Eureka! Ets a target for fibrosis!

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Abstract The oncogenic Ets family of transcription factors is now recognized to play a key role in fibroblasts as it controls the expression of a variety of pro-fibrotic genes, including the induction of CCN2 by transforming growth factor β . A recent report (Baran et al., *Am J Respir Cell Mol Biol.* 2011 May 11) shows that mice containing a version of *ets2* that is incapable of being phosphorylated are resistant to bleomycin-induced lung fibrosis. This latter paper is the subject of this commentary.

Keywords CCN2 · Ets · Bleomycin · Lung fibrosis · Scleroderma · *ctgf* · *ras* · ERK

The Ets family of transcription factors, characterized by an evolutionarily conserved Ets domain, play a key role in cell development, cell differentiation, and cell proliferation. Initially, these proteins were identified as mammalian homologues of the *ets*-region from the transforming gene of the avian erythroblastosis virus, E26 (Leprince et al. 1983; Watson et al. 1985, 1986). Ets transcription factors, in general, are activated by the oncogenic *ras*/MEK/ERK signaling cascade and activate a variety of genes involved in malignant transformation and tumor progression (Whitmarsh et al. 1995; O'Hagan et al. 1996; Oikawa 2004). Hence, it has been suggested that blocking Ets activity may represent a novel therapeutic approach to cancers (Uren and Toretzky 2005; Turner and Watson 2008).

The notion that the Ets family of transcription factors may also be a good target for anti-fibrotic therapy is in its

ascendancy, as, more recently, a role in fibrosis for the Ets family of transcription factors in promoting pro-fibrotic gene expression has been revealed. For example, *ets-1* regulates the CCN2 promoter and mediates the ability of TGF β to induce CCN2 (van Beek et al. 2006; Nakerakanti et al. 2006). The Ets family of transcription factors, and in particular Ets1, also regulates the expression of other matrix or matrix-associated genes including collagen type I (Trojanowska 2000; Hahne et al. 2011).

The potential contribution of the transcription factor Ets2 to fibrosis has not been extensively explored. Overexpression of human ETS-2 transforms NIH 3T3 fibroblasts, allowing these cells to grow in soft agar and form tumors in nude mice (Seth et al. 1989). However, mice containing a single codon mutation in Ets2 in which Ala is substituted for the critical Thr-72 phosphorylation site (Ets2A72) are viable and develop normally, yet mice show reduced tumorigenesis correlating directly with Ets2 activity and fewer stromal cells expressing matrix metalloproteinase 9 (Man et al. 2003).

A role for *ets2* in fibrosis has been uncovered using Ets2A72 mice. Ets2A72 were shown to be resistant to bleomycin-induced lung fibrosis (Baran et al. 2011). The ability of bleomycin to induce expression of fibrotic markers known to be induced by Ets proteins (e.g., collagen and CCN2) was significantly impaired in Ets2A72 mice. Fibroblasts derived from these mice also showed impaired transcriptional responses to TGF β (van Beek et al. 2006). These data are consistent with the notion that the *ras*/MEK/ERK cascade promotes fibrogenic responses in vivo and in vivo (Stratton et al. 2002; Leask et al. 2003; Lim et al. 2003; Xu et al. 2004; Chen et al. 2008; Ponticos et al. 2009).

Collectively, these data indicate that Ets transcription factors play key roles in fibrogenesis. The fundamental molecular basis underlying the resistance of Ets2A72 mice

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to bleomycin-induced fibrosis was not explored by Baran and colleagues (2011). However, bleomycin failed to significantly induce CCN2 expression in Ets2A72 mice (Baran et al., 2011). CCN2 is a direct target of Ets family transcription factors (van Beek et al., 2006); thus, the inability of bleomycin to cause lung fibrosis in Ets2A72 mice is likely to be caused by this failure (Ponticos et al. 2009; Liu et al. 2011; Leask 2011).

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