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Telomeres and their Clinical Implications in Health and Disease: An Overview

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Abstract

Telomere are the long repetitive stretch of non-coding, G rich DNA sequences, located at the distal end of linear chromosomes. These sequence are non-coding, but functional and also important regulator of the genome, as it is essential for maintenance of genomic integrity, by protecting coding genetic material from the fusion with neighbouring chromosomes. A sheltrin protein complex composed of six subunits and a telomerase enzyme, a ribonucleoprotein complex are important regulator of telomere, which protects the telomere sequences from the DNA damage response machineries and maintains the length of telomere by extension of 3′ G-overhang respectively. Telomerase activity is high in germline and stem cells, which contributes to genome stabilisation, and suppressed in somatic cells; hence with each cell division, telomere undergo age dependent incremental attrition of telomere length. Several factors are reported, which affects telomere length and telomerase activity in healthy individual as well as disease condition. A limited studies from the India have been reported on telomere length attrition and telomere gene mutations in isolated disease conditions. The present review primarily focusing on the telomeres in genetic disease and the cancers, suggesting a need of triad of telomere study including telomere length analysis, telomerase activity along with the genetic mutations using multiple approaches to enhance the clinical implication of telomeres in various diseases.

Keywords: Telomere; Telomerase; Bone marrow failure; Cancers; Clinical implications.

Key Messages: Telomeres are important in genomic integrity and telomere length can be used as biological marker for few diseases. Also, telomeres largely help in understanding disease prognosis. Since there are 29 genes associated with telomere regulation and these genes need to be studied in rare diseases and cancers.

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INTRODUCTION

Telomeres are special heterochromatic structural elements of DNA-protein content, located at the end of chromosomes, composed of guanine rich tandems repeats of DNA sequences that protects chromosomes from degradation during DNA repair and recombination activities.[1,2] Telomeres are the functional, non-coding sequences, in combination with sheltrin protein, provides a protection to the coding sequences of the chromosomal region to maintain the genomic stability.[3] Absence of complex telomeric structure provokes the abnormal

end to end fusion leading to large scale genomic rearrangements. Sheltrin and telomerase are complex proteins, essential to protect the telomere end and maintain the length respectively. Molecular studies showed association of 29 genes involved in either directly or indirectly to the telomere regulation. Several factors have been reported to cause telomere alterations such as aging, genetic alteration and epigenetic make up, environmental factors, physical activity, obesity, smoking and life style. Telomere length shortening have been reported frequently in various diseases and also been used as biological marker to understand the prognosis of the disease. Telomere length attrition and telomere regulatory gene mutations have been reported in various diseases.[4-10] Studies have also reported deficient telomerase activity in various disease conditions in the presence of telomere regulating gene mutations.[11] Understanding the clinical significance of telomeres has implications for disease diagnosis, prognosis, and potential therapeutic interventions. Monitoring telomere length and understanding telomere biology can provide insights into various aspects of health and disease, from aging and cancer to cardiovascular health and psychological well-being. In the present review, we have highlighted the importance of telomeres in disease development.

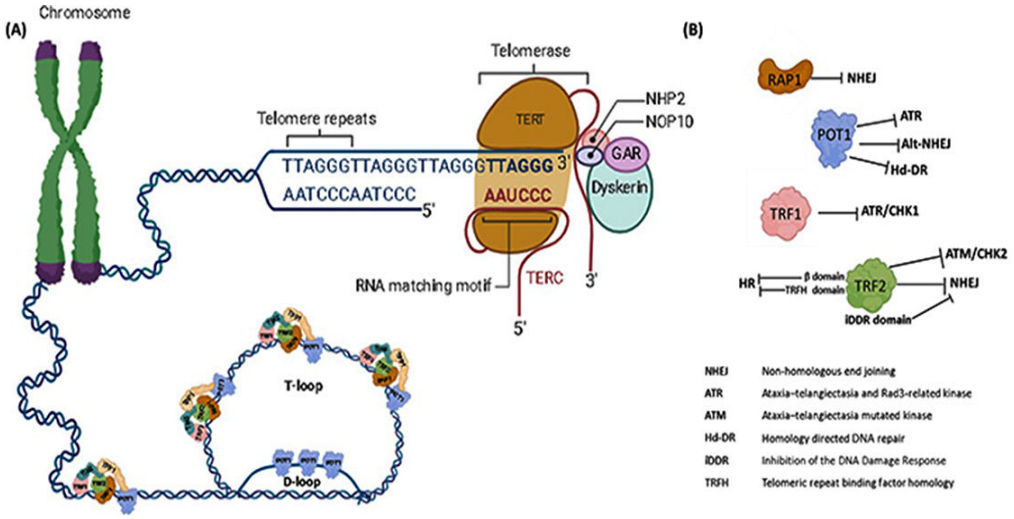

Fig. 1: (A) Schematic representation of the chromosomes, telomere structure, telomerase enzyme and its function, Shelterin protein complex along with its candidate protein to regulate telomere length and protection from degradation **(B)** Functionality of the proteins involved in the regulation and maintenance of the telomere.

Telomeres

Telomere are the conserved, short tandem repeats of GT rich sequences, structurally they are known as nucleo-protein structure, present at the end of linear chromosomes that shields them degradation, fusion and checkpoint recognition. The length of these sequences reduces during each cell division in somatic cells. Critical shortening in the length of the telomere will affect its functions and induces DNA damage response and causes cellular senescence. However a sheltrin complex protein is essential to maintain telomere length. A sheltrin complex protein is comprise of six proteins viz; *TRF1, TRF2, TIN2, TPP1, RAP1*, and *POT1*. Amongst all the proteins of sheltrin, Telomeric repeat binding factor 1 & 2 (*TRF1 & TRF2*) and protection of telomeres 1 (*POT1*) are DNA binders which binds to the single stranded G-rich overhang of telomere sequence. *TRF1*-interacting nuclear protein 2 (*TIN2*), *TIN2*-interacting protein (*TPP1*), and *RAP1* act as adaptors which is important for interaction of the all constitute. Combinely these proteins form a lariat structure, also known as t-loop. The sheltrin complex plays an essential role in protecting telomeric sequencing along with the regulation of telomere regulating enzyme i.e. Telomerase.[12] Absence of the complex telomeric structure provokes the abnormal end-to-end fusion and large scale genomic rearrangements of the linear chromosomes across the genome, considering it as pathological DNA breaks. Overall, telomere serve as biological protector of the genome; (i) by preventing the DNA degradation, as telomere length shortening at each cell division to protect the coding region of the chromosomes from

semiconservative process of the replication, (ii) maintaining chromosome stability, as the repetitive structure of telomeres helps to prevent chromosome ends from being recognized as damaged DNA and undergoing unnecessary repair processes. Without functional telomeres, chromosomes could be mistaken for broken DNA, leading to fusion events or other chromosomal abnormalities (iii) prevents the cellular senescence and apoptosis which intern prevents cells with damaged or incomplete genomes from proliferating uncontrollably, which is a hallmark of cancer. (iv) regulating cellular aging to increased cellular longevity and reduced risk of age related illnesses, and most importantly (v) regulating telomerase activity to the ends of chromosomes, counteracting telomere shortening. As, dysregulation of telomerase activity can contribute to cancer development by allowing cells to bypass senescence and continue proliferating indefinitely.

Telomeres shorten with each cell division during mitosis of cells and hence aging of organisms, leading to cell senescence, apoptosis and occasionally genomic instability.[13] However, increased risk of clinical complications associated with premature telomere shortening is frequently reported in various diseases though not completely understood. Recent findings are suggestive of the skewed megakaryocytic differentiation and exhausted hematopoetic stem cells (HSCs) function due to accelerated telomere attrition. Studies have reported that telomere dysfunction significantly affects hematopoietic progenitor differentiation.[14,15] Studies have also demonstrated telomere length attrition and telomere regulatory gene mutations in various diseases.[4–10] Along with the shorter telomere length, affected telomerase activity has been frequently reported in various diseased conditions. The studies showed that the telomere driven mutations are one of the contributors for overall genetic heterogeneity of cancers, facilitating the clonal progression and evolution of the cancer genome.[16]

Telomerase

Telomerase is complex enzyme consists 2 important component telomerase reverse transcriptase (*TERT*), and an RNA component (*TERC*) of which *TERT* act as catalytic subunit and *TERC* is a template for an extension of telomeric sequences. Protein complex including, Dyskerin (*DKC1*), nucleolar protein 10 (*NOP10*), non-histone protein 2 (*NHP2*) and encoding H/*ACA* ribonucleoprotein complex subunit 1 (*GAR1*) also contribute along with of telomerase to elongate and maintain the telomere length. Amongst all, *NOP10* and *GAR1* interacts with *DKC1* whereas, *NHP2* binds directly to the RNA. Assembly of *TERT* and *TERC* in the nucleolus forming mature telomerase complex. Telomerease complex and telomerase cajal body protein 1 (*TCAB1*) recognizes the Cajal body box and recruits mature telomerase complex to cajal body during the S-phase of the cell cycle to activate the telomerase. The active form of telomere adds the number of repeats to the telomere ends and regulated by set of a equilibrium.[17] The disruption in this process can lead to the various telomere related diseases. So far studies have reported telomerase activity to be deficient in individuals with inherited mutations in the reverse transcriptase gene (*TERT*) and the RNA template gene (*TERC*).[11] Recently, 29 telomere maintenance genes have been described, belonging directly and indirectly to telomere maintenance pathways: telomerase complex (*TERT, TERC, DKC1, GAR1, NOP10, NHP2*); shelterin–telosome protein complex (*POT1, TERF1, TERF2, TERF2IP, TINF2, TPP1*); histone binding and alternative telomere lengthening mechanism (*ATRX, DAXX, TNKS*); non-canonical telomere maintenance (*ACD, FBXO4, GPX2, MCRS1, MKRN1, NAT10, NFX1, RLIM, SMG5, SMG6, SOX7, TEP1, WRAP53, YLPM1*).

The clinical significance of telomeres

Age

Aging is precedence, as telomere naturally shorten with each cell division due to the end replication problem, leading to cellular senescence or aging and apoptosis. Hence telomere length negative correlated with the age. It has been reported that the human telomere length decreases at a rate of 24.8–27.7 base pairs per year.[18] The shortening in telomere length compared to the average telomere length of particular age group could be associated with age related diseases, or with increased risk of developing such a conditions with decreased life span.[19,20] Thus in aging-related diseases and conditions, including cardiovascular disease, neurodegenerative diseases, and cancer clinical manifestation and complications arises due to shorter telomere length.[21–28] Though the various studies are available to explain complex mechanism of telomere length shortening the exact mechanism of its alteration in an individual remains difficult to understand as, it is affected

by multiple factors, including, age, environment, social and economic status, genetic and epigenetic makeup, physical activity, obesity, smoking and life style; also aging itself is an complex phenomenon with an involvement of multiple pathways and organs of living individuals. Our unpublished data of telomere length in healthy individuals have shown that significantly shorter telomere length in elderly adults compared to young adults, though no significant difference was observed between both the genders. Though several studies have suggested to consider it as an biological marker for prediction of biological age, we suggests that it is important to consider the limitations and address the challenges in establishing telomere length as biomarker for aging, as it increases the predictive power to measure the biological age still sole measure of telomere length as biomarker for age remains inconclusive. Overall, telomeres plays a fundamental role in maintaining genomic stability, regulating cellular senescence and protecting against age related disease. Understanding telomere biology is essential for elucidating the mechanisms of aging and age related diseases and developing potential interventions to promote healthy aging.

Environmental factors and lifestyle

Telomere length is highly influenced by the external environmental factor such as environmental pollutants, chemical contaminants, radiation and infections as they modulate the cellular processing and hence affects the telomere length and telomerase activity.[29] Lifestyle, which majorly includes toxic chemicals and cancer chemotherapy agents, physical inactivity, smoking, severe prolonged stress, and obesity are causing tissue damage which demands for lot of cell division, thus increasing overall rate of telomere shortening. Though a short term follow up studies demonstrated, individuals with sedentary life experiences a more functional limitations and disabilities with progressively shorter telomere length compared to individual with active physical activity. It is also been proved that physical activity and exercise have both protective and restorative effects, with great potential to improve well-being and increase longevity as the physical activity and exercise are proved to be beneficial for telomere length maintenance in both healthy and chronically ill middle aged and older adults.[30]

Disease

Short telomeres have been associated with various age related diseases, including cardiovascular disease, diabetes, and neurodegenerative disorders; constitutional disease such as bone marrow failure, Dyskeratosis Congenita; acquired haematological conditions such as aplastic anemia, myelodysplasia and acute myeloid leukaemia; pulmonary fibrosis; and hepatic nodular regenerative hyperplasia and cirrhosis.[29,31] Telomere length serve as a biomarker for disease risk and progression. Hence telomere investigation and monitoring needs to be considered for such a conditions.

Genetic Disorders

Mutations in genes associated with telomere maintenance can lead to genetic disorders known as telomeropathies or telomere biology disorder. The primary driven force for these diseases is genetic mutations in genes encoding components of the telomere maintenance machinery which majorly include telomerase and sheltrin complex (fig. 1). The most commonly known genetic disorder is dyskeratosis congenital (DC),[32] classified as a rare inherited bone marrow failure syndrome. It is characterised by the triad of mucocutaneous features including nail dystrophy, oral leukoplakia, and abnormal skin pigmentation. They often develop tri-lineage marrow failure, leading to aplastic anemia, also an increased risk of malignant transformation. So far mutations in the genes such as, *TERT, TERC*, and *DKC1* are reported to be responsible for DC and are involved in telomere maintenance. Another disorder, idiopathic pulmonary fibrosis (IPF), also characterized by the formation of scar tissue within the lungs. With major involvement of the telomere maintenance gene particularly, *TERT* and *TERC*, which is frequently identified in IPF patients. The mutations in these genes are major contributor in premature shortening of the telomere in lung cells, eventually leading to tissue degeneration and fibrosis.

In addition to DC and IPF, telomere dysfunction has also been implicated in other genetic disorders, including Hoyeraal-Hreidarsson syndrome, Coats plus syndrome, and Revesz syndrome, among others.[33] These disorders often manifest with a variety of clinical features, including bone marrow failure, immunodeficiency, pulmonary fibrosis, and other organ dysfunction, highlighting the diverse consequences of impaired telomere maintenance. Mutation in these gene and telomere attrition collectively responsible for the genomic instability, as we have previously reported an increased telomere attrition associated with high frequency of chromosomal breakage in Fanconi's

anaemia (FA).[10] Our unpublished data on telomere attrition and telomere regulatory gene mutation from Indian patients showed an increased frequency of telomere attrition associated with high genomic instability which may manifest variable phenotypes associated with fatal marrow failure. Another unpublished finding in tri-lienage marrow failure patients, diagnosed as aplastic anaemia (AA) also showed significant telomere attrition in 41% of the AA patients, suggesting not only genetic mutations but also cellular environment, physiology and disease conditions may also affect the telomere length, eventually increasing risk of genomic instability and reduced survival. Hence understanding the role of the telomere dysfunction in genetic disorders not only provides insights into disease mechanism but also offers potential avenues for therapeutic intervention, such as telomerase activation or telomere lengthening strategies, which may help mitigate the clinical manifestations of these conditions.

Cancers

Cancer cells, unlike most of the somatic cells where telomere shortening occurs with each cell division and eventually leads to cellular senescence/apoptosis; have evolved to bypass the limitation of the telomere end replication problem.[34] One of the mechanisms to overcome telomere shortening is telomerase activation. Which adds telomeric repeats to the end of the chromosomes, avoiding telomere shortening and increasing proliferative potential of the cancer cell indefinitely. In most of the somatic cell telomerase is not typically active, however is reactivated in about 85-90% of cancers, contributing to the immortalise nature of cancer cells. In addition to telomerase activation, cancer cells also have a mechanism of alternative lengthening of telomeres (ALT), a recombination based mechanism that enables the cancer cells to elongate telomeres independently of telomerase activity. ALT can be characterised by heterogeneous telomere length with extremely long and short telomere length.[35,36] Studies have reported an increased frequency of ALT in tumours such as central nervous system, peripheral nervous system and sarcoma; but observed rarely in carcinomas. ALT pathways have a strong clinical implication in developing cancer, hence determining ALT in cancer remains important for diagnosis, prognosis and management of the cancers. As telomere length acts as a determining factor in cancer development, the telomere length monitoring and cellular achievement to reach at replicative crisis and shorter telomere length is beneficial in cases of cancer conditions. Studies have reported an elevated telomerase activity in cancer cells, whereas telomere length is found to be shorter when compared with control cells. Shammas et al have also shown telomere shortening in cancer cell lines and primary cancer cells.[37–39] This ability to maintain the telomere length is essential for cancer cells for continuous proliferation and survival. Inhibition of telomere maintenance with continuous shortening in telomere length of the cancer cell induces cell senescence and apoptosis. Several studies have indicated an individual with shorter telomere length are at high risk to develop lung, bladder, renal cell, gastrointestinal, and head and neck cancers.[27,28] Rarely but isolated cases DC with deficiency of telomerase RNA component also lead to telomere shortening leading to development of various phenotypes, vulnerability to infections, pre mature greying, progressive bone marrow failure, predisposition to cancer and premature death in adults.[40,41] Hence targeting telomeres and telomerase has been explored as a potential strategy for cancer therapy.

CONCLUSION

In conclusion, telomere plays an important role in protection of the genomic stability from the loss of genetic material and it is also reported to be affected in several disease conditions. Study of telomere length in various disease conditions will ultimately help in establishing telomere length as biological markers to understand the disease prognosis and its management. Telomere gene mutations are not frequently studied in different disease conditions in India. Hence, we suggest that the telomere length analysis along with the telomerase activity and genetic mutation with multiple approaches is essential to enhance the clinical implications of the telomere in Indian subcontinent.

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