The Role of Telomeres and Telomerase in Human Aging and Aging Associated Diseases

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الملخص

اثبات وجود رابط قوي بين التيلوميرات وكبر الخلايا في تزايد، حيث أنه مع كل انقسام خلوي خلايا الإنسان الطبيعية تفقد تيلوميراتها بشكل كبير إلي ان تبقى القليل من التيلوميرات القصيرة غير مغطاه، وهدا يعرضها للخطر ،لأن الخلايا تملك تيلوميرات قصيرة لكنها تستمر في الإنقسام مؤدية الي موت خلوي خطير و عدم ثبوت جينومي، وفي بعض الأحيان تفر الخلايا من هذا الخطر، والسبب أن هذه الخلايا تملك إنزيم يسمى التيلوميريز و الذي بدوره يحمي ويدعم ثبات الخلية على الرغم من قصر التيلومير فيها، في هذا البحث نستعرض تأثير التيلومير والتيلوميريز في كبر خلايا الإنسان والأمراض المصاحبة له.

ABSTRACT

An expanding confirmation for the existence of an imperative association between telomeres and cellular aging. With each cell division ordinary human cells dynamically lose telomeres until many telomeres become uncapped driving the cells to risk, although cells have short telomeres but continuous to dividing causing critical cell passing to cell death (apoptosis) and strong genomic variability. Infrequently a human cells get away of that risk, these cells virtually express the ribonucleoprotein, telomerase, which thought of as a component to adequate down the rate genomic instability due to damaged telomeres. This review will address the role of telomeres and telomerase in human aging and aging associated diseases.

Key Words: Telomeres, Cellular aging, Telomerase

INTRODUCTION

In 1930s investigators Barbara McClintock and Hermann Muller have proposed that the ends of chromosome have special structures essential for chromosome stability. Muller coined the term *telomere*, from the Greek for "end" (*telos*) and "part" (*meros*) (Muller, 1938). The scientist McClintock observed that the absence of these vital end structures, chromosomes would fuse or distract during mitosis and the resulting chromosome instability was harmful to cells. These founding studies documented that functional "telomeres" are essential to protect ends of chromosomes, and to ensure correct segregation of genetic material through cell division. since this work was published, a huge amount of data on telomeres and their function have been produced. Some of the major contributions are reviewed here. It is also clear that many ambiguities about telomeres and their function remain. The growing extent of detail about individual molecules and pathways involved in telomere and DNA damage responses has not at all diminished the challenge of thoughtful how telomeres are integrated and participated in DNA damage responses, and human aging. While it has become clear that telomeres play a role in the cellular response to stress and DNA damage.

In 1960s, Leonard Hayflick noted that human cells located in tissue culture stop dividing after a limited number of cell divisions by a process which known as replicative senescence (Hayflick, 1965) . Leonard suggested that the cell culture phenomenon might be used as a model to study human aging at a cellular and molecular level. Though, the role of replicative senescence in human aging and the significance of the in vitro studies stayed subject to much debate. Cells likely divide either to balance normal cell loss or in response to injury. Numerous cells in the body can divide many times more than needed during a normal lifetime. A mitotic "reserve capacity" was used as an argument against the thought that replicative senescence has any importance to human aging. Though, one would not suppose all stem cells in the body to have a comparable replicative history potential, and cells that cannot divide are easily ignored. It has also been challenging to estimate the definite turnover of the stem cells in tissues like hematopoietic and intestine stem cells with an accurateness over a typical lifespan (Potten et al., 2002), to less than 100 times for hematopoietic stem cells in humans (Lansdorp, 1997). the tight association of telomeres to overall cellular fitness does not exclude a role for telomeres even in the aging of

tissues that contain mostly long-lived post mitotic cells such as the brain, heart, or kidney. For example, it is possible that damage to telomeric DNA by reactive oxygen species (ROS) produced by either dysfunctional mitochondria (Wallace, 2005) or by signaling pathways (e.g., overexpression of oncogenes such as Ras (Mooi & Peeper, 2006) contributes or predisposes cells to apoptosis and senescence. Thus DNA damage signals originating from telomeres could be replication independent, and the sensitivity of cells to DNA damage could increase as the overall telomere length declines. More information is needed on the role of telomeres in the cellular response to various types of insults (Rubio, 2004). Watson recognized that the unidirectional nature of DNA replication poses a problem for complete replication of chromosome ends (Watson, 1972). In 1986 the first observations linking telomeres directly to aging were organized, when Cooke and Smith (Cooke & Smith, 1986) observed that the normal length of telomere repeats capping sex chromosomes in sperm cells was much longer than in adult cells. They measured the possibility that adult cells might be lacking the enzyme telomerase which discovered in the unicellular organism *Tetrahymena* (Greider & Blackburn, 1985). Additional studies later established a reduction in average telomere length with cell divisions in fibroblasts and somatic cells from the blood and colon. And this would supported the conclusion that somatic cells are actually unable to maintain telomere length. For the first time, the aging of cells could be linked to readily detectable and reproducible changes in genomic DNA. Subsequently related observations were made with cells from many other human tissues (Hayflick, 2003). The correlation between replicative potential and telomere length became a mechanistic link when it was revealed that the replicative potential of primary human fibroblasts can be extended indefinitely by artificially telomeres, Which was accomplished by or expression of telomerase reverse transcriptase (*hTERT*) gene in primary human fibroblasts (Bodnar, 1998). As had been proposed these experiments conformed that progressive telomere loss is the major cause of replicative senescence (Harley, 1992).

AGING AND EVOLUTION

Aging is the progressive reduction of tissue function that finally results in mortality. This functional decline can result from the failure to replace such cells by a stem cells to sustain replication and cell divisions , or reduced function of post mitotic cells. Aging is not disease, the aging, which varies between

individuals, is best understood in the evolution context. The Disposable Soma model offers a useful outline for such thoughts (Kirkwood, 1977). This model proposes that an increase in longevity in mammals is due to an consequent reduction in the rates of growth and reproduction . The idea that the fidelity of DNA repair is subject to selective forces and not essentially better than firmly needed for a particular cell type, tissue or species is not easily grasped. Differences in the pathways concern the fidelity of DNA repair between somatic stem cells and the germ-line cells and between comparable somatic cells from small, short-lived animals and large, long-lived species greatly complicate generalizations about the molecular mechanism of aging across different species. The progressive loss of telomeric DNA in human somatic cells is thought to act as a tumor suppressor mechanism that limits clonal proliferation, prevents clonal dominance, and ensures a polyclonal composition of (stem) cells in large, long-lived multicellular organisms. Unfortunately, limits to the clonal expansion of somatic (stem) cells also provide strong selection for cells that can ignore or bypass the "telomere" checkpoint (Verfaillie et al., 2002), that cells can grow despite the incidence of dysfunctional telomeres. The loss of telomere function in such cells effects in chromosome fusions, broken chromosomes, translocations, and aneuploidy. This genetic variability permits selection of cells with irregular growth characteristics and also assists rapid acquisition of genetic modifications that provide additional growth advantages (De Lange, 1995). Therefore, while telomere reduction may act as a tumor silencer component, it is also advances tumor development by driving selection of cells with imperfect DNA damage reactions. The aneuploidy and genomic rearrangements in cells with short telomeres and defective DNA damage responses confuse the analysis of the molecular changes that are most significant for tumor growth and development. The thought that damage of telomere function has significances both for aging and carcinogenesis. The interconnections between typical and abnormal telomere intracellular signaling pathways involved in DNA damage responses and DNA repair involving proteins such as ATM, ATR, and p53 (Vousden & Lane, 2007). support a view of telomeres as pivotal dynamic elements required for genome stability that determine how a cell responds to stress and growth stimulation.

FUNCTION OF TELOMERE

To prevent the natural ends of chromosomes from deprivation and processing as double strand breaks, covalently closed hairpin ends will formed in some bacteria, and phages (Kobryn & Chaconas, 2001) and specific transposable elements in certain insects . However, telomeres consists of G-rich repetitive DNA in organisms as protozoan, fungi, mammals, and plants, which maintained by a specialized reverse transcriptase enzyme called telomerase (Pardue, 2005).

TELOMERE BINDING PROTEIN

The component of telomeres in all vertebrates is described as a tandem repeats of (TTAGGG/CCCTAA) . Telomeric DNA typically ends in a single-strand G-rich extend of approximately 50 and 300 nucleotides at the 3 end, which has been suggested to fold back to form duplex telomeric DNA creating a "T-loop" structure (Griffith et al., 1999). The telomere length differs between chromosomes and between species. In humans and mice, the length of telomere repeats at the ends of individual cells is vastly variable (Baird et al., 2003; Lansdorp, et al., 1997). Human chromosome ends are characteristically capped with around 15 kilo base pairs of obvious telomere repeats according to the nature of tissue, the age and the replicative history of the cells. The ends of human chromosomes display marked variation in telomere length (Fig. 1) and the average length varies between chromosome ends. For example, chromosome 17p typically has shorter telomeres than most other chromosome ends (Britt-Compton et al., 2006).

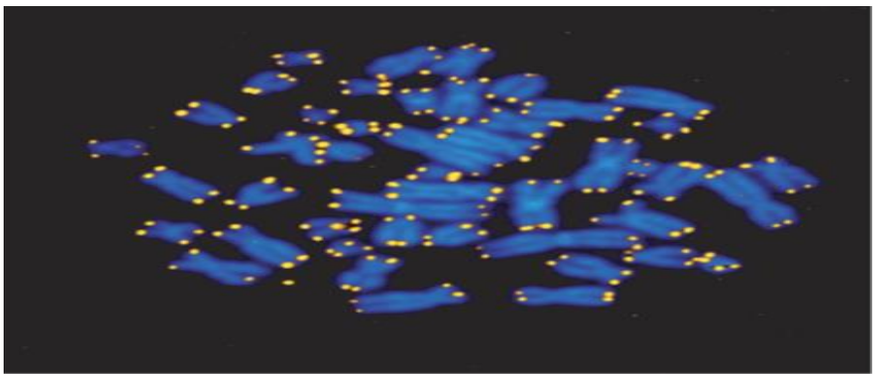

FIG. 1. The length of telomere repeats at individual chromosome ends is highly variable. Telomere repeats in a normal human lymphocyte are visualized using quantitative fluorescence in situ hybridization (Q-FISH) using peptide nucleic acid probes (Lansdorp et al., 1996). Telomeres are shown in yellow, whereas the DNA of chromosomes is shown in blue.

In nucleated blood cells of human, the average telomere length shows a highly decline with age that is most noticeable for the cells of the immune system (Fig. 2). Telomeres avoid the ends of linear chromosomes from looking as DNA double strand (ds) breaks and defend chromosome ends from degradation and fusion. It has been suggested that telomeres can shift between an open and a closed state with the likelihood of the open state inversely correlated to the length of the repeat region (Blackburn, 2001).

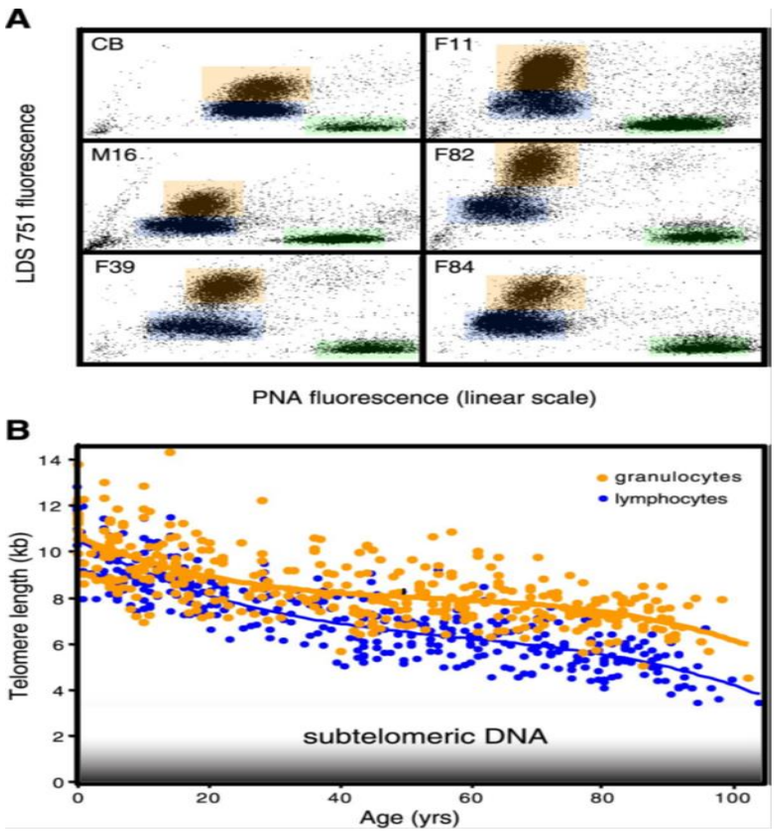

FIG. 2. The telomere length in human granulocytes and lymphocytes of human blood drops with age. *A*: bivariate flow cytometry analysis to the cells. The LDS fluorescence allows perception between granulocytes (orange shaded), lymphocytes (blue shaded) boxes, and bovine thymocytes (green shaded boxes). Results from dispersed experiments are shown to explain how inclusion of aliquots of the same internal control cells (bovine thymocytes, with known telomere length) (Baerlocher et al, 2006) , the fluorescence of telomere in lymphocytes becomes gradually short relative to granulocytes. *B*: results showed

that the telomere length is highly variable at any given age and shows a biphasic decline with age.

A huge number of proteins have been found to associate with telomeric DNA. Certain proteins, such as TRF1, TRF2, TIN2, TPP1, Rap1, and POT1 (De Lange, 2005), can be found at telomeres at any time, although the dynamic exchange between telomere-bound and unbound proteins can be high. For example, fluorescence recovery after photobleaching (FRAP) of TRF1 tagged with fluorescent protein takes less than a minute (Mattern et al., 2004). FRAP studies also showed that POT1 and TRF2 bind to telomeric DNA in two different modes: one stable (slow interchange with unbound proteins) and other unstable mode with (rapid interchange with unbound proteins). An alterations in binding modes presumably reveal alterations in structures and protein quantity at telomeres to which these proteins bind, an example, single strand G-rich DNA set against double- strand telomeric repeats (Fig. 3). Other essential telomere protein complexes, such as the telomerase enzyme complex, associate with telomeric DNA only transiently (Fig. 3). Much development has been made in the last years concerning the organization of specific proteins at telomeres and their role in telomere function (De Lange, 2005). These proteins that are recognized to (transiently) associate with telomeric DNA have roles outward telomeres, and the factors that regulate their interactions are partly understood. Most probable, posttranslational modifications of protein are critical for the accumulation of specific proteins at telomeres throughout specific phases of the cell cycle. Variation in cellular and nuclear protein levels linked to protein turnover, gene expression, and other variables that are problematic to measure separately in single cells, the increase of an integrated view of telomere function greatly complex in relation to specific proteins and function of the cell. Numerous “telomeric” proteins can be exists at cytoplasmic and non telomeric nuclear sites, and some proteins found at telomeres for yet unidentified reasons. Challenges are the differences in the employment of specific proteins to telomeric DNA between diploid cell types and the preserved cell lines that are typically observed in the laboratory. That differences confuse generalizations about the functions of the telomeric DNA proteins. (De Lange, 2005).

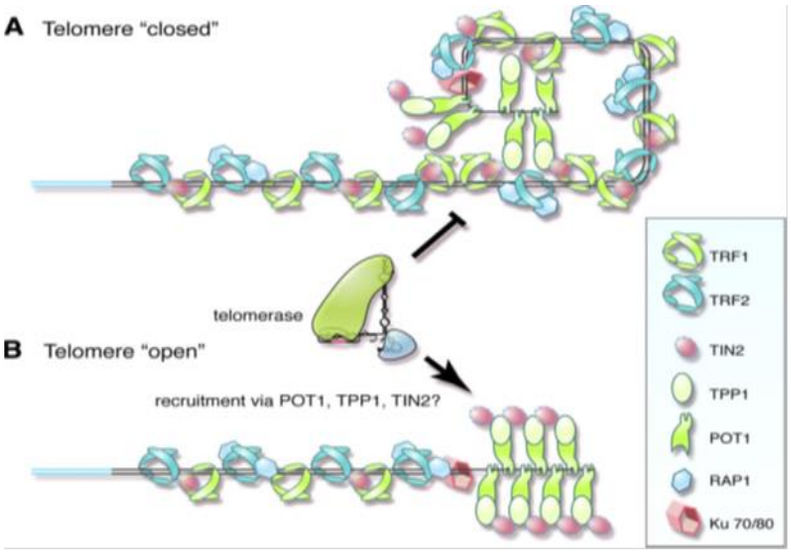

FIG. 3. Telomere function is related to telomere length through the proteins that interact with double-strand telomere repeats (homodimers of TRF1 and TRF2), proteins that bind to the 3 end single strand G-rich overhang POT1, and proteins that interact with proteins such as RAP1, TPP1, and TIN2 and the complex present at the junction of single- and double-stranded telomeric DNA. *A*: telomere "closed". TPP1 and POT1 form a complex with telomeric DNA. *B*: telomere open. The TPP1/POT1 stimulates enzymatic activity of telomerase preferentially at short telomeres (Britt-Compton et al., 2006) .

TELOMERASE

It is a reverse transcriptase enzymes capable of extending the 3′ end of chromosomes by adding TTAGGG repeats (Collins, 2006). The core enzyme contains a reverse transcriptase protein (TERT) of around 1,132 amino acids encoded by the *hTERT* gene (Nakamura et al., 1997), The ribonucleoprotein dyskerin (encoded by the *DKC1* gene on the X chromosome) is essential for suitable folding and stability of telomerase RNA (Wong & Collins., 2006) and existed to be part of the basic complex of a human telomerase enzyme (Migliaccio et al., 2000). Both the reverse transcriptase and telomerase RNA are expressed at very low levels, and haplo-insufficiency for either gene or mutations in *DKC1* can give rise to various clinical manifestations. Telomerase levels are regulated at multiple levels including transcription, alternative splicing, assembly, subcellular localization, and posttranslational modifications of various components and of the enzyme complex itself.

TELOMERES AND DNA DAMAGE RESPONSE

Studies in the areas of DNA repair and damage responses, and apoptosis have all progressed greatly, Studies of one of the major stress response components p53, have emphasized that this protein has a significance role in normal development and tumor formation, life expectancy, and overall fitness (Vousden & Lane, 2007). DNA damage signals are known to initiate from short telomeres and contribute to p53 stimulation and the cellular responses to stress. The telomere binding protein TRF2 binds to ataxia telangiectasia mutated (ATM) kinase can prevent its function (Karlseder et al., 2004), so far DNA damage signals seem to originate from telomeres with each cycle of replication (Verdun & Karlseder., 2006). It has been estimated that telomeres switch between open and closed states (Blackburn, 2001) possibly the open state is proportional to the overall telomere length of the repeat area (Verfaillie et al, 2002). As telomere length declines with age, the amount of damage signals originating from short telomeres is expected to increase.

Higher "background" levels of activated p53 could decrease the threshold for activation of senescence or apoptosis in "old" cells, in track with the increased sensitivity to stress and more delicate nature of cells and tissues from the elderly. In cellular aging the role of telomeres relative to other molecular mechanisms of aging still to be precisely defined. it has become clear that telomeres are directly responsible for continued DNA damage signals in senescent cells, and DNA damage originating from telomeres in senescent cells can readily be detected in vivo (Jeyapalan et al., 2007).

LOSS OF TELOMERE WITH AGE

Loss of telomeric DNA was shown to be associated to replicative history and life span in somatic cells. The tricky of organismal aging as a consequence of short telomeres was elevated as a concern when Dolly, "cloned" by transfer of an adult mammary gland nucleus into an enucleated egg, which revealed to have short telomeres (Shiels et al.,1999). In contrast, nuclear transfer experiments using nuclei from senescent fibroblasts produced offspring with telomeres longer than expected (Lanza et al., 2000). Differences in donor nucleus cell type, nuclear transfer methodology, or species could explain these discrepant results (Kuhholzer-Cabot & Brem, 2002). However, the growth properties of embryonic stem cell lines resulting from pre implantation embryos of various

species suggest that telomere length can be maintained in early development. the loss of telomere repeats in human cells with age varies greatly between cells and tissues, and the amount of information for different tissues is often very limited. It has been proposed that the number of cell divisions in stem cells is _100 divisions over a human lifetime and that this efficiency is achieved by a strict hierarchy at the level of stem cells with the most primitive cells dividing the least and having the longest telomeres (Lansdorp, 1997).

HEMATOPOITIC STEM CELL

Stem and progenitor cells are required to sustain blood cell formation throughout life. Hematopoietic stem cells were first described in the late 1950s with the advent of bone marrow transplantation (Thomas et al., 1959). The procedure involves the transfer of donor bone marrow containing hematopoietic stem cells to restore hematopoiesis following total marrow ablation (achieved by total body irradiation) in recipients. In 1994 it was shown that the telomere length in purified hematopoietic stem cells shows an age-related decline (Vaziri et al., 1994). This study also demonstrated (by TRF analysis) that "candidate" stem cells with a CD34,CD38 phenotype have longer telomeres than more mature CD34, CD38 progenitor cells in adult bone marrow. For this study "candidate" stem cells were purified from organ donor bone marrow cells, a scale of purification that is difficult to reproduce for stem cells of other tissues. Subsequent studies showed that CD34, CD38 cells express telomerase at high levels compared with the more primitive CD34, CD38 cells or the more mature cells (Engelhardt et al., 1997). In a murine model, telomerase expression was required to slow telomere shortening and allow consecutive serial hematopoietic stem cell transplants. Overexpression of telomerase in this model, while stabilizing telomere length, did not prevent senescence or increase the serial transplant ability of stem cells. These observations indicate the existence of telomere independent senescence pathways in hematopoietic cells, which were also postulated to limit the life span of human CD4 T cells that overexpress telomerase (Roth, 2005). Further investigations of telomere biology in human hematopoietic stem cells are challenging since these cells are not readily available for study. Even the best purification strategies do not yield pure suspensions of human stem cells, and the number of cells available for telomere length analysis is also typically very limited. The telomere length in peripheral blood leukocytes has been used as a surrogate for measurements directly in

hematopoietic stem cells. Assuming that the number of cell divisions separating stem cells from granulocytes is relatively constant, the telomere length in readily available granulocytes has been used to study the proliferation and replicative history of stem cells. The number of divisions separating lymphocytes from stem cells is more variable and increases with age, most likely reflecting a higher turnover of immune cells relative to stem cells (Fig. 2). The telomere length in both granulocytes and lymphocytes at any given age was found to be highly variable, and the overall decline in both cells types with age was found to follow a biphasic curve stabilizing in midlife with a more rapid decline in infancy and in the elderly (Figs. 2). The rapid decline in infants was most pronounced in the first years of life (Rufer et al., 1999), and this finding was recently confirmed in a longitudinal study of young primates (baboons), where a steep decline in granulocyte telomere length during the first 50–70 wk. (reflecting a high turnover of hematopoietic stem cells) was followed by a marked drop in telomere attrition. Rapid proliferation of hematopoietic stem cells is also observed in aplastic anemia (where marrow stem and progenitors are thought to be actively depleted through an autoimmune response) or in the first year following bone marrow transplantation (Rufer et al., 2001).

TELOMERE AND HUMAN AGING RELATED DISEASE

A. Telomere Dysfunction

Telomerase deficiencies were first implicated (Mitchell et al., 1999) in the inherited genetic disorder dyskeratosis congenital (DC) by the discovery of mutations in the dyskerin gene (*DKC1*) connected with the X-linked inheritance form of the disease (Heiss et al., 1998). These Mutations are responsible of the symptoms in *DKC1* which include pancytopenia, skin pigmentation, , leukoplakia, nail dystrophy and bone marrow failure or pulmonary fibrosis which finally causes death, with a possibility of bone marrow failure by age 20 exceeding 80% (Mason et al., 2005). Dyskerin is a nucleolar protein that has been involved in the modification of specific small RNA molecules, specially ribosomal RNAs and the telomerase template RNA or hTERC . In view of the studies involving mutations in *DKC1* with telomerase deficiencies and short telomere lengths (Mitchell et al., 1999), the telomerase genes were natural applicants for further examinations of younger patients with DC or bone marrow failure syndromes. patients of DC with hTERC mutations were found to have

reduced telomerase activity less than half of what can be measured in controls (Ly et al., 2005). This gene-dose effect recommends that levels of telomerase RNA are strongly regulated. Strikingly, telomerase levels also seem to be limiting in mice and yeast , showing that bi allelic expression of the telomerase RNA gene is required in a broad range of organisms. In human cell lines, concomitant overexpression of hTERT and hTERC was essential to significantly increase telomerase activity and elongate telomere length (Cristofari & Lingner, 2003).

b. Telomeres and Increased Cell Proliferation

In cellular in vitro models, for example, in the case of CD8 positive T cells overexpression of *hTERT* significantly improves proliferation and cell survival (Migliaccio et al., 2000). Comparable observations have been made with different cell types. In vivo findings in animal tumor models revealed that *mTERC* was early up regulated in tumorigenesis and the telomerase will activated in late stages of tumor development (Blasco et al., 1996). These studies explain the effects of constitutive expression or overexpression of TERT. mTert overexpression was shown to be linked with spontaneous mammary epithelial neoplasia and aggressive carcinoma in aged mice (Artandi et al., 2002), while constitutive expression of mTert in thymocytes stimulates T-cell lymphoma (Canela et al., 2004). recently, work on targeted overexpression in specific tissues showed faster wound healing and increased tumorigenesis in the skin of K5- m*Tert* mice (where m*Terc* is required for the tumor promoting effect) (Cayuela et al., 2005). In addition, it was showing that mTert causes the proliferation and mobilization of hair follicle stem cells (Sarin et al., 2005). This was fictional in situ as well as through the observation of exacerbated hair growth and faster hair regrowth in a manner independent from telomere synthesis.

C. Cancer

The connection between telomere and oncogenesis was first projected when telomerase expression was found to be a hallmark of human cancer: in which telomerase expression and activity can be noticed in 90% of tumor samples (Shay & Roninson, 2004). In mouse models loss of p53 is observed in most tumors and is tumor supporting , while mice with enhanced p53 responses display increased cancer resistance, a shortened life span, and a number of early

aging associated phenotypes (Dagarag et al., 2003; Donehower, 2002). In both models aging appears to be driven by a depletion of the functional ability of stem cells. The association between p53 and telomeres is also illustrated in Li-Fraumeni syndrome (LFS), a cancer predisposition syndrome linked with germ line *TP53* mutations. It was exposed that the progressive earlier age of cancer onset in LFS is related to a decrease in telomere length, with each generation providing the first rational biological marker for clinical monitoring of LFS patients (Tabori et al., 2007). Tumorigenesis is often associated with the up regulation of c-Myc that can be induced by retroviral insertion or translocation. c-Myc binding sequences are described within the *hTERT* promoter, and the MYC protein stimulates *hTERT* transcription (Wu et al., 1999), which may in turn contribute to tumorigenesis or tumor progression. The flip side of continued xpression or reexpression of *hTERT* in genetically stable primary cells and in animal models is enhanced longevity and a delay of senescence during in vitro culture (Gonzalez-Suarez et al., 2005). However, continuous overexpression of telomerase in T cells over longer times in culture was revealed to promote genomic instability (Roth et al., 2005). That may be directly due to hTERT overexpression or as a consequence of prolonged proliferation and replication mistakes that may be impaired by culture conditions. Moreover, gain of expression of *hTERC* due to the occurrence of multiple gene copies has also been recently connected with cervical dysplasia and aggressive cancer progression (Hopman et al., 2006).

INTERVENTIONS TARGETED AT TELOMERES

Interventions targeted at telomeres or telomerase have been the subject of many research projects over the past 20 years, and some applications are now explored in clinical trials.

Strategies to rescue human cells in vitro from senescence or prolong their life span by ectopic telomerase expression were described (Vousden & Lane, 2007) and are now routinely used in many laboratories to extend the life span of primary human cells. The approach also has appeal for cell or tissue therapies as available cell numbers are often limiting. Although many of the approaches involving ectopic expression of hTERT are still at the development stage, significant advances have already been made to enhance allografts and engineered tissue for transplantation. This type of approach may also benefit

specific T-cell immunotherapy protocols where specific T cells recognizing specific antigens (e.g., antigens specific to melanoma cells or HIV) can be purified, expanded in vitro, and infused into patients. The persistence of such tumor-infiltrating lymphocytes and their efficacy was shown to be dependent on telomere length (Leen et al., 2007). Ectopic expression of *hTERC* and hTERT in fibroblasts from DC patients was shown to rescue the proliferative properties of such cells, suggesting that similar strategies could possibly be useful for the treatment of bone marrow deficiencies linked to mutations in telomerase genes. Enhancement of telomerase activity and function is not the only attractive application that targeted telomeres: inhibition of telomerase activity remains a very interesting approach for cancer treatment. Most tumors express telomerase, and the possibility to target telomerase has generated a lot of excitement. The original focus was on the discovery of small molecule inhibitors, and moved more recently to siRNA strategies; however, issues with toxicity, half-life, modes of delivery, and the relatively long time delay to achieve telomere-dependent death of cancer cells both in vitro and in vivo remain problematic issues that may impair therapeutic success.

CONCLUSIONS

Collected documents maintenance the thought that the loss of telomere contributes to human aging. Although the gradual loss of telomere with age in cells of several tissues is not simply measured because the average telomere length exhibit a lot of variation between species and individuals of the same age. However, studies of model organisms as well as patients with telomerase mutations have shown that short telomeres result in awful consequences. It appears reasonable that, with age, the increasing numbers of proliferation of cells in normal individuals is compromised by progressive telomere loss. This is not basically a bad thing, as restrictions in the propagation of somatic cells posture a barrier for the growth of tumor cells. Unfortunately, the telomere machinery that limits the development of premalignant cells also affords strong selection for cells that no longer respond to the DNA defeat signals creating from short telomeres. Such cells are genetically unstable and have seriously increased capability to gain genetic changes that provide extra growth advantages. The difficult involvement of telomeres in both aging and cancer ensures that studies involving telomeres and telomerase will remain subject to intensive development.

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