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RESEARCH NEWS

Mechanisms of Proximal-Distal Patterning of the Lung

A review of: Lu MM, Yang H, Zhang L, *et al*. 2001 The bone morphogenetic protein antagonist gremlin regulates proximal-distal patterning of the lung. Develop Dyn 222:667–680; and Yang H, Lu MM, Zhang L, *et al*. 2002 GATA6 regulates differentiation of distal lung epithelium. Development 129:2233–2246

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The undifferentiated endodermal epithelium of the lung primordium gives rise to a variety of specialized cell types that differentiate along a proximal-distal axis either into the ciliated and secretory cells of conducting airways, or into the two cell types of gas-exchanging alveolar epithelium. The molecular mechanisms that orient precursor cells toward either a proximal or a distal fate have for long remained unknown. Two recent studies from the same group have led to identifying two proteins involved in the proximal-distal patterning mechanisms of lung epithelium, namely the bone morphogenetic protein antagonist Gremlin, and the transcription factor GATA6.

It had been formerly established from elegant *in vitro* grafting experiments (1) that epithelial cells of embryonic lung were pluripotent, displayed plasticity, and that their fate toward a proximal or distal phenotype was dictated by lung mesenchyme. The nature of molecules involved in the control of epithelial differentiation remained largely unknown, although involvement of bone morphogenetic proteins (BMPs) has been suggested by the altered proximal-distal patterning in mice overexpressing the BMP antagonist xnoggin or a dominant-negative BMP receptor (2). Based on these findings and on the recognized role of BMPs in the development of various organs, the strategy of Lu *et al*. consisted of looking for the expression of their various antagonists in the developing lung. After having evidenced the restricted expression of Gremlin (3) to proximal epithelium during late lung development, they generated transgenic mice overexpressing this protein in the distal epithelium. The transgene was targeted with the aid of the human surfactant protein C (SP-C) promoter. SP-C/Gremlin transgenic mice exhibited a disruption of pulmonary proximal-distal patterning, including expanded expression to distal epithelium of proximal markers such as the bronchiolar Clara cell secretory protein (CC10) and the transcription factor that controls ciliated-cell phenotype (4), Foxj1 (or HFH-4). Reciprocally, the expression of the alveolar marker SP-C was reduced. Furthermore, an aberrant expression around distal lung tubules was observed for α-smooth muscle actin that is normally present surrounding proximal airways but absent in the mesenchyme surrounding the distal airways in wild-type animals. These features indicate a proximalization of lung tubules. The proximally restricted expression of Gremlin in the developing lung therefore appears to play an important role in the determination of proximal epithelial cell fate, and influences in turn the differentiation of surrounding mesenchymal cells.

Yang and coworkers explored the role of GATA6, a member of the GATA family of zinc-finger transcriptional regulators, and found its expression, in contrast to Gremlin, restricted to distal epithelium. To define its role during development, a loss-of-function approach was used through expression of a GATA6-Engrailed dominant negative fusion protein targeted to distal lung epithelium of transgenic mice. Transgenic embryos lacked detectable alveolar epithelial type I cells, the attenuated cells which perform gas exchanges. The expression of Aquaporin 5, a water channel gene whose expression is restricted to this cell type, was markedly reduced. Although neither the expression of thyroid transcription factor 1, a factor essential for distal lung development, nor that of SP-A were affected, endogenous SP-C expression was not observed in the thick cuboidal epithelium where the transgene was expressed, indicating that alveolar type II cell differentiation was affected also. The authors also examined the expression of Foxp2, a winged helix transcription factor that acts as a transcriptional repressor (5). At early stages, Foxp2 is expressed in lung epithelium in a pattern similar to that of SP-C. Whereas its expression is down regulated in wild type embryos from E17.5 to E19.5, it remains high in transgenic embryos. Finally, the number of proximal airway tubules was also reduced. Together, these data implicate GATA6 as an important regulator of distal epithelial cell differentiation and as an element in the control of proximal-distal airway development.

Determination of the roles that Gremlin and GATA6 play in the differentiation of proximal and distal lung epithelium represents a crucial step in the understanding of lung patterning mechanisms. Further studies are now required to determine the mesenchymal signaling molecules that drive the differential expression pattern in the developing epithelium.

1. Shannon JM, Nielsen ND, Gebbs SA, Randell SH 1998 Mesenchyme specifies epithelial differentiation in reciprocal recombinants of embryonic lung and trachea. Dev Dyn 212:482–494
2. Weaver M, Yingling JM, Dunn NR, Bellusci S, Hogan BL 1999 Bmp signaling regulates proximal-distal differentiation of endoderm in mouse lung development. Development 126:4005–4015
3. Hsu DR, Economides AN, Wang X, Eimon PM, Harland RM 1998 The Xenopus dorsalizing factor Gremlin identifies a novel family of secreted proteins that antagonize BMP activities. Mol Cell 1:673–683
4. Chen J, Knowles HJ, Hebert HL, Hackett BP 1998 Mutation of the mouse hepatocyte nuclear factor/forkhead homologue 4 gene results in the absence of cilia and random left-right asymmetry. J Clin Invest 102:1077–1082
5. Shu W, Yang H, Zhang L, Lu MM, Morrissey EE 2001 Characterization of a new subfamily of winged-helix/forkhead (Fox) genes which are expressed in the lung and act as transcriptional repressors. J Biol Chem 276:27488–27497

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