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TRIM33 prevents pulmonary fibrosis by impairing TGF-β1 signalling

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TRIM33 has a protective role against fibrogenesis, inhibiting the TGF-β1 pathway through a direct association with HSPB5. Interactions between TRIM33, SMAD4 and HSPB5 may represent key targets to prevent the progression of pulmonary fibrosis. http://bit.ly/3aVCuxc

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ABSTRACT

Background: Idiopathic pulmonary fibrosis (IPF) is a devastating disease characterised by myofibroblast proliferation and abnormal extracellular matrix accumulation in the lungs. Transforming growth factor (TGF)-β1 initiates key profibrotic signalling involving the SMAD pathway and the small heat shock protein B5 (HSPB5). Tripartite motif-containing 33 (TRIM33) has been reported to negatively regulate TGF-β/SMAD signalling, but its role in fibrogenesis remains unknown. The objective of this study was to elucidate the role of TRIM33 in IPF.

Methods: TRIM33 expression was assessed in the lungs of IPF patients and rodent fibrosis models. Bone marrow-derived macrophages (BMDM), primary lung fibroblasts and 3D lung tissue slices were isolated from *Trim33*-floxed mice and cultured with TGF-β1 or bleomycin (BLM). *Trim33* expression was then suppressed by adenovirus Cre recombinase (AdCre). Pulmonary fibrosis was evaluated in haematopoietic-specific *Trim33* knockout mice and in *Trim33*-floxed mice that received AdCre and BLM intratracheally.

Results: TRIM33 was overexpressed in alveolar macrophages and fibroblasts in IPF patients and rodent fibrotic lungs. *Trim33* inhibition in BMDM increased TGF-β1 secretion upon BLM treatment. Haematopoietic-specific *Trim33* knockout sensitised mice to BLM-induced fibrosis. In primary lung fibroblasts and 3D lung tissue slices, *Trim33* deficiency increased expression of genes downstream of TGF-β1. In mice, AdCre-*Trim33* inhibition worsened BLM-induced fibrosis. *In vitro*, HSPB5 was able to bind directly to TRIM33, thereby diminishing its protein level and TRIM33/SMAD4 interaction.

Conclusion: Our results demonstrate a key role of TRIM33 as a negative regulator of lung fibrosis. Since TRIM33 directly associates with HSPB5, which impairs its activity, inhibitors of TRIM33/HSPB5 interaction may be of interest in the treatment of IPF.