Mitochondrial Protein Influx in Low-dose Radiation-mediated Radioprotection

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Low dose radiation (LDR) is well-defined to induce an adaptive response in a wide range of species including human. This research program aims to define a unique mechanism by which mammalian cells develop an adaptive radioprotection via activation of the prosurvival network of factor NF-kappa B (NF-κB). We have reported that blocking NF-κB activation is able to inhibit 10cGy x-ray- induced advantage of clonogenic survival in mouse and human skin cells irradiated with 5 Gy γ-ray. Further study reveals several up-stream factors responsible for NF-κB activation including ATM, HER-2 receptor and ERK. Our present study aims to define specific down-stream NF-κB effectors in LDR-adaptive radioprotection, e.g., mitochondrial antioxidant MnSOD, chaperon proteins (14-3-3s) and cell cycle elements (cyclin B1 and cyclin D1, illustrated in the Figure). Using mouse and human skin cells and whole-body irradiated mouse skin tissues, we aim to provide essential evidence to support that regulation of mitochondrial function by NF-κB target genes plays a key role in LDR-adaptive radioprotection. Adaptive radioprotection (clonogenic survival, mitochondrial membrane potential, apoptosis, etc) are investigated in mouse skin JB6P+ and human skin HK18 keratinocytes after radiation with 10cGy x-ray/5Gy γ-ray. Dynamic alterations NF-κB subunits, MnSOD, 14-3-3s (Sigma and Zeta) and cyclins (B1 and D1) are determined in isolated mitochondria and correlated with inhibition of apoptotic elements (cytochrome c, caspase 3, caspase 9) and enhanced mitochondrial translocation of MnSOD, 14-3-3s and cyclins. We have collected mitochondrial samples from JB6 and HK18 cells and western blot and mitochondrial function analysis are underway. We are planning to study animal tissue sections with low and/or high dose radiation via collaboration with Dr. Gayle Woloschak (NWU) and Dr. Dave Grdina (U Chicago). Identification of mitochondrial protein influx may generate new effective compounds to reduce radiation injury (supported by DE-SC0001271, JJL).