

# Telomeres and telomerase: Understanding basic structure and potential new therapeutic strategies targeting it in the treatment of cancer

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Received : 19-07-2013  
Review completed : 05-11-2013  
Accepted : 06-02-2014

## ABSTRACT

The impact of cancer on humanity is huge and a great deal of research is going on worldwide to find novel therapeutic targets. Telomerase is one such exciting target. Increased telomerase activity provides cancer cells with unlimited proliferative potential and is one of the hallmarks of cancer. This article provides a basic understanding of telomere and telomerase in cancer and summarizes various potential therapeutic approaches used for strategic targeting of telomerase enzyme. Medline, Medscape, EMBASE, Cochrane database, Scopus and clinicaltrials.gov were searched using terms like “telomeres”, “telomerase” and “targeted cancer therapy”. Journal articles published from 2005 to 2013 describing telomerase-based cancer therapy were screened.

**KEY WORDS:** Anticancer therapy, telomerase, telomere

## Introduction

Cancer is a major cause of death worldwide. It is estimated that 7.6 million people died in 2008 due to cancer and this figure is expected to double by 2030.<sup>[1]</sup> To conquer this disease, discovery of validated targets and new drugs is a necessity. One such attractive target is the telomerase enzyme. Telomerase-based therapies act by novel mechanisms that can provide new options for cancer therapy either alone or in combination with existing therapeutic options. Many such agents are along the drug development pipeline.<sup>[2]</sup> This article provides a basic understanding of telomeres, telomerases and various current telomerase-based therapies under investigation.

## History

Telomeres were first studied in the organism *Tetrahymena thermophila* by Elizabeth Blackburn and Joseph Gal in 1978. In

1985, Greider and Blackburn identified a “terminal transferase” enzymatic activity, which was capable of extending telomeric sequences. This activity was associated with a protein complex which was named telomerase. In 1989, Morin identified telomerase activity in human cells. A major breakthrough occurred in 1994 when a simple PCR-based assay, Telomeric Repeat Amplification Protocol (TRAP) was developed by Shay and Wright that improved the capability to detect telomere activity in human cells. Thereafter, a lot of research has been carried out in this field. In 2009, the Nobel Prize in Physiology or Medicine was awarded to Elizabeth Blackburn, Jack Szostak, and Carol Greider for their discoveries on telomeres and telomerase.<sup>[3]</sup>

## Telomere, telomerase structure and function

Telomeres are specialized structures at the ends of linear eukaryotic chromosomes. They consist of many tandem copies of a short oligonucleotide sequence in the form of G (1-4) T (1-4).<sup>[4,5]</sup> The human telomere is a repeat of the nucleotide sequence TTAGGG that occurs about a hundred times. As chromosomes are replicated during cell division, there is incomplete replication of the extreme 3' end of the lagging strand (sometimes referred to as “end replication problem”) which results in the loss of approximately 50 base pairs of telomeric material with each cell division [Figure 1]. Therefore without a special mechanism for replicating the ends, chromosomes would be somewhat shortened in each cell generation. Eventually,

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	PubMed ID: ***

telomeres would become so short that the cell would stop dividing. It is postulated that this can act as a molecular counting mechanism, marking the number of cell divisions.<sup>[6]</sup> The enzyme telomerase solves this problem by adding telomeres to chromosome ends [Figure 2]. The telomerase holoenzyme core consists of various components—the reverse transcriptase protein hTERT (human telomerase reverse transcriptase) that functions as a catalytic subunit, the RNA template-hTR (human telomere RNA) or telomerase RNA component (TERC) that serves as a template for directing the appropriate telomeric sequences onto the 3' end of a telomeric primer, and RNA-binding proteins that are involved in stabilization and maturation of the telomerase complex.<sup>[5,7]</sup> The ability to express telomerase and maintain telomeric DNA is a crucial step in carcinogenesis.<sup>[8]</sup>

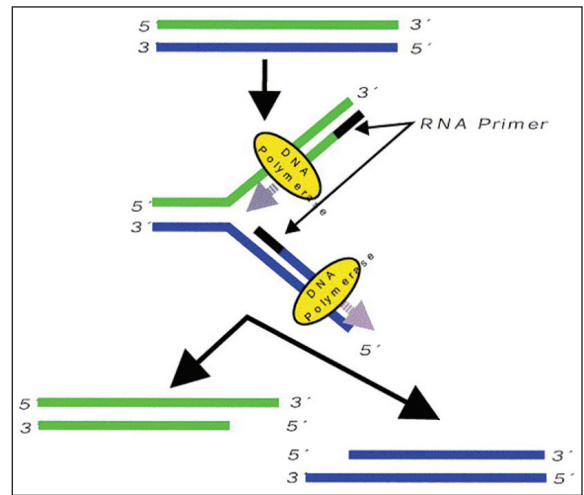
Another important role of telomeres is to protect the linear chromosome ends from being recognized as DNA damage which could initiate attack by DNA repair enzymes.<sup>[9]</sup> In adult tissues, most normal cells have low or no detectable telomerase activity. It is only in germline and embryonic stem cells that they maintain their replication capacity, such as male germ cells, activated lymphocytes, hematopoietic progenitor cells and basal keratinocytes where telomerase activity is detectable.<sup>[10]</sup> Hence normal cells undergo apoptosis when critically short length of telomeres is reached. By contrast, most cancer cells (80-90%) possess telomerase activity, which can make them immortal.<sup>[11]</sup> So targeting the telomere/telomerase machinery offers a novel and potentially broad-spectrum anticancer therapeutic strategy.

Apart from cancer, telomerase is also implicated in diseases like dyskeratosis congenita, adult-onset aplastic anemia or liver cirrhosis. It is also related to the normal aging process though its exact role in the reversal of aging is still controversial.<sup>[12]</sup>

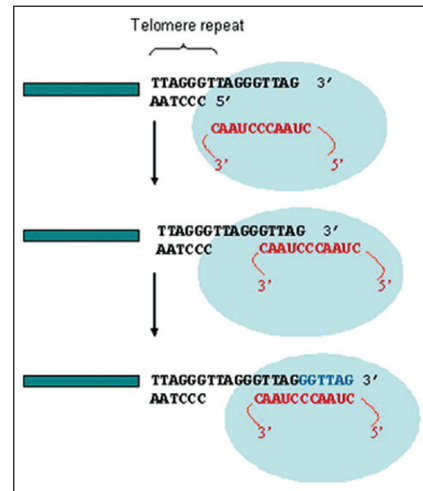
Telomerase function is highly regulated in normal cells. The molecular basis for telomerase function is highly complex. Some of the determinants include transcriptional, post-transcriptional and post-translational control of catalytic subunit hTERT.<sup>[13]</sup> Recruitment of telomerase to telomeres end and its enzymatic activity is modulated by shelterin capping and G-quadruplex stacks. These structures are found at the end of chromosomes and usually protect the ends from any loss of information or fusion with other chromosomes by forming t-loops which close the ends.<sup>[14]</sup>

**The shelterin complex and G-quadruplex**

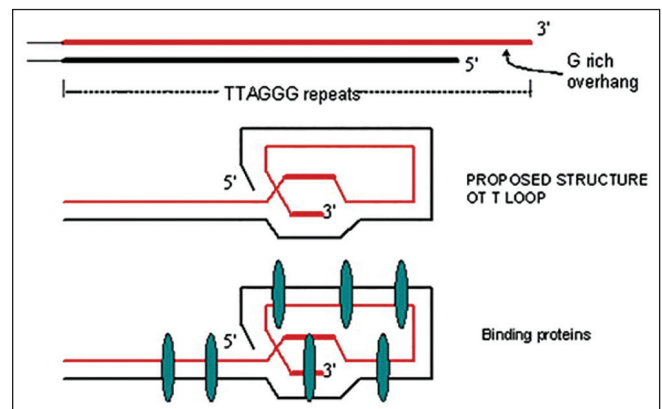
Telomeres are composed of stretches of double-stranded tandem repeat sequences and a short single stranded G rich 3' overhang. The double-stranded telomere sequence is associated with telomere binding proteins like telomeric repeat-binding factors 1 and 2 (TRF1, TRF2), TRF1 interacting nuclear factor 2 (TIN2) and Repressor/Activator protein 1 (RAP1). The single-stranded telomere sequence is associated with two proteins—Protection of Telomeres 1 (POT1) and POT1 Interacting Protein 1 (TPPI).<sup>[15]</sup> This single-stranded DNA loops back into the double-stranded part; this in turn is mediated by interaction of associated proteins which form the capped conformation of telomeres [Figure 3]. This complex is called the shelterin complex as it shelters the telomere from a series of unwanted



**Figure 1:** End replication problem of chromosomes. Each round of replication leaves 50-200 base pairs DNA unreplicated at 3' end as terminal RNA primer cannot be replicated which is removed. Each replication hence generates shorter and shorter DNA molecules



**Figure 2:** Role of telomerase. Telomerase (in light blue) adds telomeres (TTAGGG sequence) to the chromosome end with its RNA component (hTR) which serves as a template for synthesis of TG strand of the telomere



**Figure 3:** Shelterin complex forming the capped conformation of telomeres inhibiting telomerase access to 3' overhang

activities<sup>[16]</sup>, whereas the G-quadruplex is composed of planar stacks of guanine(G) residues formed by intra or intermolecular interaction of G rich single-stranded telomere ends.<sup>[17]</sup> These secondary structures have four strands and are made up of G bases; hence the name G-quadruplex<sup>[18]</sup> [Figure 4].

The telomerase enzyme complex requires the end of the telomere to be single stranded in order for effective binding to occur between the two telomerase components, hTR and hTERT. So the G-quadruplex must first be unfolded before the telomerase can initiate extension of the telomere. Thus, the G-quadruplex protects the telomeric 3' overhang from being accessed by the telomerase, thereby regulating its catalytic activity.<sup>[15,18]</sup>

The molecular mechanism of telomerase recruitment has been studied in budding yeast, but is not well understood in multicellular organisms. In human cells, TPP1 has been shown to be involved in telomerase recruitment and forms a complex with POT1. TIN2 binds TRF1 and TRF2 and recruits the TPP1-POT1 complex. TPP1 in this complex binds the TEN (Telomerase Essential N-terminal) domain of TERT, which is required for high processivity of telomerase action.<sup>[13]</sup>

#### Telomerase in normal and cancer cells

It has been observed that telomerase activity persists throughout human embryonic divisions and is needed for the large number of cell divisions required to complete embryogenesis. But at birth and in differentiated somatic cells, hTERT expression is repressed and telomerase activity is absent. However, in actively dividing cells like blood cells, epithelial cells and endothelial cells, some telomerase activity is maintained and is highly regulated.<sup>[8,19]</sup>

In human cells, there are two mechanisms to restrict cell growth: Senescence or M<sub>1</sub> and crisis or M<sub>2</sub>.<sup>[14]</sup> Senescence can be induced in part due to telomere erosion. Eroded telomeres generate a persistent DNA damage response, which initiates senescence.<sup>[20]</sup> In cancer cells, these DNA damage signals are bypassed and cells continue to divide thereby resulting in telomere shortening. Eventually, many shortened chromosome ends fuse together leading to non-homologous end joining. At anaphase, these dicentric chromatids formed due to fusions fail to segregate properly leading to loss of genomic integrity and a state of crisis characterized by p53 independent apoptosis.<sup>[19,21]</sup> Cancer cells must overcome this senescence or crisis, two anticancer protective mechanisms to become malignant. This is achieved by means of telomerase expression. Evidence suggests that cancer cells have very short telomeres. This can be attributed to the fact that cancer cells have already undergone many cell cycles with telomerase activity. Hence, normal stem cells which have relatively long telomeres are not affected to the same extent as tumor cells by telomerase inhibition. That is why telomerase is an attractive cancer therapeutic target.<sup>[22]</sup>

Telomerase activity can be detected and measured by using Telomere Repeat Amplification Protocol (TRAP) assay based on polymerase chain reaction (PCR). It has been shown that telomerase is active in 80-90% of human cancer cells. Approximately 10% of cancer cells that do not express

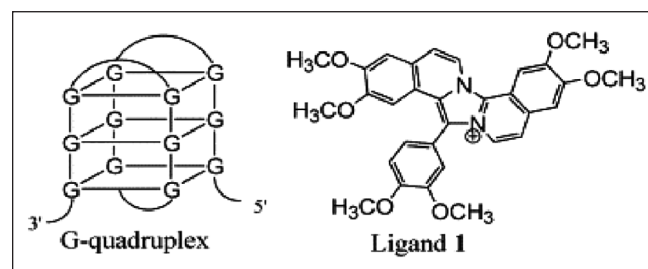
telomerase activity have been found to be mortal tumor cells or maintain their telomeres through an alternative pathway i.e. alternative lengthening of telomeres (ALT).<sup>[23]</sup> Telomerase holds great promise as a biomarker for early cancer detection as well as a prognostic index. It has been detected in many malignant cells from various samples of oral rinses, bronchial washings, colonic luminal washings or urine/bladder washings. Such tests can serve as non-invasive and cost-effective methods for detection of oral squamous cell carcinoma, lung carcinoma, colorectal carcinoma or bladder carcinoma.<sup>[24]</sup>

#### Approaches to targeting telomerase expressing cells

There are two general strategies to inhibit telomerase activity in cancer cells.<sup>[25]</sup> One is direct i.e. compounds directly causing telomerase inhibition by inhibiting the activity of the catalytic subunit (hTERT), theRNA template (hTR) or the telomere structure.<sup>[26]</sup> Indirect strategies involve blocking telomerase access to telomeres by using G-quadruplex stabilizers, or by inhibiting binding of telomerase-associated proteins leading to telomere uncapping and cell apoptosis<sup>[25]</sup> [Table 1].

#### Targeting hTERT and hTR

By the use of nucleic acid-based biologicals like small interfering RNA (siRNA), siRNA expression vectors, ribozymes and antisense oligonucleotides, telomerase catalytic subunit hTERT can be inhibited.<sup>[8]</sup> Ribozymes are small RNA molecules that have specific endoribonuclease activity. They consist of a catalytic core flanked by anti-sense sequences that function in the recognition of the target site.<sup>[27]</sup> Hyayashidan *et al.* have demonstrated inhibition of telomerase activity by ribozymes in pancreatic cell lines.<sup>[28]</sup> Among small molecule inhibitors, BIBR1532 (2-[E]-3-naphthalen-2-yl-but-2-enoylamino]-benzoic acid), a synthetic non-competitive inhibitor of hTERT



**Figure 4:** G-quadruplexes formed by the stacking of guanine tetrads. Structural example of a ligand which can stabilize G-quadruplex

**Table 1:** Some approaches for targeting telomerase as anticancer therapy

Target	Class	Examples
hTERT	Small molecule inhibitors	BIBR1532
as immune target	Antisense molecules	DNA, siRNA, Ribozymes
	Vaccines	GV1001, GRNVAC 1
hTR	Antisense oligonucleotides	GRN163L, siRNA, Ribozymes
Telomere structure	G-quadruplex ligands	BRACO-19, Telomestatin, RHPS4

hTERT = Human telomerase reverse transcriptase; hTR = Human telomere RNA; siRNA = Small interfering RNA

has been developed.<sup>[29]</sup> It directly interacts with hTERT component of telomerase. Results from various studies have demonstrated a dose-dependent inhibition of telomerase with high concentration of BIBR1532 with no significant effect on normal cells. Good results have been observed in preclinical studies on breast, prostate and fibrosarcoma cancer cell lines.<sup>[10]</sup> It also sensitizes some drug-resistant cells lines like promyelocytic cell lines to other chemotherapies.<sup>[30]</sup>

The most susceptible region for targeting hTR has been found to be the telomere repeat template sequence. It is an accessible target for oligonucleotide based inhibitors.<sup>[8,31]</sup> Stabilized analogues such as phosphorothioate oligodeoxynucleotides (PS-ODNs) directed against the hTR RNA component have demonstrated potent inhibitory effects on telomerase activity. One such compound developed, GRN163 (N<sup>3'</sup>-P<sup>5'</sup>-thiophosphoramidate), required a lipid carrier molecule to effectively traverse the cell membrane.<sup>[32]</sup> To counteract this, GRN163L (also known as imetelstat) which is a 13-mer oligonucleotide N<sup>3'</sup>-P<sup>5'</sup>-thio-phosphoramidate has been developed.<sup>[33]</sup> GRN163L, being lipid soluble, does not require any transporter for cellular intake, and demonstrated improved telomerase inhibition.<sup>[19]</sup>

#### Stabilizing G-quadruplex DNA

G-quadruplex structure must first be unfolded before the telomerase can initiate extension of the telomere. Therefore if telomeres could be stabilized using a G-quadruplex structure, the cells could be prevented from infinite proliferation characteristic of cancer. Small molecules that stabilize these structures and mimic their effect have been designed and found to inhibit telomerase activity.<sup>[34]</sup> Most of the G-quadruplex stabilizing ligands contain a polycyclic heteroaromatic structure, though it is not an essential requirement for quadruplex binding.<sup>[35]</sup> Three most commonly studied G-quadruplex stabilizing agents are Telomestatin, BRACO-19 and RHPS4.

#### Telomestatin, BRACO-19 and RHPS4

Telomestatin is a macrocyclic compound isolated from natural source *Streptomyces annulatus*.<sup>[36]</sup> It has been found to induce activation of apoptosis in acute leukemic cells and inhibit cell proliferation in various cancer cell lines like myeloma, breast, cervical, neuroblastoma cell lines. However, its use in cancer patients is still a farfetched idea because of the difficulty in the synthesis of this compound.<sup>[25]</sup>

BRACO-19 is a trisubstituted acridine derivative and RHPS4 is a polycyclic acridinium compound.<sup>[37]</sup> BRACO-19 has shown to induce marked reduction in cell growth in prostate cancer, breast cancer and uterine cancer cell lines. It works best for tumors with shorter telomeres. RHPS4 when studied in combination with other therapies like paclitaxel or doxorubicin has resulted in tumor remission.<sup>[38]</sup> One of the advantages with these compounds is the fact that they induce replicative senescence in cancer cells within a few days of exposure.<sup>[39]</sup> However, the poor pharmacokinetic properties of BRACO-19 pose a practical hindrance to its clinical testing. More hydrophobic compounds like fluoroquinolone derivative Quarfloxin/CX-3543 have been developed to make these compounds bioavailable. This agent

has completed phase II trial for treatment in low to intermediate grade neuroendocrine tumors, though results are still awaited.<sup>[40]</sup>

#### Immunotherapy

Telomerase is an attractive immune target due to almost ubiquitous expression of telomerase in cancer cells.<sup>[41]</sup> Telomerase peptides can act as universal telomerase associated antigens (TAAs). For instance, hTERT is a major histocompatibility complex (MHC) class-I restricted antigen recognized by cytotoxic CD8+ T lymphocytes. TAAs produce strong immune response by activating both CD4+ and CD8+ T cells.<sup>[25]</sup> Based on this, several vaccines have been developed that consist of antigen presenting cells that were exposed to high levels of immunogenic hTERT peptide or were modified to overexpress an immunogenic fragment of hTERT. These antigen presenting cells activate telomerase-specific cytotoxic T lymphocytes, which can then recognize and target telomerase expressing cancer cells.<sup>[19]</sup> Two of the most studied vaccines are GV1001 and GRNVAC1.

GV1001 is an hTERT peptide based vaccine. It is a 16 amino acid MHC class II-restricted peptide derived from the active site of human hTERT. It initiates both CD4+/CD8+ immune response via multiple MHC class II alleles. It is used in conjunction with adjuvant like granulocyte-macrophage colony stimulating factor (GM-CSF). It has shown good results in Phase I and II clinical trials on patients with advanced stage melanoma, non small cell lung carcinoma, hepatocellular carcinoma and pancreatic carcinoma. In the Phase II study of pancreatic cancer patients, 75% of patients showed an immune response.<sup>[42]</sup> It is now in Phase III clinical trials for treatment of non-small-cell lung cancer in combination with chemotherapy.<sup>[43]</sup>

GRNVAC1 is an autologous dendritic cell (DC) vaccine prepared from the patient's blood and is capable of activating both CD4+ and CD8+ immune responses. DC is primed ex vivo to display a multitude of hTERT fragments. It was tested in Phase I clinical trials in patients with metastatic prostate cancer and in Phase II clinical trials in patients with acute myelogenous leukemia with encouraging results. It has shown minimal effects on normal cells and no autoimmunity was detected.<sup>[25]</sup>

#### Telomerase-directed gene therapy/viral therapy

The hTERT promoter component of human telomerase is tightly regulated and is not expressed in normal cells. Hence the hTERT promoter can be used to drive the expression of a suicide gene or control the replication of a lytic virus. In a first approach, hTERT-driven genes such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) or caspase 6 was introduced into tumor to induce apoptosis.<sup>[19]</sup> Alternatively, tumors were pre-administered with an hTERT-driven prodrug activating enzyme to convert the prodrug (given for tumor lysis) into a toxin, hence selectively killing cancer cells.<sup>[23]</sup> For instance, a genetically modified viral vector encoding a prodrug activating enzyme like carboxypeptidase would replicate only in hTERT-over expressing cells and hence would activate the cytotoxic prodrug like 5-fluorocytosine only in cancer cells.<sup>[44]</sup> A second strategy involves modified hTERT promoter driven viral protein E1, which is required for replication of adenovirus. Now

as EI is controlled by the hTERT promoter, viruses can only replicate in telomerase expressing cancer cells.<sup>[45]</sup> Such viruses are called telomerase-specific replication-competent adenovirus (TRAD). Telomelysin/OBP-301 is one such adenoviral vector, which has completed Phase I clinical trial.<sup>[43]</sup>

### Problems with telomerase inhibitors

One of the problems with telomerase inhibitors is a phenomenon known as “phenotypic lag”. Telomerase inhibitors cause erosion of telomeric sequence over the cell divisions until critically short telomeres signal senescence and apoptosis in cancer cells. Most solid tumors have a population doubling time of several weeks, thereby taking months of treatment for the telomerase inhibitors to exhibit their effects.<sup>[46]</sup> Hence the more practical approach would be to develop reliable quantitative assays to measure distribution of shortest telomere in a given cancer cell population so that oncologists can select cancer patients with more chances of responding to telomerase inhibitors.<sup>[40]</sup> Scientists are now studying tumor banks to identify subtypes of solid tumors with routinely short telomeres that may respond optimally to such agents.<sup>[43]</sup>

But there are concerns that as short telomeres drive genomic instability, this might lead to increase in malignancy.<sup>[47]</sup>

### Pharmacokinetic problems

Small molecule inhibitors like telomestatin and BIBR1532 are insufficiently hydrophobic and poorly penetrate cell membranes. BRACO19 has higher water solubility but is not able to penetrate biological barriers in airways and intestinal epithelial cell culture systems.<sup>[37]</sup> Antisense oligonucleotides, siRNAs and ribozymes are even bigger molecules. Because of their negative charge, they cannot cross membranes by simple passive diffusion but require association with lipid carriers to increase their permeability into malignant cells. However, use of the carrier systems is limited due to poor understanding of safety issues.<sup>[40]</sup> Further enzymatic degradation of these molecules by endo and exonucleases is also an issue. Nuclease resistance can be achieved by chemical modifications as was done in GRN1613L by thio-phosphoramidate modification of its backbone.<sup>[19]</sup>

Last, but not the least, long-term side effects following the inhibition of telomerase activity needs to be fully evaluated as telomerase is important for the renewal capacity of normal stem and progenitor cells.<sup>[40]</sup>

### Synergy in cancer therapy

The most promising approach to fight cancer seems to be the combination of telomerase-based therapy with other conventional treatment modalities such as radiotherapy, chemotherapy or surgery. This would allow time for telomerase agents to exhibit effects or sensitize cells to other anticancer agents. Encouraging results have been demonstrated for administration of telomerase agents with chemotherapeutic agents. For instance, GRN163L potentiates the effect of etoposide in breast cancer cells<sup>[48]</sup>, and siRNA potentiates the cytotoxic effect of doxorubicin in breast cancer cells.<sup>[49]</sup> Similarly, GRN163L was shown to increase the sensitivity of resistant breast cancer cells to trastuzumab.<sup>[50]</sup>

## Conclusion

Telomerase is a very attractive molecular target for cancer therapy. Ongoing clinical trials suggest that telomerase-directed therapies have the potential to become future targeted therapies for cancer. Further advancement in the understanding of telomerase function and regulation can offer a large number of diverse opportunities to develop more molecules with therapeutic potential.

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**How to cite this article:** Sekhri K. Telomeres and telomerase: Understanding basic structure and potential new therapeutic strategies targeting it in the treatment of cancer. *J Postgrad Med* 2014;60:303-8.

**Source of Support:** Nil, **Conflict of Interest:** None declared.

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