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Review article

Telomerase reverse transcriptase promoter mutations in non-small cell lung cancer: Biology and clinical significance

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Abstract

About 85% of all lung cancers are non-small cell lung cancers (NSCLC), which are common, have a high death rate, and are usually diagnosed at an advanced stage. Recent studies have shown that mutations in the *TERT* promoter in NSCLC may be a noninvasive biomarker, enhance possible treatment approaches, and predict prognosis, especially in inoperable cases. This review comprehensively examines the present state of *TERT* promoter mutations in NSCLC, highlighting their clinical relevance, treatment approaches, challenges, and key considerations. *TERT* promoter mutations in NSCLC may offer new perspectives on the molecular pathogenesis of patients. For this reason, summarized *TERT* promoter mutations in NSCLC and current treatment strategies targeting TERT. Understanding the *TERT* effect on NSCLC may pave the way for new personalized treatment approaches.

Keywords: *Clinical significance; non-small cell lung cancer; promoter mutations; TERT*

1. Introduction

Lung cancer remains the most common cause of cancer-related mortality worldwide among all malignant neoplasms. (Lin and Park, 2024). The precise pathways leading to the development of most lung cancers are not yet fully understood. (Bertolaccini et al., 2024). It can be related to environmental variables, circle of relatives' records, tobacco smoke, and genetic elements consisting of aberrant oncogene and tumor suppressor gene law, according to analysis (Nigro et al., 2015; Qiu et al., 2019; Yu et al., 2019).

Up to 69% of patients with advanced non-small cell lung cancer are thought to have several gene alterations that can be treated (Fois et al., 2021). Based on histological capabilities, most lung cancers are split into principal subgroups: small-mobile lung cancers (SCLC) and non-small-mobile lung cancers (NSCLC) (Braicu et al., 2019). About 85% of lung cancers are within the NSCLC histology. (Sher et al., 2008). The majority of patients, however, are diagnosed at an advanced stage and need thorough care. These patients generally have poor prognoses and a brief average survival time (Spiro and Silvestri, 2005; Ma and Wang, 2024). Despite improvements in remedies, surgical procedures, and clinical processes, the five-year survival fee for NSCLC patients remains low at 10%-15% (Tan et al., 2016; Smith et al., 2017; Yeh et al., 2018; Zhang et al., 2020).

Cancer molecular biomarkers are increasingly being used to diagnose, monitor, and treat cancer (Passaro et al., 2024). Over 150 prognostic factors have been described for non-small cell lung cancer (NSCLC). The most important factors affecting survival include tumor stage at presentation, weight loss, tumor doubling time, and molecular markers (Johnson, 1995; Brundage et al., 2002; Bremnes et al., 2003). Some of this data may not be available, especially in cases of inoperable NSCLC. Therefore, research on non-invasive prognostic markers continues. Treatment for NSCLC has significantly changed with a focus on treatment strategies guided by the molecular profiles of tumor cells (Morgenstern et al., 2024). Numerous mutations that might be targeted with specific treatments were recognized through the molecular characterization of tumor cells (Alamgeer

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et al., 2013, Onur et al., 2025). Molecular targeted therapies are more effective and less toxic than treatments that conventional oncological drugs (Cheng et al., 2010; Hirsch et al., 2010; Dacic, 2011). Accordingly, molecular markers have become improving treatment strategies for NSCLC (Planchard et al., 2018).

Comprising a protein complex called Shelterin and repetitive nucleotide sequences (TTAGGG), telomeres are specialized systems observed at the ends of chromosomes. To keep genomic stability and integrity, they protect chromosome ends from deterioration and fusion with nearby chromosomes. The enzyme telomerase reverse transcriptase (*TERT*) aids in retaining the ends of telomeres (Yoo et al., 2015).

Mutations inside the *TERT* promoter location can cause expanded telomerase expression, maintaining telomere length and genomic balance, allowing cancer cells to keep away from senescence or apoptosis and keep dividing (Griewank et al., 2013). In normal cells, telomeres shorten after each cell division, and when they emerge as seriously brief, cells prevent dividing, and senescence is triggered. This is a powerful human tumor suppressor mechanism (Campisi, 2013; Inada et al., 2019; Muneer and Minhas, 2019). However, maximum tumor cells grow to be immortalized, expressing or reactivating telomerase, hence stopping senescence and permitting non-stop cell division (Kim et al., 1994).

The first promoter region of the *TERT* mutations was diagnosed in melanomas and has since been identified in various types of cancer, consisting of hepatocellular cancer, bladder most cancers, glioblastoma, and thyroid most cancers (Huang et al., 2013; Horn et al., 2013; Liu et al., 2013, El Zarif et al., 2024). The association of lung cancers and *TERT* promoter mutations has been a significant research topic in recent years.

2. Telomerase reverse transcriptase gene and protein

TERT is the catalytic subunit of the telomerase enzyme, which, at the side of the telomerase RNA portion of the telomerase RNP enzyme, forms the most essential unit in the telomerase complex (Kageler et al., 2024). The model created for the structure of *TERT* likens the TERT protein to a semi-open right hand. This model's protein includes palm, thumb, and finger areas. The RNA portion of the enzyme complicated, located within the palm region and complementary to at least 1.5 telomeric repeats, features within the extension of the G3' give up of DNA. The *TERT* gene, which is located at 5p15.33, codes for the catalytic subunit of telomerase, a specialized ribonucleoprotein enzyme necessary for eukaryotic organisms to extend their telomeres and add hexamer repeats to the ends of chromosomes for replication. Human telomerase reverse transcriptase (*hTERT*) is encoded by it (Aubert et al., 2012).

This function is essential for continuous cell division and plays a role in cellular immortality. The *TERT* gene is tightly repressed, which consequently leads to the silencing of telomerase. Cancer patients exhibit higher telomerase function, which protects telomeres and allows tumors to evade aging (Smogorzewska and de Lange, 2004).

2.1. TERT promoter mutations in non-small cell lung cancer

The *TERT* promoter region is a 260-base-pair (bp) region located between -1,800 and +2,300 relative to the ATG start codon. *TERT* promoter mutations predominantly occur at two hotspot mutation points, C228T and C250T, which mutate more frequently than other DNA regions based on genomic coordinates. The C228T region and the C250T region are located 124 bp and 146 bp upstream of the ATG region, which is the first codon of the *TERT* gene coding region, respectively (Fig.1) (Ma et al., 2014). This region is rich in GC content and lacks TATA or TCCA boxes. However, it contains multiple binding sites that regulate the transcriptional activity of *TERT* and telomerase activation (Heidenreich and Kumar, 2017). Somatic mutations in the *TERT* promoter are among the most common non-coding cancer mutations (Stern et al., 2015). In an analysis of 31 cancer types from The Cancer Genome Atlas, 27% of the samples contained these promoter mutations (Barthel et al., 2017).

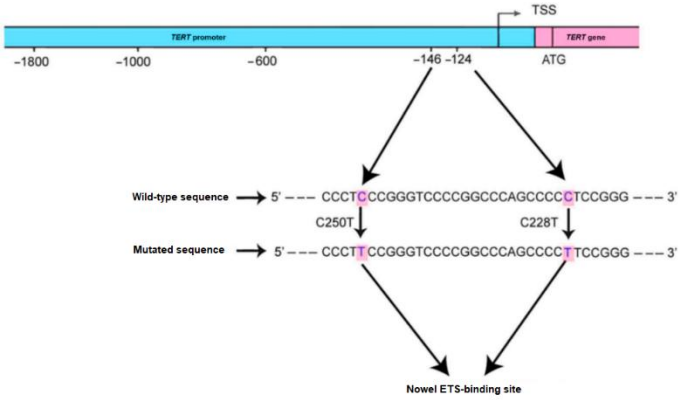

Fig. 1. *TERT* gene promoter binding sites and common promoter mutation points. ATG is the first codon, and the pink region is the coding region of the *TERT* gene. The blue region represents the *TERT* promoter region. TSS: Transcription start site. The new EST region occurs primarily at two hotspot regions, C228T and C250T, to create transcription factors. This region is located on the *TERT* promoter. TSS: transcription start site, EST: new binding site (Yang et al., 2021).

Cancer patients tend to have higher telomerase activity, which helps protect telomeres and allows tumors to evade aging. *TERT* promoter mutations generally lead to increased activity of *TERT* and telomerase in tumors (Smogorzewska and de Lange, 2004). Core promoter mutations create new ETS binding motifs, which in turn induce the upregulation of *TERT* (Wang et al., 2015). This results in the extension of telomeres in DNA sequences, enabling aging cells to bypass the Hayflick limit and, in some cases, achieve immortality, much like cancer cells. These *TERT* promoter mutations mainly occur at two hotspots, C228T and C250T, which are more frequently mutated than other regions of the genome (Hsu et al., 2006). Over 85% of *TERT* promoter mutations in various malignancies occur at these two canonical positions (Ma et al., 2014). Some reports indicate that exhibiting either mutation often demonstrates elevated levels of *TERT* and enhanced telomerase activity, implying a stimulatory effect on TERT expression (Barthel et al., 2017).

TERT promoter mutations activate telomerase expression, maintaining telomere length and genomic stability, allowing cells to continue dividing while avoiding senescence or apoptosis (Griewank et al., 2013). However, telomerase activity has also been observed in certain cancer types lacking *TERT* promoter mutations, suggesting alternative mechanisms might be at play. *TERT* promoter mutations were first identified in melanoma and subsequently found in cancers of the central nervous system, thyroid, and bladder (Akincilar et al., 2016). The frequency of these mutations varies across different cancer types. For example, liver, melanoma, and brain tumors exhibit a higher prevalence of these mutations, while they appear less

frequently in other cancers.

TERT promoter mutations have been linked to poor prognosis and lower survival rates in some cancers (Yuan et al., 2016; Spurr et al., 2024) In particular, studies indicate that these mutations are rare (~2.2-5.8%) in non-small cell lung cancer (NSCLC) patients and are typically found in older patients (Smogorzewska and de Lange, 2004; Yuan et al., 2016; Jung et al., 2017; El Zarif et al., 2024,;Werr et al., 2024). Some studies have demonstrated that these mutations are associated with poor prognoses and lymph node infiltration (Jung et al., 2017). In addition, single nucleotide polymorphisms (SNPs), consisting of rs2853669, are found in the *TERT* promoter location and are connected to telomere length and survival in NSCLC patients with *EGFR* mutations (Yuan et al., 2019; Chen et al., 2024).

2.2. Current status of TERT promoter mutation therapies and therapeutic strategies

There are numerous treatment strategies concentrated on *TERT* promoter mutations. The primary technique is based on the strategy of directly inhibiting TERT expression (Mender et al., 2018). For this, antisense oligonucleotides that bind mainly to the mutated *TERT* promoter series are used. In this way, the transcription of the *TERT* gene is blocked and telomerase expression is reduced (Ningarhari et al., 2021). Researchers are investigating this method to lower telomerase activity in cells with *TERT* promoter mutations in NSCLC malignancies (Jafri et al., 2016). It has also been reported that *TERT* mRNA can be targeted for degradation by RNA interference (RNAi) techniques using small interfering RNAs (siRNAs) that prevent telomerase production (Fekri Aval et al., 2016). Even though they are still in the early phases of research, RNAi-based treatments show a great deal of promise in preventing TERT expression.

Utilizing small molecule inhibitors, which target certain transcription sites that attach to the mutant *TERT* promoter and prevent telomerase overexpression, is an additional strategy (Brennan et al., 2013; Asangani et al., 2014). In addition, inhibitors containing JQ1, which belongs to the bromodomain and extra-terminal domain (BET) kinship circle, can prevent the assembly of transcription complexes at the mutated promoter location and thus inhibit *TERT* transcription (Filippakopoulos et al., 2010). This method focuses on disrupting the interaction between the mutated promoter and transcriptional activators.

One option is to use CRISPR/Cas9 technology to target mutations in the *TERT* promoter (Wen et al., 2020). *TERT* promoter mutations in NSCLC can be corrected by gene editing techniques targeting specific mutation sites, such as C228T or C250T, to reduce TERT overexpression and telomerase activity (Zhan et al., 2019). While this approach minimizes off-goal results, it has demanding situations in delivering CRISPR properly and efficiently to cancer cells (Liang et al., 2015).

Epigenetic cures aimed at the chromatin structure associated with the mutant *TERT* promoter may additionally have the ability to mitigate TERT expression (Barthel et al., 2017). Histone deacetylase (HDAC) and DNA methyltransferase (DNMT) inhibitors may additionally exchange chromatin accessibility and lessen *TERT* transcriptional activation. DNMT inhibitors like azacitidine and HDAC inhibitors like vorinostat, which are already used in different cancers, are being explored for their ability to regulate telomerase expression in NSCLC (Lewis and Tollefsbol, 2016).

Immunotherapy strategies also are being considered (Dosset et al., 2020). TERT-primarily based most cancer vaccines could assist the immune device become aware of and wreck TERT-expressing tumor cells, particularly in sufferers with *TERT* promoter mutations (Gridelli et al., 2020). Additionally, adoptive T-cell treatment plans involve modifying T-cells to target TERT-expressing tumor cells with the aid of recognizing neoantigens from *TERT* promoter mutations or by identifying *TERT*-derived peptides on the surface of cancer cells (Zanetti, 2017).

Lastly, the efficacy of *TERT* promoter mutation treatments may be increased by combining therapies. Telomerase inhibition may increase the susceptibility of cancer cells to immunological assaults or DNA damage when combined with traditional therapies like chemotherapy or immune checkpoint inhibitors (such as PD-1/PD-L1 inhibitors) (Yi et al., 2022). Additionally, telomerase suppression may make cancer cells more susceptible to radiation, which would hinder their ability to repair telomere damage caused by the treatment (Ali and Walter, 2023).

2.3. Challenges and considerations for therapeutic strategies targeting TERT

There are several challenges and concerns predicted for treatment strategies targeting *TERT*. Tumor heterogeneity means that not all NSCLC tumors harbor *TERT* promoter mutations, and even the ones that do could have other mutations that power resistance to telomerase-centered healing procedures (Guterres and Villanueva, 2020).

Therapeutic specificity is also an issue as concentrating on the *TERT* promoter without affecting ordinary stem cells, which depend upon telomerase for renewal, is a significant challenge. Moreover, cancer cells may develop resistance mechanisms by bypassing telomerase inhibition through alternative lengthening of telomeres (ALT), complicating the long-term efficacy of these therapies (Dilley & Greenberg, 2015). In addition, some methods for direct targeting of *TERT* present challenges in delivering the agent (e.g. CRISPR) directly and efficiently to tumor cells.

3. Conclusions

In NSCLC, mutations in the *TERT* promoter are linked to elevated production of telomerase, an enzyme that preserves telomere length and promotes the longevity of cancer cells. Therefore, targeting mutations of *TERT* promoter is a crucial area of therapeutic study in NSCLC. Most therapies that target mutations in the *TERT* promoter are currently in preclinical or early clinical development in clinical trials. Small molecule inhibitors and immunotherapy have entered early-stage studies for NSCLC and other malignancies. *TERT* promoter mutations may be used as predictive biomarkers in biomarker potential to find individuals who would benefit from telomerase-targeted treatments. Although research on how to best optimize these medicines for clinical usage continues, targeting *TERT* promoter mutations in NSCLC remains experimental but represents a potential area in cancer treatment.

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