Ind J Clin Biochem (2024) 39:151–153
https://doi.org/10.1007/s12291-024-01211-1

EDITORIAL

Recent Domains in Telomere and Telomerase Targeting for Accomplished Cancer Therapy

Rajendra Prasad[1] · Gurjit Kaur[2]

Published online: 22 March 2024

Telomerase and telomeres are attractive targets for anticancer therapy. In fact, majority of human cancers express the enzyme telomerase which is indispensable to maintain the telomere length, therapy to ensure indefinite cell proliferation, a hallmark of cancer [1]. Telomeric stability at the ends of eukaryotic chromosomes is formed via a structure composed of telomeric hexanucleotides (TTAGGGs) in human beings having a length of 15 Kb in germ line cells and a protein complex called shelterin complex (Fig. 1A). Telomerase is a ribonucleoprotein reverse transcriptase, It consists of two components viz human telomerase RNA component (hTERC) that acts as a template for the addition of new telomeric repeats and a catalytic component human reverse transcriptase (hTERT) and elongates chromosomal telomeres on the RNA template TERC [2].

Shelterin is a group of six proteins viz TRF1, TRF2, RAP1, POT1,TIN2 and TPP1 which bind to telomere, present exclusively at the ends of chromosomes accumulates at T-loop and D-loop, thereby transforms chromosomes ends into specialized structure that evade the DNA damage signalling. Henceforth shelterin complex act as protective caps of telomeres.

Cancer cells exist on the edge of catastrophe when telomere structure is disrupted. Strikingly, the unlimited proliferation capacity of cancer cells is entirely dependent upon telomere maintenance, making factors that control telomeres attractive chemotherapeutic targets. Any molecule that overturns the edge can selectively kill cancer cells. Different targets in telomere and telomerase are depicted in Fig. 1B. Various strategies to target the telomerase include hTERT inhibition, immunotherapeutic, synthetic nucleic acid against hTERT mRNA, reverse transcription inhibitors, gene therapy, inhibition of signaling pathways, hTERT inhibition using antisense oligonucleotides [3, 4]. Majority of the cancer cells upregulate telomerase enzyme whilst others use a homologous recombination based telomere elongation mechanism called alternative lengthening of telomeres [5].

Strategies to target telomere include targeting T-loops, G- Quadruplex and inhibition of shelterin complex as well as ALT-targeted approach [3, 4]. Recently, a molecule APOD53 impairs cell growth in cancer cells while sparing non-cancerous cells [6]. These molecules are excellent novel tools for fundamental research for the development of cancer therapeutics in reference to TRF 2 targets [6, 7]. Use of combination therapy that include all types of telomerase, telomere and ALT type of telomerase and ALT inhibitors may be a promising approach in future. In fact, the combination of established and new technologies include: (a) The attack on targets closely related to telomeres, telomerase and sheltering complex, a strategy named telomeres uncapping[8], (b) CRISPER/Cas9- based technique [9] (c). Novel approaches in ALT tumours, (d) the development of smart synergistic combinatory therapies. Finally, the development of more personalized concepts using state of art blood monitoring such as liquid biopsy/TELSA [10].

✉ Rajendra Prasad
fateh1977@yahoo.com

[1] Department of Biochemistry, Postgraduate Institute of Medical Education and Research, Chandigarh, India

[2] Department of Physiology, Government Medical College and Hospital, Sector 32, Chandigarh, India

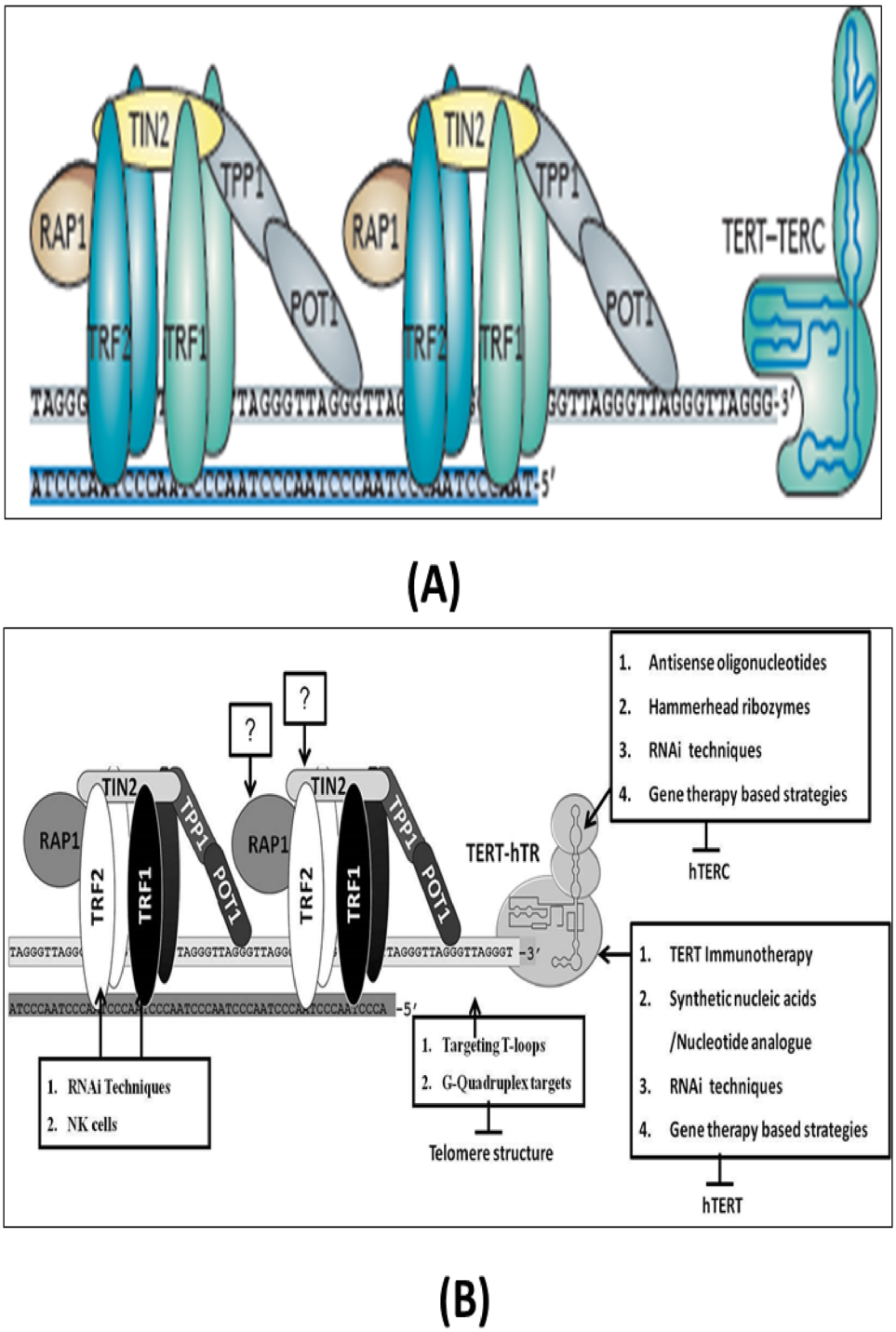

Fig. 1 **A** Schematic representation of telomerase and telomere structure. **B** Therapeutic targets

References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144:646–74.
2. Bodnar AG, Quellette M, Frolkis M, et al. Extension of life span by introduction of telomerase into normal human cells. Science. 1998;279:349–52.
3. Pal D, Sharma U, Prasad R. Therapeutic anticancer approaches targeting telomerase and telomere. In: Gandhi V, Mehta K, Grover R, Pathak S, Aggarwal A, Bharat B, editors. Multitargeted approach to treatment of cancer. Berlin: Springer; 2015.
4. Ali JH, Walter M. Combining old and new concepts in targeting telomerase for cancer therapy: transient, immediate complete and combinatory attack (TICC). Cancer Cell Int. 2023;23:197.

5. Conomos D, Pickett HA, Reddel RR. Aletrnative lengthening of telomeres: remodelling the telomere architecture. Front Oncol. 2013;3:27.
6. Sobinoff AP, Maro SD, Low RRJ. et al. Irreversible inhibition of $TRF2_{TRFH}$ recruiting functions by a covalent cyclic peptide induces telomeric replication stress in cancer cells. Technology. 2023;30:1652–65.
7. Pal D, Sharma U, Singh SK, Kakkar N, Prasad R. Over expression of telomere binding factors (TRF1& TRF2) in renal cell carcinoma and their inhibition by using SiRNA induce apoptosis, reduced cell proliferation and migration in vitro. PLoS ONE. 2015. https://doi.org/10.1371/journalpone.0115651.
8. Rousseau P, Autexier C. Telomere biology: rationale for diagnostics and therapeutics in cancer. RNA Biol. 2015;12:1078–82.
9. Fan P, He Z-Y, Xu T, Phan K, et al. Exposing cancer with CRISPR-Cas 9 from genetic identification to clinical therapy. Transl Cancer Res. 2018;7:817–27.
10. Lai T-P, Zhang N, Noh J, et al. A method for measuring the distribution of the shortest telomere in cells and tissues. Nat Commun. 2017;8:1356.