Nature Reviews Nephrology **10**, 484 (2014); published online 22 July 2014; doi:10.1038/nrneph.2014.127

FIBROSIS

Regulation of fibrotic signalling by TGF-β receptor tyrosine phosphorylation

TGF-β is a key mediator of fibrosis, and understanding the mechanisms by which this cytokine exerts its profibrotic effects is important for the identification of new antifibrotic targets. Findings from a new study show a pivotal role for integrin α1β1 signalling and TGF-β receptor II (TβRII) tyrosine phosphorylation in this process.

"The novelty of this paper resides in the fact that we show that levels of tyrosine phosphorylation of TβRII directly regulate fibrotic signalling," explains researcher Ambra Pozzi. "In addition, we show that the levels of tyrosine phosphorylation are negatively regulated by integrin α1β1 via activation of a specific tyrosine phosphatase, called TCPTP."

Pozzi and colleagues previously reported that mice lacking the integrin α1 subunit (α1KO) develop more severe fibrosis following kidney injury than do wild-type mice, suggesting that integrin α1β1 acts as a negative regulator of fibrosis. In their new study, the researchers found that this increase in kidney fibrosis is accompanied by increased TGF-β signalling. To study the mechanisms whereby loss of α1β1 leads to increased TGF-β signalling, they first generated primary cultures of collecting duct cells from wild-type, α1KO, and conditional TGF-β receptor-null mice. They then used mutagenesis assays to identify key tyrosine residues within the cytoplasmic tail of the TβRII that control profibrotic signalling.

"When we think of TGF-β receptors, we think of receptors controlled by serine and threonine phosphorylation," says Pozzi. "The cytoplasmic domain of TβRII contains five tyrosines; however, whether they have a role in controlling receptor activation and profibrotic signalling was unknown. Here we show that in cells expressing integrin α1β1, TCPTP is activated and this leads to dephosphorylation of TβRII. On the other hand, in cells lacking this integrin, TCPTP is not functional, and this results in increased TβRII tyrosine phosphorylation and activation of profibrotic signalling."

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The researchers now hope to identify the tyrosine kinases involved in TβRII phosphorylation and to determine whether other tyrosine phosphatases, in addition to TCPTP, can regulate TβRII signalling. "Finally, it is important to further confirm whether *in vivo* TβRII tyrosine dephosphorylation can be viewed as a novel tool to reduce the unwanted TGF-β receptor activation that is seen in the course of fibrosis," says Pozzi.

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Original article Chen, X. *et al*. Integrin-mediated type II TGF-β receptor tyrosine dephosphorylation controls SMAD-dependent profibrotic signaling. *J. Clin. Invest.* doi:10.1172/JCI71668