Linear And Nonlinear Tissue Signaling Mechanisms In Response To Low Dose/Low Dose-Rate Ionizing Radiation

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Program Overview (highlighting relevance to the BER SFA and strategic goals).

A central challenge of the DOE Low Dose Radiation Program is to understand whether the biological pathways linked to health effects induced by high doses of radiation behave in a nonlinear or linear manner at low doses. The goal of the Pacific Northwest National Laboratory's (PNNL's) Low Dose Radiation research program is to use an integrated, systems-level approach to understand the fundamental signaling events mediated by low dose (LD) radiation, focusing on the tissue response rather than individual cells. Using a human skin tissue model system, we are addressing the hypothesis that the normal tissue response to LD radiation supports homeostasis, and that this is achieved through intercellular signaling best understood through an integrated experimental and pathway modeling approach. The research program leverages the Laboratory's strengths in global proteomics, genomics, imaging, computational biology, and radiation biology to 1) identify functional signaling modules induced by LD radiation and quantitatively compare these to signaling induced by high dose exposures; 2) develop iterative computational/experimental strategies to model LD-induced signaling in multi-cellular systems; 3) understand the spatial flow of signaling between cell types; and 4) determine the effects of LD on key signaling intermediates, e.g., radiation induced adaptive responses. The results will provide a fundamental understanding of how LD radiation-induced signaling is coordinated through intercellular communication, and determine how these mechanisms impact the linearity of dose-response behavior at low doses.