

## Using Co-Regulation to Understand Low-Dose Ionizing Radiation Responsive Genes and Pathways.

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Genome-scale microarray expression data in conjunction with DNA sequence/pattern databases were used to identify and validate gene regulatory elements that influence cellular responses to low dose ionizing radiation. Using expression data, we identified over 500 radiation responsive genes. Computational tools were then used to identify genes that showed a pronounced pattern of expression that correlated with low and high doses of ionizing radiation (IR). Pathway analysis suggested that chromatin structure, as well as transcription control, plays a large role in linking gene regulation to DNA damage and stress responses in humans for pathways associated with the TP53 (DNA damage) and NF- $\kappa$ B (cell survival) signaling axes. The high degree of transcriptional variability was seen across individual samples irradiated both *in vivo* and *ex vivo*. Interestingly, as the dose increased, the level of transcriptional variation in these DNA damage signaling and cell survival pathways decreased, and was observed in multiple cell and tissue types. ChIP was used to confirm regulation at the level of chromatin for DNA damage associated proteins such as TP53. These results have led us to hypothesize that human population-level variation in the kinetics of chromatin modification and transcriptional regulation play a large role in understanding the low dose IR response curve across multiple tissue types. Thus, differences in the kinetics of DNA damage signaling and chromatin modification, and the subsequent up-regulation of DNA repair may influence the susceptibility of individuals to low dose IR-induced carcinogenesis. This information provides the basis for reducing the uncertainty of assessing risk at low dose levels for specific genes and pathways and may ultimately prove important for identifying susceptibility factors involved in individual responses to low dose IR.

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