

Telomere and telomerase in hematological malignancies

Ajlan Tükün¹, Güvem Gümüş Akay², Nüket Yürür Kutlay¹

¹Department of Medical Genetics, University of Ankara, School of Medicine, Ankara, Turkey

✉ tukun@medicine.ankara.edu.tr

²Department of Medical Biology, University of Ankara, School of Medicine, Ankara, Turkey

INTRODUCTION

In recent years, there has been a rapid increase in the number of researches on telomerase, since the definition of telomeres as the mitotic clock of the cell. Researchers are interested in the possible effects of telomeres and telomerase in carcinogenesis due to the relation between the telomeres and telomerase and the cell cycle. Telomere length alterations have been observed in many types of cancer and, more importantly, telomerase activation is believed to be crucial in most immortal and cancer cells ^[1,2]. Because telomerase reactivation is known to provide unlimited proliferation capability to the malignant cell, anti-telomerase therapy using special agents targeting the telomere or telomerase has become an attractive area for cancer treatment ^[3]. However, clinicopathologic significance of telomerase in cancer and the details of the mechanisms regulating its activity remain to be clarified.

Human telomere

Telomeres are the special genetic elements which are protein-associated guanine-rich repeat sequences located at the ends of linear chromosomes and which possess important biological functions. They protect the end of chromosomes against end-to-end fusion, recombination, terminal DNA degradation, and are perceived as broken DNA. Telomeres help to preserve chro-

somal organization in the nucleus and play a role in gene regulation. Telomeric DNA also serves as a molecular mitotic clock and restricts the proliferation capacities of cells ^[1,2].

In humans, the telomere is made up of tandem 5'-TTAGGG-3' repeats, and the length of telomeric DNA ranges between 1 and 12 kb. Telomeric DNA has a unique structure, different from Watson-Crick, and serves as a binding site for a number of specific DNA-binding proteins ^[3,4]. Because DNA polymerase cannot initiate synthesis from the end of lagging strand DNA, telomere length 50-200 bps shortens with each cell division. This incomplete replication is known as "end replication problem" ^[1,2].

Somatic cells divide a certain number of times in humans, and this number is known as Hayflick limit. At least one critically shortened telomere causes growth arrest at this limit. This permanent mitotic arrest is referred to as replicative senescence (mortality stage 1=M1). Cells escape replicative senescence if one of the cycle checkpoint genes such as p53 is suppressed or inactivated and mitosis continues until a second crisis, referred to as mortality stage 2 (M2). During divisions between M1 and M2, telomeres continue to shorten. These critically short and dysfunctional telomeres trigger cell death. Some of these

cells gain an ability to maintain telomere length and they can escape mortality and survive. This phenomenon is known as cellular immortalization [5]. Because stem cells maintain telomere length throughout extensive mitosis, they have an enhanced dividing capacity. In most cases this unlimited/enhanced proliferative capacity is achieved by activation of telomerase.

Human telomerase

Telomerase was first discovered in *Tetrahymena thermophila* by Blackburn et al. in 1985 [6]. It is a specialized cellular reverse transcriptase and provides unrestricted proliferative potential to the cell. This enzyme elongates the linear DNA molecules by addition of G-rich repeats to the end of telomere using its own RNA component as a template [6]. Telomerase activity has been found in most tumor cells and immortalized cells but not in normal human somatic cells [1,2].

Telomerase is composed of three essential components: 1. catalytic protein (hTERT= human telomerase reverse transcriptase); 2. the functional RNA component (hTR= human telomeric RNA); and 3. TEP1 (telomerase-associated protein 1). The genes coding these proteins were mapped to 14q11.2, 5p15.33, and 3q26, respectively [5,7].

The Catalytic Subunit (hTERT) of Telomerase requires other telomerase-associated proteins for biological function. Reverse transcriptase motifs are at the C-terminal half of the protein and it has a telomerase-specific region just N-terminal to the reverse transcriptase motifs [2,5].

The RNA Subunit (hTR) of Telomerase provides the template for telomeric repeat synthesis. In humans, the length of mature transcript of *hTR* gene is 451 nucleotides. The template for reverse transcription lies between nucleotides 46 and 53. hTR interactions with many RNA binding proteins, such as hGAR, dyskerin, hNOP10, hNHP2, hStau, L22, hnRNP C1/C1, La, and hTERT, are known. A region between nucleotides 10 to 159 appears to be the minimal-required sequence for enzyme activity [5].

Telomerase-associated protein 1 (TAP1) consists of 2,629 amino acids. TEP1 is constitutionally expressed in most tissues without any de-

tectable telomerase activity, though it was found to interact with both the RNA and catalytic components of telomerase. The function of TEP1 in the telomerase complex is still unknown [2,5].

Regulation of human telomerase activity

The regulation of telomere length and telomerase activity is a complex and dynamic process that is closely related to cell cycle regulation. Elongation of telomeres by telomerase is a multi-step process, and regulation of this process occurs at various levels of each enzyme component which are listed below [2,5].

- hTR:
 - transcription
 - mRNA splicing
 - maturation
 - processing
 - accumulation
- hTERT:
 - transcription
 - mRNA splicing
 - maturation
 - nuclear transport
 - post-translational modifications
- assembly of active telomerase
- recognition of telomeres by telomerase
- function of the telomerase on telomeres

The catalytic hTERT is the limiting factor for telomerase activity among the components of human telomerase. In most cases, hTERT is transcriptionally repressed in normal cells and is reactivated or upregulated in cancer or immortal cells. The transcriptional regulation of hTERT expression appears to be the primary and rate-limiting step in the activation of telomerase [2].

The hTERT gene is present as a single copy on chromosome band 5p15.33. The hTERT gene consists of 16 exons and 15 introns and extends over 40 kb. The hTERT gene is alternatively spliced, and several transcripts have been detected in human cells. All of the various transcripts are expressed during human development, but only the full-length hTERT transcript is associated with telomerase activity [5]. hTERT amplification activates telomerase in at least certain types of cancers [8]. Upregulation of hTERT expression

without amplification is also reported to contribute to telomerase reactivation in tumors. Several transcription factors such as c-Myc, Sp1, human Papillomavirus 16 E6, and steroid hormones are known to regulate expression of hTERT gene positively [5]. On the other hand, Mad1, p53, pRB and E2F, WT1, myeloid cell-specific zinc finger protein 2, IFN- α , and TGF- β are negative regulators of hTERT transcription [5].

The transcriptional regulation of hTERT by transcription factors is the most prominent layer in controlling telomerase activity. However, methylation of CpG islands, histone modifications, and posttranslational modifications of the hTERT protein such as phosphorylation might provide additional steps for regulation of telomerase activity. Recent studies have shown that enhancement of telomerase activity follows phosphorylation of hTERT by c-Abl, protein kinase B, and protein kinase C [5].

The regulation of telomerase access to telomeres in human cells plays an important role in telomerase activity. Recent studies show that telomere-associated proteins can regulate telomerase accessibility either positively or negatively [5]. TRF1 (TTAGGG repeat binding factors 1), TIN-2, and tankyrase inhibit telomerase access to telomeres, while TRF2 (TTAGGG repeat binding factors 2) is a positive regulator [1,2].

Telomerase activity in normal human cells

Telomerase activity is strictly regulated during development. In adults, only some tissues maintain this activity [1,2,9]. Because most normal human somatic cells are telomerase-negative, they have a limited replicative capacity. These cells withdraw from mitosis permanently when they reach replicative limit. With the exception of adult tissues, certain stem or committed progenitor cells express telomerase at low or transient levels. As expected, the germ-line cells in reproductive tissues, which is an immortal line, are also telomerase-positive in adults [5,9]. On the other hand, telomerase activity has been detected in approximately 90% of tumor samples [2,9]. With regard to telomere dynamics, there are two essential differences between normal and tumor cells. First, immortal tumor cells and most primary tumors express telomerase, whereas normal somatic cells and tissues lack this activity during development.

The second difference relates to telomere length. Tumor cells typically have relatively short telomeres, whereas normal cells have long and slowly shortening telomeres [10].

Telomerase reactivation can result in carcinogenesis/tumorigenesis if there is a causal mutation in at least one of several oncogenes [5]. The specific role of telomerase in tumorigenic transformation is provision of an unlimited dividing capacity. Furthermore, inhibition of telomerase in immortal cells leads to telomere shortening and apoptotic cell death [11,12]. All these observations indicate that telomerase reactivation is a requirement -if not cause- for unlimited proliferation, which is an essential characteristic of cancer cells [5].

Telomere and telomerase activity in hematological malignancies

Hematopoietic stem cells (HSCs) and differentiated progeny of HSCs have readily proliferative potential. Although telomerase activity is detected in these cells, telomeric shortening occurs during their replicative aging [13-15]. Despite existence of telomerase activity, telomere length progressively becomes shorter for each cell division in normal hematopoietic cells. It has been shown that the maintenance of telomeric length in HSCs depends not only on telomerase but also telomere binding proteins, the proliferative capacity of the cells, and some other determinants [16,17]. Telomerase activity has been reported to be upregulated in response to cytokine-induced proliferation and cell cycle activation in primitive HSCs, while progressive downregulation is seen in more mature clones [18-20].

Telomere length and telomerase expression alterations have been reported in various kinds of hematological malignancies and some of them appear to have prognostic significance [13]. High telomerase activity and shorter telomeres are associated with poor prognosis in both acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML) [21-23]. Elevated telomerase levels and short telomeres were reported in most patients with acute leukemia [15, 21-30]. Short telomere length with increased telomerase activity was observed in diagnosis stage of AML [21-23,30]. Telomerase activity decreases with remission and increases in relapse state in AML [24,26].

Shortening of the telomere length and increased varying degrees of telomerase activity are seen in chronic lymphocytic leukemia (CLL) patients, and telomerase activity increases during the progression of disease [31,32]. Telomerase activity is less in chronic stage with short telomere length in chronic myeloid leukemia (CML) [21-23,26,30,33-36]. Moderately increased telomerase activity in blastic crisis has been known. The telomerase reactivation has been explained as not only being triggered by shorter telomere length but also by increased blastic cell ratio [21-23]. It has been reported that immature cells ratio was not sufficient to explain telomerase reactivation because the increased telomerase activity was more than increased blastic cells [25]. It is suggested that other mechanisms, such as tyrosine kinase activity, are involved in telomerase regulation in CML [37]. Telomerase activity is negatively correlated with survival in CML patients [38]. Because telomere length is significantly reduced in blastic crisis while it appears to be normal in chronic phase, it may serve as a prognostic factor in CML [39, 40].

Telomere length and telomerase activity alterations have also been noted in myeloproliferative disorders other than CML. Regarding the previously published data, it has been suggested that telomere length for myeloproliferative disease, and telomerase activity for polycythemia vera and essential thrombocytosis can be used as prognostic markers [41,42].

Telomere length alterations are not common in myelodysplastic syndrome (MDS), but accelerated telomere shortening is associated with leukemic transformation. Furthermore, positive correlation between poor prognosis and hTERT expression in MDS patients was reported [22,43]. In contrast, telomerase expression shows heterogeneity among multiple myeloma (MM) patients, while short telomeres are known to be associated with poor prognosis [44].

Antitelomerase agents

Anti-telomerase agents that target the telomere or telomerase have become popular for

treatment, largely because of the specificity of telomerase activity in tumor cells. This is currently an attractive area for investigation and several classes of potential agents have been developed [45-52].

Many anti-telomerase agents have been defined. Antisense agents, agents targeting the G-tetrad structure, and ribozymes are the main groups. In addition, many agents such as dideoxyguanosine, cisplatin, dimethyl sulfoxide (DMSO), protein kinase C inhibitors, rubromycins and their analogs have been shown to inhibit telomerase in some cancer cells and in some immortal cell lines [45-52].

In antisense oligonucleotides, the target is the RNA component of the telomerase. It is thought that the double strand formation between antisense oligonucleotide and RNA template of the telomerase either represses the biologic function or induces degradation of enzyme [47,48,50-52].

On the other hand, the target of G-tetrad stabilizer agents, such as TMPyP4, is the telomeric repeats. They are thought to inhibit the telomerase binding to the telomere by stabilizing the G-tetrad structure of ends [45, 47, 51-53].

Interestingly, recent studies showed that a tyrosine kinase inhibitor, imatinib, decreases telomerase activity. This effect probably depends on post-translational modification of telomerase subunits by specific tyrosine kinase activity [54].

CONCLUSIONS

Recent research has focused on the telomere and its role in normal cell cycle, proliferative senescence, and carcinogenesis. The telomere and telomerase interactions appear to be an essential determinant for proliferative capacities of normal, immortal and tumor cells. It has been known that telomerase activity provides the ability of proliferation to the malignant cell; thus, targeting of tumor cells by inhibiting telomerase may be an effective therapy. Experimental data support this hypothesis.

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