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# Hmga2 is required for canonical WNT signaling during lung development

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## Abstract

Background: The high-mobility-group (HMG) proteins are the most abundant non-histone chromatin-associated proteins. HMG proteins are present at high levels in various undifferentiated tissues during embryonic development and their levels are strongly reduced in the corresponding adult tissues, where they have been implicated in maintaining and activating stem/progenitor cells. Here we deciphered the role of the high-mobility-group AT-hook protein 2 (HMGA2) during lung development by analyzing the lung of Hmga2-deficient mice (Hmga2---).Results: We found that Hmga2 is expressed in the mouse embryonic lung at the distal airways. Analysis of Hmga2-/- mice showed that Hmga2 is required for proper cell proliferation and distal epithelium differentiation during embryonic lung development. Hmga2 knockout led to enhanced canonical WNT signaling due to an increased expression of secreted WNT glycoproteins Wnt2b, Wnt7b and Wnt11 as well as a reduction of the WNT signaling antagonizing proteins GATA-binding protein 6 and frizzled homolog 2. Analysis of siRNA-mediated loss-of-function experiments in embryonic lung explant culture confirmed the role of Hmga2 as a key regulator of distal lung epithelium differentiation and supported the causal involvement of enhanced canonical WNT signaling in mediating the effect of Hmga2-loss--f-fuction. Finally, we found that HMGA2 directly regulates Gata6 and thereby modulates Fzd2 expression.Conclusions: Our results support that Hmga2 regulates canonical WNT signaling at different points of the pathway. Increased expression of the secreted WNT glycoproteins might explain a paracrine effect by which Hmga2-knockout enhanced cell proliferation in the mesenchyme of the developing lung. In addition, HMGA2-mediated direct regulation of Gata6 is crucial for fine-tuning the activity of WNT signaling in the airway epithelium. Our results are the starting point for future studies investigating the relevance of Hmga2-mediated regulation of WNT signaling in the adult lung within the context of proper balance between differentiation and self-renewal of lung stem/progenitor cells during lung regeneration in both homeostatic turnover and repair after injury. 

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## Keywords

Branching morphogenesis, GATA6, HMGA2, Lung development, WNT signaling