
Sensitivity to Radiation-Induced Cancer in Hemochromatosis

Project ID: 69939

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Research Objectives

The objectives of this pilot project using HFE-knockout homozygotes and heterozygotes are to: 1) determine whether the knock-out mice have greater sensitivity to radiation-induced cancer of the colon, liver, and breast, 2) establish the dependence of this sensitivity on accumulation of iron, 3) determine the extent to which cell replication and apoptosis occur in these target tissues with varying iron load, and 4) correlate the increases in sensitivity with changes in insulin-related signaling in tumors and normal tissue from each target organ.

Three experimental designs will be utilized in the pilot project. The sequence of experiments is designed to first explore the influence of iron load on the response and demonstrate that HFE knockout mice are more sensitive than the wild-type to radiation-induced cancer in one or more of three target tissues (liver, colon and breast). The dose-response relationships with a broader set of radiation doses will be explored in the second experiment. The final experiment is designed to explore the extent to which heterozygotes display the increased susceptibility to cancer induction and to independently assess the importance of iron load to the initiation vs. promotion of tumors.

Research Progress and Implications

Breeding pairs of HFE-knockout mice were obtained for establishing a breeding colony of HFE mice in our laboratory. A colony has now been established with sufficient numbers of mice available to support the experimental design of this project. In addition, wild-type mice (C57BL/6J) have been obtained to serve as controls for the studies. For the first experiment, thirty HFE-knockout and 30 wild-type breeding pairs were started on a low iron diet (30 mg/kg) on the first day of mating. Sufficient offspring from these matings have resulted to begin the first experiment. Groups of 20 mice (bred and raised on the low iron diet) will be fed purified iron diets as follows: 30, 300, 3000 mg/kg iron for the HFE mice and 30, 300, 3000, and 20000 mg/kg iron for the C57BL/6J wild-type mice. These mice will be irradiated (1 Gy Cobalt-60) at about 30 days of age. Two additional groups of nonirradiated mice (one HFE and one wild type) will be fed the 30 mg/kg diet and utilized as controls.

Planned Activities

If this pilot project is successful in demonstrating substantive differences in sensitivity in one or more of these organs, a larger effort will be proposed that focuses on low dose and dose rate effects of radiation with the intent of identifying non-linearity and/or thresholds in the dose-response relationships. This follow-on study would concentrate on understanding the molecular basis of interactions between this HH and radiation exposure. The additional work would allow calculation of the excess risk that would be associated with low doses of radiation in the human population under EPA's draft Cancer Risk Assessment Guidelines. More important, it should provide tools that can be applied to studying this relatively large segment of population that could have enhanced sensitivity to radiation with a focused effort in molecular epidemiology.