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PI Name:	Hall, Eric J Ph.D., D.Sc.		
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PI Email:	ejh1@columbia.edu	**Fax:**	FY 212-305-3229
PI Organization Type:	UNIVERSITY	**Phone:**	212-305-5660
Organization Name:	Columbia University		
PI Address 1:	630 West 168th Street		
PI Address 2:	Center for Radiological Research		
PI Web Page:	http://cpmcnet.columbia.edu/		
City:	New York	**State:**	NY
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Contact Email:	noaccess@nasa.gov		
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Task Description:

Radiation exposure guidelines for space are different from those on earth. Exposures in space are potentially much higher than terrestrial irradiation due to galactic cosmic radiation, trapped radiation belts near the earth and solar particle events. Radiation exposures in space are relatively difficult to reduce and impossible to eliminate entirely. Other human health risks in this inherently hostile space environment may be more acute or drastic than those of radiation exposure. For these reasons, larger annual occupational dose limits have been permitted for astronauts than are recommended for earth-bound radiation workers (though career limits of risk have been roughly equalized). Nevertheless, earlier onset of cataract has been noted in the astronaut core and exposure to space radiation appears to be an important risk factor in its development.
It is clear that there is considerable heterogeneity in the human response to radiation, which is thought to be, in part, mediated by genetic differences in susceptibility. Nevertheless, a precise understanding of the relative role of individual genes thought to be important in mediating the cellular response to radiation exposure is lacking. This proposal hypothesizes that individuals who have defects in one or more genes governing recognition or repair of DNA damage or passage through the cell cycle may be at greater risk for radiation cataract development than normal individuals.

The hypothesis upon which this proposal is based is that heavy ions mediate their cataractogenic effect through errors in division and/or differentiation arising from radiation damage and subsequent misrepair of lens epithelial cells.

We investigated the mechanisms of cataractogenesis by looking at radiation cataract formation in animals haploinsufficient for one or more genes involved in DNA damage recognition and repair or cell cycle checkpoint control.

In particular, this project examined the influence of multiple haplo-insufficiencies in the development of high-LET radiation induced opacities in mice heterozygous for Atm, Mrad9 or Brca1. Cataract incidence and progression was quantified longitudinally and compared to that from similarly irradiated wild type animals. The findings from this work support the hypothesis of a genotoxic basis for radiation cataract and establish that combined haploinsufficiency for genes regulating the DNA damage/repair response can result in more profound severe radiation cataract effects than those observed in irradiated wild-type or singly heterozygous animals.

These studies provided an opportunity to study the influence and effects of genetic heterogeneity in an organized tissue, the lens, in a genetically defined mouse model that has great relevance and similarity to human response to radiation exposure and determination of appropriate human exposure guidelines. These findings have helped shed light on the genetic control and cellular mechanisms of heavy ion induced cataractogenesis and are likely to be important in determining future exposure guidelines for radiosensitive subsets of the human population, including the astronaut core.

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:

Radiation exposures in Space are relatively difficult to reduce, and impossible to eliminate entirely. At the same time, other risks to humans in the hostile environment in space may be more acute than those of radiation. For this reason, larger annual dose limits have been tolerated for astronauts than recommended by NCRP for radiation workers on the ground, though career limits of risk have been roughly equalized. The purpose of radiation protection is to prevent deterministic effects of clinical significance and to limit stochastic effects to levels that are acceptable modulated by societal concerns. The deterministic effect already observed in a proportion of astronauts is early onset of ocular cataracts. Previous NASA funded studies from our laboratory demonstrated that mice haplo- insufficient for ATM (that contain one good copy and one bad copy of the Atm gene and a correspondingly reduced amount of ATM protein) develop high-LET (heavy-ion) radiation induced cataracts earlier and with more severity than wild type animals. This leads to speculation that the unexpected observation of cataractogenesis in the astronaut core might be explained, in part, by individual genetic differences in radiosensitivity.
The research reported here seeks to expand the library of genes involved in DNA damage recognition and repair and/or cell cycle checkpoint control and also to investigate the possible relationship(s) between heterozygosity for one or more such genes and cataractogenesis.

Findings from these studies are likely to shed light on the genetic control and cellular mechanisms of both heavy ion and proton induced cataractogenesis. More importantly, using the lens and radiation cataract induction as a model system, these findings may have important implications for radiosensitive subsets of the human population, including the astronaut core, and aid in determining future national space radiation risk policies and in determination of appropriate radiation human exposure guidelines.

We further hypothesize that that as radiation cataract is thought to arise from damaged or misrepaired DNA and subsequent errors in cell cycle control, division and differentiation, the cellular and molecular pathways of the biological response to space radiation exposure in the lens has fundamental relevance and parallels to DNA damaging processes and pathologies in other cells and tissues, including carcinogenesis.

Task Progress:

Introduction.
Radiation exposures in Space are relatively difficult to reduce, and impossible to eliminate entirely. At the same time, other risks to humans in the hostile environment in space may be more acute than those of radiation. For this reason, larger annual dose limits have been tolerated for astronauts than recommended by NCRP for radiation workers on the ground, though career limits of risk have been roughly equalized. The purpose of radiation protection is to prevent deterministic effects of clinical significance and to limit stochastic effects to levels that are acceptable modulated by societal concerns. The deterministic effect already observed in a proportion of astronauts is an early onset of ocular cataracts. Previous NASA funded studies from our laboratory demonstrated that mice haplo- insufficient for Atm (that contain one good copy and one bad copy of the Atm gene and a correspondingly reduced amount of ATM protein) develop high-LET (heavy-ion) radiation induced cataracts earlier and with more severity than wild type animals. This leads to speculation that the unexpected observation of cataractogenesis in the astronaut core might be explained, in part, by individual genetic differences in radiosensitivity.

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Project Aims.

This proposal was based on the hypothesis that, following exposure to heavy ions, aberrantly dividing and/or differentiating cells in the pre-equatorial region of the lens epithelium migrate to the posterior pole of the lens where they become opaque lens fiber cells. The plan was to investigate mechanisms of cataractogenesis by observing opacities produced by x-rays or heavy ions in mice that were haplo-insufficient for one or more genes involved in DNA damage recognition and repair and/or cell cycle checkpoint functions. The genes chosen were Atm, Brca1 and Rad9, based on experiments with cells in-vitro which indicated that heterozygosity for these genes confers radiosensitivity. There are corresponding human homologues for these genes and mutations and/or polymorphisms have been identified in a few percent of the human population. Thus, heterozygosity for these or similar genes could account for the unexpected observation of earlier onset or faster progression of cataracts in some individuals in the astronaut core.

Results.

1. RBE Studies with wild type mice and animals haploinsufficient for ATM.

Early studies demonstrated that heavy ions are significantly more effective than X-rays in producing cataracts in ATM haploinsufficient mice (Hall, 2006). ATM haploinsufficiency results in an enhanced sensitivity to X-rays compared to wild type, and this enhancement appears even larger after exposure to high-LET heavy ions. The studies demonstrated that high LET particles are much more effective than low LET X-rays in induced cataractogenesis and that this likely accounts for the reported earlier onset and faster progression of cataracts in the astronaut core.

2. Cataractogenesis in animals singly or doubly heterozygous for Atm or Brca1 exposed to x-rays or heavy ions at the NSRL in Brookhaven National Laboratory.

Mice irradiated with x-rays were utilized to examine the effect of single or dual heterozygosity for Atm and Brca1 on radiation cataract development. When average cataract stage was compared in each of the four genotypes in both irradiated and unirradiated animals, cataracts developed earlier in Atm+/- and Brca1+/- single heterozygotes than wild-type controls. However, Atm/Brca1 double heterozygotes did not exhibit faster onset of or more rapid progression of cataractogenesis as compared to the singly heterozygous animals. As compared to wildtype animals, all haploinsufficient genotypes exhibited faster onset of radiation-induced lens changes, even in unirradiated eyes. As Brca1 is known to exhibit some gender specificity, we also examined the the effect of gender on radiation cataract onset or progression. Single or doubly haploinsufficient female Brca1 mice were not any more radiosensitive to irradiation than their corresponding male counterparts. These results indicate heterozygosity for either Brca1 or Atm confers cataract radiosensitivity but that the effect of dual haploinsufficiency is not greater than that of each gene alone and for the radiation cataract endpoint, the effect of gender, and presumably sex hormonal influence, is minimal.

In a similar fashion, single and double heterozygous Atm and Brca1 mice were exposed to 50 mGy 56Fe at the Brookhaven National Laboratory NRSL facility and observed for cataract development. In contrast to the findings after low-LET x-ray exposure, double heterozygous Atm/Brca1 animals are significantly more sensitive to heavy ion induced cataractogenesis than each of the two single heterozygotes, which, in turn, are more sensitive than wild-type controls. It can also be noted that ATM haploinsufficiency has considerable effect on lens opacification even in unirradiated animals, while BRCA1appears to be of less importance in unexposed mice. It is interesting to note that animals heterozygous for Atm develop cataracts about 20 weeks earlier than wild-type animals, even at this very low dose. By contrast, heterozygosity for Brca1 appears to have little effect on cataract onset.

3. Animals singly or doubly heterozygous for Atm and Rad9

It is well established that Atm and Rad9 regulate multiple cellular responses to DNA damage, including cell cycle checkpoints, DNA repair and apoptosis. However, the impact of dual heterozygosity for Atm and Rad9 on radiation cataractogenesis in the intact animal was, until recently, unknown. To address this question, we examined whether mice haploinsufficient for the combination of both these genes might be more susceptible to the cataractogenic effects of ionizing radiation than wild type animals or those haploinsufficient for only one of these genes.

The results established that Atm+/- or Mrad9+/- animals develop spontaneous as well as radiation-induced cataracts with earlier onset and more severity than wild-type controls, which lends considerable support for the concept that radiation cataract requires misrepaired DNA damage and given the roles of Atm and mRad9 in maintaining genomic stability, are consistent with a genotoxic basis for radiation cataractogenesis. Cataracts developed earlier in X-irradiated double heterozygotes than in single heterozygotes, which were more prone to cataractogenesis than wild-type controls. Cataract onset time and progression in single or double heterozygotes were accelerated even in unirradiated eyes. These findings indicate that the cataractogenic effect of combined heterozygosity is greater than for each gene alone and the study is among the first to demonstrate radiation effects of multiple haploinsufficiency in an intact mammal. Such observations are directly relevant to explanations of observed inter-individual differential radiosensitivity in human populations and have important implications for those undergoing radiotherapy or exposed to elevated levels of cosmic radiation, such as the astronaut core.

Summary and Conclusions.

It is notable that the findings from these studies demonstrate, for the first time, the ability of two different heterozygous gene mutations to interact in a manner that increases the frequency of a radiation response. This radiation cataract model is the first higher level organ system in which it is demonstrated that heterozygosity alters the late response of a normal tissue to radiation exposure.

Three genes involved in checkpoint control and/or DNA damage recognition and repair, Atm, Brca1 and mRad9, have been examined to date. Our findings have established that single haploinsufficiency for ATM, mRAD9 or BRCA1 decreases the time of onset for cataract development following irradiation with either x-rays or heavy ions. Furthermore, combined haploinsufficiency, with either Atm/ Rad9 or Atm/Brca1, increases susceptibility for radiation induced cataract formation further still. Quantitative values for the relative biological effectiveness (RBE) of high energy 56Fe ions compared with X-rays, both for wild type and for Atm+/-mice, were determined with a clear trend toward higher RBE's in haplo-insufficient animals.

Corresponding human homologues for these genes and mutations and/or polymorphisms have been identified in a few percent of the human population. This amounts to a small but significant radiosensitive sub-population. This has wide societal implications and in the context of NASA may account for the unexpected observation of early onset of cataracts in astronauts who have flown in space.

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