Researchers discover gene network associated with vitamin A deficiency and lung birth defects

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Researchers from Boston University School of Medicine (BUSM) have discovered the mechanism responsible for the failure of the lungs to form as a result of vitamin A/retinoic acid (RA) deficiency. The study, which appears in the June issue of the *Journal of Clinical Investigation,* also shows that corrections to this network make it possible to prevent the lung defect in retinoic acid-deficient animals.

Congenital abnormalities of the respiratory system are often part of multi-organ syndromes associated with genetic, environmental or nutritional imbalances during fetal life. Developmental defects, such as tracheoesophageal fistula, pulmonary hypoplasia and failure to form one or both lungs are known for decades to be important components of the so called "Vitamin A deficiency syndrome." Researchers knew that Vitamin A, through its active form RA, is highly utilized at the time and site where the lung develops in the embryo. However, why RA is so critical and how this pathway controls lung formation has been little understood.

To tackle this problem, BUSM researchers investigated the initial stages of lung development in RA deficient mice using pharmacological and genetic models. They identified gene networks controlled by RA and characterized their role and hierarchy in this process. The researchers found that RA controls lung formation by balancing the effect of the Wnt and Tgfb pathways in Fgf10, a growth factor required for induction

of lung buds. Like two opposing forces, Wnt and Tgfb act as positive and negative regulators of Fgf10 and bud growth, respectively. The study shows that RA coordinately acts on these pathways ensuring that proper levels of Fgf10 are present at the sites of budding.

"Our data strongly suggest that disruption of Wnt-Tgfβ-Fgf10 interactions represents the molecular basis for the failure to form lung buds classically reported in vitamin A deficiency," said Wellington V. Cardoso, MD, PhD, a Professor of Medicine and Pathology and Director of the Lung Development and Progenitor Cell Biology Program at BUSM.

"Moreover, we show that simultaneously activating Wnt and repressing Tgfβ fully rescues the lung in both RA-deficient models. These findings unveil molecular interactions critical for lung progenitor cell development and sheds light into the pathogenesis of abnormalities induced by vitamin A deficiency," he added.

According to the researchers a better knowledge of the molecular pathways regulating early lung organogenesis is critical for the understanding of the pathogenesis of lung congenital malformations. This is particularly relevant in the context of conditions associated with disruption of RA signaling. Genetic mutations in RA pathway components leading lung developmental defects have been already identified in human syndromes.

"The clinical relevance of hypovitaminosis A cannot be overlooked, as it represents the third most common nutritional deficiency in the world, being found in a large population of women in child-bearing age of developing countries," added Cardoso.

Provided by Boston University Medical Center