REVIEW ARTICLE

TELOMERES RESPONSE TO LIFESTYLE - A REVIEW

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ABSTRACT
Decades of research has proven the significant role of telomeres in genomic stability and normal cellular function. Telomeres wrapped the end of chromosomes but start altering before birth and continue till adulthood by multiple socioeconomic and environmental factors or exposomes which reduces length with each cell division. An average normal cell has hay flick limit of average 50 divisions. Long expected ages are seen in children of people who practice late parenthood and can also pass this to their grandchildren. Current data on air pollution exposure confirms that the particulate matter(PM) especially $PM_{2.5}$ and PM_{10} generating reactive oxygen and nitrogen species, DNA guanine oxidation, mitochondria NADPH-oxidase function and stimulation of inflammatory cells plays a significant role in chronic health effects. Exercise can combat aging by instigating 5' AMP-activated protein kinase (AMPK) in muscles causing cell proliferation without making them immortal. Healthy Mediterranean diet and appropriate use of vitamins are supportive in reducing life threatening diseases. This review highlights recent knowledge and discoveries regarding the telomeres, with a focus on the latter-day factors altering its length.

KEYWORDS: *Telomeres, Telomerase, Particulate matter (PM), Exercise, Air Pollution.*

INTRODUCTION

Telomeres are ribonucleoprotein complexes that shield the end of chromosomes and protect interchromosmal fusion and degradation to guard genome stability[1]. Although human telomere is less than 1% of the total genome. Unlike stem cell, germ cell and cancerous cells telomere shortened every cell division in somatic cells and are considered as a marker of biological aging[2]. Telomeres are 1,500 to 15,000 base pairs long tandem repeat DNA sequences (TTAGGG) which cap at the ends of linear chromosomes with 3' G-rich single stranded overhang up to 200bp at the end of chromosomes[3]. Alexei Olovnikov in 1970 discovered telomere shortening at the chromosomes terminals. In 2009, the Nobel Prize in Physiology or Medicine was awarded **to Elizabeth H. Blackburn, Carol W. Greider and Jack W. Szostak** for the dynamic exploration on telomeres and telomerase.

Enzyme telomerase, a ribonucleoprotein containing a RNA template (with the sequence 3'-UC-CCAAUC-5') and a reverse transcriptase (TERT) add telomeric repeat sequences to the 3' ends of the chromosomes and resist the DNA length shortness in cancer and other cells[4]. A shelterin complex is formed by DNA binding proteins with telomeres "TTAGGG" repeats and can affect the telomerase function[5] , form a large duplex loop referred to as T-loop that protects the telomeres. The single-stranded overhang invades into the DNA duplex of telomeric repeats and forms a displacement loop (D-loop).

DISCUSSION

Telomere length determine the lifespan of a normal cell and act as a biological chronometer of a cell. Telomeres are longest in muscle and shortest in leukocytes and Hayflick limit of the average normal cells is 50 to 70 divisions after which cell divisions halts. Apoptosis or senescence is the fate of cell with critically shortened telomeres which involves p53 and pRb genes causing aging and ultimately cell death. Inactivation of p53 and pRb gene causes incorrect end to end joining of shortened telomeres triggering cancer initiation[6].

Older people with shorter telomeres have three and eight times increased risk to die from heart and multiple diseases[7]. Different diseases like blood pressure, fasting glucose and glycated hemoglobin(HbA1C), bone mineral density, and blood lipids, appear to be predictive of biological age[8]. The process of aging start at the younger age of life or may be before birth and prompt at mid-age. In utero exposures causes adaptive response in the fetus which result in persistent changes that influence health later in life[9].

Telomere is heritable, highly variable among individuals[10,11]. In newborns telomere length is 8,000-13,000 base pairs and each year deteriorate about 20-40 base pairs. They are longer in newborn girls by 57bp than boys which confirmed that in newborns

telomere length is highly variable[12]. It was also confirmed by Gardner M. et al., that women have greater telomere length than men[13]. Sperms of offspring's of older fathers have longer telomere lengths and have longer expected ages with healthier response to surrounding environment[14]. Sperm cells are one of only a few types of cells that maintain or even increase their telomere length over time, so the communities having the trend of late marriages and delayed parenthood have benefit of offsprings with longer life. During the first years of life, telomeres shorten at a much higher rate[15], such factors that influence telomere length in infancy causes persistent changes with less effects later in life[16].

Majority population-based studies used leukocyte telomere lengths as sample for telomere analysis[17]. Leukocyte telomere length has shown to be highly correlated with other somatic tissues from the same individual such as muscle, fat, skin, synovial tissue, indicating that a clear intra-individual synchronization in telomere length exists in adults and the rate of telomere shortening in different tissues is equal regardless of their replicative activity[18,19].

Factors Deteriorating Telomeres

Genetic makeup is not the only determinant of telomere length. Exposomes, all the lifetime exposures of an individual, affect quality of health and lifespan of an individual by accelerating premature telomere shortening and also can potentially protect telomeres and health.

Reactive oxygen species (ROS) causing DNA damage[20], production of proinflammatory cytokines, disturbance in cell signaling, homeostasis and immune system activation by exogenous factor like smoking, emotional health, prenatal stress, maternal stress, physical stress and psychological stress. Daily smoking of each pack of cigarettes, causes an additional '5 base pairs' loss in the length of telomere. Studies have proven that women exposed to stress in their daily life face early onset of age-related health problems due to release of glucocorticoid hormones that also reduces the levels of antioxidant proteins[21]. Different stress determinants prevailing in our country Pakistan like terrorism, street crimes, low finances, unemployment, traffic etc. are responsible for premature telomere shedding and early onset of aging.[23]

Obesity, illetracy, sleep quality(sleeping 5 or fewer hours)[24] , poor eating habits effect quality of life by increasing ROS causing cellular senescence and increase in the probability of diseases attack. Studies showed that South Asian men has higher leptin levels, increased body fat percentage, abdominal obesity which can leads to cardiovascular risk and decreased insulin sensitivity cause Type 2 Diabetes Mellitus. Dyslipidaemia, specifically low high-density lipoprotein cholesterol (HDL-cholesterol) and high BMI in South Asians had seen as compared with Europeans and East Asians[25].

Low income, low maternal education, unstable family structure, and harsh parenting was observed in 9-year-old boys by Mitchella C.*et al.*, and found highest genetic sensitivity scores had the shortest telomere length and genetic variants in serotonergic and dopaminergic pathways[26].Thus causing neurological disturbances which can affect over all body regulations.

Higher rate of telomere erosion and telomerase gene down regulation is seen in premenopausal period around fifty year of age due to estrogen-mediated menstrual bleeding[27].This shows the interrelation of estrogen hormone directly with aging, wrinkling of skin, mood swings, gain in weight and osteoporosis. After menopause levels of estrogen become low and is associated with increased risk for cardiovascular and cerebrovascular diseases and show a high mortality threat in women.

Telomeres Protection By Exercise And Natural Products

Physical training, cycling, daily walk, brisk walk and daily exercise have mark influence on blood pressure regulation, insulin sensitivity, abdominal fat reduction, lipid profile, hypertension and body fitness. It reduces injurious fat and decreases oxidative stress, thus protecting DNA and telomeres length. Exercise is associated with elevated telomerase activity and suppression of several apoptosis proteins, including p53 and p16. Usually athletes and hardworking laborer have high muscle mass and strength due to strenuous life. The older athletes, on the other hand, improved their leg strength by 17.9 per cent and also improved their cycling efficiency by 16.3 per cent, enough to completely eliminate their efficiency deficit compared with the younger cyclists.

Exercise and physical activities increase 5' AMP-activated protein kinase (AMPK) activation, causes increase in Telomeric repeat–containing RNA (TERRA) levels in skeletal muscles[28] which causes protection of end chromosomes. Another research nailed the positive effect of exercise and telomeres by discovering increases telomerase activity transiently (24–48 h) in fibroblasts and myoblasts proliferating cells without making them immortal cancerous cells and provide shield against aging[29]. Many natural products like fiber, soy protein and healthy fats (derived from avocados, fish, and nuts), omega 3 fats, foods such as tuna, salmon, herring, anchovies, mackerel, halibut, flounder, flax seeds, chia seeds, sesame seeds, kiwi, black raspberries, lingonberry, green tea, broccoli, sprouts, red grapes, tomatoes and olive fruits help in health control. Vitamins acting as a good source of antioxidants such as vitamin C-rich and E-rich help body metabolism to fight against xenobiotics and ROS.

Therefore, whole grains, oats, raw vegetables included in Mediterranean diet can help decreased Body Mass Index (BMI) and a healthy metabolism.

Air Pollution Altering Telomeres

Air pollution is an important determinant of chronic metabolic diseases along with lifestyle and genetic factors. In developing nation like Pakistan, air pollution from industry, traffic, and household biomass combustion are major sources of air pollutant emissions are a major threat to public health.

In this Review, focus is on the major constituents of air pollutants and their impacts on chronic respiratory and other diseases and consequences on telomeres. Long-term exposure to NO_2 and PM in air pollution in a semi-rural area resulting in an increased risk for Type 2 Diabetes Mellitus[30], and cause negative effect on pulse pressure, heart rate and cellular mechanisms. People living near a major road like motorways, highways and long-term $PM_{2.5}$ concentrations of 3 μg/m^{3}microcirculation, had 0.8 μm retinal arteriolar diameter narrowing, a reduction equivalent to that seen for a 7-year increase in age in older individuals and exacerbation of clinical cardiovascular disease[31].

Studies also proved that surface area is the most important for ultrafine particles (diameter less than 100 nm like carbon black), whereas chemical composition may be more important for larger particles[32]. These $PM_{2.5}$ and PM_{10} altered function of mitochondria or NADPH-oxidase, and activation of inflammatory cells capable of generating reactive nitrogen species and guanine oxidation in DNA[33]. So, Maintenance of mitochondrial function has been suggested to be an important mechanism for extending lifespan. Many observational studies on steel workers, truck drivers, street traffic officers, welding fumes compared with office workers and indoor workers had much lower leukocyte telomere length, which corresponds to a telomeric year equivalence of several years[34-37].

Persistent organic pollutants (POPs) are lipid-soluble, non-biodegradable compounds like lead (Pb) used in a variety of industrial applications can easily transmit in humans and animal species in the food chain by air and water. Telomere disturbance by lead can interrupt DNA structure and POPs can easily upset the endocrine system and leads to hormonal imbalance[38,39].

While going through such devastating researches scientists came across an interesting and unusual increase telomere length by short-term (less than a month) exposure to $PM_{2.5}$. Further exploration of data n sample testing helped scientist to conclude, it might be due to acute inflammatory processes that have been linked to increased telomerase activity in B-cells[40].

CONCLUSION

It was believed that decrease in the length of telomere leads to aging and cell death. Research highlighted the interplay between telomere, associated proteins, telomerase, life style, socioeconomic factors and environment have great impact on our body. Unusual response to less time exposure of PM with an increase in telomere length is still under consideration and not proven by any research. Rigorous investigation to find appropriate telomere length in different cellular stages and cell types can help in profound improvement in diseases treatment. Current industrialization, urbanization and motorization trends suggest that the air quality in Pakistan will only worsen over time unless targeted interventions are made in long term. Industries and organizations responsible for air quality management needs to strengthened their quality control checks to maintain the standards of livings.

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