

Regulation of Telomerase in Cancer Development and Progression: Implications for Cell Cycle Control and Checkpoints

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Abstract

Telomerase, a ribonucleoprotein enzyme complex, plays a critical role in maintaining telomere length and genomic stability. In most somatic cells, telomerase is tightly repressed, which limits how many times a cell can divide. In cancer, however, telomerase is often reactivated, allowing cells to bypass senescence and continue proliferating. This is important because telomerase reactivation gives cancer cells a way to escape normal cell cycle limits while also creating a possible therapeutic target. This review analyzes how telomerase is regulated during cancer development and progression, with emphasis on TERT transcription, promoter mutations, epigenetic control, post-transcriptional regulation, and checkpoint evasion. It also examines therapeutic strategies, including direct telomerase inhibition, TERT promoter-targeted therapy, telomerase-based immunotherapy, and ALT-focused approaches. Understanding how cancer cells reactivate and depend on telomerase may help explain tumor progression and guide more selective future cancer therapies.

Keywords: Telomerase, Telomere length, Genomic stability, Cancer development, Cell cycle regulators, Therapeutic intervention

1. Introduction

Telomerase is a specialized reverse transcriptase that maintains telomere length and helps regulate cellular lifespan. Telomeres are repetitive DNA-protein structures that cap the ends of chromosomes and protect them from being recognized as damaged DNA. With each cell division, telomeres become shorter because DNA polymerase cannot fully copy the very ends of linear chromosomes. This is known as the end-replication problem. Oxidative stress can also accelerate telomere shortening. When telomeres become critically short, the cell treats the exposed chromosome ends as DNA damage and activates checkpoint pathways that stop further division (Shay, 2016; Shay & Keith, 2008).

This checkpoint response is an important tumor-suppressive mechanism. The p53/p21 pathway can pause or permanently arrest the cell cycle when DNA damage is detected, while the p16INK4a/pRb pathway restricts progression from G1 phase into S phase, where DNA replication occurs. In simpler terms, these pathways act like brakes that prevent damaged or aged cells from continuing to divide. Normal human cells therefore enter replicative senescence after a finite number of divisions, a process often described as the Hayflick limit (Shay, 2016; Shay & Keith, 2008). Cancer cells must bypass these brakes in order to keep proliferating. One major way they do this is by reactivating telomerase, which restores telomere maintenance and reduces the pressure for senescence.

Figure 1 summarizes this relationship between telomere shortening, senescence, and cancer cell immortalization. In normal cells lacking telomerase, repeated divisions shorten telomeres until senescence is triggered. In contrast, cells with hTERT expression can maintain telomeres and continue dividing, which supports cellular immortalization.

Telomerase is a ribonucleoprotein enzyme composed of a catalytic protein subunit, telomerase reverse

transcriptase (TERT), and an RNA template, TERC or hTR, along with accessory proteins such as dyskerin (Wrighton, 2009). TERT uses the RNA template to add TTAGGG repeats to chromosome ends, counteracting telomere erosion (Shay, 2016; Shay & Keith, 2008). In healthy tissues, telomerase activity is mostly limited to stem cells, germ cells, and certain proliferative compartments. Most somatic cells keep TERT expression low, so telomere shortening remains a barrier to unchecked growth. Cancer cells reverse this pattern by reactivating TERT, maintaining telomeres, and gaining the long-term replicative capacity needed for tumor progression. A minority of cancers solve the same telomere problem through ALT, a recombination-based pathway that maintains telomeres without telomerase (Zhang & Zou, 2020). This review focuses on how TERT is reactivated, how telomerase activity intersects with cell cycle checkpoints, and how these mechanisms can guide telomere-directed therapies.

2. Methods / Analytical Framework

This review is a narrative review rather than a meta-analysis. Sources were chosen from peer-reviewed review articles, mechanistic cancer biology studies, and selected clinical studies that directly addressed telomerase regulation, checkpoint control, or telomere-directed therapy. The review compares evidence across several mechanisms, including promoter mutation, epigenetic regulation, transcription factors, splicing, microRNA control, and post-translational modification. It then connects these mechanisms to therapeutic strategies, with attention to biological rationale, clinical progress, tumor selectivity, and limitations such as delayed response, tumor adaptation, or toxicity in normal proliferative tissues.

3. Regulation of Telomerase Activity in Cancer Cells

Telomerase activation in cancer is a multi-step process involving genetic, epigenetic, and post-transcriptional changes that upregulate TERT or enhance telomerase function. The rate-limiting step is usually TERT expression (Liu et al., 2024), since in most cells the telomerase RNA (hTR) is constitutively present and only the TERT subunit needs induction.

3.1 Transcriptional Upregulation of TERT

Hotspot TERT promoter mutations are a prominent mechanism for telomerase reactivation in cancer. Recurrent C>T mutations at positions -124 and -146 are among the most frequent non-coding mutations in cancer. These mutations do not change the TERT protein itself. Instead, they alter the promoter region, which controls whether the TERT gene is turned on. The mutations create new binding sites for ETS transcription factors, including GABP, so transcription factors that would not normally activate TERT can now be recruited near the gene. The result is increased TERT transcription and higher telomerase activity in cancer cells (Liu et al., 2024).

Functionally, this shows that cancer cells can reactivate telomerase without mutating the coding sequence of TERT. In a pan-cancer sequencing study of approximately 30,700 tumors, about 11.3% had TERT promoter mutations and another 2% had TERT amplification. These mutations are especially common in certain tumors, including melanoma, and are associated with higher TERT expression and worse prognosis. The promoter mutation therefore acts less like a change to the telomerase enzyme and more like a new regulatory switch. By increasing TERT mRNA production, it helps cancer cells maintain telomeres and avoid the senescence response that would normally limit

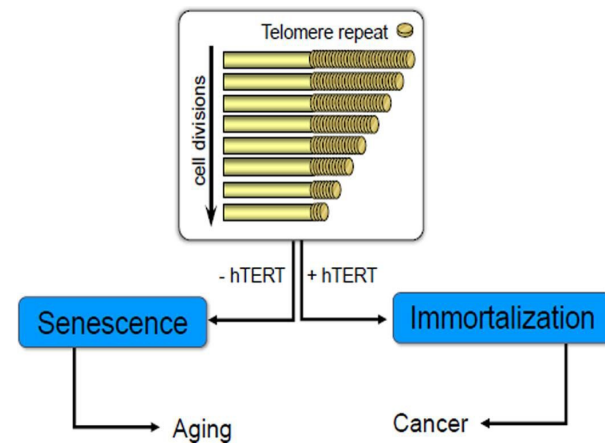


Figure 1. Telomere attrition as a barrier to cell immortality. Telomeres shorten with successive cell divisions in normal cells lacking telomerase, eventually triggering replicative senescence. Ectopic expression of telomerase prevents telomere shortening and leads to cellular immortalization (Shay, 2016). This escape from senescence is a critical step in oncogenesis, permitting unlimited proliferation.

continued division (Liu et al., 2024).

Even in the absence of promoter mutations, the TERT promoter is subject to tight regulation by multiple transcription factors. Two canonical activators of hTERT transcription are c-Myc and Sp1. c-Myc, a ubiquitous oncogenic transcription factor, binds E-box motifs in the TERT promoter and is a well-documented driver of TERT expression in many cancers (Shay, 2016). Accordingly, cells with MYC overexpression (common in lymphomas, many carcinomas) often show elevated telomerase activity. Sp1 is a zinc-finger DNA-binding protein that can activate TERT; it cooperates with other factors to enhance TERT transcription. Several oncogenic pathways converge on these factors including PI3K–AKT–mTOR and Wnt/β-catenin, which can directly upregulate TERT (Liu et al., 2024; Wrighton, 2009). Hypoxia-inducible factor 1 (HIF-1α) is another factor that can activate the TERT promoter (Nassour et al., 2021). On the flip side, there are transcriptional repressors of TERT, such as p53, which can indirectly repress TERT transcription through downstream targets, and certain tumor suppressors like Menin and WT1 that bind directly to the TERT promoter and inhibit its activity in normal cells (Liu et al., 2024). Cancer cells often lose these repressive influences. In sum, a shift in the state of transcriptional regulators is a hallmark of cancer cells acquiring TERT expression. The result is that TERT gene transcription, virtually silent in most somatic cells, becomes active in cancer cells, providing a steady supply of telomerase.

Beyond DNA sequence changes, epigenetic alterations at the TERT locus are crucial in cancer. The TERT promoter in normal cells is generally unmethylated but silenced by repressive chromatin. Paradoxically, many cancers exhibit hypermethylation in a region upstream of the core TERT promoter, referred to as the TERT hypermethylated oncological region (THOR) (Kouroukli et al., 2023; Liu et al., 2024). This methylation is thought to prevent binding of certain repressor proteins, thereby de-repressing TERT transcription. At the same time, the core promoter of TERT often remains unmethylated, which is favorable for transcription factor binding. The combination of a methylated upstream region and an unmethylated core promoter is strongly associated with active TERT expression in tumors (Kouroukli et al., 2023). Indeed, studies in thyroid cancer and melanoma have shown that high THOR methylation correlates with TERT upregulation and poor patient survival (Lee et al., 2021; Li et al., 2024). Furthermore, TERT gene body methylation, chromatin looping to distal enhancers, and histone modifications (like H3K4me3 enrichment at the promoter) also contribute to TERT's transcriptional upregulation (Liu et al., 2024). In summary, cancer cells often engineer a TERT promoter configuration that is both genetically and epigenetically optimized for high expression.

3.2 Post-Transcriptional and Post-Translational Regulation

While controlling TERT gene expression is primary, cancer cells also modulate telomerase at the mRNA and protein level. Alternative splicing of TERT pre-mRNA can yield shorter isoforms that are enzymatically inactive; some normal tissues produce mainly these dominant-negative TERT variants (Nassour et al., 2021). Many cancers shift splicing to generate the full-length active TERT mRNA or express only the active isoform. MicroRNAs provide another layer of post-transcriptional control: several tumor-suppressive miRNAs (e.g. miR-138, miR-512) directly target TERT mRNA and inhibit its translation. Downregulation of such miRNAs in tumors can relieve translational repression of TERT. For instance, loss of miR-138 has been linked to elevated TERT in gliomas. Conversely, oncogenic miR-19 has been reported to indirectly increase telomerase by repressing PTEN and activating AKT, which in turn boosts TERT activity.

At the protein level, post-translational modifications (PTMs) of TERT fine-tune telomerase. Phosphorylation by CDK1, AKT, and protein kinase C (PKC) family members can enhance TERT activity. Casein kinase 2 (CK2) also phosphorylates TERT, promoting its stability. These modifications can alter TERT's subcellular localization, stability, or assembly into the active holoenzyme. For example, AKT-mediated phosphorylation of TERT on Serine 824 and Serine 227 enhances telomerase activity by fostering TERT's nuclear localization and recruitment to telomeres. In contrast, TERT is negatively regulated by phosphorylation at certain other sites: GSK3β can phosphorylate TERT to promote nuclear export and degradation when Wnt signaling is low, and the phosphatase PP2A can dephosphorylate TERT, leading to telomerase inhibition. Another PTM is ubiquitination. TERT can be ubiquitinated and targeted for proteasomal degradation by specific E3 ligases. Cancer cells often have elevated chaperones, such as Hsp90, that bind

and stabilize TERT. Telomerase trafficking is also important because TERT must reach telomeres at the correct point in the cell cycle. Notably, phosphorylation by CDK1 in late S-phase triggers TERT to translocate to telomeres at the right time (Liu et al., 2024). Disrupting these timing cues can limit telomerase's access to telomeres and reduce its function. Overall, cancer cells support telomere maintenance not only by increasing TERT transcription, but also by controlling TERT stability, localization, and timing during the cell cycle.

3.3 Telomerase, Cell Cycle Control, and Checkpoint Evasion

Telomerase reactivation also changes how checkpoint pathways affect the cell cycle. In a normal cell, critically short telomeres are recognized as DNA damage, which activates checkpoint pathways and pushes the cell toward senescence. This means telomere shortening is not only a marker of aging but also a control system that limits risky cell division. When cancer cells restore telomerase activity, they reduce the telomere damage signal that would normally trigger these checkpoints. This does not mean telomerase alone causes every checkpoint defect, since many tumors also alter p53, pRb, or other regulators. Rather, telomerase helps cancer cells make checkpoint evasion stable over time by allowing them to keep dividing after other growth-control barriers have weakened (Liu et al., 2024). Tumors that do not activate telomerase must still solve the same telomere problem through another maintenance route, such as ALT (Zhang & Zou, 2020). This distinction matters clinically because ALT-positive tumors may respond to different telomere-directed strategies, including ATR inhibition (Flynn et al., 2015).

4. Therapeutic Strategies Targeting Telomerase and Telomeres

Given telomerase's importance in cancer cell immortality and its relative inactivity in most normal somatic cells, it has long been recognized as an appealing therapeutic target (Shay, 2016; Shay & Keith, 2008). Telomerase-targeted therapies aim either to directly inhibit the enzyme, interfere with TERT gene regulation, or use telomerase activity as a marker for targeted killing of cancer cells. The clinical question is not only whether telomerase can be blocked, but which tumor settings are most likely to respond. Telomerase-positive tumors may be treated through enzyme inhibition, promoter-targeted therapy, or immunotherapy, while ALT-positive tumors require different approaches because they maintain telomeres without telomerase (Zhang & Zou, 2020). For this reason, telomere length, TERT promoter status, telomerase activity, and ALT activity are important biomarkers for deciding which telomere-directed strategy makes the most sense.

4.1 Direct Telomerase Inhibition

The most straightforward therapeutic approach is to directly inhibit telomerase activity in cancer cells. Once telomerase is blocked, cancer cells may continue dividing for some time, but their telomeres are no longer fully maintained. With enough divisions, telomeres become too short or damaged to protect chromosome ends, which can lead to growth arrest, senescence, or apoptosis. This makes telomerase inhibition attractive because it targets the same immortality mechanism that many tumors rely on. The limitation is timing. Since the telomere signal develops gradually, treatment may require many rounds of cell division before a clear anti-tumor effect appears (Shay & Keith, 2008).

Imetelstat is one major example. It is a lipid-conjugated oligonucleotide that binds the template region of hTR and prevents telomerase from extending telomeres. Clinical studies show that telomerase inhibition can affect cancer cell proliferation, especially when tumor cells already have relatively short telomeres. Still, this approach has limitations. Normal proliferative tissues, including bone marrow, intestinal tissue, and some stem cell compartments, also depend on controlled telomere maintenance. Because of this, telomerase inhibitors can raise concerns about bone marrow suppression or impaired tissue renewal. This does not remove telomerase as a target, but it suggests that its best use may be in selected patients, combination therapy, or maintenance treatment after the tumor burden has already been reduced (Shay & Keith, 2008).

To accelerate the anti-tumor effect, researchers have developed strategies that go beyond simply blocking telomere elongation. One innovative approach is using telomerase's activity against itself. For instance, 6-thio-2'-

deoxyguanosine (6-thio-dG) is a telomerase-recognized nucleotide analog that gets incorporated into telomeres by the enzyme. Once inserted, 6-thio-dG creates dysfunctional telomeric DNA that cannot properly protect chromosomes, rapidly triggering telomere damage responses. Studies showed that 6-thio-dG causes abrupt cell death in many cancer cell lines tested, while sparing telomerase-negative normal cells. In mouse xenograft models, 6-thio-dG treatment slowed tumor growth significantly (Mender et al., 2015). 6-thio-dG is now being investigated in early clinical trials, with the FDA granting it orphan drug designation for certain cancers (Seymour, 2022). Another direct strategy is to target the telomere ends: small molecules like BRACO-19 stabilize G-quadruplex DNA structures at telomeres, making it difficult for telomerase to bind and elongate them, effectively inhibiting telomerase action at the chromosome terminus. G-quadruplex stabilizers have shown telomerase inhibition and anti-cancer activity in preclinical models, but off-target effects (since G4 DNA can form elsewhere in the genome) need careful management. Lastly, antagonists of telomerase essential protein partners are being explored. Telomerase requires association with hTR RNA and the dyskerin protein; drugs that disrupt these interactions could inactivate telomerase. For example, a compound that displaces dyskerin from hTR would destabilize the telomerase RNP. While direct telomerase inhibitors are conceptually simple, in practice an ideal inhibitor must distinguish between the enzyme in cancer vs. normal stem cells and achieve durable suppression of telomere maintenance. It may be that the best use of direct telomerase inhibitors will be in combination (for instance, with DNA-damaging chemo/radiation, to prevent repair of treatment-shortened telomeres) or as maintenance therapy to prevent minimal residual disease from regaining immortality.

4.2 TERT Promoter-Targeted Therapies

Another strategy is to use the hTERT promoter itself as a selectivity tool. In many cancers, this promoter is active because the cells depend on TERT expression to maintain telomeres. In most normal somatic cells, it remains silent or weakly active (Liu et al., 2024; Shay, 2016). Gene therapy can use this difference by placing a toxin gene or prodrug-activating enzyme under the control of the hTERT promoter and delivering it with a vector. In a cancer cell, the active promoter drives expression of the therapeutic gene. In a normal cell with little hTERT promoter activity, much less of the toxic product is made, so normal tissues are less likely to be damaged (Shay & Keith, 2008).

This same logic has also been used in oncolytic virotherapy. Telomelysin (OBP-301), for example, is an oncolytic adenovirus designed so that essential viral replication genes are controlled by the hTERT promoter. The virus can enter many cells, but it should replicate mainly in telomerase-positive cancer cells. Once it replicates, it can lyse the tumor cell and spread to nearby cancer cells. In normal telomerase-negative cells, viral replication is limited, which reduces damage to healthy tissue. This approach uses active telomerase transcription as the selectivity mechanism rather than treating telomerase only as an enzyme to inhibit (Heo et al., 2023). Clinical studies have also examined OBP-301 in gastroesophageal adenocarcinoma, including in combination with pembrolizumab (Sarkar et al., 2023; Shah et al., 2023).

Directly targeting the TERT promoter region with small molecules is another emerging idea. The G-rich TERT promoter can form quadruplex DNA structures; stabilizing those structures (with G4 ligands) may impede the binding of transcriptional activators like GABP or Myc, thus downregulating TERT expression. Molecules such as TMPyP4 that bind G-quadruplexes have been found to suppress TERT transcription in certain cancer cell lines, leading to telomere shortening and growth arrest. Another concept is CRISPR-mediated TERT silencing: using dCas9 fusions to KRAB (a repressor) targeted to the TERT promoter has shown efficient TERT knockdown in cell models, although delivering such a system in patients remains challenging. Epigenetic drugs could also modulate TERT expression – for instance, inhibitors of TERT promoter demethylation or of certain histone acetyltransferases that activate TERT could push cancer cells to a telomerase-off state. However, care must be taken as TERT repression in normal progenitor cells (hematopoietic, etc.) could have long-term consequences if those cells are required for tissue maintenance. Importantly, TERT promoter mutant cancers might be particularly susceptible to promoter-targeted therapy: the unique sequence created by mutation is a defined target that could be bound by designed nucleic acids (like triplex-forming oligonucleotides or CRISPR guides) to selectively shut down the mutant allele. Such allele-specific targeting is still mostly theoretical but holds promise for tumors addicted to TERT promoter mutations. Overall, TERT promoter-targeted strategies aim to turn the cancer cell's telomerase gene off –effectively re-engaging

the telomere-induced checkpoint that the tumor had evaded.

4.3 Telomerase-Based Immunotherapy

Telomerase is an attractive antigen for cancer immunotherapy because it is near-universally expressed in cancer cells but absent from most normal cells. The telomerase catalytic subunit hTERT contains multiple peptide epitopes that can be presented on HLA molecules to T cells, making it a possible target for T cell recognition. In fact, cancer patients sometimes naturally develop T cell responses to telomerase, but usually not enough to eliminate the tumor. Therapeutic vaccines try to strengthen this response. One of the earliest clinical trials used GV1001 (tertomotide), a 16-amino acid peptide from the active site of TERT. GV1001, when given with GM-CSF adjuvant, induces telomerase-specific CD4 and CD8 T cells in patients (Vahidi & Zabeti Touchaei, 2024). It showed initial promise in Phase I/II studies by generating immune responses, but a large Phase III trial in advanced pancreatic cancer did not improve overall survival. That result suggests that telomerase vaccines may need to be paired with other therapies or used in patients who are more likely to respond. A follow-up study found that a subset of patients with high serum eotaxin, an immune chemokine, might benefit from GV1001 (Jo et al., 2024), suggesting biomarkers could help identify responders. Newer peptide vaccines include UV1, which has shown an ability to activate CD4⁺ T helper responses and some CD8⁺ T cells in early trials, and is being combined with checkpoint inhibitors in melanoma and mesothelioma studies. Another is Vx-001, a vaccine targeting a common hTERT epitope presented by HLA-A2; it demonstrated extended survival in a subset of non-small cell lung cancer patients in Phase II, especially those who mounted strong T cell responses. UCPVax is a two-peptide vaccine that is currently in trials for lung cancer and has been associated with immune response in a Phase I trial (Vahidi & Zabeti Touchaei, 2024). Overall, telomerase peptide vaccines have shown immunogenicity, meaning telomerase-specific T cells can often be detected after vaccination (Ellingsen et al., 2021), but converting this immune response into consistent clinical benefit has been difficult. Combining vaccines with immune checkpoint blockade remains a rational strategy because it may allow vaccine-induced T cells to function more effectively in the tumor environment.

Besides vaccines, adoptive T cell therapies targeting telomerase are in development. T cells can be harvested and genetically modified to better attack telomerase-expressing cells. For instance, T-cell receptor (TCR) transduction has been used to create T cells recognizing an hTERT epitope presented by HLA-A2. Similarly, dendritic cell vaccines pulsed with hTERT peptides or RNA have been tested, where patient DCs present telomerase antigens to induce a broader T cell response. Another approach is telomerase-specific oncolytic viruses, which can lyse tumor cells and also release tumor antigens in an immunogenic context (Heo et al., 2023). One concern for telomerase immunotherapy is possible autoimmune damage to normal stem cells, which can express telomerase at low levels. So far, clinical trials have not reported severe bone marrow or gut failures clearly caused by anti-telomerase immunity, but long-term monitoring is still needed. Some patients develop immune responses to telomerase while their tumors continue to progress, suggesting that tumors can escape through HLA loss or an immunosuppressive microenvironment. For that reason, telomerase immunotherapy will likely depend on combinations, biomarkers, and patient selection rather than vaccination alone.

5. Conclusion and Future Directions

Telomerase remains important in cancer because it sits at the point where telomere biology, checkpoint control, and long-term tumor growth meet. The central pattern across the studies reviewed is that tumors do not reactivate telomerase in one single way. Some alter the TERT promoter, some change the epigenetic state of the locus, and others shift RNA processing, microRNA regulation, protein stability, or TERT recruitment to telomeres. These mechanisms are different at the molecular level, but they produce the same basic effect: they reduce the telomere damage signal that would normally push cells toward senescence and allow continued proliferation (Liu et al., 2024).

Therapeutically, this makes telomerase useful but difficult. Direct inhibitors can target the enzyme, but the response may be slow because telomeres shorten over many divisions. Promoter-based strategies are more selective in principle because active hTERT transcription is much more common in cancer cells than in normal somatic cells.

Vaccine and immune-based approaches take advantage of the wide expression of hTERT across tumors, but the clinical results so far show that immune recognition is not the same as durable tumor control (Vahidi & Zabeti Touchaei, 2024). Future work will probably need to focus less on telomerase as one universal target and more on matching the strategy to the tumor: telomere length, TERT promoter status, telomerase activity, ALT status, and immune context. In that sense, telomerase regulation is not only a mechanism of cancer cell immortality. It is also a way to decide which telomere-directed therapies are most likely to work.

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