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MicroRNA-21 as a potential therapeutic target in Idiopathic Pulmonary Fibrosis

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Idiopathic pulmonary fibrosis (IPF) is a life-threatening interstitial lung disease characterized by progressive inflammation and fibrotic remodeling. MicroRNAs are increasingly recognized as important molecular mediators that contribute to development and progression of disease. The concept of preventing fibrosis through synthetic antimiR molecules that selectively bind to a microRNA has been validated in various disease models in vivo, but only to a very limited extent in the lung. Here, we sought to determine the entire miRnome of mouse lung cells and thereby identify new therapeutic targets to treat pulmonary fibrosis.

8-12 weeks old wild type mice were subjected to intratracheal instillation of bleomycin (or PBS as control) using a microsprayer. One week later, bronchoalveolar lavage fluid (BALF) and lungs from untreated or PBS/bleomycin-treated mice were harvested and small RNA sequencing was performed. Our miRnome data revealed that, in the fibrotic lung tissue, miR-21 is the significantly upregulated (p-adj < 0.05 and log2FC > 2) microRNA with the highest expression.

To further identify the cell type in which miR-21 exerted its pathological role, different pulmonary cell types were isolated through magnetic- and fluorescence- activated cell sorting (MACS and FACS). Small RNA sequencing identified miR-21 among the top 10 expressed micro-RNAs in the total lung as well as several cell fractions, i.e., macrophages, neutrophils, T cells and epithelial cells. In endothelial cells and fibroblasts it ranked among the top 20 expressed microRNAs.

In summary, we quantified for the first time the full range of microRNAs in the main murine lung cell types at basal state and under fibrotic conditions. In particular, our data predict miR-21-expressing immune cells as key players in lung fibrotic processes and as potential therapeutic targets.