An integrated genetics approach to systemic low-dose radiation responses

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Goal: Formation of tumors is controlled by a multiplicity of genetic and microenvironmental factors (e.g. epithelial/stromal interactions), most of which remain unknown. One of the goals of Project 2 within Lawrence Berkeley National Laboratory's Low Dose SFA is to identify the combinations of genes and their functional polymorphisms that affect the susceptibility or resistance of individuals to effects of ionizing radiation. Identification of these genes will provide invaluable information, not only on biological pathways regulating whether or not low doses of radiation may cause tumor development, but also on potential mechanisms of tumor prevention.

Background and significance: The detection and characterization of multiple low penetrance genetic variants that control complex diseases are major challenges for biological research. Moreover, progress is hampered by formidable technical and conceptual difficulties. Due to the ability to control both the genetic and environmental components of risk, mouse models offer many advantages for the study of the genetic basis contributing to disease states, such as radiation-induced cancers. Utilizing mouse strains that differ in their susceptibility or resistance to cancer development will enable us to identify genes involved in low dose radiation induced damage that could potentially lead to tumor formation and cancer. Identification of human homologues of these predisposition genes and discovery of their roles in carcinogenesis will ultimately be important for the development of methods for prediction of risk and for the prevention of human cancers. Accordingly, these studies are also being extended to human cells in three dimensional culture models, which can serve as surrogates for human susceptibility.

Approach: We are using a systems genetics approach that exploits the genetic and phenotypic diversity in mouse inter-species crosses to examine the biological consequences of low-dose radiation. While the BABLB/c strain is susceptible to tumor formation, the Spret/EiJ strain has been shown to be resistant to the formation of tumors, as well as development of radiation induced lymphoma (1, 2). We have developed a breeding program that crosses the F1 generation of these two parental strains back to BALB/c females to generate an F2 generation (F1Bx) that is predicted to be genetically diverse with respect to resistance or susceptibility to tumors and radiation induced cancers. To initially characterize this mouse model, data have been collected as a function of time from blood samples of mice that have been exposed to 10cGy in order to characterize changes in metabolites and cytokines. Our results indicate that there are dramatic strain-dependent variations in serum metabolomic and cytokine profiles in response to low-doses of radiation, suggesting that genetics is a major driving force determining the radiation response in vivo. In other studies, we are investigating the potential of radiation induced mammary tumor

formation by combining our genetic diverse mouse model with the mammary gland radiation chimera model pioneered in the Barcellos-Hoff laboratory (3,4). As it takes time for the tumors to develop in this model, mammary organoid three dimensional culture assays of morphogenesis are being used as surrogates to more rapidly investigate the responses of the stromal and epithelial components to low doses of radiation.

Conclusion and Future Plans: This is an ambitious project that integrates results from many kinds of biological parameters to generate informational data-base networks that underlie responses to low doses of radiation. We plan to correlate the biological responses (including changes in metabolism, cytokine levels, and morphogenic programs observed in 3D culture models as well as the potential for tumor progression) with genetic information obtained from gene expression arrays, sequencing and SNP analysis to understand genetic controls behind the low-dose radiation response. Together this comprehensive systems biology approach will identify specific genes or pathways that are differentially controlled between mouse strains that can be extrapolated to humans in order to understand susceptibility or resistance to low doses of radiation or carcinogenesis.

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