Fiscal Year:	FY 2024	**Task Last Updated:**	FY 02/16/2024
PI Name:	Risca, Viviana Ph.D.		
Project Title:	Epigenetic State Modulation of Radiation-Induced DNA Damage: Nanoscale Modeling and Validation		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	Yes
Human Research Program Elements:	(1) **SR**:Space Radiation		
Human Research Program Risks:	(1) **Cancer**:Risk of Radiation Carcinogenesis		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	vrisca@rockefeller.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	516-728-3406
Organization Name:	The Rockefeller University		
PI Address 1:	Laboratory of Genome Architecture and Dynamics		
PI Address 2:	1230 York Ave, Box 176		
PI Web Page:			
City:	New York	**State:**	NY
Zip Code:	10065-6307	**Congressional District:**	12
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2019-2020 HERO 80JSC019N0001-HHCBPSR, OMNIBUS2: Human Health Countermeasures, Behavioral Performance, and Space Radiation-Appendix C; Omnibus2-Appendix D
Start Date:	04/01/2021	**End Date:**	04/15/2024
No. of Post Docs:	2	**No. of PhD Degrees:**	
No. of PhD Candidates:	3	**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
Contact Monitor:	Elgart, Robin	**Contact Phone:**	281-244-0596 (o)/832-221-4576 (m)
Contact Email:	shona.elgart@nasa.gov		
Flight Program:			
Flight Assignment:	NOTE: End date changed to 04/15/2024 per V. Lehman/JSC (Ed., 4/25/23) NOTE: End date changed to 03/31/2023 per NSSC information (Ed., 11/14/22)		
Key Personnel Changes/Previous PI:	Dr. Antony Jeevarajan requested that Dr. Karen Pickering be added as the institutional Co-Investigator.		
COI Name (Institution):	Plante, Ianik Ph.D. (NASA Johnson Space Center) Jeevarajan, Antony Ph.D. (NASA Johnson Space Center) Pickering, Karen (NASA Johnson Space Center)		
Grant/Contract No.:	80NSSC21K0565		
Performance Goal No.:			
Performance Goal Text:			

Task Description:

BACKGROUND

The risks of cellular dysfunction associated with exposure to space radiation, including transcriptional and epigenetic perturbations and genomic instability due to DNA breaks, have been studied in cell lines, with DNA repair foci and products as the main readouts. Such genetic and cell biological readouts show that high linear energy transfer (LET) charged nuclei, such as those found in galactic cosmic rays (GCR), cause persistent cellular changes in stress response and genomic integrity. These effects are different from the effects of low-linear energy transfer (LET) radiation such as X-rays and occur in the context of the genome-wide epigenetic landscape of each cell, which includes nucleosome positions, nucleosome modifications, and variant histone substitutions in those nucleosomes. Epigenetic states differ in chromatin fiber conformations, with transcriptionally active chromatin adopting more open, extended structures. These differences can affect DNA break patterns in response to ionizing radiation, potentially creating distinct DNA repair and signaling outcomes. The epigenetic state landscape of a cell depends on its differentiation state, cell type, and responses to external stimuli. Because it is not practical to experimentally investigate every cell type, a more generalizable approach is needed to predict how the cell's distinctive epigenetic landscape will interact with radiation to give rise to a certain pattern of DNA breaks and associated cellular response. A generalizable approach that takes local epigenetic map information into account can leverage the large and diverse epigenomic data sets available for a large number of human cell types. Previous investigations of chromatin structure's role in regulating DNA damage by radiation assumed that chromatin adopts stable, regular structures such as 30-nm fibers. Recently emerging consensus in the field suggests this single-structure view is inaccurate and the ensemble of conformational fluctuations of the fiber must be taken into account.

HYPOTHESIS

We hypothesize that the pattern and lethality of DNA breaks generated at a given genomic locus depend on the combination of (1) the incoming ionizing radiation, with differences between low LET photons and high LET GCRs, and (2) the epigenetic state of that locus, which is associated with a characteristic ensemble of chromatin fiber conformations.

DELIVERABLES

We propose to develop a generalizable mechanistic approach to determining how DNA breaks are generated by ionizing radiation including GCRs and photons. We will integrate realistic chromatin fiber ensembles with Monte Carlo simulations of photons or GCR nuclei interacting with those fibers, and Green's function based calculation of radiochemistry kinetics after the particle delivers its energy. The chromatin fiber ensembles will be generated through a coarse-grained simulation based on a stretchable shearable worm-like chain model of linker DNA between nucleosomes that is constrained by pairwise DNA-DNA contact data. We will measure chromatin fiber contact distances, simulate sub-kilobase chromatin conformation ensembles consistent with those contact distances, and predict how these ensembles give rise to ensembles of DNA break patterns. These measurements and simulations will be carried out for multiple chromatin states across several cell types as well as for in vitro reconstituted chromatin fibers in order to build a general, cell type independent model of the relationship between epigenetic state and vulnerability to radiation induced DNA damage. The resulting software package will enable the simulation of user-programmable chromatin states, to produce chromatin state specific predictions of expected DNA fragmentation patterns for each type of heavy ion or photon of incoming radiation. These fragmentation patterns can then form the basis for future mechanistic studies of the cell's differential repair and signaling responses to varied break cluster types.

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:

Our research develops technology for mapping DNA breaks caused by radiation onto the human genome and studies how the sensitivity to radiation varies across the human genome. Our data and methods will have direct applicability to determining cell type specific sensitivity to radiation therapy used to treat many cancers. We anticipate that our results will also aid cancer prevention here on Earth in addition to helping to advance our understanding of the health risks associated with space travel.

Task Progress:

In the last reporting period, we have characterized how the chromatin structure ensembles we generate with a coarse-grained chromatin model and Monte Carlo simulations depend on the geometric parameters of chromatin, namely nucleosome wrapping by DNA and spacing of nucleosomes along the DNA. We found that the spacing and wrapping parameters can be determined from synthetic RICC-seq data predicted from a large number of simulated structures using a simple regression model. These parameter estimates help us match simulated structures against experimental data from different epigenetic states and can be used to build chromatin structure ensembles based on nucleosome spacing measurements from a variety of orthogonal epigenomic methods, such as MNase-seq. Continuing to work with the version of RITRACKS described in the last reporting period, we have made an additional update to add elastic scattering cross-sections for DNA and estimate them for amino acids.

We have then run simulations with photons and several different ions of varying LET values to benchmark the code against other codes and against experimental data. These simulations were performed with single nucleosomes. Chromatin fiber simulations with multiple nucleosomes and different densities of nucleosomes will be started in the next month.

We have performed simulations with and without histones and observed that the yield of DNA breaks is approximately twice without histones as with histones, showing that our simulation recapitulates the well-known role of histones in protecting genomic DNA from radiation. Although the yield of double-strand breaks (DSBs) without histones is higher than predicted by other codes and observed in experiments, when histones are incorporated, the RITRACKS predictions for DSB yield agree with the other codes and experiments.

On the experimental side, we have adapted two protocols for use with cells irradiated with ionizing radiation: END-seq, which maps DNA DSBs, and GLOE-seq, which maps DNA single-strand breaks (SSBs), onto genomic DNA coordinates. These methods use single-ended mapping of breaks and do not depend on regions of high break density or on spatially correlated breaks to generate DNA fragments that can be sequenced, in contrast to RICC-seq, the method we were using in the prior reporting period.

In pilot experiments with X-rays, we have shown that by combining these protocols with normalization by irradiated

	genomic DNA controls, we can obtain estimates of DNA break density by epigenetic state that is different from that in scrambled genomic feature controls. Our results from X-ray and preliminary ion experiments indicate that the density of both SSBs and DSBs varies between epigenetic states by approximately 10%, with less compact states, such as active promoters, exhibiting the highest break densities. We have performed 200 Gy gamma ray and Fe ion irradiations at NASA Space Radiation Laboratory (NSRL) on four cell types: K562 leukemia cells, BJ fibroblasts, IMR90 fibroblasts, and RPE-1 retinal pigment epithelial cells. The DNA sequencing libraries resulting from these experiments are still being processed and we anticipate that sequencing data will be available for analysis in late spring 2024.
Bibliography Type:	Description: (Last Updated: 03/15/2024)
Abstracts for Journals and Proceedings	Canaj H, Scortea A, West D, Plante I, Risca VI. "Mapping DNA damage propensity by low and high LET ionizing radiation with respect to epigenetic states." 2023 American Society for Cell Biology Annual Meeting, Boston, Massachusetts, December 2-6, 2023. Abstracts. 2023 American Society for Cell Biology Annual Meeting, Boston, Massachusetts, December 2-6, 2023. , Dec-2023
Abstracts for Journals and Proceedings	Plante I, Risca VI. "Simulation of radiation-induced DNA damage show histone protection." 2024 NASA Human Research Program Investigators' Workshop, Galveston, Texas, February 13-16, 2024. Abstracts. 2024 NASA Human Research Program Investigators' Workshop, Galveston, Texas, February 13-16, 2024. , Feb-2024
Abstracts for Journals and Proceedings	Canaj H, Scortea A, Rendleman J, West D, Plante I, Risca VI. "Mapping DNA damage propensity by ionizing radiation with respect to epigenetic states." 2024 NASA Human Research Program Investigators' Workshop, Galveston, Texas, February 13-16, 2024. Abstracts. 2024 NASA Human Research Program Investigators' Workshop, Galveston, Texas, February 13-16, 2024. , Feb-2024
Articles in Peer-reviewed Journals	Soroczynski J, Risca V. "Technological advances in probing 4D genome organization." Curr Opin Cell Biol. 2023 Oct 23;84:102211. https://doi.org/10.1016/j.ceb.2023.102211 ; PMID: 37556867 PMCID: PMC10588670. , Oct-2023