Mechanisms of Low-Dose and Adaptive Responses in Radiation Sensitive Tissues

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The goals of this project are to understand the molecular mechanisms by which low-dose exposures may alter cancer processes in cancer target cells or their microenvironment (non-target cells), how low-dose damage responses may deviate from linearity, and the basis for variability in individual risks from low-dose exposure with emphasis on breast cancer. Our project has investigated the radiation regimen and genetic factors that lead to non-linearities in expression profiles, molecular pathways and networks of the cellular damage responses within irradiated tissues of mice. We have demonstrated that neighboring component cell types within the mammary gland can differ markedly in their molecular responses depending on the genetic background of the animal.

Our project is part of the LBNL SFA that supports a coordinated, systems biology approach to the elucidation of mechanisms by which complex systems respond to low-dose radiation and transduce that exposure into disease-linked damage in order to guide regulatory decision making. The LBNL SFA investigates the relative contributions of genetic and epigenetic factors in cellular and tissue damage processing in tissues that have been exposed to low and adapting exposure regimens. We have introduced a parallelogram system biology model for guiding the research toward estimating non-linearities of risk modification after low-dose and adaptive response exposures on human breast cancer by utilizing complementary human and mouse in vitro and in vivo model systems..

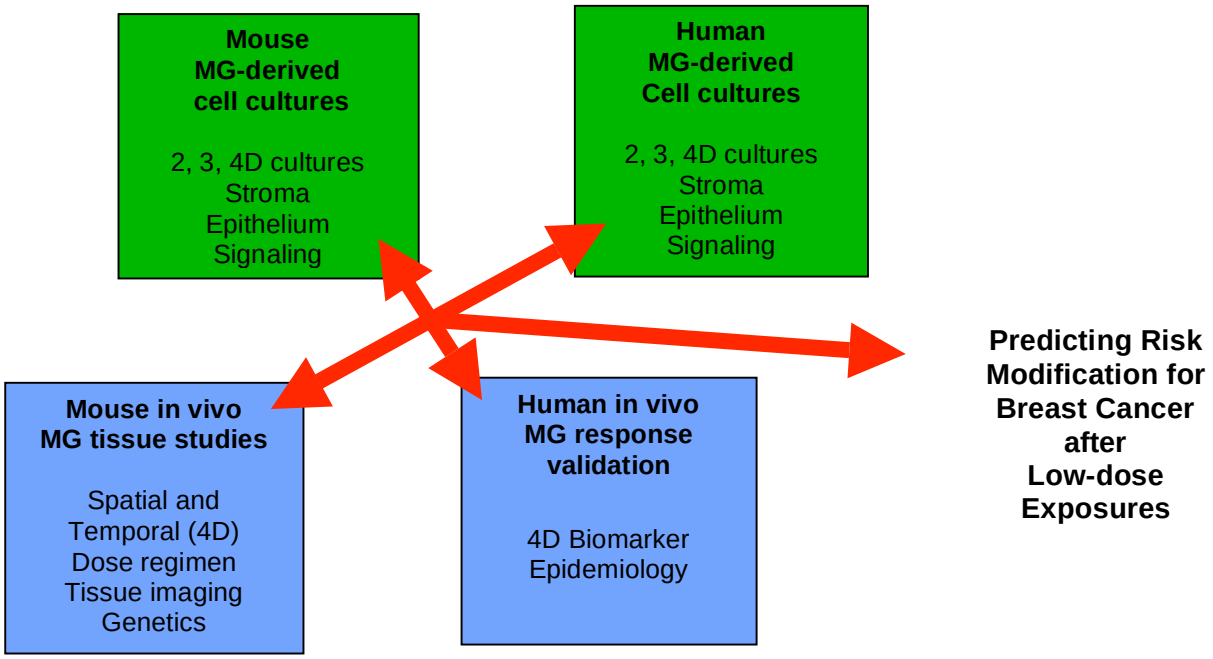

Figure. Integrated Spatial and Temporal System Biology Parallelogram approach to estimating low-dose risk modification from low dose and AR exposures

Our hypothesis is that the induction of damage response pathways after low dose and adaptive exposure regimens differ between stromal versus epithelial cells, and that there are genetically determined dose and dose-rate dependent barriers to pathway induction that are predictive of low dose non-linearities in mammary gland cancer risks among individuals.

The Adaptive Response (adaptation, or AR) to ionizing radiation is a well-documented but highly variable protective phenomenon in which cells or individuals exposed to low-dose or low-dose-rate ionizing radiation are transiently protected against a variety of effects from subsequent radiation exposures, including DNA and chromosomal damage, cell and tissue toxicity, and cancer. However, the molecular mechanism(s) remain unknown, and such information is essential for incorporating adaptive responses into estimation of risk from low dose exposures. Our project is designed to characterize the early temporal, spatial, and dose characteristics of early molecular signaling pathways and metabolic networks of the low-dose damage responses in mammary gland tissue, to compare the damage response mechanisms in epithelial versus stromal cells within the mammary gland, and to identify early molecular signatures that are predictive for enhanced resistance or sensitivity for radiation-induced breast cancer risk. Our project utilizes low-dose regimens that have been shown to modify risks for lymphoma and breast cancer in sensitive inbred strains of mice, and a multi-disciplinary system biology approach with advanced molecular and tissue technologies for assessing molecular damage signatures, cellular damage and differentiation defects in irradiated tissues, utilizing three inbred strains (BALB/c, C57BL/6 and Spretus SPRET/Ei) that differ in their susceptibilities for radiation-induced mammary gland cancer. These strains of mice include the parental lines used in the genetics backcross project of this SFA.

In prior studies with human cells in culture and with tissues of irradiated mice, we showed that exposures to single acute doses of low dose ionizing radiation (<10cGy) induced different expression profiles that suggest that low-dose exposure induce qualitatively and quantitatively different damage response mechanisms when compared with single high dose exposures. We recently extended this work to investigate expression profiles from tissues of mice exposed to a regimen of repeated low-dose exposures (4 weekly exposures to 7.5cGy) which has been reported to protect mice against radiation induced thymic lymphoma from higher doses (4 x 1.8Gy). Mammary gland tissues from irradiated female C57BL/6 mice and BALB/c were isolated at 4 or 10hrs and 1 month after exposure and analyzed for transcript and metabolomic profiles, development of the epithelial ducal tree, and for epithelial branching potential in culture.

We recently completed gene expression profiling in blood, lymph nodes, and mammary glands of young adult female BALB/c and C57BL/6 mice, and performed comparative pathway enrichment analyses of modulated genes. There were substantial strain differences in the signaling pathways after the adapting regimen. Cluster and pathway analyses suggest that the low-dose radiation response, at least for a number of genes, is highly dependent on exposure context and genetic background. Metabolomic profiling of mammary gland tissue isolated from both strains of mice is in progress. Also the effect of low dose radiation on mammary gland outgrowth in 3-D cultures is in progress. Our progress report will be presented at the workshop.

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