



Review Article

ROLE OF TELOMERES IN CAUSING CANCER AND TARGETING TELOMERASE IN TREATMENT OF CANCER AS BETTER THAN CONVENTIONAL THERAPY

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ABSTRACT

Telomere that is a part of chromosome can play a vital role in causing cancer in human beings by targeting that part the treatment becomes easy and majority of the investigations are showing that the activation/expression of hTERT in body is the main cause for the carcinoma condition that occurred in the patient. It has discussed about the percentage of cancer cases that has diagnosed with carcinoma condition occurred due to the expression of hTERT and also discussed about the therapies can be given are that can be used to target the telomeres to treat carcinomic stages in cancer patients.

Keywords: Telomeres, telomerase, htert expression, immune therapy, viral therapy, limitations of telomerase

INTRODUCTION

Telomeres

Each chromosome has a cap like structure at their ends composed of DNA- protein for the protection of chromosome these protective structures were called as telomeres. Each telomere is a repeated DNA sequence of guanine and is repeated shortly. 5'-TTAGGG-3' is the repeated sequence of telomere^{1,2}. The stability and the length of the telomere are maintained by the DNA proteins only³⁻⁵. Nearly nucleotides about 200 were present in the 3' end of telomere part of a chromosome, they serves as a substrates to the added repeats of telomeres⁶. Telomeres maintenance is required for escaping the cells from senescence of replication and achieving the proliferation status indefinitely⁷.

Telomerase

In most of the somatic cells except in some stem cells (pleuri-potent cells) the activity of telomerase is not known. Later the enzymatic activity was found in about 90 % of the primary tumors of human cancer cell lines. It was found that the activity of telomerase is counter acting against the progressive replication of telomere ends that causes shortened ends during the replication of cells by synthesizing the new repeats DNA at the terminal part of the chromosome⁸. The expression of hTERT in all human cells has limited the activity of telomerase which was found only in the cells where telomerase activity can be detected^{9,10}. The levels of telomerase must be maintained for the homeostasis of telomeric length, if the elongation of telomeres were continued the htr and hTERT were over expressed in all the human cancer cell lines and primary tumors¹¹. The activity of telomerase can be measured and detected by a polymer chain reaction assay that is very sensitive as it can detect the telomerase activity even from a very less sample size; it is called as the TRAP (Telomerase Repeat Amplification Protocol)¹²⁻¹⁴.

Role of Telomerase in Different Cancers

It was estimated that about 13 millions of deaths will occur by 2030 due to cancer. About 7.9 million deaths will occur every year. About

70 % of new deaths across the world were due to cancer. Here the different types of cancers were discussed¹⁵.

Renal Carcinoma

The activity of telomerase in renal carcinoma was investigated and found that about 70 % of positive samples of cancer cases are with the activated telomerase¹⁶. The activity of telomerase in renal carcinoma is not associated with any clinical profile^{17,18}, but in some cases it was found that the increased activity of telomerase occurs at PT4 stage of renal cancer¹⁹. In the upper U.T.I also the telomerase role was identified²⁰. The potential antigen nature of telomerase is another major important role in renal carcinoma. In the stage of carcinoma the renal cancer cells lacks the specific antigens for tumors to induce immunotherapy specifically. Recent study has revealed that the metastatic stage of renal carcinogenic cells can induce cytotoxicity against the same telomerase of primary culture that is positive in nature²¹.

Prostate Carcinoma

Telomerase activation in androgen cells is more strongly expressed in cell lines of androgen sensitive cell lines while it is absent in both androgen independent and normal cells²². About 92 % of studies reveled telomerase activation in prostate tumors is positively resulted²³. The activity of telomerase on prostate tumors is related to many pathological and clinical factors²⁴⁻²⁶. RT-PCR is used to measure the catalytic hTERT subunit quantitatively in the prostate cancer cell lines²⁷. In about 67 % of the hTERT expression was detected²⁸. PFNB (Prostate Fine Needle Biopsies) is the technique used to detect the cancer cells with high expression of hTERT/ activated telomerase^{29,30}. Recently it was found that the analysis of urine samples serves as the major tool for detecting the non-invasive prostate cancer³¹.

Bladder Carcinoma

About 90 % of bladder cancer cases are reported with the presence of activated telomerase^{32,33}. The RT-PCR is the assay technique used to measure the expression of hTERT m-rna quantitatively that is associated according to grade and stage of cancer tumors in the

bladder³⁴. Urine diagnosis is the prognostic tool for the detection of bladder carcinoma, which is a non-invasive tool for diagnosing the cancer^{35,36}.

Telomerase acting as a Diagnostic Marker

In early days telomerase was considered as the one of the important tool for diagnosis of cancer but it was limited due to the presence of its activity even in normal healthy cells^{37,38}. Among the reported breast cancer cases about 79 %-95 % of cases were found to be positive for the telomerase activity. Though it was found that the activation of telomerase is associated with breast cancer, it is not sufficient for any of the purposes either prognostically or diagnostically^{39,40}. Where as in the case of lung cancer it was found that the analyzing metastasis stage of NSL (non-small-lung) cancer by K-ras mutations is compared to the detection of telomerase activity in lung carcinoma and also compared to the P53 detection. The activity of telomerase in lymph nodes are undetectable, where as the histopathological conditions were reported as about 54 %⁴¹. In case of bladder carcinoma about 85 % of cases were shown positive results for the telomerase activity in specimens of urine than compared to the other available screening tests and cytology also⁴²⁻⁴⁴.

Therapeutics of Telomerase

Generally the advanced stages of cancer are treated by surgical, chemotherapy and radiation or the combination of all the three therapies. Treatment for cancer is considered as the identical therapy if at all it is targeting only on the cancer cells specifically. In such cases the detection of telomerase activity is considered as the ultimate target for the cancer therapy. Targeting telomerase is considered as the novel therapeutic approach when compared to the general conventional treatments to cancer patients as it shows the less side effects and toxic conditions, and has a greater specificity towards the cancer tissues only. These features of the telomerase have directed the therapy towards the clinical trials to evaluate its safety measures, to obtain its T.I (Therapeutic index) / tolerable dose rate^{45,46}. Telomerase inhibitors are considered as the selective agents that acts selectively only on the carcinogenic cells but not on the normal healthy cells. This was proved by the activities done on the human and mice cells⁴⁷. These telomerase inhibitors acts by completely inhibiting the (cell cloning) telomerase activity that further undergoes shortening of telomere length and finally leads to the death of cell caused by instability in the chromosomes^{48,49}. Another method that is discovered recently that causes cell death is inhibition of telomerase along with the analogs of oligonucleotides⁵⁰. Two types of therapies can be done on targeting on the telomerase they are

- a. Immunotherapy
- b. Viral therapy

Immunotherapy

Anti – Telomerase cancer therapy is considered as the rapidly progressing therapy for cancer which acts by targeting on the immune system of the patient^{51,52}. The therapy targeting on the immune system of the patient and makes the immune system to target and kill the telomerase activated cells^{52,53}. In this type of therapy the immune cells are sensitized to the cells expressing hTERT peptides as the surface antigens through class-I pathway of HLA (Human Leukocyte Antigen) that leads to the expression of expanded CD8 + cytotoxic T-Lymphocytes that further initiates the patient's immune system⁵⁴.

Viral Therapy

Tumors with positive telomerase are targeted by suicide genes that are driven by hTERT to express the gene of pro-apoptotic (suicide

gene). It is considered as the alternate gene therapy driven by telomerase⁵⁵⁻⁵⁹.

Limitations of Therapy Targeting on Telomerase

Therapy targeting on telomerase is limited because it needs more generations of cells that are required to obtain the in-viable cell, for which it takes a long period and during that period the cancer cells may become lethal to the body. The cell lines of hTERT positive tumors may get lysed due to the responses of T-Lymphocytes that are cytotoxic but these responses were not clinically proven and their responses on the normal cells were not known. Further investigation on the telomerase targeting therapy is required⁶⁰.

CONCLUSION

In this review we discussed about the different types of cancers that are caused due to the length of telomere that can't be maintained, that further causes limit less proliferation of cancer cells. To treat such cases targeting telomerase is considered as the best way of treatment. The present and ongoing research shows that the telomerase based therapies have an increased potential to treat cancer cases than the conventional therapy.

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