NIH Award from the National Heart, Lung, and Blood Institute

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- **Project:** Effects of Hypoxia on Alveolar Epithelial Cytoskeleton
- **Start Date:** June 1, 2009
- **Total Award Amount:** $18,675

How the results of this project will benefit society:
Alveolar hypoxia, or lack of oxygen in the tissue of the lungs, is observed in many physiological and pathological conditions including chronic obstructive pulmonary disease, cardiogenic pulmonary edema, acute respiratory distress syndrome, and high altitude sickness. This research will provide novel insights on the role of keratin intermediate filaments, which form a fibrous polymer network that helps epithelial cells withstand external mechanical forces. These filaments are important in the pathogenesis of hypoxia-induced alveolar epithelial dysfunction, which is of biological and physiological importance in patients with pulmonary edema.

The problem the project is trying to solve:
The effects of hypoxia on the function and cytoskeleton of the alveolar epithelium, the tissue that covers the external surface of the alveoli in the lung, have yet to be elucidated. The cytoskeleton is largely responsible for a cell’s structural support, and keratin intermediate filaments (IFs) are known to play an important role in maintaining the integrity of epithelial cells. In alveolar epithelial cells (AEC), keratin IFs are the major structural proteins. An intact keratin IF network is important for optimal alveolar epithelial function.

How this project will work:
This proposal is focused on determining whether hypoxia-induced changes in the keratin IF network lead to dysfunction of alveolar epithelial cells (AEC). We hypothesize that hypoxia generates mitochondrial reactive oxygen species in AEC, which activate protein kinases that phosphorylate keratin proteins and regulate the organization, disassembly and degradation of the keratin IF. Modifications to keratin IFs in the alveolar epithelial cell may contribute to impaired alveolar epithelial function. We will study the hypoxia-induced regulation of keratin IFs in the alveolar epithelium. The proposed experiments will determine the molecular mechanisms that regulate the hypoxia mediated reorganization and/or disassembly of keratin IFs. The consequences of this reorganization on alveolar epithelial function will be examined both in vitro and in vivo.

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