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.

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 erythroblasts 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 Toretsky, 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 TGFβ 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 tumorogenesis 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 TGFβ (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 to bleomycin-induced fibrosis was not explored by Baran and colleagues (2011). However, bleomycin failed to significantly induce CCN2 expression in Ets2A72 mice; 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).

REFERENCES


