FINAL TECHNICAL REPORT

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This past year we have made substantial progress in modeling the contribution of homeostatic regulation to low-dose radiation effects and carcinogenesis. We have worked to refine and apply our multistage carcinogenesis models to explicitly incorporate cell cycle states, simple and complex damage, checkpoint delay, slow and fast repair, differentiation, and apoptosis to study the effects of low-dose ionizing radiation in mouse intestinal crypts, as well as in other tissues. We have one paper accepted for publication in 'Advances in Space Research', and another manuscript in preparation describing this work. I also wrote a chapter describing our combined cell-cycle and multistage carcinogenesis model that will be published in a book on stochastic carcinogenesis models edited by Wei-Yuan Tan. In addition, we organized and held a workshop on 'Biologically Based Modeling of Human Health Effects of Low dose Ionizing Radiation', July 28-29, 2005 at Fred Hutchinson Cancer Research Center in Seattle, Washington. We had over 20 participants, including Mary Helen Barcellos-Hoff as keynote speaker, talks by most of the low-dose modelers in the DOE low-dose program, experimentalists including Les Redpath (and Mary Helen), Noelle Metting from DOE, and Tony Brooks.

It appears that homeostatic regulation may be central to understanding low-dose radiation phenomena. The primary effects of ionizing radiation (IR) are cell killing, delayed cell cycling, and induction of mutations. However, homeostatic regulation causes cells that are killed or damaged by IR to eventually be replaced. Cells with an initiating mutation may have a replacement advantage, leading to clonal expansion of these initiated cells. Thus we have focused particularly on modeling effects that disturb homeostatic regulation as early steps in the carcinogenic process.

There are two primary considerations that support our focus on homeostatic regulation. First, a number of epidemiologic studies using multistage carcinogenesis models that incorporate the 'initiation, promotion, and malignant conversion' paradigm of carcinogenesis are indicating that promotion of initiated cells is the most important cellular mechanism driving the shape of the age specific hazard for many types of cancer. Second, we have realized that many of the genes that are modified in early stages of the carcinogenic process contribute to one or more of four general cellular pathways that confer a promotional advantage to cells when these pathways are disrupted.

Four general cellular pathways that can increase the promotional advantage of cells are:
1.) Cell signaling pathways that cause diminished homeostatic control, including Wnt/APC/beta-catanin, TGF-beta, BMP, Notch, Par that lead to cancers such as colo-rectal, liver, breast, and other epithelial cancers;
2.) Sensing, repair of DNA damage pathways that cause continued cycling, and genetic instability, including Rad9/Rad1/Hus2, ATM, DNA-PK, ATR, BRCA1, Rad 51, Rad52 that lead to cancers such as colon, breast, gastric, and thyroid.
3.) Checkpoint control pathways with disruption causing reduced repair, faster cycling, instability, involving P21, P53, BRCA1, Rb/p16INK4a, Chk1, Chk2, ATM/ATR that lead to cancers such as non-small cell lung cancer, melanoma, ovarian, and prostate.
4.) Apoptosis pathways with reduced apoptosis causing a promotional advantage and more surviving mutations, involving Bcl-2, P53, PI3K/AKT/Survivin, and Ki67, as seen in leukemias, astrocytic, small cell lung, breast, and gastric cancers.

Disruption of any of these four general pathways can be modeled within the framework of our combined cell cycle and multistage carcinogenesis model.

We have initially applied the model to study mouse intestinal crypts because of their sensitive radiation response, and because of the ability to knockout specific genes regulating apoptosis, checkpoint control, and other cell cycle regulatory features.

In modeling the mouse intestinal crypts, we incorporate homeostatic regulation at the individual crypt level to maintain a target of approximately 16 stem cells per crypt. As this target number is approached, the model causes the rate of progression out of the G1 cell cycle state to diminish. Thus cells in G1 stage become blocked, effectively going into G0 state. The model incorporates differentiation out of G1 based on a circadian rhythm, with homeostatic regulation then leading to division of a few stem cells. The dividing cells are much more susceptible to radiation. Thus the model predicts a few (3-4) highly sensitive stem cells that apoptosis with low-dose IR, with the remaining stem cells in G0 highly resistant to radiation. These model results are in general agreement with experimental data.

If future funding becomes available, we plan to collaborate with Chris Kemp here at FHCRC, who is an expert in these mouse systems. In anticipation of this, we have worked with Chris on a preliminary analysis looking at changes in mitotic index as a function of IR dose for p27 +/+, +/-, and -/- mice to study the effects of disregulation of the G2/M checkpoint. The early results appear promising, but we need extended funding to pursue our preliminary findings.