CHAPTER

76

Telomere and Ageing

VN Mishra, Nalini Mishra, Ishan

WHAT IS AGEING?

Over the years Ageing has been defined by scientific thinkers, workers and organizations in their own way, from the biological standpoint most definitions of aging indicate that it is a progressive process associated with declines in structure and function, impaired maintenance and repair systems, increased susceptibility to disease and death in near future. Ageing is not inevitable, indeed there are some species of plants and animals that do not appear to age as they undergo an extremely slow aging process termed "negligible senescence" conversely there are some living creatures that undergo programmed death immediately after reproduction such as annual plants and semelparous animals. However majority of others from yeast to humans undergo a gradual aging process leading to death that is surprisingly similar at the cellular and biochemical level.

Ageing is particularly apparent in organisms where growth is completed before reproduction commences, such as insects, birds and many mammals including humans. Understanding ageing is demanding, time consuming and to be honest we are still not well equipped mentally and technically to understand this complex puzzle of Life and Death, the biggest secret of nature. There is little evidence that death is programmed into our genes and substantial evidence that it is malleable, it is proved by the fact that lifespan has been lengthened by a variety of means in many living species including human beings. Recent studies on mice have shown a 20% rise in life expectancy in mice following genetic modification.

THEORIES OF AGEING

One has to agree with the logic that all living creatures have only two options to maintain their existence: immortality or reproduction. It seems that in the situation of ever changing environment, they have adopted strategy of reproduction combined with a finite lifespan which has proved to be successful. Many evolutionary theories related to aging are linked by their attempts to explain this interaction between reproduction and longevity. Most of the mainstream aging theories stem from the fact that evolution is driven by early reproductive success whereas there is minimal selection pressure for late life reproduction or post reproductive survival. Aging is seen as the random degeneration resulting from the inability of evolution to prevent it i.e. the non adaptive consequence of evolutionary neglect. This conclusion is supported by recent studies that restricted reproduction to later life in the fruit fly Drosophila melanogaster thus permitting natural selection to operate on later life traits leading to an increase in longevity

It seems that there is still no consensus about the mechanism of ageing but there is general agreement that it is unlikely that any single mechanism would explain the process. Following quote by some anonymous worker explains the fact that how complex the process is and how little we know about it till now *"Rather than getting closer to understanding the systems (of ageing), science is getting further away, because we are learning it's more complicated than we thought it was."* Many theories have been put forward by workers from time to time to explain why and how ageing happens. These are not mutually exclusive theories but differ in the perspectives of their analysis. One of the important theories of ageing is "Telomere Shortening theory of ageing."

WHAT IS TELOMERE?

Telomeres are the strands of DNA with same repetitive nucleotide sequences at each end of a chromosome. Telomeres have been compared with the plastic tips on shoelaces, because they keep chromosome ends from fraying and sticking to each other or from fusion with neighbouring chromosomes which would scramble an organism's genetic information. Its name is derived from the Greek nouns telos means 'end' and meros means 'part.' For vertebrates the sequence of nucleotides in telomeres is TTAGGG. Because of the way in which DNA is replicated, the length of the telomeres shortens each time the cell divides. Consequently, the length of telomeres in the cells of older people tends to be shorter than in younger people. In human white blood cells length of telomere ranges from 8,000 base pairs in newborns to 3,000 base pairs in adults and as low as 1,500 in elderly people. (An entire chromosome has about 150 million base pairs.) Each time it divides, an average cell loses 30 to 200 base pairs from the ends of its telomeres.

In 1965 Leonard Hayflick's showed the limit to which cells duplicate themselves before aging. Hayflick established what subsequently is called the Hayflick limit, which states that a cell can divide forty to sixty times before it cannot divide further and begins to age. Although Blackburn helped discover telomeres in 1975 two years before in 1973, Olovnikov had hypothesized the existence of telomerase, the length of telomeres, and their connections to cellular aging during his study on the Hayflick Limit, later on Blackburn isolated and cloned telomeres in Tetrahymena DNA. Blackburn with the help of Carol Greider identified telomerase in 1984 and isolated it from

Tetrahymena in 1989. This discovery was so important that Blackburn, Jack Szostak, and Carol Greider received the Nobel Prize in Medicine in 2009 for their work to identify and isolate telomeres and telomerase. Telomere shortening has been identified as a factor that could contribute to ageing. However, the relationship is not a simple one and although short telomeres may contribute to early ageing, they are not a good predictor of how long an individual will live or how healthy they will be before they die. Research into this field is still at an early stage.

WHAT IS TELOMERASE?

Telomerase is a ribonucleoprotein DNA polymerase complex that maintains telomere length. The complex comprises the protein human Telomerase Reverse Transcriptase (hTERT) and a catalytic RNA (TERC). In the absence of telomerase activity telomeres progressively shorten. Telomerase activity is absent in most normal human somatic cells because of the lack of expression of TERT whereas TERC is usually present. Without telomerase, telomere shortening eventually limits the growth of cells, leading to senescence. Expression of TERT in cells that otherwise lack telomerase activity cause cells to bypass senescence and crisis, such cells are usually termed "immortalized." The absence of telomerase activity in most human somatic cells results in telomere shortening during aging. Telomerase activity can be restored to human cells by hTERT gene transduction or potentially via drug therapy.

CAN TELOMERASE REVERSE AGEING PROCESS?

It is becoming apparent that reversing shortening of telomeres through temporary activation of telomerase may be a potent means to slow aging. This could possibly extend human life by increasing Hayflick limit. Three routes have been proposed to reverse telomere shortening: drugs, gene therapy, or metabolic suppression, so-called, torpor/hibernation. So far these ideas have not been proven in humans. Turbill in the year 2013 demonstrated that telomere shortening is reversed during hibernation and thus aging is slowed in rodents prolonging life span. In recently conducted studies on mice it has also been demonstrated that telomere extension could successfully reverse some signs of aging. Those mice that were engineered to lack the enzyme telomerase became prematurely decrepit but they bounced back to health when the enzyme was replaced. The finding hints that some disorders characterized by early ageing could be treated by boosting telomerase activity. It also offers the possibility that normal human ageing could be slowed by reawakening the enzyme in cells where it has stopped working. This has implications for thinking about telomerase as a serious anti ageing intervention. Other scientists however point out that mice lacking telomerase are a poor stand in for the normal ageing process. Moreover, ramping up telomerase in humans could potentially encourage the growth of tumours.

Role of Telomere Extension in Reversing Aging in Cultured Human Cells

Scientists working at the Stanford University have developed a new procedure which involves the use of a modified type of RNA, this can quickly and efficiently increase the length of human telomeres, human cultured fibroblast cells treated with this procedure behave as if they are much younger than untreated cells, multiplying with abandon in the laboratory dish rather than stagnating or dying. Skin cells with telomeres lengthened by this procedure were able to divide up to 40 more times than those cells which were untreated. This will improve the ability of researchers to generate large numbers of cells for study or drug development. This research may show the new path to treat diseases caused by shortened telomeres in the coming days.

TELOMERE AND LIFE STYLE MODIFICATIONS

Some of the lifestyle factors which increase risk of developing cancer have also been associated with shortened telomeres including stress, smoking, physical inactivity and diet high in refined sugars. Diet and physical activity influence inflammation and oxidative stress. These factors are thought to influence telomere maintenance. Psychological stress has also been linked to cell aging, and telomere shortening appears to be accelerated in people living more stressful lives. In a study by Epen on peripheral blood mononuclear cells from healthy premenopausal women, women with the highest levels of perceived stress have telomeres shorter on average by the equivalent of at least one decade of additional aging compared to low stress women. These findings have implications for understanding how, at the cellular level, stress may promote earlier onset of age related changes. In 2012 Blackburn published the influence of lifestyle on the length of telomeres and cellular aging in humans. He found that stress, nutrition and personality influence the length of telomeres and telomerase enzyme activity. The authors noted that those who perceived events as less stressful had longer telomere lengths compared to individuals who perceived events as more stressful behaviours, smoking or eating processed meats also correlated with shorter than normal telomere lengths. Also those who took vitamin C or E supplements had longer than normal telomere lengths. The results of Blackburn and her team's experiment verified that environmental factors affect the length of telomeres. It has been suggested that a combination of lifestyle modifications, including healthy diet, exercise and stress reduction, have the potential to increase telomere length, reverse cellular aging, and reduce the risk for aging related diseases. In a recent clinical trial on early prostate cancer patients comprehensive lifestyle changes resulted in a short term increase in telomerase activity and long term modification in telomere length. Lifestyle modifications have the potential to naturally regulate telomere maintenance without promoting tumorigenesis.

TELOMERE AND CANCER

Telomeres are critical for maintaining genomic integrity.

Studies have shown that telomere dysfunction or shortening is commonly acquired during the process of tumour development. Short telomeres can lead to genomic instability, chromosome loss and the formation of non reciprocal translocations. It has been observed that telomeres in tumour cells and their precursor lesions are significantly shorter than surrounding normal tissue. As a cell begins to become cancerous, it divides more often and its telomeres become very short. If its telomeres get too short, the cell may die. Observational studies have found shortened telomeres in many cancers including pancreatic, bone, prostate, bladder, lung, kidney, head and neck. In addition, people with many types of cancer have been found to possess shorter leukocyte telomeres than healthy controls. Recent meta-analyses suggest 1.4 to 3.0 fold increased risk of cancer for those with the shortest vs longest telomeres. However the increase in risk varies by age, sex, tumour type and differences in lifestyle factors.

Quite often these cells escape death by making more telomerase enzyme, which prevents the telomeres from getting shorter. Measuring telomerase may be a way to detect cancer. And if we could learn how to stop telomerase, we might be able to fight cancer by making cancer cells age and die. In one experiment, researchers blocked telomerase activity in human breast and prostate cancer cells growing in the laboratory, prompting the tumour cells to die. But there are risks. Blocking telomerase could impair fertility; wound healing, and production of blood cells and immune system cells. A 2013 pilot study from University of California San Francisco on early stage prostate cancer studied the lifestyle changes and experienced a significant increase in telomere length of approximately ten percent. Cancer cells require a mechanism to maintain their telomeric DNA in order to continue dividing indefinitely (immortalization). A mechanism for telomere elongation or maintenance is one of the key steps in cellular immortalization and can be used as a diagnostic marker in the clinic. The largest comparative study of telomeres and telomerase, involving over 60 mammalian species found that smaller, short lived species tend to have long telomeres and high levels of telomerase. This suggests that short telomeres and suppression of telomerase are necessary for the evolution of large body sizes and longevity, presumably by suppressing cancer.

CONCLUSION

Telomere plays an important role in natural senescence and aging. Telomerase is probably not the sole factor in determining differences in aging rate among various species. Cellular senescence is primarily caused by cumulative effect of various kinds of cellular stress but perhaps telomere shortening might play some role in aging and age-related diseases. They might be contributors or intermediaries by enhancing the effects of other types of molecular cellular damage. Reactivation of telomerase could be useful in some forms of cell therapy but safety issues are a concern as activation of telomerase removes barrier to the continued growth and developing cancers. Lack of telomerase activity provides a tumour suppressor function. Targeting the telomeres and/or telomerase by itself does not seem to have effect on human aging at present but it might be helpful in the case of some specific pathologies. It is unquestionable that cellular senescence and telomere biology are important in understanding pathogenesis of cancers and it may be of some help in developing newer anti cancer treatments in near future.

REFERENCES

1. Finch C. E. 1990 Longevity, senescence and the genome Chicago, IL: University of Chicago Press.
2. Vaupel J. W., Baudisch A., Dolling M.et al. The case for negative senescence. *Theor Popul Biol* 2004; 65:339–351.
3. National Institutes of Health. Single gene change increases mouse lifespan by 20 percent [Internet]. 2013. http://www.nih.gov/news/health/aug2013/nhlbi-29.htm
4. Bernardes de JB, Vera E, Schneeberger K, et al. Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer. *EMBO Mol Med* 2012; 4:691–704.
5. Sadava D, Hillis D, Heller C, & Berenbaum M. (2011). Life: The science of biology. (9th ed.) Sunderland, MA: Sinauer Associates Inc.
6. Peter J. Hornsby. Telomerase and the aging process. *Exp Gerontol* 2007; 42:575–581.
7. Shay J, Wright W. Hallmarks of telomeres in ageing research. *J Pathol* 2007; 211:114–23.
8. Turbill C, Ruf T, Smith S, et al. Seasonal variation in telomere length of a hibernating rodent. Biology Letters. 2013; 9:20121095.
9. Wentzensen, IM; Mirabello, L; Pfeiffer, RM; et al. "The association of telomere length and cancer: a meta-analysis". *Cancer Epidemiol Biomarkers Prev* 2011; 20:1238–1250.
10. Lin, Jue, Elizabeth B et al. "Telomeres and lifestyle factors: roles in cellular Aging." *Mutation Research* 2012; 730:85–9.
11. Ornish, D; Lin, J; Chan, JM; et al. "Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study". *Lancet Oncol* 2013; 14:1112–20.
12. Willeit P, Willeit J, Mayr A, et al. "Telomere length and risk of incident cancer and cancer mortality". *JAMA* 2010; 304:69–75.