Telescoping Telomeres

By Mary Ann F. Kirkpatrick

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"Telescoping Telomeres" was delivered to the Winchester club on April 6, 2016.

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Your liver is less than a year old.

Your skin is less than a month old.

Your stomach is less than a week and a half old.

Your body is composed of cells, as you likely know. You probably also know that the cells in your body today are not those you were born with; cells re-create themselves. Telomeres are a crucial part of that process.

Telomeres are tiny protective caps at each end of our 46 chromosomes. During cell division, they ensure that the genetic information from parent cells is accurately passed on and that chromosomes do not fuse with each other to form mutations. Their length is controlled by the protein enzyme telomerase and RNA subunits, sometimes referred to as a "cellular immortalizing enzyme" ("Overview"). However, each time a cell divides, some telomere length is lost. When it becomes too short, the chromosome can no longer replicate, and the cell dies.

Even though telomere length and its biology are not well-known concepts for the vast majority of people, telomeres have a major impact on our overall health and life quality as we age. Research findings indicate that overall telomere length has implications affecting our health. Longer length is associated with longer life expectancy, while shorter length has been associated with early onset of conditions such as heart disease, diabetes, osteoporosis, and reduced life expectancy. Indications suggest that lifestyle choices such as proper nutrition, exercise, and stress reduction may promote longer telomeres. Conversely, short length may have positive benefits in cancer treatment, where tumor cells can be deprived of the immortalizing telomerase, thus preventing tumor cells from subdividing.

Telomeres and Aging

With aging, overall telomere length tends to decrease: "Telomere length in humans seems to decrease at a rate of 24.8-27.7 base pairs per year" (Shammas). Telomere shortening, some have proposed, may be "a molecular clock mechanism that counts the number of times a cell has divided and when telomeres are short, cellular senescence (growth arrest) occurs" ("Overview").

Masood A. Shammas of the Harvard Cancer Institute writes, "Telomere length, shorter than the average telomere length for a specific age group, has

been associated with increased incidence of age-related diseases and/or decreased lifespan. Telomere length is affected by a combination of factors including donor age, epigenetic make-up and environment, social and economic status, exercise, body weight, and smoking." For these variables, "Gender does not seem to have any significant effect on the rate of telomere loss."

Dr. Shammas summarizes:

> Certain lifestyle factors such as smoking, obesity, lack of exercise and consumption of an 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, heart failure, diabetes, increased cancer risk, and osteoporosis.

Individuals whose white blood cell telomeres are shorter than the corresponding average telomere length for persons in the same age group have a three-fold higher risk of developing myocardial infarction. In these examples, oxidative stress is the culprit causing the telomere shortening.

Consider this concrete example: women who smoke a pack of cigarettes per day for 40 years lose an average of five more base pairs of telomere per year than non-smoking women. This translates into losing 7.4 years of life. In obese women, an estimated 8.8 years of life are lost (Shammas).

Exposure to similarly harmful agents likewise leads to oxidative stress and thus telomere shortening. Traffic police officers who are exposed to daily pollution, defined as toluene and benzene, have shorter telomeres than office workers who are the same age. Additionally, coke-oven workers exposed to polycyclic aromatic hydrocarbons have significantly shorter telomeres, as well as more DNA damage and genetic instability, than a control group of men. The decrease in telomere length in the coke-oven workers significantly correlates with the number of years the workers were exposed to harmful agents (Shammas). As in the case of cigarette smoking, telomere shortening in coke-oven workers appears to be dose-related.

Family instability has also been linked with shorter telomeres in children.

Family instability—e.g., family incarceration, suicide of a family member, witnessing violence—has also been linked with shorter telomeres in children. In a study of 75 African American families with children ages 5 to 15, researchers found the more family instability a child had experienced, the shorter his or her telomeres were. The researchers "took into account other factors that could influence a child's development, such as body mass index, age, maternal education as an indication of socio-economic status, household monthly income and more. Almost none of these factors had any bearing on telomere length except a few peculiarities around gender and age" (Hunt). In this study, remarkably, family instability appears to affect girls more than boys (other studies had shown no gender differences). Boys who actually witnessed violence appear to be more affected than those who experienced other types of family instability. Interestingly, maternal education appears to provide a protective barrier for boys ten years old or younger. However, the older a boy is when he experiences family instability, the shorter his telomeres appear to be (Hunt).

African-American men tend to have shorter life expectancies than any other racial or gender group in the United States and to have more chronic diseases compared with the rest of the population. Older African-American men who perceive they have experienced racial discrimination and who also hold negative in-group racial bias have shorter telomeres relative to the rest of the population, even when other variables are controlled. Although past discrimination cannot be eliminated, there is hope that reducing or eliminating in-group racial bias could help lengthen their telomeres and lessen their chronic disease burden in their later years (Chae et al.)

Life style changes that lengthen telomeres may also improve overall health. In a small, five-year study of 35 men with localized, early-stage prostate cancer, researchers investigated the relationship between comprehensive lifestyle changes and telomere length and telomerase activity. Ten of the subjects were assigned to lifestyle changes that included a vegetarian diet (high in fruits, vegetables and unrefined grains, and low in fat and refined carbohydrates), a moderate exercise regimen (walking 30 minutes a day, six days a week), stress reduction (gentle yoga-based stretching, breathing exercises, and meditation) and increased social support through group sessions. The group that made lifestyle changes experienced a "significant" increase in blood sample telomere length of approximately 10%. (Note: the researchers saw the positive telomere lengthening in blood rather than prostate tissue.) Further, the greater the behavioral changes, the more significant the improvements in telomere length (Fernandez).

Similar positive results from exercise have been demonstrated in post-menopausal women who were primary caregivers for a family member with dementia and women with a history of childhood abuse. The short telomeres of women who were primary caregivers had a probable link to holding a pessimistic outlook, which is associated with high levels of pro-inflammatory protein. Pessimism scores were lower and telomeres were longer for the caregivers who exercised regularly. Women with histories of childhood abuse who did not exercise had telomeres shorter than those of women with no history of abuse. However, "in women who exercised regularly, there was no link between childhood abuse and telomere length, after controlling for body mass index, income, education and age" (O'Brien).

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Intriguing as these findings are, the relationship between telomeres and exercise requires further investigation. The Mayo Clinic Health Letter reported the length of time a person stands is more predictive of longer telomeres than the amount of time spent exercising (Mayo Clinic 4). Earlier studies that showed a lengthening of telomeres with exercise, such as the study in which men walked 30 minutes per day, six days per week, were investigating the *presence* or *absence* of exercise and not necessarily studying the *type* of exercise.

Entrepreneurs have been quick to connect the link between nutrition and telomere length. By simply searching the web for telomere lengthening supplements, one can find many opportunities to purchase supplements guaranteed to extend telomeres, reverse aging, cure cancer, and deplete your bank account. This, however, is not part of my discussion—you are on your own with that one.

Telomerase and Cancer

In over 85% of cancers, regardless of the type, telomerase is responsible for maintaining the length of telomeres, which allows tumor cells to proliferate. Therefore, detecting telomerase may be helpful in diagnosing certain types of cancer, as a predictor of outcomes and as a marker of minimal remaining disease following standard cancer therapy. Since most cancer cells must maintain their telomeres, any treatment or strategy that prevents telomere maintenance also prevents precancerous cells from immortalizing, or forces immortal cells into a normal pattern of senescence or cell death, and therefore is a potentially important anti-cancer treatment (Shay, "What are telomeres").

The molecular structure and subunits of telomerase are well defined, so researchers can target specific areas of the enzyme in an effort to manipulate activity. Short chains of nucleic acids called oligonucleotides, researchers have shown, can bind with a specific region of telomerase RNA (called the template region), causing an inactivation of telomerase in cancer cells. "In addition to approaches directed at

telomerase RNA," according to a University of Texas Southwestern website, "other strategies include specifically targeting the catalytic reverse transcriptase subunit or telomerase as well as its associated proteins. Identification of the cellular genes that regulate the telomerase repression pathway offers an independent tactic for developing telomerase antitumor drugs. In this regard, there is substantial evidence that a gene on chromosome 3p contains a telomerase repressor" (Shay, "What are telomeres").

Findings at the Salk Institute indicate that yeast telomerase has an "on/off" switch. This means that simply having telomerase present may not keep telomeres from shortening. Since most cancer cells require telomerase to allow uncontrolled cell growth, manipulation of the "off" switch could potentially keep telomerase activity below the required threshold for tumor cell proliferation ("Flip the Telomerase").

In pediatric patients who have spontaneous remissions from neuroblastoma 4s and low-grade gliomas, researchers have learned, telomerase is *not* activated. These children are born with advanced cancer; however, for those tumors to grow, a mechanism to maintain telomere length must be established, and establishing such a mechanism requires telomerase. Thus, inhibition of telomerase in these children could be a "potent, almost universal, anticancer therapeutic target" (Shay, "Short Telomeres").

According to an article by Jerry Shay, Roger Reddel, and Wooding Wright, "0 to 15% of human cancers lack detectable telomerase activity, and many of these use an alternative lengthening of telomeres (ALT) mechanism":

> Cells that use ALT to overcome telomere shortening have many unusual characteristics such as highly heterogeneous telomere lengths and abundant extrachromosomal telomeric DNA. […] These ALT-expressing tumors would not be expected to respond to anti-telomerase therapies, and the telomerase-expressing tumors could become resistant by switching to an ALT mechanism, as has recently been seen in mice.

Less is known about ALT structures than is known about telomerase. A critical unanswered question to date is whether or not there is more than one type of ALT mechanism. Theoretically, combinations of ALT plus telomerase inhibitors should be ideal cancer treatments, but too little is known to date about ALT.

There are three very different strategies under investigation for telomerase-expressing cancer treatments: telomerase inhibition; telomerase-targeted immunotherapy; and telomerase-targeted oncolytic viruses. Each of these treatment strategies have been useful for specific types of cancer. Telomerase inhibition is useful in small cell lung cancer, multiple myeloma, and breast cancer, phase 2. Immunotherapy targeting telomerase has shown positive results in mice implanted with human pancreatic cancer, while phase 3 cells and virotherapy is showing promise for lung, prostate and liver cancers. Some telomerase inhibitors have even been used in concert with traditional treatments to suppress growth of new tumors when post-treatment residual cancer cells have managed to survive after multiple rounds of cell divisions (Ouellette, Wright, and Shay).

The Long View of Telomeres

Our understanding of telomeres is growing but far from complete. If we had a telescope that could look into the future of biological research into telomeres, what might we see?

Biochemically, the telomere is a rather simple structure, but research has revealed its importance to our health and viability. We cannot simply assume, however, that one could live a very long healthy life based solely on the length of our telomeres, so long as one has a healthy life style, free from environmental toxins and over whelming personal stresses. The telomere story is more complicated. Researcher Jerry Shay observes:

> There is increasing evidence that telomeres are heritable, and mutations in telomere regulatory genes have a causal role in human diseases, such as bone marrow failure and idiopathic pulmonary fibrosis. These have been referred to as

> telomeropathies or telomere syndromes. It is becoming recognized that these telomere maintenance disorders are a spectrum of diseases, and thus it is too early to draw general conclusions about the causative versus correlative role of telomere biology in most human disease. ("Short telomeres")

Further complications arise from the ways telomeres can be measured and their data compared. Methods of measurement vary; investigators select a method based on the specific research question to be answered, the material available for analysis, and the accuracy of the measurements. As for data comparison, the research questions may be the same, but the materials available and/or types of measurement may be different (Aubert, Hills, and Lansdorp). For example, in a meta-analysis involving 36,230 subjects to determine if females have longer telomeres than males and if the association becomes stronger with advancing age, results were surprising. The overall results indicated yes, telomere length is longer in females than males as expected (since females tend to live longer), but no differences are found in studies that do not use the same methods of determining specific DNA sequences in the analyses (Gardner et al.). So, even after a meta-analysis, the question remains, do females really have longer telomeres than men?

To further complicate our understanding, some types of cancer and disease occur in individuals long before their telomeres should have shortened, based on time from birth to disease presentation, to the point of losing their protective capability.

Future investigators have plenty of unanswered questions to address, in short. However, until more information is available, I will keep my telescope trained on my telomeres and try to live a healthy life style and hope that I began life with extra-long telomeres.

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