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Review

Telomeres and lifestyle factors: Roles in cellular aging

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ABSTRACT

Recent research has demonstrated that telomere maintenance might be a key integrating point for the cumulative effects of genetic, environmental and lifestyle factors on aging and aging-related diseases. It is timely to 'take stock' of where this work has led the field. This review summarizes studies that have examined associations between lifestyle factors and telomere length and telomerase activity. In most of the studies described in this chapter, telomere length was measured in leukocytes (LTL) or peripheral blood mononuclear cells (PBMCs), taken from blood draws from the study subjects. Much of this chapter focuses on psychological stress, a widespread factor often intimately tied in with lifestyle or behavioral factors that in turn are related to risks of clinical diseases. Together, these findings suggest that cellular aging is linked to a range of influences, with an individual's life events and lifestyle parameters playing significant roles. Lastly, we propose possible biochemical mechanisms that mediate these associations and discuss future directions.

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1. Perceived stress and adverse life events

Severe or chronic psychological stress is known to accelerate biological aging, as defined in broad sense, although the mechanisms by which this occurs have been elusive. A 2004 study by Epel et al. first reported a novel correlation between short telomere length, low telomerase activity and perceived chronic psychological stress in mothers, some who had a healthy child and some who were caregivers of chronically sick children [1]. Those who scored high on a 10-item questionnaire assessing their perceived stress

level in the past month had shorter telomere length and lower basal telomerase activity in their peripheral blood mononuclear cells (PBMCs). Although the finding was based on cross-sectional analysis, and therefore was not able to establish a cause-effect relationship, the authors found that years of caregiving were inversely related to telomere length, suggesting that the cumulative burden of psychological stress in caregiving may have caused the shorter telomeres observed. This finding was replicated in a different group of caregivers, spouses of Alzheimer's patients [2]. In this study, caregivers had significantly shorter telomere lengths in PBMCs as well as in T lymphocytes and monocytes. Caregiving is a prototypical example of chronic life stress, since it is typically full time, demanding, and continues for years. There are many other indices of chronic life stress, and here we review studies including low socio-economic status (SES), exposure to intimate partner violence, and childhood trauma.

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Several studies have examined the relationship between adverse socio-economic status and telomere length, but the results so far have been mixed. In one study, 1552 female twins aged 18–75 were compared for their leukocyte telomere length, and it was significantly shorter in lower SES groups. The mean difference in terminal restriction fragment length (TRFL) between non-manual (high SES) and manual SES (low SES) groups was 127 base pairs (bp) (approximating 3–5 years of accelerated shortening), after adjusting for body mass index, smoking and exercise [3]. A recent study of the Whitehall cohorts found a positive correlation between telomere length and educational attainment, but not current socioeconomic status [4]. However, Adams et al. [5] investigated the association between telomere length and life-course socio-economic status at age 50 in 318 participants in the Newcastle Thousand Families study and did not see correlations between telomere length and multiple measures of socio-economic position. Two other studies – 1542 men in the West of Scotland Coronary Prevention Study and 624 individuals in the National Long Term Care Survey (NTLCS) – also failed to detect a correlation between telomere length and socio-economic status [6,7]. Moreover, a survey of 958 men and 978 women aged 65 years and over living in Hong Kong showed that – in men only – after adjustment for age and other confounding factors, a higher ranking in community standing was associated with shorter telomere length [8], which is the opposite direction of the findings reported by Cherkas et al. and Steptoe et al.

Several distinct differences exist between these different reports. First, a larger sample size of 1552 twins in the Twins UK study compared to the 318 participants in Newcastle study and 624 participants National Long Term Care Survey. Given that the Twins UK study found a relative small difference of 127 bp between the low and high SES with a marginal statistical significance of $p < 0.047$, it is probable that Newcastle study and National Long Term Care Survey did not have enough statistical power to capture the small effect even if such a difference existed. The age, sex and racial compositions of each cohort may also play an important role as these factors are all known to be associated with telomere length [9–11]. Finally, different socio-economic status markers were used to assess socio-economic status and this may determine whether an association can be found.

Exposure to severe psychological trauma, early or late in life, may have lasting effects on hematopoietic stem cell integrity and thus on circulating leukocyte telomere length. Women who had previously experienced inter-partner violence (at least one year before the PBMCs were collected for telomere length measurements) had significantly shorter mean telomere length compared to controls. Length of time in the abusive relationship and having children were associated with telomere shortness after controlling for age and body mass index, suggesting that the stress caused by inter-partner violence and raising children in the abusive relationship causes accelerated telomere shortening [12].

Several studies show associations between childhood trauma and telomere length. Tyrka and colleagues [13] evaluated the effects of childhood adversity in a community-based sample of 31 men and women with and without a history of childhood maltreatment, and with no current depression. Participants reporting a history of maltreatment (mostly neglect rather than abuse) had significantly shorter telomeres than those who did not report such maltreatment independent of the effects of age, gender, smoking, body mass index (BMI), or other demographic factors known to be associated with shortened telomeres. Likewise, Kananen and colleagues [14] also reported that childhood adversity was associated with telomere shortening in adults in the Health 2000 Survey in Finland. Kiecolt-Glaser et al. reported that in 132 healthy older adults including 58 dementia family caregivers and 74 noncaregivers, the presence of multiple childhood adverse events was

related to shorter telomeres after controlling for age, caregiving status, gender, body mass index, exercise, and sleep [15]. In a recent study of young to middle-aged adults with post-traumatic stress (PTSD), those with PTSD had shorter LTL. Early exposure to adverse events may have accounted for the difference in LTL between those with PTSD and controls; all those exposed to multiple events and types of trauma in childhood were in the PTSD group and had shorter leukocyte telomere length than those without such exposure [16]. The findings between short telomeres and childhood adverse event were replicated in a large study of ethnically homogenous population of 4441 women of the UK EPIC-Norfolk study [17]. However, one study reported a null finding between physical and/or sexual abuse in childhood and telomere length [18]. Here, like the findings for socio-economic status, the specific measurement tool used for assessing childhood trauma may be an important determinant of whether an association with telomere shortness is found. Those reported an association used a broad range of measurements including physical, sexual, emotional abuse, physical and emotional neglect [13,15,16]. Kananen et al. used a series of 11 questions about the subject's childhood social environment, which has an even broader scope that includes the financial situation of the family, physical and mental health of parents as well as the child, and the conflicts within the family and in school. It should be noted that the most significant childhood adversity in the Kananen et al. study was the person's own chronic or serious illness during childhood. Therefore, it is possible that physiological, rather than psychological adverse events in childhood are associated with shorter telomere length.

2. Stress and stress-related psychiatric conditions

Depression and post-traumatic stress disorder (PTSD) are closely linked to, and attributable to, exposure to chronic or severe psychological stress (reviewed by [19]. Several reports have found shorter telomere length in patients with mood disorders including major depressive disorder, and bipolar depressive disorder with and without anxiety [20–22]. In a small study, Wolkowitz et al. found only marginally shorter telomeres in individuals with major clinical depression compared with controls [23]. However, a significant inverse relationship was observed between telomere length and total cumulative lifetime duration of depression. This result suggests that telomere shortening may progress with longer exposure to depression. Interestingly, the major depression subjects in the Simon et al. studies had on average 31.8 ± 11.2 years of disease history, while patients in Wolkowitz's study had a shorter average disease duration (13.0 ± 11.2 years). It is possible that the lack of association between depression and short telomere length in the Wolkowitz study was due to the short disease duration in some subjects. Childhood trauma appears to set one up for both vulnerability to stress related mental health conditions, like PTSD and depression, but also for short TL. It is also likely that early trauma and later life PTSD and MDD may interact to contribute to accelerated cell aging.

3. Telomere length and temperament

Damjanovic et al., when examining LTL in older caregivers, found that simply being a caregiver was related to shorter LTL and our recent study on dementia caregivers replicates this finding (O'Donovan et al., under review). However, many studies of stressor exposure find that it is individual differences, such as perception of stress, or personality, that are linked to stress-related physiology. For example, Epel et al.'s 2004 study first demonstrated that level of perceived stress, as opposed to the inherently stressful caregiving situation itself, was correlated with shorter telomere length,

suggesting that individual differences in stress vulnerability may be an underlying reason for the differences in telomere length between high and low stress groups. The older age of the dementia caregivers may also contribute to vulnerability to stressor-induced aging.

O'Donovan et al. investigated whether dispositional traits are correlated with telomere length and found that pessimism is negatively associated with telomere length, regardless of caregiving status [24]. The personality characteristics assessed in these studies – perception of stress and pessimism – are relatively stable personality traits and thus may be operative over much of an individual's life, suggesting that they may have cumulative effects on cell aging, as reflected by telomere maintenance, over relatively long periods.

4. Dietary biomarkers and nutritional intake

Unhealthy life style factors including smoking [25–30], consumption of processed meat [31] and high BMI [32–37] have been reported to correlate with short telomere length. Several studies have now reported relationships between dietary biomarkers and telomere length. Higher plasma vitamin D level was associated with longer telomere length in women [38]. Another study reported high plasma homocysteine was associated with shorter telomere length [39], while higher folate was associated with longer telomeres [40]. Farzaneh-Far et al. found that in a cohort of patients with coronary artery disease, there was an inverse relationship between baseline blood levels of marine omega-3 fatty acids and the rate of telomere shortening over the subsequent 5 years, independent of other factors. The Sisters Study examined the intake of multivitamins [41] participants aged 35–74 and found that multivitamin use was associated with long telomere length. Specifically, higher intake of vitamins C and E from food was associated with long telomere length even after adjusting for multivitamin use. A detailed review on the topic of diet, nutrition and telomere length was recently published [42]. It should be noted that these studies have been observational and most of the studies mentioned were biased to retrospective analysis. Furthermore, people who take nutritional supplements are more likely to lead a healthy life style that also includes exercise and a healthy diet. Therefore the impact of individual nutritional marker on telomere length needs to be assessed in this context. There is a need for both intervention studies, as well as for a more systematic analysis of macro- and micro-nutrients in relation to cell aging.

5. Interventions

Cross-sectional correlations between healthy life style factors and telomere length and telomerase activity have been reported in various studies, and provide the compelling possibility that LTL is malleable and partly under our control. For example, in a sample of 318 subjects, 40–64 years old, with no previous diagnosis of coronary heart disease, stroke, diabetes or cancer, shorter LTL was related to presence of coronary artery calcium (CAC) [43]. However, greater fruit and vegetable consumption, lower meat consumption and having high social support independently attenuated the relationship between short telomere length and presence of coronary artery calcium (CAC). Physical activity during leisure time was correlated longer telomere length in the UK Adult Twin Registry [44]. Puterman et al. found that the relationship between stress and short telomeres was attenuated in women who exercised the recommended amount by Center for Disease Control and Prevention (an average of 75 min of vigorous activity per week) [45].

There are two reports on interventional effects on changes in telomerase activity. Ornish et al. found telomerase activity in PBMCs

in early stage prostate cancer patients increased after 3 months of a comprehensive lifestyle change program compared with activity levels at the beginning of the study [46]. This intervention included dietary modification, moderate aerobic exercise, stress management and group support. Although this pilot study does not include a control group not enrolled in the program, the extent of telomerase activity increase over the 3 months correlated with the 3-month decreases in low density lipoprotein (LDL) cholesterol and in psychological distress, indicating that increased telomerase activity may be a biomarker of improved health. In another study, participants in a 3-month meditation retreat had higher telomerase activity than controls at the end of retreat (no baseline telomerase measure was available). The effect of the retreat on telomerase was mediated by increases in Perceived Control (associated with decreased stress) and meaning in life, and decreases in Neuroticism (associated with increased subjective distress) during the 3 month study period [47]. These results are consistent with earlier findings linking perceived chronic stress to low baseline telomerase activity in peripheral leukocytes of healthy individuals, but add the possibility that increases in well being (not just reductions in distress) can also influence telomerase.

6. Possible mechanisms mediating relationships between life style factors and telomere length

What potential mechanisms and pathways mediate the relationship between life style factors and telomere length? Research has focused on several inter-related biochemical pathways: stress hormones, inflammation and oxidative stress. Treatment of stimulated T-cells with the stress hormone cortisol *in vitro* causes decreases in cell proliferation, decreased telomerase activity and lower hTERT mRNA levels after cell activation [48]. *In vivo*, elevated levels of epinephrine, norepinephrine and cortisol were found to be associated with short telomere length in PBMCs [49,50]. Chronic stress and depression have also been linked to high levels of 8-hydroxy-deoxyguanosine (8-OHdG) and decreases in anti-oxidant enzymes [51–55]. Oxidative stress preferentially damages telomeric versus other genomic DNA regions (reviewed by [56]) and inhibits telomerase activity *in vitro* in various cell types [57,58]. Micronutrients like vitamin C, E, folate acid and marine omega-3 fatty acids are associated with anti-oxidative function [59,60], and thereby may be associated with long telomeres due to their anti-oxidative property. Stressed individuals have high levels of proinflammatory cytokines including IL-6 and TNF- α [61–63]. IL-6 has been shown to stimulate telomerase activity in cultured cells whereas TNF- α negatively regulates telomerase activity [64]. The concerted effects of these various biochemical mediators on telomerase may contribute to the observed associations between lifestyle factors and telomere length.

7. Is telomerase activation a compensatory mechanism induced by telomere shortness?

The Epel et al. 2004 study showed that low basal telomerase activity in unstimulated PBMCs is associated with worse stress in women without frank disease. This correlation was confirmed in a more recent study with women caregivers of dementia patients by the same author [65] as well as in other studies that showed increases in telomerase activity over a 3 month period were associated with improved health profiles [46,47]. However, other studies have found the opposite relationship. In a different and older group of caregivers, who were primary caregivers for Alzheimers' patients, unstimulated telomerase activity in PBMC and T cells was higher in caregivers than in controls [2]. Telomerase activity was higher in depressed individuals compared to the controls and was

directly correlated with depression and stress ratings across both groups of subjects [66].

It was proposed that the elevated PBMC telomerase activity was an unsuccessful attempt of cells to compensate the excessive loss of telomeres in caregivers [2]. This appears to support the notion that elevated telomerase activity is reactive to short telomere length. In vitro studies showed that telomerase preferentially add telomeric sequences to short telomeres [67–69]. Whether this also happens in vivo remains to be found. Telomerase activity in PBMCs is dynamic in response to acute psychological stress. When a group of post-menopausal women were exposed to a brief laboratory psychological stressor [70], telomerase activity was found to increase within one hour after the acute stressor and this increase was associated with greater cortisol increases in response to the stressor [65]. At the organism level, tight regulation of telomerase activity is essential for health as haploinsufficiency of telomerase activity due to genetic mutations is the cause of several human diseases, summarized as the syndromes telomere shortening reviewed by [71]. However, this does not rule out the possibility of temporal dynamic changes of telomerase activity in response to various stimuli.

8. Future directions

While cross-sectional studies are abundant, there have been very few longitudinal studies of telomere length [72–77]. One consistent finding from the published longitudinal data is that the rate of telomere length change over time is inversely related to the baseline telomere length [72,76,77]. The mechanisms that regulate this phenomenon are of great interest. The available studies have shown that telomere length trajectory over time predicts health outcome. For example, in the McArthur aging study, elderly men who showed telomere shortening over a 2.5 year period had a 3-fold higher chance of death from cardiovascular disease in the subsequent 9 years compared with those in the same cohort whose telomere length was maintained or lengthened [74]. More studies are clearly needed to establish cause-effect relationships between lifestyle factors, white blood telomere length and health outcomes.

A large remaining puzzle in human populations is the relationship of telomerase activity (measured in blood lymphocytes) to life style factors and disease risks and states. As described above, results have been indicative of a complex relationship. Whether the heightened levels of telomerase reflect the cells' unsuccessful attempt to compensate for shorter telomere length, as was first suggested by Damjanovic et al. [2], remains to be seen. Many of the studies of telomerase activity in white blood cells have involved a variety of study subject populations, with different disease and other characteristics, making comparisons between these studies difficult. It is known that the rate of telomere length change over time is inversely proportional to the baseline telomere length [72,76,77] although whether the rate of change of length is associated with telomerase activity has not been investigated in the population at large. It is also possible that elevated telomerase activity is a response to the proinflammatory cytokine environment associated with immunosenescence [78,79]. Whether epigenetic changes that result from changes in the cellular environments establish more long-lasting changes in telomerase and telomere length regulation is a question open for investigation.

How much do lifestyle factors contribute to telomere length differences? Telomere length is determined by the collective effects of genetic, environmental, life experience and lifestyle factors. Several papers have estimated that genetics contribute to 30–80% of the variabilities in telomere length between individuals [80–82], leaving 20–70% of the variability unaccounted for, which presumably comes from external factors including environmental and lifestyle factors. Among these factors, interactions – with additive, syner-

gistic or opposing effects on telomere maintenance – are likely to occur. Lifestyle and environmental factors are the potentially modifiable elements in this equation. However, as discussed earlier, stress vulnerability and perception may be shaped by early life experience, such as childhood trauma, and may also partly be genetically predetermined, as in the case of personality traits. Lifestyle changes that have an impact on telomere length are likely to contribute to lower disease incidences and risks and healthy life. Indeed, in at least one elderly study cohort, long telomeres have been associated with years of healthy life [83].

In summary, accelerated cell aging, at least as indexed by short leukocyte telomere length, is emerging as a strong determinant of early onset of diseases of aging. The converging picture from correlational studies of humans shows that cell aging is also intricately related to early life experience, and daily behavior. These studies provide compelling reasons to conduct intervention studies, to examine how much we can capitalize on these malleable relationships to reduce early illness and extend years of healthy living.

Conflict of interest

Drs. Jue Lin, Elissa Epel and Elizabeth Blackburn are co-founders of Telome Health Inc., a diagnostic company measuring telomere biology.

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