Telomeres are the ends of linear chromosomes and are composed of TTAGGG hexanucleotide repeats. In somatic cells, telomeres shorten upon each cell division ultimately resulting in activation of DNA damage response followed by senescence or cell death. However, cancer cells activate telomere length maintenance mechanisms (TMM) to overcome telomere attrition and attain replicative immortality which therefore represents one of the principle hallmarks of cancer. Two major pathways are employed by cancer cells to maintain telomeres. First is activation of telomere elongating enzyme called telomerase and second is alternative lengthening of telomeres (ALT). In addition, telomeres are bound by an end protection complex called as shelterin which has an essential role in regulating telomere length maintenance. Thus, TMM and telomere structure and function regulatory pathways represent an attractive target for development of anticancer therapeutics.

Telomerase in Cancer
Telomerase is a specialized reverse transcriptase that elongates telomeres and thus maintain telomere length. It is a multi-subunit complex composed of telomerase reverse transcriptase (TERT), telomerase RNA component (TR) which serves as a template for telomere synthesis, dyskerin, NHP2, nop10, gar1, reptin and pontin which are involved in the biogenesis and maturation of active telomerase (Dey and Chakrabarti, 2018).

Normal somatic cells display a limited lifespan due to the end replication problem that arises due to absence of telomerase activity that occurs due to TERT transcriptional repression during differentiation process (Kim et al., 1994). Telomerase activity is observed in stem...
cells, immune cells and germ cells and 85 to 90% of cancer cells (Shay and Wright, 2011). Based on this observation it is hypothesized that cancer cells may have originated from cancer stem cells however evidences also suggest that somatic cells and de-differentiated progenitor cells acquire stem cell like properties to progress into cancer (Armanios and Greider, 2005; Marusyk and Polyak, 2010). Telomerase activity enables neoplastic cells to replicate endlessly and acquire more genetic alterations in order to achieve cancer development and progression.

TERT gene expression is an important regulatory factor in reconstituting telomerase activity since TR and other telomerase assembly components are ubiquitously expressed (Bodnar et al., 1998; Counter et al., 1998). The major mechanisms reported for TERT activation and telomerase activity in cancer include transcriptional activation of TERT expression through mutations in TERT promoter, amplification of TERT gene and epigenetic pathways (Akincilar et al., 2016). Two most common somatic mutations in TERT promoter include C228T and C250T, mapping to -124 and -146 bp upstream of transcription start site (Horn et al., 2013; Huang et al., 2013). These mutations create a de novo motif for ETS transcription factor binding and thus activate TERT transcription reconstituting telomerase activity in cancer cells. These mutations are reported to occur in several cancers including melanomas, glioblastoma, bladder cancer, thyroid carcinomas and liver cancers. Amplification of TERT gene is reported to occur in breast cancer (Gay-Bellile et al., 2017). Epigenetic modulation through methylation and histone modification has also been reported to be involved in the regulation of the TERT gene however exact molecular mechanisms are not known (Sui et al., 2013).

Targeting telomerase in cancer is an attractive therapy since it is specific to cancer cells and is not detectable in normal somatic cells. Currently, one telomerase inhibitor, imetelstat (GRN163L) has advanced to clinical trials (Akiyama et al., 2003; Asai et al., 2003; Harley, 2008). Imetelstat is a 13-mer oligonucleotide conjugated to lipid with thio-phosphoramidate as backbone. The sequence of the oligonucleotide is complementary to TR component of telomerase and it competitively inhibits telomerase activity by forming stable
complexes with TR. Several other compounds have also been reported to inhibit telomerase activity for example nucleoside analogues (zidovudine, stavudine, tenofovir), synthetic non-nucleoside inhibitors (BIBR1532), natural compounds (rhodocyanine, EGCG, MST-132, curcumin, quercetin, xanthones, oleanane, berbarine, boldine), G-quadruplex stabilizers (BRACO-19, telomestatin, RHPS4), isothiazolone derivates (TMPI) and HSP90 inhibitors (geldanamycin, novobiocin, radicicol) (Ganesan and Xu, 2017). However, they have not advanced to clinical trial step due to lack of the specific molecular action for these compounds and further they exhibit cytotoxicity and non-specificity.

**ALT in Cancer**

ALT involves synthesis of telomeres using homologous recombination (HR) pathway. The template for recombination may be the telomere of another chromosome or sister chromatid telomere or another region from the same telomere through t-loop formation (Cesare and Reddel, 2010). Several reports suggest that loss of ATRX/DAXX function is required for ALT activity (Heaphy et al., 2011). ALT activity is observed in 10 to 15 % of cancers which include osteosarcomas, undifferentiated pleomorphic sarcomas, leiomyosarcomas and glioblastomas while it is low to undetectable in several other cancers (Henson and Reddel, 2010).

Targeting ALT in cancers could be lethal as it involves HR and DNA synthesis which are vital cell processes. Several molecular details of ALT pathway for example causes and consequences of ALT activation remain open areas of investigation and could be potential targets in cancers displaying ALT activity.

**Shelterin in Cancer**

Shelterin complex is present at the telomeres and it consists of six protein complex which include telomere repeat binding factor 1 (TRF1), TRF2, POT1, TPP1, TIN2 and RAP1. Telomeres may be recognized as double stranded breaks by DNA damage machinery in the cell therefore shelterin essentially functions in blocking the DNA damage response emanating from telomeres. Shelterin blocks three major DNA damage pathways which include non-homologous end joining (NHEJ), homology directed repair (HDR) and activation of ATM and ATR (Kibe et al., 2018).
Expression of several shelterin components has been reported to be altered in human cancers suggesting them as potential targets in cancer (Martinez and Balsco, 2017). Mutations in POT1 have been linked to development of familial melanoma, familial glioma, mantle cell lymphoma and chronic myelogenous leukemia (Bainbridge et al., 2015; Ramsay et al., 2013; Robles-Espinoza et al., 2014). Mutations in RAP1 and TPP1 have been found to be associated with familial melanoma (Aoude et al., 2015).

Recently, a chemical inhibitor of TRF1 was reported to inhibit binding of TRF1 to telomeres and it blocked the growth of already established lung carcinomas in mice by inducing acute telomere uncapping and rapid DNA damage response induction (Garcia-Beccaria et al., 2015). Further research is required to explore telomere uncapping as an attractive anti-cancer chemotherapeutic approach.

**FUTURE PROSPECTS**

Telomere maintenance mechanisms have been extensively investigated as targets in cancer and some have reached the clinical trial stage. Figure 1 shows the schematic of various telomere maintenance mechanisms highlighting targets whose therapeutic potential has been investigated. However, further research is required to translate the knowledge of telomere biology to advance into cancer therapeutics.

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**Figure 1:** Schematic representation showing telomere length maintenance mechanisms. Potential cancer targets currently under investigation are indicated.
REFERENCES


