

James & Esther King Biomedical Research Program

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Medicine
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2008 Program
New Investigator (3-year project)

Project Title: Involvement of Arginase in the Response of Endothelial Cells to Hypoxia

Project Summary: Cigarette smoking is a major cause of chronic obstructive pulmonary disease (COPD) which is characterized by poor gas exchange in the lungs. This inadequate pulmonary ventilation is associated with cellular hypoxia, a reduced availability of oxygen for cellular functions. Lung endothelial cells release nitric oxide (NO), which acts to dilate blood vessels and maintain normal blood pressure in the pulmonary circulation. Hypoxia induces a decrease in NO production. NO production is regulated by a variety of mechanisms, one of which is the availability of L-arginine, the substrate for NO production by endothelial nitric oxide synthase (NOS). L-arginine is also metabolized by intracellular arginases. Sharing a common substrate, arginase and NOS compete for L-arginine. The exposure of cultured endothelial cells to hypoxia activates arginase, and we suggest that this upregulation of arginase activity leads to a decrease in NO production. The objective of this grant is to study the effects of hypoxia on arginase activity and, in turn, NO production in endothelial cells and to investigate possible mechanisms for the action of hypoxia on arginase activity. Elucidation of the role arginase plays in the regulation of NO production and the subsequent development of endothelial cell dysfunction under hypoxic conditions would be a new step in our understanding of endothelial physiology with implications for tobacco-related disease such as COPD.