

Human In Vivo Dose Response to Controlled, Low-Dose Low LET Ionizing Radiation Exposure

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The effect of low doses of ionizing radiation (LDIR, ≤ 10 cGy) on human tissue when exposure is under normal physiological conditions is of significant interest in many scientific and medical disciplines. Yet, to date there has been no direct assessment of response of human tissue to LDIR when exposure is under normal physiological conditions of intact 3-dimensional architecture, vasculature, and cell-cell contacts (between epithelial cells and between epithelial and stromal cells). Here, we present the first data on the response of human tissue exposed in vivo to LDIR with precisely controlled and calibrated doses. We evaluated transcriptomic responses to a single exposure of LDIR in the normal skin of men undergoing therapeutic radiation for prostate cancer (research protocol: HIPAA compliant, IRB approved). Using newly developed biostatistical tools that account for individual splice variants and the expected variability of temporal response between humans even when the outcome is measured at a single time, we demonstrate a dose-response pattern in gene expression in a number of pathways and gene groups that are biologically plausible responses to LDIR. Examining genes and pathways identified as radiation responsive in cell culture models, we found 7 gene groups and 5 pathways that were altered in men in this experiment. These included the Akt/PI3 kinase pathway, the growth factor pathway, the stress/apoptosis pathway and the path initiated by TGF β signaling, while gene groups with altered expression included the keratins, the zinc finger proteins and signaling molecules in the MAPK gene group. We demonstrate that there is considerable individual variability in radiation response that makes detection of effects difficult, but still feasible when analyzed by gene group and pathway. These results demonstrate for the first time that low doses of radiation have an identifiable biosignature in human tissue, irradiated in vivo with normal intact 3-dimensional architecture, vascular supply and innervation. The genes and pathways show that the tissue (a) does detect the injury, (b) initiates a stress/inflammatory response, (c) undergoes DNA remodeling, as suggested by the significant increase in zinc finger protein genes expression, and (d) initiates a ‘pro-survival’ response. The ability to detect a distinct radiation response pattern following LDIR exposure has important implications for risk assessment in both therapeutic and national defense contexts.

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