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Telomeres and Lifestyle Choices

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1. Introduction

Telomeres, the specific DNA–protein structures found at both ends of each chromosome, protect genome from nucleolytic degradation, unnecessary recombination, repair, and interchromosomal fusion. Telomeres therefore play a vital role in preserving the information in our genome. As a normal cellular process, a small portion of telomeric DNA is lost with each cell division. Telomeres shorten with age. When telomere length reaches a critical limit, the cell undergoes senescence and/or apoptosis. Shorter telomeres have also been implicated in genomic instability and oncogenesis. People older than 60 with short telomeres have three and eight times increased risk to die from heart and infectious diseases, respectively [Starr et al., 2007.] Rate of telomere shortening is therefore critical to an individual's health and pace of aging. Telomere length may therefore serve as a biological clock to determine the lifespan of a cell. The telomere length limits a cell proliferative ability in cultured human primary cells. Telomere shortens in the absence of telomerase in non-ALT cells. Certain agents associated with specific lifestyles may expedite telomere shortening by inducing damage to DNA in general or more specifically at telomeres and may therefore affect health and lifespan of an individual.

Smoking [McGrath et al., 2007; Morla ´ M et al., 2006; Song et al., 2010; Valdes et al., 2005], exposure to pollution [Hoxha et al., 2009; Pavanello et al., 2010.], lack of physical activity [Cherkas et al., 2008; Werner et al., 2009], obesity [Valdes et al., 2005], stress [Von et al., 2002], and an unhealthy diet [Jennings et al., 1999; Jennings et al., 2000.] increase oxidative burden and the rate of telomere shortening. To preserve telomeres and reduce cancer risk and pace of aging, we may consider to eat less; include antioxidants, fiber, soy protein and healthy fats (derived from avocados, fish, and nuts) in our diet; and stay lean, active, healthy, and stress-free through regular exercise and meditation. Foods such as tuna, salmon, herring, mackerel, halibut, anchovies, catfish, grouper, flounder, flax seeds, chia seeds, sesame seeds, kiwi, black raspberries, lingonberry, green tea, broccoli, sprouts, red grapes, tomatoes, olive fruit, and other vitamin C-rich and E-rich foods are a good source of antioxidants. These combined with a Mediterranean type of diet containing fruits, and whole grains would help protect telomeres.

2. Structure and function of telomeres

Telomeres, the DNA–protein complexes at chromosome ends, protect genome from degradation and interchromosomal fusion. Telomeric DNA is associated with telomere-

binding proteins and a loop structure mediated by TRF2, which protects the ends of human chromosomes against exonucleolytic degradation [Van Steensel et al., 1998], and may also prime telomeric DNA synthesis by a mechanism similar to 'gap filling' in homologous recombination [Griffith et al., 1999]. Telomere shortening occurs at each DNA replication, and if telomere length reaches below a critical limit, this leads to chromosomal degradation and cell death [Shin et al, 2006]. Telomerase activity, the ability to extend telomeres, is present in germline and certain hematopoietic cells, whereas somatic cells have low or undetectable levels of this activity and their telomeres undergo a progressive shortening with cell proliferation [Kim et al., 1994; Wright et al., 1996.]. Telomerases are reactivated in most cancers and immortalized cells. However, a subset of cancer/ immortalized cells lack telomerase activity and maintain telomere length by alternative mechanisms, probably involving genetic (homologous) recombination [Dunham et al., 2000], which is elevated in most immortal/cancer cell lines [Shammas et al., 2009].

3. Telomere shortening, cancer, and aging

Telomeres shorten with age and rate of telomere shortening may indicate the pace of aging [Epel et al., 2004; Irie et al., 2003; Patel et al., 2002; Von et al., 2002.].

3.1 Telomere length decreases with age and may predict lifespan

Normal human somatic cells lose telomeres with each cell division and therefore have a limited lifespan in culture. Telomeres protect chromosome ends from being recognized as DNA damage and chromosomal rearrangements. Conventional replication leads to telomere shortening, but telomere length is maintained by the enzyme telomerase that synthesizes telomere sequences de novo onto chromosome ends. Telomerase is specialized reverse transcriptase, requiring both a catalytic protein and an essential RNA component. In the absence of telomerase, telomeres shorten progressively as cells divide, and telomere function is lost. For this reason, telomerase is required for cells that undergo many rounds of divisions, especially tumor cells and some stem cells. [de Lange et al., 1990; Harley et al., 1990.]. Human liver tissues have been reported to lose 55 base pairs of telomeric DNA per year [Takubo et al., 2000]. The expression of stathmin and EF-1a, the biomarkers for telomeric dysfunction and DNA damage in a cell, increases with age and age-related diseases in humans [Jiang et al., 2008; Song et al., 2010]. Telomere length negatively correlates with age whereas the expression of p16, [Song et al., 2010; Takubo et al., 2000]. p16 represents a cell cycle inhibitor that is up-regulated in senescent cells [Alcorta et al., 1996; Stein et al., 1999]. Functional studies on senescent fibroblasts have shown that p16 appears to be upregulated in a p53 and telomere independent manner [Herbig et al., 2004]. Transgenic induction of a telomerase gene in normal human cells extends their lifespan [Bodnar et al., 1998]. Cawthon et al. [Cawthon et al., 2003] showed that individuals with shorter telomeres had significantly poor survival due to higher mortality rate caused by heart and infectious diseases. Progressive shortening of telomeres leads to senescence, apoptotic cell death, or oncogenic transformation of somatic cells in various tissues [Gilley et al., 2005; von Zglinicki et al., 2002]. Telomere length, which can be affected by various lifestyle factors, may determine overall health, lifespan, and the rate at which an individual is aging [Babizhayev et al., 2010].

3.2 Accelerated telomere shortening may increase the pace of aging

As a normal cellular process, telomere length decreases with age [Brouilette et al., 2003; Valdes et al., 2005;]. Telomere length in humans seems to decrease at a rate of 24.8–27.7 base pairs per year [Brouilette et al., 2003; Valdes et al., 2005]. Telomere length is affected by a combination of factors including donor age [Frenck et al., 1998], genetic background, epigenetic make-up, environment [Benetti et al., 2007; Celli et al., 2005; Munoz et al., 2005; Steinert et al., 2004], social and economic status [Adams et al., 2007; Cherkas et al., 2008], exercise [Cherkas et al., 2008], body weight [Nordfjall et al., 2008; Valdes et al., 2005], and smoking [Nawrot et al., 2004; Valdes et al., 2005]. Gender does not seem to have any significant effect on the rate of telomere loss [Brouilette et al., 2003]. When telomere length reaches below a critical limit, the cells undergo senescence and/or apoptosis [Gong et al., 1999; Stiewe et al., 2001]. Certain lifestyle factors such as smoking, obesity, lack of exercise, and consumption of unhealthy diet can increase the pace of telomere shortening, leading to illness and/or premature death.

Accelerated telomere shortening is associated with early onset of many age-associated health problems, including coronary heart disease [Brouilette et al., 2007; Fitzpatrick et al., 2007; Zee et al., 2009], heart failure [Van der Harst et al., 2007], diabetes [Sampson et al., 2006], increased cancer risk [McGrath et al., 2007; Wu et al., 2003], and osteoporosis [Valdes et al., 2007]. The individuals whose leukocyte telomeres are shorter than the corresponding average telomere length have three-fold higher risk to develop myocardial infarction [Brouilette et al., 2003]. Evaluation of telomere length in elders shows that the individuals with shorter telomeres have a much higher rate of mortality than those with longer telomeres [Cawthon et al., 2003]. Excessive or accelerated telomere shortening can affect health and lifespan at multiple levels. Shorter telomeres can also induce genomic instability [Chin et al., 1999; De Lange et al., 2005] by mediating chromosome end-to-end fusions and may contribute to telomere stabilization and development of cancer [Chin et al., 1999; Meeker et al., 2006]. Several studies indicate that shorter telomeres are a risk factor for cancer. Individuals with shorter telomeres seem to have a greater risk for development of lung, bladder, renal cell, gastrointestinal, and head and neck cancers [McGrath et al., 2007; Wu et al., 2003]. Certain individuals may also be born with shorter telomeres or may have genetic disorder leading to shorter telomeres. Such individuals are at a greater risk to develop premature coronary heart disease [Brouilette et al., 2003; Brouilette et al., 2007] and premature aging. Deficiency of telomerase RNA gene in a genetic disorder dyskeratosis congenita leads to shorter telomeres and is associated with premature graying, predisposition to cancer, vulnerability to infections, progressive bone marrow failure, and premature death in adults [Vulliamy et al., 2001].

4. Impact of smoking and obesity on telomeres and aging

Smoking and obesity seem to have adverse effect on telomeres and aging.

4.1 Smoking may accelerate telomere shortening and process of aging

Excessive telomere shortening can also lead to genomic instability [De Lange, 2005; Chin et al., 1999] and tumorigenesis [Chin et al., 1999; Meeker, 2006]. Consistently, the telomeres in

most cancer cells are shorter relative to normal cells. Smoking is associated with accelerated telomere shortening [Song et al., 2010]. The dosage of cigarette smoking is shown to negatively correlate with telomere length [Song et al., 2010]. A dose dependent increase in telomere shortening has been observed in blood cells of tobacco smokers [Morla et al., 2006; Valdes et al., 2007]. A study conducted in white blood cells of women indicates that telomeric DNA is lost at an average rate of '25.7–27.7 base pairs' per year and with daily smoking of each pack of cigarettes, an additional '5 base pairs' is lost [Valdes et al., 2005]. Therefore, the telomere attrition caused by smoking one pack of cigarettes a day for a period of 40 years is equivalent to 7.4 years of life [Valdes et al., 2005]. Babizhayev et al. [Babizhayev et al., 2010] have proposed that telomere length can serve as a biomarker for evaluation of the oxidative damage caused by smoking and may also predict the rate at which an individual is aging. The authors also propose that oxidative damage leading to telomere shortening can be prevented by antioxidant therapy [Babizhayev et al., 2010]. In summary, the smoking increases oxidative stress, accelerates telomere shortening, and may increase the pace of aging process.

4.2 Obesity is associated with excessive telomere shortening

Obesity is also associated with increased oxidative stress and DNA damage. Furukawa et al. [Furukawa et al., 2004] showed that the waist circumference and BMI significantly correlate with the elevated plasma and urinary levels of reactive oxygen species. Song et al. [Song et al., 2010] have shown that BMI strongly correlates with biomarkers of DNA damage, independent of age. The obesity related increased oxidative stress is probably due to a deregulated production of adipocytokines. Obese KKAy mice display higher plasma levels of reactive oxygen species and lipid peroxidation, relative to control C57BL/6 mice [Furukawa et al., 2004]. The elevated levels of reactive oxygen species in obese mice were detected in white adipose tissue but not in other tissues, indicating that the oxidative stress detected in plasma could be attributed to oxidizing agents produced in the fat tissue. Moreover, the transcript levels and activities of antioxidant enzymes including catalase and dismutase were significantly lower in white adipose tissue of obese relative to control mice. The authors propose that a lack of antioxidant defense and elevated NADPH oxidase pathway in accrued fat probably led to increased oxidative stress in obese animals. Telomeres are not merely 'cell-division counters'. A proportion of the oxidative damage inflicted upon telomeres remains unrepaired and determines the amount of shortening in the next round of replication. This proportion is related to the total amount of damage in the bulk of the genome. Although most of that damage has been repaired, it is the residual, unrepaired fraction that determines the probability to mutation. Thus, telomere shortening counts not only cell divisions but also the cumulative probability of mutations occurring, and short telomeres trigger senescence in response to oxidative stress and mutational probability [von Zglinicki et al., 2002.].Oxidative stress can induce DNA damage and may therefore accelerate telomere shortening. Telomeres in obese women have been shown to be significantly shorter than those in lean women of the same age group [Valdes et al., 2005]. The excessive loss of telomeres in obese individuals was calculated to be equivalent to 8.8 years of life, an effect which seems to be worse than smoking. Together these data indicate that obesity has a negative impact on telomeres and may unnecessarily expedite the process of aging.

5. Impact of environment, nature of work, and stress on telomeres and aging

Environment, nature of profession, and stress can also affect the rate of telomere shortening and health.

5.1 Exposure to harmful agents and nature of profession may affect telomere shortening

Hoxha et al. [Hoxha et al., 2009] evaluated telomere length in the leukocytes derived from office workers and traffic police officers exposed to traffic pollution. Exposure to pollution was indicated by the levels of toluene and benzene. The investigators found that telomere length in traffic police officers was shorter than that in office workers within each age group,. Similarly the lymphocytes of coke-oven workers, exposed to polycyclic aromatic hydrocarbons, had significantly shorter telomeres and increased evidence of DNA damage and genetic instability, relative to control subjects [Pavanello et al., 2010]. Reduction in telomere length in these workers, although did not correlate with age and markers of DNA damage, significantly correlated with the number of years the workers were exposed to harmful agents. Telomere attrition has been associated with increased cancer risk [Wu et al., 2003; McGrath et al., 2007] and coke-oven workers are at a greater risk to develop lung cancer [Pavanello et al., 2010.]. Telomere attrition in lymphocytes is also associated with aging [Frenck et al., 1998]. Consistently, the reduced telomere length in the lymphocytes of coke oven workers was also associated with hypomethylation of p53 promoter [Pavanello et al, 2010], which may induce the expression of p53 [Esteller et al., 2006], leading to inhibition of growth or induction of apoptosis [Chin et al., 1999]. Thus the exposure to genotoxic agents, which may induce damage to DNA in general or more extensively at telomeres, can increase cancer risk and pace of aging.

Stress increases the pace of telomere shortening and aging [Epel et al., 2004]. The stress is associated with release of glucocorticoid hormones by the adrenal gland. These hormones have been shown to reduce the levels of antioxidant proteins [Patel et al., 2002] and may therefore cause increased oxidative damage to DNA [Irie et al., 2003] and accelerate telomere shortening [Von Zglinicki et al., 2002]. Consistently, women, exposed to stress in their daily life had evidence of increased oxidative pressure, reduced telomerase activity, and shorter telomeres in peripheral blood mononuclear cells than women in the control group [Epel et al., 2004]. Importantly, the difference in telomere length in these two groups of women was equivalent to 10 years of life, indicating that the women under stress were at a risk for early onset of age related health problems. Eventually, stress would adversely affect health and longevity.

6. Impact of diet, dietary restriction, and exercise on telomeres and aging

What we eat and how much we eat can significantly affect our telomeres, health, and longevity.

6.1 Dietary biomarkers and nutritional intake

Unhealthy lifestyles such as smoking [Babizhayev et al., 2010; McGrath et al., 2007; Mirabello et al., 2009; Morla et al., 2006; Nawrot et al., 2010; Valdes et al., 2005],

consumption of processed meat products [Nettleton et al., 2008], and high body mass index [Al-Attas et al., 2010; Nordfjall et al., 2008; Lee et al., 2011; O'Callaghan et al., 2009; Zee et al., 2010] have been reported to correlate with the length of the shorter telomeres. Several studies have reported the association between diet and telomere length and human telomerase activity (Gunduz et al., 2005; Avci et al., 2007, 2011; Sahin et al., 2010; Cogulu et al., 2009). Higher plasma vitamin D was associated with increased telomere length in women [Richards et al., 2007]. Another study reported elevated plasma homocysteine is associated with decreased telomere length [Richards et al., 2008], while higher folate was associated with longer telomeres [Paul et al., 2009]. Farzaneh-Far et al. found that in a cohort of patients with coronary artery disease, there was an inverse relationship between baseline levels of marine omega-3 fatty acids and the rate of telomere shortening over the next five years, regardless of other factors [Farzaneh-Far et al., 2010.]. The Sister Study examined the intake of multivitamins [Xu et al., 2009] participants aged 35-74 years and found that multivitamin use is associated with longer telomere length. Specifically, higher intake of vitamins C and E from food associated with long telomere length, even after adjustment for multivitamin use. It should be noted that these studies are observations and most of those studies were biased to the retrospective analysis. In addition, people who take supplements are more likely to lead a healthy lifestyle that includes exercise and a healthy diet. Therefore, the effects of individual nutrients marker of telomere length has to be assessed in this context. There is a need for both intervention studies and for a more systematic analysis of macro-and micronutrients in relation to cell aging. [Paul et al., 2011].

6.2 Impact of fiber, fat, and protein on telomeres

Cassidy et al. [Cassidy et al., 2010] studied the association of leukocyte telomere length with various lifestyle factors in a relatively large group of women. Telomere length positively correlated with dietary intake of fiber and negatively associated with waist circumference and dietary intake of polyunsaturated fatty acids, especially linoleic acid. Reduction in protein intake also seems to increase longevity. Reduction in the protein content of food by 40%, led to a 15% increase in the lifespan of rats. The rats subjected to a protein-restricted diet early in life displayed a long-term suppression of appetite, reduced growth rate, and increased lifespan [Jennings et al., 1999; Jennings et al., 2000], and the increased lifespan in such animals was associated with significantly longer telomeres in kidney [Jennings et al., 1999]. Consistently, the highest life expectancy of Japanese is associated with low protein and high-carbohydrate intake in diet [Matsuzaki et al., 1992].

6.3 Dietary intake of antioxidants reduces the rate of telomere shortening

A study by Farzaneh-Far et al. [Farzaneh-Far et al., 2010] indicates that a diet containing antioxidant omega-3 fatty acids is associated with reduced rate of telomere shortening, whereas a lack of these antioxidants correlates with increased rate of telomere attrition in study participants. The authors followed omega-3 fatty acid levels in blood and telomere length in these individuals over a period of 5 years and found a direct correlation, indicating that antioxidants reduce the rate of telomere shortening. Similarly, the women who consumed a diet lacking antioxidants had shorter telomeres and a moderate risk for development of breast cancer, whereas the consumption of a diet rich in antioxidants such as vitamin E, vitamin C, and betacarotene was associated with longer telomeres and lower

risk of breast cancer [Gammon et al., 2009]. Antioxidants can potentially protect telomeric DNA from oxidative damage.

6.4 Dietary restriction reduces the pace of aging

Dietary restriction or eating less has an extremely positive impact on health and longevity. Reducing food intake in animals leads to reduced growth rate [Jennings et al., 1999; Jennings et al., 2000], reduced oxidative burden and reduced damage to DNA [Jennings et al., 2000], and therefore keeps the animals in a biologically younger state and can increase their lifespan by up to 66% [Jennings et al., 2000]. It has been shown that dietary restriction in rodents delays the onset of age-associated diseases and increases the lifespan. Rats subjected to a protein-restricted diet early in life displayed a long-term suppression of appetite, reduced growth rate, and increased lifespan [Jennings et al., 1999; Jennings et al., 2000]. The increased lifespan in such animals was associated with significantly longer telomeres in kidney [Jennings et al., 1999]. Because oxidative stress can substantially accelerate telomere shortening, the reduction in oxidative stress by dietary restriction is expected to preserve telomeres and other cellular components.

7. Exercise may preserve telomeres and reduce the pace of aging

Song et al. [Song et al., 2010] have demonstrated that duration of exercise inversely correlates with biomarkers for damage to DNA and telomeres and with p16 expression, a biomarker for aging human cell. Exercise can reduce harmful fat and help mobilize waste products for faster elimination, leading to reduced oxidative stress and preservation of DNA and telomeres. Werner et al. [Werner et al., 2009] showed that exercise was associated with elevated telomerase activity and suppression of several apoptosis proteins, including p53 and p16, in mice. Consistently, in humans the leukocytes derived from athletes had elevated telomerase activity and reduced telomere shortening than non-athletes [Werner et al., 2009]. Exercise seems to be associated with reduced oxidative stress and elevated expression of telomere stabilizing proteins and may therefore reduce the pace of aging and age-associated diseases.

8. 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 [Epel et al., 2004]. 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 [Damjanovic et al., 2007]. 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 studies including low socio-economic status (SES), exposure to intimate partner violence, and childhood trauma had been reviewed. 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 [Cherkas et al., 2006]. A recent study of the Whitehall cohorts found a positive correlation between telomere length and educational attainment, but not current socioeconomic status [Steptoe et al., 2011]. However, Adams et al. [Adams et al, 2007] 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 [Batty et al., 2009; Risques et al., 2010]. 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 [Woo et al., 2009], 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 was studied 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 [Aviv et al., 2002; Aviv et al., 2005; Hunt et al., 2008]. 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 [Humphreys et al., 2011]. Several studies show associations between childhood trauma and telomere length. Tyrka and colleagues [Tyrka et al., 2010] evaluated the effects of childhood adversity in a community-based sample of 31 men and women with and without a history of childhood mal-treatment, 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 [Kananen et al., 2010] 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 [Kiecolt-Glaser et al., 2011]. In a recent study of young to middle-aged adults with post-traumatic stress (PTSD), those with PTSD had shorter leukocyte telomere length 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 LTL than those without such exposure [O'Donovan et al., 2011]. 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 [Surtees et al., 2011]. However, one study reported a null finding between physical and/or sexual abuse in childhood and telomere length [Glass et al., 2010]. 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 [Kiecolt-Glaser et al., 2011; O'Donovan et al.,2011; Tyrka et al., 2010]. 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.

8.1 Stress and stress-related psychiatric conditions

PTSD are closely linked and related to, exposure to chronic or severe psychological stress [Wolkowitz et al., 2008]. Several reports have found shorter telomere length in patients with affective disorders, including depression and bipolar depression with and without anxiety [Hartmann et al., 2010; Lung et al., 2007; Simon et al., 2006]. In a small study, Wolkowitz et al. found only slightly shorter telomeres in subjects with major clinical depression compared to controls [Wolkowitz et al., 2011]. There was a significant inverse correlation between telomere length and the total cumulative lifetime period of depression. These results suggest that telomere shortening may develop with longer exposures to depression. Interestingly, depression subjects in Simon et al. studies had an average of 31.8 ± 11.2 years of history, while patients in Wolkowitz study had a shorter mean disease (13.0 ± 11.2 years). It is possible that the lack of correlation between depression and short telomere lengths in Wolkowitz study was due to the short disease duration in some

subjects. It is also likely that early trauma and later in life PTSD and MDD may interact to contribute to faster aging of cells.

9. 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 stress exposure show individual differences, such as the experience of stress, or personality, those 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 dementia caregivers may also contribute to vulnerability to stress-induced aging. O'Donovan et al. investigated whether dispositional characteristics are correlated with telomere length and found that pessimism negatively associated with telomere length, regardless of nursing status [O'Donovan et al., 2009]. The personality characteristics assessed in these studies - the experience of stress and pessimism - are relatively stable personality traits and thus may be operating over much of an individual's life, suggesting that they may have cumulative effects on cell aging, as reflected in telomere maintenance, during the relatively long periods.

10. 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 interrelated 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 [Choi et al., 2008]. In vivo, elevated levels of epinephrine, norepinephrine and cortisol were found to be associated with short telomere length in PBMCs [Epel et al., 2006; Parks et al., 2009]. Chronic stress and depression have also been linked to high levels of 8-hydroxy-deoxyguanosine (8-OHdG) and decreases in anti-oxidant enzymes [Forlenza et al., 2006; Irie et al., 2002; Irie et al., 2003; Liu et al., 1999; Tsuboi et al., 2004]. Oxidative stress preferentially damages telomeric versus other genomic DNA regions [Zglinicki et al., 2002] and inhibits telomerase activity in vitro in various cell types [Haendeler et al., 2003; Haendeler et al., 2004]. Micronutrients like vitamin C, E, folate acid and marine omega- 3 fatty acids are associated with anti-oxidative function [Jolly et al., 2001; Romieu et al., 2008], 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- alpha [Graham et al., 2006; Kiecolt-Glaser et al., 2003; Kiecolt-Glaser et al., 2005]. IL-6 has been shown to stimulate telomerase activity in cultured cells whereas TNF- alpha negatively regulates telomerase activity [Liu et al., 2010]. The concerted effects of these various biochemical mediators on telomerase may contribute to the observed associations between lifestyle factors and telomere length.

11. 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 [Epel et al., 2010] as well as in other studies that showed increases in telomerase activity over a 3 month period were associated with improved health profiles [Ornish et al., 2008; Jacobs et al., 2011]. 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 [Damjanovic et al., 2007]. 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 [Wolkowitz et al., 2011]. It was proposed that the elevated PBMC telomerase activity was an unsuccessful attempt of cells to compensate the excessive loss of telomeres in caregivers [Damjanovic et al., 2007]. 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 [Teixeira et al., 2004; Chang et al., 2007; Britt-Compton et al., 2009]. 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 [Kirschbaum et al., 1993], 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 [Epel et al., 2010]. 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 of telomere shortening reviewed by [Armanios et al., 2009]. However, this does not rule out the possibility of temporal dynamic changes of telomerase activity in response to various stimuli.

12. Future directions

While cross-sectional studies are abundant, there have been very few longitudinal studies of telomere length [Aviv et al., 2009; Ehrlenbach et al., 2009; Epel et al., 2009; Nordfjall et al., 2009; Svenson et al., 2009; Farzaneh-Far et al., 2010]. 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 [Aviv et al., 2009; Svenson et al., 2009; Farzaneh-Far et al., 2010]. 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 [Epel et al., 2009]. 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. [Damjanovic et al., 2007], 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 [Aviv et al., 2009; Svenson et al., 2009; Farzaneh-Far et al., 2010] 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 [Akiyama et al., 2002; Parish et al., 2009]. 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 [Slagboom et al., 1994; Vasa-Nicotera et al., 2005; Andrew et al., 2006], 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, synergistic or opposing effects on telomere maintenance – are likely to occur. Lifestyle and environmental factors are 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 [Njajou et al., 2009]. 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.

As a result, a strong argument can be made to strengthen healthcare on a number of fronts that involve improvements in preventative care and diagnosis, appropriate lifestyle modifications, and the initiation of new investigative platforms to understand the complexities of specific disorders as well as foster new avenues that can promote growth and maturation, mitigate aging-related disorders, and extend longevity.

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