



Boston University
School of Medicine

For Immediate Release: March 8, 2005

Contact: Gina M. DiGravio, 617-638-8491, gina.digravio@bmc.org

BUSM RESEARCHERS FIND KEY PATHWAY LINKING OXIDATION CHEMICAL REACTION TO HEART FAILURE

(Boston) – Enlargement (or hypertrophy) of the heart muscle is a disease process underlying heart failure. Although reactive oxygen species (ROS) are known to be involved in this process, relatively little is known about precisely how ROS -- highly reactive molecules that arise from incomplete chemical reaction of oxygen -- activate the pathways that direct cardiac myocytes to enlarge. ROS can cause tissue damage but also are involved in the regulation of cell growth, consequently they are important for the study of biochemical processes in normal and diseased cells.

Stimulation of the α -adrenergic receptor causes hypertrophy in adult rat cardiac myocytes in culture, thus providing a useful model to study the cellular mechanisms of cardiac hypertrophy. A small protein, Ras, that contains sulfur molecules (thiols), is known to be activated following α -adrenergic receptor stimulation and to mediate molecular signaling events leading to hypertrophy. Ras was studied to understand the precise mechanisms of ROS interactions with its thiols.

According to a study published in this month's issue of *Circulation*, researchers at Boston University School of Medicine (BUSM) found that α -adrenergic receptor stimulation produces ROS that modify thiols of Ras. In chemical terms, this is known as an "oxidative modification" of Ras thiols. Furthermore, they found that the chemical reaction of ROS with Ras thiols can be prevented if the endogenous level of thioredoxin-1, a protein capable of protecting protein thiols in the cell, is increased by viral gene transfer. It was further shown that preventing the oxidative modification of Ras thiols also inhibited α -adrenergic receptor-stimulated hypertrophy.

“This is the first direct demonstration that an oxidative modification of a small signaling protein, Ras, mediates myocyte hypertrophy,” said lead author Wilson Colucci, MD, chairman of the department of cardiology at BUSM, and chief of cardiology at Boston Medical Center. These observations he said, show how those ubiquitous ROS molecules that we get from incomplete cellular processes can interact with protein thiols in a damaging way, playing an important role in cardiac disease. Furthermore, according to the researchers, these observations raise the possibility that by knowing the way in which the interaction takes place, new treatments may be developed to protect thiols from oxidative modification.

This project was funded with Boston University and Federal funds to Dr. Colucci through NIH/NHLBI and as part of the NHLBI Proteomics Initiative from the National Heart, Lung, and Blood Institute, National Institutes of Health, under Contract No. N01-HV-28178.