Low-Dose Radiation Cataract and Genetic Determinants of Radiosensitivity

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The lens of the eye is one of the most radiosensitive tissues in the body. Ocular ionizing radiation exposure results in characteristic, dose related, progressive lens changes leading to cataract formation. While initial, early stages of such opacification may not cause visual disability, the severity of such changes progressively increases with dose until vision is impaired and cataract extraction surgery may be required. The latency of such changes is inversely related to dose.

Within the past few months, both the ICRP and the NCRP have released new guidelines and recommendations concerning ocular ionizing radiation exposure. ICRP significantly lowered the presumptive threshold for radiation cataract to 0.5 Gy, regardless of whether exposure was acute, protracted or chronic. Similarly, the occupational lens exposure limit was lowered, from 150 mSv/yr to an average of 20 mSv/yr over 5 years, with no single year exceeding 50 mSv. These new recommendations are likely to have significant implications for occupational exposure and the need for eye protection, for example in fields such as interventional cardiology.

Nevertheless, despite recent human epidemiological findings concerning human radiation cataract risk, considerable uncertainties remain concerning the relationship between cataract development, threshold dose and the role of genetics in determining radiosensitivity.

Our research utilizes radiation cataract as a model system to study the effects of low-dose ionizing radiation exposure in a complex, highly differentiated tissue. We believe radiation cataract is a useful model to determine the genetic and individual basis for risk from ionizing radiation with particular relevance to carcinogenesis and radiation induced DNA damage, repair and cell cycle control. These studies are also designed to help elucidate the mechanistic nature of radiation induced biological damage and determine the relative contribution of genetic defects affecting radiosensitivity. The unique morphology of the lens and the ease of non-invasive observation of its radiation response facilitate molecular and mechanistic investigations resulting in unrepaired or misrepaired DNA damage.

Our recent work has demonstrated dose-related significant lens opacification to as little as 100 mGy X-rays and preliminary data suggests that animals haploinsufficient for *Atm*, *p53* or both may have even lower threshold doses and that time of cataract onset and rate of progression is significantly altered. In addition, histological examination of micronuclei frequency in lens epithelium from these animals suggests more frequent occurrence of such clastogenic events. Additional work from the laboratory, examining the effect(s) of single or multiple haploinsufficiency for *Atm*, *Brca1, Rad9, PTEN* and *p21* suggest expression of these genes, which have important roles in recognizing and repairing radiation induced DNA damage, inducing cell cycle arrest and initiating apoptosis, are also related to onset, latency and progression of radiation cataract.

Such animal experimental work has broad implications for human exposure and risk assessment and suggests that individual human genetic differences in radiosensitivity might help explain the wide variation in reported time of cataract onset, degree of opacification and subsequent progression to visual disability among exposed populations. More importantly, these findings have important implications for both radiotherapy and occupational exposure in radiosensitive subsets of the human population. We hypothesize that cellular and molecular pathways of the biological response to ionizing radiation exposure in the lens has fundamental relevance and similarity to that in other tissues and that radiation cataract arises from damaged or misrepaired DNA and subsequent errors in cell cycle control, division and differentiation, similar to that observed in carcinogenesis.

This view is supported by the 2011 report from the ICRP which states *"The precise mechanism of radiation cataractogenesis is not known, but genomic damage resulting in altered cell division, transcription and/or abnormal lens fibre cell differentiation is considered to be the salient injury, … heterozygosity for genes involved in cell cycle checkpoint control, DNA damage recognition, or DNA repair might also contribute to this phenomenon"*.

Technical assistance and support from Drs. Adam Rusek and Peter Guida (BNL; NSRL & Medical Department) is gratefully acknowledged. This research is supported by the Department of Energy, Office of Science, Low Dose Radiation Research Program, DE-FG02-07ER64334 (NJK) and NASA grant, NNJ05HI38G (EJH).