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BITS AND BYTES

Targeting the jagged/notch pathway: a new treatment for fibrosis?

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Abstract There is no treatment for fibrotic disease. TGFβ is known to promote fibrogenesis in vivo and in vitro, however, development of anti-fibrotic strategies targeting the TGFβ axis is problematic owing to the pleitropic nature of TGFβ action. Two recent papers (Kavian et al. 2010; Nyhan et al. 2010) suggest that the jagged/Notch pathway may selectively mediate fibrogenic properties of TGFβ and thus may represent a novel therapeutic approach to fibrosis for scleroderma and kidney fibrosis; these papers are the subject of this commentary.

Keywords Scleroderma · EMT · Kidney fibrosis · TGF beta

Fibrosis is one of the largest groups of diseases for which there is no therapy; nearly 45% of all deaths in the developed world are caused by chronic inflammatory and fibrogenic disorders including lung, kidney and liver fibrosis, scleroderma (systemic sclerosis, SSc) and inflammatory bowel disease (Pinzani 2008). It is well-established that transforming growth factor (TGF) β is a prime driving force in fibrogenesis (Leask and Abraham 2004). The basic, canonical TGFβ signaling pathway in fibroblasts involves the activation of the TGFβ type I receptor kinase (ALK5) by TGFβ ligand resulting in the phosphorylation of Smad2/3, which enables Smad2/3 to dimerize with Smad4, migrate into the nucleus and activate transcription.

The cell type responsible for fibrosis is a differentiated form of fibroblast, termed the myofibroblast which is highly contractile and expresses α-smooth muscle actin (α-SMA) as well as overexpressing genes encoding the extracellular matrix (Hinz et al. 2007; Krieg et al. 2007). Although the exact origin of the myofibroblast in fibrosis is unclear and is controversial, an increasing body of evidence has implicated epithelial/mesenchymal transition (EMT) in fibrogenesis especially in the kidney (Hinz et al. 2007; Zeisberg and Kalluri 2008; Zeisberg and Duffield 2010; Liu et al. 2010). [Although the importance of pericytes in this process is also understood (Rajkumar et al. 1999, 2005; Shiwen et al. 2009; Liu et al. 2010; Humphreys et al. 2010; Zeisberg and Duffield 2010)]. EMT is defined as a process whereby epithelial cell layers undergo disassembly of cell–cell contacts, reorganization of actin cytoskeleton, and cell–cell separation resulting in fibroblast-like cells that express molecular markers of cells and show enhanced cell migration (Hay 1995). Not surprisingly, TGFβ has been implicated as being a prime driving force for EMT (Hills and Squires 2010). Broad pharmacological targeting of the TGFβ pathway to combat disease is likely to be problematic due to the pleitropic nature of TGFβ action; thus understanding the fundamental mechanism specifically behind how TGFβ stimulates fibrogenesis is essential (Leask and Abraham 2004).

One of the critical signaling pathways that appears essential for epithelial function and appears to contribute to EMT in embryogenesis and cancer is the jagged ligand/notch receptor signaling pathway (Moustakas and Heldin 2007). This pathway controls the formation of boundaries between groups of cells and regulates cell fates, and elements of the Notch signaling pathway, including Jagged1 and Notch1 and 2, Hes1 and Hey1 have been identified as TGFβ1-responsive genes for example in kidney epithelia (Morrissey et al. 2002; Zavadil et al. 2004). TGFβ-induced EMT was blocked by RNA silencing of jagged 1 or by chemical inactivation of Notch indicating an essential role for this pathway (Zavadil et al. 2004).

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A critical step in assessing whether a particular pathway is appropriate to target with drugs to combat a disease (e.g. fibrosis) is to investigate whether the pathway specifically or selectively affects the processes associated with the disease (e.g. the profibrotic effects of TGFβ on cells). A recent paper published by Nyhan and colleagues (2010) used proximal tubule epithelial cells (HK-2) to begin to address this question. Although the use of global genome-wide expression profiling (e.g. using the Affymetrix system) is the best way of addressing this question in a truly unbiased fashion, the authors used real time polymerase chain reaction and Western blot analyses and an inhibitor of γ-secretase (an enzyme required for Notch receptor cleavage and transcription regulation) to show that the ability of TGFβ1 to induce expression of genes associated with epithelial-mesenchymal transition such as E-cadherin and vimentin were blocked affected by γ-secretase inhibition, but other TGFβ1 targets such as CCN2/connective tissue growth factor (CTGF) and thrombospondin-1 (THBS1) were not. Crucially, the ability of TGFβ to induce α-SMA protein was also prevented by γ-secretase inhibition. Moreover, another recent manuscript published by Kavian and colleagues (2010) assessed Notch activation in the skin of patients with the fibrotic disease scleroderma and in mice subjected to hypochlorous acid. The Notch pathway was hyperactivated in the scleroderma skin and in the skin, lung and leukocytes of diseased mice. γ-secretase inhibition reduced the skin and lung fibrosis seen in hypochlorous acid-treated mice as well as in mice subjected to bleomycin-induced skin and lung fibrosis.

Although more experiments need to be conducted to truly assess the specificity of jagged/Notch action in promoting EMT and fibrosis, collectively, these data suggest that inhibition of the jagged/Notch pathway to combat fibrosis is a useful concept, and warrants further investigation.

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