

How the vasculature delivers lung epithelia from an incorrect fate

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Cross talk between pulmonary endothelia and epithelia prevents abnormal differentiation into liver cells.

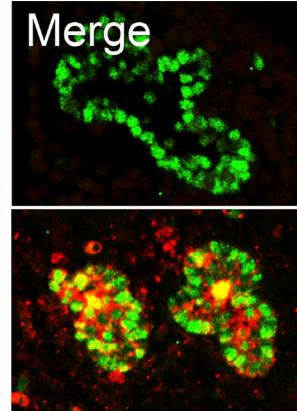
Signaling between epithelial and endothelial cells is crucial for the development of many different organs, with each cell type capable of regulating the proliferation and differentiation of the other. Communication between these cell types is particularly important in the lungs, where the development of blood vessels and pulmonary epithelia must be intricately coordinated in order to form the alveolar units that mediate gaseous exchange. In this issue, Yao et al. reveal that, in the absence of a BMP signaling inhibitor called MGP, the cross talk between pulmonary endothelia and epithelia goes awry, resulting in the abnormal differentiation of lung epithelial cells into hepatocytes (1).

MGP is expressed throughout the body's vasculature and its deletion causes a variety of phenotypes, including calcification of elastic arteries such as the aorta (2). "Every vascular bed is abnormal in MGP knockout mice," says Kristina Boström, from the David Geffen School of Medicine at UCLA. "But the precise defect differs in each bed." In the lungs, BMP signaling induces MGP expression, creating a feedback loop that sets the correct level of BMP activity for pulmonary development. Overexpressing MGP limits BMP signaling and inhibits pulmonary vascular growth (3). Loss of MGP, in contrast, causes vascular overgrowth and arteriovenous malformations in the lung (3).

Boström, Yao, and colleagues were surprised, however, when they analyzed the gene expression profile of lungs from MGP knockout mice (1). "We saw that knockout lung had a similar expression pattern to liver," explains co-corresponding author Yucheng Yao.

The researchers, led by first author Jiayi Yao, confirmed that many different liver cell markers were up-regulated in the lung epithelial cells of MGP knockout mice, while hepatocyte growth factor (HGF) was elevated in pulmonary endothelial cells.

Yao et al. determined that, in the absence of MGP, the resulting increase in BMP-4 signaling induces both VEGF and the HGF receptor c-Met in epithelial cells, as well as



Focal Point (left to right) Jiayi Yao, Kristina Boström, Yucheng Yao, and colleagues reveal that, in the absence of the BMP inhibitor MGP, signaling between endothelial and epithelial cells in the developing lung goes awry, resulting in the induction of hepatic rather than pulmonary epithelial differentiation. For example, compared with a wild-type mouse embryo (top), the hepatocyte marker albumin (red) is up-regulated in the airway progenitor cells (green) of an MGP knockout embryo (bottom). The researchers find that the increase in BMP signaling caused by MGP deletion stimulates elevated hepatocyte growth factor expression in pulmonary endothelial cells and the subsequent induction of the hepatic transcription factor Hnf4a in epithelial cells drives hepatic gene expression. PHOTOS COURTESY OF THE AUTHORS.

the VEGF receptor Flt1 in endothelial cells. VEGF activates Flt1 to stimulate the production of HGF by pulmonary endothelial cells, which, in turn, activates c-Met on the surface of epithelial progenitors to induce their differentiation into hepatocytes. Removing the *Hgf* gene from the endothelial cells of MGP knockout mice limited this ectopic differentiation.

"We saw that knockout lung had a similar expression pattern to liver."

The researchers then investigated how elevated HGF levels induce the differentiation of lung epithelial cells into hepatocytes. The transcription factors Hnf4a and Foxa2 bind to each other and drive hepatic differentiation (4). In lung epithelial cells, however, Foxa2 usually binds to a different transcription factor, Nkx2.1 (5). Yao et al. discovered that HGF induces Hnf4a in the pulmonary epithelia of MGP knockout mice and that this transcription factor outcompetes Nkx2.1 for binding to Foxa2, resulting in the transcription of liver-specific genes.

During development, the lungs and liver arise in close proximity to each other from the foregut endoderm, and local signals are crucial for specifying the two distinct fates. Yao et al.'s study suggests that MGP is one of these signals, limiting local BMP activity to ensure that endothelial-epithelial cross talk promotes pulmonary development and suppresses hepatic differentiation. Accordingly, MGP is not expressed in the liver, but is produced by both epithelial and endothelial cells in the lung. Yao et al. found that MGP from either source is sufficient to suppress hepatic gene expression during pulmonary specification.

The researchers now want to investigate how MGP affects the cross talk between endothelia and neighboring cell types in other parts of the vasculature, and whether these effects contribute to the various phenotypes, such as aortic calcification, that are observed in MGP knockout mice.

1. Yao, J., et al. 2017. *J. Cell Biol.* <http://dx.doi.org/10.1083/jcb.201612122>
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3. Yao, Y., et al. 2011. *J. Clin. Invest.* 121:2993–3004.
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