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Inter-Individual Variability in Human Response to Low-Dose Ionizing Radiation
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In order to investigate inter-individual variability in response to low-dose ionizing radiation, we are working with three models, 1) in-vivo irradiated human skin, for which we have a realistic model, but with few subjects, all from a previous project 2) ex-vivo irradiated human skin, for which we also have a realistic model, though with the limitations involved in keeping skin pieces alive in media, and 3) MatTek EpiDermFT skin plugs, which provides a more realistic model than cell lines, which is more controllable then human samples.

In-Vivo Irradiated Human Skin

We have two papers from data derived from the human in-vivo low-dose studies. The actual sample collection was funded under the predecessor grant to this one (DOE DE-FG03-01ER63237. The first (Berglund et al. 2009) examined transient changes in expression over time from a low dose. We analyzed nineteen gene groups and seven pathways for transient response, defined here as a transcriptional response that is elevated or depressed at 3 and 8 hours compared to the baseline at 0, and at 24 hours. We found nine gene groups that showed such transient differential expression.

The second (Kalanetra et al. 2016) is a more detailed examination of time-course behavior of gene expression from in-vivo exposed skin. In this new data set, we have split observations at 0, 3, 8, and 24 hours post irradiation by 10cGy (eight samples per subject) and eight patients with usable samples. We obtained comprehensive gene expression data using the Illumina platform and utilizing a complex data analysis strategy we obtained 1766 differentially expressed genes. We found that pathways associated with apoptosis and survival, development, cell adhesion, DNA damage, immune response, signal transduction, cytoskeleton remodeling, G-protein signaling, cCTP/CTP and cUTP/UTP metabolism, cell cycle, ATP and ITP metabolism, GTP and XTP metabolism, and CFTR folding and maturation were all significantly affected. This paper is currently in review.

MatTek EpiDermFT Skin Plugs

Despite being widely investigated, cell lines grown as monolayers provide a limited insight on the biological processes occurring under a given condition. EpiDermFT is a three-dimensional skin model which is composed of normal human epidermal keratinocytes (NHEK) and normal human dermal fibroblasts (NHDF). This skin model is mainly utilized for studying human skin responses to cosmetics and topical agents. We aimed to test and validate it by assessing its gene expression following LDIR exposure against known responses of actual human skin irradiated in vivo. The plugs were irradiated with 0, 10, and 100 cGy at a dose rate of 50 cGy/min. Skin plugs were harvested at 0, 3, 8, and 24 hours post irradiation, with duplicates at each combination of

dose and time, for a total of 32 samples. RNA was extracted and gene expression assessed using the Illumina platform. Results from this analysis appear in Yunis et al. (2012) and identify pathways responsive to radiation in this model. A further development of the methodology for analysis of such studies was provided in Ray et al. (2012) in which a graph-based approach was used.

Ex-Vivo Irradiated Human Skin

We have used discarded surgical skin to evaluate the transcriptional response to ionizing radiation. This model is less realistic than the in-vivo-irradiated skin, but more realistic than the MatTek skin-plug model. We used Illumina expression data from two subjects at baseline and at doses of 5 and 500 cGy at 2, 8, and 30 hours following irradiation. There were 3–4 replicates per person per condition, resulting in 80 samples total. We identified sets of differentially expressed genes by time by dose and by subject, and have analyzed the pathways and gene groups that are most significantly represented in the differentially expressed genes across individuals and with dose and time across individuals. The results from this study were published in *Radiation Research* (Albrecht et al. 2012).

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