***In Vivo* Effects of Low Dose γ- Rays on Mitochondrial Function**

Min Li[1], Sonia M. de Toledo[1], Debkumar Pain[2,] and Edouard I. Azzam[1]

Departments of [1]Radiology and [2]Pharmacology and Physiology, New Jersey Medical School Cancer Center, Newark, NJ

Mitochondria consume about 90% of the body's oxygen and are the richest source of reactive oxygen species (ROS). They play an integral part in signaling events that occur in response to oxidizing agents, including ionizing radiation. To gain insight into radiation-induced effects on mitochondria, we investigated the *in vivo* effects of low dose γ-rays on mitochondrial protein import, aconitase activity and modulation of antioxidants in tissues of whole body-irradiated mice. Mitochondrial protein import is a fundamental mechanism of mitochondrial biogenesis, and the TCA cycle in the mitochondrial matrix is a central pathway of oxidative metabolism. Mitochondrial aconitase (ACO2), one of the eight enzymes that participate in the TCA cycle, is highly vulnerable to oxidative stress. Furthermore, antioxidants are essential for the homeostatic control of ROS.

Our data consistently indicated that *in vivo* mitochondrial protein import is highly sensitive to ionizing radiation. Exposure to acute γ-ray doses as low as 1cGy decreased protein import in mitochondria isolated from cells of liver, spleen and heart of C3H/HeJ or C57BL/6 mice. Protein import decreased as a function of time during the first 48h after exposure and began to recover around 120h. The magnitude of the decrease was tissue specific and the recovery was associated with increased level of Tom20, a 20 kDa translocase of outer mitochondrial membranes. A similar trend of decrease and recovery in the activity of aconitase was observed. These effects occurred in conjunction with increasing activity of the antioxidant enzyme Mn-superoxide dismutase (Mn-SOD) and a decrease in protein oxidation.

The above changes in mitochondrial function occurred in normal cells, but not in genomically unstable cells, which suggests that the observed decreases in mitochondrial functions may be part of the protective responses of healthy/normal organisms to mitigate radiation-induced oxidative stress. Mitochondrial protein import, aconitase activity and SOD activity are likely to serve as sensitive markers to examine radiation effects.

Supported by Grant DE-FG02-07ER64344 from the U.S. Department of Energy, Low Dose Radiation Research Program