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JOURNAL OF GASTROINTESTINAL CANCER Volume: 52 Issue: 2 Pages: 431-447 Published: JUN 2021

Early Access: JAN 2021

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Journal of Gastrointestinal Cancer
https://doi.org/10.1007/s12029-020-00565-y

REVIEW ARTICLE

TERRA Gene Expression in Gastric Cancer: Role of hTERT

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Accepted: 6 December 2020

Abstract

Purpose One of the most important serious malignancies is gastric cancer (GC) with a high mortality globally. In this way, beside the environmental factors, genetic parameter has a remarkable effective fluctuation in GC. Correspondingly, telomeres are nucleoprotein structures measuring the length of telomeres and they have special potential in diagnosis of various types of cancers. Defect protection of the telomeric length initiates the instability of the genome during cancer, including gastric cancer. The most common way of maintaining telomere length is the function of the telomerase enzyme that replicates the TTAGGG to the end of the 3′ chromosome.

Methods In this review, we want to discuss the alterations of hTERT repression on the modification of TERRA gene expression in conjunction with the importance of telomere and telomerase in GC.

Results The telomerase enzyme contains two essential components called telomerase reverse transcriptase (hTERT) and RNA telomerase (hTR, hTERC). Deregulation of hTERT plays a key role in the multistage process of tumorigenicity and anticancer drug resistance. The direct relationship between telomerase activity and hTERT has led to hTERT to be considered a key target for cancer treatment. Recent results show that telomeres are transcribed into telomeric repeat-containing RNA (TERRA) in mammalian cells and are long noncoding RNAs (lncRNAs) identified in different tissues. In addition, most chemotherapy methods have a lot of side effects on normal cells.

Conclusion Telomere and telomerase are useful therapeutic goal. According to the main roles of hTERT in tumorigenesis, growth, migration, and cancer invasion, hTERT and regulatory mechanisms that control the expression of hTERT are attractive therapeutic targets for cancer treatment.

Keywords Telomere · Telomerase · Human telomerase reverse transcriptase (hTERT) · Telomeric repeat-containing RNA (TERRA)

Introduction

Importance of Epigenetic and Mutations in Gastric Cancer

The function of epigenetic modifications has an impressive role in human diseases. Relatively, the epigenetics research has helped understand various bio-activities including methylation of DNA, the structure of chromatin, transcription, and histones [1]. DNA methylation and chromatin remodeling are two significant epigenetic modifications. Considering that alterations of DNA methylation help to molecular heterogeneity changes in gastric cancer, the importance of DNA methylation in pathogenesis gastric cancer is proven. In the diagnosis and prevention of all cancers, especially gastric cancer, the calculation of the amounts of methylated and unmethylated parts of DNA is important [2]. While DNA methylation is a chemical change in the DNA sequence, chromatin restructuring is caused by N-terminal terminus of histone modifications which eventually affect the interactions between DNA and chromatin-modifying proteins. Conspicuously, DNA methylation and histone changes are linked to the silencing of critical tumor-suppressing genes and the activation of cancer oncogenes [3]. DNA methylation as epigenetic factors is very important for carcinogenesis. It can generally be stated that

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Published online: 07 January 2021

cancer possesses a complex mechanism and generates at least 6 mutations or oncogenes in cells that cause functional changes in certain efficient genes associated with various signaling pathways such as WNT, SHH, and Notch. Also, DNMT1 enzyme plays an important role in maintaining DNA methylation. DNMT2 or TRDMT involved in mutation repair, recombination of DNA, and DNA damage. Perhaps the flexibility and reversibility of the mechanism of epigenetics are the main cause of major variations between DNA methylation and mutation can be demonstrated. Accordingly, the absence of detectable DNA methylation leads to an instability of the genome and activation of an oncogene in cancer [4, 5] (Table 1). However, further research is recommended, especially studies of epigenetic factors such as DNA methylation alongside with gene expression [6].

By using analyses of genomic, expressional, and mutation researches, in particular, possible clinically significant driver mutations led to the discovery of a change in gastric cancer [7, 8]. For example, TP53 is encoded by a tumor suppressor called p53, a mutated gene common in gastric cancer and TP53 codes in addition to apoptosis and affects in cell cycle interruption when activating p53 in the determination of cell stress, oxidative stress, and damages to the DNA. Loss of function mutation in the TP53 gene is indeed a prevalent pathogenic in gastric cancer. CDH1, which codes for the cell adhesion molecule E-cadherin, is another traditionally mutated gene associated with gastric cancer. CDH1 was found to function as the fourth most commonly mutated gene after TP53, ARID1A, and PIK3CA [8–10]. In this way, BRCA2 acts for maintaining the genome stability [9, 11] (Table 2).

Importantly, telomerase is responsible for maintaining telomere length and plays a central key role in malignant transformation. Additionally, hTERT as a subunit of telomerase acts as an important function in telomerase activation. In other words, hTERT expression level was shown to have a direct relationship with telomerase. Many studies have shown high levels of hTERT expression in gastric cancer. The findings also confirm the association of hTERT expression with lymphatic metastases in patients with gastric cancer [12].

Table 1 List of some genes altered by epigenetic in gastric cancer

Gene	Function	Reference
hMLH1 MGMT PMS2 MSH2	DNA repair	[13]
p15 p16 CDKN1A CHFR	Cell cycle/checkpoint	[14, 15]
CDH1 GRIK2	Cell migration, cell invasion	[16, 17]
APC DKK3 SFRPS	Wnt signaling	[18–20]
RUNX3 hTERT	Transcriptional regulation, tumor suppressor	[21–23]
H3K27me3	Cell proliferation	[24, 25]
H3K3me3	Tumor suppressor	[26]
H19 HOTAIR	Cell proliferation/cycle	[27]
MiR-21	Cell proliferation and invasion	[28, 29]
miR-27a	Tumor metastasis	[30, 31]

Telomeres

Historical Context

When the structure of the genetic material was still obscure, in 1938 Hermann Muller proposed the presence of a particular structure at the end of the chromosomes [43]. Correspondingly, Leonard Hayflick in 1961 suggested that senescence or cellular aging is a natural feature of cells [44]. In 1972, James Watson described the theory of the end-replication problem, and he observed that the ends of chromosomes are not able to be completely replicated throughout replication because of removing the RNA primer from the end. DNA polymerases only synthesize DNA from 5′ to 3′ direction and require RNA primer for this purpose [45]. Alexey Olovnikov pointed out that the ends of chromosomes of linear DNA reduced with every cell division and highlighted the possible connection between the shortening of the chromosome and Hayflick observation [46]. Elizabeth Blackburn's research in DNA sequencing in 1978 led to the discovery of the end of a chromosome or telomere that was made of repeating DNA sequencing. They also found that this mechanism was prevalent in maintaining telomeres in a eukaryote. In 1981, Jack Szotak and Blackburn showed telomeric function in Tetrahymena and *Saccharomyces cerevisiae*. In 1985, an enzyme called telomerase was identified in the Blackburn lab. This enzyme adds telomeric repeats TTAGGG, at the end of the chromosomes and leads to the maintenance of telomeres in Tetrahymena and yeast. However, it conserved structure across all eukaryotes—G-rich DNA replicate sequence at the chromosome ends which, in humans, was later exposed to be consists of 5′-TTAGGG-3′ repeats [47, 48].

In 1990, it became clear that due to the end-replication problem and absence of telomerase, the telomere length was shortened in human primary fibroblasts. In contrast, telomere length is maintained in germ cell and cancer cells due to telomerase activity [49].

Table 2 List of some mutated genes in gastric cancer

Gene	Function	Reference
Tp53	Cell cycle regulation, tumor suppressor	[32]
CDH1	Cell cycle arrest, apoptosis, cell adhesion, cell migration	[33]
APC RNF43 CTNNB1	Wnt signaling	[34, 35]
SMAD4 ELF3	TGF-β pathway	[36, 37]
ERBB2 ERBB3 PINK3CA KRAS	RTK pathway	[38, 39]
CTNNA2 CTNNB1 FAT4	Cell adhesion	[40, 41]
hTERT	Transcriptional regulation	[41, 42]

Telomere Structure

Telomeres are nucleoprotein structures that have been discovered at the ends and perform a "capping" function by guarding the ends of chromosomes against destruction and fusion (8).

This is an important factor in maintaining the stability of chromosomes. Researchers have also suggested that chromosome ends have specific structures necessary for chromosome stabilization. The word telomere was innovated by Muller. McClintock observed that without telomere, chromosomes might fuse and usually break upon mitosis, and she has seen that the resulting chromosome instability was detrimental to cells (9).

Telomeres are important structures at the ends of most eukaryotic chromosomes. The telomeric DNA, the shelterin complex, and the telomerase complex are essential in telomere length maintenance. In humans, telomeric DNA includes a duplex area consists of extended areas of double-stranded G-rich TTAGGG repeats and a telomere-particular protein complex, shelterin. The shelterin complex contains six protein subunits: telomeric replicate presenting factor-1 (TRF1), TRF2, TRF1-interacting protein-2 (TIN2), repressor/activator protein 1 (RAP1), TINT1/PIP1/PTOP 1 (TPP1), and protection of telomeres 1 (POT1), and regulates the preservation of telomere length and protects normal chromosome ends from being recognized as broken DNA [50, 51]. TRF1 and TRF2 directly bind double-stranded telomeric repeats, while POT1 identifies the single-stranded telomeric G-rich 3′ overhang. TIN2 binds to TRF1 and TRF2 through specific domains and also recruits a TPP1-POT1 heterodimer, therefore linking various shelterins to arrange the telomere cap. Eventually, RAP1 is recruited to telomeres by TRF2, but may also bind during chromosome arms to manage transcription [52, 53]. All shelterins except RAP1 are important for a lifetime. Actually, RAP1 is the only real shelterin dispensable for telomere protection [54]. Shelterin complex protects chromosomes from end-to-end fusions and destruction by building particular T-loop–like structures. T-loops are formed through string invasion of the extended 3′ overhang at the telomere end to the double-stranded telomeric DNA. This 3′ overhang is recreated following DNA replication through the exonucleolytic destruction of the 5′ ends of the telomeres [51, 55]. Therefore, the T-loop sequesters the ends of chromosomes and supplies, a process to avoid the entire activation of a DNA damage response generally seen at ends [56].

The six subunits of shelterin complex associate with telomeric DNA which are responsible for telomere preservation. The length of telomeric repeats may be preserved by telomerase, which consists of telomerase reverse transcriptase (TERT), telomerase RNA template part (TERC), and a few additional proteins. TERT synthesizes telomeric DNA applying TERC as a template, and other proteins involved in this structure include dyskerin (DKC); Gar1, TRF1-interacting nuclear component 2 (TIN2); telomeric repeat-binding factor (TRF), nucleolar protein 10 (NOP10); protection of telomeres 1 (POT1);repressor/activator protein 1 (RAP1);non-histone protein 2 (NHP2); and telomerase Cajal human body protein 1 (TCAB1) [51] (Fig. 1). G-quadruplexes(G4) are other complex structures that have already seen to create in the G-rich single-stranded telomeric DNA in vitro and in vivo. The association of four guanines results in a square-planar agreement (G-tetrad), wherever numerous G-tetrads then collected over one another to make a G4. They are major conserved structures and may suppose a few confirmations. Telomeric G4s seem to possess regulatory functions in telomere elongation and preservation by rendering the G-rich single-stranded overhang unavailable to telomerase, therefore inhibiting telomere extension [57, 58].

Telomere Length

The human telomere length is about 10-15 kb, which shortens the throughout cell division about 50-200 bp [59, 60]. Telomeres lose their protective role by shortening their length.

Ribonucleoprotein telomerase enzyme inhibits the shortening of telomere length by adding telomeric repeats to the end of the chromosome. The telomere maintenance mechanism (TMM), also termed alternative lengthening of telomeres (ALT), is another mechanism involved in maintaining telomere length, which happens in almost 10–15% of human cancer cells [55, 61]. Generally, a significantly short telomere length may induce the cell to enter replicative senescence with a consequence of cell death; alternatively, cells continue steadily to divide if death does not happen, which benefits in genomic instability and chromosomal abnormality. Thus, telomere length acts as a mitotic clock for eukaryotic cells and probably presents a number of cell replications performed by each cell throughout its lifetime [62]. Insufficient physical

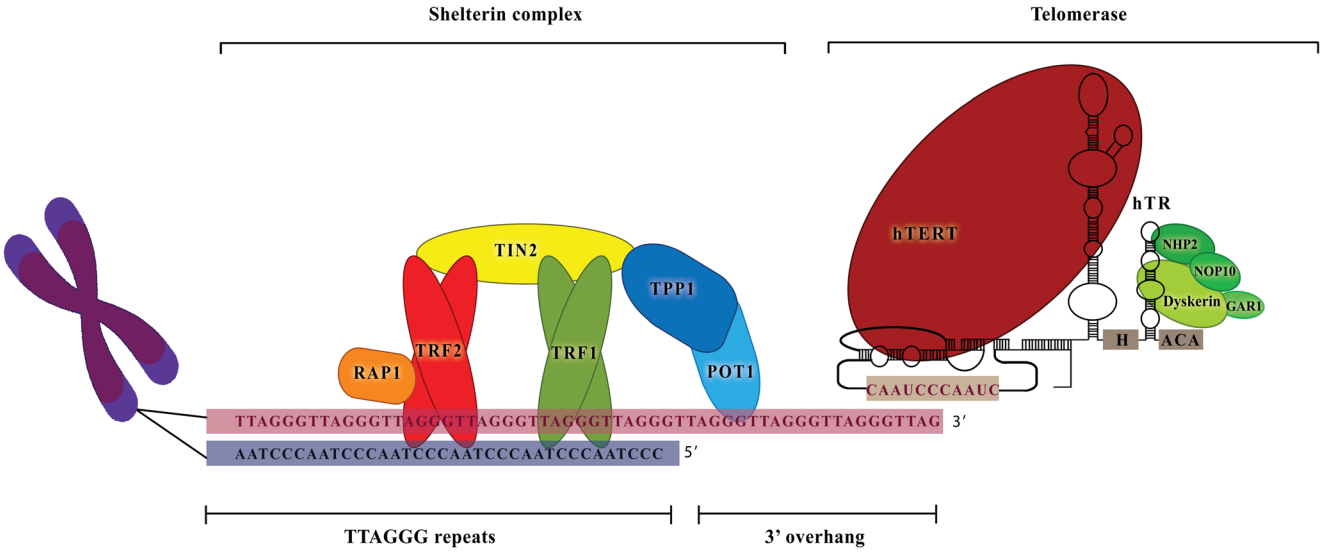

Fig. 1 Human telomere structure

activity, overweight, smoking, and use of inappropriate feeding may raise the speed of telomere shortening.. In this account, accelerated telomere shortening is related to some diseases including cancer, coronary cardiovascular disease, heart failure, diabetes, increased cancer risk, osteoporosis, pulmonary fibrosis, aplastic anemia, and hepatic cirrhosis [63–69]. In this way, several studies have shown that the alteration in telomere lengths including abnormally short and long telomere length is associated with an increased risk of developing many cancers including gastric, colorectal, neuroblastoma, melanoma, esophageal, neuroblastoma, renal, lung, ovarian, and bladder (43, 44). In other words, when telomeres reach significantly short lengths, it leads to the cessation of division and cell death. Nevertheless, in several cancers, activation of telomerase or ALT pathway drives to abnormal telomere lengthening. Due to this association between telomeres and cancers, telomerase subunit (TERT) is investigated as a target for cancer therapeutics [64].

Telomere Functions and Genomic Stability

Telomeres are considered a telomeric cap due to the essential features it serves for linear DNA. Through the years, researchers have discovered that telomeres perform an essential role in the stability and mobility of the genome and reduce erosion of coding DNA. Telomeres serve numerous features in preserving chromosome stability, including protecting the ends of chromosomes from destruction and avoiding chromosomal end fusion. The progressive loss of telomeric replicate sequence because of insufficient telomerase activity is exemplified by the telomere shortening that happens in telomerase-deficient somatic cells with each cell division, even though because of cell senescence or apoptosis, this does not typically lead to chromosome instability. Knowledge of the mechanisms of telomere preservation and the different factors that promote telomere instability must offer valuable ideas into both human genetic diseases and cancer [70]. While the telomeric tumor suppressor pathway can be an effective mechanism to restrict the growth of cancer, the inability of transformed cells to experience senescence can contribute to a telomeric crisis under which the cells may not increase. In such positions, the cells' fight against genome instability as well as telomerase activation provides a way out of the telomere crisis, which finally attends to tumor formation. Telomerase activation provides an outcome from telomere crises, leading ultimately to a cancer clone synthesis with a highly rearranged genome. In cells that are absent from the p53 and RB tumor suppressor systems, continued growth beyond the senescence barrier can make their cell cycle transitions impossible by ATM and ATR signaling. Cells in the telomere crisis cause mitotic missegregation and genomic instability. Cells in the telomere crisis undergo regular cell death. A typical prognosis is that chromosome harm and missegregation can cause a lack of viability, while an increased mitotic charge in a number of cells can require extra telomere deprotection [51].

End-Replication Problem

Due to inability of DNA polymerase, telomeres are shortened in each cell division which is known as the chromosome end problem. A short oligonucleotide is required for DNA replication. Due to the limitations of the replication machine, the last sequence of lagging strand cannot be converted to a DNA

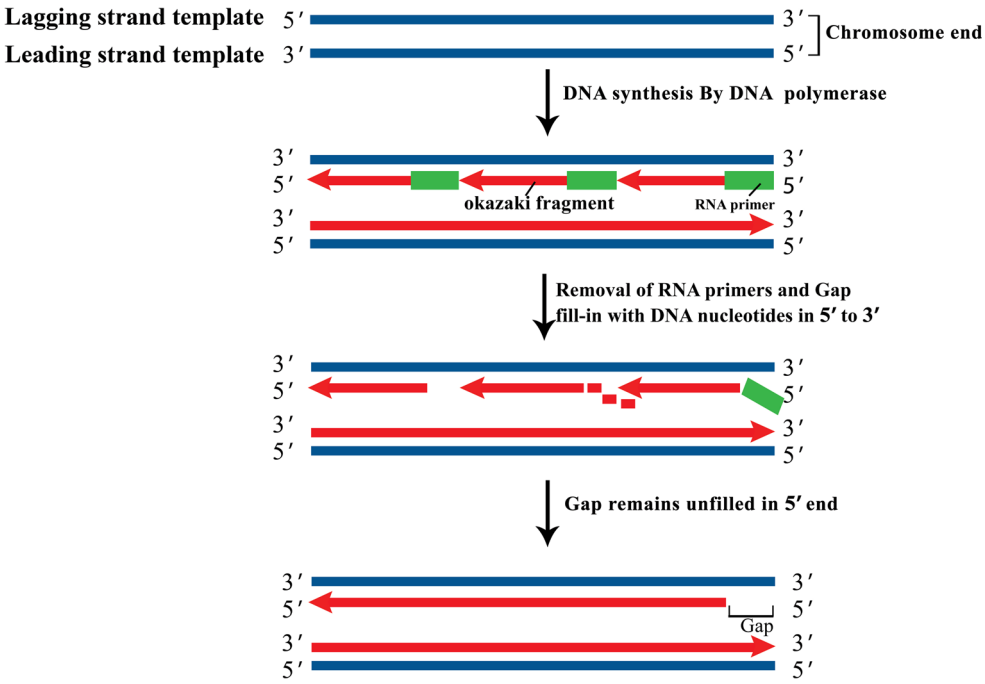

Fig. 2 Telomeres shorten during each cell division due to the process of end-replication problem

sequence. For this reason, the stability of the DNA end is lost (Fig. 2). Although telomerase is inactive in most human cells except germ cells and stem cells, it is used as one of the appropriate solutions to solve the end-transcription problem [56, 71, 72].

The Relationship Between Telomere Length and Cancer

Telomere length and telomerase activity are related to cellular longevity and cancer. It is believed that the increased loss of proliferative capacity seen in human cells leads to missing telomerase and might have evolved or maybe not to create decrepitly but to greatly help to prevent cancer. Cancers occur whenever a cell takes numerous genetic mutations that together induce the cell to escape from regular regulates on replication and migration. The idea is that telomerase deficiency can delay the growth of tumors and cause cells to continually divide to reduce their telomeres. If telomerase were produced by cancer cells, the telomeres would remain indefinitely. The activity of telomerase in short telomeres contributes to the cell survival and immortality, as well as causing chromosomal alterations and genetic mutations in promoting cancer.

However, if the genetic confusion of the pre-crisis period causes the production of telomerase, cells will not absolutely eliminate their telomeres. Alternatively, the shortened telomeres are going to be recovered and maintained. In this way, genetically upset cells may obtain the immortality characteristic of cancer. Clearly, some tumors do not have telomerase activity, whereas telomerase activity has been observed in some somatic cells [73, 74].

Telomerase

Historical Context

In 1985, Greider and Blackburn observed that enzymatic activity is involved in enhancing telomere length [47]. Morin in 1989 has shown that human telomeres added the repeated sequence TTAGGG at the end of the telomere [75]. In 1994 and 1998, Shay revealed telomerase activity and hTERT expression in most human cancers which contribute to cell immortality. The 2009 Nobel Prize winner, Szostak, nominated telomerase as the protector of telomere length [76]. Telomerase is really a ribonucleoprotein accountable for maintaining telomere length. Telomerase has two parts: catalytic telomerase reverse transcriptase (TERT) and telomerase RNA (TERC or TR). TERT uses the template location (3′-CAAUCCCAAUC-5′) of TERC to include TTAGGG DNA repeats and expand single-stranded 3′ telomeric strands [77].

In 1980, RNA subunit TR with reverse transcriptase property was identified [78]. TR is found in high levels in all tissues that have telomerase activity, while it is normally absent or low levels in somatic cells. The half-life for hTR is 5 days in somatic cells, while in cancer and stem cells, it is suggested to be between 3 and 4 weeks. The half-life of hTERT mRNA has been also defined as 2–3 h [79]. It is obvious that the defect in hTR and hTERT is associated with genome and chromosome instability, shortening of telomere length, DNA, and damage. As a result, in most human tumors and immortalized cell lines, telomerase activity and telomere conservation become increased highly [80].

Telomerase Activity and Function

Telomerase activity is various in numerous human cells and tissues. Telomerase is active throughout early embryonic progress but it is inactive in the majority of cells before 20 weeks of pregnancy [81, 82]. In embryonic stem cells, the deacetylation of histone H3 in the hTR and hTERT promoter and H4 only in hTERT promoter leads to a decrease of telomerase activity. Telomerase has been gradually repressed through differentiation in many human adult tissues except stem cell lymphocytes, human fibroblasts, and endothelial cells [83]. Upregulation of hTERT in human embryonic stem cell lines led to the suppression of cellular in vitro differentiation while downregulation counteracted pluripotency and proliferation. Most of these benefits show an essential function of telomerase activity in telomerase-positive cells [84].

Human Telomerase Reverse Transcriptase

The human telomerase reverse transcriptase (hTERT) gene is located on the short arm of chromosome 5 (5p15.33), 1.2 MB away from the telomere, with 16 exons and 15 introns [85]. hTERT expression in different cells and tissues is regulated by various factors. Upregulation of hTERT in most human cancer cells, indicating that hTERT is associated with cancer development and progression by causing irruption and telomere lengthening, prevents senescence and apoptosis [86, 87].

TERT Telomere-Independent Activities

In humans, telomerase is early active in embryonic advancement, and offsets the loss of telomere throughout rapid proliferation which is crucial for tissue development and differentiation. In most of the cancerous cells, telomerase is upregulated or reactivated. Meaningly, telomerase activation is essential for immortalization and plays an important role during the malignant development of cancer cells [88, 89]. TERT expression could promote cell growth, proliferation, and elongation of the telomere and allows the cells to multiply by a characteristic of cancer cells [90].

Mechanisms of hTERT Regulation

New developments in DNA sequencing technologies have allowed genome sequencing reports across different tumor types. Several alterations in protein-coding genes have already been recognized [91, 92]. On the other hand, only a small number of the mutations in noncoding parts have recently been identified [93]. Recurrent mutations and chromosomal rearrangements in hTERT promoter have more established the significance of telomerase activation in human cancers [94].

hTERT Promoter Mutations

hTERT promoter mutation is a genetic modification which is located 124 and 146 bp upstream of the translation start site [94, 95].

hTERT Promoter Mutations in Different Types of Human Cancers

hTERT promoter mutation has been shown in many cancers, including glioblastoma, thyroid, gastric, melanomas, hepatocellular, bladder, liposarcomas, and urothelial cancers, which is indicative of its association with the high expression of hTERT [96, 97]. In contrast, TERT promoter mutations in colon, lung, esophagus, kidney, pancreatic, breast, and prostate cancers are less prevalent [98].

Enhanced Telomerase Levels by hERT Promoter Mutations

Hotspot mutations produce a transcription factor-binding site which can increase the expression of hTERT. It stimulates the transcriptional activity of hTERT promoter by activating NF-κB signaling pathway.

Transcription Activators of hTERT

c-Myc

One of the most important genes in this category is c-Myc which is a member of the MYC family that plays a role in cell adherence, proliferation, differentiation, and apoptosis. c-Myc binds the histone acetyltransferase (HAT) to regulatory elements called the E boxes to exact the active effect on various gene transcriptions. By connecting E-box sequences to the promoter of hTERT, c-Myc leads to high gene expression and telomerase activity. The c-Myc activating function of the hTERT gene is assisted through the recruitment of the SPT3-TAF9-GCN5 acetyltransferase (STAGA) complex and the mediator complex of transcript coactivators. GC boxes which are binding sites for specificity protein 1 (Sp1) transcription factor are also present within the key hTERT promoter [99]. This also illustrates the finding that the expression c-Myc and Sp1 correspond to hTERT transcript in various cancer cell lines. AP-1, which binds as a transcription repressive, AP-2, which exhibits tumor-specific upregulation hTERT, and HIF-1, an upregulated hTERT expression in hypoxic cases, are also important binding points of the hTERT promoter. The p53, p63, and p73 tumor suppressors are powerful hTERT repressors, as transient overexpression of human embryonic renal cell variables results in less c-myc expression and reduced hTERT promoter activity. However, numerous c-Myc inhibitors and suppressors can counteract the activity of beneficial regulators with c-Myc-induced hTERT activation.

The findings also show breast cancer 1 (BRCA1), prostate, and ovarian cancers through the binding of hTERT promoter and c-Myc. Wilms tumor 1 (WT1) and TGFβ, by attaching to the hTERT promoter and suppression of the c-Myc, inhibit hTERT expression [80, 100, 101].

STAT Proteins

STAT3 acts a significant performance in regulating hTERT gene expression in cancer. As a result, with the decrease in the expression of STAT3 by siRNA, the expression of the hTERT gene is also significantly reduced. The upregulation of hTERT expression by STAT3 also needs the activity of DNA methyltransferases (DNMTs) in gastric cancer which indicates that DNMT1 and DNMT3 are responsible for the maintenance of methylation in CpGs [4, 80, 100, 102–104].

NF-κB

The NF-κB pathway can be described to regulate TERT transcription. NF-κB is really a transcription factor complex whose activity is caused in several cell forms by different stimuli such as for example inflammation, cellular differentiation, tumorigenesis, and apoptosis. It is demonstrated to perform an activating role in telomerase expression and activity by regulating hTERT gene transcription via binding to the proximal promoter of the target gene, or ultimately by modulating the expression of transcription factors recognized to affect hTERT expression [105]. Activation of NF-κB in human monocyte cells by causing inflammation leads to increased binding to the hTERT promoter, which further improves telomerase activity, depleting NF-κB levels by disrupting the binding of NF-κB to hTERT promoter by reducing its response factor-induced upregulation of hTERT expression. It absolutely was also planned that there exists a regulation between NF-κB and telomerase while binding to p65, and modulates its transcription activity on its target genes, including factors which are essential for inflammation and cancer progression [106]. Taken together, NF-κB indirectly contributes to increased expression of hTERT [80, 101, 107].

Paired Box Proteins (Pax)

Pax protein family includes paired box- and homeobox-containing transcription factors expressed in early development. Deregulation of PAX genes particularly PAX2, PAX5, PAX8, PAX3, and PAX7 has been related to a variety of cancers, including melanoma, astrocytoma, medulloblastoma, lymphoma, and tumor of Wilms, human malignancies, such as renal tumors, and medullary thyroid carcinoma rhabdomyosarcoma. pax8 plays an important role in telomerase activation and also, hTERT and hTR expression levels [108, 109].

Estrogen Receptor

At least two members of the nuclear hormone receptor superfamily, the estrogen receptors (ERs) ERα and ERβ, are mediated with the physiological reactions to estrogens in certain tissues [110]. Telomerase and transcriptional activities are observed only in estrogen receptor-positive cells. In addition, several biomolecules have been shown to inhibit ER hTERT activation in human cancer cells, for example, ovarian, breast, colon, and endometrial cancer [80, 100].

Telomerase Therapeutics Strategy

Telomerase and telomere therapeutics are considered the primary purposes of cancer treatment [111]. Despite extensive research, only a few of them were performed in clinical studies with promising results [112].

Telomeres as an aging agent become shortened at each time of cell division in mature somatic cells, such as mutations in telomerase and telomerase-associated genes, and inappropriate lifestyle such as unhealthy nutrition, obesity, and smoking, which will shorten the length of telomeres and consequently promote diseases such as telomeric syndrome. Breast cancer treatment showed a decrease in the tumor and invasiveness of the cells. Studies using immortalized breast cancer cells for altered oligonucleotides as inhibitors of telomerase show that telomere reduction is reversible and may have restricted side effects on stem cells. Thus, the approach should be closely characterized in patients with a deficiency in tumor suppressor systems and age-related patients [113].

Nevertheless, the adverse effects on normal stem cells, which functions rely on the telomerase activity, are not appropriate to telomerase therapeutics. Present in clinical trials, only a single telomerase inhibitor impacts the activities of telomerase and the elongation of telomeres, by connecting them to TERC [114, 115].

It has been noted that TERT protects cells from stress-induced DNA damage. Thus, this could be one of the reasons why radiotherapy or DNA damage-targeted chemotherapy does not generally result in the whole eradication of cancer cells. Nevertheless, hTERT is a good candidate against the previously failed candidates. There are some drugs currently binding to the RNA template of telomerase (hTR) to inhibit telomerase. Telomerase reactivation systems at mutant TERT promoters can be a more efficient and promising method of inhibiting telomerase, particularly in cancer cells while preventing the cytotoxic effects to normal stem cells that do not include TERT promoter mutations. Thus, more biochemical characterization of the complex and multi-faceted systems of mutant TERT promoter activation in various cancers is essential only at that early stage [83] (Fig. 3).

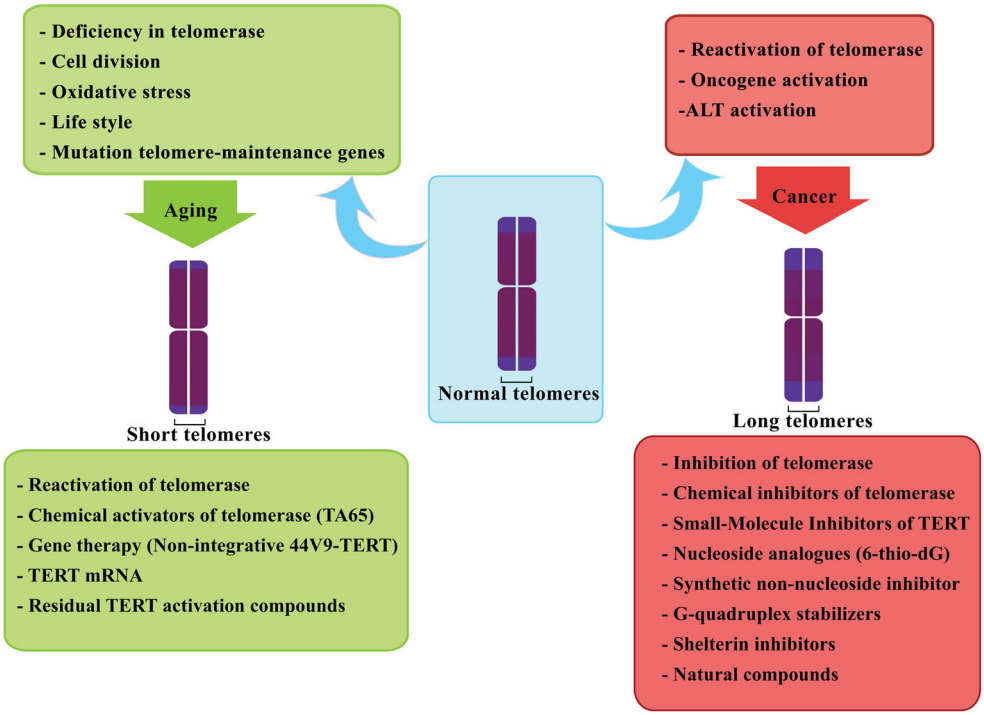

Fig. 3 Targeting telomerase for cancer therapeutics and aging

Noncoding RNA

Noncoding RNAs (ncRNAs) are type of RNAs without protein-coding function which is commonly expressed in organisms. ncRNAs consist of housekeeping ncRNAs and regulatory ncRNAs. Relating to size, the latter may further be divided into three forms:

1. Short ncRNAs (sncRNAs), consisting of small-interfering RNAs (siRNAs), microRNAs (miRNAs), and Piwi-interacting RNAs (piRNAs).
2. Mid-sized ncRNAs.
3. Long noncoding RNAs (lncRNAs) [116, 117].

The ncRNAs which are between 50 and 200 nt known as mid-sized ncRNAs and lncRNAs are longer than 200 nt [118, 119].

New reports on ncRNAs have helped us gained knowledge of their biogenesis and functions. An essential result of the research knowledge is that the expression of numerous ncRNAs is regulated by diverse epigenetic, transcriptional, and post-transcriptional systems. Consequently, the noncoding RNA is currently bestowed with an exceptional diversity in function and response to environmental changes [120].

ncRNAs are transcribed by RNA polymerase II (RNAP II), which is responsible for the synthesis of various types of noncoding RNAs (ncRNAs), including snoRNAs and miRNAs. However, a range of important ncRNAs, for example, tRNAs and 5S rRNAs, has also been developed by Pol III [121].

In addition, long-coded RNAs (lncRNAs) and small snoRNAs (RNAs) are as unusual determinants of initiation, development, and metastasis [122].

Short Noncoding RNAs

In general, short noncoding RNAs (sncRNAs) cover tiny nuclear (sn) RNAs, ribosomal 5S and 5.8S RNAs (rRNAs), transfer RNAs (tRNAs) and small nucleolar (sno) RNAs, and others, including miRNAs, siRNAs, and piRNAs [123]. snoRNA executes a significant role in human diseases, especially cancer [124, 125]. However, snoRNAs may also be associated with the late stages of cancer development. snoRNAs have been considered to act as "housekeeping" genes in measuring the expression of miRNAs in cancer samples [126].

The RNA Interference and Small-Interfering RNAs

The RNA interference (RNAi) system was found in *Caenorhabditis elegans* when double-stranded RNA exogenously presented caused a transitory depression of gene expression. As the silencing mechanism was systemic, it had been hypothesized that the RNAi effect was facilitated by a stable intermediate. It offered the idea that there can be an active intermediate that facilitated gene silencing [127]. Therapeutic programs of RNAi make use of a conserved pathway for gene expression regulation that includes the potential for sequence specificity through the complementarity of siRNAs due to their objectives [128]. These intermediates

involved the dicer enzymes and the RISC which really is a complex of proteins and the siRNA molecules with a highly conserved Argonaute protein. The mechanism of siRNA-mediated gene silencing may have a particular repression effect. In more detail, the primary sequence particular cleavage system has already been recognized as siRNAs may be identified the following: endogenous dsRNA which is recognized by dicer which cleaves it into small double-stranded fragments of 21 to 23 base pairs in length with nucleotide overhangs at the 30 ends. They include a passenger strand and a guide strand, which are linked together by an active protein complex named RISC. Following binding to RISC, the guide strand is directed to the target mRNA, to cleave it into small parts which are between bases 10 and 11 relatives to the 50 end of the siRNA guide strand by the cleavage enzyme Ago2. Therefore, the procedure of mRNA translation may be disrupted by siRNA (Fig. 4) [129].

siRNA Against Cancer Targets

Cancer continues to be the second major reason for deaths throughout the world. There have been several advances in the gene sequencing of cancer cells which have resulted in the progress of synthetic siRNA for delivering personalized medicine. Because of their finding, siRNA therapeutics have already been pursued actively due to their high specificity, easy modification, and unlimited therapeutic targets. Nevertheless, its instability in blood is a major problem [129]. RNAi methods may be employed against cancer targets including insulin growth factors (IGF), cyclin-dependent kinases (CDKs), vascular endothelial growth factors (VEGF), and anti-apoptotic factors that govern uncontrolled cell proliferation. Overexpression of cyclins manages within the cell cycle and disturbs the cell cycle causing the progress of cancer. Cyclin B1 has been associated with cancers such as for example prostate adenocarcinoma, renal, and breast cancer. siRNAs have already been used in in vivo trials to silence the expression of cyclin B1 for prostate and lung cancer. Proliferation signals are developed by growth mediators like IGF that promote cell division, proliferation, and survival and provide a suitable growth environment for cancer cells. Angiogenesis is really an important component of cancer development. Meaningly, without angiogenesis, cancer growth could be restricted. Thus, tumor growth might be managed by inhibiting the antigenic system promoted by VEGFs [130–132].

Concerns of siRNA Application in Cancer

Regardless of the promising nature of siRNA as cancer medicine, the therapeutic application of siRNAs has increased protection concerns, and studies have underscored potential drawbacks. Variations in oncogenic mRNA expression levels between different cancer cells and also non-cancerous cells pose a challenge for developing an acceptable therapeutic dosage without causing part effects. The probable inhibition of tumor-suppressive mRNA by siRNA can cause spontaneous cancer development. Moreover, the siRNA could obtain entry into non-target cells causing undesired off-target effects. Getting of resistance against siRNA by tumors is really a reason for concern, despite the present effectiveness against tumors. Thus, important roles in cancer resistance development must be characterized so as to predict the results of siRNA treatment. The foreign nature of siRNA could provoke an immune reaction by the body's immune system to eliminate the siRNA and avoid the targeted localization of siRNA. Protein with a high turnover rate or an extended half-life will restrict the utility of siRNA as a tool for a proper knockdown. This is because of the siRNA targeting the mRNA used to synthesize the oncogenic protein but it generally does not directly reduce the total amount of current oncogenic protein [132–134].

siRNA Cancer Therapeutic Strategy

In cancer therapeutic category, siRNAs are used as a new technique with a remarkable ability. The key strategy used in siRNA therapeutics is inhibiting the expression of target protein of cancer cells, but it does not change the nature of the genome. siRNAs' efficacy and safe and specific delivery inside specific cells are important in this cancer approach [132, 133].

microRNAs

MicroRNAs are small (20–24 nucleotides) noncoding RNA gene products that post-transcriptionally modulate gene expression by negatively regulating the stability or translational performance of their target mRNAs. Aberrant expression of miRNAs has been noted to be concerned in tumorigenesis, variously as possibly oncogenes or tumor suppressors [135]. Many genes encoding miRNAs are a single copy, and numerous copies of gene clusters associated with important biological procedures, including progress, differentiation, proliferation, apoptosis, invasion, and metastasis [136, 137]. In addition to biomarkers, miRNAs are used as potential therapeutic targets for cancer [123, 138].

Long Noncoding RNA

Improvements in genome sequencing and analysis have generated the finding of many RNA transcripts that have similar properties to mRNAs but are not translated into proteins, known as long noncoding RNAs (lncRNAs), that is longer than 200 nucleotides. Due to this broad classification, lncRNAs are heterogeneous in their biogenesis, stability, abundance, and progress. Certainly, while some lncRNAs

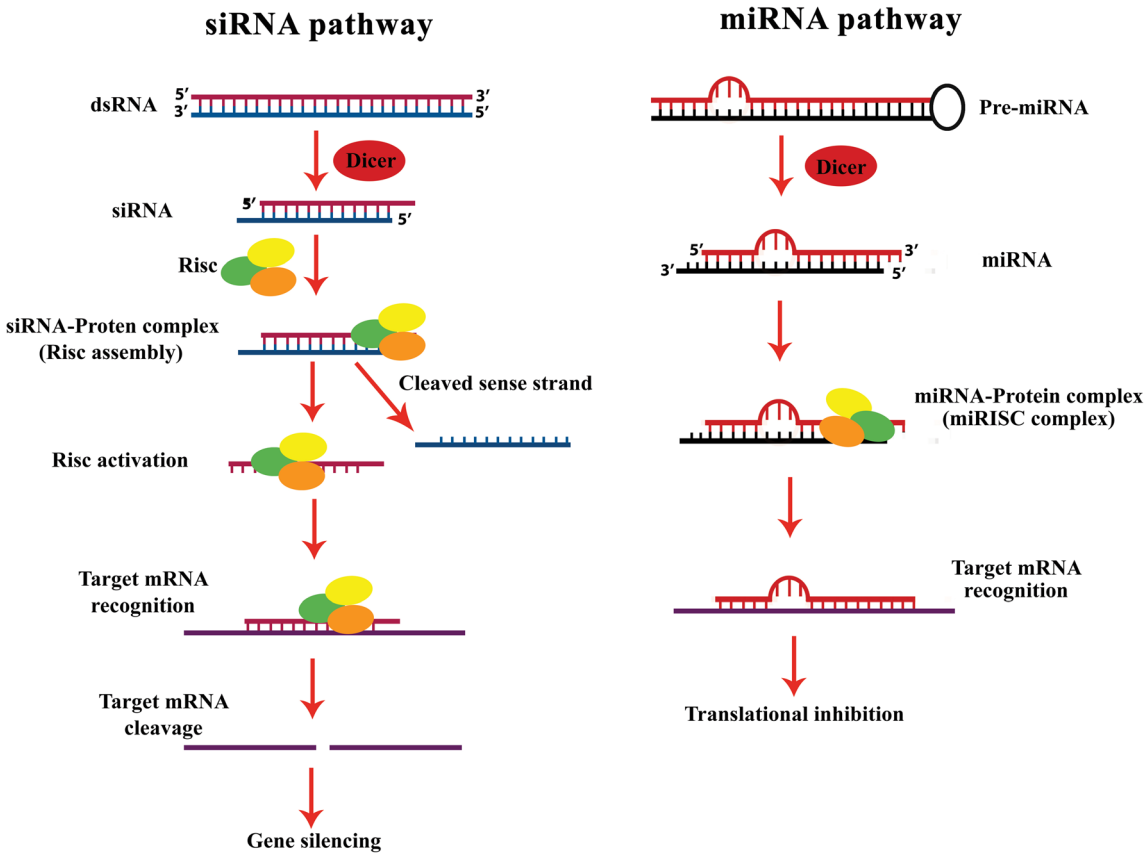

Fig. 4 siRNA and miRNA pathway

become functional RNA molecules, the others appear to be non-functional byproducts of underlying cis-regulatory components such as enhancers. Actually, lncRNAs are identified to act as regulators of gene expression programs in diverse biological procedures [139–142]. lncRNA loss-of-function recommended that may have broad effects on gene expression [143, 144].

Several lncRNAs getting together with proteins make macromolecular complexes. These interactions are mediated by particular components in the RNA sequence, including short RNA sequence motifs or larger secondary structures. An essential function of lncRNAs is usually included in many discrete domains that interact with various proteins [145].

LncRNAs lacked a significant ORF (usually less than 5 amino acids) and may be transcribed by RNA polymerase II or RNA polymerase III and may consist of only one exon. Some lncRNAs, just like miRNAs, may be affected by processes such as capping in 5′ UTR and polyadenylation in 3′ UTR. These long regulatory RNAs as key molecules are involved in regulating processes such as chromatin structure rearrangement, transcriptional regulation, post-transcriptional regulation, epigenetic alteration, small RNA processing, cell cycle regulation, and apoptosis [146]. The overexpression, deficiency, or mutation of lncRNA genes have been implicated in several human diseases. These regulatory molecules can act as a scaffold for the storage of several proteins as well as a guide in the application of proteins to a particular locus of chromatin or affect the local structure of chromatin [146]. A key function of lncRNAs appears to be to regulate the different epigenetic states of their distant and near protein-coding genes through cis-trans mechanisms that involve applying chromatin rearrangement sets to specific genomic loci and thus regulating chromatin structure in the single gene promoter, single gene cluster, or the whole genome [147].

Telomeric Repeat-Containing RNA

Telomeres have long been characterized by heterochromatin markers such as trimethylated lysine 9 of histone H3, trimethylated lysine 20 of histone H4, histone hypoacetylation, HP1, and cytosine hypermethylation of CpG islands in the subtelomeric regions which were considered heterochromatin regions [50, 56, 148]. Therefore, telomeres are thought to be transcriptionally silent due to the presence of heterochromatin markers and gene deficiency in the telomeric region. Recent studies have shown that despite telomeric heterochromatin structure, mammalian telomeres are transcribed into telomeric repeat-containing RNA (TERRA) [149]. In fact, TERRA is a long noncoding RNA that has been identified in mammals,

fungi, trypanosomes, and birds which forms all of the telomeric heterochromatin components [150–152]. TERRA not only consists of the UUAGGG repeats in the telomere region, but also includes a portion of the subtelomere DNA that has been transcribed. The direction of TERRA transcription is from the centromere to the telomere. The synthesis of TERRA in mammals and yeast is performed by RNA polymerase II [153, 154]. In a similar manner to long noncoding RNAs (lncRNAs), TERRA participates in the fine regulation of cell biology, which opens a new field in the understanding of telomeric functions and related diseases. TERRA molecules localize to telomeres and regulate telomerase activity, telomere length, and associated heterochromatinization. Improvements in the expression level of TERRA are related to altered telomeric length and promote genome instability and cellular senescence [50].

There are some signs that a number of telomere-bound proteins, together with the heterochromatic marker organization of the protective cap of telomeres, are connected with the management of the TERRA concentrations, which are accountable for the transcriptional regulation of the TERRA system. Shelterin complex includes TRF1, TRF2, Rap1, TIN2, TPP1, and POT1 which protects telomeres. Curiously, TRF1 may interact. It has been noted that whenever TRF1 was depleted using small-interfering RNA (siRNA), TERRA's total levels reduced, which shows that TRF1 helps TERRA transcription. Nevertheless, TRF1 acts as a conventional transcriptional activator. First, TRF1 depletion is not linked to telomeric DNA due to an associated absence of RNAPII. Secondly, TRF1 is limited to the telomeric area and likely not to the subtelomere, where transcription is assumed to begin. Ultimately, TRF1 overproduction in less TERRA generation is more effective than telomere elongation after TRF1, which can also influence TERRA transcription TRF1 [155, 156].

TERRA, Telomere, and Cell Cycle

TERRA molecules are transcribed from the subtelomeric regions toward the chromosome ends and include subtelomeric-derived sequences and G-rich telomeric repeats. TERRA promoter regions have already been recognized at CpG islands contained in a subset of human telomeres in proximity with their telomeric repeats tract. Constantly, DNA methylation at subtelomeric regions typically associates with the lowered expression of TERRA [157]. Recently, the second type of TERRA promoters located 5–10 kilobases far from the telomeric repeats of 10 distinct human telomeres has already been recognized [158]. The current presence of various kinds of promoters probably plays key role in the length heterogeneity of TERRA transcripts. Many lines of evidence show that modifications of the heterochromatic state of chromosome end manage the expression of TERRA [159]. TERRA is regulated in human cells during the cell cycle and at the G1 stage and is at the highest level and decreases throughout the cell cycle until it enters the S phase. At the end of the S and the G2 phase, it reaches to its lowest level. As cells complete the mitosis division, TERRA expression levels increase again [160]. In general, TERRA has the lowest expression in the late S and early stages of the cell cycle. This is because of the telomeres that are at this stage of replication and telomerase developed at the end of the chromosome. As such, TERRA as a telomerase suppressor is outside the S phase [161].

TERRA and Telomere Maintenance

The potential for telomere dysfunction to be initiated by cancer is inhibited by the function of p53 and p16. Meaningly, tumor cells must overcome this repressive mechanism. Therefore, tumor cells protect and maintain their telomeres. Otherwise, the rapid and unplanned proliferation of tumor cells can lead to chromosome shortening and subsequent loss of genetic information. To prevent this, tumor cells must have a mechanism to maintain the length of the telomere. In this way, two types of telomere length maintenance mechanisms have been identified in this process and are including telomerase and homologous alternative telomere length maintenance mechanisms based on homologous recombination. About 85–90% of tumor cells utilize telomerase function. On the other hand, telomerase is not expressed in at least 10–15% of immortalized tumors and cell lines and these cells use a telomerase-independent mechanism called the ALT mechanism. Especially, the particular procedures and protocols for the analysis of the expression of TERRA can be added to the various outcomes achieved in various studies. TERRA expression from various chromosome ends has been recorded in all research on TERRA with telomerase-positive human cancer cells [158]. Ending the various components of the NMD or hnRNPs that bind TERRA increases TERRA's location at chromosome ends without influencing the general or stable TERRA concentrations. TERRA molecules are actively displaced from telomeres and can thus be recruited at chromosome ends by interacting with stable telomeric structural components. The expression of TERRA causes the formation of heterochromatin in the telomeres. TERRA interacted with several protein-like TRF1, TRF2, H3K9me3, and origin replication complex 1 (ORC1), HP1, and MORF4L2 that acts as a chromatin restorer in chromosome end (Figs. 5 and 6) [158, 162, 163].

TERRA and Telomerase

It seems that decreased expression of TERRA is related to telomerase activity, which may indicate TERRA inhibitory role on telomerase [152]. It is confirmed that the TERRA binds to the TERT enzymic subunit and acts as a natural

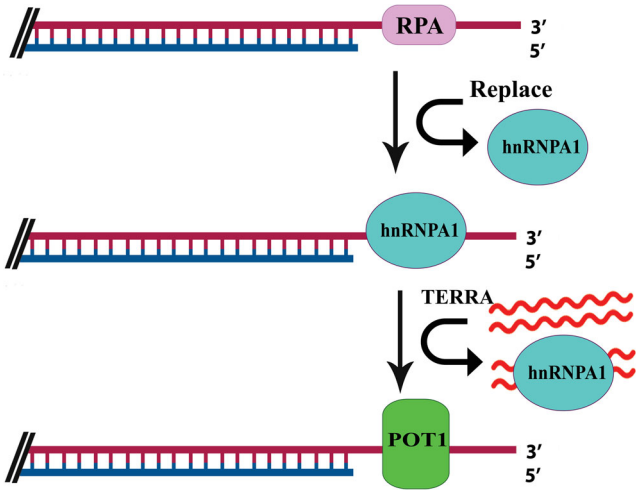

Fig. 5 TERRA expression is essential for the capping of telomeres. RPA replace with hnRNPA1 from telomeric single-stranded overhangs. The interaction between TERRA and hnRNPA1 removes hnRNPA1 from chromosome ends and permitting POT1 binds to telomere end in single-stranded overhangs

ligand and an inhibitor of human telomerase. Although their interaction is still unclear, three models have been proposed for them; TERRA blocks telomerase access by telomere molecule binding to proximal telomeric segment, TERRA binds to telomeric heterochromatin and blocks telomerase access to 3′ end of telomeres, and finally TERRA binds to telomerase and prevents it from binding to telomeric chromatin [152]. In some cancers that the telomerase as a mechanism to maintain telomere lengths is employed, such as advanced stages of the larynx, stomach, colon cancer, and lymph node tumors, TERRA expression is reduced compared to normal tissues [157]. On the other hand, overexpression of TERRA has been observed in tumors with long telomere and lacking telomerase activity. These results suggest that elevated levels of TERRA can be a marker of ALT. Accordingly, telomerase inhibitors and activators and ALT may be important as a specific therapeutic agent [164].

Conclusion

The shortening of telomere lengths plays a role in genome instability and leads to the formation of malignant cells. However, shorter telomere lengths are lethal for cancer cells. For this reason, at the last stage of tumorigenesis, telomere lengths are maintained by telomerase. Changes in telomere length are affected by several factors. Hence, shortening and lengthening of telomeres are associated with an increased risk of cancer. Telomerase has an increasing regulation in cancer cells, but it is not detectable in most normal somatic cells and targeting telomerase selectively removes tumor cells and prevents side effects. Some studies show that hTERT plays an important role in tumorigenesis, growth, migration, and cancer invasion. Most studies are currently focusing on the regulation of hTERT and gene transcription. The overall amount of evidence suggests that post-transcriptional regulation, especially due to long noncoding RNA (lncRNA), is another

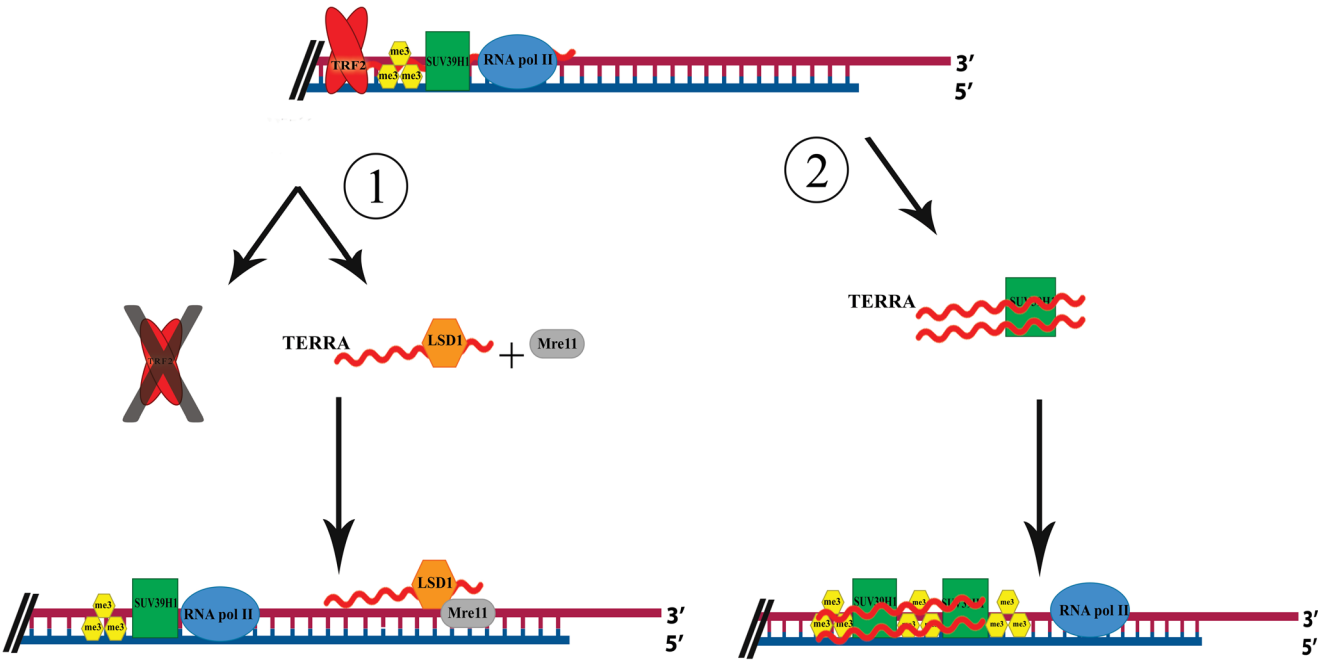

Fig. 6 TERRA participates in DNA damages. 1. The elimination of TRF2 leads to the ineffectiveness of telomeres and increased TERRA expression. TERRA interacts with LSD1-Mre11 complex at chromosome ends and enhances DNA degradation. 2. TERRA interacts with SUV39H1. Also, this interaction leads to promote HSK9me3 in dysfunctional telomeres

level of control. Comparably, TERRA is transcribed as an lncRNA from CpG-island promoters. TERRA plays a significant role in telomere length adjustment and genome stability. Of course, some observations indicate that there is no relationship between TERRA expression and telomere length. lncRNAs are important in the regulation of target gene molecules. Consequently, many observations indicate that TERRA plays an important role in inhibiting telomerase, and that is why it is involved in shortening telomere length. Importantly, in cancer cells with short telomere lengths, the levels of the TERRA increased. In other words, increasing the length of telomeres in cancer cells leads to suppressing the TERRA. TERRA is associated with telomerase enzyme via binding to the RNA. Conclusively, hTERT and regulatory mechanisms that control the expression of hTERT are attractive therapeutic targets for cancer treatment.

Acknowledgments The authors express their appreciation to all people who contributed to this manuscript. We express our gratitude and appreciation to Dr. Ali Ashraf, Mrs. Sedigheh Samimian, and Mrs. Seyedeh Elham Norollahi for their contribution to this manuscript.

Author Contributions SV accomplished the data processing, investigated the informatics database, performed the statistical analyses, and wrote the whole manuscript. AAS revised and managed the manuscript and compiled some sections of the article. All authors revised the article comprehensively and confirmed the final edited version of the paper.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Issues There are no ethical problems for this review article.

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