

## **Evidence for the involvement of fibroblast growth factor 10 in lipofibroblast formation during embryonic lung development**

Al Alam D., El Agha E., Sakurai R., Kheirollahi V., Moiseenko A., Danopoulos S., Shrestha A., Schmoldt C., Quantius J., Herold S., Chao C., Tiozzo C., De Langhe S., Plikus M., Thornton M., Grubbs B., Minoo P., Rehan V., Bellusci S.

*Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia*

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### **Abstract**

© 2015. Published by The Company of Biologists Ltd. Lipid-containing alveolar interstitial fibroblasts (lipofibroblasts) are increasingly recognized as an important component of the epithelial stem cell niche in the rodent lung. Although lipofibroblasts were initially believed merely to assist type 2 alveolar epithelial cells in surfactant production during neonatal life, recent evidence suggests that these cells are indispensable for survival and growth of epithelial stem cells during adulthood. Despite increasing interest in lipofibroblast biology, little is known about their cellular origin or the molecular pathways controlling their formation during embryonic development. Here, we show that a population of lipid-droplet-containing stromal cells emerges in the developing mouse lung between E15.5 and E16.5. This is accompanied by significant upregulation, in the lung mesenchyme, of peroxisome proliferator-activated receptor gamma (master switch of lipogenesis), adipose differentiation-related protein (marker of mature lipofibroblasts) and fibroblast growth factor 10 (previously shown to identify a subpopulation of lipofibroblast progenitors). We also demonstrate that although only a subpopulation of total embryonic lipofibroblasts derives from Fgf10+ progenitor cells, *in vivo* knockdown of Fgfr2b ligand activity and reduction in Fgf10 expression lead to global reduction in the expression levels of lipofibroblast markers at E18.5. Constitutive Fgfr1b knockouts and mutants with conditional partial inactivation of Fgfr2b in the lung mesenchyme reveal the involvement of both receptors in lipofibroblast formation and suggest a possible compensation between the two receptors. We also provide data from human fetal lungs to demonstrate the relevance of our discoveries to humans. Our results reveal an essential role for Fgf10 signaling in the formation of lipofibroblasts during late lung development.

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### **Keywords**

Fgf10, Lipofibroblasts, Lung, Mesenchyme