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| **Fiscal Year:** | FY 2017 | **Task Last Updated:** | FY 07/07/2017 |
| **PI Name:** | Grabham, Peter Ph.D. | | |
| **Project Title:** | Combined Effects of Space Radiation and Microgravity on the Function of Human Capillaries and the Endothelial Barrier: Implications for Degenerative Disorders | | |
| **Division Name:** | Human Research | | |
| **Program/Discipline:** | | | |
| **Program/Discipline--Element/Subdiscipline:** | HUMAN RESEARCH--Biomedical countermeasures | | |
| **Joint Agency Name:** | | **TechPort:** | No |
| **Human Research Program Elements:** | (1) **HHC**:Human Health Countermeasures | | |
| **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:** | 10032-3702 | **Congressional District:** | 13 |
| **Comments:** | | | |
| **Project Type:** | Ground | **Solicitation / Funding Source:** | 2013 HERO NNJ13ZSA002N-Crew Health (FLAGSHIP & NSBRI) |
| **Start Date:** | 08/27/2014 | **End Date:** | 09/30/2018 |
| **No. of Post Docs:** | 1 | **No. of PhD Degrees:** | |
| **No. of PhD Candidates:** | | **No. of Master' Degrees:** | |
| **No. of Master's Candidates:** | | **No. of Bachelor's Degrees:** | |
| **No. of Bachelor's Candidates:** | | **Monitoring Center:** | NASA ARC |
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| **Flight Program:** | | | |
| **Flight Assignment:** | NOTE: Extended to 9/30/2018 per NSSC information (Ed., 12/13/17)<br>NOTE: Extended to 9/30/2017 per PI and NSSC information (Ed., 7/22/16) | | |
| **Key Personnel Changes/Previous PI:** | | | |
| **COI Name (Institution):** | Sharma, Preety Ph.D. ( Columbia University ) | | |
| **Grant/Contract No.:** | NNX14AR22G | | |
| **Performance Goal No.:** | | | |
| **Performance Goal Text:** | | | |

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| **Task Description:** | This proposal is aimed at determining the effects of space radiation combined with microgravity on the function of human blood vessels and capillaries. The average human body contains tens of thousands of miles of vessels that permeate every tissue down to the microscopic level; therefore, it is an important target for radiation and is also influenced by gravitational forces. The vascular system is crucial to healthy functioning of the tissues and its dysfunction is not only a primary event in a range of degenerative diseases but also an important influencing factor in many others. The two functions of the human vascular system that greatly affect human health and disease are 1) angiogenesis -- the growth of new vessels to replace damaged vessels, and 2) Barrier function – the process that allows nutritious molecules to cross from the blood to tissues and waste molecules to be cleared out from tissues. Disruption of these processes is known to cause degenerative disease.<br>We have shown that space radiation inhibits angiogenesis and disrupts endothelial barrier function using human endothelial cells in 2- and 3-dimensional human tissue models. The doses and time course for radiation-induced events are now known which makes it possible to assay for joint effects with other environmental influences. Angiogenesis and barrier function are also affected by microgravity so there is a potential for further dysfunction of the human vasculature when applied in combination with radiation. Here, we propose a ground-based study using simulated microgravity to determine the combined effects of space radiation and microgravity on human blood vessel models and its impact on degeneration by testing for angiogenesis and endothelial barrier function using our established assays. |
| **Rationale for HRP Directed Research:** | |
| **Research Impact/Earth Benefits:** | Tissue models<br>The development of 3-Dimensional human tissue models from normal human cells and stem cells has great potential in many fields of medical research. Tissue models can more accurately depict human tissue since the cells can be arranged spatially as they would be in vivo and can interact with each other as they would in the human body. A neurovascular unit can be used for basic research on many aspects of the human brain. These include regeneration, synaptic function, and degeneration. Because the tissue model is derived from individual cells, each cell type can be altered genetically before it is incorporated into the model. The effects of radiation combined with simulated microgravity can be of benefit to the health of astronauts. |
| **Task Progress:** | We have shown that space radiation inhibits angiogenesis and disrupts endothelial barrier function using human endothelial cells in 2 and 3-dimensional human tissue models. The doses and time course for radiation-induced events are now known which makes it possible to assay for joint effects with other environmental influences. Angiogenesis and barrier function are also affected by microgravity so there is a potential for further dysfunction of the human vasculature when applied in combination with radiation. Here, we describe a ground-based study using simulated microgravity to determine the combined effects of space radiation and microgravity on human blood vessel models and its impact on degeneration by testing for angiogenesis and endothelial barrier function using our established assays.<br>Task progress<br><br>Experiments addressing the effect of simulated microgravity alone on the development of human capillaries (angiogenesis) and the effects on mature capillary models are now completed. This material is being prepared as a manuscript for submission to the new Journal – npgMicrogravity. Both angiogenesis (capillary formation) and the effect on mature vessels were examined.<br><br>Effects of microgravity on developing microvessels<br><br>We first tested the effect of a 3D clinostat spin on the activity of motile tips – the initial structures that facilitate the extension of pioneer tunnels, which later become capillary tubes. The results showed little effect--only a slight increase in the number of motile tips in vertical and 3D rotations.<br><br>A second set of experiments investigated the effects of simulated microgravity (SMG) on the entire process of capillary formation, from seeding of cells in the matrices to the final vessels structure after 7 days of culture. In this case there was a significant effect on capillary formation. We tested several types of rotation including vertical spins at 1, 5, and 10 rpm, a horizontal spin at 10 rpm and 3D clinostat rotation at 10 rpm for each axis. There was a clear inhibition of vessel formation after all vertical rotations and the 3D rotation whereas vessel formation after horizontal rotation was unaffected and similar to the stationary control. There are 2 main conclusions from these data. 1) Since vertical rotation is as effective as 3D rotation, the data indicates that removal of the vector of gravity is sufficient to cause an inhibition of vessel formation. It is not necessary to distribute the vector of gravity globally to cause an effect; removal by vertical spin is sufficient. This suggests that a mechanism is held in place by the force of gravity on Earth can be disrupted by rotation and cause the kinds of effects seen in the space environment. 2) Since a 1 rpm spin was as effective as faster rotations even though there is little turbulence at such a speed it is unlikely that turbulence is causing the inhibition. Further experiments showed that vessel development in disruptive spins was normal for up to 3 days but affected after this point in development when the vessels became more mature with widened. Examining the history of microvessel growth by looking at the collagen deposited by microvessels shows that microvessels complete maturity before collapsing.<br><br>Effects of microgravity on mature vessels<br><br>Human capillary models were first grown to maturity and then subjected to the same variety of rotations used in the angiogenesis studies. These models represent the capillaries already present in vivo. The effect of rotation on these cultures is similar to that on developing cultures, that is, all the vertical and the 3D rotations are effective at changing the final capillary structure. After 48 hours rotation there was a reduction in total vessel length although further studies are required to determine how this response translates in vivo. Morphological studies show that mature vessels collapsed. These studies and the angiogenesis studies do, however, prove that in isolation, human capillaries are responsive to alterations in gravity. Therefore, it highly likely that there is some kind of response in vivo.<br><br>Low dose inhibition of human angiogenesis by charged particles: LET (linear energy transfer) ranges and synergistic effect<br><br>Since both space radiation and simulated microgravity are disruptive to human capillary models we expected that their combined effects would occur at lower doses of charged particle radiation. Previous data from several years ago indicated that heavy and light ions inhibit angiogenesis with a 50% effect at around 40 cGy for both types of radiation |

albeit via distinct mechanisms. In order to investigate the combined effect we carried out experiments with much lower doses than previously used with an improved assay. Surprisingly, we found that even without simulated microgravity the charged particles inhibited angiogenesis at much lower concentrations than previously detected.

For angiogenesis: Light and heavy ions show distinct responses at different stages of angiogenesis and LET range studies showed that light ion effects occur with an LET of < 3 KeV/AMU and heavy ion effects occur with an LET of > 8 KeV/AMU or greater. Light ions caused significant inhibition at 1.25 cGy and Heavy ions coincidentally also caused significant inhibition at 1.25 cGy. These doses were considered to be much more relevant to those in space and because of the nature of mixed ion species in the space environment, experiments were carried out using mixed heavy and light ion beams at NASA Space Radiation Laboratory (NSRL). For angiogenesis, a surprising result was seen. A 1:1 ratio of light and heavy ions shows a synergistic effect that is significant at a dose of 0.3 cGy (0.15 cGy each of Fe ions 1GeV and protons 1GeV). This is the lowest known dose effect of space radiation at the cell and tissue level and represents a novel synergistic effect of heavy and light ions.

Experiments using mixed ions experiment have been repeated with different ions- Helium (1GeV) and Si ions (600 MeV) and a similar result confirms the synergistic response.

This is considered this an important unexpected finding and a manuscript is being prepared together with data on LET ranges from a previous grant award. Acknowledgements will be made to both grant awards. Combined effect of microgravity and space radiation on developing vessels

Since the LET range studies delineated the response to radiation into 2 groups we used both heavy ions and light ions in combination with SMG for these studies. Vessel models were exposed to radiation on day 1 after seeding the cells in 3D matrices then either grown to maturity while stationary or revolving vertically at 5 rpm. For all particle radiation (including 1 GeV He ions, 1 GeV protons, and 1 GeV Fe ions) combined with SMG there is an additive effect--the shape of the dose curve is the same but shifted lower in the presence of SMG. Thus, there is the potential for the combined effects of the space environment to cause more damage to micro-capillaries.

Combined effect of microgravity and space radiation on mature vessels

The data prove that simulated microgravity together with heavy ion radiation is at least additive in breaking down the structure of mature vessels. There was a distinct morphology when both agents are applied together. There are a number of vessels ending in dead ends and in fact very little tube structure left. Experiments with protons and Helium ions, which do not affect vessels up to 4 Gy showed that the microgravity acts alone in this case.

In conclusion we have shown that simulated microgravity alone has little effect on the early motile tip stage of angiogenesis but does have an effect on the entire process of capillary formation and is also effective on mature vessels. Both light and heavy ions are more effective than previously thought and can inhibit angiogenesis detectible at 1.25 cGy and that there is a synergistic response of mixed ions that brings the effective doses even lower (lowest significant effect with 0.15 cGy each ion). In mature vessel models, simulated microgravity has a profound effect of reducing full width vessel models at 1.25 cGy. Furthermore, the combined effect of microgravity is additive to that of charged particles making the space environment. Taken together the radiation and microgravity in the space environment have the potential to damage the microvasculature, which could cause pathologies such as cardiovascular disease (CVD) and neurodegeneration in astronauts.

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