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Mesenchymal adenomatous polyposis coli plays critical and diverse roles in regulating lung development

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Abstract

© 2015 Luo et al. Background: Adenomatous polyposis coli (Apc) is a tumor suppressor that inhibits Wnt/Ctnnb1. Mutations of Apc will not only lead to familial adenomatous polyposis with associated epithelial lesions, but will also cause aggressive fibromatosis in mesenchymal cells. However, the roles of Apc in regulating mesenchymal cell biology and organogenesis during development are unknown. Results: We have specifically deleted the Apc gene in lung mesenchymal cells during early lung development in mice. Loss of Apc function resulted in immediate mesenchymal cell hyperproliferation through abnormal activation of Wnt/Ctnnb1, followed by a subsequent inhibition of cell proliferation due to cell cycle arrest at G0/G1, which was caused by a mechanism independent of Wnt/Ctnnb1. Meanwhile, abrogation of Apc also disrupted lung mesenchymal cell differentiation, including decreased airway and vascular smooth muscle cells, the presence of Sox9-positive mesenchymal cells in the peripheral lung, and excessive versican production. Moreover, lung epithelial branching morphogenesis was drastically inhibited due to disrupted Bmp4-Fgf10 morphogen production and regulation in surrounding lung mesenchyme. Lastly, lung mesenchyme-specific Apc conditional knockout also resulted in altered lung vasculogenesis and disrupted pulmonary vascular continuity through a paracrine mechanism, leading to massive pulmonary hemorrhage and lethality at mid-gestation when the pulmonary circulation should have started. Conclusions: Our study suggests that Apc in lung mesenchyme plays central roles in coordinating the proper development of several quite different cellular compartments including lung epithelial branching and pulmonary vascular circulation during lung organogenesis.

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Keywords

Adenomatous polyposis coli, Ctnnb1, Lung branching morphogenesis, Lung development, Lung mesenchyme, Lung vasculogenesis, Pulmonary circulation, Versican