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

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- **Project:** Role of the Mitochondrial Atp-Binding Cassette Protein-1 in Cellular Protection
- **Start Date:** July 15, 2009
- **Total Award Amount:** $245,007

**How the results of this project will benefit society:**
Ischemic heart disease (IHD) is a major epidemic throughout the developed world, yet the molecular mechanisms that lead to myocardial cell death in this disorder are not completely understood. Evidence indicates that the mitochondria play an important role in regulating ischemic-induced cellular injury. Successful completion of our studies will have potential impact on our understanding of the role of mitochondria in cardiovascular disease, and may open new avenues for the treatment of IHD.

**The problem the project is trying to solve:**
We previously demonstrated that overexpression of a mitochondrial protein, the mitochondrial ATP-binding cassette protein-1 (mABC1) protects against oxidant-induced cell death, while its downregulation causes an increase in cell death at baseline. The primary function of mABC1 is unknown, thus it is unclear how this protein exerts protection against oxidant stress. The yeast homolog of mABC1, Mdl1p, has also been shown to exert protection against oxidant-induced cellular injury and plays a role in mitochondrial iron homeostasis. Intracellular iron accumulation can be a source of oxidative stress, which is thought to be the underlying mechanism for the protective effects of Mdl1p.

**How this project will work:**
In this proposal, we will follow up on our key observation that mABC1 is protective against oxidant injury and propose to elucidate the underlying mechanism for this process. Furthermore, we will attempt to extend our studies to intact animals and determine whether mABC1 can also protect against ischemic injury in the heart. Our main hypothesis is that mABC1 plays a role in the maintenance of the mitochondrial iron homeostasis and that it protects against ischemic damage in the heart. In order to test this hypothesis, we propose three interrelated specific aims. In Aim 1, we will determine whether mABC1 plays a role in the maintenance of mitochondrial iron homeostasis and generation of intracellular reactive oxygen species. The levels of mABC1 will be modulated in neonatal rat cardiomyocytes (NRCM) using various molecular biology techniques, followed by measurement of the mitochondria iron and intracellular ROS levels. In Aim 2, we will determine whether the protective effects of mABC1 are through inhibition of the mitochondrial permeability transition pore (mPTP). This channel is believed to be a pivotal player in oxidant-induced cell death. By altering the levels of mABC1 in NRCM, we will study the effect of mABC1 on cell viability and mPTP opening. In Aim 3, we will make transgenic mice that overexpress mABC1, followed by induction of ischemia/reperfusion (I/R). The effects of mABC1 overexpression on I/R-induced cell death will then be examined by various techniques. These lines of investigation promise to advance our knowledge of the molecular mechanisms of myocardial cell death in ischemic heart disease.

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