Concept Clearance

Branch: HSRB

Council Period: 201801

Concept Title: Research Network on Telomeres as Sentinels of Environmental Exposures, Psychosocial Stress, and Disease Susceptibility

Introduction

A growing number of investigators across a range of scientific fields have become intrigued by the role of telomeres in health and aging. In addition to their direct role in certain diseases, telomeres, and more specifically their maintenance, also appear to be both a facile sensor of insult, "sentinel" for environmental exposures and psychological stress, and potentially a marker of life history readout in response to the totality of exposure events of an individual. For example, changes in telomere length have been associated with exposure to cadmium, arsenic, and non-dioxin-like PCBs (Zota et al. 2015, Fillman et al. 2016, Gao et al. 2015, Mitro et al. 2016) However, inconsistent epidemiological findings, concerns about comparability of telomere assessments across multiple studies, and emerging findings about the more prominent role that early life exposures play in setting telomere length suggest that more research is needed to understand the role of exposures and telomeres in health.

Research Goals and Scope

A recent NIEHS/NIA workshop brought together experts from basic telomere biology, medicine, biopsychology, epidemiology, and related fields to explore and discuss a number of questions including how assays of the status of telomeres can best be used, what research/technology advances are needed in the field, how best to use telomere measurement in the study of environmental and stress exposures, and what role telomeres play in disease susceptibility as detected in population-based research. Experts discussed how basic researchers can help epidemiologists/clinicians and vice versa. Discussions also addressed factors that need to be measured alongside of telomeres: interactions between genes and the environment (including both the physical and the social environment) on health, tissue-specific effects, and the potential to use surrogate tissues in situations where the "true" tissue of interest (e.g., the brain) is inaccessible. Building on this productive dialogue, attendees continued discussion about the immediate need to compare results using different assays and for different cell types, set standards for sample preparation, DNA extraction, and reporting of assay protocols, and make recommendations for conducting telomere assessments in different research contexts (lab-based, population based). Continued dialogue across disciplinary lines will be essential to move this agenda forward. Consensus emerged about the need for definitive studies about methods and universal standards for laboratory protocols, involving a wide range of labs working together and bringing in biostatistics expertise. Participants also recommended that distinct sets of recommendations be developed for laboratory, clinical, and population-based studies given that no single approach would simultaneously meet the needs of all types of studies.

Continued transdisciplinary dialogue can support a more coordinated research strategy to address:

- Whether telomere length (TL) and other markers are early sentinels of premature aging or early disease processes because they encapsulate the life history of the individuals. What studies are necessary to enhance the quality of data that allows us to test this hypothesis? Is the telomere a marker of the exposures or is it a cumulative index of overall health status? If it's a marker of cumulative exposure, what is driving that measure?
- Given accumulating evidence that initial setting of TL at birth and exposures in early development play important roles in predicting long-term outcomes: What governs the fast range of shortening early in life and why is there a window of susceptibility? Is there a set-point during early development and is this universal? What are the reasons for race and sex differences, observable already early in life? What are the best time/conditions to measure telomeres?
- How should we think of TL as an "integrative marker"? Does focusing on telomeres have advantages/disadvantages relative to other r biomarkers related to aging or exposures? What is the most important set of assays for determining cell aging in healthy humans? What other markers can be combined? Should we examine TL in addition to other indices of cellular aging such as inflammation, senescence-associated secretory phenotype (SASP), genetic index, or epigenetic aging? Mitochondrial function? In what contexts do replicative senescence and TL matter most?
- Given that longitudinal data in well-characterized cohorts will be necessary to advance this agenda to determine the impact of a range of stress and environmental exposures on health and aging, what are the next steps for this field?

Mechanism and Justification

This consists of three proposed initiatives, two are linked and planned as cooperative agreements and the third would be released later while the U24 is still active. The two linked activities will be supported using funding from NIA and NIEHS and the third will be supported primarily by NIEHS, hopefully with support from other ICs, and released after the first two initiatives. A Network/Collaboratory is proposed to allow for a flexible range of activities (meetings, pilot studies, collaboration across laboratories, commissioned analyses, outreach, etc.) to facilitate continued dialogue between basic biologists and scientists

wanting to use telomere assays as markers to drive more specific analyses. In addition, there is a need for cross-validation between studies using different methods. This initiative would also support a study involving multiple labs, with input from experts across the telomere field, to develop recommendations for assay protocols for telomere measurement for different types of studies. Results would yield a set of recommendations and standards for the field. This initiative is planned as a cooperative agreement and will involve two linked activities. The first is a methods study (U01) involving several labs. The second is an interdisciplinary network/collaboratory (U24) to both (1) serve as a coordination platform for the methods study and (2) create infrastructure for the collaboration and coordination between NIEHS and NIA researchers and facilitating transdisciplinary advances in exposure science.

This will be important for informing a prevention agenda to address the following questions:

- If telomere length and other markers are early sentinels of premature aging or early disease processes to determine the impact of a range of stress and environmental exposures on health and aging, what are the next steps for this field?
- Is the telomere a marker of the exposures or is it a cumulative index of overall health status? If it's a marker of cumulative exposure, what is driving that measure?

In addition, there is a need for cross-validation between studies using different methods. This initiative would also support a study involving multiple labs, with input from experts across the telomere field, to develop recommendations for assay protocols for telomere measurement for different types of studies. Results would yield a set of recommendations and standards for the field.

A third initiative is envisioned that will focus on research to understand relationship between environmental exposures and telomere biology. To fully take advantage of the standards developed and research advances made from the above two linked initiatives, this third initiative is expected to be released in the Spring 2021, during the course of the U24, but after the U01s are completed. The RFA would be for more hypothesis-driven research and likely be for R01s, and R21s, as appropriate. Program staff from other ICs will be contacted to see if they would be interested in joining this RFA, and if so, what specific topics that would be interested in.

Initiative (per year)	NIEHS Contribution	NIA Contribution	Contribution from other ICs
Telomere Network/Collaboratory (U24) and Methods Development (3-4 U01s)	$2M	$3.75M	
EHS-focused Initiative	$5M		To be determined

Total Costs for Three Initiatives $10.75M
NIEHS Contribution $7M