Role of *TERT* gene mutation in the pathogenesis of anaplastic thyroid carcinoma (Review)

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Abstract. The present review provides a comprehensive analysis of the significance of telomerase reverse transcriptase (TERT) promoter mutations in the progression of anaplastic thyroid cancer (ATC). The significance of these mutations lies in their role in reactivating telomerase, and when combined with BRAF and RAS mutations, they contribute to heightened aggressiveness in ATC. The clinical implications of TERT promoter mutations were discussed, evaluating their potential role as prognostic biomarkers and targets for therapeutic intervention. The present review also emphasizes recent developments in our comprehension of TERT's role in the progression of ATC, offering insights that may guide future investigations focused on improving patient management for this condition.

Contents

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1. Introduction

The majority of thyroid cancers have a fairly favorable prognosis, while anaplastic thyroid cancer (ATC) is among the most aggressive of all solid malignancies. Although ATC accounts for <2% of thyroid cancers, it causes 1/3- to 50% of thyroid cancer-related deaths (1). The aggressive behavior of ATC creates an unmet need for in-depth molecular understanding in the development of potential therapies (1). Telomerase, a reverse transcriptase, maintains the telomeres at the end of chromosomes by using template RNA from the telomerase reverse transcriptase (TERT). Normal somatic cells exhibit low or undetectable telomerase activity, which results in a reduction in the quantity of deoxynucleotides associated with cell division, ultimately leading to cellular senescence (1).

Among the genetic mutations implicated in the pathogenesis of ATC, mutations in the *TERT* gene have attracted significant attention. The *TERT* gene, which encodes the catalytic subunit of telomerase, plays a crucial role in cellular immortality by maintaining telomere length (2). Aggressive thyroid cancers, particularly ATC, frequently exhibit TERT promoter mutations, accounting for ~40-70% of cases (2-4). These mutations lead to increased TERT expression and enhanced telomerase activity, allowing cancer cells to evade senescence and continue proliferating (Fig. 1). Furthermore, TERT mutations have been linked to other oncogenic mutations, including BRAF and RAS, suggesting that they function together to render cancer more aggressive (1,5,6).

New targeting therapies comprise telomerase activity inhibitors. They aim to inhibit cancer cells from becoming immortal when they activate TERT (7). The association of TERT mutations with distinct types of tumors could also serve as a biomarker for diagnosis and prognosis, influencing the choice of therapy. More studies are necessary to investigate the implication of the *TERT* gene in ATC for developing effective interventions to improve the dismal outcome in this disease (3).

The present review highlights the significant impact of the *TERT* gene on the aggressive transformation of ATC. Additionally, the authors are interested in investigating the

rare solid tumors classified as rare in Saudi Arabian population, with ATC being one such example. Consequently, it was sought to investigate the significance of TERT mutations in the development and progression of ATC, focusing on their effects on telomere maintenance, cellular immortality and tumor growth. Furthermore, the possible therapeutic ramifications of targeting TERT and associated pathways in the management of ATC were examined.

2. Biology of the TERT gene

Telomerase and telomere maintenance. Telomeres are repeating nucleotide sequences found at the ends of chromosomes. These sequences generally consist of TTAGGG (8,9). They perform the function of a protective cap, which inhibits the recognition of chromosomal ends as damage to DNA. There is a gradual shortening of the telomeres that occurs after each division of the cell; when the telomeres get too short, the cell will either be eliminated or enter a state of senescence. The enzyme known as telomerase is a ribonucleoprotein that is responsible for extending telomeres by adding telomeric repeats to the ends of chromosomes (10). This process helps offset the gradual shortening of telomeres. As a result, cells are capable of eternal division.

TERT and the function of telomerase. Telomerase is a ribonucleoprotein enzyme that extends the repetitive nucleotide sequences at chromosome ends, which are called telomeres. As a result of low or undetectable activity of telomerase in most somatic cells, these cells usually develop shorter telomeres and eventually become senescent or undergo apoptosis (9). By contrast, during tumorigenesis, cancer cells that succeeded in reactivating telomerase maintain their telomeres and acquire unlimited replicative potential, one of the well-known characteristics of cancer cells. TERT is the catalytic unit of telomerase, which confers activity. Normal cells express TERT from a highly regulated gene, but cancerous cells can upregulate this gene due to a mutation in the promoter region (8,10). The increased levels confer a survival advantage to cancerous cells, causing them to fail in normal cell division limits and consequently avoid apoptosis (11).

TERT promoter mutations. The identification of mutations in the promoter of *TERT* gene is the most significant observation in cancer biology (3,11). Mainly, researchers have identified these mutations at positions -124 and -146 bp upstream of the transcription initiation site, which create two novel binding sites for transcription factors such as ETS, thereby activating TERT expression. Very aggressive cancers including ATC, glioblastoma and melanoma commonly exhibit these mutations. Indeed, >60-70% of the cases of ATC have shown TERT promoter mutations, whose presence correlates with poorer outcomes and a more aggressive disease course (5). In addition, 70% of melanomas, 80% of glioblastomas and ~60% of bladder cancers have TERT promoter mutations.

Typically, somatic mutations in the TERT promoter occur in conjunction with other oncogenic mutations, such as those in the genes *BRAF* or *RAS*. When the mutation of the TERT promoter was combined with these other genetic changes, they worked together to render these tumors turn cancerous and develop to cancer (1,3,12). For example, as will be mentioned in the next section, a large number of ATC cases express the concomitance of TERT promoter mutations with the BRAFV600E mutation, demonstrating highly aggressive tumor behavior and insusceptibility to standard therapies.

TERT promoter mutations in ATC. Mutations in the TERT promoter region are some of the most common genetic alterations found in ATC. These often occur at positions -124 C>T and -146 C>T from the TERT transcription start site and create novel binding sites for transcription factors such as members of the ETS family (2,13). Consequently, there is a remarkable induction in TERT expression and telomerase activity.

Reactivation of TERT via promoter mutations is an important step in the tumorigenesis of ATC (3,6). TERT promoter mutations enable unlimited cellular replication in cancer, enabling cells to maintain their telomeres (8,10). The ability of telomerase to support the length of the telomeres contributes significantly to the aggressive nature of ATC disease, which is characterized by rapid tumor growth and invasion. Reactivating TERT further helps ATC cells live forever and develop a more aggressive phenotype by making them more resistant to apoptosis, invasion and metastasis (9). This partly occurs because TERT may interact with other pathways, such as PI3K/AKT and MAPK signaling pathways, which are often aberrantly activated in ATC (14). These contribute to the high proliferative capacity, metastatic potential and chemoresistance observed in ATC (6).

As previously described, mutations in the TERT promoter almost always occur together with mutations in other oncogenes, notably BRAF and RAS (15). The BRAFV600E mutation is considered one of the major driver mutations in numerous kinds of thyroid cancer, leading to the constitutive activation of the MAPK/ERK pathway, which promotes cell proliferation and survival. BRAF mutations in ATC cells increased telomerase activity and made them even more aggressive when combined with TERT promoter mutations (16,17). Consequently, other mutually co-occurring mutations in the RAS family of oncogenes, which activate the MAPK and PI3K/AKT pathways, further enhanced the oncogenic potential of TERT by promoting cellular proliferation and survival in a telomerase-dependent manner (5).

Most somatic cells tightly restrict TERT expression, resulting in low or undetectable telomerase activity. However, stem cells, germline cells and some immune cells express TERT, enabling them to maintain telomere length and promote tissue regeneration. When TERT is turned back on in cancer, cells can copy themselves more than they should be able to, which causes the tumor to grow and take on more aggressive traits (11).

3. TERT plays a crucial role in the pathogenesis of ATC

Tumorigenesis and progression. In ATC tumorigenesis, activating mutations of the TERT promoter represent an important step (18). These TERT promoter mutations confer telomere maintenance in such cells and fulfill one of the hallmarks of cancer: Infinite cellular replication. The maintenance of telomere length, facilitated by telomerase activity, plays a crucial role in the aggressiveness of the disease, particularly when ATC

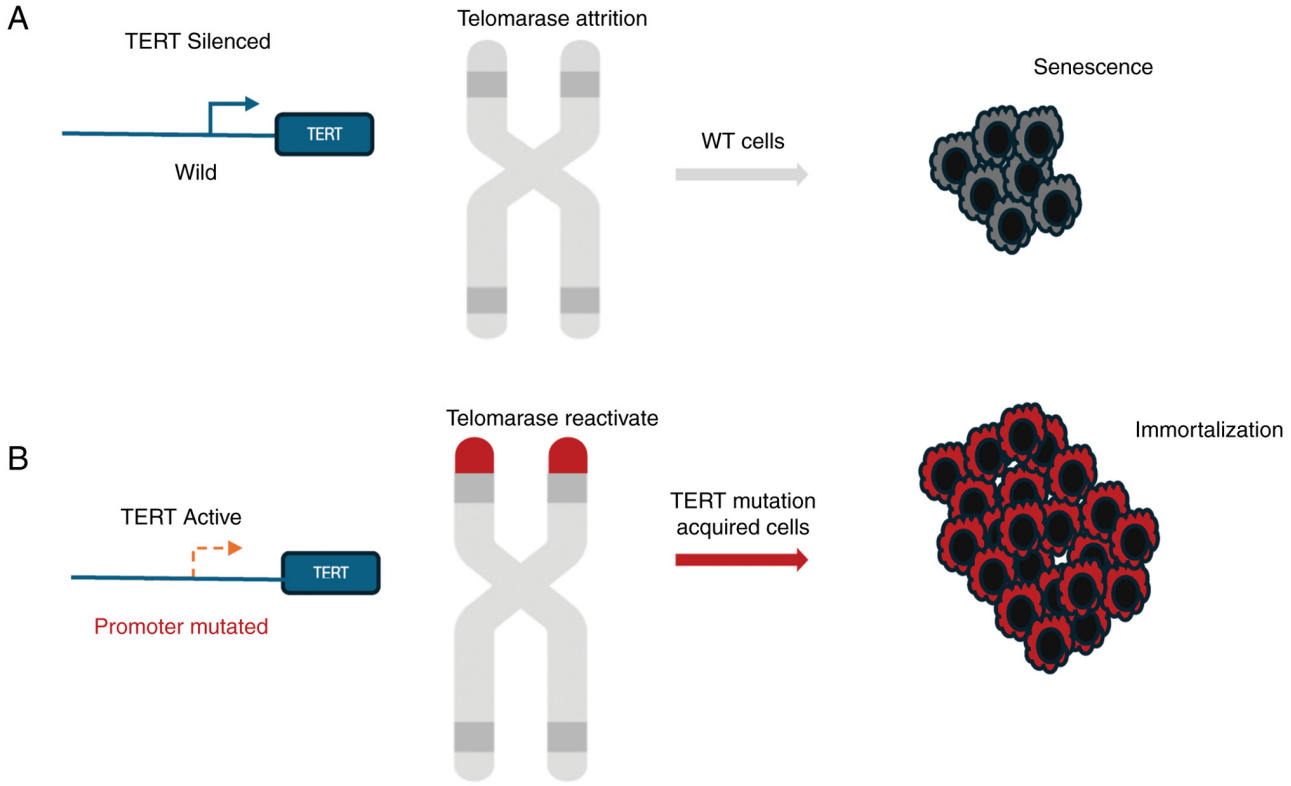

Figure 1. Mutant TERT promoter, which is found in the majority of anaplastic thyroid cancer cells. (A) Normal cells that do not express TERT shorten their telomeres progressively with each cellular division. (B) By contrast, in tumor cells with TERT promoter mutations, TERT is activated, and telomeres are maintained, facilitating cellular immortality. The figure generated by Microsoft® PowerPoint (version 16.9.3; Microsoft Corporation). TERT, telomerase reverse transcriptase; WT, wild-type.

experiences typical rapid tumor growth and invasion. Moreover, in ATC, TERT reactivation promotes not only cellular immortality but also other cancer-related processes, including invasion, metastasis and resistance to apoptosis. TERT partially achieves this through its interactions with a wide range of signaling pathways, such as PI3K/AKT and MAPK cascades, frequently dysregulated in ATC. These pathways collectively contribute to the high proliferation rate, metastatic potential and resistance to therapy observed in ATC (18).

Interaction with other oncogenic drivers. As previously mentioned, mutations of other oncogenes, particularly BRAF and RAS, almost always accompany TERT promoter mutations. The BRAFV600E mutation is the most important driver mutation in thyroid cancers. It permanently activates the MAPK/ERK pathway, which in turn activates downstream effectors that usually help cells proliferate and survive (3,14,17). As a result of a mutation in the TERT promoter, BRAF-mutated ATC cells had higher levels of telomerase activity and were very aggressive (1). In the same way, oncogenic mutations in the RAS family genes, which turn on both the MAPK and PI3K/AKT pathways, often happen together with TERT promoter mutations in ATC. These make the cancer-causing effect of TERT even stronger by helping cells proliferate and stay alive in a way that depends on telomerase (3,4,11,17).

Diagnostic and prognostic Implications of TERT mutations. Whereas TERT promoter mutations exhibit a very high prevalence in ATC, their detection may hence have a significant impact on diagnosis and prognosis (19,20). There is a chance that molecular tests for mutations in the TERT promoter and other common mutations such as BRAF and RAS could help diagnose ATC, at least in cases where histology is not completely clear (19). Along with this, the presence of TERT promoter mutations may also provide useful prognostic information, since these mutations are linked to worse clinical outcomes, such as a higher rate of recurrence and metastasis, as well as overall mortality (21). Besides their diagnostic potential, TERT promoter mutations might also become useful biomarkers for treatment stratification. As an example, patients with ATC carrying TERT promoter mutations would likely have improved response to treatment that targets telomerase or the signaling pathways that interact with TERT, such as the MAPK and PI3K/AKT pathways. This highlights a significant shift in personalized treatment approaches for ATC, considering the molecular profile of the tumor (2,22).

4. Therapeutic targeting of TERT in ATC

Telomerase inhibitors. Given the central role of TERT in ATC pathogenesis, targeting telomerase has emerged as a potential therapeutic strategy (23-25). Telomerase inhibitors, such as imetelstat, have shown promise in ATC models before they are tested on humans. They accomplish this by decreasing telomerase activity and shortening telomeres (8,24,26). These agents function by binding to the RNA component of telomerase, preventing the addition of telomeric repeats to the ends of chromosomes. Inhibition of telomerase leads to

progressive telomere shortening, eventually triggering cellular senescence or apoptosis in cancer cells that rely on telomerase for survival (23,27,28).

While telomerase inhibitors have shown some efficacy in other cancers, their use in ATC remains experimental (24). Developing telomerase inhibitors for clinical use presents a challenge due to the delayed onset of their effects, as telomeres must shorten over several cell divisions before the therapeutic impact becomes apparent. Telomerase inhibitors may require combination with other therapies to achieve meaningful clinical outcomes in rapidly progressing cancers such as ATC, where immediate tumor control is critical (9,24).

Targeting associated pathways. In addition to directly targeting telomerase, another therapeutic approach involves targeting the signaling pathways that interact with TERT. ATC frequently dysregulates the MAPK and PI3K/AKT pathways, and preclinical and early clinical studies have shown promise for inhibitors of these pathways (29). For example, BRAF inhibitors, as BRAF gene, more especially the BRAFV600E mutation, is mutated in between 30-50% of ATC cases. In these individuals, targeted treatments that block the BRAF protein, such as dabrafenib and vemurafenib, have demonstrated notable therapeutic efficacy. The FDA has authorized these medications for the treatment of ATC caused by the BRAF V600E mutation. Dabrafenib and vemurafenib, have demonstrated efficacy in patients with ATC carrying the BRAFV600E mutation, particularly when combined with MEK inhibitors. By blocking the MAPK pathway, these drugs may also indirectly affect TERT activity and reduce the tumor's proliferative capacity (30).

Researchers are exploring PI3K and AKT inhibitors as potential treatments for ATC, especially for patients with mutations in the PI3K/AKT pathway (29,31). Stopping this pathway might not only slow down the growth of tumors, but it might also enable other treatments, such as radiotherapy and chemotherapy, to work better by avoiding resistance mechanisms that are linked to TERT activation (32).

Kinase inhibitors are being investigated as therapeutic agents due to the mutation of TERT along with BRAF and RAS. Vemurafenib and dabrafenib are drugs that work well in ATC with a BRAF V600E mutation (31,33). Researchers have conducted combination studies with MEK inhibitors such as trametinib to overcome resistance. Preclinical combination drug studies have yielded promising results, with some demonstrating long-term effects. The activation of the MAPK pathway in TERT mutant ATC may inhibit tumor growth and prolong survival (34).

Given the crucial role of telomerase in TERT-mutant ATC, telomerase inhibitors could serve as effective therapeutic drugs (31). In the development process, telomerase-targeting drugs also aid in inhibiting the enzyme's activity, thereby further limiting the maintenance of telomeres in cancerous cells. As aforementioned, telomerase inhibitors such as imetelstat have been promising in the preclinical models, and more studies are required to establish their efficacy and safety for treating patients with ATC. Although these drugs are promising, they work best with other targeted therapies.

Despite advances in targeted drugs, improving ATC results requires a comprehensive approach. Numerous approaches are needed: Precision medicine is required, as ATC is molecularly heterogeneous. A complete genetic profile may identify TERT, BRAF and RAS mutations, enabling tailored treatments. Personalized treatment regimens will also focus on the features of the tumor and reduce collateral damages (31,35,36).

Since anaplastic thyroid carcinoma is such an aggressive cancer, monocytic therapies are almost never successful (37). Using a mix of kinase inhibitors, immunotherapies, or telomerase inhibitors in treatment may be able to overcome resistance mechanisms and render therapy more complete. Clinical trials are studying combination therapies in TERT-mutated ATC.

The identification of TERT mutations along with other oncogenic factors in patients with ATC may accelerate the process of finding novel treatment strategies. TERT expression biomarkers may indicate a virulent disease, prompting early targeting to improve survival and reduce metastases (3). However, the aggressiveness of the ATC demands palliative care along with other supportive care. Patients and families could be instructed about treatment options and the expected consequences of new medications, potentially enhancing their quality of life and autonomy. Combined medical and psychological treatments assure overall management of the sickness.

Immunotherapy and TERT. Previous advances in immunotherapy have opened new avenues for treating ATC, particularly with the advent of immune checkpoint inhibitors targeting programmed cell death protein 1 and programmed death-ligand 1 (38). Immunotherapy harnesses the power of the immune system to recognize and destroy cancer cells. Researchers are investigating TERT-specific immunotherapy approaches, such as T-cell therapy (25). These approaches aim to stimulate an immune response against TERT-expressing ATC cells, leading to their elimination (39). The role of TERT in immune evasion is still being explored, but strong evidence suggests that TERT may contribute to an immunosuppressive tumor microenvironment by promoting the expression of immune checkpoint molecules. This raises the possibility that combining telomerase inhibitors with immunotherapy could enhance the antitumor immune response and improve outcomes in patients with ATC (40).

TERT mutations can lead to increased neoantigen expression, making cancer cells more recognizable to the immune system. Studies have demonstrated the benefits of immune checkpoint drugs such as pembrolizumab in ATC, particularly when combined with kinase inhibitors or radiotherapy. Emergent data suggest that immunotherapy using targeted drugs could potentiate immune response and provide an improved prognosis for patients bearing the TERT mutation in ATC. Nonetheless, research on ATC pathogenesis and clinical management is not only working on understanding every aspect of this disease but also exploring various immunotherapy strategies.

5. Conclusion

The multifunctional enzyme TERT is involved in the pathogenesis of ATC by playing a significant role in the preservation of telomeres, the transmission of cellular signals, and the

growth of tumors. Given the very high incidence of TERT promoter mutations in ATC, it is likely that these events play a significant driving role in the development of this severe form of chemotherapy. These alterations result in an overabundance of TERT, which, at present, permits cancer cells to keep their telomere length intact and escape replicative senescence, which ultimately results in an endless proliferation of cells.

In addition to this, TERT is involved in a variety of oncogenic signaling pathways, and it is responsible for stimulating the development, invasion and metastasis of other tumors. The fact that TERT participates in actions beyond telomere preservation highlights the intricacy of its involvement in cancer biology. These activities include regulating gene expression and modifying apoptotic pathways.

TERT targeting is a promising therapeutic method since it has the ability to interrupt the maintenance of telomeres, inhibit oncogenic signaling, and induce ATC cells to die. All these characteristics are commonly associated with cancer. This might open the way for the development of innovative therapeutic options for ATC, which is often resistant to current medications. The development of particular inhibitors that target TERT or its related pathways could be advantageous.

Understanding the specific processes that underlie the function of TERT in the advancement of ATC should be a top priority for future research on ATC, in order to identify successful techniques to target TERT mutations. It will be essential to conduct clinical studies that investigate TERT inhibitors in order to determine whether or not they are effective and safe as potential therapy choices. It is possible that therapeutic targeting of TERT might improve outcomes for patients who have ATC and significantly extend the understanding of the formation of ATC tumors themselves.

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Availability of data and materials

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Authors' contributions

AGA, OA, NA, DA and ROS contributed equally for the article conception and design, data collection and manuscript preparation. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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