A Novel Hollow Fiber Model System and the Study of Oxygen Sensitive Genes in the Alveolar Epithelium of Marine Mammals

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Pulmonary surfactant, a complex mixture of phospholipids and proteins, is critical for lowering surface tension levels in the alveoli and preventing lung collapse. The molecular and cellular mechanisms that regulate surfactant secretion are numerous and complex. During fetal lung development, *in utero* surfactant production is essential for successful lung inflation and function upon birth. In fact, abnormal surfactant is the major problem associated with premature births and the development of respiratory distress syndrome (RDS). When compared to the airway of the newborn, the fetal lung develops under conditions of lower oxygen tension. Similarly, during deep diving activities of marine mammals, the lung is collapsed, resulting in a state similar to that of the neonate *in utero,* rapidly becoming hypoxic and further complicated by increasing hyperbaric pressure due to diving depths of 90 to 2,000 meters. Pulmonary surfactant is crucial in allowing for proper reinflation and restoration of lung oxygen tension upon surfacing. Studies from our laboratory and others have indicated specific oxygen-sensitive genes may have roles in the regulation of surfactant production, especially during times of low oxygen tension. Due to the complex nature of lung architecture that prevents easy access, studies of the alveolar epithelium are extremely difficult. Through the establishment of a novel lung model system that more accurately represents *in vivo* conditions by incorporating the three-dimensional nature and air-liquid interface of the native lung epithelium (both marine and terrestrial), this study provides the opportunity to elucidate the roles of specific oxygen-sensitive genes in the regulation of surfactant production. Our data indicate a direct relationship between hypoxia-inducible factor and the expression of hemoglobin and surfactant proteins and suggest a role for hemoglobin in ATII cells in the oxygen-sensing pathway in alveolar epithelial cells. The information gathered will facilitate the elucidation of particular genes that may be useful in the development of new therapeutics to treat and prevent airway disease associated with disruption of surfactant production.

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