Rac1 protein critical for lung development

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A study by researchers from The Saban Research Institute of Children's Hospital Los Angeles reveals a promising therapeutic target for improving lung function in infants. Their study, now published online by the *American Journal of Physiology-Lung Cellular and Molecular Physiology*, shows that a protein called Rac1 is critical for the proper development of mammalian lung.

Normal lung development - lung branching morphogenesis - is an essential process occurring in early development that eventually leads to the formation of the right number of alveolar sacs, where gas exchange takes place. While Rac1 has been shown to play an important role in lung cancer, its role in lung development had not yet been investigated. It is known that Rac1 orchestrates a multitude of cellular events required for normal cell function; the new study shows that this includes modulation of the Wnt signaling pathway that is important to lung branching morphogenesis.

Lung branching abnormalities underlie the etiology of many lung diseases including pulmonary hypoplasia (PH), a congenital state of incomplete development of the lungs. PH can result in fatal complications, due to improperly formed alveoli or air sacs that are not capable of generating air exchange. To date, there are no cures available for PH. Little is known about the mechanisms underlying these diseases, an understanding essential to development of therapeutic strategies.

Using a specific chemical inhibitor of this protein, the research team showed that Rac1 inhibition severely hinders branching of the lung, and

disrupts the formation of the vascular system and the expression of other proteins ((Vegfa, Fgf10, AXIN2, and FGF receptor 2B) involved in lung development. The inhibition of Rac1 also led to cell death in mouse lungs cultured in the lab. The authors developed a model of human lung culture and validated these results in the context of human lung growth. They demonstrated that, similar to mouse, Rac1 inhibition resulted in impaired branching and decreased expression of AXIN2 and FGFR2b in human lung cultures.

"We concluded that RAC1 regulates lung branching morphogenesis, in part through the so-called canonical Wnt signaling pathway, which leads to the regulation of the transcription of many genes," said principal investigator Denise Al Alam, PhD, of the Department of Surgery and the Developmental Biology and Regenerative Medicine Program at The Saban Research Institute. Al Alam, who is also assistant professor at Keck School of Medicine of the University of Southern California, added that the exact mechanism by which the protein and signaling pathway interact still require further investigation.

More information: Soula Danopoulos et al, Rac1 modulates mammalian lung branching morphogenesis in part through canonical Wnt signaling, *American Journal of Physiology - Lung Cellular and Molecular Physiology* (2016). DOI: 10.1152/ajplung.00274.2016

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