Telomerase Activity in Hematological Malignancies

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Abstract: Telomerase expression and telomere maintenance are critical for cell proliferation and survival, and they play important roles in development and cancer, including hematological malignancies. Transcriptional regulation of the rate-limiting subunit of human telomerase reverse transcriptase gene (hTERT) is a complex process, and unveiling the mechanisms behind its reactivation is an important step for the development of diagnostic and therapeutic applications. Here, we review the main mechanisms of telomerase activation and the associated hematologic malignancies.

Keywords: telomerase activity; hematological malignancy; amplification; epigenetic; polymorphism; mutation; virus

1. Introduction

The ends of all linear genomes are comprised of a unique and genetically stable structure, termed telomere, which preserves genome integrity [1,2]. Due to the “end replication problem”, telomeric sequences shorten after every cell division, triggering the activation of DNA damage pathways that result in senescence and cell death. Telomere erosion and replicative senescence/apoptosis, limits the replicative capacity of cells, which is considered an important tumor-suppressive mechanism [3]. Shortening of telomeres may be counteracted by telomerase, an enzyme specialized in the elongation of telomeric ends [4]. Although the major function of telomerase is telomere elongation, accumulating evidence suggests that telomerase also possess telomere independent functions like enhanced survival, chemo-resistance, invasion and metastasis of malignant cells [5–8].

Telomerase consists of two core components: a catalytic subunit, human telomerase reverse transcriptase (hTERT) with reverse transcriptase activity and an RNA component, human telomerase RNA component (hTR), used as a template for the elongation of telomeres. In vivo telomerase activity requires additional components that associate with hTERT and hTR to form the holoenzyme [9]. Somatic cells do not display detectable telomerase activity, with the exception for germ cells, stem cells and some immune cell types with high proliferative needs. However, in such cells, the telomerase activity is only sufficient to delay, but not to completely prevent telomere shortening [10]. In about 85%–90% of all cancer cells, telomerase is reactivated, allowing the cells to circumvent senescence and divide indefinitely [11]. The remaining cancer cells, preserve the telomere length by a non-telomerase mechanism, known as alternative lengthening of telomeres (ALT), which involves the use of a DNA template [12].
It is believed that the limiting factor for telomerase activity is the level of hTERT [13]. Corroborating this idea is the fact that hTERT expression is transcriptionally shut-off in somatic cells, but the other telomerase associated components are constitutively expressed in most mammalian cell types; expression of hTERT mRNA in somatic cells is sufficient to reconstitute telomerase activity; and the expression levels of hTERT show strong correlation with telomerase activity [14–16].

The expression of hTERT is primarily determined by the transcriptional activity of the hTERT gene promoter. The hTERT promoter does not have typical transcription regulatory elements like TATA and CAAT boxes, but it contains a number of binding sites for multiple important transcription factors, which integrate hTERT transcriptional responses with many important pathways that are deregulated in various tumor types [17]. Transcriptional factors and signaling pathways frequently activated in tumor cells, like c-Myc, specific protein 1 (SP1), upstream transcription factor 1 (USF1), signal transducer and activator of transcription 3 (STAT3), phosphoinositide 3-kinase (PI3K), and nuclear factor of activated T-cells (NFAT), can positively stimulate hTERT promoter expression.

In contrast, Mad, histone deacetylases, E2F1, transforming growth factor-β-activated kinase 1 (TAK1), Wilms’ tumor 1 (WT1), p53, mothers against decapentaplegic homolog (Smad3), and Menin signaling negatively regulate hTERT promoter expression [18]. Even if there are a lot of transcription factors involved in telomerase expression regulation, none of them clearly account for the cancer specificity of hTERT expression [19]. The hTERT gene has a GC rich promoter and may therefore be under epigenetic regulation [20,21]. DNA hypomethylation or histone methylation around the transcription start site of the hTERT promoter triggers the recruitment of histone acetyltransferase (HAT) activity, allowing hTERT transcription [11]. It is also described in childhood brain tumors that hypermethylation in specific CpG sites upstream of hTERT transcription start site, results in telomerase expression [22]. There are also exogenous factors influencing hTERT transactivation: several viruses or virus proteins that interact with telomerase are known to be involved in tumorigenesis of infected tissues [23]. Since telomerase activity is a hallmark of the immortal cell phenotype, unveiling the mechanism of telomerase reactivation is an important step for the development of diagnostic and therapeutic applications [24]. This review aims to summarize the mechanisms utilized by hematological malignancies to reactivate telomerase expression.

2. Telomeres and Telomerase in Hematologic Malignancies

While hTERT expression and telomerase activity are increased in both virus-driven and virus-unrelated lymphoproliferative disorders, telomeres are generally short in virus-unrelated malignancies, and several data suggest that virus-associated tumors and/or pre-neoplastic disorders are characterized by longer telomeres [25–27]. This observation may reflect differences in the timing of hTERT activation and, therefore, telomere length stabilization. Indeed, from a theoretical perspective, shorter or longer telomeres could both contribute to oncogenesis [28]. On one hand, long telomeres suggest an early activation of hTERT that may contribute to a delay in replicative senescence and prolonged time to acquire genetic alterations critical for the induction of a fully transformed phenotype [23]. On the other hand, telomere shortening ultimately results in genetic instability and activation of hTERT may thus occur as a subsequent step, necessary for the immortalization of cells with acquired oncogenic potential. Accordingly, in adult T-cell leukemia/lymphoma (ATLL), telomerase activity appears as a key event in the development and progression of the disease, whereas in acute myeloid leukemia (AML), in chronic myeloid leukemia (CML) and in B-cell diseases, it was demonstrated that telomerase activity is not required for the initiation of disease, but it is required for its maintenance [29–32]. High telomerase activity is related with progressive disease, worse prognosis, or chemotherapy resistance in the group of hematologic neoplasias [33]. In addition, inhibition of telomerase in leukemia cell lines induces progressive telomere shortening and eventual proliferative arrest or cell death via apoptosis in vitro and in vivo [29,34–36]. The observed functional requirement of telomerase in established hematologic malignancies provides a rationale to therapeutically target telomerase in these diseases.
3. Mechanisms of Telomerase Reactivation in Hematologic Malignancies

Although the transcription factors known to bind to hTERT promoter may regulate hTERT transcription on specific cell type and physiological conditions, none of them are sufficient on their own to promote immortalization of somatic cells [37].

3.1. hTERT Amplification

The hTERT gene is frequently amplified in human tumors, including hematological malignancies [38]. In most cases, the amplified region encompassed most or all of the chromosome 5p region. In several cases, chromosomal break points were mapped to regions close to the hTERT promoter, suggesting that chromosomal rearrangements could either relieve the promoter from its stringent repressive epigenetic environment or place it in the proximity of enhancers at different chromosomal sites [39,40]. The telomerase reverse transcriptase-cleft lip and palate transmembrane protein 1-like protein (TERT-CLPTM1L) locus including the gene encoding hTERT gene is rarely but recurrently targeted by somatic chromosomal translocations to immunoglobulin heavy (IGH) and non-IG loci in B-cell neoplasms, including acute lymphoblastic leukemia, chronic lymphocytic leukemia, mantle cell lymphoma and splenic marginal zone lymphoma. In addition, tumors bearing chromosomal aberrations involving hTERT showed higher TERT transcriptional expression and increased telomerase activity [41,42].

Multiple copies of the hTERT gene are unlikely to yield a sufficient amount of the hTERT transcript, so the marked activation of hTERT transcription during tumorigenesis may be a combination of gene amplifications with other genetic or epigenetic mechanisms [37].

3.2. Epigenetic Regulation of hTERT Gene

Epigenetic modifications imply reversible changes in the genome of cells without any alteration in the DNA sequence. Increasing evidence suggests the epigenetics as an important mechanism involved in cancer initiation, progression, treatment and prognosis. There are three major epigenetic mechanisms that are known to regulate gene transcription in carcinogenesis: modified DNA methylations, histone modifications, and deregulated microRNA (miRNA) expression [43].

The epigenetic plasticity of the hTERT gene promoter is a determinant for the control of telomerase activity, and it has been shown that epigenetic modulation may repress hTERT transcription in hematological malignancies and may provide an additional level of enzyme regulation [44].

3.2.1. DNA Methylation

There are conflicting studies regarding the correlation between hypermethylation of the hTERT promoter, hTERT gene expression and telomerase activity [45,46].

Regarding hematological malignancies, in a cohort of childhood acute lymphoblastic leukemia (ALL), it was reported that the tumor samples had a methylated promoter, and that the hTERT promoter methylation status defines specific ALL subgroups [47]. In addition, in some T cell lymphomas, hTERT expression goes along with hTERT promoter hypermethylation [48]. It is believed that the promoter hypermethylation interferes with the binding of inhibitors, such as the CTCF transcription factor, which allows the hTERT gene to be transcribed [49]. On the contrary, some cells of the lymphoid system seem to escape methylation-dependent mechanism of hTERT regulation. Leukemias and lymphomas, including B cell chronic lymphocytic leukemia (CLL), express high levels of telomerase but exhibit low levels of hTERT promoter methylation [50]. Moreover, ALL (HL-60) and Burkitt’s lymphoma (Raji) cell lines, were found to have hypomethylated hTERT promoters [45,51]. In telomerase-positive B cells, hTERT is targeted by paired box 5 (PAX5), a B cell-specific factor, which is sufficient to activate TERT expression [48].

It is believed that the unusual correlations between DNA methylation and expression in cancer cells may, in part, result from the varied methods used to study differing regions of the hTERT
promoter. Indeed, it was observed that a small region around the transcription start site has little or no methylation, while there is a densely methylated region 600 base pairs upstream the transcription start site [45]. The core promoter demethylation is required for hTERT transcription in tumor cells, while the hTERT promoter in many normal cells and tissues is either unmethylated or hypomethylated, indicating that hTERT silencing does not require extensive CpG methylation at its promoter [46]. In addition, treatment with DNA methyltransferase inhibitors (DNMTIs), including decitabine (DAC) and azacitidine (AZA), is able to cause a reduction in hTERT gene expression and telomerase activity [52–54]. These two types of drugs are the first molecules that have been approved for the treatment of patients with AML and myelodysplastic syndrome (MDS) [55].

3.2.2. Histone Modifications

Another prevalent epigenetic mechanism that affects hTERT transcription is histone modification that includes histone acetylation, methylation, phosphorylation and ubiquitination. Histone deacetylation/methylation, in particular, have been reported to be responsible for the repressive status of the hTERT promoter [56].

The native chromatin environment is critical for the tight regulation of the hTERT gene, as the induction of hTERT transcription and telomerase activity in some telomerase-negative cells, was observed upon a treatment with trichostatin A (TSA), a histone deacetylase (HDAC) inhibitor [57,58]. The histone acetylation confers an opened chromatin structure, allowing transcription factors to bind to the DNA [59,60]. HDAC inhibitors are agents that have attracted interest due to their ability to induce not only cell differentiation, but also to promote growth arrest, apoptosis and sensitivity to certain chemotherapeutic reagents. Some HDACs were approved by the United States Food and Drug Administration (U.S. FDA) for the treatment of certain hematological diseases [61]. Modest clinical activity has been reported using HDACs as single-agent therapy, but they appear to be synergistic in vitro and improve response rates in vivo when combined with other agents [62]. Regarding hematological malignancies, the functional impact of HDAC inhibitors on hTERT transcription impairment was reported. TSA has an antiproliferative and apoptosis inducing effect on the human leukemic cell line U937, associated with the inhibition of hTERT expression and telomerase activity [63]. In leukemia cells it was verified that hTERT promoter DNA methylation and histone deacetylation status may contribute to the transcriptional repression of the hTERT gene and associated cell differentiation induction, observed during all trans retinoic acid (ATRA) treatment [50,64]. Furthermore, it was reported that the epigenetic modification of the distal domain of the hTERT promoter, determines the retinoid capacity to repress telomerase in maturation resistant acute promyelocytic leukemia cells during cellular differentiation [44].

Imatinib (IM) is a tyrosine kinase inhibitor selective for the BCR-ABL fusion gene, the cytogenetic hallmark of CML [65]. IM administration also inhibits telomerase activity independently of its effect on the BCR-ABL protein, and is mainly caused by hTERT post-translational modifications caused by the downregulation of various members of the phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase B (PI3K/AKT) pathway [66,67]. IM resistance is a major problem in therapy and disease relapse of CML. Recent studies have shown that by targeting telomerase expression using a dominant negative form of hTERT, or by the treatment with HDAC inhibitors, the risk of IM resistance may be reduced and the IM induced apoptosis in leukemia cells may be enhanced [68,69].

Histone methylation also plays a role in hTERT regulation. SMYD3, a histone methyltransferase (HMTase), is capable to induce hTERT transcription and telomerase activity in normal human fibroblasts and cancer cell lines through histone H3 K4 trimethylation [70]. H3-K4 methylation may function as a critical licensing element for transcription factors, such as c-Myc, through which the trans-activation of the hTERT gene is initiated [71].
3.2.3. MicroRNAs (miRNAs)

MiRNAs are a family of 19–24 nucleotide non-protein-coding RNA molecules that regulate the stability and translation of target mRNAs [72]. Various studies have revealed that loss- or gain-of-function of specific miRNAs contributes to cellular transformation and tumorigenesis, including hematological diseases [73,74]. The main mechanism that underlies the aberrant miRNA expression is that they are frequently localized in fragile sites prone to translocations and cancer-associated genomic regions (CAGRs) such as minimal regions of loss of heterozygosity (LOH), minimal regions of amplification and common breakpoint regions [75,76]. Many studies propose miRNAs as novel biomarkers and predictors of treatment response of hematological malignancies due to the specific miRNA signatures that allows for discrimination between different subtypes of leukemia and lymphoma with a greater degree of accuracy compared to traditional gene expression analysis [73,77,78].

Besides the effort to identify and catalog aberrantly expressed miRNAs in disease, very little is known about the functional consequences of miRNA dysregulation. It has been demonstrated that miRNAs are implicated in the regulation of hTERT expression through a regulatory network which is interconnected with other pathways also involved in tumor development. The miRNAs that target the hTERT 3′UTR have been identified as tumorigenesis inhibitors, and, consequently, are commonly found downregulated in many types of cancer [79]. The functional impact of miRNAs in B-cell ALL was reported with the restoration of miR-196b expression, which led to significant down-regulation of c-myc and its effector genes, including hTERT, suggesting a tumor suppressor function role for miR-196b [80].

Among all the factors regulating telomerase expression and activity, a few polymorphisms and mutations were also identified.

4. TERT Polymorphisms

The presence of single nucleotide variants (SNVs) in the hTERT locus, including the promoter and downstream introns, may be an alternative or additional mechanism influencing enzyme’s expression and activity. The genetic variability in the hTERT genomic region may affect telomerase function and can modulate telomere length and contribute to the development of cancer as well as the outcome of chemotherapy [81,82]. There are some TERT promoter polymorphisms associated with increased risk of developing hematological diseases, and even suggested as prognostic markers of survival [83,84].

Regarding hTERT transcription activation, the TERT promoter region SNP rs2735940 was associated with risk of childhood ALL. The rs2735940 T allele increased the levels of the TERT mRNA compared with the C allele [84]. The role of the mechanism of hTERT regulation was also demonstrated via MNS16A polymorphism in patients with Non-Hodgkin Lymphoma (NHL) [85]. The polymorphic element MNS16A, located downstream of exon 16 of the TERT gene and upstream of the putative promoter region of an antisense TERT transcript, has promoter activity depending on the number of tandem repeats. Carriers of the MNS16A short (S) allele display higher telomerase activity than the long/long (LL) genotype carriers. In fact, longer alleles at MNS16A exhibit stronger promoter activity compared to the shorter alleles, but this leads to increased expression of antisense TERT mRNA with a conceivable, or at least partial, silencing of the sense telomerase transcript [86].

5. hTERT Subunit Mutations

 Clinically, loss-of-function mutations in hTERT or hTR might increase the risk of chemotherapy resistance and predisposal to specific human diseases, like bone marrow failure or dyskeratosis congenita and acquired aplastic anemia, diseases that predispose to MDS and AML [87–89]. These clinical observations suggest that telomerase deficiency may contribute to the development of hematopoietic malignancy. Although most cancer cells express telomerase to maintain their proliferative capacity,
telomerase deficiency may lead to telomere attrition, hypothesized as a molecular mechanism that promotes genomic instability and predisposition to cancer development including leukemia [90,91].

Analysis of MDS/AML cases, secondary to bone marrow failure or dyskeratosis congenita allowed the establishment of an association between hTERT mutations and poor prognosis [92,93]. In addition, screening of de novo cases of MDS and AML for telomerase mutations have reported the existence of loss-of-function and non-synonymous mutations in the hTERT gene implicated as risk factors for AML [94,95].

6. TERT Promoter Mutations

Recently, two hot spot mutations in the TERT promoter, (−124 G > A and −146 G > A, C > T on the opposite strand) were reported in several different solid tumors [96,97]. These mutations have strong clinical implications with worse prognosis and poor survival and may represent a novel therapeutic target in solid tumors [96–99]. However, hematological malignancies are not reported to be subjects for somatic promoter mutations in the TERT gene [83,94,97,100].

7. Virus-Driven Lymphoid Malignancies

Viruses involved in lymphomagenesis may directly up-regulate telomerase expression and activity [23,101,102].

7.1. HTLV-1-Associated Lymphomas

Infection with the human T-lymphotropic virus type I (HTLV-I) is associated with the development of an aggressive form of T-cell leukemia known as adult T-cell leukemia/lymphoma (ATLL) [103]. High telomerase activity is associated with disease progression, so reactivation of telomerase seems to be a critical event in the development and progression of ATLL [27,104]. HTLV-I virus can directly induce endogenous telomerase up-regulation through the viral protein Tax that plays a central role in the modulation of hTERT expression [105]. Indeed, Tax represses hTERT promoter in proliferating cells, while it activates it in quiescent cells, allowing the cell cycle progression [106]. Notably, in ATLL cells, Tax expression is very low-to-undetectable, yet these cells retain strong telomerase activity. This suggests that alternative/additional mechanisms, independent of Tax protein, may induce hTERT expression and telomerase activity. Additionally, the viral protein HTLV-1 basic leucine zipper (HBZ) expressed in ATLL cells increases transcriptional activity of JunD, an AP-1 protein, while, HBZ in association with JunD activates the hTERT promoter [107]. Furthermore, it has also been shown that interleukin-2 (IL-2) signaling was associated with a PI3K-dependent transcriptional up-regulation of the hTERT promoter in HTLV-1 transformed cells. Activation of the PI3K pathway mediates cytoplasmic sequester of the WT1 protein, a strong hTERT promoter suppressor [108].

7.2. EBV-Associated Lymphoproliferative Disorders

Epstein-Barr virus (EBV) is involved in the pathogenesis of several lymphoproliferative disorders, including Burkitt’s and Hodgkin’s lymphomas, post-transplant lymphoproliferations, and a subset of T/natural killer (NK) cell lymphomas [109]. Among EBV latency gene products, latent membrane protein 1 (LMP-1) is considered the strongest oncprotein, being essential for immortalization of B cells. A crucial prerequisite for EBV-driven transformation is the induction of latent EBV genes and the down-regulation of lytic EBV gene expression, concomitantly with the induction of hTERT expression and activity [110]. LMP-1 activates TERT at the transcriptional level via NF-kB and (Mitogen-Activated Protein Kinase/Extracellular signal-Regulated Kinases) MAPK/ERK1/2 pathways [111].

8. Conclusions

The regulation of the hTERT gene is a very complex process. The repressed hTERT promoter can be activated by multiple mechanisms in different hematological malignancies. In addition
to a variety of transcription factors that bind and promote hTERT transcription/inhibition, the chromatin environment and nucleosomal conformation appear to be among the major mechanisms that tightly regulate the hTERT gene in the majority of hematological malignancies. Through epigenetic modulation, the hTERT locus is able to adopt a decondensed state, and then allow the binding of sequence-specific transcription factors that will activate its transcription. Chromosomal translocations of the hTERT locus may, in fact, be an important mechanism of telomerase activation, as it allows the escape of the promoter from its native repressive chromatin environment. Amplification of the hTERT gene was reported in hematological malignancies, and combined with other genetic or epigenetic mechanisms, results in a marked activation of hTERT transcription during tumorigenesis. In virus-driven lymphoid malignancies, the hTERT promoter may also be activated directly by viral proteins.

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