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Telomerase activity and telomere on stem progeny senescence

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ABSTRACT

The end of linear chromosomes is formed of a special nucleoprotein heterochromatin structure with repetitive TTAGGG sequences called telomere. Telomere length is regulated by a special enzyme called telomerase, a specific DNA polymerase that adds new telomeric sequences to the chromosome ends. Telomerase consists of two parts; the central protein part and the accessory part which is a RNA component transported by the central part. Regulation of telomere length by this enzyme is a multi-stage process. Telomere length elongation is strongly influenced by the level of telomerase and has a strong correlation with the activity of telomerase enzyme. Human Telomerase Reverse Transcriptase (hTERT) gene expression plays an important role in maintaining telomere length and high proliferative property of cells. Except a low activity of telomerase enzyme in hematopoietic and few types of stem cells, most of somatic cells didn't showed telomerase activity. Moreover, cytokines are secretory proteins that control many aspects of hematopoiesis, especially immune responses and inflammation. Also, the induction of hTERT gene expression by cytokines is organized through the PI3K/AKT and NF/kB signaling pathways. In this review we have tried to talk about effects of immune cell cytokines on telomerase expression/telomere length and the induction of telomerase expression by cytokines.

1. History of telomere study

The telomere was described, for the first time, as a protective structure at the end of the chromosomes in 1930 by Hermann J. Muller and Barbara McClintock to prevent the end-to-end fusion that may occur in the chromosomes and lead to cell death [1]. In 1960, Hayflick described a biological view of aging. He concluded that human diploid cells indicating a limitation in proliferation and Hayflick's limit is considered to be the maximum number of cell divisions [2,3]. In 1970, James D. Watson defined the End Replication Problem during DNA replication. Indeed DNA polymerase couldn't completely replicate the end of the 5' chromosome [4]. Then, in 1973, Olovnikov linked the cell senescence with the end replication problem in the "Theory of Marginotomy". In this theory, telomere shortening was considered as an internal hourly mechanism of aging. later in 1980 this theory had approved and they observed the shortening of telomere length during *in vitro* cell proliferation conditions [5]. Elizabeth Blackburn found that the molecular structure of Tetrahymena pyriformis telomeres has a rich of guanine (G) and thymine (T) nucleotide [6] and in 1984 Elizabeth Blackburn et al. isolated an enzyme that called telomerase. They proved, this enzyme is responsible for telomere length regulation and later reported that the presence of telomerase activity in human cancer cells have led to the immortality of these cells [7]. This is true that telomerase enzyme is not alone in telomere length regulation and another mechanism such as alternative telomere length has an important [8] and telomere and telomerase have been studied extensively because of its important role in physiologic aging, cancer pathology and premature aging syndrome.

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2. Telomere structure

The ends of linear chromosomes have been formed with a special heterochromatin structure that called telomere and this structure protect the end of the chromosome from degradation and act as DNA repair mechanism, therefore, the telomere is a structure that is essential for the stability of the chromosome [9,10]. The mammalian telomeres consist of several kilobases, for example, telomere length in humans is 10–15 kb and 25–50 kb in mice that consisting of repetitive TTAGGG sequences [1,11,12]. This specific rich region of guanine structure is characterized by the presence of 30–400 nucleotides at the end of the 3′ chromosome [13,14]. Telomeres are linked to specific structures that called Shelterin, which is essential for telomere length regulation, telomere protection from the DNA damage response system and keep the chromosome end of the DNA repair machine [15]. The Shelterin Complex consists of six central proteins; TRF1 (telomeric repeat binding factor 1), TRF2 (telomeric repeat binding factor 2), TIN2 (TRF1-interacting protein 2), POT1 (protection of telomeres protein 1), TPP1 (TIN2- and POT1-interacting protein) and RAP1 (repressor/activator protein 1) [16–19]. Homodimers of TRF1 and TRF2 bind to double-strand telomeric DNA in one side and TIN2 on the other side which form Shelterin core complex [20]. Other proteins such POT1 binds to single strand telomeric DNA sequence [21,22]. TIN2 binds to TRF1 and TRF2 and acts as a bridge between Shelterin components [23–26]. TPP1 binds to TIN2 and POT1 that is essential for binding and calling telomerase to the ends of chromosomes [27,28]. finally, RAP1 align with TRF2 to binds the telomere and in addition, this factor binds to non-telomeric regions and plays a role in processes such as gene expression regulation [17,29,30] (Fig. 1).

3. Telomerase holoenzyme complex

Telomerase enzyme is a specific DNA polymerase enzyme that adds new telomeric sequences to the chromosome ends [4,7,31–34]. This enzyme consists of two parts, the central part is TERT (Telomerase Reverse Transcriptase) protein and the accessory part is TERC (Telomerase RNA component) an RNA component that is transported by the central part and both of these parts provide a pattern for the synthesis of telomeric sequences [35–37]. Telomerase enzymes seem to be assembled in Cajal bodies, where the protein component (TERT) and its RNA component (TERC) get together to form the enzymatic ribonucleoprotein complex [38,39]. Another accessory component of this protein enzyme is Dyskerin, which forms a central complex with three other small proteins, NHP2, NOP10 and GAR1. Dyskerin is essential for the function of the telomerase [40,41]. Cajal body telomerase-1 (TCAB1) is another protein that binds to the enzyme and adjusts its transit [42]. In vertebrates, the RNA that transmitted by telomerase enzyme has about 382–559 nucleotides [43]. The number of RNA nucleotides transmitted by the human telomerase enzyme is about 451 nucleotides and its nucleotide sequence composed of 5'-CUAACCCU AAC-3' sequences, which is responsible for coding the telomere sequences [44] (Fig. 2).

4. Telomere length regulation

Telomere length in humans is regulated by telomerase enzyme and the telomerase enzyme by attaching to the end of the guanine-rich area changed the telomere length [45]. during embryonic development, this enzyme has highly expressed, but its expression is suppressed in most somatic cells several weeks after birth, however, high levels of telomerase expression are observed in cells with high generative potentials, such as stem cells, lymphocytes, germ cells and cancer cells [46] (Fig. 3). The DNA polymerase-1 is a one-way enzyme that can't replicate all of the bases at the 3' end of chromosome, consequently in each cycle of the replication process, one of the chromosome ends can't be fully synthesized and part of its structure disappears and if cells can't solve this replication problem, they are not able pass on their genetic content to the next generation [47,48] (Fig. 4).

The telomere length regulation by the telomerase enzyme is a multi-stage process. In the first step, nucleotides present at the end of the 3' end DNA telomeres form a hybrid with the RNA transported by the telomerase enzyme. In the second step, the gap at the end of leading strand is filled and finally, the newly synthesized strand moves in the direction of 5', allowing the creation of a new gap and this cycle is repeated [25,47]. Telomere length regulation is done throughout the cell cycle and telomerase adds telomere sequences at S stage of the cell cycle [49] (Fig. 5).

5. Telomere length and cell senescence

As Hayflick et al. [50] showed, the cells stopped their divisions after several passages and these process are referred to "Replicative Senescence". This condition causes a lot of alteration such as morphology, gene and protein expression changes in the cells [51]. There are several important factors to suppress proliferation of the cells, most notably, telomere length shortening, DNA damage and tumor suppressor signaling [52,53]. Although telomere shortening may not be the primary factor in acute cellular senescence but the reduction in telomere length and oxidative stress together can increase the probability of cell entering to the senescence condition [52]. Telomere length shortening in

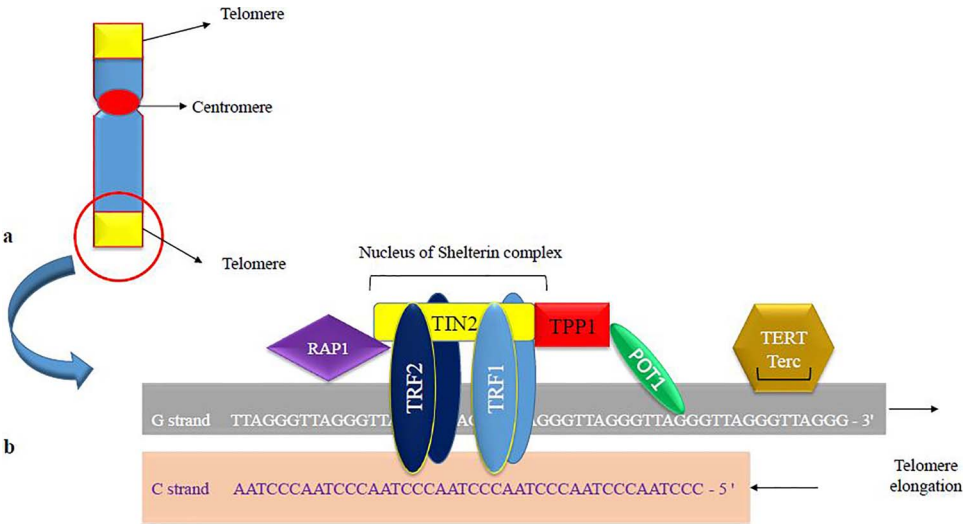

Fig. 1. Human telomere structure and telomerase recruitment. (a) linear chromosome that shows the position of telomere at the end of the chromosome (b) Telomeric DNA is bound by the sheltering complex consisting of six proteins: TRF1, TRF2, POT1, TIN2, TPP1 and RAP1. TRF1 and TRF2 bind to double-stranded telomeric DNA, TIN2 forms a bridge with TRF1 and TRF2 and TPP1. POT1 bind to single-stranded telomeric DNA. On the other hand, the figure shows telomerase recruitment to the chromosome end for telomere length regulation.