

Lens Epithelium and Proton-Induced Cataractogenesis

Radiation induced cataract is one potential late effect from exposure in space flight to charged particles, the most prevalent of which are protons. The aim of the proposed research is to elucidate further the underlying molecular basis for proton induced radiation cataractogenesis, and to develop strategies to diminish the incidence or severity of these changes. We have developed and characterized an *in-vitro* model of differentiating human lens epithelial (HLE) cells grown on extra cellular matrix (ECM) derived from bovine corneal endothelial cells. The HLE cells undergo fiber cell differentiation as proven by the expression of molecular markers, including lens-specific γ -crystallin, and the cyclin-dependent kinase inhibitor (CKI) p⁵⁷ KIP². Being involved in cell cycle control during development and terminal differentiation maps to a region implicated in human cancers and the Beckwith-Weidemann syndrome, in which there is an increased incidence of tumor and cataract formation. As we have novel evidence for the enhanced expression of basic fibroblast growth factor (FGF-2) by X-rays and accelerated protons in differentiating HLE cells we are now proposing to delineate the specific molecular role(s) of FGF-2. In proliferating HLE cells we will test the hypothesis that upregulation of FGF-2 is an early proton-induced event promoting a specific G1/S cell cycle delay that interferes with radiation-induced apoptosis. In non-proliferating human lens fiber (HLF) cells we hypothesize that radiation-induced FGF-2 expression alters normal enucleation and crystallin protein expression due to misregulation of cell adhesion molecules (CAMs). We will determine the dose-dependent expression of BAX/p⁵³/p^{RB} mediated nuclear signaling and membrane production of ceramide, cell cycle delay and apoptotic index with and without FGF-2 neutralizing antibody. We will measure dose-dependent enucleation, alterations in β 1-integrin and ICAM-1 and changes in differentiation as indicated by protein makers.