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Project Title:	Telomeres and the One Year Mission Project		
Division Name:	Human Research		
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Program/Discipline--Element/Subdiscipline:			
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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Comments:			
Project Type:	FLIGHT	**Solicitation / Funding Source:**	2017-2018 HERO 80JSC017N0001-BPBA Topics in Biological, Physiological, and Behavioral Adaptations to Spaceflight. Appendix C
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Task Description:	The ultimate goal of the studies proposed here is to establish temporal profiles of human telomere length dynamics and DNA damage responses of importance for maintenance of human health and performance during long-duration deep space missions. We hypothesize that telomere length dynamics (changes over time) represent a particularly relevant and informative biomarker of health for the astronauts, as it reflects the combined experiences and exposures encountered during spaceflight. That is, an astronaut's individual genetic susceptibilities, unique lifestyle stresses encountered (e.g., nutritional, psychological, physical), and particular environmental exposures (e.g., altered atmospheres, microgravity, space radiations) are all integrated and captured as changes in telomere length. Thus, the rate at which telomeres shorten provides a general measure of health that can be linked to aging, as well as to risk of developing age-related pathologies, ranging from reduced immune function and dementia, to cardiovascular disease and cancer. Importantly, functional telomeres are also essential for maintaining genomic integrity and stability, as they protect chromosomal termini from inappropriate degradation, and prevent these natural DNA ends from being recognized as broken DNA and triggering inappropriate DNA damage responses (DDRs). To identify trends in adaptations to human health and performance during long-duration low-Earth orbit, we propose telomere length and DDR/cytogenetic measures pioneered and validated in the NASA Twins Study/first One Year Mission, across the Integrated One-Year Mission Project onboard the International Space Station and the concurrent ground analog (prolonged isolation) component.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Identifying interactive effects of genetic and nongenetic telomere length determinants and DDRs will improve understanding of aging and aging trajectories (disease risk), as well as guide future studies and development of potential strategies for improving health-span, not only in astronauts on long-duration missions, but for those on Earth, as well.
Task Progress:	Astronauts live and work in an extreme environment fraught with extraordinary hazards and chronic stressors, including space radiation exposure, microgravity and/or altered gravity, confinement and isolation (psychologically stressful), a closed environment (biologically hostile), altered nutrition and microbiome – all in addition to intermittent bouts of acute stress, e.g., extravehicular activities (EVAs), and endurance/aerobic exercise to maintain bone and muscle mass. Considering the combination of unique stressors and chronic space radiation exposures associated with long-duration spaceflight, as well as the adverse health effects experienced by multiple physiological systems (e.g., dysregulated immunity, inflammation, infection), we proposed that monitoring of telomere length dynamics and persistent DDRs (DNA damage responses) (genome instability) would be of particular relevance for astronauts because these informative biomarkers provide insight into individual health status during a mission, as well as potential implications and predictions for aging and disease risk later in life. The successful mission of Artemis 1 carried with it the hopes and dreams of returning to the Moon and venturing beyond to Mars. As the number and diversity of space travelers increase in the coming years, a better understanding of how long-duration spaceflight affects human health is essential to maintaining individual astronaut performance during and improving disease and aging trajectories following, future exploration missions. Findings from our NASA Twins Study and Telomeres investigations provided clues suggestive of potential mechanistic roles for chronic space radiation exposure underlying changes in telomere length dynamics and persistent DNA damage responses associated with long-duration spaceflight (see publications below). Exposure to the space radiation environment contributes to a number of fundamental biological features of spaceflight, including mitochondrial dysregulation and elevated oxidative stress, increased DNA damage, and dramatic shifts in telomere length dynamics. Spaceflight-specific telomere elongation was confirmed in three unrelated astronauts during one-year and six-month missions onboard the International Space Station (ISS) using multiple assays (including sequencing), and in all samples and cell types evaluated (including urine). Rapid and significant telomere shortening after return to Earth was also observed in the vast majority of crewmembers. Interestingly, a mutational analysis of C. elegans flown on the ISS for 11 days found no significant differences in mutation rates but did report slightly elongated telomeres in the worms. We proposed that in the context of chronic exposure to the space radiation environment, persistent DDRs to increased reactive oxygen species (ROS) production by dysfunctional mitochondria, elevated levels of oxidative damage and replication stress, and low dose rate high linear energy transfer (LET) space radiations, conspire at damaged telomeres, acting to either enhance telomerase activity, or perhaps more likely, particularly in blood lymphocytes with very low levels of telomerase activity, transiently activate telomerase-independent alternative lengthening of telomeres (ALT) or ALT-like recombinational pathways that are at least partially responsible for the striking shifts in telomere length dynamics observed. Interestingly and in support of such a view, we also found longer telomeres in a cohort of prostate cancer patients immediately following fractionated exposures associated with radiation therapy. Individual differences in response were observed in both cohorts, underscoring the importance of developing personalized approaches for evaluating human health effects and long-term outcomes associated with radiation exposure scenarios, whether on Earth or living in the extreme environment of space. Ionizing radiations are exquisite in their ability to induce DNA damage in the form of prompt double-strand breaks (DSBs), which when mis-repaired can result in a variety of well-described chromosome rearrangements. Utilizing the strand-specific methodology of directional genomic hybridization (dGH), and for the first time in astronauts, we detected increased frequencies of intra-chromosomal inversions during spaceflight, which persisted after spaceflight, potentially suggestive of stem-cell damage, clonal hematopoiesis, and/or genome instability. Also consistent with exposure to the space radiation environment, strong relationships between post-spaceflight chromosome aberration frequencies, specifically inversions, and lifetime radiation dose estimates were identified, providing additional evidence of their persistence after exposure, and further support of inversions as informative biomarkers of radiation exposure associated with spaceflight. Chronic radiation exposure is one of the primary hazards of long-duration space travel, particularly as astronauts venture deeper into space and outside of the protection the Earth provides. The mechanistic links between chronic exposure to the space radiation environment and the telomeric and DNA damage responses we observed, as well as radiation dose-dependent decreases in white blood cell (WBC) counts post-spaceflight, provide support for the development of effective radiation mitigators and individualized countermeasures for upcoming deep space exploration missions. Furthermore, a major conclusion from our previous studies is that inter-individual differences in response to the combined stressors and exposures associated with spaceflight predominate over general trends of individual factors and highlight the critical need for personalized monitoring and precision medicine strategies for future astronauts.

	While the definitive mechanisms involved in these processes remain elusive, we propose a testable model based on our foundational findings: chronic exposure to the space radiation environment results in genomic DNA damage and instability, as well as transient activation of telomerase-dependent and/or independent pathways in response to chronic oxidative damage specifically to telomeres, which together with lymphocyte radiosensitivity, particularly those with short telomeres (55), and the resulting redistribution of leukocyte subsets (56), contribute to the telomere elongation observed during spaceflight. Our current studies as part of the Complement of Integrated Protocols for Human Exploration Research (CIPHER) will assess a larger, more diverse cohort of astronauts, on various duration missions (ranging from several months to one year), will serve to further elucidate and confirm underlying mechanisms of the dramatic changes in telomere length dynamics associated with spaceflight, and provide additional insight into individual differences in response and outcomes, and guide future development of effective mitigation strategies. Data collection and analysis is progressing successfully, with many sample collections (pre-flights, in-flights, and post-flights) completed and/or planned.
Bibliography Type:	Description: (Last Updated: 04/25/2024)
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