ACTIVATION OF LATENT TGFβ BY A_VB_1 INTEGRIN: OF POTENTIAL IMPORTANCE IN MYOFIBROBLAST ACTIVATION IN FIBROSIS

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ABSTRACT

Cell-mediated activation of latent TGF-β1 is intimately involved with tissue repair and fibrosis in all organs. Previously, it was shown that the integrin β1 subunit was requred for activation of latent TGF-β1 and skin fibrosis. A recent study by Henderson and colleagues (Nature Medicine 19,1617–1624, 2013) used three different in vivo models of fibrosis to show that integrin αv subunit was required for fibrogenesis. Through a process of elimination, the authors conclude that in vivo, the little-studied $\alpha_v\beta_1$ could be the major integrin responsible for TGF-β activation by myofibroblasts. Thus targeting this integrin might be a useful therapy for fibrosis.

It is fairly well-established that, in connective tissue, the myofibroblast is the key cell type essential for tissue repair and fibrosis (Hinz et al., 2012). Transforming growth factor beta (TGF-β) plays a key role in causing resident fibroblasts to differentiate into myofibroblasts and therefore plays a key role in fibrogenesis (Varga and Whitfield, 2009; Leask, 2010). Myofibroblast differentiation in response to TGF-β occurs only in adherent cells, and requires focal adhesion kinase, which is activated by integrin-dependent adhesion (Thannickal et al., 2003). More recently, it has been shown that integrins are essential for activation of latent TGF-β1, which is bound to the extracellular matrix and integrins via a RGD peptide located within the latency associated peptide (LAP) which is bound to TGF-β1 (Wipff et al., 2007). Mechanical loading and contraction is believed to generate a conformational change in latent TGF-β resulting in the liberation of active TGF-β which can then bind to its receptor and elicit profibrotic signaling responses.

In a series of elegant experiments summarized nicely by Hinz (2013), Henderson and colleagues (2013) use platelet derived growth factor receptor β (PDGFRβ)-Cre mice to delete αv integrin, an activator of latent TGF-β1, leading to suppression of carbon tetrachloride–induced fibrosis in the liver [Induction of PDGFRβ occurs early during myofibroblast differentiation from pericytes; that is, hepatic stellate cells (HSCs) which are major source of myofibroblasts in the liver). Pericyte-specific deletion of αv integrin also prevented bleomycin-induced lung and ureteric

obstruction-induced kidney fibrosis in mice. [Please see a recent commentary by Tsang (2013) in this journal for a discussion on the potential perictye/progenitor cell orgin of myofibroblasts in fibrosis]. Deletion of individual β integrin subunits β3, β5 and β8 did not protect against liver fibrosis (Henderson et al., 2013); the only remaining αv integrin that binds or activates latent TGF-β1 would be αvβ1. These results support prior data showing that fibroblast-specific integrin β1 knockout mice are resistant to bleomycin-induced skin fibrosis and show impaired cutaneous tissue repair concomitant with significantly reduced ability to activate latent TGF-β1 (Liu et al., 2009, 2010).

In contrast to mice deficient in integrin β1 which show defects in adhesion, extracellular matrix/CCN2 gene expression dermal homeostasis, vasculogenesis and repair (Liu et al., 2009, 2010; Liu and Leask, 2012, 2013), blocking of αv integrin with a peptide inhibitor did not show any adverse effects on HSC adhesion and migration, vascular pericyte numbers or neovascularization (Henderson et al., 2013). These results suggest that anti-αv integrin therapy may represent a novel approach to selectively modulate fibrosis.

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