Activation of latent TGF β by $\alpha_v\beta_1$ integrin: of potential importance in myofibroblast activation in fibrosis

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Abstract Cell-mediated activation of latent TGF- β 1 is intimately involved with tissue repair and fibrosis in all organs. Previously, it was shown that the integrin β 1 subunit was required for activation of latent TGF- β 1 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 α_v 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.

Keywords Fibrosis · Integrin · Myofibroblast · Bleomycin · TGF beta

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- β 1, 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- β 1 (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 (PDGFR β)-Cre mice to delete α_v integrin, an activator of latent TGF- β 1, leading to suppression of carbon tetrachloride-induced fibrosis in the liver (Induction of PDGFR β 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 α_v 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 pericyte/progenitor cell origin of myofibroblasts in fibrosis]. Deletion of individual β integrin subunits β 3, β 5 and β 8 did not protect against liver fibrosis (Henderson et al. 2013); the only remaining α_v integrin that binds or activates latent TGF- β 1 would be $\alpha_v\beta_1$. These results support prior data showing that fibroblast-specific integrin β 1 knockout mice are resistant to bleomycin-induced skin fibrosis and show impaired cutaneous tissue repair concomitant with significantly reduced ability to activate latent TGF- β 1 (Liu et al. 2009, 2010).

In contrast to mice deficient in integrin β 1 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 α_v integrin with a peptide inhibitor did not show any adverse effects on HSC adhesion and migration, vascular pericyte numbers or neovascularization

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(Henderson et al. 2013). These results suggest that anti- α v integrin therapy may represent a novel approach to selectively modulate fibrosis.

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