Telomeres

NANCY ADLER and AOIFE O'DONOVAN

Abstract

Telomeres cap the ends of chromosomes in the cell and their length provides a marker of cellular aging. As people age, their telomeres generally shorten, a process that is accelerated by exposure to chronic stress as well as by health behaviors such as smoking, lack of exercise, and poor diet. Individuals who are lower on the social hierarchy have shorter telomeres on average, providing evidence of the health-damaging effects of social disadvantage.

INTRODUCTION

Biomarkers alert patients and providers to incipient disease to allow early intervention and monitor the efficacy of treatment. For example, elevated levels of glycated hemoglobin (HbA1c), reflecting the concentration of glucose in the blood, signals increased risk of diabetes and may trigger attempts to reduce risk through diet, exercise, and weight loss. If diabetes occurs, HbA1c levels help monitor whether health behaviors and/or pharmaceutical treatments are effective in controlling the disorder. Biomarkers also provide information on the health of populations and enable us to link social factors to internal biological process that can affect health.

Biomarkers are frequently used to assess stress responses and assess the extent to which social circumstances trigger and modify these responses. Most commonly used is cortisol, a hormone that mobilizes resources to allow the body to activate "fight or flight" responses to deal with an immediate threat. Cortisol levels have been linked to a range of social factors including low social rank in nonhuman primates, negative social evaluations in laboratory settings, and low income. However, cortisol is more useful as a measure of acute stress than of chronic stress and researchers have sought a more stable biomarker that can better inform us about cumulative lifespan effects.

Emerging Trends in the Social and Behavioral Sciences. Edited by Robert Scott and Stephen Kosslyn.
 ISBN 978-1-118-90077-2.

In this context, telomere length, a biomarker for cellular aging, has emerged as a highly promising candidate. Unlike biomarkers that capture byproducts of biological responses in specific systems, telomere length in white blood cells may capture cumulative processes at the cellular and molecular level throughout the body. White blood cells comprise various types of immune cells that circulate in the system and serve important immune system functions across bodily systems and tissues. Although it has not been unequivocally shown that telomere attrition is a mechanism by which social disadvantage leads to earlier development of chronic age-related diseases and higher rates of mortality, white blood cell telomere length has been linked both to experiences of chronic stress and disadvantage, and to increased risk for specific diseases and mortality. We focus primarily on disadvantage resulting from low socioeconomic status as reflected in low income and education.

FOUNDATIONAL RESEARCH

Telomeres

Telomeres are DNA–protein complexes that form protective caps on the ends of chromosomes. Analogous to how the cap on the end of a shoelace protects it from unraveling and fraying, the telomere on the tip of the chromosome protects against damage to the DNA that encodes our genes. Over time, as cells divide and are subject to biochemical stress, telomeres shorten. When their length falls below a certain critical threshold, cells can become functionally impaired and unable to divide, and can undergo apoptosis or cell death. Telomere length has been described as a "molecular clock" and the shortening of telomeres with age is thought to play a mechanistic role in age-related functional decline and increased risk for disease.

The number of studies of telomeres in humans has grown since the dawn of the 21st Century. Such research has been facilitated by the fact that telomeres in white blood cells can be easily measured in blood samples. Although we do not yet know how strongly correlated telomeres from white blood cells are with telomeres from other cell types, white blood cell telomere length has emerged as a powerful biomarker. Prospective studies have shown that individuals with shorter white blood cell telomeres are more likely to develop age-related diseases such as cardiovascular disease (including myocardial infarction and stroke), some types of cancer, autoimmune disorders, and dementia.

The precise causes of telomere shortening in humans are not fully understood. However, there is evidence that telomere shortening is accelerated by oxidative stress, the imbalance between oxidizing molecules and antioxidant

defenses, and by chronic activation of the inflammatory response of the immune system. There is also some evidence that high levels of the stress hormone cortisol may downregulate processes that maintain telomeres.

Oxidative stress and chronic inflammation, which are linked to greater telomere attrition, are elevated among individuals who smoke, are physically inactive and/or have high body mass index. Because socially disadvantaged groups show higher rates of all these risk factors, they may be a pathway by which social factors get into the body to affect health and longevity. In addition, socially disadvantaged individuals experience greater chronic psychological stress, which can also increase inflammation and oxidative stress, may accelerate telomere attrition.

Stress and Telomere Length. Accumulating evidence links psychological stress exposure with short telomere length. A groundbreaking study found shorter telomeres among women experiencing greater distress as a result of caring for a chronically ill child, and the longer the duration of the caregiving, the shorter her telomeres. Subsequent studies have linked shorter telomeres to other chronic stresses across the lifespan. One study found shorter telomeres in the adult offspring of women who were exposed to stress during pregnancy. Another found a faster rate of telomere shortening from age 5 to age 10 among children exposed to maternal domestic violence, physical maltreatment and frequent bullying than among children without such exposure to violence.

It is not simply exposure to threatening or stressful conditions that leads to accelerated telomere attrition, but the individual's appraisal and cognitive-emotional response to the situation. For example, among the mothers caring for a chronically ill child in the study described, shorter telomeres were found primarily among those who experienced higher levels of perceived psychological stress and comparison group mothers who reported relatively high levels of perceived stress. Perceived psychological stress appears, in fact, to be more robustly related to short telomere length than is objective stress exposure. This stands to reason because stress gets "under the skin" only to the extent that it activates the biological stress response, which in turn is dependent on stress perception.

Social Determinants. Studies linking stress and telomere length suggest a possible pathway by which social disadvantage results in disease. Socially disadvantaged individuals—those with less education and lower incomes and members of some minority groups—experience greater chronic stress. However, findings to date linking telomere length to specific aspects of social status are mixed.

Much of the research on social status and health, including telomere length, has been done in the United Kingdom. Shorter white blood cell telomere length was observed among British women in manual versus nonmanual occupational classes and in unemployed versus employed Scottish men. However, in these samples, telomere length was not associated with income or education, or with neighborhood deprivation. In contrast, lower income was associated with shorter telomere length in a study of Scottish men and women, and two other studies in Britain found an association of shorter telomere length with lower educational attainment, but not other indicators of social disadvantage.

In the United States, studies have examined telomere length in relation to race and ethnicity as well as to socioeconomic status. African-Americans are exposed to greater chronic stress and have poorer health status than do other groups. Within samples of African-Americans, the relationship between psychological stress and short telomere length appears to hold. However, African-Americans appear to have relatively longer telomeres than whites. A recent study of older black and white adults demonstrated the importance of considering the combination of race/ethnicity and socioeconomic status in assessing telomere length. Although, overall, individuals with more than a high school education had longer telomeres than those with a high school education or less, this effect was moderated by race. There was relatively little difference in telomere length by educational levels for whites, but a marked difference for blacks. Indeed, the telomeres of blacks with more than a high school education were not only significantly longer than those of lesser-educated blacks but were also significantly longer than those of whites no matter their level of education.

CUTTING-EDGE RESEARCH

Mechanisms of the Stress–Telomere Relationship

The vast majority of studies linking the social environment with telomere length focus on stress as a mediator of the association. Much research on the health effects of chronic stress has focused on "allostatic load," the accumulated wear and tear on the body of repeated exposures to stress. Allostatic load represents dysregulation of multiple systems within the body and predicts future risk of morbidity and mortality. The same processes that contribute to allostatic load are related to telomere shortening. Consequently, studies are currently making links between social disadvantage and exposure to uncontrollable threatening situations on the one hand and dysregulation of biological systems and accelerated cellular aging on the other.

These studies reveal the biological effects of frequent cycles of threat and disadvantage associated with lower social status. Social threats activate the hypothalamic-pituitary-adrenal axis and increase production of cortisol and proinflammatory proteins. These responses are functional in the short term in preparing the body for "fight or flight" as well as for injury and infection. However, repeated and prolonged activation of these responses in the socially disadvantaged can promote chronic biological changes that accelerate telomere shortening.

In addition to direct physiological effects of repeated and prolonged activation of biological stress systems on telomeres, recent studies reveal an indirect path from social status to cell aging through behavioral responses individuals use to cope with stressful circumstances. Individuals with fewer socioeconomic resources encounter more uncontrollable stressors than do the more advantaged. Animal models have shown that exposure to uncontrollable stress promotes greater ingestion of foods containing fats and sugars. As with the stress response, this behavioral response is functional because consuming such foods can downregulate cortisol release. Among humans, stress-inducing exposures may not only elicit the ingestion of energy dense "comfort foods" but also use of tobacco and other substances. These bring short-term emotional relief and can dampen down the stress response, but over time, can damage telomeres and the body.

Individuals who have encountered repeated exposures to threatening and uncontrollable situations may become more vigilant for information that may signal potential threats. Such vigilance is advantageous in dangerous environments. However, sensitivity to threat can be costly, leading to more frequent and prolonged activation of biological stress systems even when threats are absent or mild. When adolescents from different socioeconomic backgrounds were asked to interpret videos of various kinds of social situations they made similar interpretations of clearly positive or clearly negative scenarios. However, adolescents from families of lower socioeconomic status interpreted ambiguous situations as more threatening than did their more advantaged peers. Adolescents making more negative attributions to ambiguous videos appeared to pay a price for their vigilance, exhibiting higher blood pressure in overnight monitoring.

Biological stress responses to anticipated and actual threat—both of which may be more common in socially disadvantaged individuals—may promote telomere shortening. This pathway would explain recent finding that women who rated a standardized acute laboratory stressor as more threatening had significantly shorter telomeres than those making more benign appraisals.

Buffers of the Stress–Telomere Relationship. Although stress appears to accelerate telomere shortening, individuals who are experiencing chronic stress may be able to lessen its impact on their telomeres through engagement in healthy behaviors. For example, physical activity may slow telomere attrition, especially in the face of stress. In one study, women who were physically active showed no relationship between their reported levels of stress and the length of their telomeres, while among those who did not exercise, those reporting greater stress had significantly shorter telomeres.

Emerging evidence indicates that a lifestyle including physical activity, good sleep and a diet enriched with fresh fruit and vegetables and lower processed meat intake may slow telomere attrition. An important next step will be translating findings into effective interventions. This will be challenging. It is difficult to get people to maintain a healthy lifestyle, and even more so when people are enduring high stress that requires attention to immediate survival goals and emotional needs. Moreover, individuals who are from socially disadvantaged groups have more limited access to resources for engaging in health-promoting behaviors.

KEY ISSUES FOR FUTURE RESEARCH

Telomere Lengthening

One of the most exciting but also puzzling stories to have emerged in the telomere field in recent years is the finding that telomeres may lengthen as well as shorten. Although telomeres are longest at birth and shortest in old age, accumulating evidence suggests that some individuals show telomere lengthening over periods ranging from 1 to 5 years. The enzyme telomerase, a reverse transcriptase that builds telomeric DNA and lengthens telomeres, may be responsible for this occurrence. In cells cultured in the laboratory, telomeres shorten with each cycle of cell division until they reach a critical shortness called the Hayflick limit. At this critical point, cells become functionally impaired and are unable to divide and produce daughter cells. However, when telomerase is added to such cultures, telomeres are maintained for longer, allowing the cells to continue dividing. This process is tightly regulated to allow for damaged and older cells to die and leave the system. The exception is found in cancer cells, which have short telomeres, but can become immortal by expressing very high levels of telomerase. Thus, at the same time that telomerase is beneficial in allowing healthy cells to stay functional and proliferate, it can also be problematic by promoting thriving in cancer cells.

In general, however, higher levels of telomerase are associated with better health in humans, suggesting that increased telomerase is advantageous

overall. For example, when prostate cancer patients engaged in comprehensive lifestyle improvements, their levels of telomerase increased. Physical activity also activates telomerase and there are recent reports that mindfulness meditation interventions increase telomerase. Future studies are needed to understand the factors that promote telomerase activity, and to elucidate its ability to slow biological aging.

Telomere Length Measurement

Telomere length is generally assessed from white blood cells using either the "Southern blot" or the "quantitative real-time polymerase chain reaction" (Q-PCR) approach. Southern blot was the first method established for telomere length measurement and subsequent developments have increased its sensitivity. It serves as the "gold standard" for calibrating new methods, but it is costly and labor intensive and requires a large amount of DNA. In contrast, the Q-PCR approach and monochrome multiplex Q-PCR methods require less DNA and lend themselves to the high throughput needed for large studies.

More recent and more controversial is the use of buccal cells rather than blood to assess telomere length. Buccal cells, obtained through cheek swabs, are easier to obtain and may be more acceptable, especially in work with children, than is collecting blood. Advances in telomere measurement from dried blood spots also have the potential to reduce the burden of collecting blood samples, especially in nonclinical settings.

Recent studies show that telomere length varies even within cells, and suggest that the shortest telomere within a cell may play a particularly important role in influencing cell responses. Thus, newer approaches to telomere length measurement that allow the measurement of individual telomeres and the quantification of short telomeres within cells are likely to yield important new insights.

Public Health Implications

Research linking social disadvantage with telomere length provides a strong foundation for designing interventions to improve health and diminish disparities, but much remains to be done before the findings can be translated into real-world applications. We do not yet know how and when to intervene to slow down cellular aging. While biological researchers seek ways to target the telomere maintenance system directly, social and behavioral scientists may find ways to slow telomere shortening by improving social conditions and/or psychological and behavioral responses to disadvantage. Such interventions need to be informed by knowledge of modifiable mechanisms of

telomere shortening, the conditions that foster these mechanisms and the policies that can affect these conditions.

Greater understanding of the dynamics of telomere shortening over the life course can inform the timing and targets of interventions. Most research on telomeres has been in older people because diseases of aging linked to telomere shortening occur in this population. However, strategies that affect early-life determinants of telomere length may have a greater payoff. The length of a person's telomeres in older adulthood is a function of the length of the telomeres with which they were endowed at conception as well as by environmental exposures from the womb onward. Investment in enhancing the early-life environment may hold much promise in changing trajectories and promoting longevity and better health into old age.

FURTHER READING

Adler, N. E., & Stewart, J. (2010). Health disparities across the lifespan: Meaning, methods, and mechanisms. *Annals of the New York Academy of Sciences*, *1186*, 5–23.

Adler, N., Pantell, M., O'Donovan, A., Blackburn, E. H., Cawthon, R., Koster, A., … , Epel, E. (2013). Educational attainment and late life telomere length in the health, aging and body composition study. *Brain, Behavior, and Immunity*, *27*, 15–21. 10.1016/j.bbi.2012.08.014

Aubert, G., Hills, M., & Lansdorp, P. M. (2012). Telomere length measurement-Caveats and a critical assessment of the available technologies and tools. *Mutation Research*, *730*, 59–67.

Entringer, S., Epel, E. S., Kumsta, R., Lin, J., Hellhammer, D. H., Blackburn, E. H., … , Wadhwa, P. D. (2011). Stress exposure in intrauterine life is associated with shorter telomere length in young adulthood. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(33), E513–518.

Epel, E. S., Blackburn, E. H., Lin, J., Dhabhar, F. S., Adler, N. E., Morrow, J. D., & Cawthon, R. M. (2004). Accelerated telomere shortening in response to life stress. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(49), 17312–17315.

Puterman, E., Lin, J., Blackburn, E., O'Donovan, A., Adler, N., & Elissa, E. (2010). The power of exercise: Buffering the effect of chronic stress on telomere length. *PLoS ONE*, *5*(5), e10837. doi:10.1371/journal.pone.0010837

Shalev, I. (2012). Early life stress and telomere length: Investigating the connection and possible mechanisms: A critical survey of the evidence base, research methodology and basic biology. *Bioessays*, *34*, 943–952.

NANCY ADLER SHORT BIOGRAPHY

Nancy Adler, PhD is Lisa and John Pritzker Professor of Psychology in the Departments of Psychiatry and Pediatrics, Vice-Chair of the Department of

Psychiatry, and Director of the Center for Health and Community at the University of California, San Francisco. A social psychologist, her early research examined the utility of decision models for understanding health behaviors with particular focus on reproductive health. Subsequently, she directed the MacArthur Foundation Research Network on SES and Health in which an interdisciplinary group of researchers identified and tested possible mechanisms by which socioeconomic status gets into the body to affect health. In addition to documenting effects of objective socioeconomic status, she demonstrated the importance of subjective social status. A special issue of the Annals of the New York Academy of Sciences on the Biology of Disadvantage provides an overview of this work. While continuing to conduct empirical research on social determinants of health, she has become increasingly interested in methodological challenges in assessing the relationship of social disadvantage and health and in policy and interventions that could affect these processes.

AOIFE O'DONOVAN SHORT BIOGRAPHY

Aoife O'Donovan, PhD is a Society in Science—Branco Weiss Fellow and Assistant Professor in the Department of Psychiatry at the University of California, San Francisco, and the San Francisco Veterans Affairs Medical Center. She received her undergraduate education in psychology and philosophy at University College Cork and subsequently completed a Masters in Health Psychology at the National University of Ireland, Galway. During her Masters, she conducted experimental research examining the effects of subtle manipulations of social support on cardiovascular responses to acute stress. Following this, she pursued a PhD in Clinical Psychobiology at University College Dublin focused on uncovering associations between threat-related psychological variables and indices and mechanisms of biological aging. Dr. O'Donovan's laboratory is focused on uncovering how chronic and traumatic stress exposure increase risk for psychiatric and physical disorders, by studying both the psychological and biological consequences of stress. The ultimate goal of this work is to inform the development of new interventions that reduce the negative effects of psychological stress on health.

RELATED ESSAYS

Social Epigenetics: Incorporating Epigenetic Effects as Social Cause and Consequence *(Sociology)*, Douglas L. Anderton and Kathleen F. Arcaro
Inefficiencies in Health Care Provision *(Economics)*, James F. Burgess *et al*.
Self-Fulfilling Prophesies, Placebo Effects, and the Social-Psychological Creation of Reality *(Sociology)*, Alia Crum and Damon J. Phillips

Genetic and Environmental Approaches to Political Science *(Political Science)*, Zoltán Fazekas and Peter K. Hatemi
Evolutionary Approaches to Understanding Children's Academic Achievement *(Psychology)*, David C. Geary and Daniel B. Berch
Genetics and Social Behavior *(Anthropology)*, Henry Harpending and Gregory Cochran
An Evolutionary Perspective on Developmental Plasticity *(Psychology)*, Sarah Hartman and Jay Belsky
Niche Construction: Implications for Human Sciences *(Anthropology)*, Kevin N. Laland and Michael O'Brien
Immigrant Health Paradox *(Sociology)*, Kyriakos S. Markides and Sunshine Rote
Rationing of Health Care *(Sociology)*, David Mechanic
Health and Social Inequality *(Sociology)*, Bernice A. Pescosolido
Social Relationships and Health in Older Adulthood *(Psychology)*, Theodore F. Robles and Josephine A. Menkin
The Role of Cultural, Social, and Psychological Factors in Disease and Illness *(Sociology)*, Robert A. Scott
Incarceration and Health *(Sociology)*, Christopher Wildeman