenesis of pulmonary fibrosis. Therefore, to determine of the pathogenesis of IPF, identification of functional fibroblasts is warranted. This study was aimed to determine the role of fibroblasts positive for meflin, identified as a potential marker for mesenchymal stromal cells, during the development of pulmonary fibrosis.

Research Results

We characterized meflin-positive cells in a single cell atlas established by single-cell RNA

sequencing (scRNA-seq)-based profiling of 243,472 cells from 32 IPF lungs and 29 normal lung samples. scRNA-seq combined with in situ RNA hybridization identified proliferating fibroblasts positive for meflin in fibroblastic foci, not dense fibrosis, of fibrotic lungs in IPF patients. We determined the role of fibroblasts positive for meflin using bleomycin (BLM)-induced pulmonary fibrosis. A BLM-induced lung fibrosis model for meflin-deficient mice showed that fibroblasts positive for meflin had anti-fibrotic property to prevent pulmonary fibrosis. Although transforming growth factor-β-induced fibrogenesis and cell senescence with senescence-associated secretory phenotype were exacerbated in fibroblasts via the repression or lack of meflin, these were inhibited in meflin-deficient fibroblasts with meflin reconstitution.

Research Summary and Future Perspective

These findings provide evidence to show the biological importance of meflin expression on fibroblasts and myofibroblasts in the active fibrotic region of pulmonary fibrosis.

Publication

Nakahara Y,* Hashimoto N,*# Sakamoto K,* Enomoto A, Adams TS, Yokoi T, Omote N, Poli S, Ando A, Wakahara K, Suzuki A, Inoue M, Hara A, Mizutani Y, Imaizumi K, Kawabe T, Rosas IO, Takahashi M, Kaminski N, Hasegawa Y. Fibroblasts positive for meflin have anti-fibrotic property in pulmonary fibrosis. Eur Respir J. 2021 DOI: 10.1183/13993003.03397-2020.

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