NSCOR The contribution of non-targeted effects in HZE cancer risk

M. H. Barcellos-Hoff[2], A. Balmain[1], S.V. Costes[3], S. Demaria [2], J. H. Mao[3],

[1] Helen Diller Comprehensive Cancer Center, University of California, San Francisco School of Medicine, Box 0128, San Francisco, CA 94143-0128, USA.

[2] Department of Radiation Oncology, New York University School of Medicine, 566 First Avenue, New York, NY 10016, USA.

[3] Department of Cancer and DNA Damage Response, Lawrence Berkeley National Laboratory, 1 Cyclotron Road, MS977, Berkeley, CA 94720, USA.

This multi-institutional NSCOR focuses on experimental and modeling studies to define the efficiency and physiological context in which high LET radiation increases epithelial cancer risk. Our experimental data and that of others suggest that radiation carcinogenesis is a two-compartment problem: ionizing radiation can alter genomic sequence as a result of damage due to targeted effects from the interaction of energy and DNA, and alter phenotype and multicellular interactions that contribute to cancer by poorly understood non-targeted effects (NTE). Rather than being accessory or secondary to DNA damage and mutations that can initiate cancer, we hypothesize that radiation NTE create the critical context to promote cancer. We hypothesize that both targeted and non targeted effects (NTE) contribute to radiation carcinogenesis. Targeted effects of ionizing radiation result from interaction of energy with DNA, leading to DNA damage response and changes in genomic sequence. On the other hand, poorly understood NTE alter phenotype and multicellular interactions that could contribute to cancer. Our ongoing studies are focused on three approaches: evaluating the contribution of NTE in mammary carcinogenesis (Project 1, NYU), systems genetics of radiation carcinogenesis (Project 2, UCSF), and modeling radiation effects (Project 3, LBNL), all of which are supported by a bioinformatics team.

Project 1 has completed two mammary carcinogenesis studies in which mice were exposed to different fluences of 350 MeV/amu Si or 600 MeV/amu Fe particles prior to transplantation with a mammary epithelium oncogenically primed by deletion of *Trp53*. Histologically and molecularly diverse carcinomas spontaneously arose over the course of 16 months in this radiation chimera model (see Illa-Bochaca et al. poster). We found that tumor latency was decreased when the host was irradiated with 30 cGy Fe and 80 cGy Si particles but not by 10 or 30 cGy Si or 80 cGy Fe, indicating that NTE are not proportional dose. Tumor expression profiling shows that Si particle irradiation of hosts induces a metaprofile within the subsequent tumor, even though host irradiation and tumor development are more than 6 months apart. Pathway analysis of expression profiles from irradiated tissues and tumors suggest that inflammation, stem cell regulation, metabolism and cell growth regulation are important NTE processes.

The use of systems genetics enable the identification of genes and pathways associated with susceptibility to radiation-induced cancer. Project 2 uses various mouse models in which p53 activity is affected. Germline deletion of a small N-terminal proline-rich region of p53 in an *in vivo* mouse model (ΔP) causes no spontaneous tumors. However, upon exposure of the ΔP mouse to either low or high LET radiation, a wide range of solid tissue tumors develops, including those of the skin, liver, lung and kidney (see Adams et al. poster). This striking increase in radiation-induced solid tumors, in the absence of confounding by spontaneous tumors as seen in the *Trp53* null mouse on the same genetic background, will facilitate comparative genetic analysis of epithelial tumors induced by either high or low LET radiation. In addition, the breeding of the p53ΔP and the corresponding null allele on to different mouse strain backgrounds will enable us to address the strain-dependence of these effects, as a means of identifying susceptibility factors for radiation tumorigenesis.

Stem and progenitor cells are thought to be important targets for cancer initiation by ionizing radiation (IR) because they have the greatest long-term proliferative potential and mutagenic events persist in multiple daughter cells. Current studies have identified enrichment of mammary stem cell signatures in Si particle irradiated mammary tissue and tumors arising in Si particle irradiated hosts, which motivated agent-based modeling in Project 3 to test the contribution of different mechanisms (see Tang et al. posters). The ABM modeling indicates that self-renewal induced by radiation can increase stem cell frequency, while radiation-induced cell death or senescence cannot. Studies in cultured cells show that this response is likely mediated by radiation-induced Notch and TGFβ.

Together, these NSCOR studies are generating a more complex view of radiation effects on carcinogenesis. Ongoing studies evaluate radiation quality dependence of NTE, with particular emphasis on regulation of tissue stem cells, inflammation and immune responses. Our integrated approach using complex mouse models, systems biology, and modeling will provide novel insights into the mechanisms by which radiation increases cancer.