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Mesodermal ALK5 controls lung myofibroblast versus lipofibroblast cell fate

Li A., Ma S., Smith S., Lee M., Fischer A., Borok Z., Bellusci S., Li C., Minoo P.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© 2016 Li et al.Background: Epithelial-mesenchymal cross talk is centerpiece in the development of many branched organs, including the lungs. The embryonic lung mesoderm provides instructional information not only for lung architectural development, but also for patterning, commitment and differentiation of its many highly specialized cell types. The mesoderm also serves as a reservoir of progenitors for generation of differentiated mesenchymal cell types that include αSMA-expressing fibroblasts, lipofibroblasts, endothelial cells and others. Transforming Growth Factor β (TGFβ) is a key signaling pathway in epithelial-mesenchymal cross talk. Using a cre-loxP approach we have elucidated the role of the TGFβ type I receptor tyrosine kinase, ALK5, in epithelial-mesenchymal cross talk during lung morphogenesis. Results: Targeted early inactivation of Alk5 in mesodermal progenitors caused abnormal development and maturation of the lung that included reduced physical size of the sub-mesothelial mesoderm, an established source of specific mesodermal progenitors. Abrogation of mesodermal ALK5-mediated signaling also inhibited differentiation of cell populations in the epithelial and endothelial lineages. Importantly, Alk5 mutant lungs contained a reduced number of αSMApos cells and correspondingly increased lipofibroblasts. Elucidation of the underlying mechanisms revealed that through direct and indirect modulation of target signaling pathways and transcription factors, including PDGFRα, PPARγ, PRRX1, and ZFP423, ALK5-mediated TGFβ controls a process that regulates the commitment and differentiation of αSMApos versus lipofibroblast cell populations during lung development. Conclusion: ALK5-mediated TGFβ signaling controls an early pathway that regulates the commitment and differentiation of αSMApos versus LIF cell lineages during lung development.

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Keywords

Lipofibroblast, Lung development, Mesoderm, Myofibroblast, Pdgfrα, Pparβ, Zfp423