

# INTEGRATED EXPERIMENTAL AND COMPUTATIONAL STRATEGY TO DEVELOP A PREDICTIVE UNDERSTANDING OF RADIATION INDUCED MATRIX REMODELING IN A HUMAN SKIN TISSUE MODEL

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One of the early events following exposure to ionizing radiation is the activation of cell signaling pathways. These signaling pathways in turn elicit diverse proximal responses such as proliferation, apoptosis, activation of pro-survival programs and tissue remodeling. Radiation can in fact simultaneously activate several signaling pathways within cells leading to the induction of both protective effects as well as adverse consequences. However a key question is whether signaling cascades initiated by low doses are fundamentally different relative to high dose exposures. Understanding the link between radiation dose and dose rate to the pattern of cell signaling is an important prerequisite for developing a mechanistic understanding of radiation risk.

We are investigating the mechanisms whereby radiation stimulates signaling cascades in a skin tissue culture model. We are currently pursuing an integrated experimental and computational strategy to develop a predictive understanding of the link between cell signaling, gene expression and proximal tissue responses to low dose/low dose rate radiation exposures. We are quantitatively measuring variables that represent these processes and using the experimental data to construct a mathematical model of the relationships between the measured variables. The constructed model will provide us with a mechanistic understanding of the effect of low dose radiation exposure on tissue responses. Experiments are specifically designed to obtain information on how low dose/low dose rate exposures modify radiation induced signaling pathways important to maintaining tissue homeostasis.