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A Significance Correlation between Malignant Tumors and Telomerase

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Abstract

Telomeres are the ends of humans linear chromosomes that comprise repetitive nucleotide sequences.Telomeres help to maintain chromosomal stability. Telomere length reduces with each somatic cell division, ultimately telomere length will be shortened. Telomere shortening can be avoided by the activity of telomerase enzymatic reaction,which are present in germ line, stem, and immune cells but are unavailable in somatic cells. A shelterin complex connects telomeres, controlling their span and keeping them from damage. Cancer uses telomere conservation to persist an unregulated replicative process.As a result, it's critical to clarify how telomeres and associated proteins play a role in tumor development, growth, and treatment.The present article emphasizes the importance of various telomerase functions, including cancer features that were recently described. Emerging mechanisms for recognizing multiple elements of telomere.

Keywords : Telomere, Telomerase, Tumor, anticancer.

Introduction

Chromosome terminal nucleotides have a critical value in order to retain its stability, The main propose was achieved by Barbara McClintock, that conducted her experiment about maize during 1930s(1), and H. Muller, who studies fruit flies(2).Those researchers hypothesis included that chromosomal ends composed of essential forms required for genome integrity. McClintock observed that chromosomes would fuse and may be break during mitosis in the absence of these specific end structures. The functional units of these complexes are essential to preserve the chromosome terminus, support chromosome cohesion, and ensure faithful segregation of genetic element upon cell division into new daughter cells.At the first of 1960s, Hayflick discovered that cultivation of homosapin cells in tissue culture avert cleavage through a proliferative

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senescence mechanism upon a some of cell creating(3,4,5). Cell culture, he suggested, On a cello-molecular basis, it could be used as a framework for understanding human aging. In vitro models and the role of replicative senescence in human aging have also been extensively debated.Cells are thought to divide in order to regulate normal cell loss. Several cells in the body replicate faster than they should during a normal lifespan(6).In the United States, approximately 606880(7) was died with cancer, while the world cancer statistics of 2018, revealed that approximately seventeen million new cancer cases and nine and six tenths millions of people are expected to die.Efforts to discover a proper cancer cure have shown less finding that fall short of the ultimate target of eradicating the disease.The emphasis is on developing successful anticancer drugs that can target particular genes and signal pathways occurring only in cancer cells.The mechanism of inexhaustible replication is a crucial stage in the growth of tumor mass.Telomerase is a reverse transcriptase that synthesized a significance sequences of DNA to telomeres at the ends of chromosomes(8,9,10).Whereas telomeres significance has been determined (11,12), and telomeres sequence is one of the most important DNA discoveries. (13,14).

Mammalian Telomeres composed of frequencies of sixth nucleotides units (TTAGGG) and related protein category named shelterin(15,16). As a mask-like structure covering the chromosome end, the previous complex protects chromosomes from end separating (17,18).When some telomeres are diminished, at this point cell growth is halted, and a DNA damage signs and cellular senescence are induced(19-21). When there isn't any such improvements, cells can stay in a quiescent state for prolong time, here can be called a tumor regrresion mechanism in long-lived organisms including homosapins. Although it is a general thought that conventional senescent cells undergo apoptosis. it has now been discovered that some factors are arise from senescent cells that affect age-related phenomenon, and still viable, but not duplicating for an extended period of time As seen in figure 1(22).

Figure (1): Homosapin Somatic normal cells show gradual telomere shortening, with increased cell division. During absence of telomeres repairing mechanism , cells undergo replicative senescence(aging). The TERT is a catalytic subunit of the telomerase enzyme is required to maintain telomere length and immortalize normal cells. Ordinary cells, whether they have or have no telomerase activity, aren't transformed. Normal cells can up regulate telomerase, but they can altered in the presence of other oncogenic modifications.

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The telomere cap

The telomere mask of human (10 to 15kb) persists as double stranded, protect linear chromosomal end and recapping of them(23),which stills linked to shelterin protein at the telomere's double-stranded end(24).On the other hand,the single stranded guanine rich telomere field,(Some hundred nucleotides)modify in the form of a T-loop. Shelterin complex composed of six proteins, as they are detailed in table1(25,26).

Table (1): The telomere proteins and their role

No.	Item.	Purpose
1	TRF1	DNA down length regulation activity.
2	TRF2	Formation t-loop and support chromosome stability.
3	POT1	Protect telomere stability.
4	RAP1	Regulate telomere length and protect chromosome.
5	TIN2	Suppress telomere elongation.
6	PTOP1	Telomere length regulating.

Telomerase and cell transformation relationship

Through up regulating telomerase, cellular survival and DNA damage-induced inhibitory signaling pathways are almost never encountered in human carcinomas, by telomerase up regulating. The behavior of telomerase is an increase in transit-replicating stem cells, after cell differentiation it goes through a silent phase. Oncogenic modifications can accumulate in transit-duplicating cells in some cases, causing them to be transformed to become tumorigenic, as well as overexpressing telomerase.

Investigation of cell-proliferation checkpoint genes confirmed its evasion from senescence pathway, which contributed to increased percentages of cell divisions and prompted premalignant or transformed cells, such as certain oncogenes and onco-suppressors(27,28).

On the other hand, cells undergo "crisis," pathway, which is a time in which a cell's division and death are in balance. During the crisis, as a serious of cell conversion, chromosome end fusions, genomic instability, chromosome re-arrangement, there will be telomerase activation, and the tumor will proceed to a malignant state(figure 2).

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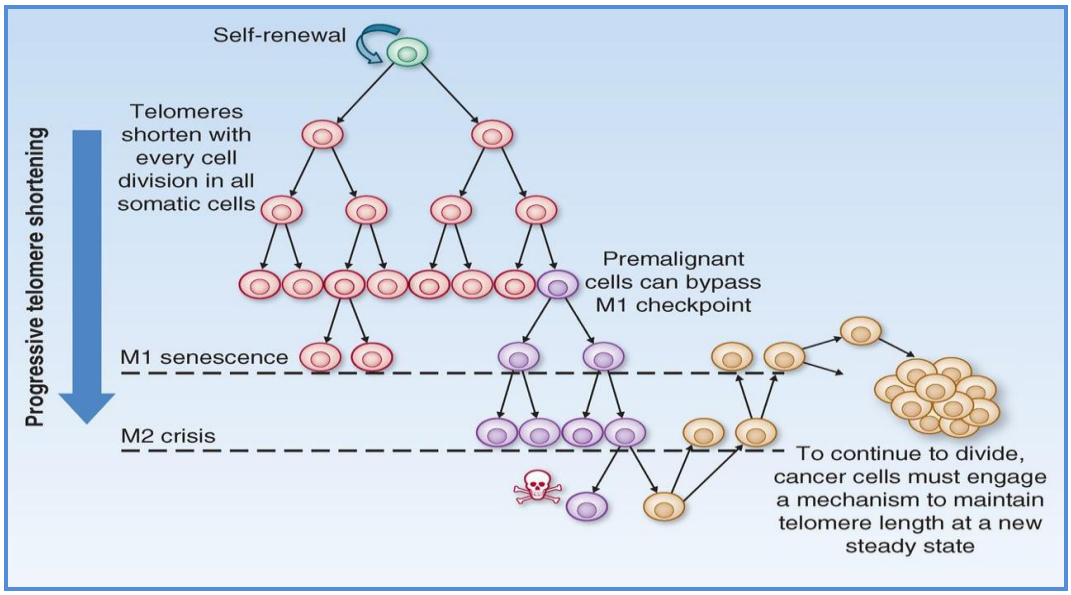

Figure (2): Except in stem cells, there is a noticeable shortening of telomeres as a result of accelerated cell division. After a limited number of cell doublings, it has short telomeres and enters a growth arrest called senescence or the mortality phase (M1). Transformed cells with a variety of oncogenic mutations can skip M1 and live for an extended period of time. Even then, there will be a slowing of cell proliferation and a balance between cell growth and apoptosis over a period of time known as crisis, after which the vast majority of the cell population will die.

According to many studies overall the world, some cases of cancer types documented telomerase activity associated with telomere degradation, for example, pri-melanomas(up to 85%), glio-blastomas(up to 82%), and urogenital tumor(up to47%) involve mutations in TERT promoter nucleotides sequence that lead to telomerase over expression, while new forms of tumors are discovered almost every week(up to 44). It isn't determined why other cancer kinds, like lung, why other cancer forms, such as lung adenocarcinoma, colorectal and ovarian cancer don't have a high incidence of mutations in TERT sequences(29).

In certain cases, these cancer forms have little or just a small percentage of promoter mutations. TERT promoter mutations, on the other hand, are more common in tissues with a low cell turnover rate(30), These mutations are thought to cause telomerase activity, allowing cancer to progress by promoting continuous cell replication. It was previously reported that many tumors

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could be unable to discern telomerase activity, resulting in cancer remission(31,32). These examples show how a lack of telomerase activity will lead to cancer(33).

Moreover, some telomerase is needed to retain the shortest telomeres and it has previously been revealed that 1% of the telomerase present in progressive cases of cancer is needed to retain the shortest telomeres(34).Telomerase expression in untransformed cells for a short period of time is enough to improve the proliferative life of cells by several folds(35). These studies indicate that telomeres shortening depend on telomerase activity, These concerns have important consequences for the advancement of telomerase therapeutics(36).

Recently, TERT expression have been correlated with induced chromatin marks in cells due to TERT promoter mutations (37). Whereas, the wild-type TERT allele is still around chromatin mark in silence stat and doesn't recruit its transcription factor. The mutant TERT promoter in human embryonic stem cells (hESC) that express telomerase elevate telomerase level activity, whereas wild-type hESCs depress telomerase activity during cell differentiation, under various conditions, this mean that telomerase still in active form in hESCs with mutant TERT promoter(38).

Telomerase's Role in Cancer Transformation

In homosapin transformed cells, the enzyme of TERT is programmed to suppress telomere shortening by blocking end extension problems and increasing telomere nucleotides sequences(39).Due to its role is senescence, aging and oncogenic metabolic pathway, Telomerase's primary role is to bind telomeric repeat sequences to the 3′ end of chromosomes, allowing unregulated cell cycling and maintaining telomere length(40,41), in addition, cell proliferation check point genes are a significant cancer hallmark and effective therapeutic targets(42).

Homo sapins telomerase RNA, heat shock protein 90,Human TERT, telomerase linking protein1,Tp23, and dyskerin are all subunits of telomerase that use their internal hTR to create telomeric DNA. Adult replicative cells release HTR and hTERT, while somatic cells remain silent(43). The hTR and hTERT core subunits are both essential for telomere duration maintenance. Dyskerin binds to nuclear RNA, and this complex binds to telomerase's hTR internal domain(44). As seen in figure 4, a long transcript of 451 nucleotides forms the hTR domain, which contains 11 (5′CUAACCCUAAC)nucleotides as the hTR template region.

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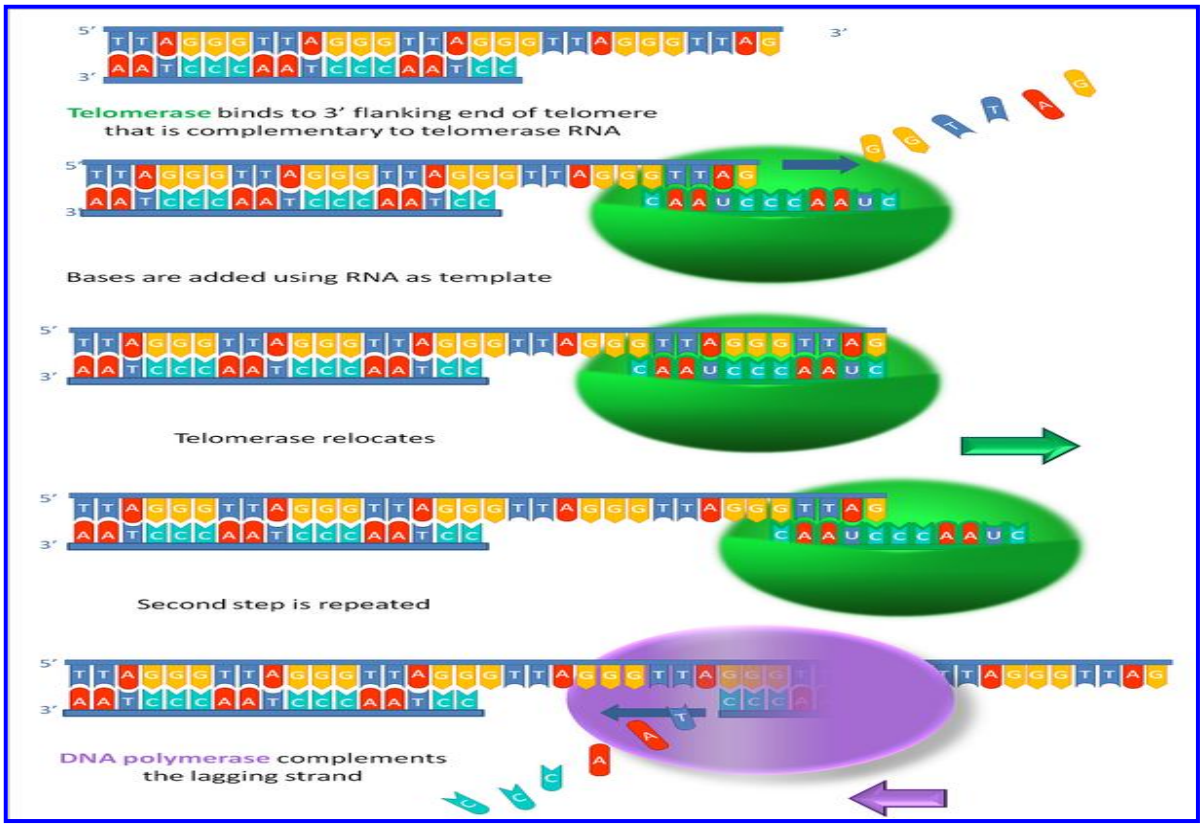
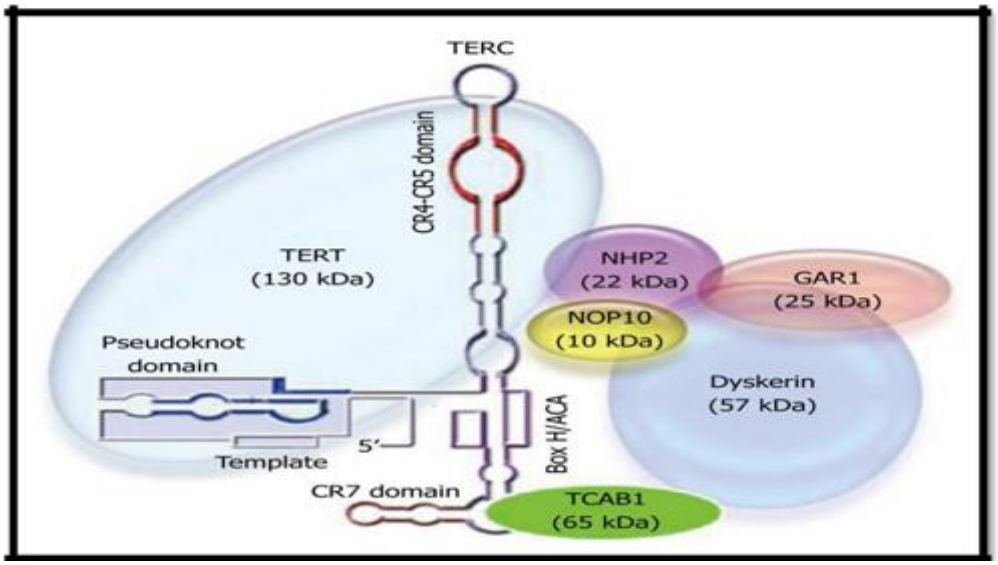


Figure(4): Telomerase, telomere, RNA template complex

hTERT is made up of four distinct subdomains: the N domain, the TERT-RNA binding domain(TRBD) RT domain, and the C-terminal extension(CTE), as seen in figure 5.



Figure(5): Telomerase is a telomerase enzyme. The key components of the telomerase enzyme were shown in a diagram.

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Telomerase hTERT catalytic process acts as a transcriptional factor in tumor signaling pathways, regulating target gene expression required for tumor survival and growth.With hTERT transcription initiation and telomerase activity induction, the Wnt/-catenin and NFB deregulation pathway is related to human carcino-genesis(45,46). Many approaches to producing therapeutic particles have emerged as a result of these findings, some of which are mentioned in the table below.

Table(2):hTERT enhancer protein blockers.

No.	hTERT activator protein	hTERT activator protein inhibitors	Ref.
1.	AKT	Perifosine, Capivasertib, Miransertib, Uprosertib	62, 64,69,71
2.	EGFR	Dacomitinib, Osimertinib, Afatinib, Erlotinib, Cetuximab	75,76,77,78,79
3.	HSP90α	Luminespib, HSP990	81,82
4.	PKC	Dasatinib, Staurosporine, Calphostin C, Tamoxifen	83,84,85,86
5.	FGF	Tamoxifen, Nintedanib, Pazopanib HCl	87,88,89
6.	STAT3	APTSTAT3-9R, S3I-201, C188-9	91,92,93

AKT ,Protein kinase B;EGFR,Estimated glomerular filtration rate; HSP90α,Heat shock protein alpa;PKC,Protein kinasC (PKC);FGF, Fibroblast growth factors and STAT3,signal transducer and activator of transcription3.

Extratelomeric functions are telomere independent functions performed by Telomerase,they are in charge of the development of transformed cells. Telo-merase preserves the nucleus and mitochondria by reducing cellular autolysis and enhancing tolerance stress, chromatin binding. The DNA damage response facility and activation of neuro-protective signaling.These telomerase activities that aren't even dependent on telomeres could impact cancer cell drug resistance. As a consequence, inhibiting telomerase's extra-telomeric role is required for the production of effective telomerase inhibitors.(47,48).

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Targeting Telomeric Components in malignant tumors

various anti-telomere have been designed as cancer therapy. Given the essential and crucial function of telomeres in cancer.Telomere uncapping causes rapid cell death or senescence, which is thought to be a cancer-regression option (49-50). TRF1 can play a role in tumor suppression. The combination of a DNA depletion trigger and a cell cycle arrest inhibited lung cancer cell proliferation without disrupting the mice's survival(51).

Telomerase Inhibitors

Nucleoside Analogs

The earliest antagonists were nucleoside analogs, which incorporated telomeric DNA and inhibited telomerase production to obstruct the telomerase activity. Such as abacavir(52,53).Telomerase chooses the analog 6-thio-dG as a significance coal, it causes telomere dysfunction in cell line,which contributes to death of pulmonary carcinoma(54,55), as well as pediatric brain malignancies. (56,57).

Chemically Modified Oligonucleotides

Imetelstat is a 13-mer oligonucleotide sequence with a thiophosph-oramidate backbone and a covalently connected group of 50 palmitoyl lipids. It has a high affinity for TERC and prevents telomerase from interfering with telomeric DNA. Imetelstat eliminates telomere lengthening and promotes telomere shortening as cells multiply(58). So, after a lag period, cell replication is suppressed in order to achieve short telomeres. The thiophos-phoramidate backbone provides resistance to cell nuclease effects, improved plasma and tissue stability, and increased binding affinity to its target. Lipids increase cell permeability, which increases potency while also enhancing pharmaceutical ability. Imetelstat's function and effectiveness against certain cancerous cell lines and in laboratory animals are the subject of subclinical research. Imetelstat inhibited telomerase activity in NSLC(59), hepatocarcinoma (60) and breast carcinoma(61), as well as leukemia and myeloma(62-64).

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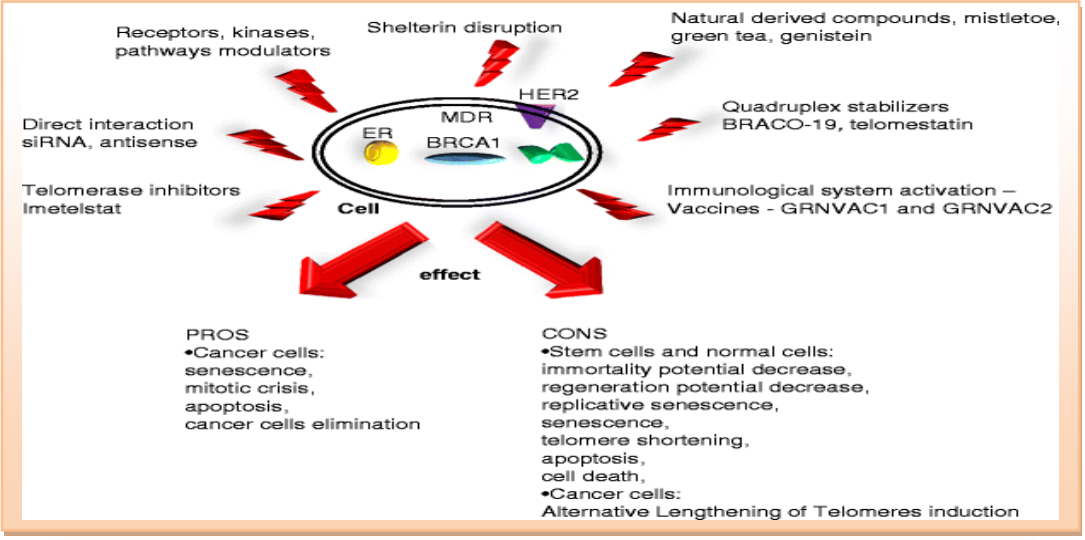
Mixture of uncompetitive chemically Inhibitor

These inhibitors were discovered through the use of chemical references and regression in TRAP behavior. TNQX and DPNS, for example, bind to telomerase and inhibit telomerase-dependent telomere elongation(65,66), as seen in figure 6.



Figure(6): Human cancers can gain from targeting telomeric factors and telomerase.

Non synthesized therapy

Telomerase activity has been shown to be controlled by a series of biological compounds, shorten telomeres, and affect the checkpoint for cancer cell proliferation. Polyphenols and resveratrol, as well as alkaloids, are among them (67). These compounds have also been shown to have antioxidant properties, but the mechanism by which they affect telomerase remains unknown. Synthetic compounds that inhibit telomerase have also been produced based on natural compound structures(68-70).

G4-DNA Stabilizers

From the standpoint of drug discovery and architecture, telomeric G4 is an attractive molecular target for preclinical studies, They have also been shown to disrupt telomerase synthesis, telomere capping, and apoptosis by affecting telomere maintenance(71). They may also use the ALT pathway to restrict cancer cell proliferation in a telomerase-independent manner.(72,73).Sun and colleagues discovered a G4-interacting compound called 2,6-diamido-anthra-quinone analog, which could help to prevent cell senescence (74,75).DIZ-3, a dimeric

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aryl-substituted imidazole, inhibited cell proliferation in the ALT-positive cancer cell line U2OS, demonstrating selectivity for multi-meric G4 cells (76).A synthetic derivative of carboline-benzimidazole was found to be involved in stabilizing G4 DNA over dsDNA, decreasing telomerase activity, and inducing apoptosis in the Hela cervical cancer cell line (77).Instead of dsDNA, a di-nuclear phenanthroline complex showed positive results for different functional classes of G4-DNA(78).

Human TERT Targeting Immunotherapy

1. Immunotherapy Using TERT-Derived Peptide Vaccines

Several studies have looked at using immunogenic peptides extracted from TERT as cancer immunotherapy goals(79,80).TERT-derived peptides have been shown to contain tumor-specific MHC I and MHC II epitopes in a number of vaccines(81,82).

GV1001 and GRNVAC are two vaccines that have been extensively tested against human cancers. GV1001 is a 16-mer peptide vaccine restricted to MHC class II that requires GM-CSF to activate cytotoxic CTL, T-helper cells, and naive T cells(83,84). GV1001 has a major impact on cells. As per some studies, GV1001 is localized in the cytoplasm after crossing cell membranes and decreases the amount of intracellular and surface HSPs, HIF-1a, and VEGF in tumor cells under hypoxic conditions. (85,86).GV1001 has been shown to induce apoptosis of prostate cancer and renal carcinoma cells in the lab(87). GV1001 was the first TERT peptide vaccine to be studied in human cases for melanoma, pancreatic, lung, and liver carcinoma.88,89,90(Fig.7).

Figure (7): Telomerase-based immunotherapy and the role of the immune system in eliminating cancer cells. Several telomerase-based immunotherapies including peptides and plasmids have been developed to eradicate the tumor cells expressing human TERT peptides on their surface. CD8+ and CD4+ T cells accept these antigenic peptides through the main histocompatibility complex class I and class II, respectively. This causes cancer patients' telomerase-mediated cytotoxic T lymphocyte responses to be amplified.The hTERT peptide in GV1001 is MHC class II-restricted and is picked up by antigen-presenting cells (APCs) to represent it as an MHC class I peptide, activating both CD4+ and CD8+ immune cells.Both CD4+ and CD8+ immune responses are generated by GX30, UV1, and INVAC-1. CD4+ and CD8+ T cells are triggered by GRNVAC1 and Vx001 to destroy hTERT-expressing cancer cells, respectively. CD8: cluster of differentiation 8; hTERT: human telomerase reverse transcriptase.

UV1 is a vaccine that incorporates three TERT-specific peptides in a multi-peptide shape. UV1 was offered to patients with prostate cancer who had metastasis in phase I and IIa classes, along with GM-CSF,91-95(Fig.9).

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2. TERT-Immunotherapy Targeting Dendritic Cells (DCs.)

Dentric cells are the potent APCs, functioning as a link between the innate and adaptive immune systems.Transfection of mature DCs with TERT mRNA and the lysosomal derived membrane protein 1,LAMP1, resulted in the synthesis of GRNVAC1, a DC-based tumor vaccine (96).Prostate cancer metastases inoculated with GRNVAC1 developed a strong CTL response.Patients infected with GRNVAC1 did not develop autoimmunity, and the vaccine was well tolerated even after repeated administration. GRNVAC1 also produced antigen-specific cytotoxic and helper T cells (97,98).

Mehrotra and colleagues created a pulsed DC vaccine that included three different HLA A2-restricted TERT peptides, CEA, and survival. In a phase I trial for pancreatic cancer treatment, this was tested. In half of the patients, the procedure elicited unique T-cell responses, resulting in stable disease and a median overall survival of 7.7 months. The vaccine was well tolerated, with transient nausea and influenza-like symptoms being the most common side effects (99,100).There was also a hybrid vaccine made with mannan-modified adenovirus that expressed both TERT and vascular receptor-2 endothelial growth factor. It triggered CTL responses against TERT and VEGFR-22, which resulted in high antitumor immunity and prevented intra tumor angiogenesis (101,102).

3. DNA Vaccines

TERT peptides can be improved to produce more efficient epitopes on the surface of APCs. APCs can be directly implanted with recombinant plasmids using electroporation and a gene gun. A DNA vaccine like phTERT is an example. PhTERT contains TERT-versus-full-length DNA. PhTERT was first electro-porated into mice and nonhuman primates, causing a long-lasting and significant TERT-specific CD8+ T-cell reaction with IFN-, TNF-a, and CD107a expression. The immune monkeys produced a lot of IFN- and perforin, indicating that phTERT caused cytotoxicity. (103-104).

4. Cell-Based Approaches

TERT and lentiviral transduction is used to immortalize human umbilical vein endothelial cells. To prevent cellular growth, updated HUVECs were irradiated and then subcutaneously injected into murine models of lung and colorectal cancer, where they retained high telomerase activity and expressed CD31, integrin a5, and VEGFR-II(105).

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5. Gene-Modified T-Cell Therapy

This involves genetically altering or engineering T cells to produce T cell receptors that directly recognize cancer antigens and epitopes for successful cancer therapy(106,107).

For genetically modified T cells, there are two well-established methods: the first uses tumor TCRs originating from tumor-specific T cells, and the second uses chimeric antigen receptors, whose extracellular region contains a single-chain antigen recognition receptor made up of variable regions of a monoclonal antibody that recognizes the tumor-specific antigen, and whose intracellular region contains a costimulatory molecule that binds to the intracellular component of the TCR (108-110).

Conclusion

The depletion of telomere repeats in (stem) cells and lymphocytes causes human ageing, according to accumulating proof.This description is not widely known, owing to the difficulty of quantifying the progressive depletion of telomere repeats with age in cells of various tissues, as well as the fact that the total length of telomere varies greatly between species and individuals of the same age.Short telomeres, on the other hand, have been shown to have dire implications in both model organisms and telomerase mutation patients. It's likely that as people get older, progressive telomere depletion puts the proliferation of an increasing number of cells in jeopardy.Limits on somatic cell proliferation are an impediment to the development of aspiring tumor cells, so this isn't always a bad thing.

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