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Title: Inhibition of the sonic hedgehog pathway at the primary cilium prevents the effect of TGF-beta 1 on alveolar epithelial cells

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Body: Introduction. The mesenchymal differentiation of alveolar epithelial cells induced by Transforming Growth Factor-beta1 (TGF-beta1), also called Epithelial Mesenchymal Transition (EMT), may contribute to Idiopathic Pulmonary Fibrosis (IPF). The Sonic Hedgehog (SHH) pathway is involved in epithelial cells-fibroblasts interaction during fetal lung development and lung fibrogenesis in adult lung. Previously, our laboratory has demonstrated that the SHH pathway is necessary to the action of TGF-beta 1 in human pulmonary fibroblasts (Cigna et al. in revision). Aims.We hypothesized that the SHH pathway could play a role in mesenchymal differentiation of alveolar epithelial cells induced by TGF-beta 1. Methods. The A549 cell line or primary alveolar epithelial murine cells are pre-treated 1h with agonists (recombinant SHH, Smoothened Agonist) or with inhibitors of the pathway (Cyclopamine, HPI-4, GANT61) in the absence or presence of TGF-beta 1 (1-5 ng/ml) for 48h in serum-free medium. The expression of E-Cadherin, N-Cadherin, and fibronectin is evaluated by real-time PCR, Western blotting and immunocytochemistry. The migratory capacity of A549 is also measured in these conditions. Results. Inhibition of the pathway via SMO/GLI abolishes the effect of TGF-beta 1 on the migration of epithelial cells but do not influence the effect of TGF-beta 1 on cell differentiation. By contrast, the inhibition of the HH pathway in the primary cilium with HPI-4 prevents and reverts the effect of TGF-beta 1 on epithelial cell differentiation. Conclusions. Our results indicate that the primary cilium controls the effect of TGF-beta 1 on A549 cells in vitro.