A Novel Hollow Fiber Model System to study Gene and Protein Regulation during Stress in the Alveolar Epithelium of Marine Mammals

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Studies of the alveolar epithelium are extremely difficult due to the complex nature of lung architecture that prevents easy access. Marine mammals have a respiratory system that is physiologically similar to terrestrial mammals with the exception of an increased respiratory air exchange volume and an increased flow rate. While there are a number of obvious morphological differences, the alveoli of marine mammals are similar to those of terrestrial mammals in that they posses alveolar epithelial type I and type II cells, which function similarly in surfactant production.

One of the major differences with regards to marine mammalian lungs is the ability to completely collapse the lung under circumstances such as swallowing and diving. This results in the removal of all air from the alveoli and prevents the absorption of compressed gas by the blood and, subsequently, protects the animal from Caisson disease (the bends). During deep diving activities and increasing hyperbaric pressure, the lung alveoli of marine mammals collapse and experience low oxygen tension in blood and tissue. Pulmonary surfactant is crucial in allowing for proper reinflation and restoration of lung oxygen tension upon surfacing. Recent observations suggest that marine mammals have an incredibly high surfactant turnover production rate during these times of hypoxic stress. These observations in coordination with data from our laboratory confirm a link of hypoxia to surfactant production as well as the role of oxygen sensitive genes, including HIF-2α and hemoglobin, in such surfactant synthesis and/or secretion. Thus, studies of the marine mammal alveolar epithelium could prove highly useful in further elucidating the complex mechanisms that play a role in surfactant regulation, especially during times of hypoxia.

Current cell models using cultured alveolar cell systems do not accurately mimic the *in vivo* cellular microenvironment lacking air-liquid interface and dynamic stretching characteristics of native lung tissue, which are important for normal phenotypic gene expression and cellular function. Thus, there is a critical need for the development of new model systems, particularly for marine mammals. We have established a novel, selectively semi-permeable hollow fiber membrane-based model system that more accurately mimics the microenvironment of the mammalian (both marine and terrestrial) alveolar epithelium. 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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