A two-pronged weapon in the fight against fibrosis

Focus on “Inhibition of Wnt/β-Catenin Signaling Promotes Epithelial Differentiation of Mesenchymal Stem Cells and Repairs Bleomycin-induced Lung Injury”

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Pulmonary fibrosis was first described in the 1930’s, and while its etiology has become somewhat more clear in recent years, the disease remains virtually untreatable (1, 5). The etiology of pulmonary fibrosis has stirred considerable debate over the years. Initially, pulmonary fibrosis was treated as an inflammatory disease. However, poor clinical response to anti-inflammatory therapy made evident that the inflammatory responses seen in histological examination of biopsied fibrotic tissue are “paraphenomena” (4). The more contemporary hypothesis is that progression of pulmonary fibrosis is due to defects in organ repair processes and/or alterations in the intricate cell-cell signaling events that mediate normal wound healing (3, 10). While debates have raged over the pathogenesis of pulmonary fibrosis, all have agreed that new therapeutic approaches, preferably ones that target multiple aspects of the disease, are clearly needed.

Pulmonary fibroblasts and alveolar epithelial cells play central roles in the formation and maintenance of lung structure and function. Fibroblasts establish and maintain pulmonary architecture through the synthesis of collagens and other extracellular matrix proteins. These cells are also responsible for scar formation following tissue injury, as they migrate to sites of inflammation and rapidly proliferate. Following lung injury, scar formation must eventually give way to regeneration of normal alveolar structure, including the epithelial barrier. Dysregulated production of extracellular matrix and persistent fibroblast proliferation and migration are hallmarks of pulmonary fibrosis. Thus, impaired apoptotic responses and/or persistent activation signals in fibroblasts could interfere with alveolar epithelial regeneration (healing) and alter alveolar structure and function.

Understanding the function and regulation of alveolar epithelial cells and fibroblasts, including the origin of these latter cells during the injury/repair process, is key for developing therapeutic strategies for treating pulmonary fibrosis. Much effort has focused on classical fibrogenic mediators, including TGF-β, TNFα, PDGF and others (10). These entities modulate wound repair processes such
as immune cell invasion, epithelial-mesenchymal transition, differentiation of mesenchymal stem cells and activation of fibroblasts (2, 12). While significant progress has been made in understanding these processes, no effective treatment for pulmonary fibrosis has emerged.

More recently, the Wnt/β-catenin signaling pathway has been studied as central to the wound healing process. This pathway modulates activation and differentiation of fibroblasts as well as the differentiation of alveolar epithelia from mesenchymal stem cells (9). In this issue of AJP Cell, Wang and coworkers employ a Tankyrase inhibitor, XAV939, to suppress Wnt/β-catenin signaling in mice subjected to bleomycin-induced lung fibrosis. Tankyrase mediates poly-ADP-ribosylation of Axin2 to facilitate Axin2 proteolysis, which leads to fewer β-catenin degradative complexes and increased β-catenin signaling (Figure 1). They observe increased survival and a significant reduction in lung fibrosis, despite administering the therapy 10 days after induction of the fibrotic process with bleomycin. Using cell culture studies, these investigators found that XAV939 treatment inhibited the proliferation of fibroblasts and reduced their differentiation into activated myofibroblasts. Moreover, the authors found that this inhibitor promoted the differentiation of bone marrow-derived mesenchymal stem cells into an epithelial-like phenotype when co-cultured with alveolar type II epithelial cells.

The study by Wang and co-workers, along with prior publications from this group and others (6, 11, 13), makes clear that the Wnt/β-catenin signaling pathway plays a major role in pulmonary fibrosis. This pathway appears to affect two key cell types involved in lung injury and repair: it activates fibroblast proliferation and inhibits mesenchymal stem cell differentiation into epithelia (instead promoting differentiation into a fibroblast-like phenotype). Therefore, inhibition of Wnt/β-catenin signaling gives a two-pronged effect in reversing pulmonary fibrosis (Figure 1). This feature may prove to be critical, since other therapeutic approaches that target a single pathway have fallen short in clinical trials of pulmonary fibrosis. Perhaps equally important, multiple druggable targets
exist in the Wnt/β-catenin pathway (as evidenced by the different inhibitors used in this and other studies). While targeting different aspects of the pathway may not prove to have equivalent effects, it does spur optimism that an effective but tolerable therapy with a small molecule will emerge.

Many questions, though, remain unanswered. First, the authors use a co-culture approach to demonstrate the effect of XAV939 on epithelial differentiation, so it is not certain that this process also occurs \textit{in vivo}. Future studies should seek to quantify the degree of epithelial differentiation that occurs in this disease model and determine if inhibition of β-catenin signaling has these same effects \textit{in vivo}. Second, while there is evidence that Wnt signaling is increased in humans with pulmonary fibrosis (7), the degree to which the Wnt/β-catenin pathway is dysregulated in the disease is not clear. Alterations in the pathway in humans with the disease may make certain therapeutic approaches unfeasible (e.g. if Tankyrase expression is down-regulated, an inhibitor targeting this protein would have limited efficacy). Finally, many other biological processes are regulated by Wnt/β-catenin signaling, including hematopoiesis, homeostasis of gut, and synapse formation in peripheral and central nerves. Defining the off target effects of drugs inhibiting this pathway will be critical for determining if the side effects will be tolerable in the setting of pulmonary fibrosis.

Inhibition of Wnt/β-catenin signaling may be useful for treatment of other fibrotic diseases since certain mechanisms are common across multiple organs (14). Given that the effects of Wnt/β-catenin inhibition on epithelial regeneration appears critical in pulmonary fibrosis, it is tempting to speculate that this approach could be particularly useful in various forms of kidney or gastrointestinal disease in which epithelial regeneration is essential. Cardiac and liver fibrosis lack clear epithelial components, but Wnt/β-catenin may still be a key player by regulating fibroblast activation and possibly differentiation of invading immune cells (8). More studies are required to investigate these
possibilities, but the work by Wang et. al. should spur considerable interest in the Wnt/β-catenin pathway.

In summary, the work by Wang et. al. highlights the potential therapeutic value of inhibiting the Wnt/β-catenin signaling in pulmonary fibrosis and accentuates the need to understand the diverse aspects of lung injury and repair. Effective treatment of pulmonary fibrosis will need to address multiple components of the reparative process, including immune system response, fibroblast activation and function, epithelial regeneration and stem cell recruitment and differentiation. Inhibiting Wnt/β-catenin signaling may not be the sole answer for treating pulmonary fibrosis, but it does provide a potentially effective two-pronged weapon in the fight.
Figure 1: Tankyrase stimulates degradation of Axin2, so the Tankyrase inhibitor XAV939 increases the abundance of Axin2 in the cell. Axin2 promotes the assembly of β-catenin degradative complexes and thereby, reduces Wnt/β-catenin signaling. The beneficial effect of XAV939 treatment in the setting of pulmonary fibrosis is two-pronged: it inhibits fibroblast activation (reducing extracellular matrix production) and promotes mesenchymal stem cell differentiation into lung epithelia (facilitating wound repair).


