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Telomerase Gene Therapy: Repercussions In Preventing Aging And Curing Cancer

Amandeep Kaur and Jeena Gupta

Department of Biochemistry, School of Bioengineering and Biosciences, Lovely Professional University, Phagwara, Punjab (India) – 144411

*Address correspondence to: Dr. Jeena Gupta, Assistant Professor, Department of Biochemistry, School of Bioengineering and Biosciences, Lovely Professional University (LPU), Jalandhar - Delhi G.T. Road, Phagwara, Punjab (India) - 144411

Phone: +91-1824-404404, Fax: +91-1824-506111,

E-mail: jeena.20104@lpu.co.in

Short Title: Telomerase and aging

Abstract

Telomerase plays a major role in end replication problem. Telomerase with help of his disciples TERT, TER and dyskerin helps in preventing chromosome shortening. But with increase in age the telomerase expression decreases and leads to replicative senescence. With the advent of new technology, gene therapy can be the solution to overcome the replicative senescence. Inhibiting TERT or TERC expression by targeting their RNAs or utilizing TERT or TERC promoters for expression of exogenous vectors the decreased expression of the telomerase can be restored again. Experiments have been carried in mice and they have shown a significant increase in the telomeric expression, by increasing the expression the aging of the cells can be de-escalated. So, with the use of gene therapy cell life can be increased by increasing telomeric expression.

Keywords

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Vol-22-Issue-16-August-2019

Telomeres; Telomerase; hTERT;Gene therapy;Dyskeratosiscongentia

Introduction

Every living being is made up of biology code language called DNA. DNA is a double-stranded, parallel, helical coiled structure made by the combination of four nucleotides(a sugar attached to phosphate backbone and nitrogenous bases) in minuscule organisms to billions of nucleotides in enormous organisms. With cell division in an organism, DNA also replicates which requires some key enzymes [1].DNA replication takes place in one direction only that is from 5' to 3'. When the DNA unzips with helicase (breaks hydrogen bonds), the 3' to 5' strand DNA synthesis takes place towards and of 5' to 3' takes place away from the unzipped fork. Because of this, the 5' to 3' strands form Okazaki fragments also called lagging strand and are slower in the synthesis process as compared to the leading strand (3' to 5'). So at the end of replication, one strand of DNA is fully synthesizedwhile the other is not which can lead to the shortening of the chromosome. But nature has a phenomenon to prevent this, by a repeated sequence which forfends losing essential parts of the chromosome. This repeated sequence is called Telomeres and the enzyme responsible for its synthesis is called Telomerase. Telomerase helps in the addition of bases at the end of telomeres [2].

Telomeres come from Greek words *telo* referringto "end" and *meros*to "part". Herman J.Muller gave the term *telomere.* He observed that telomerespossess some unique characteristics. A linear chromosome has two ends and at each end telomeres are present [3]. A telomere is a special set of sequences present at the end of a linear chromosome called telomeric sequence (also called the cap of chromosomes). The telomeric sequence consists of repeats which can be 100-1000 copies long depending upon the organism. These repeated sequences are called tandemly repeated DNA sequences. In all vertebrates, the sequence is 5'-TTAGGG-3' (conserved).

Nobel laureate Barbara McClintock (Nobel Prize in Physiology and Medicine 1983) saw that new ends of a broken chromosome in the study of maize are sticky i.e able to fuse with each other. However, the ends of a normal chromosome are stable and show no propensity of fusing with other native or broken ends. These results denoted that telomeres have some peculiar structure different from the ends generated by the breakage of chromosomes [4].Another

ISSN:0971-1260
Vol-22-Issue-16-August-2019

rationale for claiming that telomeres have unique structure is that the known mechanism of replication of linear DNA molecules does not allow duplication of both strands of DNA at the ends of the molecules. Therefore, telomeres must have some specialty to ease the replication process or a special enzyme must be present to solve the inscrutable replication [5].

Telomeres truncate every time cell divides and eventually the cell stops dividing as chromosome reach a crucial length after which it cannot replicate. Telomeres avert this in some kind of cells like stem cells by lengthening of telomeres. People having a rare disease called "Dyskeratosiscongentia" have short telomeres due to disabling of enzyme telomerase andage prematurely [6]. In the year, 2011 scientists of Harvard Medical School engineered mice that lack telomerase completely. This result in their telomeres shrank successively over several generations. The mice aged quickly than the normal mice and suffered from age-related problems and died young [7]. This highlights that telomeres play a starring role in the ageing process.

Most primary cells of humansare not able to divide regularly. After some time, due to the depletion of the telomerase enzyme, no longer lengthening of telomeres takes place [8]. Research is being carried out to manipulate telomerase, to increase telomeres length and decrease aging. The telomerase gene therapy with human telomerase reverse transcriptase (hTERT), shows potential significance in expanding the population of cell lines for consecutive therapeutic transplantation. This is important for age damaged organs and tissue replacement [9].Butan increase in telomerase expression can increase the chances of cancer-producing cells as it has been observed that cancerous cells have high telomerase activity [8].Telomerase gene therapy is still in its early stages. Although a lot of work has been done but many things still need to be identified for its potential role in aging. Moreover, telomeres are not the sole reason for aging, many other factors do contribute regardless of telomere length which serves as a biomarker of aging with reference to physical and cognitive abilities.

Telomerase

Replicative senescence,cell's incapability to divide, was first defined by Hayflick[10].Hayflick observed that after several numbers of cell divisions, cells in culture ceased to propagate.

ISSN:0971-1260
Vol-22-Issue-16-August-2019

Telomeres are known to play a crucial role in cellular replication, as with the loss of telomeres, cellsare unable to divide. There are two mechanisms employed by cells to maintain telomere and thereby immortality. First through enzyme telomerase, a ribonucleoprotein complex, which catalyzes the addition of nucleotides resulting in synthesizing de novo TTAGGG repeats and thus telomeres elongation. In most of the somatic cells, the levels of telomerase are very low or almost undetectable, however, high levels are detected in actively dividing cells and during embryonicdevelopment[11, 12). High levels of telomerase are also detected in cancerous cells required for their unlimited proliferation. The second mechanism of maintaining telomere by cells involves homologous recombination dependent mechanism of DNA replication called Alternative-Lengthening-of-Telomeres (ALT) pathway[13].4-15% of the cancerous cells in humans employ the ALT pathway to overcome the shortening of telomeres. The epithelial carcinomas are although rare in ALT but it is present in various types of tumors [14].

Components of telomerase

There are three components present in Telomerase complex-1)An enzyme Telomerase-Reverse-Transcriptase (TERT), a dyskerin protein and an RNA component (TER,also known as TR or TERC), (Table 1). The mutations occurring in genes coding for any of these i.e.- TERT, TER, or dyskerin; or telomerase-associated proteins can lead to compromised telomerase activity resulting in its low level and insufficient telomere maintenance. These changes become apparent in causing telomere syndromes like idiopathic pulmonary fibrosis (IPF) and dyskeratosiscongenita (DC) [15].

Telomeric replication

Telomericreplication follows the semi-conservative mode of DNA replication. Ergo, one telomere is generated by the synthesis of leading-strand and othersby the synthesis of lagging-strand. Although telomere of leading-strand is blunt-ended, the abstraction of RNA primer from the telomeric lagging-strand leads to loss of the small amount of the telomeric DNA during each DNA replication round. To neutralize the incessant DNA loss, telomerase is used for the lengthening of telomeric DNA[16].Telomerase helps in RNA-dependent elongation. TERC serving as RNA template consists of AAUCCC repeats with which the 3’ overhang of

ISSN:0971-1260
Vol-22-Issue-16-August-2019

chromosome binds and complement synthesis take place. After the elongation chromosome dissociates from the complex and the chromosome ends folding takes place (Figure 1).

Replicative senescence

Replicative-senescence is a cellular phase illustrated by changes in cell morphology and P-galactosidase activation at acidic-pH, and the previous work had highlighted that the cell's DNA damage response machinery is activated in senescent cells. The mortal cells in the human body display the shortening of telomeres with each consecutivecell division rounds while the stable lengths of telomeres are maintained by immortal cells. It is suggested from these observations that while approaching a critical telomeres length, replicative senescence occurs due to telomeres shortening. The constitutive hTERTexpression in human cells which led to increased telomerase maintains the length of telomere and allows these cells expressing telomeraseto bypass the senescence[11].

Telomere shortening leads to aging

In consideration of telomeres, each round of cell division led to its shortening imparting the mortality to normal untransformed-cells. The cancerous cells however, maintain the telomere length turning them immortal by explicit telomerase. The name ‘‘molecular clock’’ is hypothesized for telomeres for their influence on mammalian aging. This model got strong support from the analysis conducted on mice deficient in telomerase, in which the loss of premature viability was observed due to telomere shortening[17]. Another study relates stem cell mobilization to telomere shortening [18], where the stem cells start losing their functioning due to the abrasion of telomere underlying aging process. A recent study highlighted that the patients of Major depressive disorder (MDD) which is associated with accelerated aging showed shorter lengths of telomeres as compared to controls[19]. Even the patients of chronic-obstructive-pulmonary-disease were found to have shorter telomeres [20]. The mechanistic insights highlight that the dysfunctioning of telomerase is responsible for disrupting BMP/pSmad/P63 signaling, which impaired specification of epidermal stem cell and skin /hair folliclesdifferentiation resulting in accelerated skin aging [21].

ISSN:0971-1260
Vol-22-Issue-16-August-2019

The excessive telomere shortening is a common cause of premature-aging-syndromes.Additionally, excessive telomerase activity is associated with cancer. The activation of telomerase replenishesthe tumor with the capacity of infinite growth [22].Telomerase uninterrupted expression with the use oftransgenesis in adult mouse tissue had spotted a role of telomerase in obviating age and tissue fitness but at the disbursement of an increased chance for occurrence of cancer[23-25]. However, a study had shown that when canceling the enhanced incidence of cancer byaccumulating the tumors suppressor genes dosage (*p53*,*p16*,and *Arf*) in a mice cohort, with constitutive expression of transgenic telomerase results in improved lifespan extension by 43% compared to the corresponding wild mice [26].

Tackling telomere shortening with gene therapy

The use of non-integrative gene therapy using adeno-associated-virus (AAV) in adult and aged mice, results in delaying aging and reveal significant elongation of lifespan decreasing the cancer susceptibility. Even a single TERT treatment was sufficient in mice to emancipate the age-dependent degeneration and to hold the morphological aging of the mouse. During this study, a 24% increase in lifetimein a year-old mice and 13% lifespan extension in 2 years old animals was observed[27]. This study validates that using gene therapy to change telomerase expression, could be considered as a practical approach for extending lifespan without the increase in cancer incidence.

Old mice, treated with TERT had shown metabolic fitness, better skin and less bone loss, the traits associated with aging progression. Furthermore, mice with TERT treatment interestingly showed a propensity for memory improvement, coordination, and balance which are compromised in aged mice. Impressively, the non-occurrence of cancer in adult mice ensures the safety of this strategy. The reason may be because of non-integrative AAV vectors used, compared to the lost expression of TERT even in severely proliferating cancer cells. Another interpretation could be that AAV preferably targets post-mitotic cells of peripheral tissues which are assumed to be more recalcitrant to cancer than the highly proliferative tissues. With this technique re-introducing telomerase in models with high loss of telomerase, rescues the “aging-phenotype” with the absence of any rise in cancer. This perhaps could be of the reason that cells

ISSN:0971-1260
Vol-22-Issue-16-August-2019

deficient in telomerase are resistant to cancer initiation[28, 29]. Also, the study supports the significant role of telomerase in tissue rejuvenation of adult organisms and these are solid evidence that age reversal is possible to carry out. Novel therapeutic scheme affecting the expression of telomerase could reveal potential mechanisms upon the deterioration of tissue n.A chemical compound, TA-65 extracted from *Astragalusmembranaceus*, had been observed to trigger telomerase both*in vitro* and *in vivo*[30, 31].

Role of telomerase in cancer

The telomerase role has been significantly studied in cancer. Cancerous cells have high activation of telomerase so as to enable the infinite cell proliferation of tumor cells [32]. For preventing cellular senescence induction or apoptosis, the tumor progression is stimulated by telomerase by assuring sustenance of telomeres above a critically short length (Figure 2). There are various mechanisms that had been reported responsible for telomerase activation in cancer[33]. It had been observed that mice having intact p53 pathways are resistant to cancer development due to dearth of telomerase activity, while on the contrary forced TERT overexpression in distinct mouse models is associated with an escalated frequency of spontaneous tumors [34, 35]. The depletion of hTERT was found to exert growth inhibition of cancerous cells (K-562 cells) and also potentiates the anticancer activity of imatinib (tyrosine kinase inhibitor) leading to cell senescence[36]. *Exvivo* studies carried out on human tissues showed telomerase expression of about 90% in all malignant tumors, makes it a potential biomarker for various cancers. Also, epidemiological studies executed on the relationship between cancer occurrence and polymorphisms in the 5p15.33 locus, which expresses TERT, robustly suggest that variation of the TERT gene affects individual cancer susceptibility [37]. The concerted overexpression of various genes that are directly related to telomere function was found to activate Telomere-Maintainance-Mechanisms (TMM), which is a hallmark for most cancers [38].

Targeting telomerase for anticancer strategies

As it has been observed that telomerase activity is linked to tumor development and progression, the array of methods are being devised for targeting telomerase as a novel therapy against cancer.

ISSN:0971-1260
Vol-22-Issue-16-August-2019

Immunotherapy-It includes vaccination (active immunization) against the tumor-associated antigens (TAAs), so far the results of using this technique are disappointing. Most patients affected with different tumors and when vaccinated with telomerase peptides show immunological response.

Gene therapy-Involvement of TERT or TERC in gene therapy can be classified into two: Inhibiting TERT or TERC expression by targeting their RNAs.By using siRNAs (small interfering RNAs; double-stranded RNA molecules which regulatemRNA translation and degradation), antisense oligonucleotides(single-stranded RNA or DNA sequences showing complementarity to the target RNA), ribozymes(RNA enzymes having the capability to cleave specific mRNAs).

Utilizing TERT or TERC promoters for expression of exogenous vectors-With this approach TERT promoter can be exploited to deliver oncolytic viruses or 'suicide' genes selective to the malignant cells oncogenes [33].

G-quadruplex stabilization- It is an indirect strategy for the inhibition of telomerase expression by stabilizing G-quadruplexes (rich in guanine, has folded structure conformation). Stabilization is achieved by introducing a molecule that binds to G-quadruplex. It prevents hydroxyl group recognition at 3' end of single-stranded telomere[39].

Conclusion

To prevent chromosome shortening repeated sequence called telomeres are present. Telomeres are synthesized with the help oftelomerase, an enzyme that synthesizes tandem repeats of a particular sequence.Telomere shortening takes place with every cell division and with increasing age telomeres eventually shorten enough that the important function of the cells is not able to be carried out leading to senescence.A rare condition called dyskeratosiscongentia, leads to inactivation of telomerase. With gene therapy, telomere shortening can be prevented. TERT treatment carried out in old mice with gene therapy showed significant results. But the excessive increase in the telomeric activity can lead to cancer as cancerous cells show a high level of telomerase activity. There are different mechanisms that lead to the activation of telomerase in cancer cells.Gene therapy can also be used to decrease the level of telomerase in cancerous cells.

ISSN:0971-1260
Vol-22-Issue-16-August-2019

It can be concluded that gene therapy plays an important role in anti-aging, many technologies and methods have been used for fulfilling the dream of achieving cell immortality without triggering cancer, telomere gene therapy is one of the important aspects to diminish aging.

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Table1: Telomerase components

TER/TERC	Non-coding RNA, serves as a template.
TERT	Has conserved catalytic domains, helps in elongation of telomeric G-rich strand.
Dyskerin	It plays an active role in telomerase stabilization and maintenance

ISSN:0971-1260
Vol-22-Issue-16-August-2019

Figure 1:

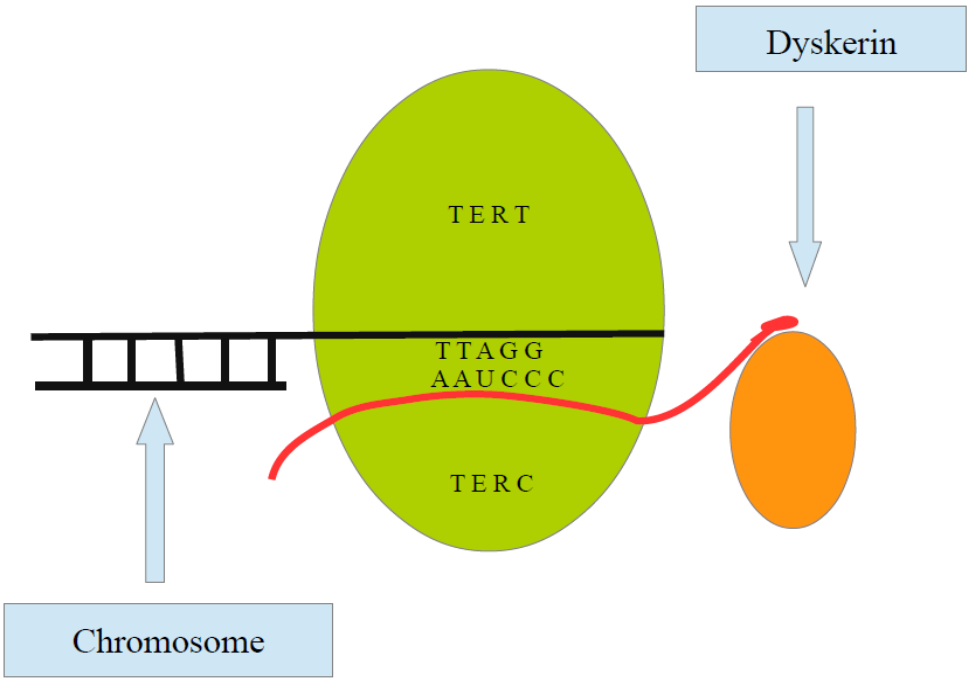

Fig.1. TERT with TERC and dyskerin helps in the chromosome end replication problem by synthesizing repeats of TTAGGG (in humans).

ISSN:0971-1260
Vol-22-Issue-16-August-2019

Figure 2:

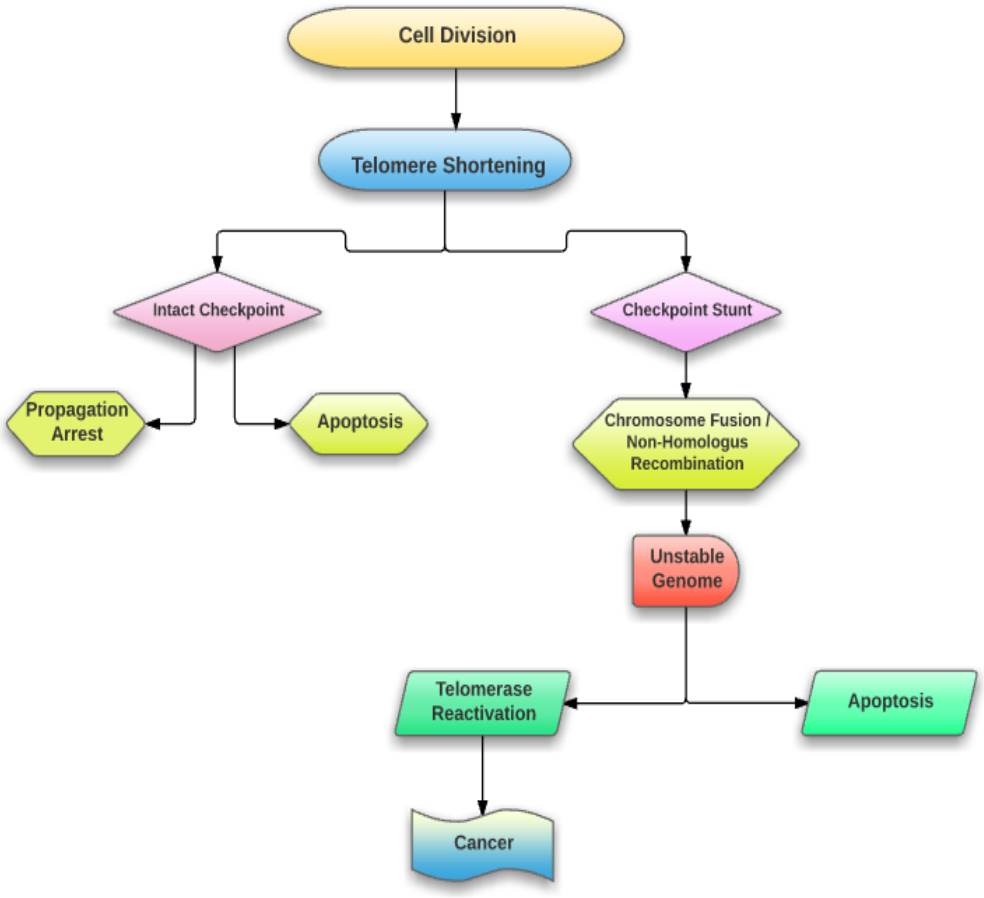

Figure 2. Role of telomerase in cancer:

Subsequent cell divisions can lead to telomere shortening which makes the cell enter intact checkpoint for cell propagation arrest or apoptosis, or enter checkpoint shunt where chromosome fusion can occur which can lead to genome instability and cause either apoptosis or telomerase reactivation which can cause uncontrolled cell growth i.e. cancer.