Minireview

On the road to immortality: hTERT upregulation in cancer cells

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Received 2 February 2004; revised 18 March 2004; accepted 18 March 2004

First published online 1 April 2004

Edited by Varda Rotter

Abstract Telomere attrition limits the replicative potential of most somatic cells. In contrast, tumor cells acquire immortality by continuous telomere maintenance which is predominantly due to the transcriptional upregulation of the limiting component of telomerase, hTERT (human telomerase reverse transcriptase). Recent findings have provided mechanistic insight into how oncogenic activation as well as derepression, often due to the inactivation of tumor suppressors, stimulate the hTERT promoter. Knowledge gained from the study of hTERT transcriptional regulation may prove instrumental in the development of cancer therapies directed at the suppression of telomerase activity in tumor cells.

Key words: Cancer; Human telomerase reverse transcriptase; Oncoprotein; Telomerase; Tumor suppressor

1. Introduction

Telomeres are situated at the ends of linear chromosomes and protect them from degradation as well as end-to-end fusions [1]. In humans, telomeres are typically 10 kb long and consist of TTAGGG repeats. Due to the end-replication problem telomeres erode by 50–200 bp during each round of cell division in most somatic cells. Once telomeres shorten down to a critical length, growth arrest or senescence is induced thereby limiting the replicative potential of cells. This may cause aging and aging-related diseases in human beings, and accordingly greater telomere length has recently been correlated to decreased mortality [2].

In contrast to most somatic cells, germ, stem and tumor cells have the ability to maintain telomere length, a prerequisite for their unlimited replication potential. This is predominantly due to the enzyme telomerase that consists of an RNA subunit, a catalytic subunit (hTERT, human telomerase reverse transcriptase) and telomerase-associated proteins [3]. In vitro, the RNA subunit and hTERT are sufficient to elongate telomeres and thus constitute the core of telomerase. Whereas the RNA subunit of telomerase is expressed in most cells, hTERT expression is repressed. Thus, hTERT is the limiting component with regard to telomerase activity. Although some tumor cells maintain telomere length by the alternative lengthening of telomere pathway involving recombination processes, >85% of all tumor cells rather do so by inducing telomerase activity through hTERT transcriptional upregulation [4]. Other ways of regulating telomerase activity, for instance by differential splicing of the hTERT transcript or posttranslational modification of the hTERT protein, also exist [5] but appear to be more of a fine-tuning on top of hTERT promoter regulation.

Ectopic expression of hTERT has been shown to facilitate immortalization of human cells [6] and to be required for the transformation of human primary cells by the H-Ras and SV40 large T antigen oncoproteins [7]. Thus, hTERT expression resulting in telomerase activity is critical for tumorigenesis. Furthermore, inhibition of telomerase activity leads to senescence or apoptosis in tumor cells [8–10], indicating that telomerase activity is required for the long-term viability of tumor cells. However, at least in some human cell types, transformation of cells and initial tumor formation may occur in the absence of telomerase activation [11,12].

Altogether, telomerase expression due to the stimulation of hTERT gene expression has clearly emerged as one hallmark of cancer. The cloning of the hTERT promoter in 1999 [13–16] facilitated the identification of possible mechanisms of how hTERT transcription is upregulated in tumor cells leading ultimately to their immortalization. This review focuses in particular on how hormone stimulation, dysregulated activity of two families of transcription factors (E-box binding proteins and ETS proteins) or viruses and, on the other hand, loss of tumor suppressors can lead to hTERT upregulation.

2. Regulation of hTERT transcription by nuclear hormones

Estrogen is a positive regulator of cell growth in several tumors, in particular those of the breast. Accordingly, antiestrogens like tamoxifen are often applied in the treatment of breast cancer. One of estrogen's tumor promoting effects could be the activation of hTERT gene expression, since it can stimulate the endogenous hTERT gene and concomitantly induce telomerase activity [17,18]. Two sites in the hTERT promoter have been found that interact with the estrogen receptor (ER). The first one at −2677 to −2665 (GGTCAAGCTGATC; Fig. 1) matches nearly the consensus ER binding site, GGTCAN$_3$TGACC. In vitro ER specifically bound to this site and its deletion reduced hTERT promoter-mediated reporter gene activity [17]. The second hTERT sequence (−873 GGGCGGGATGTGACC −859) mediating estrogen stimulation and binding ER in vitro and in vivo [18,19] consists of a half-site for ER binding next to a canonical recognition sequence for the transcription factor

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0014-5793/04/$30.00 © 2004 Published by Elsevier B.V. on behalf of the Federation of European Biochemical Societies.
doi:10.1016/S0014-5793(04)00356-4

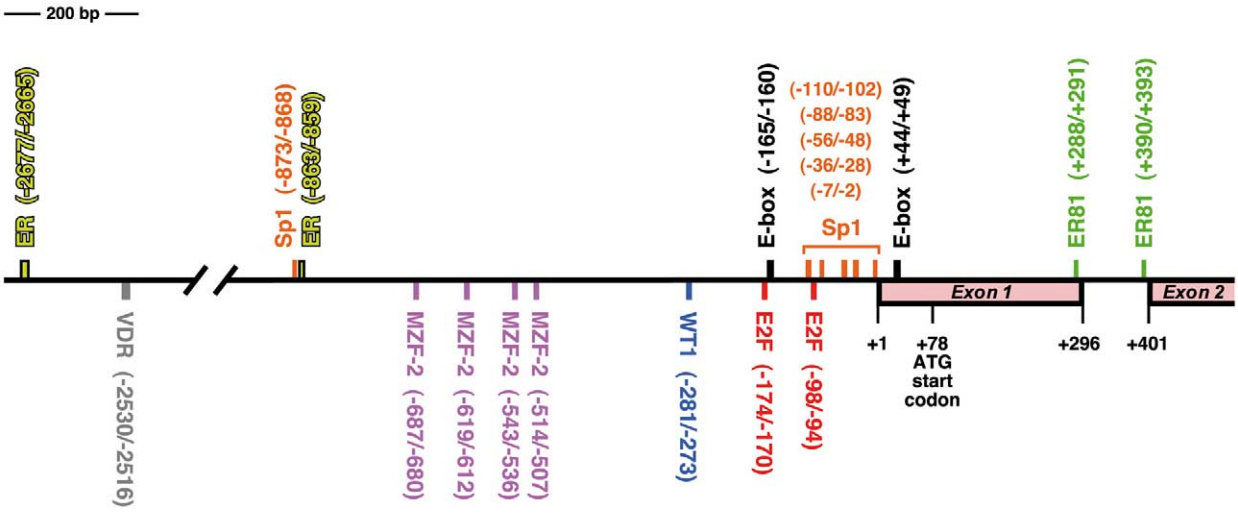

Fig. 1. Scheme of the human hTERT promoter. Documented binding sites for transcription factors regulating the hTERT promoter are indicated.

Sp1, GGGCGG; this juxtaposition of binding sites often allows complexes of ER and Sp1 to collaboratively bind to DNA [20]. Expectedly, tamoxifen countered estrogen-mediated hTERT upregulation in breast tumor cells, but also consistent with its estrogen-agonistic action in the endometrium, tamoxifen activated hTERT expression in an endometrial cancer cell line [21]. Therefore, utilization of tamoxifen to suppress estrogen-induced telomerase activity will only be beneficial in certain cancers such as those of the breast.

Similar to estrogen, progesterone has been shown to activate hTERT transcription in breast cancer cells, yet it remains unclear whether this is due to a direct activation of the hTERT promoter by the cognate hormone receptor [22]. Also, androgen stimulates the hTERT promoter and telomerase activity in LNCaP prostate cancer cells, but this is a delayed response to androgen and therefore most likely an indirect effect of androgen on hTERT expression [23,24]. In conclusion, steroid hormones may induce hTERT transcription in several hormone-dependent tumors. However, hTERT expression might also be repressed by some nuclear hormone receptors including the vitamin D receptor (VDR), which binds to a respective response element in the hTERT promoter (Fig. 1), and retinoic acid receptor [25,26].

3. Significance of the E-boxes within the hTERT promoter

E-boxes (CACGTG) are binding sites for the Myc/Max/Mad network of basic helix-loop-helix/leucine zipper transcription factors. Central is Max that can both homodimerize and form heterodimers with Myc and Mad proteins, resulting in gene activation (Myc/Max) or repression (Mad/Max). Accordingly, Myc and Mad antagonize each other, and therefore their expression levels appear to be inversely regulated, with the proto-oncogene c-Myc being activated in proliferating and many neoplastic cells whereas Mad genes are more prominently expressed in differentiating and resting cells [27]. Two E-boxes within the hTERT promoter were identified (Fig. 1) that mediate Myc/Max binding and transactivation [14,15,28,29]. Expectedly, those two E-boxes also mediate repression of hTERT transcription by Mad [30,31]. Indeed, switching from Myc/Max to Mad/Max occupancy at the hTERT promoter has been observed during differentiation of promyelocytic leukemic HL60 cells that is accompanied by hTERT downregulation [32]. A reverse switch has been noted upon transformation of WI-38 fetal lung fibroblasts that thereby acquire telomerase activity [33]. Thus, the antagonism between Myc and Mad proteins may be a crucial determinant of hTERT expression and telomerase activity.

Two canonical and three degenerate binding sites for the transcription factor Sp1 are localized within 110 bp upstream of the hTERT transcription initiation site (Fig. 1) that all interacted with Sp1 and whose mutation reduced hTERT transcription [15,34]. Interestingly, c-Myc cooperated with Sp1 to induce the hTERT promoter, and both transcription factors may be overexpressed once cells pass the stage of replicative senescence [34]. However, Sp1 and the related protein Sp3 may also under some circumstances recruit histone deacetylases to and thereby inhibit the hTERT promoter [35].

The c-Myc gene is downregulated through the transforming growth factor-β (TGF-β)/Smad pathway [36,37]. This may account for how TGF-β stimulation can suppress hTERT expression [38,39] and thereby exert one of its anti-tumorigen-

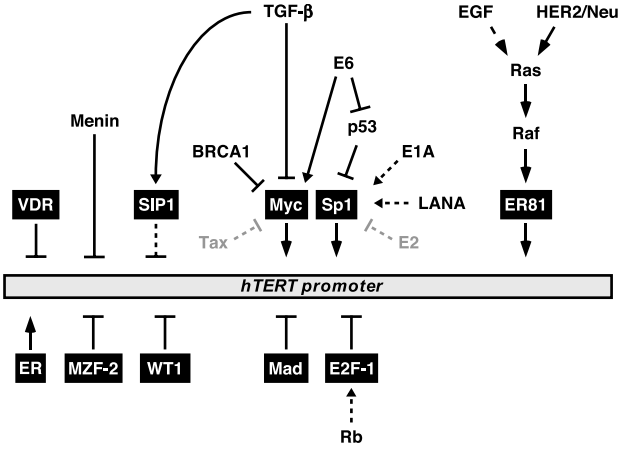

Fig. 2. Regulation of hTERT transcription in tumor cells. hTERT promoter binding proteins are boxed. Dashed arrows indicate hypothetical regulatory pathways.

ic actions (Fig. 2). Another potential way of reducing the amount of c-Myc capable of binding to the hTERT promoter would be by sequestering or masking of c-Myc. This may explain how the tumor suppressor BRCA1, which forms complexes with c-Myc, downregulates hTERT expression [40–42].

E-boxes are not only binding sites for Myc/Max/Mad, but also for other proteins such as upstream stimulatory factor (USF). Indeed, binding of both E-boxes by USF in vitro and in vivo as well as activation of hTERT promoter constructs by USF have been reported [43–45]. Interestingly, USF overexpression was unable to stimulate the hTERT promoter in telomerase-negative cells as opposed to telomerase-positive ones, indicating that USF in itself is not sufficient to upregulate the hTERT gene during cell transformation. It may even be that USF prevents binding of Myc/Max and thereby inappropriate stimulation of hTERT in normal somatic cells [45]. Finally, there are probably other E-box binding proteins that interact with the hTERT promoter [44,46] and their contribution to hTERT regulation remains to be determined.

4. ETS proteins and hTERT transcription

ETS proteins are a family of transcription factors characterized by a conserved DNA binding domain. The protagonists of this class of proteins, Ets1 and Ets2, can be activated through phosphorylation by MAP kinases [47], which themselves are stimulated through the epidermal growth factor (EGF) receptor and its homolog, the HER2/Neu proto-oncoprotein [48]. Interestingly, EGF stimulation can lead to hTERT upregulation involving a promoter region encompassing two juxtaposed ETS sites at −22 to −14 [49]. It was speculated that Ets1 and Ets2 directly mediate the response of the hTERT promoter to EGF stimulation, but at present this hypothesis has not been supported by the demonstration of binding of Ets1/Ets2 to the ETS sites at −22/−14. Furthermore, other ETS sites may be involved in the regulation of the hTERT promoter by Ets1/Ets2 [50], but again a more rigorous analysis is required before their significance can be evaluated.

Recently, oncogenic HER2/Neu, Ras and Raf that all lead to the activation of MAP kinases and its downstream effector, the ETS transcription factor ER81, have been implicated in hTERT upregulation. Importantly, while neither HER2/Neu (or Ras or Raf) nor ER81 alone could elicit hTERT transcription in telomerase-negative cells, they together did so. Furthermore, ER81 bound to two ETS sites at the end of exon 1 and intron 1 (Fig. 1), and mutation of these sites severely suppressed hTERT promoter activity. In addition, blocking signaling from HER2/Neu to ER81 or a dominant-negative ER81 molecule suppressed telomerase activity in a HER2/Neu-positive breast cancer cell line [51]. Taken together, these results may explain how activation of ER81 via the HER2/Neu → Ras → Raf → MAP kinase pathway elicits telomerase activity in the plethora of cancer cells characterized by oncogenic HER2/Neu, Ras or Raf.

5. Viral activation of hTERT expression

Viral DNA often integrates at chromosomal sites where viral enhancers then drive the inappropriate expression of a neighboring gene. This type of viral activation of hTERT gene expression has recently been observed for hepatitis B virus (HBV), which is an important risk factor for the development of liver cancer, and human papillomavirus (HPV) that is one major cause of cervical cancer [52–55].

In addition, viral proteins may directly contribute to hTERT upregulation (Fig. 2). The HPV type 16 E6 protein, which primarily exerts its oncogenic effects by inhibiting p53, can also associate with c-Myc and thereby activate hTERT transcription [56–59]. Adenovirus E1A protein and the latency-associated nuclear antigen (LANA) of Kaposi's sarcoma-associated herpesvirus have also been reported to activate hTERT transcription, which probably involves the Sp1 binding sites close to the transcription initiation site [60,61]. On the other hand, hTERT transcription is downregulated by the T-cell leukemia virus type 1 oncoprotein Tax and HPV E2 that presumably is mediated through the E-boxes and Sp1 binding sites, respectively [62,63]. On first sight, this latter finding of hTERT transcription repression by tumor-associated viral proteins appears counterintuitive. However, telomere attrition during early phases of tumorigenesis promotes chromosomal aberrations and aneuploidy which may be required to cause the accumulation of mutations necessary to establish a transformed phenotype [64]. Only after this pro-cancer period, telomerase activation is required to maintain a stable malignant cell phenotype, and accordingly Tax expression is downregulated upon progression to the leukemic stage [65] and similarly E2 during progression to cervical cancer [66].

6. Repression of the hTERT promoter

The hTERT promoter is GC-rich and located in a CpG island, suggesting that it is regulated by methylation. However, no coherent correlation between hTERT promoter methylation and telomerase activity could be found, indicating that CpG methylation is not the cause for the repression of hTERT transcription in most somatic cells [67,68]. Yet, methylation may still be important for the downregulation of hTERT expression in some cell lines [69,70] and, unexpectedly, in some instances hypermethylation may even contribute to hTERT promoter activation [71].

On the other hand, hybrids of hTERT-positive tumor cells with normal hTERT-negative cells displayed a shut-down of all hTERT expression, suggesting that dominant repressors mediate hTERT downregulation. Similarly, introduction of several individual chromosomes from normal somatic cells into tumor cells led to the suppression of hTERT expression [72]. As such, several independent repressors of hTERT gene transcription have been postulated to exist in normal somatic cells.

In search of these repressors, several candidate molecules have been identified. The Wilms' tumor suppressor 1 (WT1) bound to one site in the hTERT promoter (Fig. 1) and thereby suppressed hTERT transcription [73]. Similarly, myeloid-specific zinc finger protein 2 (MZF-2) interacted with a cluster of four sites in the hTERT promoter (Fig. 1) and downregulated hTERT activity [74]. However, due to the limited or preferential expression of WT1 in kidney, gonads and spleen and of MZF-2 in myeloid cells, those transcription factors are unlikely to mediate hTERT suppression in most somatic cells.

A more general repressor of hTERT expression could be p53 [75,76]. However, p53 has not been shown to directly bind and repress the hTERT promoter. Rather, p53 forms com-

plexes with Sp1 and may thereby prevent Sp1 from binding to and activating the hTERT promoter [77]. Another transcription factor, E2F-1, may also contribute to hTERT repression as E2F-1 bound to the hTERT promoter at two sites (Fig. 1) and reduced hTERT promoter activity in human squamous carcinoma cells [78]. Similarly, its relatives E2F-2 and E2F-3 repressed hTERT transcription in tumor cells, whereas E2F-4 and E2F-5 did not. Stunningly, in non-transformed hTERT-negative cells hTERT activation was observed with all of the tested E2F-1 to -5 proteins [79] which may reflect the paradox that E2F can both promote and inhibit cell proliferation and transformation. Furthermore, recruitment of the retinoblastoma tumor suppressor (Rb) by E2F-1 to the hTERT promoter might account for the fact that Rb downregulates telomerase activity [80,81]. Two further proteins implicated in the repression of hTERT are SIP1, a DNA binding and TGF-β-regulated transcription factor, and Menin, a tumor suppressor which binds in vivo to the hTERT promoter, most likely via to-be-identified DNA binding transcription factors [82].

7. Conclusions

Telomere attrition contributes to genomic instability and may thereby promote the development of malignant cell transformation. However, continuous telomere erosion would be fatal even for tumor cells, which is why at later stages of tumorigenesis telomeres are maintained in the vast majority of cancer cells by telomerase [64]. Furthermore, telomerase may exert functions beyond telomere lengthening during tumorigenesis [83,84], but at present it is unclear how it does so.

Telomerase activity is dependent on hTERT upregulation that can be elicited in many different ways, of which probably more than one is utilized in a tumor type-specific manner. However, two common principles have emerged for hTERT upregulation: (i) the activation of the hTERT promoter through oncoproteins or viral integration, and (ii) the derepression of the hTERT promoter through the loss of tumor suppressors (Fig. 2). A caveat is that the participation of many transcription factors in hTERT regulation has been inferred from studies utilizing in vitro cell cultures and should be corroborated by studying the involvement of these transcription factors in the regulation of the endogenous hTERT gene in human tumors.

Knowledge gained from the study of hTERT transcriptional regulation may help us to design therapies directed at the suppression of hTERT transcription and concomitantly telomerase activity in cancer cells. Examples are the inhibition of the EGF receptor or HER2/Neu leading to the suppression of hTERT transcription [51,85], probably by abrogating the activation of the transcription factor ER81; the inhibition of hTERT promoter activity through VDR upon treatment with 1α,25-dihydroxyvitamin D_3 and 9-cis-retinoic acid [25]; and the cell type-specific repression of hTERT expression by the ER antagonist, tamoxifen [21]. Finally, the tumor-specific upregulation of the hTERT promoter destines it for targeted cancer gene therapy. Cytotoxic or pro-apoptotic genes under the control of the hTERT promoter will only be activated in tumor cells and thereby protect normal cells from the indiscriminate delivery of these genes via viral vectors [86].

Acknowledgements: This work was supported by grant CA085257 from the National Cancer Institute.

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