National Institute of Environmental Health Sciences
Division of Extramural Research and Training

NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL
September 1-2, 2010

Concept Clearance

Identification of Biomarkers for Early Detection of Mitochondrial Dysfunction

Overview:

Mitochondrial dysfunction is associated with numerous chronic diseases including Type II diabetes, metabolic syndrome, neurodegenerative diseases, blindness, cardiovascular disease, and cancer. Although it is known that mitochondria are a target for numerous environmental compounds, including pesticides, bacterial and fungal toxins, and multiple industrial chemicals, there are only a few well-studied links between disease and mitochondrial dysfunction resulting from environmental exposures. Research in this area is hampered by a lack of tools to measure early markers of mitochondrial dysfunction in human studies, particularly with respect to ambient environmental exposures. Current clinical markers for mitochondrial dysfunction are typically associated with advanced symptoms of tissue injury and disease. There is therefore an urgent need for reliable, informative markers of early mitochondrial dysfunction associated with environmental stressors, as these will enhance the mechanistic understanding of environmentally-induced mitochondrial toxicity and disease and enable prevention and intervention in the subclinical stages of disease.

Background:

In addition to their central role in cellular bioenergetics, mitochondria also play a major role in apoptosis, control of cytosolic calcium concentrations, and metabolic cell signaling. Through normal energy production by oxidative phosphorylation and ATP generation via the electron transport chain, mitochondria proteins and mtDNA are vulnerable to damage from reactive oxygen species (ROS). Mitochondria are also susceptible to damage from over 60 natural and synthetic compounds that exert their toxicity by affecting the integrity of mtDNA, inhibiting complexes in the electron transport chain, altering membrane potential, affecting calcium homeostasis, and by modulating induction of apoptosis. Mitochondrial dysfunction is associated with numerous chronic diseases, and may reflect, in part, the vulnerability of mitochondria to environmental influences. For example, the organic pesticide rotenone is a potent Complex I inhibitor, exhibits selective toxicity for dopaminergic neurons, and is associated in human studies with increased risk of Parkinson's disease (PD).

The identification of mitochondrial impairment in clinical settings is challenging. Acute exposure to mitochondrial toxicants causes short-term and nonspecific clinical symptoms that include muscle weakness, fatigue, hypotension and shortness of breath. Current clinical markers used to identify mitochondrial dysfunction in diseases include measurement of serum lactate, histological and genetic markers from muscle biopsies, and imaging (including

magnetic resonance spectroscopy brain imaging of lactate accumulations). These markers are typically detected in patients with advanced symptoms of mitochondrial dysfunction. Such markers have limited application to large-scale population studies to detect mitochondrial dysfunction at a stage where intervention is possible. There is therefore an urgent need for reliable, informative markers of early mitochondrial dysfunction associated with environmental stressors. For application to large-scale population studies, biomarkers of mitochondrial dysfunction will need to be developed in easily accessible tissues, including blood, buccal mucosa, and urine. However, mitochondrial biology varies between tissues and at different stages of development. Before development of biomarkers for human studies, a number of research questions need to be addressed including: Why are some tissues or cell types more susceptible to mitochondrial dysfunction from environmental exposures or genetic mutations? Why do certain mitochondrial diseases show such tissue specificity? Are there less severe systemic effects that are detectable in surrogate tissue? How do protein, metabolite or other biochemical markers differ by cell type?

DERT sponsored a workshop on June 25, 2009 in conjunction with the United Mitochondrial Disease Foundation annual meeting held in Tyson's Corner, Virginia to explore the state of the science and technology with experts in the field of mitochondrial physiology and function with the goal of developing recommendations on how to advance the field by developing improved biomarkers of mitochondrial dysfunction related to genetics and environmental exposures. Workshop participants recommended support for the development of new and improved animal models and other experimental models to better understand tissue-specific effects of mitochondrial toxicants and develop assays in less-invasive biospecimens that reflect mitochondrial alterations in target tissues. The overall goal of such research efforts in experimental models would be to identify promising approaches and candidate markers that can subsequently be developed for use in human population studies.

Objectives:

The goal of this program is to develop animal models and other experimental models that can 1) help to identify environmental stressors that inhibit normal mitochondrial function through a number of possible mechanisms, 2) improve our understanding of the tissue-specific effects of mitochondrial toxicants, 3) provide a more comprehensive understanding of the role of genetics and environment on mitochondrial dysfunction through the use of transgenic and "trans-mitochondrial" models, 4) help to set standards for analysis of mitochondrial endpoints to determine the best or most widely accepted endpoints that signal mitochondrial dysfunction, and 5) develop approaches and candidate markers that will serve as the basis for developing early biomarkers of mitochondrial dysfunction in human population studies linking exposure to disease. Approaches can include, but are not limited to:

- Developing gene expression, protein, metabolomic or biochemical signatures of mitochondrial dysfunction that are detectable in both target and surrogate tissues
- Improving methods for detecting mtDNA mutations and rearrangements induced by environmental stressors
- Enhancing imaging methods for tissue-specific effects of mitochondrial defects
- Developing novel markers of mitochondrial defects (e.g., autophagy, fission/fusion, changes in mitochondrial motility, or markers of mitochondrial biogenesis).

- Using transgenic or transmitochondrial approaches to simulate effects of aging or chronic oxidative stress together with the effects from mitochondrial toxicants

Anticipated outcomes of this program will be the identification of a set of tools and biomarkers that can be further developed and adapted to large-scale human population studies.

Program Management, Implementation, and Budget:

NIEHS intends to contribute up to $2.5M to this program to support 6-8 R01 projects. Other participating NIH Institutes may include NIDDK and NIA.