PARTICLE RADIATION-INDUCED DYSREGULATION OF PROTEIN HOMEOSTASIS IN THE BRAIN

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Protein modification by ubiquitin is a highly regulated post-translational modification process that is catalyzed by a series of three enzyme families known as E1, E2, and E3, which are capable of modifying the correct protein in the correct cellular location at the correct time in order to control important processes such as the maintenance of genomic stability, removal of damaged or misfolded proteins, autophagy, apoptosis and gene transcription. Impaired or dysregulation of the function of ubiquitin-proteasome system is implicated in normal aging process and also in several age-related neurodegenerative disorders that are characterized by increased accumulation of oxidatively modified proteins and protein aggregates. High-energy particle radiation is known to produce rapid and sustained increases in reactive oxygen species that can lead to a variety of cellular damage in different tissues.

In a new project to be initiated in May 2014, we hypothesize that when neuronal cells/tissues are exposed to particle radiation, abnormal and persistent changes in cellular ubiquitin pools occur both in the short term, as part of damage repair processes, in response to oxidative stress mediated by the Nrf2 pathway, and in the long term when irreparable damage is present in neuronal tissues. The identification of the ubiquitin-modified proteins and the exact sites at which the target proteins are modified is predictive of an increased risk of specific adverse health consequences. Depending on the radiation dose and beam quality, particle radiation may cause significant damage to proteins in neuronal cells and as well as supportive cells that constitute the tissue environment, such as vascular endothelial cells. These changes, which can produce alterations in protein homeostasis, apoptosis, cell proliferation, secretion, and cell surface receptor expression, may be of fundamental importance in causing the physiological damage leading to CNS pathology. Using the methodology that we have developed previously for in-depth analysis of ubiquitin-related pathways and networks employing liquid-chromatography coupled to a hybrid, high resolution linear ion-trap/Orbitrap tandem mass spectrometry (LC-MS/MS) system, we aim to assess particle-radiation induced cellular protein turnover to uncover alterations in pathway-specific cellular ubiquitin pools and protein modification *in vitro* using cultured primary neuronal stem cells and in vivo using brain tissues from normal mice and Alzheimer Disease (AD) transgenic mice to establish mechanisms associated with particle-radiation induced development and progression of age-related neurodegeneration.