Fiscal Year:	FY 2014	**Task Last Updated:**	FY 09/19/2014
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Project Title:	Mechanisms, early events, and dose dependence of radiation-induced atherosclerosis		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Radiation health		
Joint Agency Name:	**TechPort:**		No
Human Research Program Elements:	(1) **SR**:Space Radiation		
Human Research Program Risks:	(1) **Cardiovascular**:Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	35205-4831	**Congressional District:**	7
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2009 Space Radiobiology NNJ09ZSA001N
Start Date:	02/01/2011	**End Date:**	07/31/2015
No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	1	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 7/31/2015 per PI and NSSC information (Ed., 8/27/14) NOTE: End date changed to 7/31/2014 per NSSC information (Ed., 4/10/14) NOTE: End date changed to 4/30/2014 per NSSC information (Ed., 1/22/14)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Kabarowski, Janusz Ph.D. (University of Alabama at Birmingham)		
Grant/Contract No.:	NNX11AC61G		
Performance Goal No.:			
Performance Goal Text:			
Task Description:	Radiation causes vascular inflammation, which is a known risk factor for atherosclerosis. Epidemiological studies have shown that radiation from many sources, including cancer treatments, atomic bombs, and excessive occupational exposure all increase the risk for atherosclerosis. Previous studies, using gamma and/or X-ray radiation, have demonstrated that radiation causes increased white blood cell (WBC) adhesion to the blood vessel wall, an essential early event in atherosclerotic plaque formation. What is not known is whether the cosmic radiation astronauts will be exposed to on missions to the moon and Mars will similarly increase the risk for atherosclerosis. In our last project, we established that X-ray, 56Fe (iron ion), and proton irradiation of blood vessel cells increase adhesiveness of the vessel wall, and that X-rays and 56Fe accelerate development of atherosclerosis in a mouse model (results of proton experiments are pending). The molecular mechanism for this, however, is not yet known. In addition, it remains to be determined how fractionation of doses and irradiation of other tissues affect the dose dependence of both cell adhesion and development of atherosclerosis. With the hypothesis that radiation in general and cosmic radiation in particular directly alter the adhesive properties of vascular endothelium, and resultant vascular inflammation accelerates atherosclerosis, we propose to systematically investigate mechanisms of radiation effects on vascular cells, using both isolated cells and whole mice, to better predict risk and to provide the basis to develop possible future countermeasures. Our specific aims are: Aim 1: Determine whether atherogenic effects of radiation are limited to local effects on vascular endothelium, or if other systems contribute to disease progression and/or modify dose dependence. Aim 2: Determine the molecular mechanism of acute activation of leukocyte-endothelial cell adhesion in response to radiation. Aim 3: Determine how fractionation of doses affects dose-dependence of progression rates, latency periods, and surrogate endpoints.		
Rationale for HRP Directed Research:			
Research Impact/Earth Benefits:	Therapeutic radiation is a well-established risk factor for cardiovascular disease and stroke. Head and neck cancer patients who undergo radiation treatment are at significantly elevated risk of stroke, even in young patients whose risk would otherwise be near zero. For women with early breast cancer, the benefit of radiotherapy can be nearly offset by the increased risk of mortality from vascular disease. Moreover, new modalities of therapeutic radiation include the use of proton and carbon ion irradiation. Little is known about the adverse effects of these types of radiation, but early results from cell and animal studies suggest that the consequences for cardiovascular disease could be equal to or greater than those for gamma- and X-rays. The risk from accidental exposure is similar. For example, atomic bomb survivors have an increased incidence of coronary artery disease and stroke. Risk for cardiovascular disease after radiation exposure at Chernobyl was increased for those who were exposed to less than 1 Gy. Even radiation technologists in the 1950s (when shielding was less rigorous) had an increased risk of death from cardiovascular disease, demonstrating that repeated exposure at low doses results in significant risk years later. Currently, the principal strategy for reducing risk is avoidance of exposure. Completion of our specific aims will advance the knowledge of the molecular mechanisms of radiation-induced atherosclerosis, enabling better prediction of cardiovascular risk from exposure, facilitating early detection through the use of surrogate biomarkers, and pointing the way toward potential countermeasures to mitigate the cardiovascular consequences of radiation exposure, both in space and on Earth.		

Task Progress:	In this reporting period, we made substantial progress on all three specific aims. Our work demonstrates progress in answering the following CPR questions: Degen-1, “How can tissue specific risk models be developed for the major degenerative tissue risks, including heart, circulatory, endocrine, digestive, lens and other tissue systems in order to estimate GCR and SPE risks for degenerative diseases?” ; Degen-2, “What are the mechanisms of degenerative tissues risks in the heart, circulatory, endocrine, digestive, lens, and other tissue systems? What surrogate endpoints do they suggest?” Progress on each aim is summarized below. Aim 1: Determine whether atherogenic effects of radiation are limited to local effects on vascular endothelium, or if other systems contribute to disease progression and/or modify dose dependence. We performed studies examining 56Fe-induced thickening of the wall of the carotid artery for both radiation targeted to the chest and neck and radiation of the whole mouse. Ten week old male ApoE -/- mice (a well-characterized animal model of atherosclerosis) were anesthetized by injection of the drugs ketamine and xylazine and irradiated with either 0 Gy , 2.0 Gy , or 5 Gy 56Fe (accelerated iron ions). The mice were returned to our home institution and fed a normal mouse-chow diet and housed under standard conditions. At 13 weeks post-irradiation (when the mice were 23 weeks of age), mice were euthanized and dissected. Increased thickness of the intimal layer of the wall of the carotid artery, an atherosclerotic change, was compared between mice that received radiation only to the chest and neck and those that received radiation to the entire body. In addition, atherosclerotic changes in the aortic root (where the aorta connects to the heart) were also examined. Results of this study are now complete and are being prepared for publication. Aim 2: Determine the molecular mechanism of acute activation of leukocyte-endothelial cell adhesion in response to radiation. We showed previously that both x-irradiation and 56Fe increase the adhesiveness of vascular endothelial cells (the cells that line the inside of the vessel wall), an important, early step in the development of atherosclerosis. We also demonstrated that this effect depends on chemokines, a family of signaling molecules that is involved in both cell adhesion and atherosclerosis. In the past year, we worked to identify the particular chemokine responsible. For this study, endothelial cells from human aortas were grown in dishes to simulate the lining of the aorta. First, cell-growth media, the liquid that nourishes cells grown in dishes, was collected from the human aortic endothelial cells (HAECs) 24 hours after irradiation from both x-irradiated and sham-irradiated control cells (cells that were manipulated exactly as the irradiated cells, but not actually irradiated). A Luminex assay was then used to determine the concentration of several chemokines, focusing on those that were likely to be secreted by endothelial cells and known to be involved in atherosclerosis. From this, we could determine which chemokine(s) were secreted in response to radiation. When candidate chemokines were identified, we tested for their importance in the mechanism of adhesiveness changes by inhibiting their action using specific antibodies. This was to determine how necessary the candidate chemokines are for the increase in adhesion. We also tested whether each chemokine was sufficient by itself to reproduce the radiation effect. That is, we added individual chemokines to un-irradiated cells to determine whether they could increase adhesiveness by themselves. This study is also complete and is being prepared for publication. Another important question concerning the mechanism of radiation effects on atherosclerosis is how different types of radiation affect the disease process. This is very important, because cosmic radiation is very different from the x-rays used in diagnostic medicine (that is, the x-rays and CT scans used to see inside the body) and in cancer treatments. Most of what we know about radiation effects on atherosclerosis comes from studies of such terrestrial radiation sources. In space, however, astronauts will be exposed to accelerated ions as well as x-rays, and these ions interact with human tissue very differently than do x-rays. An understanding of the similarities and differences between different types of radiation with respect to the arterial damage they cause will be essential to enable us to predict risk to astronauts. The knowledge gained will also be important for understanding new types of radiation therapy, such as proton therapy, that patients are now receiving in leading hospitals in the USA and abroad. To address this question, we irradiated mice with x-rays or either 56Fe or 28Si, two different ions found in cosmic radiation. We used the same 10-week old ApoE -/- mouse model that we had used in previous studies. Again, we waited 13 weeks after radiation to assess atherosclerosis-related radiation effects. When the mice were 23 weeks old, they were euthanized and atherosclerotic changes were examined in the carotid artery, the aortic root, and in other parts of the aorta. We have now determined that there are both similarities and differences in the effects of these three types of radiation. The results are to be presented and their consequences discussed in an upcoming publication, now in preparation. Aim 3: Determine how fractionation of doses affects dose-dependence of progression rates, latency periods, and surrogate endpoints. We also compared 10-week old male mice that were either un-irradiated, irradiated with a single dose of 2 Gy iron ions on one day, or irradiated with 5 doses of 0.4 Gy iron ions on each of 5 consecutive days. The experiments are finished, but the data are still being analyzed. Results will be included in the final progress report to be written after the conclusion of this funding period on July 31, 2015.
Bibliography Type:	Description: (Last Updated: 04/12/2018)
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