

GENE EXPRESSION SIGNATURES FOR HIGH-THROUGHPUT MINIMALLY-INVASIVE RADIATION BIODOSIMETRY.

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In response to the recognized need for improved biodosimetry methods for use in potential radiological triage situations, the Center for High-Throughput Minimally-Invasive Radiation Biodosimetry has been developing approaches for automation of well-established cytogenetic assays, as well as newer approaches based on metabolomic and gene expression signatures. The Phase I RABiT (Rapid Automated Biodosimetry Tool) can score micronuclei in up to 6000 blood samples per day and requires only 10-30 μ l blood from a fingerstick. Small molecule metabolites that distinguish between irradiated and non-irradiated samples are being identified in urine and saliva, providing the potential for completely non-invasive assays. Work is also progressing in the identification of informative gene expression signatures that can be measured in microliter quantities of peripheral blood.

Human peripheral blood represents an easily biopsied tissue that is one of the most responsive to ionizing radiation in terms of gene expression. We had identified a number of genes in early *ex vivo* studies with expression levels increasing linearly with dose between 0.2 and 2 Gy up to 48 hours post-exposure (1). Many of the same genes also responded *in vivo* in patients undergoing total body irradiation, although not all *in vivo* responding genes were seen in the *ex vivo* experiments (2). Since these early studies, we have measured global gene expression profiles at 6, 24 and 48 hours after *ex vivo* exposure of human peripheral blood to 0.5, 2, 5 and 8 Gy gamma-rays, a dose range relevant to medical decision-making in a radiological triage situation. The gene expression signatures identified could be used to predict radiation exposure dose without reference to individual pre-exposure controls using linear discriminant analysis, nearest neighbor or nearest centroid classifiers. For instance, a nearest centroid classifier using a set of 74 genes correctly predicted 98% of 6- and 24-hour samples as unexposed, exposed to 0.5 Gy, to 2 Gy, or to 5 Gy and above (3).

Continuing studies will attempt to better characterize *in vivo* responses to radiation exposure, and will examine the impact of potential confounding factors, such as smoking, pre-existing disease and inflammatory conditions, on performance of our dosimetric classifier. These efforts remain integrated with the development of a self-contained microfluidic biochip for rapid measurement and interpretation of gene expression signatures. Our findings to date continue to support the potential of gene expression signatures as an informative approach for rapid high-throughput radiation biodosimetry.

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References:

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