Telomeres and *Telomerase* as Natural Therapeutic Targets

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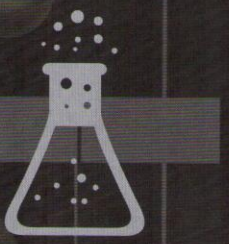

Introduction

The Nobel Prize for Medicine (2009) was awarded to EH Blackburn, CW Greider and JW Szostak for scientific research on telomeres and their controlling enzyme telomerase (www.nobelprize.org). Research into the biological significance of telomeres and telomerase has proceeded at a frenetic pace over the past couple of decades. This area of science remains "embryonic", but it holds the promise of providing new frontiers and foundations for the understanding of the emergence of chronic disease, cancer and aging. The purpose of this article is to highlight concepts that are most relevant to the introduction of a natural clinical protocol to support the structure and function of telomeres.

The Basics

Telomeres are DNA caps on linear chromosomes that function to prevent aberration or loss of genetic information during cell division(1-4). These "protective regions" of DNA shorten with repeated cell division in somatic cells. The enzyme telomerase (a reverse transcriptase) acts to extend telomeres and reduce their attrition.

Shortened telomeres may reach a point where they cannot support normal division of chromosomes, resulting in cell senescence (replicative arrest) and abnormal chromosomal function. These changes can result in altered or loss of normal functions of genes, cancer propagation, immune dysfunction, aging of tissues and the emergence of chronic disease(5-12).

If telomere shortening correlates with age and telomerase can sustain or lengthen telomere, then simple logic dictates that interventions to modulate the telomere/telomerase "duo" present a promising and novel strategy for anti-aging or disease prevention or treatment. While tampering with telomeres and telomerase enchants many scientists and clinicians, matters are not quite as simple as some individuals may have hitherto supposed.

Observations on Telomere Tampering

Telomere length and telomerase expression appear to be linked in many, but not all studied species of life(1-10). While telomeres shorten with age, some people start with longer telomeres than others. Shortened telomeres tend to "push" a cell towards senescence prior to apoptosis (cell death) and this chain of events can be variably corrected in vitro and/perhaps, in a safe manner, in vivo.

Telomerase activity may lengthen telomeres, but this enzyme is found to be expressed preferentially in cancer, certain germ cells and stem cells (immortal cells). This leaves an unanswered question "will direct telomerase induction lead to cancer?" We know relatively little about selective telomerase enhancers and this selective approach for telomere support is an important target for pharmaceutical or nutraceutical development as the potential longevity promoting properties of telomere support emerge (1-10).

Shortened telomeres exert a "telomere position effect" which alters genetic expressions at the cellular level. In this circumstance, DNA repair genes do not exert optimum function and those genes that promote cellular aging may emerge. The aging cell with its shortened telomere, seems to lead to a circumstance that facilitates or favors mistakes. However, one must pause and think about the induction of cellular senescence with age as a potential defense mechanism against the occurrence of age-related cancer. Senescence and apoptosis serve both aging and disease prevention options. The gene that regulates telomerase expression is "silenced" in healthy cells. "Switching on" or "switching off" this gene, to a variable degree, is possible by genetic manipulations and the administration of certain compounds.

Telomere loss or compromise is not consistently shown to be telomerase dependent and it may not always show a linear relationship with advancing years. For example, loss of telomere length is accelerated in childhood (up to the age of 20 years) and in the elderly (greater than 65 years). While telomerase is not expressed in most somatic cells, some cells (expanding immunocytes, germ cells and cancer cells) express high levels of telomerase. Does telomerase shortening in laboratory tests of white blood cells (T-lymphocytes) mirror telomere shortening in other cell types? Further research is required(1-17).

Telomeres loss is associated with sedentary lifestyles, oxidative stress, cancer, insulin resistance and chronic inflammatory disease…to name a few disorders, but some degree of "chicken and egg" arguments prevail. To add to the conundrum, laboratory studies of germinal centers, that produce B cells (lymphocytes), show that telomere length can increase, in spite of intense cell replication. Furthermore, some studies imply that telomere loss may not always exhibit a clear correlation with certain cells history of replicative activity. These factors, and other concerns, may question the sensitivity and specificity of some measures of telomere length as a reliable measurement of physiological age(1-20).

A general consensus has emerged that telomere length has reasonable clinical predictive value, but it is only one of several useful biomarkers of age e.g. immune function or the detection of immune senescence. That said, immune senescence seems to be closely related to telomere shortening. The presence of high numbers of certain T-lymphocygtes (CD8 and CD28+) in elderly individuals is associated with blunted immune response and this circumstance has been labeled as an "immune risk phenotypes" that a predictor of all causes of mortality in the elite elderly >80 years of age(10-13). Telomerase induction may be a solution to this "immune risk phenotype".

The telomere/telomerase literature is replete with promises of the potential benefit of targeted therapeutic interventions(1-17). While no pharmaceutical is approved for telomere modulation, natural approaches are emerging with the use of specific dietary supplements (e.g. Astragalus extracts). While this long term safety or efficacy of nutraceutical interventions for telomere support remains unknown, the desirability of telomere retention or lengthening strategies are so appealing that the use of safe and simple strategies to achieve this outcome seems to be a reasonable intervention.

I propose that this therapeutic approach with a natural protocol for "telomere support" that can be applied with optimistic caution by healthcare

TABLE 1: Factors that alter telomere length. The asterisk (*) denotes somewhat amenable to intervention (References 1-17)

FACTOR	COMMENT
GENDER	Tend to be longer in women
AGE	Children have longer telomeres
AGE OF PARENTS	Older parents may deviate shorter telomeres to their offspring (e.g. Dolly the sheep)
SEDENTARY LIFESTYLES*	Exercise tends to cause retained telomere length
CHRONIC INFLAMMATION*	Clear evidence e.g. rheumatoid disease
OXIDATIVE STRESS*	Emerging studies on antioxidants for retention of telomeres
MENOPAUSE AND ANDROPAUSE*	Predictable loss of telomere length with milestones of aging. Hormone dependency of telomere length discovered.
TELOMERASE*	Activity can be induced
INSULIN RESISTANCE*	Emerging association with telomere shortening.
	Metabolic Syndrome X and Type 2 Diabetes are clearly a disorder of premature aging.

TABLE 2: An emerging evidence base for nutraceuticals that support the structure and function of telomeres.

NUTRACEUTICAL	EVIDENCE-BASE-FOR USE
ASTRAGULUS	Astragalosides (cycloastragenol) or the specific molecule TA-65 are proposed as telomeres. A clinical trial that showed improvements in immune function, eyesight, sexual function and skin color characteristics. (Reviewed at TASciences.com accessed February 6, 2010).
OMEGA 3 FATTY ACIDS	In a group of patients with coronary heart disease there was an inverse relationship between blood levels of marine omega 3 fatty acids and telomere shortening over a five-year interval. (Raimin F, et al, JAMA, 303, 250-257, 2010)
ANTIOXIDANTS	The rate of telomere shortening is modulated by oxidative stress (certain in vitro) (Saretzki G, Von Zglinicki, T, Ann NY Acad Sci, 959, 24-9, 2002). Breast cancer risk may be affected by telomere length in women with low intake of antioxidants or antioxidant supplements (Shen J et al, Int. J. Cancer, 124, 1637-43, 2009)
VITAMIN D	Higher Vitamin D concentrate in serum is associated with longer telomere length (Richards JB et al, Am. J. Clin. Nutr., 86, 5, 1420-1425, 2007)
FOLATE/B12	Folate status alters telomere length in a non-linear manner probably by its effects on the integrity of DNA and epigenetic influences (Cattaneo PL, et al, J Nutr., 139, 7, 1273-1278, 2009) Plasma homocysteine elevation due to folate and vitamin B12 deficiency is associated with decreased telomere length in older males (Bull CF et al, Rejuvenation R. Sep. 28, 2009)
NICOTINAMIDE	Nicotinamide extends the lifespan of human fibroblasts as a presumed consequence of reduced mitochondrial production of reactive oxygen species (Kang HT et al, Aging Cell, 5, 423-36, 2006)
MULTIVITAMINS	Epidemiological evidence associates multivitamin use with longer telomere length (Xu, Q et al, Am J Clin Nutr. 89, 6, 1857-63, 2009)
CHINESE GINGER ROOT	Evidence is emerging that ginger root may support telomerase lengthening and have other beneficial actions.
ALPHA-TOCOPHEROL	Demonstrated to inhibit telomere shortening and retain telomerase activity in microvascular endothelial cells in the brain. (Tanaka Y et al, J. Cell Biochem, 102, 3, 689-703, 2007)
N-ACETYLCYSTEINE	N-acetylcysteine blocks the nuclear export of h TERT into cell cytoplasm and delays replicative senescence of endothelial cells that are attracted by reactive oxygen species (Haendeler J, et al Clinc. Res, 94, 768-775, 2004)
STATINS	Treatment with statins increases lymphocyte telomere length (Brouillette SW et al, Lancet, 39, 107-114, 2007) Statins interfere with redox balance of endothelial cells (Haendeler J et al, Clin Res, 94, 768-775, 2004) and (Spyridopolens I, et al circulation, 110, 3136-3142, 2004)
GINGKO BILOBA	Extracts of Gingko biloba extracts have been show to delay the onset of cellular senescence by activating P13k/Akt signaling pathways that augment telomerase activity (Xu D et al, D X et al, J Cardiovasc. Pharmacol, 4-9,111-115, 2007).

givers. I recommend patient monitoring and surveillance with this novel intervention strategy. However, the protocol that I suggest involves nutritional support and multipronged interventions using natural approaches that have an established precedent of safety. In the essence of any longitudinal safety or efficacy studies outcome should be monitored on an individual basis by a care-giver.

Chemical Telomere Support

Processes that may increase loss of net telomere length or rebuilding of a shortened telomere (Table 1). Several factors act to shorten telomere length, some are amenable to intervention as shown in Table 1.

Telomere Support Protocol

Research data and clinical outcome observations permit the recommendation of a clinical protocol for telomere support (References 1-17 and Table 2). The existence of other "natural protocols" for telomere lengthening may be superseded by a more comprehensive approach to telomere support and age management. This proposed protocol for the natural clinician is best summarized in line item statements:

- Initial telomere testing is recommended. There are laboratories across the US that offer telomere testing. These laboratories provide a "telomere score", by measuring telomere length on T lymphocytes. The score is derived from comparisons of the measurement to results obtained from the American population within the same age range. This test is generally accepted as an efficient method to assess biological age (with certain reservations) and it can be interpreted with other biomarkers of aging e.g. cardiorespiratory functions, skin characteristics, eyes, renal function, immune function, sexual functions etc. Interval telomere scores may be obtained on an annual basis and biomarkers of aging can be monitored regularly by the caregiver.
- Lifestyle Change Many positive lifestyle changes may inhibit

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telomere shortening. These include optimum nutrition, weight control, stress reduction, withdrawal of substances of abuse (simple sugar, tobacco, alcohol, unnecessary prescription or over the counter or illicit drugs) and the restoration of normal sleep patterns (Table 1).

- Dietary Supplements A number of nutraceuticals are associated with supporting telomere structure and function including, specifically: extracts of Gingko biloba, Astragalus, Chinese Ginger root, vitamin D, folic acid (and perhaps Vitamin B12), nicotinamide and omega 3 fatty acids (Table 2). Studies imply that taking multivitamins and or antioxidant use may be associated with enhanced telomere length or interference with telomere shortening. Elevated levels of blood homocysteine should be addressed (Folic acid, Vitamin B12 etc.).

Dietary supplementation is not a substitute for specific dietary guidelines in the quest for telomere support. In brief, the anti-aging, telomere supporting diet should involve:

- Reductions in simple carbohydrate intake with increase in dietary fiber intake (to counter insulin resistance).
- Nutrient dense food selections that are low in calories. Calorie restriction enhances maximum and average lifespan and this process may be enhanced by the use of calorie restriction mionetic compounds.
- High antioxidant load in a diet rich in fruit and vegetables. Multivitamins taken in greens, berries, fruit and vegetable mixes are a preferred form of general nutritional support. Phytonutrients are vitamin co-factors and provide an antioxidant food.
- Enrich sources of omega 3 fatty acids in active forms e.g. cold water fish, salmon etc.
- Decreased sources of saturated fat, hydrogenated oils and trans-fatty acids.
- Average balance protein intake with rotation among meat, dairy, vegetable and fish protein sources (not greater than 1gm/kg of body weight per day, unless otherwise indicated).
- Intermittent short periods of fasting and methods for body detoxification (dietary and otherwise) may support telomere structure and function.
- Disease Management A clear association exists between common diseases (cancer and degenerative diseases) and shortening of telomere length e.g. cardiovascular disease (atherosclerosis), hypertension, insulin resistance (Metabolic Syndrome X), diabetes mellitus and diseases associated with cognitive decline (dementia). Meticulous management of co-morbid conditions is obligatory. Metabolic Syndrome X and diabetes are classic disorders of premature aging.
- Miscellaneous Factors Every attempt should be made to tackle the following issues with appropriate medical interventions: Attempts to eliminate coronary heart disease and atherosclerosis risk factors must be applied e.g. reduce LDL (target <90 mg%>, reduce oxidized and dense particle size LDL, increase HDL. Control blood glucose (important in both established and prediabetes or Metabolic Syndrome X), control blood pressure, keep blood homocysteine in check, reduced chronic inflammation (monitor C-Reactive Protein, maintain HS-CRP<1).
- Institution of an exercise program is obligatory, linked to levels of aerobic fitness (professional trainers recommended). Control of weight with holistic interventions

of diet, exercise, behavior modification and supplement adjuncts are mandatory. Interventions that support stem cell functions, increase nitric oxide signaling, improve mitochondrial function, detoxify the body and optimize hormonal controls (e.g. bio-identical hormone therapy) may be valuable adjunctive approaches to telomere support.

Specific Nutraceutical Interventions

I propose a synergistic combination of herbs, botanicals and nutrients for the nutritional support of telomere structure and function (compatible with guidelines of the US Dietary Supplement Health and Education Act, 1994). This nutraceutical approach is based on evidence of good scientific agreement in reviewed medical literature. It is not possible to provide a detailed overview of all nutritional agents that are putative agents for telomere support in this short article. Table 2 summarizes an evidence-based nutraceutical approach, within the limits of current research and knowledge in natural therapeutics. Key references are present within Table 2.

A combined use of the natural agents is proposed as more versatile and powerful than the use of single agents alone in the nutritional support of telomeres. A consensus has not emerged on the best nutraceutical approach for telomere support, but the author proposes the use of combinations of natural agents that act on different aspects of the cascades of events that support telomere structure and function. This is a synergistic approach.

Much attention has been paid to the phenomenon of telomerase activation in therapeutics. Gingko biloba extracts, Astragalus extracts and perhaps Chinese ginger root have been proposed as botanical approaches that may activate telomerase. The Astragalus extract showed an ability to enhance immune function (a known consequence of the use of Astragalus species) and improve certain biomarkers of aging.

The association of vitamin D, marine omega 3 fatty acids and stations (HMG-CoA reductase inhibition) with positive affects on telomere-dependant senescence appears to be supported by credible scientific studies. "Statin effects" can be achieved in natural therapeutics by using red yeast rice which contains lovastatin. The nutritional co-factors folic acid and vitamin B12 are important for the maintenance of DNA integrity.

The value of antioxidants (or multivitamin) administration in telomere support is apparent in recent population studies and N-acetylysteine has been shown to block the nuclear loss of hTERT into cell cytoplasm. This latter action of N-acetylsteine was shown in endothelial cells that take on early senescent properties when attached by reactive oxygen species (oxidant molecules). Similar findings are apparent with the administration of alpha-tocopheral (Vitamin E components), which has been shown to inhibit telomere shortening (with retention of telomerase enzyme activity) in endothelial cells that are present in the microsvasculature of the brain. (see references in Table 2)

I propose an evidence-based natural protocol that can be applied to support the structure and function of telomeres by telomerase-inducing and non-telomerase dependent mechanisms that are not completely defined. In summary this protocol (www.naturalclinician.com) involves: positive lifestyle change, nutritional support with combinations of dietary supplements to contribute to the healthy telomere structure and function, monitoring of clinical outcome.

Conclusion

In my educational columns on natural therapeutics, I have focused on three very important issues in anti-aging or regenerative medicine. These areas include stem cell support, the use of calorie restriction mimetics and support for telomere structure and function (The Anti-Aging Trilogy). I believe that these three areas of longevity medicine interdigitate in a manner that creates the most important and promising frontier for "turning back the clock" in the field of aging medicine. ◆

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