DOE Final Report

Title: Individual Genetic Susceptibility
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We have finalized the study of radiation induced oncogenic transformation, apoptosis and ocular cataracts in mice haplo-insufficient for one or more genes involved in DNA repair. Several papers have already been published and two more have been submitted as detailed in the attached list.

Oncogenic Transformation and Apoptosis

Apoptosis experiments were repeated using thymocytes from animals irradiated in vivo, rather then the in vitro assay which was found to be unreliable. Haplo-insufficiency of Atm, BRCA1 or mRad 9 resulted in an increase in the incidence of radiation induced oncogenic transformation in mouse embryo fibroblasts and a corresponding decrease in the proportion of thymocytes dying an apoptotic death, compared with cells from wild-type animals. Haplo-insufficiency for two genes either Atm/mRad 9 or Atm/BRCA1, resulted in an even larger effect on apoptosis, transformation and micronuclei formation. The conclusions are that, under stress conditions, the efficiency and capability for DNA repair mediated by either cell signaling network depends on the expression levels of both proteins.

Ocular Cataracts

Using X-rays as an environmental insult and cataractogenesis as an endpoint, this study examined the effect of heterozygosity in mice. In addition, double heterozygotes were studied namely Atm/mRad9 and Atm/BRCA1. Posterior subcapsular cataracts, characteristic of radiation exposure, 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. This is the first demonstration of the effects of multiple haplo-insufficiency in an intact mammal.

Significance

Current radiation protection guidelines assume that the human population is homogeneous in radiosensitivity, with the exception of a minority of individuals, such as AT homozygotes, who are hypersensitive but easily recognized by their clinical symptoms. Our research has shown that haplo-insuficiency for several rare, high penetrant genes confers a measure of radiosensitivity in animals while not resulting in any health detriment that can be easily recognized. Individuals who are haplo-insufficient for the three genes studied to date, (Atm, BRCA1, and Rad 9) already comprise a small, but significant, sub-population that are abnormally radiosensitive, and there may well be other genes not yet identified in the human population. In the past year or so, two clear instances from human epidemiological studies, have emerged where a radiosensitive sub-population has been detected. One involves the clustering of meningiomas in certain families that were epilated with x-rays in the course of the treatment of Tinea Capitis. The other involves a study of breast cancer in young people monitored by frequent diagnostic x-rays in the management of scoliosis. In this case, the dose-response was significantly greater for women who reported a family history of breast cancer in first or second degree relatives. While in each of these instances there is clear evidence of a radiosensitive sub-group, the gene(s) involved have not been identified, though there are obvious suspects. The genes we have identified in mice might be the ones involved in the human epidemiology studies.

At the very least, a radiosensitive sub-group would distort the shaped of the dose-response relationship for carcinogenesis, tending to make it non-linear and concave downwards. Another implication of a radiosensitive sub-population is that it would be unethical to choose such individuals for tasks involving the risk of exposure to substantial does of radiation.

Hall, E.J. *Intensity-modulated radiation therapy, protons, and the risk of second cancers.* Int, J. Radiation Biol. Phys. 65:1-7, 2006

Hall, E.J., Worgul, B.V., Smilenov, L.B., Elliston, C.D. and Brenner, D.J. *The relative biological effectiveness of densely ionizing heavy-ion radiation for inducing ocular cataracts in wild type versus mice heterozygous for the ATM gene.* Radiat. Environ. Biophys. 45:99-104, 2006

Travis, L.B., Rabkin, C.S., Brown, L.M., Allan, J.M., Alter, B.P., Ambrosone, C.B., Begg, C.B., Caporaso, N., Chanck, S., DeMichele, A., Figg, W.D., Gospodarowicz, M.K., Hall, E.J., Hisada, M., Inskip, P., Kleinerman, R., Little, J.B., Malkin, D., Ng, A.K., Offit, K., Pui, C.H., Robison, L.L, Rothman, N., Shields, P.G., Strong, L., Taniguchi, T., Tucher, M.A., Greene, M.H. *Cancer survivorship-genetic susceptibility and second primary cancers: research strategies and recommendation.* Review J.Natl Cancer Inst. 98: 15-25, 2006.

Hall, E.J. *The Inaugural Frank Ellis Lecture: Iatrogenic Cancer: the impact of IMRT.* Clinical Oncology, 18:277-282, 2006.

Smilenov, L.B., Hall, E.J., Bonner, W.M. and Sedelnikova, O.A.. *A microbeam study of DNA double-strand breaks in bystander primary human fibroblasts.* Radiat. Prot. Dos., 1-4, 2006.

Hall, E.J. Editorial. *Antiprotons for Radiotherapy?* Radiotherapy and Oncology, 81: 231-232, 2006.

Hall, E.J. *Cancer cause by X-rays-a random event?* Lancet Oncology. (In press).

Brenner, D.J., and Hall E.J. *Computed Tomography: An increasing source of Radiation Exposure.* New England Journal of Medicine, 357, 2277-2284, 2007.

Smilenov, L.B., Zhan, G., Mitchele, S.A., Ludwig, T. and Hall, E.J. *Heterozygosity for Atm and BRCA1 influence, the balance between cell transformation and apoptosis* (submitted).

Kleiman, N.J., David, J., Elliston, C.D., Hopkins, K.M., Smilenov, L.B., Brenner, D. J., Worgul, B.V., Hall, E.J.and Lieberman, H.B., *Mrad9 and Atm Haploinsufficiency Enhance Spontaneous and X-ray-Induced Cataractogenesis in Mice.* Radiation Research, 168, 567-573, 2007.

Hall, E.J. and Brenner, D.J. *Cancer risks from diagnostic radiology.* Br. J. Radiol, 81: 362-378, 2008.

Smilenov, L.B., Zhou, G., Mitchell, S.A., Ludwig, T., and Hall, E.J., *Heterozygosity for Atm and Brca1 influence the balance between cell transformation and apoptosis.* (submitted)

Zhou, G., Smilenov, L.B., Lieberman, H.B. and Hall, E.J. *Radiosensitivity to high energy iron ions is influenced by heterozygosity for Atm, Rad9 and Brca1*. (submitted)