Sonic Hedgehog signaling in pulmonary fibrosis: a spiky issue?

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THIRTY-TWO YEARS AGO, Christine Nusslein-Volhard et al. (12) first described the secreted Hedgehog factor (Hh) as a segmentation pattern control gene in Drosophila. Since then, the involvement of the Hedgehog (HH) signaling pathway in development and diseases is undeniable in chordates. Sonic Hedgehog (SHH), Desert Hedgehog, and Indian Hedgehog are the three mammalian orthologs of Drosophila Hh (21). For instance, the key role of the Sonic Hedgehog pathway in lung development is well documented. Shh is required for lung branching morphogenesis. SHH controls the growth and the survival of the embryonic lung mesenchyme as well as the expression of other critical morphogenetic genes during lung patterning (1, 13). Beyond embryonic development, HH pathway deregulations are directly implicated in various diseases including, among others, liver fibrosis (18) and cancers such as small cell lung carcinoma (20), medulloblastoma, and skin basal cell carcinoma (11).

Recently, Bolaños and colleagues (2) described the possible involvement of the Sonic Hedgehog pathway in idiopathic pulmonary fibrosis (IPF). The mechanisms leading to alveolar destruction by the accumulation of fibroblast and extracellular matrix in the distal lung are still poorly understood in this deadly disease (9). IPF prognosis is very poor with a median survival of 3–5 yr owing to the lack of effective therapies (9). IPF is a chronic lung disease characterized by fibrosis and the progressive destruction of the alveolar epithelium from an unknown trigger and concomitant IPF is hypothesized to result from repeated injury to the lungs (9).

From a cellular point of view, recent studies have shown that several components of the Hedgehog signaling pathway were localized to the primary cilium (21). The primary cilium is a nonmotile organelle grown from the mother centriole that is described as a microtubule-based antenna-like structure at the cell surface (21). This conserved organelle is required for appropriate transduction of the HH signaling pathway. In the absence of SHH (Fig. 1A), the HH receptor Patched (PTCH1), a 12-transmembrane domain protein, is localized to the primary cilium. PTCH1 prevents the translocation of the 7-transmembrane domain protein, Smoothened (SMO), from cytoplasmic vesicles into the cilium (Fig. 1A) and thereby inhibits downstream HH signaling by the zinc finger transcription factor family GLI1, GLI2, and GLI3 (11). In the “off” state, GLI1 is not expressed while GLI2 and GLI3 are processed into, respectively, a weak and a strong transcriptional repressor (21). The binding of SHH ligand to its receptor PTCH1 excludes PTCH1 from the primary cilium (Fig. 1B).

Therefore, SHH relieves the inhibition of PTCH1 on SMO that translocates into the primary cilium. SMO then promotes the formation of GLI2 transcriptional activator. After translocation into the nucleus, GLII induces the expression of GLI downstream targets such as the activator GLI1 transcription factor and the receptor PTCH1 (21).

In this study, Bolaños and colleagues (2) confirmed with others (4, 7) the reactivation of the Hedgehog pathway in IPF and provide evidence of nuclear accumulation of the transcription factors GLI1 and GLI2 in fibrotic areas and increased expression of Hedgehog target genes. But this feature is probably not specific to IPF since SHH pathway reactivation has previously been observed in other interstitial lung diseases (7). Because IPF is a chronic lung disorder characterized by fibroblast proliferation and extracellular matrix accumulation (9),...
Bolaños and colleagues next investigated the effects of SHH on lung fibroblast function. Remarkably, in vitro treatment of control and IPF lung fibroblasts with recombinant SHH stimulated their proliferation, extracellular matrix synthesis (collagen and fibronectin) as well as their migration. All these basic functions are critical to fibrogenesis. However, it remains to be determined whether these functions, in particular the migratory effect, are downstream of either canonical GLI activation or noncanonical SHH pathways. Indeed, recent studies have shown that SHH influences actin dynamics by activating the Rho pathway downstream of SMO in a GLI-independent manner during mouse embryonic fibroblast migration (14) and during in vitro tubulogenesis of human umbilical vein endothelial cells (3).

Unlike TGF-β, SHH stimulation was not sufficient to fully differentiate lung fibroblasts into myofibroblasts since α-smooth muscle actin expression was not upregulated in presence of SHH. However, a recent study showed that a cross talk between the HH and TGF-β pathways was involved during the myofibroblastic differentiation of lung fibroblasts upon TGF-β stimulation. Inhibition of GLI activation at the level of the primary cilium or in the nucleus abrogated TGF-β1-induced myofibroblast differentiation in control and IPF lung fibroblasts (4).

The most salient feature of this study is the apoptosis resistance observed in lung fibroblasts treated with SHH (2). SHH stimulation decreased the extrinsic apoptosis induced by TNF-α/INF-γ/FAS treatment, probably by upregulating the expression of, among others, several members of inhibitor of apoptosis protein family (XIAP, cIAP1, and cIAP1). Insights into IPF pathogenesis have revealed that an imbalance in apoptosis may also participate in the development of lung fibrosis (15). In addition to the accumulation of activated fibroblast aggregates in fibroblastic foci, IPF is also characterized by evidence of alveolar epithelial cell injury and excessive epithelial apoptosis (19). By contrast, it has been shown in vitro and in vivo that fibroblasts in IPF can eventually acquire resistance to apoptosis during the differentiation process (5, 9). This singular dichotomy between increased alveolar epithelial cell apoptosis and reduced fibroblast cell death has been coined “the apoptosis paradox in IPF.” Therefore, the reactivation of the Sonic Hedgehog developmental signaling pathway may also participate to the apoptosis paradox in IPF. Altogether these findings support a profibrotic role for the SHH pathway in IPF.

In conclusion, an additional important developmental signaling pathway, namely Sonic Hedgehog, is reactivated in IPF. This factor secreted by epithelial cells may participate in the aberrant epithelial-fibroblast cross talk and the apoptosis paradox in IPF. More importantly, there is still an urgent need to develop an effective therapeutic for IPF. The Hedgehog/SMO pathway is highly druggable and pharmacological agents are available to possibly modulate this pathway in IPF.

GRANTS

This work was supported by the European Commission (FP7 project no. 220224, European Idiopathic Pulmonary Fibrosis Network), the French National Research Agency (ANR Physio 2006, FIBROPNEUMO), the LABEX “Inflamex,” and the Chancellery of Paris Universities (Poix Legacy). E. F. Moshai was supported by a grant from LVL Medical and by the “Respiratory Health Research” endowment fund (“Philippe Godard” promotion). This work was conducted within the “FIRE” University Hospital Department (DHU).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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