Invited Review

Telomeres: Implications for the Future

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Abstract

Telomeres are located at the ends of chromosomes and contain proteins and tandem repeats of DNA hexanucleotides. This DNA repeats shorten with each cell division, and the telomere length is an indicator of how many divisions the cell has undergone so far. So, telomere length is a sign of several biological pathways in many different era of medicine. Psychiatric disorders are good candidates and have not been fully understood in terms of the telomeres and its association with them. This review will give a sense of importance of telomere length in the era of medicine, hematology, and psychiatry. This hot topic will be deeply discussed in this review.

Introduction

In 1938 Herman Muller, observed inversions and segment loss in the chromosomes of the vinegar fly (Drosophila melanogaster) when exposed to X-ray. Interestingly this observation was not true for the ends of the chromosomes. Hence, he described a cap protect end of the chromosomes and called it as telomeres. Two years after this observation Barbara McClintock found broken chromosomes fuse with each other and she postulated that telomeres are necessary for chromosomal integrity and stability (1, 2).

In 1962, American biologist Leonard Hayflick demonstrated normal mammalian cells were able to divide for certain numbers (approximately 50 cell divisions). He called this restriction in cell division Hayflick Phenomenon. Even some morphological changes observed in old cells those cells were able to maintain their life. He called that as “cell senescence or replicative senescence”. In 1970s when DNA replication mechanism enlightened it turns out DNA polymerase is not able to repair and replicate end of the linear chromosomes. In 1972, James D. Watson called this as “end replication problem (ERP)”. In 1973, Russian scientist Alexey Olovnikov suggested ERP is because of the telomere shortening and according to his idea ERP was main responsible factor for Hayflick phenomenon. At the end of the 1970s, Joseph G. Gall and Elizabeth H. Blackburn sequenced telomeric region from a single cell organism with cilia (Tetrahymena). In 1988, they showed that telomeres composed of repeated nucleotide series. Those repeated regions of DNA were similar in all creatures. Since DNA polymerase was not able to synthesize telomeres a specialized enzyme called telomerase discovered by Elizabeth Blackburn and Carol W. Greider in 1985. Telomeres are unique sequence of DNA discriminate DNA from double stranded DNA breaks. Since DNA repair enzymes is actively looking for double stranded DNA breaks this specialized end of chromosomes allows the DNA travel safely throughout DNA replication journey. This review covers the description and roles of telomeres and telomerase in the biology of normal tissue stem/progenitor cells and in the development of cancer and psychiatric and ageing disorders (3-6).

Function and Structure of Telomeres

The unchanged structure of chromosome ends need to be discriminated from DNA double-strand breaks (DSBs), which are a target for DNA repair pathways and activate the major DNA damage-induced checkpoint kinases such as ATM and ATR. Telomeres protect chromo-
some ends from degradation and activation of double strand break repair system. These functions achieved with these exceptionally ordered nucleoprotein complexes. In humans, telomeres contain thousands of TTAGGG tandem repeats. DNA synthesis is initiated by DNA polymerase which requires 3’ OH end to initiate the replication process. This end usually provided by primers. The leading strand is synthesized continuously whereas the lagging strand synthesized with small base groups as known Okazaki fragments. With each DNA replication lagging strand shorten, because DNA polymerase cannot fill the last primer of DNA machinery at the end of this replication journey. This problem called end replication problem (ERP). ERP is main responsible for shortening of telomere in each cell division (6,7).

A Look to Telomere World

Efforts to uncover the underlying mechanisms driving genome instability in cancer have revealed a prominent role for telomeres. Telomeres are nucleoprotein containing structures that protect the ends of linear chromosomes and are particularly vulnerable due to progressive shortening during each round of DNA replication and, thus, a lifetime of tissue renewal process put the organism at risk for increasing chromosomal instability. In fact, telomere erosion has been demonstrated in aging tissues and hyper proliferative diseases, these conditions highly associated with increased cancer risk.

Furthermore, telomere dysfunction in the degenerative diseases of aging and cancer particularly results from the dysfunction of DNA damage checkpoint responses. Mostly advanced cancers have a feature reactivated telomerase and serves to maintain telomere length and supportive data have also shown the capacity of telomerase to directly regulate cancer-promoting pathways (8).

Extremities of chromosomes, contain a main telomeric region and subtelomeric region. Subtelomeric region usually contains 40-60 kb of repeated TTGGGG or TGAGGG. Main telomeric region range from 5-15 kb length and composed with hundreds to thousands repeats of the TTAGGG. Altruistic telomeres give their base pairs instead of these comprehensive genes. It is important to emphasize that those regions is G rich which allows telomeres to bind the protective proteins easily (9).

Studies has done by Olovnikov elicited the mystery behind cell division limit and shortening of chromosomes. Basically he proposed that cell division shorten telomeres which eventually restrict the cell division number and explain Hayflick phenomenon. When telomeres become critically short this arise a signal, this signal put the cells whether in apoptosis tunnel or senescence (10).

Several diseases have been linked with aging and most of them cause increased cost to the health system. Most of the cardiovascular and neurodegenerative diseases are very common and cause increased health expenses. Discovery of telomeres has raised this question; does aging can be manipulated? Substantial data has linked telomere with aging and senescence of the cells. Telomeres are very important in cell senescence theory, source of this theory first, telomerase overexpression immortalize the cells, another data has demonstrated stable telomere length maintain cell dividing in cancer cells, stem cells, and germ cells such as sperm or eggs (9, 11).

As a rule of the aging process telomeres become shorter and cause an arrest of the signaling pathway of the dividing cells. A recently published study illustrated that telomere can be manipulated with a male hormone, testosterone. In this study hematologic stem cells were able to recover from telomere shortening they even statistically increased their telomere length via telomerase enzyme which is essential way of the elongating telomeres. Thus another study has been conducted at the NIH named as Danazol treatment in patients with genetic telomere diseases. Unpublished data has shown that patients with the vulnerable genetic background who candidate to develop whether blood disease (aplastic anemia) or lung and liver fibrosis responded well to the therapy and longer telomeres have helped those patient population to recover from their diseases (12).

Telomeres have so many features. They are sometimes an aging factor, sometimes a predictor for the mortality, sometimes a cause for disease, sometimes key factor in some cancers. To date telomeres have been overwhelmingly studied and marked as a disease marker.

Diseases of Telomeres

Bone Marrow Failure

Since telomeres are lost in each consecutive cell division, bone marrow cells mostly prone to develop telomere diseases as a result of a genetic mutation. Telomere disease manifestations are very broad which can
range from very minimal disease to catastrophic results. These diseases are inherited but penetrance may vary, even in the same pedigree (3).

**Dyskeratosis Congenita**

A syndrome of ectodermal dysplasia which characterized by specific triad includes, dystrophic nails, patchy skin hyper pigmentation, and oral leukoplakia. Family studies have revealed and led to the discovery of mutations in telomere maintenance system. This syndrome initially present with mucocutaneous findings and followed by fatal aplastic anemia in first or second decade (13).

**Acquired Aplastic Anemia**

Substantial declines in all three blood cell line occur. Pancytopenia is fatal if not treated. Telomere maintenance system mutation has found in telomerase enzyme complex in this disease. Roughly 10% of the acquired aplastic anemia patients carry this mutation (3).

**Pulmonary Fibrosis and Liver Disease**

Approximately one fifth of patients with dyskeratosis have features of pulmonary fibrosis. After this association found, idiopathic pulmonary fibrosis (IPF) cases were deeply analyzed for telomere pathology. 15% of patients with familial IPF were found to have telomerase mutation. Some patients with dyskeratosis again has liver fibrosis, nodular hyperplasia, and portal hypertension features (14).

In conclusion, even though telomere mutations seem to affect mostly bone marrow cells, a clear relation with the other fast divided cells was explained. Skin, lung, and liver are other targets for telomere diseases.

**Telomeres and psychiatric disorders**

Even though till date telomeres have been thought very important marker and well studied particularly for hematological disorders and cancer, recent publications demonstrated the importance of this marker for psychiatric and ageing disease or disorders.

Recent publications regarding psychiatric disorders have demonstrated, shorter leukocyte TL (LTL) associated with short sleep duration, phobic anxiety, schizophrenia and depression. Previous studies also proposed that the frequency of depressive episodes is associated with shorter LTL and cellular ageing and antidepressant pharmacological treatment preserve against telomere loss and shortening. Additionally, in schizophrenia poor response to drug therapy has been linked with shorter LTL. Furthermore, the study was done for bipolar disorder (BD) patients and their data has suggested that long-term lithium treatment in BD patients results in longer LTL. This study was also supported by a previous one which tested the association between lithium and LTL with mechanistic pathway in vitro (15,16).

**Conclusion**

Although heterogeneous background, telomere shortening is one common pathway of bone marrow failure syndrome particularly in constitutional and acquired aplastic anemias. Telomere shortening, which caused by genetic mutations, is responsible for reduced hematopoietic stem cell numbers as well as its proliferation capacity and eventually causing hypoplastic bone marrow.

Telomere disease is very recently identified; excitement about those pathologies has led to many discoveries in other areas of medicine. Telomere journey ended with Nobel Prize for the discovery of it in 2009. There has been substantial concentration in the field of cancer, hematology and ageing. Telomere has opened many doors for clever brains, psychiatric disorders and ageing diseases are very good surrogated for researching regarding telomere and telomerase complex.

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