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LETTER TO THE EDITOR

Recent advances of Blood telomere length (BTL) shortening: A potential biomarker for development of cancer

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Abstract
Telomeres, the specific DNA–protein structures remains at both ends of each chromosome and are crucial in the maintenance of chromosome integrity and genomic stability with protection of the chromosome from damage and degradation.. Increasing evidences suggest the correlation between telomere length and the development of cancers, but the findings remain obscure. Generally, the average length of telomere repeats at the ends of chromosomes that gives a clue in providing indirect information about their mitotic history. It plays immense role in preventing genome from nucleolytic degradation, unnecessary recombination, repair, and interchromosomal fusion. It has major role in storing the information in the genome. Telomere attrition during successive cell divisions induces chromosomal instability and contributes significantly to genomic rearrangements that can result in tumorigenesis. Convincing evidence documented that a meagre portion of telomeric DNA is expelled out during mitotic stage of cell division. But accelerated shortening telomere length at critical level triggers senescence and/or apoptosis. Various harmful agents with bad lifestyles are responsible in inducing shortening of telomere length with damage of DNA resulting to occurrence of disease with shortening of lifespan. Besides, telomerases, the specialized polymerase that synthesizes new telomere repeats and is strongly associated with cancer facilitating malignant transformation. Therefore, in the study, it is highlighted that the telomeres may play diverse roles in different cancers whereas shortening of telomere length may be risk factors for the development of tumors.

Keywords Telomere length · Shortening · Cancer · Cisease · Biomarker

Telomeres, the specialized structures comprising of tandem repeats of a repetitive DNA sequence (TTAGGG) and associated proteins that protect the ends of eukaryotic linear chrosomes. It comprises of repetitive DNA sequences at the ends of linear chromosomes bound by specialized proteins i.e. shelterin proteins. Because of the end replication problem regarding linear chromosomal DNA, telomeres shorten with each cell division [1]. In addition, telomerase plays immense role in telomere maintenance by protecting this acquired altered genetic information ensuring immortality without losing eukaryotic linear DNA. Telomere length and telomerase activity have been attributed in the control and maintenance of cell proliferation and genomic stability with genetic (homologous) recombination [2]. It is well documented that telomeres consist of several thousand DNA repeats of TTAGGG with a protein complex (i.e. shelterin) at the ends of chromosomes in eukaryotic cells [3]. Jafri et al. [4] reported that telomere has a major role in maintaining genomic integrity in normal cells, and rapid shortening during successive cell divisions at mitotic stage induces chromosomal instability. They also revealed that cancer is generally an age-related genetic disease, manifesting only when normal cells accumulate genomic instability over a period of time and acquire the capability of replicative immortality [4]. Moon and Jarstfer [5] indicated that telomere has a beneficial role in maintaining chromosome integrity and genomic stability through prohibiting nucleolytic degradation, chromosomal end-to-end fusion and irregular recombination. Shortening of telomere length can trigger cell to enter replicative senescence with a result of cell death with genomic instability and chromosomal abnormality. Zhu et al. [6] reported that it is a biomarker to elucidate the mitotic clock in eukaryotic cells, with cell replications undertaken by each cell during its lifespan. Emerging studies reported that telomeres are strongly

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associated with different tissues and contributes significantly to genomic rearrangements resulting to tumorigenesis with multiple cancers. Shay [7] revealed that telomeres are controlled by an enzyme called telomerase with an important mechanisms underlying telomere length (TL) maintenance and telomerase expression involve transcriptional, post-transcriptional and epigenetic regulation. Shortening of telomere length may be risk factors in the initiation and progression of cancer with antiproliferative barrier, senescence and/or apoptosis and telomeric DNA damages. at each DNA replication, and if continued leads to chromosomal degradation and cell death. The mechanism undergoing critical shortening of telomeres with DNA damage is the important target. Jafri et al. [4] revealed that dysfunctional telomeres, arising by in normal somatic cells during progressive cell divisions, elicit DNA damage responses (DDRs) that trigger cellular senescence. Epidemiological evidences suggest that short telomeres were associated with increased cancer risk. Emerging studies also reported that misbalance of telomerase-mediated telomere extension promotes genomic instability and enhances carcinogenesis with development of malignancy [8]. The aim of the study was to assess the association between blood telomere length and risk of both cancer manifestation as well as cancer mortality.

Increasing evidence suggest that telomeres are long repetitive DNA sequences of TTAGGG situated at the end of the linear chromosomes and surrounded by telomeric DNA protein complex i.e. shelterin proteins [9]. Emerging studies reported that telomeres are strongly associated with different tissues and contributes significantly to genomic rearrangements resulting to tumorigenesis with multiple cancers. Repetition of telomere length is dependent on the type of tissue, the age of the donor and the replicative history of the cells. Khan et al. [10] demonstrated that sheltering proteins are composed of telomere repeat binding factors 1 and 2 with negative regulators (TRF1 and TRF2) that causes protection for the loop structure of telomere by preventing the chromosome ends uncapped; resemble a DNA break and activating DNA repair mechanism. Van Steensel et al. [11] revealed that telomeric DNA is associated with telomerebinding proteins and a loop structure mediated by TRF2 protects the ends of human chromosomes against exonucleolytic degradation. There are another four types of shelterin proteins that include tripeptidyl peptidase 2 (TIN2), protection of telomeres 1 (POT1), repressor activator protein 1 (RAP1), and tripeptidyl peptidase 1 (TPP1) [11]. Generally, it is composed of G-rich hexanucleotides repeats which enable the single-stranded telomere G overhangs form G-quadraplexes safeguarding the integrity of genomic material with activation of enzyme telomerase by preventing telomere shortening, suppression of recombination and inhibition of telomerase-dependent telomere extension [12]. Telomeres prevents chromosome from degradation and interchromosomal fusion by activating the efficiency of telomerase that is ribonucleoprotein complex with RNA and protein components [1, 13]. Telomere length is hampered by a wide spectrum of endogenous and environmental factors viz. oxidative stress, aging, unhealthy lifestyle and genotoxic stress. It is reactivated in most cancers and immortalized cells with probably involving genetic (homologous) recombination through various mechanisms.Telomere length is hampered by a wide spectrum of endogenous and environmental factors viz. oxidative stress, aging, unhealthy lifestyle and genotoxic stress. Telomere dysfunction results breakage of telomere structure with chromosomal instability through propagation of breakage-fusion-bridge (BFB) cycles and genetic aberrations. The shortening also causes cancers, through various mechanism including aneuploidy, loss of heterozygosity, gene amplification and gene loss [14]. In another study, Cheung and Deng [15] revealed that an alternative telomere lengthening (ALT) mechanism alleviates chromosome instability with genetic alterations for malignant transformation and cancer development. Cottliar and Slavutsky [16] revealed that of telomere length shortening causes metaphase telomeric associations (tas) and chromosome instability with disturbance of telomere separation in mitosis properly. Shortening of telomere length with alerted telomerase activity triggers chromosome instability, DNA damage and development of cancer. Genetic variation of several genes was closely associated with telomere length. Thus, the study helps to explain more insight to detect cancer. It could be a prevalent and specific tumor biomarker for adopting novel and excellent target for anti-cancer therapy.

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Compliance with ethical standards

Conflict of interest statement The author declares no conflict of interest.

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