

Scientists show gene mutation may cause immature lungs in newborns

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Scientists have identified a gene critical to lung maturation in newborns and the production of surfactant, which lines lung tissues and prevents the lungs from collapsing.

In a study posted online by the *Proceedings of the National Academy of Sciences (PNAS)*, investigators at Cincinnati Children's Hospital Medical Center deleted the *Foxm1* gene in embryonic mice.

Although lung development in the mice progressed through early stages after the gene was deleted – a finding that surprised the research team – the lungs did not completely mature. The immature lungs also did not produce two critical surfactant proteins (SP-A, SP-B) and the mice died shortly after birth from respiratory distress.

"Our findings demonstrate the *Foxm1* gene's central importance to lung maturation and surfactant production in mice," said Vladimir Kalinichenko, M.D., Ph.D., a physician and researcher in the division of Pulmonary Biology at Cincinnati Children's and the study's senior investigator. "Ultimately, this information is important to newborn survival, as infants must breathe on their own at birth instead of getting oxygen from the mother's umbilical cord blood."

In the study, Dr. Kalinichenko and his colleagues also wrote that, "identifying critical regulators of lung maturation, such as *Foxm1*, may provide novel strategies for diagnosis, prevention and treatment of respiratory distress syndrome (RDS) in preterm infants."

RDS is a common cause in death in preterm infants, and Cincinnati Children's helped pioneer the clinical use of surfactants to improve lung function in premature babies. Previous research has shown that Fox genes (a group of transcription factors that control the transfer of genetic information to regulate proteins within cells) are important for the embryonic development of lungs and other organs.

To study the role of Foxm1 during embryonic lung development, investigators in the current study generated transgenic mice, which are engineered to allow genetic manipulation. The researchers deleted Foxm1 in developing lung epithelium – tissue that coats the surface of air sacs. Deletion did not impact the initial budding and branching or the growth of the lung. This suggests Foxm1 is not critical to replicating genetic information in the development of epithelial cells, the researchers said. Deletion of the gene did, however, inhibit anatomic and biochemical maturation of the lung, where air sacs did not fully form and surfactant production was compromised.

Dr. Kalinichenko said the research team is working to find pharmacological compounds that can activate Foxm1. The compounds could be used to create new drugs that treat a variety of human diseases involving Foxm1 deficiency. He said pharmacological activation of Foxm1 in premature babies may be beneficial to treat RDS by inducing lung maturation and surfactant production.

Source: Cincinnati Children's Hospital Medical Center

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