Hedgehog Dysfunction in Fibrosis: Insights in the Pathogenesis of Scleroderma

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Introduction

The Hedgehog (HH) pathway has been repeatedly linked to the development of fibrosis in different tissues in conditions like liver fibrosis, pancreatic cancer, idiopathic pulmonary fibrosis and more recently Scleroderma. Transforming growth factor-β (TGF-β) is the main signal that activates fibroblasts to contract and deposit collagen and other extracellular matrix proteins. These specialized cells, myofibroblasts, are very abundant in fibrotic conditions. In this commentary we will discuss the evidence that links the HH and TGF-β pathways and will discuss their potential dysfunction during the pathogenesis of Scleroderma.

Aberrant Activation of the HH Pathway in Fibrotic Conditions

In human idiopathic pulmonary fibrosis there is a paradoxical reduction of expression of the HH proteins SHH and IHH in the alveolar and bronchiolar epithelia with a specific increase of SHH in fibroblast in the fibrotic regions [1]. Nuclear staining of Gli1 and Gli2, the transcription factors that mediate the canonical HH pathway [2], and the pattern of expression of negative regulators of HH signaling in idiopathic pulmonary fibrosis indicates activation of the pathway in the fibrotic loci and the surrounding alveolar epithelium by the paracrine action of SHH secreted by activated fibroblasts. Studies in primary lung fibroblasts indicate that SMO, the central transducer of the HH pathway, and Gli activity are required to induce the expression of α-smooth muscle actin (αSMA), collagen1a (COL1a), and fibronectin-1 (FN1), markers of TGF-β induced fibroblast activation. Interestingly, TGF-β treatment of lung fibroblasts isolated from patients affected by pulmonary fibrosis undergo myofibroblastic differentiation in a Gli-dependent manner but partially independently of SMO, suggesting an alternative pathway leading to Gli activation in a pro-fibrotic environment. Interestingly, this observation was limited to profibrotic fibroblasts and not reproducible on fibroblasts subcultured from healthy lungs.

Activation of the HH pathway has also been implicated in the desmoplastic response in pancreatic cancer [3]. Expression of SHH in an orthotopic model of pancreatic cancer in mice contributes to the fibrogenic reaction, as administration of SHH blocking antibody almost prevented the resulting fibrosis [3]. SHH enhanced pancreatic stellate cell proliferation and differentiation and enhanced pancreatic myofibroblast invasion in a paracrine manner. As a proof of principle, developmental overexpression of SHH or IHH in acinar cells in zebrafish also leads to a dramatic fibrotic response [4]. In this model, the fibrotic regions contained elevated numbers of proliferating myofibroblasts characterized by expression of αSMA and proliferating cell nuclear antigen (PCNA). The fibrotic region also showed an increase in TGF-β in ductular cells and of αSMA and Gli1 and Gli2 in the myofibroblasts. SHH and IHH also increased the expression of some matrix metalloproteases (MMPs), which are necessary for the extracellular matrix remodeling that promotes migration of activated HH-responsive fibroblasts. This study also revealed that Hh ligands recruit and activate myofibroblasts from several sources, which is in agreement with the reported migratory and chemotactic effect of SHH on fibroblasts [5,6].

Similar studies on post injury liver fibrosis indicated that deletion of SMO in liver fibroblasts was sufficient to suppress the fibrotic reaction [7]. Moreover, HH proteins mediate liver fibrosis in conditions as diverse as radiation injury, schistosomiasis, and fatty liver disease [8-10].

Altogether, these and several other studies in the literature indicate that regardless of the cause leading to tissue fibrosis or the organ affected, HH pathway plays a central role in the activation of tissue fibroblasts, the key cellular elements of fibrosis, and that this activation is selective and does not extend to other cell types such as epithelial or endothelial cells.

Regulation of HH Signaling by TGF-β

One of the key cytokines upregulated during tissue fibrosis is TGF-β. The HH pathway transcription factor Gli2 is one of the targets of TGF-β signaling, providing a direct way to stimulate Gli-dependent transcription even in the absence of HH ligands. Upregulation of Gli2 leads to induction of Gli1 for a strong activation of HH-target genes in normal fibroblasts and other cell types [11]. The mechanism involves recruitment of Smad3 and β-catenin to distinct elements of the gli2 gene promoter in response to TGF-β and is blocked by ALKS inhibitors or Smda3 siRNA [11,12].

Dysfunctional SHH Activation in Scleroderma

Besides its role in the activation of tissue fibroblasts, SHH is a key signaling molecule for epithelial cell proliferation and angiogenesis [13]. The discovery of this common pathway in the function of epithelial cells, endothelial cells and fibroblasts led to implement therapeutic approaches using recombinant SHH to improve tissue regeneration during wound healing [14,15].

Indeed, during wound healing the activation of tissue fibroblasts and deposition of extracellular matrix is finely tuned with epithelial cells proliferation and angiogenesis [16]. In contrast, during tissue fibrosis in Scleroderma both epithelial cell proliferation and angiogenesis...
are impaired in favor of aberrant fibroblast activation. In this sense it is rather intriguing to note that the activation of SHH pathway, noted in Scleroderma as well as in many other fibrotic conditions, is not accompanied by increased proliferation of epithelial cells and angiogenesis [17-19].

If SHH is clearly activated during tissue fibrosis, why angiogenesis and epithelial cell proliferation are impaired? Does TGF-β play any role in the cell-type selective SHH function during fibrosis?

Indeed, the work of Jung et al. [4] clearly demonstrates that during fibrogenesis there is an intricate paracrine signaling involving fibroblasts and epithelial cell types. The study of the cell specific crosstalk of TGF-β in the cell-type selective SHH function during fibrosis?

References


