

# Chapter 2

## Telomerase: Basic and Clinical Approaches

S. Saied Hosseini-Asl

**Abstract** Telomerase enzyme is responsible for compensating telomere shortening occurred during cell proliferation and found to be reactivated in about 90 % of tumor cells. Telomerase activation could be regulated in two manners, including pretranslation and posttranslation. Some proteins including Akt kinase, PKC, and IP6 could induce telomerase activity. However, it may be suppressed by another group including c-Abl, and PP2A. In this chapter, some fundamental elements were highlighted. Furthermore, within a clinical based data, telomerase activity and expression of its RNA component; expression of hTR and hTERT in human primary breast cancer patients were discussed.

**Keywords** Telomerase · Regulation · hTERT · hTR · Breast cancer

### 2.1 Introduction

Telomeres are nucleoprotein structures found in the end of eukaryotic linear chromosomes. Telomere DNA ranges in length 100–300 bp in ciliates and yeasts, up to 100 kb in mice, and 5–15 kb in humans.

The short repeating duplex sequence terminates in a short G-rich single strand overhang (De Lange 2006). TRF2 facilitates invasion of the G-overhang to the duplex at an upstream position and creates a telomeric loop (T-loop) (Sealey et al. 2010).

In human, telomere is a repeating sequence of TAAGGG hexanucleotide located at the ends of chromosomes and has many important roles on chromosome integrity and cell proliferation. According to “Hayflick limit”, telomere limits the cell proliferation ability with every cell division. About 85 % of cancer cells revealing TMM

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(Telomere length maintenance mechanism), demonstrate the chromosome ends renewal mechanism involving telomerase (Henson and Akbar 2010).

## 2.2 Telomerase Structure

Telomerase is a ribonucleoprotein complex which composed of catalytic protein subunit (hTERT) and its RNA component (hTR, hTERC) (Greider and Blackburn 1989; Lingner and Cech 1996; Nakamura et al. 1997; Meyerson et al. 1997).

Treatment with RNase inactivation of telomerase could be achieved, therefore, an RNA molecule could provide the template for nucleotide addition. The gene encoding RNA was cloned in 1989, and the sequence of CAACCCCAA (complementary to the *Tetrahymena* telomeric repeat) could emphasize on this mechanism (Greider and Blackburn 1989). The RNA component of telomerase (TER, TR) has been cloned from different organisms and shows great variability considering length, sequence, and structure (Theimer and Feigon 2006). In addition, all TERs have a short template sequence complementary to the telomeric repeat (Osterhage and Friedman 2009).

Joachim Lingner and Thomas Cech identified two proteins (p123 and p43) that co-purified with the ciliate telomerase RNA (Lingner and Cech 1996). At nearly the same time, a yeast genetic screen performed by Victoria Lundblad's group yielded several genes that caused an EST (ever-shorter telomere) phenotype when mutated. Cloning of *EST2* and p123 revealed homologous proteins with motifs similar to known RTs2 (Lingner et al. 1997). Interestingly, in 1997, the catalytic subunit was identified in humans (hTERT) (Nakamura et al. 1997).

The RNA component of telomerase acts as the template for the catalytic subunit in order to telomeric repeat synthesis. hTR (human TER) is transcribed by RNA polymerase II and its mature transcript consists of 451 nucleotides (Feng et al. 1995). The hTR gene was cloned and localized to chromosome 3q26.3 in 1998 (Soder et al. 1997; Zhao et al. 1998). The template for hTERT activity lies in nucleotides 46–53. Although there is a variation of hTR RNA sequences among telomerase RNAs, there is a remarkably conserved secondary structure from ciliates to vertebrates. This indicates an essential role for the structure in enzyme function (Chen et al. 2000). hTR is a single-copy gene that lacks poly A and does not contain any introns, so RT-PCR for hTR gene is considered to be prone to errors. DNA contamination of RNA extractions could be amplified by PCR and therefore could give rise to a false positive result for hTR transcription affecting the correlation between hTR expression and telomerase activity (Januskiewicz et al. 2003; Kameshima et al. 2001).

The N-terminus of human TERT (hTEN) exhibits a length- and sequence dependent affinity for telomeric DNA in an electrophoretic mobility shift assay (EMSA). Human TEN also interacted with, and restored catalytic potential to an hTERT truncation mutant lacking the N-terminus in Trans. It was identified that point mutations in hTEN strongly impaired telomerase activity and the ability of telomerase to immortalize cells in culture, but did not impair the interaction with telomeric DNA or the hTERT C-terminus (Sealey et al. 2010).

## 2.3 Telomerase Regulation

### 2.3.1 *Pretranslational Regulation*

Transcriptional regulation of hTERT has an important role in the control of telomerase activity. Alternative splicing is suggested to play a crucial role in hTERT regulation. So far, ten different splice variants of hTERT have been identified (Kilian et al. 1997; Ulaner et al. 1998; Hisatom et al. 2003). Among them, two variants have been widely studied:  $\alpha^-$ , which contains deletion of 36 bp from exon 6 within RT motif A (Kilian et al. 1997; Wick et al. 1999), and  $\beta^-$ , deletion of 182 bp in exons 7 and 8 (Nakamura et al. 1997; Lingner et al. 1997).

The  $\alpha^-/\beta^+$  variant acts as a dominant-negative inhibitor of telomerase activity (Yi et al. 2000; Colgin et al. 2000; Wojtyla et al. 2011).

### 2.3.2 *Posttranscriptional Regulation*

Another way to regulate the telomerase activity is through the posttranscriptional stage. It can occur by phosphorylation of hTERT catalytic subunit at serine/threonine or tyrosine residues. It may affect the telomerase structure, localization and enzyme activity (Cong et al. 2002).

### 2.3.3 *Telomerase Activators*

#### 2.3.3.1 Akt kinase

The Akt kinase (Protein kinase B) induces phosphorylation of hTERT on its serine/threonine residues and so, enhances telomerase activity. Therefore, it has crucial roles on protecting cells from apoptosis and enhancing the capacity of cell proliferation. In melanoma cells, this modification is carried out on serine residue at position 824 (Wojtyla et al. 2011).

#### 2.3.3.2 Protein kinase C and IP6

In breast cancer, PKCa phosphorylates hTERT and hTEP1. Also, IP6 could repress the telomerase activity via deactivation of Akt and PKCa in cells derived from prostate cancer. Binding the hTERT to its nuclear translocator requires to hTERT phosphorylation. Therefore, IP6 may decrease the level of proteins involved in telomerase transport to the nucleus (Li et al. 1998; Jagadeesh and Banerjee 2006; Wojtyla et al. 2011).

**Table 2.1** Human telomerase regulation factors. (Adapted from Wojtla et al. 2011)

Factor	Up/down regulation	Factor	Up/down regulation
Akt	Up	Mistletoe lectin <sup>a</sup>	Down
Estrogen <sup>a</sup>	Up	IP6 <sup>a</sup>	Down
IGF1 <sup>a</sup>	Up	Oxygen <sup>a</sup>	Down
IL-6 <sup>a</sup>	Up	14-3-3 Signaling proteins	Up
IL-2 <sup>a</sup>	Up	NF- $\kappa$ Bp65	Up
PKC	Up	Shp-2	Up
Ionizing radiation <sup>a</sup>	Up	Nucleolin	Up
UV	Up	H <sub>2</sub> O <sub>2</sub> <sup>a</sup>	Up
Dimethyl sulfoxide <sup>a</sup>	UP	Ran (GTPase) <sup>a</sup>	Down
Abl	Down	hPinX1	Down
PP2A	Down	hnRNPA1	Up
Imatinib mesylate <sup>a</sup>	Down	TCAB1	Up
PTEN <sup>a</sup>	Down	POT1	Up
Gambogic acid <sup>a</sup>	Down	TPP1	Up
Retinoic acid <sup>a</sup>	Down	Ku	Down
TRF1, TRF2	Down	hRap1 <sup>a</sup>	Down

<sup>a</sup> Indirect influence on telomerase activity

### 2.3.4 Telomerase Repressors

#### 2.3.4.1 c-Abl

It was found that specific phosphorylation site at TERT is present at proline rich region (Cong et al. 2002). The c-Abl tyrosine kinase phosphorylates hTERT at specific tyrosine residue and decreases the telomerase activity. Moreover, overexpression of c-Abl causes cell cycle arrest and so, inhibits cell growth (Sawyers et al. 1994). Exposure of cells to ionizing radiation led to a significant increase in TERT phosphorylation by c-Abl. It was also demonstrated that c-Abl phosphorylated TERT leading to inhibition of telomerase activity and decrease in telomere length (Kharbanda et al. 2000) suggesting a direct association between c-Abl and TERT. A crosstalk between Bcr- Abl tyrosine kinase, protein kinase C and telomerase was also suggested as a potential reason for resistance to Glivec in chronic myelogenous leukemia (Bakalova et al. 2003; Wojtla et al. 2011).

#### 2.3.4.2 PP2A

Protein phosphatase 2A (PP2A), is contributed to the negative control of cell growth and division. In addition, its inhibitory function on telomerase activity in human breast cancer- PMC42 cells was reported. PP2A remarkably abolished telomerase activity in nucleus while the other main cellular protein phosphatases 1 and 2B were not applied (Li et al. 1997). When active, PP2A dephosphorylates TERT protein on ser and/or thr residue (Avci et al. 2007; Wojtla et al. 2011) (Table 2.1).

## **2.4 Telomerase Activity and Expression of Its RNA Component (hTR) in Breast Cancer Patients (Adapted from Hosseini-Asl et al. 2006a)**

### **2.4.1 Methods**

The standard guidelines including the ethical approval and consent form were considered. Fifteen tumour samples from patients with primary invasive breast cancer treated surgically during 2004–2005 at Day General Hospital were investigated. Breast tissues were collected and stored at  $-70^{\circ}\text{C}$ . Telomerase activity was analyzed using standard TRAP assay, as previously described (Bachand et al. 2001).

In order to detect the false-negative samples containing PCR inhibitors, such as CHAPS, an internal control was studied. Negative control samples avoid false-positive results (characterized by variation in band intensity). They were produced by heating the protein extract (to remove the enzyme activity) or using any telomerase negative sample.

Total RNA was extracted from samples. One microgram of the extracted RNA was used to create cDNA. In order to avoid the probable DNA contamination (Remained through RNA extraction), a solution containing the same materials used for cDNA synthesis excluding reverse transcriptase enzyme (negative control 1) was prepared. Such product includes DNA only, but characterized by an alternative concentration, comarible with the cDNA products.

DNase treatment was the other strategy for avoiding DNA contamination. Approximately half of DNase treated RNA sample could be used to create cDNA. The negative control group 2 (containing all of the materials excluding the reverse transcriptase enzyme) was prepared for validating the accuracy of DNase treatment process. The cDNA, DNase treated cDNA and two control groups were amplified by RT-PCR. GAPDH and PGM1 were amplified as housekeeping genes.

The statistical analysis of the data was carried out by Pearson, Chi-square and Fisher Exact tests, using the SPSS software package. The significance levels were considered as results with p value less than 0.05.

### **2.4.2 Results**

Telomerase activity was determined in 36 out of 50 (72 %) samples. The hTR gene expression was observed in 64 % (32 out of 50) of samples of which 93.7 % (30 out of) samples revealed telomerase activity. In six samples without hTR expression, telomerase activity was detected (Table 2.2). There was a significant association between telomerase activity and hTR expression ( $p < 0.001$ ).

**Table 2.2** The frequency of telomerase activity between either sample with hTR expression or without expression. (Adapted from Hosseini-Asl et al. 2006a)

Telomerase activity	hTR expression		
	Positive	Negative	Total
Positive	60 % (30) <sup>a</sup>	12 % (6)	72 % (36)
Negative	4 % (2)	24 % (12)	28 % (14)
Total	64 % (32)	36 % (18)	50

<sup>a</sup> The outcomes presented as percentage (number);  $p < 0.001$

Seventy-two percent (36 out of 50) of RNA extracts revealed DNA contamination. In total, 36 samples (with DNA contamination) demonstrated hTR expression, whereas after DNase treatment, 17 samples did not show it.

### 2.4.3 Discussion

The GAPDH pseudogene could be amplified with GAPDH cDNA primers which seems to be as same as the current GAPDH gene cDNA. Usually, RNA is contaminated with DNA and could create a positive result that arises from the presence of a pseudogene in the sample. The detected subject was not considered in most previous studies in those GAPDH housekeeping was used as a positive control to assess the accuracy of cDNA synthesis. In fact, the positive result of GAPDH-PCR may be due to the amplification of the pseudogene which was as the result of DNA contamination, but not related to the cDNA template. If GAPDH primers are used for DNA samples, then positive results could be occurred. Therefore, this characteristic of GAPDH was used to ensure the accuracy of DNase treatment procedures.

Most investigators have not paid any attention to intronless domain of hTR gene (Kuniyasu et al. 1997; Kyo et al. 1999; Liu et al. 2001; Nowak et al. 2003; Onada et al. 2004; Rohde et al. 2000; Hu et al. 2002; Ulaner et al. 2000; Wang et al. 2001; Wu et al. 1999; Yan et al. 2001). Therefore, the reported results were representative of a high expression of this gene and hence no association were detected considering hTR expression and telomerase activity (Table 2.3).

In our study, the accuracy of the procedures were checked with GAPDH and PGM1 housekeeping genes. In the case of having a positive result for negative control groups, or a negative result for DNase treated cDNAs, the DNase treatment was repeated.

A false estimation of our result, through a procedure without DNase treatment, would be expected, i.e., instead of observing 98 % (49 out of 50) with hTR expression, the outcome could be decreased to 64 %.

**Table 2.3** The results of some previous studies on hTR expression using RT-PCR method without doing the DNase treatment. (Adapted from Hosseini-Asl et al. 2006a)

Detect hTR expression (%)	Sample type	Reference
93.6	Skin neoplasm	Hu et al. 2002
100	Stomach cancer	Kunuyasu et al. 1997
100	Normal human Endometrial and endometrial cancer	Kyo et al. 1999
100	Prostate cancer	Liu et al. 2001
100	Colonic cancer	Nowak et al. 2003
100	Parathyroid lesions	Onada et al. 2004
100	Renal cell carcinoma	Rohde et al. 2000
100	Ovarian adenocarcinoma	Ulaner et al. 2000
90.7	Nasopharyngeal carcinoma	Wang et al. 2001
93.3	Skin tumors	Wu et al. 1999
100 <sup>a</sup>	Colorectal carcinoma	Yan et al. 2001 <sup>a</sup>

<sup>a</sup> DNase treatment was performed, but, the accuracy of DNase digestion and probable effect of remaining DNase activity on the genes PCR had not assayed

**Table 2.4** hTR and hTERT expression in 46 malignant samples. (Adapted from Hosseini-Asl et al. 2006b)

	hTR expression	hTERT expression
Positive	31	38
Negative	15	8

## 2.5 Expression of hTR and hTERT in Human Breast Cancer Patients: A Clinical Based Data (Adapted from Hosseini-Asl et al. 2006b)

### 2.5.1 Results

The methods are described earlier in Sect. 2.4.1. The telomerase associated genes expression were detected in 38 (82.6 %) and 31 (67.4 %) of breast tumors respectively (Table 2.4). The hTR gene was expressed in all breast cancer tissues obtained from patients aged  $\leq 40$  years (10 out of 10) compared to 60 % (21 out of 35) of patients aged more than 40 years ( $p = 0.019$ ). This significant observation was not detected for hTERT. Furthermore, there was a significant association between hTERT- and hTR-expression when comparing patients aged  $\leq 40$  with olders. ( $p = 0.018$ ).

There was no significant association between tumor size and expression of hTR and hTERT (Table 2.5). Moreover, no association was seen between their expression status and tumor's grade, stage, axillary node status and pathological type of the tumor.

Two of the benign breast lesion revealed hTERT expression. However, hTR expression was not detected in any benign breast samples.

**Table 2.5** Correlation between hTR, hTERT and clinicopathological parameters. (Adapted from Hosseini-Asl et al. 2006b)

Parameter	Fre- quency	hTR expression			hTERT expression			hTERT <sup>+</sup> samples hTR expression			
		Neg.	Pos.	<i>p</i> value	Neg.	Pos.	<i>p</i> value	Neg.	Pos.	<i>p</i> value	
		Age	≤40	10	0	10	<b>0.019</b>	0	10	0.168	0
range	>40	35	14	21		8	27		11	16	
Pathol.	IDC	43	15	28	0.593	8	35	0.798	12	23	0.602
	ILC	1	0	1		0	1		0	1	
	Muc.	1	0	1		0	1		0	1	
Stage	I	9	4	5	0.087	2	7	0.941	3	4	<b>0.045</b>
	IIA	7	2	5		2	5		1	4	
	IIB	7	5	2		1	6		5	1	
	IIIA	6	0	6		1	5		0	5	
	IIIB	1	0	1		0	1		0	1	

### 2.5.2 Discussion

To understanding a new angle of telomerase regulation in breast cancer, the present study was designed. That was the first study to examine the association between hTR and the prognostic factors in human breast cancer. The DNase treatment method was engaged for the detection of hTR gene expression in order to avoid DNA contamination in RNA extracts. Such contamination may result in false positive findings while RT-PCR technique is used alone in those intronless genes or genes containing pseudogene (such as GAPDH housekeeping gene).

It was found that benign breast lesions showed no expression of hTR. Such an observation is in concordance with other studies which showed that any detected hTR expression in stromal cells, including those in fibroadenomas, was negative. However, increased hTR expression was observed in some foci of apocrine metaplasia and atypical hyperplasia.

(Yashima et al. 1998). Moreover, a multistage tumorigenic study in transgenic mice has shown up-regulation of TER in the first stages of tumorigenesis (Blasco et al. 1996). Therefore, up-regulation of hTR may be attended as a predictive marker for invasive tumor development.

By finding the association between hTR expression and younger age could lead to implicate a telomerase gene based therapy or cancer treatment strategies in young patients with breast cancer. This could be achieved by targeting the template region of hTR with anti hTR which may inhibit cell telomerase activity and can lead to a profound induction of programmed cell death (Yashima et al. 1998; Blasco et al. 1996).

It could be concluded that hTR expression probably plays a valuable role in mammary tumorigenesis in younger women (≤ 40 years). Tumors in older patients may develop telomerase independent mechanisms for survival.

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