How "Reversible" Is Telomeric Aging?
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Abstract
A critical question in human health is the malleability of telomere length. Telomere length, sampled at one point during adult life, is predictive of certain types of cancer and other immune and metabolic-related diseases. We now know from basic studies that the telomere/telomerase maintenance system plays a causal role in accelerating biologic aging and promoting disease processes. One can develop short telomeres for a multitude of reasons. Historical factors such as genetics, prenatal conditions, and early adversity, contribute to adult telomere length; however, current stress and lifestyle are also associated. If these modifiable predictors are causal factors in telomere shortening, there is a tremendous opportunity to improve maintenance and possibly even lengthen telomeres with behavioral interventions. This minireview discusses our current understanding of telomere lengthening and questions facing the field. Several small-scale stress reduction/wellness studies show promising findings, suggesting that cell aging can be slowed or reversed in vivo over short periods. Moreover, possible mechanisms are discussed, that take into account actual telomeric lengthening, such as that which occurs through telomerase-mediated elongation, or mechanisms resulting in "pseudo-telomeric lengthening" as might occur from changes in cell type distribution. There is a strong need for more translational clinical to bench research to address mechanistic questions in experimental models. In addition, well-designed intervention research that examines both telomeres and potential mediators of change can further enhance our understanding of malleability, mechanism, and clinical implications of telomere lengthening. Cancer Prev Res; 5(10); 1163–8. ©2012 AACR.

A rapidly growing body of research suggests that one snapshot measure of leukocyte telomere length is predictive of age-related physiologic decline, onset of diseases of aging, such as cancer and dementia, and early mortality (1–3). Thus, it is not surprising that when people learn about telomeres, one of the most common questions is "Can telomeres be lengthened?" The answer is not so simple. While the quick answer is "yes," it is one that requires qualification and explanation. Here, we review what is known so far about telomere shortening and elongating in humans, and address important questions to understand the mechanisms of apparent telomere lengthening.

Telomeres Shorten . . . and Lengthen
Telomeres tend to shorten slowly over years of aging but are active and dynamic, especially when examined over short periods. In the early studies of telomeres in single-celled organisms called protozoa, Blackburn and Greider observed, "telomeres are dynamic structures in vivo, being acted on by shortening and lengthening activities" (4). They discovered telomerase, an intracellular enzyme that has an RNA reverse transcriptase component that lengthens telomeres. Telomerase-mediated elongation of telomeres occurs through de novo synthesis of telomeric DNA. The telomerase protein and transcriptase component, plus end-repair activities, together lengthen and stabilize telomeres (5).

In complex living beings, telomerase-dependent lengthening occurs, but this activity is difficult to measure in vivo. This is partly because we are trying to measure telomere length in a moving target, that is, leukocytes, the mix of diverse immune cells in the circulating blood. When telomeres are lengthened by telomerase, this could be called "actual lengthening" or "reversal" of telomeric aging. In contrast, when average telomere length increases but is due to a redistribution of cell subpopulations (the changes in percentages of cell types in the blood due to trafficking between blood, tissue and storage sites), this mimics a literal reversal and might be called "pseudo-lengthening." In either case, there is an apparent lengthening, and it is this apparent lengthening across cells types that has been observed in longitudinal and intervention studies that warrants closer examination.
We now have an emerging picture about telomere dynamics over time in people. The most commonly observed pattern when examined over a short period of 2 to 6 years is that while some individuals shorten or maintain their telomere length, around 15% to 25% of people tend to show average lengthening (6–8) even when buccal cells are examined (9). However, when observed over a decade or more, we are less likely to see lengthening (10).

Longitudinal studies in humans show a strong inverse relationship between baseline telomere length and change. While some of this could be measurement error or regression to the mean, as argued by Chen and colleagues (6), in some studies it is clearly not due to error, and the phenomena is consistent with the biological regulation of telomere length by telomerase. Over the short term, cells prevent short telomeres from shortening further and uncapping by responding with high telomerase activity. Telomerase targets short telomeres causing them to lengthen more than the long telomeres (11) striving to prevent critically short telomeres. In the only study so far that examined changes over six months, around half the sample showed lengthening. Further, shortening tended to occur in the longest telomeres (10). Thus, over short periods telomere length oscillates, and these dynamic patterns must be studied to understand the potentials and limits of reversals of telomeric aging.

**Telomeres Reflect Personal History**

To what extent can we extend telomeres? Telomere length in adulthood is influenced by both personal history and recent events. Some of these early factors are simply out of our control. Thus, an important consideration in understanding the potential limits to lengthening is that some factors that shaped adult telomere length are not modifiable but may still exert their influence in some ways. Genetic variation, a younger paternal age at conception, gestational age, and prenatal maternal stress are all associated with shorter adulthood telomeres (12–15). Childhood is another time of apparent imprinting, where early adversity, such as exposure to trauma or neglect or low parental socioeconomic status predicts childhood or adulthood telomere length (16–18).

Thus, early developmental events set us on a trajectory that influences the limits of cellular replication—in immune cells and possibly other mitotic cells—in adulthood. It is not clear how the memory of these early events is transmitted, but given how short-lived many immune cells are, it is possible these events are affected through alteration of the immune cell source—the hematopoietic stem cells. But to determine this, experimental animal studies would be required. Hematopoietic stem cells determine the offspring cells’ telomere length, particularly for granulocytes and monocytes (19). In animal models, insufficient telomerase leads to accelerated senescence of stem cells, which can be remedied with antioxidants (20). Thus, it is conceivable that excessive stress and the remediation of stress might influence these critical stem cells in humans as well.

**Telomeres Reflect Mindset and Lifestyle**

The more hopeful part of the telomere story is that our current behavior and mental health, both modifiable factors, are associated with telomere length. Lower stress, exercise, good nutrition (omega-3 free fatty acids, antioxidants, less processed red meat), and good sleep are related to longer telomeres as reviewed elsewhere (21, 22). In longitudinal studies, abdominal obesity predicts telomere shortening, whereas high omega-3 free fatty acid levels predict less attrition over a 5-year period (8, 23). This fuels the hope that if people can master the challenge of altering certain lifestyle habits, they may be able to lengthen their telomeres. These observational studies still leave us far from understanding if the relationships with lifestyle are causal. Exercise is likely one of the most potent components and has been related to higher telomerase activity in rodents (24), however, most of the intervention efforts in humans to date have been focused on stress. Can we reduce stress and improve well-being, and do these changes predict lengthening?

**The Promise of Interventions**

It has been a common belief that telomeres are stable structures that change slowly in a unidirectional manner—shortening over years. Cross-sectional studies across age ranges do indeed verify this trend. Thus, in our first intervention studies, we made the assumption that telomere length would not change within months and subsequently measured only telomerase activity changes. While this has led to some missed opportunities, these studies have been informative nevertheless.

Four small-scale intervention studies suggest that telomerase activity is responsive to lifestyle and mindset. In an uncontrolled study of intensive lifestyle modification for men with prostate cancer, including a low fat diet, increased activity, and stress reduction (yoga, meditation, social support), there was a 30% increase in peripheral blood mononuclear cell (PBMC) telomerase activity over 3 months (25). In a stress reduction/mindful eating intervention for overweight women, telomerase activity increased 18% in a treatment group versus waitlist group, although nonsignificantly (26). Across the sample, those who showed the largest decreases in psychologic distress, cortisol, and glucose also showed the greatest increases in telomerase activity. In a study of dementia caregivers, a meditation group showed a 43% increase in telomerase activity as compared with a relaxation control group (27). Finally, a 3-month trial of intensive concentrative and compassion-oriented meditation found 30% significantly higher telomerase activity as compared with the waitlist control group (28).

Each of these preliminary studies has limitations, particularly based on their small size or lack of ideal control group. However, there was a pattern across all 4 studies, in which decreases in aspects of psychologic distress (intrusive thoughts, anxiety, depressive symptoms, and neuroticism, respectively), were significantly associated with increases in, or higher posttreatment, telomerase activity. This suggests
that PBMC telomerase activity, at least as measured across the mix of circulating cells under controlled resting conditions, is malleable and responsive to changes in psychologic well-being. But also, given the novelty of this field, and lack of larger controlled trials, there may be a publication bias toward positive results.

Biegler and colleagues have now reported the first study to show that changes in telomere lengthening are associated with changes in distress over a 4-month period (29). Using the Flow-FISH method which allowed them to look at telomere length changes in specific cell types, they found that those subjects who had increased lymphocyte telomere length also showed an increase in naive T cells, which provides insight into one possible mechanism of apparent telomere lengthening. While this type of lengthening may not be a literal “reversal” of telomeric aging, it may nevertheless have a positive clinical impact through rejuvenating immune system robustness.

There is now a striking new finding from what appears to be the first nutritional intervention on telomere length. Kiecolt-Glaser and colleagues found that after four months of omega-3 polyunsaturated fatty acid supplementation, lower blood levels of n-6/n-3 polyunsaturated fatty acids were associated with longer peripheral blood mononuclear cell telomeres, controlling for baseline telomere length. This did not appear to be telomerase-mediated, at least as measured at the two timepoints. The greater the improvements in the ratio the greater the reductions in oxidative stress and proinflammatory factors, etc. and low adiponectin, is associated with shorter telomere length (36, 37). Targeting the comorbidity between psychologic stress and metabolic stress might be more powerful than reducing them individually, as they are often interdependent (31). In particular, interventions that reduce both stress and overeating should be more effective than a strictly dietary-focused intervention. Antioxidants may also be an important mechanism in behavioral interventions, as they can buffer oxidative stress-related shortening in vitro and in animal models (20).

**Decreasing activation of latent viral load**

Most people are positive for common latent viruses, such as Epstein–Barr virus and cytomegalovirus. Chronic stress enhances viral replication (38), which in turn can dampen telomerase activity and shorten telomere length (39). Stress reduction may reduce reactivation of latent viral load and slow replicative senescence. It is not clear if this mechanism can have meaningful effects in very short-term reversal states or just over longer periods.

**Redistribution (Changes in circulating immune cell subsets)**

Immune cells are a moving target throughout the body. Leukocytes in the blood comprise diverse populations of cells including granulocytes, T and B lymphocytes, natural killer cells, and monocytes. Leukocyte telomere length therefore is comprised of the average telomere length across all immune cell subpopulations present in the sample studied. Importantly these subsets are not of equal frequency in the blood of a given person nor between persons. Thus, leukocyte telomere length may mask important differences in subpopulations. This does not seem to matter in terms of clinical use, as it is leukocyte telomere length (vs. telomere length in specific cell types) that has been most studied and is predictive of early disease and mortality. However, to further understand the mechanism of telomere shortening with stress and lengthening with intervention, it is important to know whether there are specific cell types that are causing the changes observed. For example, stress reduction might reduce numbers of presenescent or senescent cells, such as CD8⁺CD28⁻ T cells, which become proinflammatory (40). Because they make up a very small percentage of the total number of immune cells, they should not statistically influence leukocyte or PBMC telomere length. However, having a greater percentage of these cells is associated with shorter average PBMC telomere length (41), which suggests that they are influential, and bulk measures of PMBC telomere length may, in part, reflect the level of CD8 replicative senescence.

Stress induces dramatic changes in immune cell distribution throughout the body. As Dhabhar and colleagues explain, immune cells start in what might be thought of as the barracks—the synthesis and storage sites (marginalized pool, spleen, bone marrow, etc.)—and under acute stress
move to the boulevards or the blood vessels—our main window into the system—on their way to the battle stations, the target tissue, such as skin and the gastrointestinal tract (42). During acute stress, there are also acute increases in telomerase activity in PBMCs observed that do not seem to be dependent on cell type subpopulation (43). However, during chronic stress, which is of most relevance to the question of reversibility, there are fewer cells circulating, and these cells show impaired mobilization to tissue (44). Changes in the types of cells that are mobilized during chronic stress may in turn influence whether lengthening is observed or not in the circulating blood.

**Increases in "younger" cells**

Within redistribution, there can be increases in numbers of naïve cells regardless of cell type. Biegler and colleagues’ (29) findings suggest that lengthening was associated with an influx of naïve T cells. Thus, rather than elongation of telomere length on a per cell basis, it seemed to be in part due to replenishment of cells in circulation. Naïve T cells naturally have longer telomere length than memory T cells but may also have longer telomere length than granulocytes (45). Any factors that stimulate more naïve T-cell influx may lead to lengthening of average telomere length (mimicking the reversal typically associated with telomerase-mediated per cell increases in base pairs).

Improvements in health behaviors might promote short term lengthening as well. Exercise may be one of the important factors shaping apparent or actual lengthening, as it is related to greater numbers of naïve cells as well as longer telomere length (36, 46). Increasing well-being through dampening stress and concomitant increases in growth and restorative factors might induce a specific pattern of adhesion molecule-stimulated trafficking patterns and result in cells with longer telomeres—either more naïve cells or fewer senescent cells.

**Caveats:** Telomere Length and Telomerase can Increase or Decrease in States of Chronic Stress: Implications for Detecting Intervention Effects

An important paradox exists in that severe stress may lead to apparent telomere lengthening, as relief of stress appears to (reviewed earlier). Stress might stimulate re-populations from hematopoietic cells (with longer telomere length), particularly in the myeloid (granulocyte) vs. lymphoid (lymphocyte) compartment. In a critical study addressing short term changes of telomere length in different cell types, extreme exposure to oxidative stress over 5 months led to a selective and dramatic increase in telomere length in granulocytes and naïve T-cells, followed by a rapid decline over the next 7 months (47). There were no changes in memory or B cells, which have slower turnover. This pattern fits predictions and argues against measurement bias (which would have affected all cell types equally). Authors suggest a model of dynamic telomere equilibrium under stress: Severe stress might first lead to increased turnover and depletion of circulating cells, and compensatory re-population of granulocytes from bone marrow, resulting in acute telomere lengthening. This is followed by a high level of replication and turnover in these new cells, leading to dramatic shortening over the next period of time (47). A repeating oscillatory pattern of responding to severe stress may lead to earlier depletion of stem cell resources, replicative senescence and accelerated aging of tissues. This possibility emphasizes the importance of understanding short term telomere dynamics, since short term lengthening could be either salutary or a bellweather for early senescence. There are inconsistent findings on leukocyte telomere length and cancer risk, and it is possible that the oscillatory dynamics of telomere length may be contributing to the complex picture.

Telomerase levels under stress also present a paradox, as they can be high or low. Given the difficulty in accurately measuring basal state telomerase in human cells, little is known about telomerase regulation *in vivo*. Telomerase has more functions than just elongating telomeres. Higher telomerase, while probably always beneficial for telomere protection, might also serve as an indicator of a high level of cellular stress. Telomerase appears to increase during acute stress (43) and certain states of chronic adversity, such as low education, depression, and caregiving (48–50), presumably to combat oxidative stress and to protect the telomere. In depressed people, although they had elevated telomerase at baseline, treatment with an antidepressant led to further increases in telomerase activity, and this telomerase increase was associated with a greater reduction in depressive symptoms (49). Chronic adversity can lead to short telomeres and high telomerase activity—likely compensatory to maintain stable telomeres. But will reducing stress increase or decrease telomerase? Stress reduction for groups with elevated telomerase could theoretically reduce telomerase if it is also reducing aspects of cellular stress. So far, the few small-scale interventions seem to increase telomerase. However, given these observations from cross-sectional studies, the opposite, a decrease in telomerase, might be expected as well during stress reduction for those experiencing high chronic stress. Nevertheless, telomere maintenance or lengthening might still be observed if the net effect on cells is a reduction of factors that promote shortening.

**Conclusions: How Malleable Is Telomere Length?**

Life experiences are reflected in telomere length. Early development and childhood exposures have repercussions throughout life. But interventions might act as an intense resetting or induce critical periods where we can “shake up” our immune system toward a healthier, younger state characterized by longer telomeres, through either true reversal of telomeric aging or addition of younger cells, or both.

It is still unclear how much people can actually change categories—from having short to long telomeres, resulting...
from improvements in mental well-being or metabolic health. These are unresolved issues due to the vacuum of longitudinal data addressing this question and the absence of clear reference standards for what a short telomere length value is. It is also unclear how much short-term changes in one’s mental and physical health can actually improve telomere length in a clinically meaningful way, by promoting sustained increases in telomere length that should in turn predict relatively reduced risk of disease. While over decades, most telomeres will shorten, temporary increases, especially if sustained over time, could alter the trajectory of age-related shortening. In animal models, dramatically replenishing telomerase activity increases telomere length and induces a reversal of clinical aging (51). In people, modest increases in telomerase after behavioral interventions co-occur with improvements in metabolic health (25, 26). Since tumors are immortalized by high telomerase, one might wonder if such increases in telomerase in leukocytes might elevate risk of cancers. Our focus is on behavioral interventions, where telomerase-associated increases don’t come close to the high levels linked to cancer.

It has become clear that telomeres shorten over time in an oscillatory rather than linear fashion. Although we do not fully understand how telomere length changes over short periods, there may be clinical significance regardless of mechanism. Longer telomeres, if sustained, indicate greater potential for replication and less senescence and associated pathology. It is also intriguing to consider that what we observe in the immune system may be an example of what is happening throughout many of the body’s mitotic cells. For example, senescent fibroblasts, which have short telomeres, and create a fertile ground for cancer (52), might also respond to these interventions. We cannot easily measure telomeres in organs or tissues deeper than skin, but studies suggest that there is coordination of aging across tissue compartments.

Most of the questions raised earlier are low-hanging fruit that can be answered by basic and intervention research. We need to distinguish between true reversal of telomere shortening (actual lengthening) and replenishment of younger cells (pseudo-lengthening) and whether these forms of lengthening slow clinical signs of aging. We need larger trials that examine telomerase and telomere length in key cell types—acknowledging that the state of these immune cells’ aging is dynamic. We need to peer into the workings of the mind, behavior, and the cell simultaneously and repeatedly. Then, the next generation of telomere intervention research can help us identify and test the most effective intervention components and determine just how much we can intentionally lengthen our telomeres. And finally, if such changes are a true reversal of telomeric aging with the expected benefits to our well being and healthspan.

Disclosure of Potential Conflicts of Interest
E. Epel is a cofounder and consultant/advisory board member of Telome Health, Inc., a telomere measurement company. E. Epel also has ownership interest in a UCSF Patent.

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