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Mad about Smads in Pulmonary Fibrosis and Hypertension

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The transforming growth factor (TGF)-β superfamily is comprised of growth factors essential during embryo- and organogenesis [such as TGF-βs themselves, activins, and bone morphogenic proteins (BMPs)]. Biological effects of TGF-β and BMP isoforms are mediated via similar signaling pathways, including the sequential activation of two serine-threonine kinase receptor isoforms (a type II and type I receptor) and subsequent phosphorylation of pathway specific Smad transcription factors. Kinetics of Smad translocation processes to the nucleus, a prerequisite of their biological function, however, remain largely unknown.

Two pulmonary diseases are associated with perturbations of the TGF-β system. Pulmonary hypertension has recently been linked with heterozygous germline mutations in *BMPR2*, the gene encoding the type II receptor for BMPs, predicted to lead to a loss of Smad signaling. In contrast, pulmonary fibrosis represents a disease which is presumably due to enhanced expression and activity of the TGF-β system components.

Here, we characterized the expression patterns of smads in the human lung and characterized their biological roles. All receptor-smads (smad1, 2, 3, 5, and 8), as well as the co-smad (smad4), were highly expressed in whole human lung, and in primary human pulmonary arterial smooth muscle cells and fibroblast, as assessed by RT-PCR of their full-length coding sequences and Western Blot analysis. Novel Smad isoforms were identified in human lung and characterized. Real-time imaging of smad2 translocation kinetics to the nucleus was assessed by live cell microscopy, and occurred immediately and rapidly subsequent to receptor interaction. Our studies therefore represent a first step towards elucidation of transcription factor translocation kinetics in live cells using the TGF-β/BMP system, and open up novel possibilities for pharmacological intervention of this system.