Data integration reveals key adaptive mechanisms in human 3D skin model after low dose exposure to ionizing radiation

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Our goal is to determine the key signaling pathways perturbed by Low Dose Radiation, how they may create a new cell/tissue state that is more or less sensitive to other perturbations, and how they relate to cell transformation and carcinogenesis. Using an *in vitro* 3-D human skin tissue model system, we have examined the temporal response of isolated keratinocyte and fibroblast layers exposed to 10cGy of ionizing radiation using global transcriptomics and protein microarrays, as well as secreted effectors in the media. The data have been integrated to determine regulatory mechanisms in the transcriptome data that influence down-stream signaling events represented in the protein data, and dose-response data has been used to determine how transitions in signaling pathways might be happening between low and high doses. We identified an interaction between IL-8 and somatostatin, which potentially explains a low dose-specific phenomenon. Our data indicate that IL-8 is secreted in response to 10cGy irradiation, but not significantly at 200cGy, and that somatostatin transcription is up-regulated by irradiation. Somatostatin is a known inhibitor of IL-8 synthesis, so we hypothesize that IL-8 is secreted at low doses due to oxidative stress, but at high doses, the synthesis of somatostatin reaches a critical level necessary to shut down IL-8 synthesis. In addition, gene expression data collected from cultured cells that elicit a cell transformation response to diverse stimuli can also be used to link our mechanistic data in the skin model to potential outcomes related to the development and/or susceptibility of cancer. Integrating these data, we have identified critical regulatory nodes representing adaptive responses after radiation, which when silenced create a permissive environment for radiation-induced stress response. Our data suggest that adaptive responses may occur in the skin after exposure to low doses of ionizing radiation, the result of which is determined by paracrine events in the surrounding tissue.