Su, Yunchao

Department of Medicine *2001 Program*
University of Florida College of Medicine *New Investigator (3-year project)*

Project Title: Effect of cigarette smoke on lung endothelial nitric oxide synthase - the role of calpain.

Project Summary: Cigarette smoke has been implicated as a major risk factor in chronic obstructive pulmonary disease (COPD). The relaxation and density of lung blood vessels is diminished in human cigarette smokers and in the lungs of individuals with COPD. Cigarette smoke extract (CSE) causes inhibition of an enzyme called nitric oxide synthase, which is involved in the relaxation and growth of lung blood vessels. The objective of this project is to study the role of calpain in the CSE-induced inhibition of nitric oxide synthase. The project has measured calpain activity and protein changes in CSE-treated lung endothelial cells. Two pathways in the regulation of protein and activity of nitric oxide synthase by calpain were studied in CSE-treated lung endothelial cells by using calpain inhibitors and molecular biology technique. The effects of CSE on endothelial cells growth were also studied. A better understanding of the mechanism responsible for dysfunction of nitric oxide synthase and vessel growth in the lungs of cigarette smokers and patients with COPD will advance the ability to prevent or attenuate the pulmonary vascular complications, such as pulmonary hypertension and cor pulmonale, that develop in these individuals.

Project Successes: The project found that CSE induced an inhibition of calpain activity. The inhibition of calpain activity by CSE is caused by an increase in calpastatin protein, an endogenous calpain inhibitor. Four antisense nucleotides of calpastatin were designed. One of the antisense nucleotides has been found to be able to prevent smoke-induced increase in calpastatin protein and smoke-induced inhibition of calpain activity as well as smoke-induced decreases in protein of nitric oxide synthase and endothelial cell growth in lung endothelial cells. The antisense nucleotides of calpastatin also prevent CSE-induced decrease in gene transcription of nitric oxide synthase. Decreased activity of nitric oxide synthase and endothelial cell growth caused by CSE may be responsible for the increased risk of COPD and vascular dysfunction in cigarette smokers. Identifying the mechanism of CSE-induced inhibition of nitric oxide synthase will advance the understanding of the pathophysiology of pulmonary vascular disease and dysfunction in cigarette smokers.

Publications from BRP funded research in Peer Reviewed Journals:

Su Y, Cao W, Han Z, Block ER. Cigarette smoke extract inhibits angiogenesis of pulmonary artery endothelial cells: the role of calpain. Am J Physiol Lung Cell Mol Physiol. 2004;287:L794-L800.

Su Y, Edwards-Bennett S, Bubb MR, Block ER. Regulation of endothelial nitric oxide synthase by the actin cytoskeleton. Am J Physiol Cell Physiol. 2003;284:C1542-C1549.

Presentations from BRP funded research:

Cao W., **Su Y**, Block ER. Cigarette smoke extract inhibits lung endothelial angiogenesis induced by growth factors. Am J Respir Crit Care Med. 2004;169(7):A165.

Han Z, **Su Y**, Block ER. Involvement of acetylated histone 3 in cigarette smoke extract-induced inhibition of nitric oxide synthase gene transcription in pulmonary artery endothelial cells. Am J Respir Crit Care Med. 2004;169(7):A395.

Kondrikov D, **Su Y**, Han H. and Block ER. Direct Interaction of Endothelial Nitric Oxide Synthase with the Actin Cytoskeleton. FASEB J 2004;15(5):1026.

Qiu K, **Su Y**, Block ER. Calpain siRNA function in pulmonary artery endothelial cells. FASEB J. 2004;15(5):1026.

Su Y, Cao W, Block ER, Cigarette smoke extract inhibits the production and effects of vascular endothelial growth factor. Circulation 2003; 107(19):e172. American Heart Association Second Asia Pacific Scientific Forum: New Discoveries in Cardiovascular Disease and Stroke: Bench to Bedside to Community, June 8-10, 2003, Honolulu, Hawaii.

Qiu K, **Su Y**, Block ER. A calpastatin anti-sense ODN potentiates the hypoxic effects on calpain in pulmonary artery endothelial cells. Am J Respir Crit Care Med. 2003;167(7):A927.

Su Y, Edwards-Bennett S, Bubb MR, Block ER. Regulation of endothelial nitric oxide synthase by the actin cytoskeleton. FASEB J. 2003;17(5):A118.

Han Z, **Su Y**, Block ER. The role of calpain in cigarette smoke extract-induced inhibition of endothelial nitric oxide synthase. Am J Respir Crit Care Med. 2003;167(7):A120.

Cao W, **Su Y**, Block ER. Cigarette smoke extract inhibits angiogenesis of pulmonary artery endothelial cells (PAEC) — Role of calpain and endothelial nitric oxide synthase. Am J Respir Crit Care Med. 2003;167(7):A118.

New grants based in part on BRP-funded work:
Flight Attendant Medical Research Institute
Title: Clinical Innovator Award, Effect of side-stream cigarette smoke on lung endothelial angiogenesis induced by epidermal growth factor
Project period: 07/01/2004 – 06/30/2006
Award amount: $200,000