

Fiscal Year:	FY 2023	Task Last Updated:	FY 04/03/2023
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		
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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:		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
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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:			

	<p>BACKGROUND</p> <p>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.</p> <p>HYPOTHESIS</p> <p>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.</p> <p>DELIVERABLES</p> <p>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.</p>
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	<p>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.</p>
Task Progress:	<p>Over the last year, we have updated computational for studying how the local structure and epigenetic state of chromatin, the packaged form of DNA found in cells, affects the density and type of DNA breaks caused by space radiation. We have also performed experiments using gamma rays and ions at NASA Space Radiation Laboratory (NSRL) to determine how break density varies as a function of epigenetic state in two cell types.</p> <p>1. We have updated the radiochemistry code in RITRACKS, a NASA-designed software tool that simulates DNA damage events caused by ionizing radiation to support two new types of interactions with DNA and amino acids. We are working on ensuring that the new RITRACKS produces double-strand DNA break yield estimates that are consistent with the experiment.</p> <p>2. We used RITRACKS to demonstrate that it can reproduce experimentally observed protection of DNA by histone proteins.</p> <p>3. We have validated coarse-grained simulations of chromatin against experimental results from in vitro reconstituted chromatin and generated ensembles of chromatin structures with constant or variable linker DNA lengths.</p> <p>4. We have performed ion irradiations in two cell lines and obtained preliminary data for calculating the relative sensitivity of different genomic loci to DNA damage by photons and ions. We have encountered several technical challenges in making this measurement that we are now addressing by changing the DNA break mapping protocol and one of the two cell lines, from an endothelial cell to a fibroblast.</p>
Bibliography Type:	Description: (Last Updated: 03/15/2024)
Abstracts for Journals and Proceedings	<p>Plante I, West D, Risca VI. "Simulation of radiation-induced DNA damage using the code RITRACKS: initial results show histone protection." Radiation Research Society 68th Annual Meeting, Waikoloa Village, Hawaii, October 16-19, 2022.</p> <p>Abstracts. Radiation Research Society 68th Annual Meeting, Waikoloa Village, Hawaii, October 16-19, 2022. , Oct-2022</p>

Abstracts for Journals and Proceedings	Plante I, West D, Risca VI. "Simulation of radiation-induced DNA damage show histone protection." NASA Human Research Program Investigators' Workshop, Galveston, Texas, February 7, 2023. Abstracts. NASA Human Research Program Investigators' Workshop, Galveston, Texas, February 7, 2023. , Feb-2023
Abstracts for Journals and Proceedings	Canaj H, Scortea A, West D, Plante I, Risca VI. "Heavy ion damage on chromatin: break mapping across genomic compartments." NASA Human Research Program Investigators' Workshop, Galveston, Texas, February 7, 2023. Abstracts. NASA Human Research Program Investigators' Workshop, Galveston, Texas, February 7, 2023. , Feb-2023
Articles in Peer-reviewed Journals	Canaj H, Scortea A, West DW, Plante I, Risca VI. "Heavy ion damage on chromatin; break mapping across genomic compartments." Mol Biol Cell. 2023 Feb 1;34(2):ab1. https://doi.org/10.1091/mbc.E22-12-0555 ; PubMed PMID: 36637911 ; PubMed Central PMCID: PMC9930526 , Feb-2023
Articles in Peer-reviewed Journals	Mansisor AR, Risca VI. "Chromatin accessibility: methods, mechanisms, and biological insights." Nucleus. 2022 Dec;13(1):238-78. https://doi.org/10.1080/19491034.2022.2143106 ; PubMed PMID: 36404679 ; PubMed Central PMCID: PMC9683059 , Dec-2022