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Inhibition of MRTF activation as a clinically achievable anti-fibrotic mechanism for pirfenidone

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Abstract

Background Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic disease characterised by aberrant fibroblast/myofibroblast accumulation and excessive collagen matrix deposition in the alveolar areas of lungs. As the first approved IPF medication, pirfenidone (PFD) significantly decelerates lung function decline while its underlying anti-fibrotic mechanism remains elusive.

Methods We performed transcriptomic and immunofluorescence analyses of primary human IPF tissues.

Results We showed that myocardin-related transcription factor (MRTF) signalling is activated in myofibroblasts accumulated in IPF lungs. Furthermore, we showed that PFD inhibits MRTF activation in primary human lung fibroblasts at clinically achievable concentrations (half-maximal inhibitory concentration 50–150 µM, maximal inhibition >90%, maximal concentration of PFD in patients <100 µM). Mechanistically, PFD appears to exert its inhibitory effects by promoting the interaction between MRTF and actin indirectly. Finally, PFD-treated IPF lungs exhibit significantly less MRTF activation in fibroblast foci areas than naïve IPF lungs.

Conclusions Our results suggest MRTF signalling as a direct target for PFD and implicate that some of the anti-fibrotic effects of PFD may be due to MRTF inhibition in lung fibroblasts.

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