“Lung Development and Disease: Lessons from Newborn Infants"

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The cellular and molecular processes that enable us to keep our lung inflated, fight infections, and avoid pulmonary diseases like pulmonary fibrosis and cancer as we age, may be the very same ones that enabled us to take our first breaths at birth.

The origin of this insight begins with Drs. Mary Ann Avery and Jerry Mead’s discovery in the 1950s when they identified of the role played by pulmonary surfactant in respiratory distress syndrome in preterm babies, a disorder that was usually fatal in the U.S. Three decades later, Dr. Whitsett and his research team discovered surfactant proteins B and C, small molecules that interact with lipids in surfactant to allow the alveoli to dynamically expand and contract without collapsing. This work helped bring surfactant replacement therapy to infants in the U.S. Dr. Whitsett’s laboratory identified and cloned genes encoding from surfactant proteins (SP-A, B, C, D) and studied their roles in lung function. Together these proteins were found to play critical roles in innate host defense of the lung and in control of surfactant function and homeostasis.

In collaboration with many other laboratories, these discoveries made it possible to identify mutations in newborn infants that cause respiratory failure in full-term babies. “Through cellular and molecular biology, we learned that the pathogenesis of the diseases caused by changes in the genes regulating the surfactant system function within cellular and molecular networks that are relevant to respiratory diseases throughout life.”

Genetic mechanisms controlling lung development provide important insights into the functions of lung cells in health and disease throughout our lives. Advances in elucidating the genetic causes of lung disease will provide knowledge that may one day lead to the correction of life-threatening lung diseases, for example, using gene or cell replacement, or gene editing that may someday enable correction of pulmonary diseases that are only treated by lung transplantation at present. Likewise, knowledge of the signaling and transcriptional programs regulating normal lung repair will provide the basis for new treatments for lung disease.

Even before those milestones are reached, study of lung’s early development will benefit research related to lung disease. “It is remarkable that the lung develops late in fetal life. During much of lung development in utero, the lung is a solid tissue, more like liver than the air-filled lung after birth. Near the time of birth, lung saccules dilate, and future air spaces form. In the weeks after birth, alveolarization begins, and small lung saccules become increasingly divided, “septated,” and surface area increases markedly.” “When things go wrong, it's the loss of alveoli that leads to chronic lung diseases like bronchopulmonary dysplasia (BPD) a chronic disease of extremely preterm infants, emphysema or pulmonary fibrosis in older patients. Understanding how the normal alveoli are formed is critically important to understanding how to prevent lung injury or to repair the damaged lung at any age.”

Dr. Whitsett developed some of the first transgenic mouse models for study of human lung diseases, deleting or mutating genes critical for lung formation and function. These studies, in concert with identification of patients with lung diseases caused by mutations or alterations in critical gene networks, have provided insights into the pathogenesis of diverse respiratory disorders, cancer, pulmonary fibrosis, pulmonary alveolar proteinosis and asthma.