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Telomeres in a Life-Span Perspective: A New “Psychobiomarker”?

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ABSTRACT—*In order to more fully understand associations between psychological stress and health, it is helpful for researchers to identify “psychobiomarkers,” or biological measures that are regulated in part by psychological function and that predict longevity. Telomere length appears to be such a measure. Telomeres, the protective caps at the tips of chromosomes, shorten with age, and this shortening predicts disease and longevity. Leukocyte telomere length may be best viewed through a life-span approach, as it reflects in part the cumulative number of cell divisions that have occurred and the long-term biochemical environment. Recently, a critical mass of studies demonstrated that telomeres appear to shorten with chronic stress, although the mechanisms are unknown. This paper reviews what appear to be malleable determinants of rate of telomere attrition, focusing on early life chronic stressors and metabolic adversity (poor nutrition during development, and obesity). The next generation of research will benefit from experimental and longitudinal models integrating genetic variation, social environments, life experience, and health behaviors.*

KEYWORDS—*chronic stress; aging; telomeres; psychobiomarker; life-span approach*

TELOMERES AS A PSYCHOBIO-MARKER?

While chronological aging occurs at a constant predictable rate, biological aging, its related consequence, can in some cases have a course of its own. It is helpful to have biomarkers of age in order to predict health status and longevity. While true biomarkers change with age and predict mortality, many have no known relationship with psychological factors. “Psychobio-

marker” might be a helpful label for a biomarker that is also known to be influenced by one’s psychological state and, thus, social and environmental context. In the search to understand the mechanistic links between how social environments and psychological processes impact how we age, validated psychobiomarkers are essential to provide a window into how our social environment gets under our skin.

Telomeres may be such a measure. Telomeres are repeat sequences of DNA that cap the end of chromosomes and protect the cell’s genomic stability. The molecular structure of telomeres, discovered by Elizabeth Blackburn and colleagues, solves the end-replication problem, which is that the enzymes that replicate chromosomes cannot do so fully at the tips, which could cause us to lose parts of genes when cells replicate. Instead, the telomeres serve as a buffer of DNA at the ends of chromosomes, so that with cell replication, the telomeres shorten. The telomere caps have many other functions, including preventing recombinations and fusions of the ends of genes with fragments of DNA from broken chromosomes, which could typically lead to cancer. Telomeres that are shortened past a critical length cause the cell to enter a state of arrest (cell senescence) when cells can no longer divide. Senescent cells tend to underlie tissue aging and possibly organismal aging. Telomeres tend to shorten with age, although rate of shortening depends on levels of *telomerase* activity; telomerase is an enzyme that can lengthen and protect telomeres.

In the last decade, there has been an explosion of epidemiological research on telomere length (TL) and disease. Shorter TL in leukocytes (white blood cells) has been consistently associated with chronic disease states, primarily cardiovascular-related diseases, and is predictive of clinical disease and, in several studies, of early mortality (Fuster & Andres, 2006).

TELOMERE MAINTENANCE THROUGH A LIFE-SPAN PERSPECTIVE

Telomeres appear to lengthen and shorten in response to sociobiological signals during critical developmental or

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stressful periods, described below. Thus, it may be helpful to view TL maintenance through a theoretical framework of lifespan development (Baltes, 1987). For example, TL adaptation shows plasticity—lengthening or shortening at different rates depending on stage of growth or aging—which occurs from conception to death. Adaptation over the life span involves changes in the allocation of resources used for growth, maintenance, and restoration. Last, adaptation is influenced by ontogenic and biopsychosocial forces. As described below, telomeres can lengthen in people as well as shorten, depending on the extent of the fluctuations of the dynamic biochemical environment as it responds to the demands of the external environment.

Although no prospective studies have been conducted from infancy to adulthood, given the small changes in TL over time within a cell, average leukocyte TL may prove to have a strong “tracking record” over the life span. While TL likely tracks over time, it does not change at a constant rate. For example, people have long telomeres in infancy (around 10,000 base pairs), show rapid loss early on, and then show slower loss during adulthood—roughly 30 to 60 base pairs a year (Zeichner et al., 1999). Life experience may also alter rate of loss, as I will describe. Thus, to understand the etiological forces that have shaped TL at any one point in time, it is helpful to consider both early developmental periods or events that influence TL trajectories, and current factors that modulate the rate of TL attrition versus TL lengthening.

A REVIEW AND RESEARCH AGENDA

In what follows, I list the presumed biochemical pathways regulating TL and review other influences, including early-life exposures, metabolic health, chronic stress, and sociodemographic factors.

Biochemical and Other Regulators of TL

Several factors, including genetic effects and immune challenges (antigen exposure leading to higher telomerase and T-cell turnover and thus telomere shortening), are known to influence TL and telomerase. Changes in telomere length may also be due to changes in hematopoietic stem cells, the precursor cells to leukocytes (Lansdorp, 2006). Recent research has pointed to a broad set of candidate biochemical factors. Oxidative stress is the best-established factor, as it causes telomere shortening in laboratory experiments and is associated with shorter telomeres in people. Several studies in adults have now linked telomere shortness or telomerase to the stress hormones cortisol and catecholamines, and to metabolic factors such as obesity and insulin (Epel et al., 2006; Gardner et al., 2005), and cortisol has been found to dampen telomerase in laboratory experiments (Choi, Fauce, & Effros, 2008). It is thought that certain immuneregulating proteins called cytokines promote telomere shortening. It is logical evolutionarily that this array of biochemical

regulators ensures that signals about an organism’s state of stress (metabolic or psychological) can influence telomere maintenance and thus cell longevity versus early senescence. Unfortunately, most human studies are merely correlational, and there is little direct evidence that metabolic or other biochemical factors play a causal role in telomere shortening. While animal studies can provide the best models for elucidating causal pathways, this remains a largely untouched research area.

Metabolic Health in Childhood and Adulthood

Aspects of health are transmitted across generations, not just through genetics and health behaviors but also through the prenatal environment (fetal programming). For example, a woman’s nutritional status during pregnancy affects the birth weight of her infant, which in turn will affect the child’s catch-up growth and later obesity or metabolic disease. There are some hints that TL may be affected by similar early factors as well. In rodents, poor maternal nutrition during pregnancy (reduced protein), compared to poor nutrition after birth, leads to low birth weight, rapid catch-up growth later, and the development of shorter telomeres in kidney tissue (Jennings, Ozanne, Dorling, & Hales, 1999) and aortic tissue (Tarry-Adkins, Martin-Gronert, Chen, Cripps, & Ozanne, 2008) in early life. So far, one study compared leukocyte TL in preschool-age children who had been normal-birth-weight infants to that in children who had been low-birth-weight infants, and found that the low-birth-weight group had shorter TL (Raqib et al., 2007), possibly analogous to the rodent studies described above. The first 5 years of life (at least) are characterized by a dramatic rate of telomere attrition, thought to be due to anatomical and functional changes in the immune system (Frenck, Blackburn, & Shannon, 1998). However, this period is largely unstudied in terms of nutrition or psychosocial factors. Figure 1 models these isolated effects, suggesting they may leave imprints on TL in later life. As described above, there are clues that telomere maintenance in adulthood may be similarly influenced by metabolic pathways (Gardner et al., 2005), and thus one would expect synergistic effects between early experience and later health on TL trajectories (not shown in Fig. 1).

Stress and TL

Given the malleability of TL, and its vulnerability to an adverse biochemical environment, my colleagues and I hypothesized that years of chronic stress and associated stress arousal would dampen telomerase and lead to prematurely shortened leukocyte telomeres in young adulthood. Chronic stress leads to dysregulation of allostatic systems (McEwen, 2007) and could affect rate of shortening through lifestyle, biochemical milieu, and/or greater vulnerability to immune challenges. In our first test of this hypothesis, we found that perceived stress and duration of a chronic stressor (parenting a child with a chronic condition) were associated with lower telomerase and shortened leukocyte telomeres (Epel et al., 2004). These findings have been extended by others,

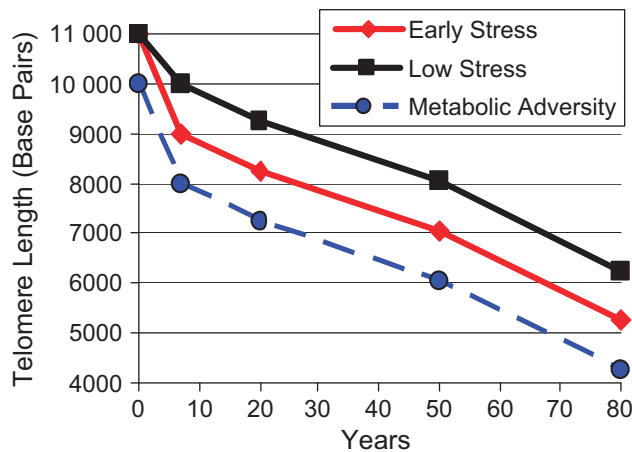


Fig. 1. Hypothetical telomere length (TL) trajectories over the life span in three hypothetical individuals—one born to a high-stress environment (early stress; red), one born to a low-stress environment (black), and one having experienced poor fetal nutrition (metabolic adversity; blue). The high-stress person has equivalent TL at birth to the low-stress person but is exposed to greater stress arousal and possibly has greater antigen exposure, which result in accelerated attrition in the first 5 years of life, the most dynamic period of change. The person with metabolic adversity is both born with shorter TL and has a greater rate of attrition during catch-up growth. (The model does not take into account changing levels of stress throughout the life span.) By late life, the hypothesized effects from the early exposures has led to 15% shorter TL for the high-stress individual and 30% shorter TL for the individual who experienced metabolic adversity. These estimates of telomere size and rate of attrition are roughly based on several studies (e.g., Zeichner et al., 1999) but should be viewed as theoretical, since such estimates vary significantly from study to study.

comparing dementia caregivers and people with depression to controls (Damjanovic et al., 2007; Simon et al., 2006). Genetics also modulate influence of stress exposure. For example, a certain gene variant (monoamine-oxidase-A promoter polymorphism) is linked to shorter telomeres, and this effect is especially present in those with current major depression (Lung, Chen, & Shu, 2007).

Can telomeres lengthen in people? TL may not change in a unidirectional fashion, simply shortening over time. We still know little about telomere attrition *in vivo*, which has been determined almost solely by cross-sectional studies. One would assume TL could not change appreciably in adults over just a few years. But TL appears to be more dynamic than initially thought, when sampled over short periods. In the first mouse study examining stress effects, telomeres shortened as expected after mice were exposed to 4 months of stress, but actually lengthened in the control mice (Kotrschal, Ilmonen, & Penn, 2007). Our preliminary data across two samples of healthy older adults suggests that average TL increased over time in a sizable minority, and in one study, where stress was repeatedly measured, lengthening was correlated with decreases in life stress over the same time period. On the surface, it may seem counterintuitive that what appears to be a cumulative marker of aging doesn't move in just one direction, toward age-related shortening, but may actually lengthen. However, we must postpone assumptions about telomere dynamics until there is a critical mass of longitudinal data. Last, observed changes could be due to increases

per cell or due to changes in a certain subset of circulating cells or in stem-cell dynamics.

Stress works indirectly through promoting smoking, obesity, and sedentariness, which have all been linked to shorter TL. Can behavioral interventions increase TL? So far, one pilot study found that intensive lifestyle modification was associated with a significant improvement in leukocyte telomerase activity levels in men with prostate cancer (Ornish et al., 2008). Although this study lacked a control group, the greater the reduction in intrusive thoughts and distress about cancer, the greater the increase in telomerase, suggesting a possible stress pathway. Smoking cessation, exercise, weight loss, and stress reduction all merit examination.

Thus, there now appears to be a critical mass of studies demonstrating effects of severe stress on TL and a suggestion that telomeres can lengthen. It will be helpful to know how individual differences and interventions affect TL, especially in interaction with stress exposure, and through which pathways.

Sociodemographic Contexts and TL

The life-span perspective considers how people's health is influenced by their environment, including neighborhoods, socioeconomic status (SES), and social changes. One would expect those of lower SES, which is a proxy for greater exposure to a range of stressors, to have shorter TL. Indeed, in one study, lower occupational status was linked to shorter TL in women, even after controlling for body mass index, smoking, and exercise (Cherkas et al., 2006), although replication is needed. This research opens up the possibility that a range of factors embedded in SES, such as neighborhood and childhood SES, may also have effects on TL.

Studies on racial differences are in progress, testing the hypothesis that telomere attrition is the biological mechanism for Arline Geronimus' construct of "weathering"—stress-induced early aging that might underlie the persistent U.S. racial health inequity. It will be a challenge to parse out sources of observed differences (e.g., genetics or culturally or SES-patterned factors such as diet and stress exposure).

Gender differences can also be better understood through a developmental perspective. Although females do not have longer telomeres at birth than men, they are significantly longer by adulthood, and it is unclear when this sex difference emerges or how it may relate to gendered social experiences or biological differences over the life course. The gender gap in telomere length most likely reflects the greater rate of telomere attrition in men compared to women, at least in early adulthood. In later adulthood, after women experience menopause, women's rate of attrition may become more similar to that of men.

Do Developmental Periods Affect Telomere Maintenance? A Life-Span Approach

Perinatal or early childhood influences on TL are a ripe area for research and possibly intervention. It is conceivable that

common factors such as a mother's obesity, stress, depression, or substance use could affect TL in utero. Animal studies show early life stressors (e.g., maternal separation) can alter stress response systems and immune function years later (McEwen, 2007). In turn, it is possible these factors may hasten telomere-induced cell senescence. Low SES is related to greater childhood infectious disease and later susceptibility to colds (Cohen, Doyle, Turner, Alper, & Skoner, 2004). Excessive childhood infections lead to T cell turnover, and such turnover, without sufficient telomerase, presumably leads to shorter TL. In this way, if tracking of telomere length is strong, early infections might also promote earlier replicative senescence of the immune system in adulthood. On the other hand, telomere length may be quite malleable even late in life. A recent study showed that in the elderly, over a mere 2.5-year period, some had telomere shortening as expected, but some also had telomere lengthening. Furthermore, greater rate of shortening predicted earlier mortality in men (Epel et al., 2009).

Early infancy may be a unique period, given the dramatic rate of telomere attrition, but it is likely not the only period of dynamic change. We need studies closely examining other potentially critical periods, such as later childhood, puberty, and menopause. Given the effects of estrogen exposure, which can increase telomerase in laboratory studies, it is conceivable that telomeres may show lengthening after puberty and accelerated attrition after menopause. This is speculative, and studies are needed to test these periods characterized by dramatic changes in hormones.

If a mother's poor nutrition, depression, and damaging health behaviors during pregnancy prove to play a role in setting up a lifelong trajectory of rapid telomere attrition in her child, it will be warranted to test effects of interventions, such as enhanced prenatal care, parenting skills, and enrichment programs for preschoolers, during these critical developmental periods.

SUMMARY AND CONCLUSIONS

TL appears to be a promising psychobiomarker. It appears to reflect an individual's recent past and cumulative history, possibly starting as early as the prenatal environment. Biochemical signals appear to shape telomere maintenance throughout the life span, making TL responsive to allostatic demands. Thus TL is best viewed through a life-span approach, which emphasizes life circumstances, adverse exposures, and health behaviors across time, as well as sociocultural context.

Given the novelty of research on TL in humans, there are numerous unanswered questions, such as the ones above. The first generation of human telomere research has examined cross-sectional relations in large cohorts. This led to novel information, showing that telomeres are associated with lifestyle and social context. Integrating findings from the studies available provides a tentative model to promote a longitudinal perspective and generate a research agenda that moves beyond correlations

and serves as a starting point for a life-span perspective. Figure 1 shows hypothesized effects of extreme exposures to early chronic stress or adverse prenatal environments on TL, which will likely interact with later lifestyle and stress.

There is still much to learn from well designed cross-sectional studies in terms of identifying correlates that may serve as potential predictors and consequences of TL. However, an investigation of how nature interacts with nurture over time requires translational research models. Experimental studies that manipulate presumed regulators of telomerase and TL in people are necessary. A single level of analysis focusing on genetic variation or biological-, psychological-, or social-level factors will be limiting, as these factors do not work in isolation but rather in interaction. The next generation of studies should thus move toward longitudinal multilevel and experimental perspectives. Measuring the complex network of one's social, biological, and genetic contexts over time will ultimately provide the most predictive models of telomere maintenance throughout the life span.

In the near future, however, the field requires answers to basic questions: What are the rates of telomere attrition in different developmental periods? In which cell types? And how do these differ by individual differences and across sociodemographic groups? Collaborations between basic, clinical, social, and epidemiological scientists can promote this type of research and deepen our understanding of TL maintenance throughout the life span.

Recommended Reading:

- Blackburn, E.H. (2000). Telomere states and cell fates. *Nature*, *408*, 53–56. A seminal review for readers wanting more technical background on cell aging, by one of the discoverers of telomerase.
- Graham, J.E., Christian, L.M., & Kiecolt-Glaser, J.K. (2006). Stress, age, and immune function: Toward a lifespan approach. *Journal of Behavioral Medicine*, *29*, 389–400. Reviews seminal studies in the field of psychoneuroimmunology and aging, which is helpful background for understanding the significance of stress effects on leukocyte telomeres.
- Gardner, J.P., Li, S., Srinivasan, S.R., Chen, W., Kimura, M., Lu, X., et al. (2005). (See References). One of the few published studies with longitudinal data on TL; it finds that a minority of people show increases over time and that insulin resistance tracks with TL.
- Lin, J., Epel, E., & Blackburn, E. (in press). Telomeres, telomerase, stress, and aging. *Handbook of neuroscience for the behavioral sciences*. New York: John Wiley & Sons. A very comprehensive review of influences on the telomere/telomerase maintenance system, from genetics to psychosocial factors.
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