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Transcriptional profile of immediate response to ionizing radiation exposure

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ABSTRACT

Astronauts participating in long duration space missions are likely to be exposed to ionizing radiation associated with highly energetic and charged heavy particles. Previously proposed gene biomarkers for radiation exposure include phosphorylated H2A Histone Family, Member X (γH2AX), Tumor Protein 53 (TP53), and Cyclin-Dependent Kinase Inhibitor 1A (CDKN1A). However, transcripts of these genes may not be the most suitable biomarkers for radiation exposure due to a lack of sensitivity or specificity. As part of a larger effort to develop lab-on-a-chip methods for detecting radiation exposure events using blood samples, we designed a dose–course microarray study in order to determine coding and non-coding RNA transcripts undergoing differential expression immediately following radiation exposure. The main goal was to elicit a small set of sensitive and specific radiation exposure biomarkers at low, medium, and high levels of ionizing radiation exposure. Four separate levels of radiation were considered: 0 Gray (Gy) control; 0.3 Gy; 1.5 Gy; and 3.0 Gy with four replicates at each radiation level. This report includes raw gene expression data files from the resulting microarray experiments from all three radiation levels ranging from a lower, typical exposure than an astronaut might see (0.3 Gy) to high, potentially lethal, levels of radiation (3.0 Gy). The data described here is available in NCBI's Gene Expression Omnibus (GEO), accession GSE64375.

Specifications	
Organism/cell line/tissue	*Homo sapiens*
Sex	Mixed
Sequencer or array type	Affymetrix® Human Gene 1.0 ST v1 Arrays
Data format	Raw; CEL files
Experimental factors	0.3 Gy exposure vs. 0.0 Gy (low radiation response); 1.5 Gy exposure vs. 0.0 Gy (mid-radiation response); 3.0 Gy exposure vs. 0.0 Gy (high radiation response)
Experimental features	Gene expression profiling of radiation exposure using: 0.0 Gy (control; n = 4); 0.3 Gy (low radiation; n = 4); 1.5 Gy (mid radiation; n = 4); 3.0 Gy (high radiation; n = 4)
Consent	Not applicable
Sample source location	Not applicable

1. Direct link to deposited data

Data is available in the Gene Expression Omnibus (GEO) [1,2] accession GSE64375 through the direct link http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE64375

2. Value of the data

- Available data on transcriptional profiling of ionizing radiation exposure is sparse at best and this dataset provides novel data on immediate transcriptional responses for both coding and non-coding RNAs at

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Table 1
Concentration and purity data for microarray samples.

Sample Number	Volunteer Number	Radiation Level	Concentration ng/ul	260/280	260/230	RIN
1	1	0.0 Gy	81	2.08	2.20	8.20
2	2	0.0 Gy	99	2.09	2.02	5.90
3	3	0.0 Gy	93	2.08	2.13	6.60
4	4	0.0 Gy	62	2.08	2.05	7.90
5	1	0.3 Gy	67	2.06	2.14	8.30
6	2	0.3 Gy	130	2.08	2.23	5.40
7	3	0.3 Gy	97	2.03	2.04	6.70
8	4	0.3 Gy	68	2.08	2.14	7.30
9	1	1.5 Gy	68	2.06	2.19	7.90
10	2	1.5 Gy	167	2.08	2.13	6.50
11	3	1.5 Gy	99	2.09	2.13	6.20
12	4	1.5 Gy	77	2.07	2.18	7.50
13	1	3.0 Gy	62	1.99	2.06	7.30
14	2	3.0 Gy	88	2.11	2.06	6.90
15	3	3.0 Gy	94	2.09	2.02	6.70
16	4	3.0 Gy	68	2.10	2.04	6.80

three distinct levels of radiation: 0.3 Gy (low), 1.5 Gy (medium), and 3.0 Gy (high).

- Immediate transcriptional response biomarkers to radiation exposure can be elucidated by combining the radiation exposure data and determining common transcriptional responses.
- Dose-specific transcriptional responses immediately following radiation exposure can be determined using the available dataset which can be used to extract sensitive and specific biomarkers.
- Identification of appropriate biomarkers for general radiation exposure as well as dose-dependent markers found within blood plasma samples makes it possible to design appropriate diagnostic tests for measuring radiation exposure. Such a test could be employed on long-term space flights to diagnose whether or not an astronaut has been exposed to radiation and at what level so appropriate treatment options can be explored.

3. Experimental design, materials and methods

3.1. Experimental design

All procedures were performed in accordance with published NASA and NIH Guidelines, the University of Louisville Institutional Review Board (IRB), and the University of Louisville Institutional Biosafety Committee (IBC). In this study, we sought to understand transcriptional changes in human blood samples resulting from exposure to three different levels of radiation. The experimental design consisted of blood draws from four volunteers which was separated into four samples. Blood from each volunteer was then exposed to 0.0 Gy, 0.3 Gy, 1.5 Gy, and 3.0 Gy of radiation independently as described in Section 3.2.

3.2. Sample preparation

Whole blood was drawn from four (4) volunteers using a Safety Winged IV blood draw set (Exel International, St. Petersburg, FL) in 7-ml lavender topped Ethylenediamineteraacetic acid (EDTA) anticoagulant-containing vacutainers. Blood samples were aliquoted and kept at room temperature throughout the radiation and white blood cell (WBC) isolation process.

Whole blood samples were radiated at the Kentucky Lion Eye Center using a Gammacell 1000 Elite (Cs-137) (Best Theratronics Ltd., Ottawa, Canada) for 0 s (control — 0.0 Gy exposure), 3 s (0.30 Gy exposure), 16 s (1.5 Gy exposure), or 32 s (3.0 Gy exposure).

Approximately 30 min after completion of the radiation cycle, red blood cells (RBC) were lysed by adding 15 ml of NH_4Cl RBC lysis buffer for each ml of whole blood (1:15 v/v dilution) in order to isolate leukocytes. The tubes were agitated for 5 min on a rocker platform and centrifuged for 5 min at 1500 RPM at room temperature. Cells were suspended in 10 ml of phosphate-buffered saline (PBS) and centrifuged again twice for 5 min at 1500 RPM. WBCs were suspended in 2 ml PBS, equivalent to the initial volume of the whole blood. WBCs were centrifuged 5 min at 1500 rpm. Supernatant was discarded and cell pellets were suspended in 600 ul RLT lysis buffer (Qiagen, Venlo, The Netherlands) and tubes were vortexed vigorously and stored at −70 °C until RNA purification. Purification of total RNA was performed using the RNAeasy Mini Kit (Qiagen). Optional on-column DNase digestion was performed to eliminate genomic DNA contamination. Total RNA was eluted in 60 ul of RNase-free water. The quantity analysis of the total RNA was performed with a Nanodrop spectrophotometer (Thermo Fisher Scientific, Wilmington, DE). The quality of the total RNA was checked using an Agilent 2100 Bioanalyzer (Agilent Technologies, Inc., Santa Clara, CA) (Table 1).

Biotinylated cDNA were prepared according to the standard protocol for Affymetrix® GeneChip® WT Expression protocol (Affymetrix® Inc., Santa Clara, CA) from 100 ng total RNA, which includes an Ambion WT Expression kit followed by a GeneChip® WT Terminal Labeling and Hybridization kit. Following fragmentation, microarrays were hybridized at the University of Louisville Genomics Core Facility in a single batch. cDNA were hybridized for 16 h at 45 °C to Affymetrix® GeneChip® Human Gene 1.0 ST v1 Arrays (GEO platform GPL6244) according to the GeneChip® WT Terminal Labeling and Hybridization User Manual from Affymetrix®.

3.3. Data acquisition

GeneChips® were scanned using an Affymetrix® GeneChip® Scanner 3000 7G (Affymetrix®) and the GeneChip® Command Console® software version 3.1 (Affymetrix®), resulting in 16 raw CEL files

Table 2
Sample information.

Sample number	Sample name	CEL file	Volunteer number	Dose	GEO sample ID
1	SAMPLE_0.0Gy_1h-1	PS_Vol1_0.0GY.CEL	1	0.0 Gy	GSM1569806
2	SAMPLE_0.0Gy_1h-2	PS_Vol2_0.0GY.CEL	2	0.0 Gy	GSM1569807
3	SAMPLE_0.0Gy_1h-3	PS_Vol3_0.0GY.CEL	3	0.0 Gy	GSM1569808
4	SAMPLE_0.0Gy_1h-4	PS_Vol4_0.0GY.CEL	4	0.0 Gy	GSM1569809
5	SAMPLE_0.3Gy_1h-1	PS_Vol1_0.3GY.CEL	1	0.3 Gy	GSM1569810
6	SAMPLE_0.3Gy_1h-2	PS_Vol2_0.3GY.CEL	2	0.3 Gy	GSM1569811
7	SAMPLE_0.3Gy_1h-3	PS_Vol3_0.3GY.CEL	3	0.3 Gy	GSM1569812
8	SAMPLE_0.3Gy_1h-4	PS_Vol4_0.3GY.CEL	4	0.3 Gy	GSM1569813
9	SAMPLE_1.5Gy_1h-1	PS_Vol1_1.5GY.CEL	1	1.5 Gy	GSM1569814
10	SAMPLE_1.5Gy_1h-2	PS_Vol2_1.5GY.CEL	2	1.5 Gy	GSM1569815
11	SAMPLE_1.5Gy_1h-3	PS_Vol3_1.5GY.CEL	3	1.5 Gy	GSM1569816
12	SAMPLE_1.5Gy_2h-4	PS_Vol4_1.5GY.CEL	4	1.5 Gy	GSM1569817
13	SAMPLE_3.0Gy_2h-1	PS_Vol1_3.0GY.CEL	1	3.0 Gy	GSM1569818
14	SAMPLE_3.0Gy_2h-2	PS_Vol2_3.0GY.CEL	2	3.0 Gy	GSM1569819
15	SAMPLE_3.0Gy_2h-3	PS_Vol3_3.0GY.CEL	3	3.0 Gy	GSM1569820
16	SAMPLE_3.0Gy_2h-4	PS_Vol4_3.0GY.CEL	4	3.0 Gy	GSM1569821