Low dose and bystander responses in a 3-D human skin model.

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Significant structural abnormalities develop within several days of exposure of the 3-dimensional normal human skin tissue model EPI-200 (MatTek) to high or low doses of low LET radiation. Disruption of the basal layer occurs following high radiation doses, and premature cornification is evident after both high and low dose exposures. In bystander tissue that is near irradiated portions of the tissue, but is not itself irradiated, we also observe premature cornification, increased apoptosis and micronucleus formation. Changes in global gene expression also occur in both directly irradiated and bystander EPI-200 tissue. Although the unfolding over time of the gene expression response in 3-dimensional tissue is complex, in general the patterns of gene expression response are consistent with the observed structural alterations in the tissues. At 16 hours after irradiation, the gene ontology functional categories related to cell cycle control and replication dominated the response to both high and low dose direct irradiation, while functions related to signal transduction dominated the response in bystander tissue.

In directly irradiated tissue, a more profound disturbance of cell cycle is suggested following high dose exposures, followed by a shift toward terminal differentiation at 24 hours. A more protective response is suggested by the gene expression patterns in tissues exposed to low doses, which return to a state similar to that of the un-irradiated controls within the first 24 hours. Network analysis of gene expression responses to high and low dose revealed TP53 as the major hub involved in response to high dose exposure, and a new potential regulator of low dose response, HNF4A. An increase in the active phosphorylated form of HNF4A was confirmed in HCT116 cells, and a complex regulatory relationship with p53 was suggested. In bystander tissue, NFκB was the major hub involved in the gene expression response, consistent with findings in 2-dimensional primary cell cultures. Signal transduction related processes were the most significantly enriched functions in bystander tissue, and enhanced expression of g-protein coupled receptor genes was also prominent in network analysis.

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