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PI Name:	Wang, Ya M.D., Ph.D.		
Project Title:	NSCOR: Mechanisms underlying the risk of HZE particle-induced solid tumor development		
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Human Research Program Risks:	(1) Cancer :Risk of Radiation Carcinogenesis		
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Space Biology Special Category:	None		
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COI Name (Institution):	Doetsch, Paul (Emory University) Orloff, Gregg (Emory University) Sun, Shi-Yong (Emory University) Vertino, Paula (Emory University) Wang, Huichen (Emory University) Dyman, William (Emory University)		
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Task Description:	<p>The Emory University-Georgia Health Sciences University NSCOR will investigate the mechanisms by which high charge and energy (HZE) particles, a component of space radiation, induce lung cancer. HZE exposure elicits complex DNA damage, together with a broader cell/tissue stress response that likely includes changes in expression of tumor suppressor proteins, persistent elevation of reactive oxygen species, and alterations in the pattern of DNA methylation. The central hypothesis of this NSCOR is that this broader stress response amplifies the carcinogenic risk from a primary DNA damage event. Preliminary studies suggest that a small noncoding RNA, microRNA-21 (miR-21) plays a key role in coordinating the HZE particle-associated stress response. Center investigators will use genetic, epigenetic, and biochemical approaches to address the role of miR-21 dependent and independent stress responses in HZE particle-induced lung cancer. There are four projects:</p> <ol style="list-style-type: none">1. Determine whether the lung cancer suppressor, Gprc5a, protects against HZE particle-induced lung carcinogenesis, and whether miR-21 overexpression blunts this protective effect.2. Determine whether HZE-particle radiation exposure results in hyper-reliance on error-prone DNA repair pathways, whether miR21 mediates this effect, and whether dysregulation of DNA repair contributes to lung carcinogenesis.3. Determine the nature of the HZE-particle induced ROS stress response, whether it contributes to HZE particle-induced lung carcinogenesis, and the role of miR-21 in this process.4. Determine the scope of HZE-particle radiation-induced alterations in DNA methylation patterns, whether these alterations contribute to lung carcinogenesis, and the role of miR-21-dependent targeting of DNA methyltransferase 1 (DNMT1) in this process. <p>These four projects have a synergy through their collaboration on studying the mechanism underlying how mammalian respond to HZE particle-induced DNA damage, which contributes to tumor development.</p>		
Rationale for HRP Directed Research:			
Research Impact/Earth Benefits:	<p>Space radiation from HZE-particles with high-LET is different from radiation with low-LET on Earth. Understanding the mechanism by which mammalian cells respond to space radiation induced the DNA damage is a key issue for us to evaluate the risk of space radiation on astronauts' health at any endpoint. Lung cancer is the most common fatal cancer among men and women worldwide. Lung cancer is believed to be one of the major risks of HZE-particle exposure-induced carcinogenesis, although a quantitative and mechanistic understanding of this risk is lacking. The Emory NSCOR will address this important knowledge gap. In addition, our NSCOR team will answer the question concerning whether and how different qualities (LET) of radiation affects lung tumorigenesis. These results will not only provide important information that will aid in the facilitation of the NASA Mars project, but will also provide the public with useful information concerning lung carcinogenesis and the benefits of cancer prevention.</p>		

1. Overview of the Emory NSCOR main achievements:

1) We successfully held a retreat during January 17-18, 2013 in Emory University. Besides the key personnel of our NSCOR team and related lab members, the following people attended the retreat:

Internal Executive Advisors: Walter Curran, MD, Executive Director, Winship Cancer Institute of Emory University, Associate Vice President of Cancer, Woodruff Health Sciences Center, Professor and Chair, Department of Radiation Oncology, Emory University School of Medicine; Fadlo Khuri, MD, FACP, Deputy Director, Winship Cancer Institute of Emory University, Professor and Chair, Department of Hematology and Medical Oncology, Emory University School of Medicine.

External Consultants: Carlo Croce, MD, Professor and Chair, Depts. of Human Cancer Genetics, Molecular Virology, Immunology and Medical Genetics; Director, Human Cancer Genetics Program, Ohio State University Medical Center (assigned for project 1); George Iliakis, PhD, Professor, Director, Institute of Medical Radiation Biology, University of Duisburg-Essen, Medical School, Essen, Germany (assigned for project 2); Peter O'Neill, PhD, Professor, Gray Institute for Radiation Oncology & Biology, Department of Oncology, University of Oxford, Oxford, UK (assigned for project 3); Marco Durante, PhD, Professor, GSI-Biophysik, Darmstadt – Germany (assigned for project 4).

NASA Executive Advisors: D. Marshall Porterfield, PhD, Division Director, NASA Life and Physical Sciences, Human Exploration and Operations Mission Directorate, NASA Headquarters, Washington, DC; Francis Cucinotta, PhD, Chief Scientist, Human Research Program Space Radiation Element, NASA Lyndon B. Johnson Space Center, Houston, Texas.

From this retreat, we obtained evaluations provided by the external consultants. We summarized the consultants' main points as follows:

The consultants concurred in the goals of this NSCOR grant that were carefully selected and founded on promising hypotheses that are likely to generate valuable information towards the central aims of the NASA space radiation program. The consultants also believed that the progress made to date towards these goals was significant and the grant was very well managed and directed overall. The consultants noted that attention should be paid to the following aspects:

(1). Use the same cell lines that have been exposed to the same doses of HZE or X-ray among projects; (2). Study the global miRNA dysregulation in HZE particle-irradiated cells; (3). Focus on study the mechanism of HZE-induced lung tumor.

These evaluations provide valuable information, which allows us to better follow the major goal of NASA radiation program for estimating the risk of space radiation on astronauts' health and exploring approaches to reduce the risk. After this retreat, we submitted a report to NASA radiation program.

2) We finished the mid-term evaluation that is organized by NASA radiation program on October 21, 2013 at the NASA Headquarters.

On October 21, 2013, the Emory NSCOR key personnel (the leaders of each project and education component) reported our project progress to the review panel that includes Drs. Colin Hill (USC Keck School of Medicine), Raymond Meyn (M.D. Anderson Cancer Center), Janice Huff (USRA/NASA JSC), Noelle Metting (DOE), and Walter Schimmerling (USRA). We also answered the questions raised by the panel members. We expect to obtain the final review report by December, 2013. Again, we believe that the mid-term evaluation will facilitate our NSCOR team to better follow the major goal of NASA radiation program for estimating the risk of space radiation on astronauts' health and exploring approaches to reduce the risk. 3) We have finished the animal radiation exposure for long-term tumorigenesis. In this NSCOR proposal, we used several mouse models to perform the radiation-induced tumorigenesis study. The mouse strains include wild type C57BL/6 mice, miR-21 knock-in mice, Gprc5a^{-/-} mice, miR-21 knock-in and Gprc5a^{-/-} double mutant mice, miR-21^{-/-} mice. X-ray exposure was performed in the Department of Radiation Oncology, Emory University and the HZE-particle exposure was performed at NASA Space Radiation Laboratory (NSRL), Brookhaven National Laboratory (BNL). We originally planned to sacrifice the mice at 8 months after irradiation; however, due to the fact that no significant tumorigenesis was observed at this time point from 3 irradiated miR-21 mice, we decided to extend the observation period from 8 months to 1.5 years to obtain the results of IR-induced tumorigenesis. Until now, we have obtained some tumorigenesis results from the irradiated mice. We expect to obtain the entire tumorigenesis results by end of 2014. 1,320 mice in total are used for the long-term project.

2. Progress from each project: This proposal has four projects and one education component. The progresses from these projects are described as follows:

Project 1: The main purpose of this project is to identify the targets of miR-21 and their regulation and effects on IR-induced carcinogenesis. Recently, we collaborated with Dr. Doetsch and H. Wang (project 3) to study the effects of miR-21 on the generation of radiation-induced reactive oxygen species (ROS); the results have been published (Cancer Res, 72:4707-4713, 2012). We found that miR-21 could directly target SOD3 and indirectly target SOD2 to enhance HZE particle-induced ROS and transformation in the human lung epithelial cells. We have finished this study and published the results. Also, we are collaborating with Dr. Dyanan (project 2) and have found that the miR-21-EGFR loop is over-activated in the DNA double strand break (DSB) repair deficient cells and mice, which is stimulated by endogenous DNA DSB formation that occurs during DNA replication. We found that the increased level of miR-21 and EGFR is correlated with an increased frequency of radiation-induced tumorigenesis. These results demonstrate for the first time that DNA DSBs have a functional link with the up-regulation EGFR-miR-21 loop. These findings provide an important explanation for why DNA DSB repair deficient mice have a high frequency of spontaneous tumorigenesis, and also provides additional explanation concerning why radiation-induced DNA DSBs enhances tumorigenesis. In addition, we are collaborating with Dr. Vertino (project 4) as to how miR-21 affects cell response to HZE particles via targeting DNMT1. We plan to complete these studies in the next two years.

Project 2: The hypothesis underlying project 2 is, "exposure to HZE-particle radiation, or altered miR-21 expression status, results in hyper-reliance on error-prone repair pathways, which accounts for the excess relative risk of HZE-particle radiation in lung carcinogenesis." The experimental approach is to test whether a history of HZE radiation exposure influences the fidelity (and not just the efficiency) of the response to future DNA damage. These experiments used a reporter cell line that has been engineered to report mutagenic repair of enzymatically-induced DNA double-strand breaks. We exposed replicate cultures to HZE particle radiation and challenged at intervals by expression of a rare-cutting nuclease that cuts within integrated reporter transgenes. In this system, deletion of a sequence within one of the reporter transgenes leads to green fluorescence, and translocation between two transgenes integrated into different chromosomes leads to red fluorescence. Highlights of the past year include:

- Publication of a manuscript showing that exposure to 1 Gy of 600 MeV/u 56Fe increases nuclease-induced translocations by 3-fold and deletions by a more modest but nevertheless significant amount. The effect persists for up to two weeks, is associated with presence of chronic DNA damage, and is not seen with low-LET radiation.

- Extension of findings to 1000 MeV/u 48Ti, which also increased the frequency of nuclease-induced translocations by 3-fold, although the duration of the effect is shorter.

- Demonstration that 600 MeV/u 56Fe, 1000 MeV/u 48Ti induce a characteristic set of mRNAs encoding secreted factors, including IL-1b, IL-6, IL-8. Preliminary data show that co-culture of HZE-irradiated cells with naïve bystander cells increased the frequency of mutagenic repair in the bystanders.

Together, results suggest a model depicted in the figure, where HZE exposure activates a biological stress response. Persistent DNA damage and the secretory response each contribute to activation of a mutagenic double-strand break repair pathway. This in turn leads to genomic instability and promotes tumor development. Results are of particular interest because they provide a new potential mechanism for the radiation bystander effect, based on dysregulation of DNA repair in bystander cells. For the past several months, we have been working to develop a new version of the reporter system in non-transformed bronchial epithelial cells, which are more representative of the target cells for lung carcinogenesis. We plan to test these in the coming year. We also plan further experiments to identify the mechanistic basis of the mutagenic repair phenotype.

Project 3: DNA damage inflicted by radiation or chemotherapeutic drugs induces a cellular stress response by as yet undefined mechanisms and consequences for cell survival and genomic stability. The goals for Project 3 are to determine the nature of HZE-particle induced stress response and the resulting DNA damage and genomic instability that contributes to HZE-particle induced lung carcinogenesis. In the third year we have accumulated a critical mass of experimental results for one publication (Oncogene, in revision) about the cellular context where elevated ROS levels persist, elevated up to two weeks following HZE particle exposure in the progeny of surviving cells. We found that elevated ROS co-exist with biomarkers of cellular senescence, genomic instability and nitric oxide (NO). We found that Fe particle irradiation, but not an equivalent X-rays dose, induced a senescence-like response, which increases genomic instability and can be abrogated by p38MAPK inhibition. We have initiated measuring nitric oxide production, which, following radiation exposure follows a temporal pattern overlapping with ROS, but does not appear to affect genomic instability or the senescence-like response. For the next year of support we will complete and publish studies about the ROS responses observed at earlier times following radiation exposure and effects on genomic instability. We will pursue our studies about the persisting effects of PARP-1 inhibition at early times following exposure to HZE. We will follow-up on the response leading to NO production as this is a potential, convenient biomarker that is easy to measure in exhaled air, reporting such persistent responses and signaling lung distress.

Project 4: Studies and Results: The primary goal of this project is to define the epigenetic determinants of HZE radiation exposure induced lung carcinogenesis and the extent to which this is mediated by miR-21. Our hypothesis is that there may be an epigenetic "memory" of high LET radiation exposure wherein alterations in DNA methylation resulting from acute radiation exposure and local DNA damage have the potential to become "fixed" if they are subsequently replicated, leading to permanent changes in DNA methylation and new gene expression programs. To test this hypothesis, triplicate cultures of immortalized human bronchial epithelial cells (3KT) were exposed to low LET (X-ray) (onsite at Emory) or high LET of various doses (0, 0.3, 1.0 Gy) and sources (Si, Fe) at the Brookhaven National Laboratory facility. Samples were collected from a fraction of the exposed population after 48hrs and the remaining cells were maintained in continuous culture for an additional 20 population doublings (~3 months) with weekly collection for genomic DNA, RNA, and cellular protein. Unexposed cultures underwent the same handling procedures and were maintained in parallel. The methylation status of > 485,000 CpG residues across the human genome was analyzed using the Illumina Infinium Human Methylation 450K platform. Two independent experiments have been performed for the high LET Fe series, with a 0.1 Gy dose added to the second series.

An analytical pipeline was developed to identify statistically significant changes in DNA methylation associated with dose, source, or time after exposure. A linear mixed-effects model was applied using an in-house tool ("CpG assoc") wherein Beta values (methylation level) were treated as the outcome (dependent variable), with various co-variables considered including dose, time elapsed, chip position and a random effect for chip number. We considered the Fe, Si, and X-ray exposed cohorts separately in the analyses. Significance was assessed by the Holm, and Benjamini-Hochberg methods, and permutation analyses were incorporated to test for robustness of the results.

Our results indicate that the most significant association is with time; more than 100,000 CpG sites underwent a significant drift in methylation over time in culture, independently of the type or dose of radiation exposure. Nevertheless, high LET radiation exposure led to alterations in DNA methylation at a subset of these sites, with both hyper and hypomethylation events observed. In particular, we identified 124 CpG sites for which a change in methylation was significantly associated with Fe radiation dose (FDR<0.05).

We identified 934 sites whose methylation status was significantly associated with Fe dose (849 hyper; 86 hypo); 299 sites whose methylation status was associated with Si dose (158 hyper, 142 hypo) and 1150 that were associated with X-ray dose (252 hyper; 898 hypo). Interestingly, the effects of radiation on genome-wide methylation patterns were dependent on both LET and radiation quality. Exposure to Fe ions resulted in a genome-wide trend towards hypermethylation and tended to affect sites that start out with lower DNA methylation levels (mean~21.9%); whereas exposure to X-ray resulted in a genome-wide trend towards hypomethylation and affected sites that tended to start out with a higher methylation level (median~61.9%). Indeed, Fe and X-ray exposure tended to affect different genomic compartments: sites whose methylation status was affected by Fe exposure were enriched in CpG island promoters and 'shores' (44.3% obs vs. 39.3% exp) whereas sites affected by X-ray exposure were enriched in gene bodies and intergenic regions (64.4% obs vs 60.4% exp). Importantly, radiation-induced methylation changes were observed early (48h after exposure) and persisted over time, indicating a stable and heritable change had occurred in the epigenome.

Taken together these data suggest that both high and low LET radiation exposure can induce stable and heritable changes in DNA methylation, but that these effects are distinct in mechanism, and may also have distinct biological consequences related to carcinogenesis. Hypermethylation of CpG islands like that observed in Fe exposed cells is observed in human cancers and has been linked to the silencing of tumor suppressor and other genes. The genome-wide hypomethylation of gene bodies and intergenic regions seen with X-ray exposure is also observed in human cancers and is associated with in genome instability, large scale chromosomal aberrations, and reactivation of transposable elements. The above findings are currently in preparation for publication. Our goal is for submission of a manuscript before the end of 2013.

Plans for upcoming year: At this point all of our exposure and methylation analyses have been on cell populations. If the DNA methylation changes observed are consequent to localized DNA damage or ROS effects at the track site, then these effects would be randomly distributed in a cell population and thus the methylation effect diluted out across the ~10e6 cell equivalents analyzed. To determine whether HLET radiation induced DNA damage leaves an epigenetic 'scar' that is subsequently perpetuated, or more generally affects DNA methylation in random patterns (due to more global effects like increased cellular ROS), we will attempt clonal studies where individual cells will be isolated immediately after exposure and clonally expanded prior to methylation analysis. We also plan to work with Project 2 to assess DNA methylation and chromatin structural changes in and around an induced DSB following the compromised repair observed in flow sorted high LET exposed cells.

We also plan to do more analytical work to probe the significance of our findings with respect to human cancer. Planned are experiments to compare our observed high and low LET methylation "signature" with the methylation patterns of hundreds of primary human lung cancers of different genetic and pathologic backgrounds that have been analyzed as part of the NCI's Cancer Genome Atlas project. Integrated analyses of DNA methylation with gene expression, mutation profiles and copy number alterations will allow for an assessment of the relationship between DNA methylation changes associated with radiation exposure and those associated with specific tumor classifications and subtypes, outcomes etc.

Education Component: The main goal of the education and outreach plan is designed to maximize the immediate and long-term impact of the work performed by the NSCOR network (Network), which will greatly enhance the influence of the NASA education programs. For this purpose, the education component has the following activities:

(1) Public Outreach. A. Emory NSCOR Website: We are now filming/editing/presenting interviews with Emory NSCOR project PIs and undergraduate student researchers. We plan to film additional interviews over the coming year. We have worked to maintain the Emory NSCOR website (http://nskor.emory.edu). The website contains information about the research being done (and the researchers performing the work), educational materials for students (see below), and allows participants to keep up with events related to the Emory NSCOR; B. Radiation Education for Students and the Public: We are currently developing a new curricular unit on lung cancer. The topics covered include risks and prevention of lung cancer, including terrestrial radiation exposures (i.e. radon). The possible effects of space radiation, as researched by NASA NSCORs, will also be covered. We continue to disseminate the radiation curricular unit. The unit includes a PowerPoint presentation, vocabulary list, and more. All material is designed to meet the Georgia Science Standards. The PowerPoint is also well suited for education of the general public; C. Facebook®: Our Facebook® page has over 9,500 fans (as of 10/23/13) and is actively used to promote research related to the work of the Emory-NSCOR, our educational materials, and Emory NSCOR events. To reach the widest possible audience, we are actively promoting the page via Facebook® advertising. In the future we hope to collaborate with other NSCORs and promote their work as well.

Task Progress:

	<p>(2) Internal Communication/Research Facilitation. A. Virtual Bioinformatics Team: The purpose of the team is to facilitate the shared use of datasets created by NASA NSCOR researchers. Eventually, the standardized data will be made available to the greater research community; B. Blackboard®: The Emory NSCOR Blackboard® site contains pertinent grant-related documents including meeting agendas and minutes, and lists of shared reagents/cell lines. Access is restricted to those individuals currently working on the project.</p> <p>(3) Student Engagement. A. Training of Undergraduate Researchers via the SURE program: One goal of the education unit is to encourage students to pursue science technology and mathematics (STEM) careers. To achieve this, we work with the Emory SURE Program. SURE is a 10-week long research program. The program is administered by the Emory College Center for Science Education. Our students participated in all SURE activities and presented their work via posters at the conclusion of the program. Emory NSCOR researchers hosted three SURE students during the summer of 2013.</p> <p>(4) Administration. A. Participation in Monthly Meeting: The education products are presented and discussed along with the results/plans of the research projects. B. Attendance/Presentation at NASA NSCOR Review January 2013: The Education unit provided multimedia equipment and support for the two-day event.</p>
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