

Review

Telomerase: A Crucial Player in HTLV-I-induced Human T-cell Leukemia

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Abstract. *One in seven types of human cancer is associated with an oncogenic virus infection. Most human tumors have high telomerase activity but very short telomeres, yet the maintenance of these short telomeres is critical to avoid telomere end fusion or senescence and to support active proliferation. Oncogenic viruses have evolved a wide repertoire of strategies to stimulate telomerase functions at the transcriptional and post-transcriptional levels. Since telomerase activity is absent in somatic cells, the inhibition of telomerase is an attractive target for cancer therapeutics.*

Telomerase and Cancer

The “end replication” problem model states that the ends of chromosomes cannot be replicated due to the lack of a downstream template for DNA polymerase. This eventually leads to a loss of the very distal ends of DNA with successive replication cycles, leading to telomere attrition, cell cycle arrest, and cellular senescence or apoptosis (1). This normal physiological aging process ensures that proliferating cells that accumulate genetic defects over time are replaced by new undamaged cells and protects against potential pre-cancerous cells. However, this process needs to be tightly regulated because shortened telomeres can also lead to chromosomal instability characterized by end-to-end fusions, chromosomal translocations and DNA damage responses, increasing the risk of cellular transformation (2).

In tumor cells, the existence of a mechanism for the maintenance of telomere length is critical and the up-regulation of telomerase expression and activity has a well

established role in carcinogenesis. In fact, nearly 90% of all tumours demonstrate an increase in telomerase expression (3, 4). The remaining 10% of tumors use a telomerase-independent alternative lengthening of telomeres (ALT) pathway (5).

Telomerase is composed of *hTR*, a 451 nucleotide stretch of RNA, which serves as a template for the RNA-dependent DNA polymerase, telomerase (*hTERT*). Through repetitive binding to *hTR*, *hTERT* is able to lay down tracts of TTAGGG, 10-15 kbp in length, which serve to protect and sustain chromosomal ends. Telomerase expression alone, however, is not sufficient to sustain telomeres, as the shelterin complex, composed of the DNA binding proteins TRF1, TRF2, and POT1, and their partners TIN2, hRAP1, and PTP, have been shown to have a definitive role in regulating and protecting telomere lengths (6, 7). These telomere binding proteins prevent recognition of telomere structures by DNA damage response proteins, repress recombination mechanisms by altering the shape of telomeric DNA and protect telomeres against the action of exonucleases.

A proven role for telomerase in the transformation process is still ongoing. The ability of telomerase to avoid cellular senescence is evident in early *in vitro* studies, in which telomerase-negative cells and human endothelial cells reconstituted with telomerase, and telomerase transduced CD8+ T-cells were able to prolong growth, sustain longer telomeres, and in the case of CD8+ T-cells, maintain a normal karyotype through successive cycles of growth (8-10). However, telomerase expression alone may not be enough to induce a tumorigenic state in normal cells, as somatic cells expressing telomerase are unable to form tumors in nude mice, nor colonies in soft agar (11). Recent studies have shown that forced overexpression of *hTERT* and Ras^{G12V} proteins, along with the small and large T-antigens of simian virus 40 (SV40), are fully capable of transforming human cells (12). Transformation could also occur in the absence of the viral SV40 proteins, if RB, p53, Ras and c-Myc are overexpressed along with *hTERT* (12). These findings suggest

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that the overexpression of telomerase can prevent cellular senescence, thereby contributing to the transformation process, and once fully transformed can then extend the proliferative capacity of these cells, ensuring successive generations of growth. As the transformation process depends upon the deregulation of host cellular proteins and pathways, the ability to circumvent these processes is vital to the survival of the evading pathogen. Deregulating host mechanisms is a hallmark of all viruses, as they have proven exceptional at perturbing host cell homeostasis, including deregulation of telomerase activity.

Transformation of ATLL Cells by HTLV-I: The Case for Achieving Clonal Expansion

Human T-cell leukemia virus type 1 (HTLV-I) is the etiological agent of adult T-cell leukemia/lymphoma (ATLL), a lymphoproliferative disorder of infected CD4+ T-cells (13). ATLL develops in less than 5% of infected individuals after a long latency of 20 to 30 years. The lack of proofreading and subsequent high error rates of viral reverse transcriptase (RT) enzymes have been associated with the diversity observed in retroviruses. HTLV-I is unusual in that the observed genetic variability among isolates is unusually low. Thus, it has been hypothesized that HTLV-I provirus replication occurs mainly with the high-fidelity process of cellular DNA replication during the division of infected cells (14). This concept is supported by the fact that treatment with AZT, a reverse transcriptase inhibitor, does not reduce proviral loads in infected patients over a short period of time.

ATLL disease progression is linked to the proviral load, which in turn depends on long term survival and proliferation of the infected cells. To efficiently achieve clonal expansion, HTLV-I-infected cells must gain an extended life span while avoiding elimination by the host immune responses. Increased longevity may in part be explained by an increased expression of anti-apoptotic Bcl-2 and Bcl-xL in HTLV-I-transformed T-cells *in vitro* and of Bcl-xL in uncultured peripheral blood mononuclear cells (PBMCs) isolated from ATLL patients (15, 16). Escape from immune defenses may result from a combinatorial effect of the regulatory proteins p30 and p12 that reduce viral expression and down-regulate MHC expression, respectively (17, 18). Yet to achieve clonal expansion, HTLV-I-infected cells must also acquire an increased capacity to replicate their DNA and telomeric ends.

HTLV-I Infection Subverts Transcriptional Control of the *hTERT* Promoter

Regulation of the *hTERT* promoter is complex and subject to positive c-myc, Sp1, USF1/2, 14-3-3 and negative Mad1,

phosphorylated-Rb, PTEN regulators (19, 20). Regulation of the *hTERT* promoter can also occur by hypermethylation or acetylation (21). Many oncoviruses have evolved proteins that target the *hTERT* promoter to stimulate telomerase expression and promote transformation. The E6 protein of human papillomavirus (HPV) and the LMP1 protein of Epstein-Barr virus (EBV) have been shown to transactivate the *hTERT* promoter (22-24). HPV E6 was also found to promote acetylation of histone H3 and HPV can integrate near the *hTERT* gene (25, 26). Hepatitis B virus (HBV) has also been shown to integrate viral DNA into the *hTERT* promoter, allowing for cis-activation of telomerase (27).

A recent report suggests that the HTLV-I oncoprotein Tax may repress transcription from the *hTERT* promoter and lower telomerase activity under specific cell culture conditions (28). Yet, such a function of Tax is difficult to reconcile with its capacity to immortalize T-cells and the increased transcriptional regulation of the *hTERT* promoter in HTLV-I and Tax expressing human T-cells. These discrepancies may simply depend on the activation status of infected cells found in other studies. We found that Tax suppressed *hTERT* mRNA expression only when Tax-expressing cells were subject to PHA mitogenic stimulation and that in the absence of exogenous stimulation, Tax always stimulated expression from the *hTERT* promoter (29). We propose that in response to antigen stimulation, interference of Tax with the full induction of *hTERT* expression may result in transient genetic instability during mitosis. Once the mitogenic effect has vanished, Tax-mediated activation of *hTERT* gene expression offers a long term proliferative advantage to those cells that have acquired chromosomal abnormalities, increasing their chances to repeat this cycle. Successive repetition of the transient proliferation and stabilization phase may be required for the development of ATLL. This model is supported by *in vitro* HTLV-I infection of activated PBMCs, as PBMCs stimulated by coculture with MT2 (HTLV-I producer T-cell line), showed a significant decline in telomerase activity by week 4, with undetectable levels reached during the 5th and 6th weeks of culture. By week 7, however, telomerase activity began to increase and was significantly elevated by week 13. Telomerase detection by week 7 occurred before the cells escaped from crisis and therefore was not attributed to a general loss of PBMC cells as they died, but rather as a possible mechanism for selection and maintenance of transformed cells (29, 30). In addition, PBMCs cocultured with MT2 cells produced strong telomerase activity that correlated with viral load (29). Further analysis of this model of Tax-mediated *hTERT* regulation is required in order to more fully appreciate the contribution of telomerase in mediating transformation of HTLV-I infected T-cells. Real-time PCR analysis detected *hTERT* mRNA expression in all HTLV-I established cell lines, whether IL-2 dependent or independent. Increased expression of *hTERT* mRNA can be

detected in PBMCs following coculture with lethally-irradiated MT2 cells, suggesting that HTLV-I activates endogenous *hTERT* expression (29). Surprisingly, our laboratory found that Tax-mediated NF- κ B activation was responsible for the increased *hTERT* expression. Chromatin immunoprecipitation (ChIP) assays demonstrated an increased binding of the transcriptional activators, c-Myc and Sp1 onto the *hTERT* promoter, thereby acting as downstream effectors of the NF- κ B responses (29). *In vivo* studies also support the idea of HTLV-I-induced telomerase expression, as telomerase activity is consistently detected in acute, smoldering and chronic ATLL patients (31, 32). In fact, disease progression, as exemplified from asymptomatic to acute stages of disease, correlates with increased telomerase activity, as acute/chronic patients exhibit a higher percentage of telomerase activity than asymptomatic carriers (33).

Post-transcriptional Regulation of Telomerase by HTLV-I Tax Oncoprotein

There is abundant evidence that telomerase expression and activity is constrained at multiple levels. Several reports have identified a lack of correlation between *hTERT* mRNA levels and telomerase activity measured using the telomeric repeat amplification protocol (TRAP) assays. Although the half-life of *hTERT* mRNA and the telomerase complex differ significantly, one and eighteen hours respectively, these observations suggest additional post-transcriptional regulation of the enzymatic activity. The region surrounding Ser-824 in *hTERT* contains a consensus sequence for phosphorylation by Akt and Akt kinase enhances human telomerase activity through phosphorylation of *hTERT* (34). Telomerase must be translocated from the cytoplasm to the nucleus in order to act upon telomeric DNA. TNF α modulates telomerase activity by inducing nuclear translocation of *hTERT* protein bound to NF- κ B p65/RelA phosphorylated on Ser-536. A specific IKK inhibitor, PS-1145, which prevents p65/RelA phosphorylation, or a specific NF- κ B nuclear translocation inhibitor, SN-50, both block TNF α -induced *hTERT* nuclear translocation and stimulation of telomerase activity (35). In addition, EBV's LMP1 increases telomerase activity in nasopharyngeal carcinoma cells post-transcriptionally through NF- κ B-mediated phosphorylation and nuclear localization of *hTERT* (36). Finally, 14-3-3 protein can also enhance the nuclear localization and activity of *hTERT* (37).

ATLL Cells have Short Telomeres Despite Strong Telomerase Activity

Both HTLV-I immortalized and transformed cell lines and *in vivo* ATLL patient samples have high telomerase activity when compared to non-infected PBMCs and asymptomatic carriers. However, measurements of telomere lengths show

a decrease in size in both *in vitro* and *in vivo* HTLV-I infected samples relative to normal human T-cells (31, 32). This paradox is not entirely surprising, as telomere length does not solely depend upon the expression of telomerase and most cancer cells have short telomeres.

Telomere length is also regulated by several key positive and negative regulators that have been discovered of late, which act either directly on telomerase or indirectly by binding to the telomeric DNA itself. These proteins can then prevent telomerase extension by blocking access of the reverse transcriptase to the now "closed" ends of telomeric DNA. While the functions of most of these telomeric regulators are still being elucidated, it is clear that the complex they form (shelterin) can negatively affect the extent of telomere elongation by inhibiting the access of telomerase to the ends of DNA (38). In fact, three components of the shelterin complex the TTAGGG repeat binding factors TRF1 and TRF2, and the TRF1-interacting nuclear protein 2, TIN2, are overexpressed in ATLL patients. Studies have shown that overexpression of either TRF1 or TRF2, results in rapid telomere shortening. In addition, TRF1, TRF2 and TIN2 can inhibit apoptosis and cell cycle arrest due to DNA damage (39, 40). It is possible that the telomeres of transformed ATLL cells reach a critically short length but the cells are prevented from initiating apoptosis and senescence, due to the overexpression of key members of the shelterin complex. Further investigations into the roles of these proteins in allowing the continuous proliferation of ATLL cells is warranted as it could explain how ATLL cells continue to survive, despite short having telomeres.

Treatment of ATLL patients with Telomerase Inhibitors

The clinical significance of telomerase activity in ATLL disease progression can readily be demonstrated upon treatment with telomerase inhibitors. Azidothymidine (3'-azido-3'-deoxythymidine, AZT), is a thymidine analog, that has been shown to inhibit cancer growth and telomerase activity. AZT is used to treat several virus associated human cancers including, AIDS-related Kaposi sarcoma, Kaposi sarcoma associated primary effusion lymphoma (PEL) and EBV-associated lymphoma and primary central nervous system lymphoma (PCNL). However, until recently, the mechanism of AZT action was unclear and thus reasons for treatment failure unknown. The poor prognosis of ATLL patients is associated with the resistance of neoplastic cells to the conventional combination of high-dose chemotherapy and radiotherapy. Recently, a higher response rate following AZT/IFN alpha treatment of ATLL patients was reported in several human trials (41). Long-term treatment of HTLV-I infected cells with AZT (or ddG, an additional telomerase inhibitor) inhibits telomerase activity, induces telomere attrition and

promotes cellular senescence, in absence of apoptosis (42). HTLV-I infected cells undergo senescence during long-term AZT treatment, due to the reactivation of tumor suppressor p53 transcriptional activities. This effect is dependent upon telomere shortening. *In vivo* patient samples of AZT-treated ATLL patients show decreases in telomerase activity and telomere lengths. Further analysis of ATLL patients at varying disease stages demonstrates that those patients with a transcriptionally functional p53 gene are able to undergo partial or complete remission following AZT/IFN alpha treatment (42). However, those patients with a mutated p53 do not respond to AZT treatment and die (42). These results demonstrate that AZT treatment causes telomere attrition leading to the reactivation of a functional p53. Reactivated p53 is then capable of driving senescence in ATLL cells, allowing for patient remission, underscoring the importance of telomerase and telomeres in ATLL disease status.

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