A TALE OF LOBSTERS:
TELOMERE AND TELOMERASE
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Abstract – lobsters don't appear to age. How can we be more like lobsters. Immortality can be decoded by understanding telomere and telomerase clinically and biologically. In this paper, we will review the current knowledge of telomere and telomerase and their influence on cellular senescence, cell proliferation, cancer therapy, tumor and laying emphasis on human aging. Preventing our telomeres from shorting will prevent us from disease and increase our life span. Deactivation of the enzyme telomerase in tumor and cancerous cells will be an alternative to chemotherapy or treatment for cancer and tumor cells.

Keywords: telomere, telomerase, aging, cancer, tumor.

INTRODUCTION

The tip of a eukaryotic chromosome has a special structure called the telomere. They are Repetitive DNA sequences at the ends of all human chromosomes. They consist of repeats of the DNA sequence TTAGGG and some proteins [1] They protects the chromosomes from enzymatic end degradation and keeps their stability [2]. They achieve this by effectively "capping" the end of a chromosome in a manner similar to the way the plastic on the ends of our shoelaces "caps" and protects the shoelaces from unraveling. Without telomeres, the ends of the chromosomes would be "repaired", leading to chromosome fusion and massive genomic instability. Telomeres not only give stabilization and protection of the chromosome, their structure allows the tip of linear DNA to be replicated completely, thus, Telomeres are also thought to be the "clock" that regulates how many times an individual cell can divide. Telomeric sequences shorten each time the DNA replicates. When the replication of linear chromosome is taking place, the DNA polymerase will replicate DNA termini in 5’ to 3’ direction using an RNA primer for the initiation. The RNA primer is removed after the DNA has replicated, then the telomeric DNA sequence is lost from the ends [2]. Telomere length varies within species. In humans the length of the telomere is 8-14 kilobasepairs and in mice they have as much as 150 kilobasepairs [1]. The mechanism of DNA replication differs for the leading and the lagging DNA Strand. The leading strand replicates continually and for the lagging strand to replicate, DNA polymerization have to start with several RNA primers which elongates to produce a DNA fragment called Okazaki fragments. The RNA sequence will later be degraded and replaced by DNA sequence.

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TELOMERASE

Telomerase is a ribonucleoproteic enzymatic complex and it catalyzes the addition of telomeric repeats to the tip of chromosomes DNA [3]. This makes them to prevent the loss of telomeric sequence that occur normally at each cell division. Whenever there is telomerase activity, there is stabilization of the chromosome length, replication of the cell is not limited and cells are immortal. Telomerase is an enzyme needed for continuous growth of the cell [4]. It is inactivated in most of the somatic cells except for cells that reproduce rapidly (Proliferating cells) and telomerase is activated in 85% of the human cancer tissues. Its activity is needed as a cancer detecting marker in some of the cancers. It is also a useful Prognostic detector in cancel cells in which it has become unregulated from the progression of tumor. Telomerase activity at the telomere is also regulated at the level of telomerase recruitment to the telomere [5]. But the mechanism in which it recruits telomere is not fully known, but is likely a part of negative feedback loop caused by shelterin proteins that bound at the telomere as act as negative regulators of telomerase extension of telomere. Inhibition of telomerase has the features to be used as a selective anti can therapy that stops the multiplication capacity of telomerase positive cancer cells.

CELL PROLIFERATION

Proliferation competent somatic cell don't show any noticeable telomerase activity in them and their telomere shorten with each cell division [6] In cancer and stem cells of renewal tissues, telomerase activity levels correspond with the rapid reproduction state of the cells. The presence of this telomerase enzyme is needed for unlimited proliferation (immortality) and it's absence leads to a finite life span (senescence).

CELLULAR SENESCENCE

Olovnikov in 1971 proposed that the loss of telomeric DNA through the end replication process could serve as the mitotic clock, and this induces senescence once a shortening to a certain value has reached [7]. He states that telomere shorten as somatic cells divides. This was supported by the measurement of telomeres in different cell types which was done indirectly. We cannot measure telomere directly in most organism including humans because their telomeric repeats and subtelomeric DNA don't have a recognition site for any known restriction enzyme. When telomeres get damaged and fail to function, it leads to DNA damage. This DNA damage is characterized by the binding of DNA damage response proteins to the uncapped telomere [8]. Considering the cell type, genetic information and level of the telomeric damage, the cell can enter permanent cell cycle arrest which is senescence. These cellular responses may have important effects on the organism, especially for complex eukaryotic organism that have both mitotic and post mitotic cells. The most important effect of the telomere dysfunction is carcinogenesis which comes from mitotic cells.

HUMAN AGING
Shortening of the telomere is followed by human aging and there is also some premature aging diseases that is associated with short telomere. From this you can note that telomere length directly influences longevity [9]. No other Chromosome has been linked to major human health issues expect telomere and this has to do with their length. Telomere length is now taking to be the reference point for anyone discussing the impact of any factor into human fitness. Short telomeres has been said to be associated with aging, high risk of premature death and development of vascular and colon disease. For us to decide if shorten of telomere is really the cause of many vascular disease that is linked to aging or short life span is not an easy thing to do. The presence of short telomere starts cell senescence in vivo, and this affects organ and tissue function. Senescence can be caused by other factors and not only telomere shortening, it marks a need to for us to study more on this. A recent study with baboons shows that the first time their telomere is being seen as damaged, it increases with age in the skin whereby this increase is not present in muscle cells. This supports the notion that telomere shortening is highly responsible for cell senescence in organs with high proliferative potential. This is also seen in aged humans. It has been seen that telomere length is an indication of biological aging [2]. The incomplete replication of linear chromosomes by DNA polymerase, telomeric repeats at the end are lost each time there is a cell division. This dysfunction of telomere is has associated itself with the pathogenesis of many age related diseases. Telomere length can be changed by nutrition in human and animals.

ANTICANCER THERAPY

The telomeres of mortal cells shorten during each round of cell division, cancer cells don't and they possess indefinite growth capacity and maintain their telomeres [10]. We see immortality of these cells as an escape from senescence, deregulation of cell cycle and proliferation of the cells. Telomerase has been suggested as an important target for the production of new anti cancer drugs. Processes based on the reversal of tumor growth by telomerase inhibition. A therapeutic anticancer approach is needed that will inhibit telomerase function will be able to deny unlimited progeny [11]. Telomerase contain a catalytic protein unit, human telomerase reverse transcriptase (hTERT) and the human telomerase RNA (hTR) and they provide the template for the telomeric repeat sequence. Telomerase is found at the 3' telomere end and they add new sequence by the release of DNA according to the RNA template. Using telomerase inhibition as a cancer treatment has a limitation. It takes weeks for telomeres at the lag phase to shorten to a critical value and start the cellular senescence. Telomerase inhibition is a new method of cancer treatment and there are also several potential targets acting in either stabilization of the telomere end protective structures or proteins involved in telomerase activity regulation. In the process of carcinogenesis, there is activation of telomerase at different stages [12]. Sometimes, they are activated gradually through out the progression of the cancer where in some other instances the enzyme is expressed in precancerous stages and this affects the clinical utilization of telomerase as a diagnostic marker. Most cells exhibit telomerase activity and this make it difficult to know if the telomerase activity is coming from the tumor cells. To over come this, an in situ TRAP assay that employs fluorescent dyes and microscopy to visualize telomerase activity in the nuclei of cells being investigated is required to determine if the telomerase expression seen is gotten from normal telomerase positive cells or malignant cells. Since telomerase activity is also detected in premalignant tissue, it is important for physicians to noted that testing for telomerase activity is
important for detection of cancer in high risk patients. hTR subunit is found in all cells and its expression in cancer cells are high. hTERT expression correlates with telomerase activity since its presence is needed for enzymatic activity. From this we can see that early detection of hTERT mRNA is needed for the detection of cancer cells in clinical samples.

**TUMOUR**

Tumors require telomeric consistency to maintain viability conferred by adequate length of telomeric DNA replenished by telomerase and binding of telomere binding proteins (TBPs) [13]. Levels of TBPs in tumor tissue might have effects for drug development if they make some cancers more sensitive or resistant to telomere targeted agents. In contrast to somatic cells, 85 - 90% tumor cells have telomerase enzyme over expressed and activated. In some other tumors an alternative recombination mechanism (ALT) maintains telomere length [14]. However the maintenance of telomere length is important for the survival of tumor cells and any means of stopping this process is an important new approach to the therapy [13].

**CONCLUSION**

Telomere and Telomerase are important in somatic cells. This review has helped us to understand that telomere shortening are the most causes of aging and some other vascular disease. When multiple cell divisions take places, the telomere is shorten to a critical length in which it cannot divide again. At this time, senescence or apoptosis takes effect. Telomerase activation leads to the integrity of telomeres and causes cell proliferation which is the hallmark of carcinogenesis and tumorgenesis. Inhibition of telomerase enzyme in somatic cells will be the hallmark for anti cancer therapy drugs. Changing our lifestyle by eating right, and exercising will help in maintaining a healthy telomere length, there reducing the shorting of telomere length and making human somatic cells immortal and increasing long life span.

**REFERENCES**

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