Inter-individual variations in the human transcriptome following in vivo exposure to low dose ionizing radiation

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Human exposure to low dose ionizing radiation (LDIR), defined as equal or lower than 0.1 Gy, can occur through a variety of sources, including natural (cosmic rays, radionuclides in Earth's crust), medical (diagnostic imaging and therapy), occupational (nuclear factory and medical workers), and accidental (nuclear catastrophe, terrorist act). However, the biological effects and molecular mechanisms involved in the human response to LDIR are still poorly understood. Since the effects of radiation in humans are best studied in humans, our laboratory has pioneered analysis of human skin following in vivo exposure to LDIR. In essence, normal skin from consented men undergoing radiotherapy for early stage prostate cancer is used. Studying the effects of IR in human skin is highly relevant since skin is the most abundant organ in humans, and the first organ exposed to IR during occupational, therapeutic and accidental exposures.

Methods. The present study included 7 patients and a total of 4 skin punch biopsies were collected per patient: one prior IR exposure and one each at 3, 8 and 24h following exposure to 0.01 Gy, as determined by MOSFET (metal-oxide semiconductor field-effect transistor) dosimetry. Transcriptional changes in duplicate samples (obtained by splitting each biopsy) of control skin and IR exposed skin were assessed by global gene expression analysis using Illumina Human Ref-8 beadchips (24,526 RefSeq curated gene probes). While the same original data set has been previously analyzed to identify common biological responses following in vivo exposure to a 0.01 Gy dose of Xrays, here we focused on the inter-individual variability in response to LDIR. Linear mixed effects modeling was used to select genes with the most variability between patients in response to radiation over time. Genes were classified into functional groups with DAVID (http://david.abcc.ncifcrf.gov/), and MetaCore by GENEGO® was used to map differentially expressed genes to functional pathways.

Results. Following background subtraction, probes with a detection P-value < 0.05 for all arrays were selected, resulting in a data set with a total of 21145 probes. Out of these, 4257 probes (20%) had a raw P-value < 0.05 for the likelihood ratio test of a patient-treatment interaction effect (indicating significant variability among patients in response over time), and 1011 (5%) had a false discovery rate (FDR)-adjusted P-value < 0.05. For most probes, the variability in gene expression between patients at a given time point was greater than the mean change in expression between time points. Genes and pathways represented in these inter-individual variable gene expression profiles will be discussed.

Analysis of the inter-individual transcriptional changes induced by in vivo exposure to LDIR is expected to contribute to a better definition of the biological effects of LDIR in humans, and thereby enable risk assessment to assist with public policy decisions.