Telomere shortening: A marker of atherosclerosis?

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Telomeres are nucleoprotein complexes at the ends of chromosomes, consisting of tandem arrays of TTAGGG nucleotide repeats[1] (Figure 1). They are essential for chromosomal stability and for preventing degradation and abnormal chromosomal recombinations. Telomeres are considered as a replicometer, which counts cell divisions and ultimately triggers replicative senescence, and they act as cellular 'sentinels' for genomic damage (Box 1). The fact that telomeres trigger replicative senescence has been supported by three observations. First, telomeres shorten with each population doubling in primary human cell cultures, but stop shortening in non-dividing cells[2]. Second, immortal cells, whether single-cell organisms, germ line cells or tumour cells express in their vast majority active telomerase, the enzyme that binds to the single-stranded 3′ end of the telomere and re-elongate it[3]. Third, human fibroblasts, which display telomere shortening and senescence, can be immortalized solely by transfection with the catalytic subunit of human telomerase, hTERT; this transfection results in the restoration of functional telomerase and elongation of telomeres[4]. *In utero*, telomere length is similar in most tissues[5] but during extrauterine life, telomeres progressively shorten in proliferative somatic cells and their length diminishes with age. Based on studies in twins, telomere length seems to be familial[6,7] and recently, its mode of inheritance has been described to be X-linked[8].

Recent studies propose that telomere shortening is a marker of biological ageing

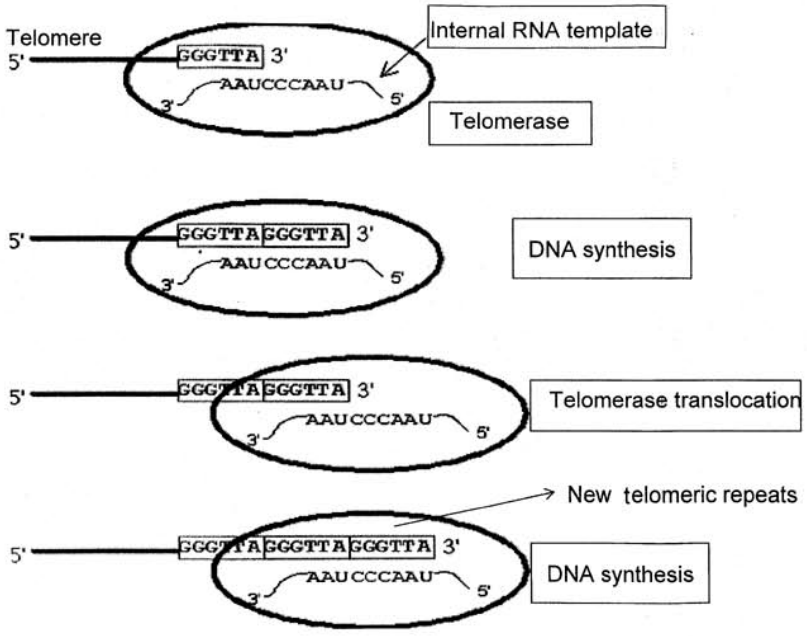

Figure 1. Telomere in a human chromosome is composed of the tandem repeat sequence TTAGGG. The telomerase contains an essential RNA component which is complementary to the telomere repeat sequence. Therefore, the internal RNA can serve as the template for synthesizing DNA. Through telomerase translocation, a telomere may be extended by many repeats. This protects the genome from the potential loss of information. In the absence of telomerase, the telomere will become shorter after each cell division. When it reaches a certain length, the cell may cease to divide and die. The successive shortening of the chromosomal telomeres with each cell cycle is also believed to influence the vitality of the cell, thus contributing to premature cellular senescence in various cell types.

Box 1. Telomeres

Telomeres are snippets of DNA at the ends of chromosomes that function in part like the plastic tips on the ends of shoelaces, preventing chromosomal fusions and offering genomic integrity and stability. Apart from ensuring chromosome stability, telomeres also provide a mechanism for 'counting' cell divisions, and thus signal replicative senescence. Since DNA polymerase requires a labile primer to initiate unidirectional 5′–3′ synthesis, some bases at the 3′ end of each template strand are not copied unless special mechanisms bypass this telomere 'end-replication' problem. Immortal eukaryotic cells, including transformed human cells, apparently use telomerase, an enzyme that elongates telomeres, to overcome incomplete end-replication. However, telomerase has not been detected in most normal somatic cells, and these cells lose telomeres with age.

Box 2. A long story on short telomeres

- In 1961, Leonard Hayflick reported that human cells in culture divide a certain number of times, reaching a maximum 'Hayflick limit'.
- In 1972, James Watson described the 'lagging strand problem' (end-replication problem), which predicts telomere shortening with each division.
- In 1972, Alexy Olovnikov connected Hayflick's and Watson's ideas and proposed that each DNA replication depletes telomere material to a point that signals the cell to stop dividing and attain cellular senescence.
- In 1987, Blackburn and Greider named the enzyme 'telomerase' – a reverse transcriptase that elongates the telomeres.
- In 1990, scientists identified the six-base sequence (TTAGGG) repeats in human telomeres – which become a yardstick to measure telomeres in 'telomere restriction fragment' assay.
- During the 1990s, cancer cells were shown to ignore the 'Hayflick limit' by having long telomeres and active telomerase. In addition, transfecting telomerase genes into cultured human cells gave them an unlimited capacity for cell division. In contrast, telomeres in most somatic cells in multicellular organisms, including humans, shorten with each cell division and they lack telomerase or telomerase is undetectable in those cells.
- In 1995, Chang and Harley observed short telomeres as a marker of accelerated aging in cells forming blood-vessel inner linings. Subsequent studies to-date strongly support that telomere length might be useful in predicting the onset of atherosclerosis and other cardiovascular diseases.
- Recent research[19] suggests that the relationship between telomere length and cell/organism longevity is strong. Worms/birds with longer telomeres have been shown to have long lifespan.

and atherosclerosis, and that individuals with shorter telomeres than might be expected based on their chronological age, are prone to various diseases. Alterations in cellular turnover of cardiovascular tissue contribute to the many factors leading to cardiovascular diseases, and none of the conventional biomarkers directly measures them. In this context, recent investigations have demonstrated the potential of employing telomere length measurements (expressed in terms of mean telomere restriction fragment (TRF) length) as a marker of replicative history and future replicative capacity of normal somatic cells[2]. It is likely that not only the loss of replicative capacity, but also the alteration in gene expression seen in senescent cells contributes to age-related cardiovascular disease. If senescent endothelial cells accumulate at focal sites of high cell turnover, then their reduced ability to divide and form a continuous monolayer will expose the underlying media to blood-derived mitogenic and adhesive factors, which would contribute to the formation of the expanded intimal morphology characteristic of an atherosclerotic plaque[9].

TRF length was shorter in patients with atherosclerotic heart disease than in age-matched controls[10]. It is also demonstrated that telomere shortening could be involved in the development of atherosclerotic disease in patients with metabolic diseases such as hypercholesterolemia and diabetes mellitus[11]. Shortened telomere length was also observed in white blood cells of patients with Type 1 diabetes[12] and Type 2 diabetes[13].

It appears that there are common molecular mechanisms accounting for atherosclerosis in which expressions of genes related to glucose metabolism, lipid metabolism and vascular function are altered. Oxidative stress could be one such common mechanism[14] underlying insulin resistance, diabetes and cardiovascular disease. Telomeres are less efficient in single-strand break repair than the bulk of the genomic DNA[15] and oxidative stress accelerates telomere loss, whereas antioxidants decelerate it[16]. In fact, telomeres, as triple-G-containing structures, are highly sensitive to damage by oxidative stress[17]. It will be interesting to know the causal relationship between the molecular mechanisms underlying the metabolic/cardiovascular diseases and telomere shortening.

Interestingly, several studies[6,8,13] indicate that age-adjusted telomere length is longer in women than in men. Independent of age and mean arterial pressure, arterial stiffness and pulse pressure were also inversely correlated with TRF length in men[18]. Such enigmatic findings suggest that the biology of aging differs between men and women and warrant further investigations.

Accelerated telomere shortening appears to be related to 'lifestyle diseases' that accompany certain concomitant metabolic factors such as obesity, hypernutrition and lack of exercise. Will this accelerated telomere shortening be prevented by tight control of blood glucose, pressure and lipids and/or by caloric restriction and antioxidant supplementation? The answer heavily relies upon advancing telomere biology research (Box 2). Given that aging is a multifactorial and highly variable entity and that biological aging (premature cellular senescence) may alter functional status of several tissues, the use of telomere length provides a new dimension to the study of metabolic and cardiovascular diseases with special reference to atherosclerosis.

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