

Telomerase and Cancer Research

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Abstract

Telomerase activity has always been an exciting subject to many fields of scientific research. Since its description by Blackburn's group in 1985 as a telomere synthesizer, many therapeutic applications have been speculated. Once telomerase is capable to delay the biological clock imposed by telomeres, it has already been considered as a possible fountain of youth. But, when researchers discovered its over-activity in more than 90% of tumors, the possibility of its use as a senescence inhibitor had to be reviewed with caution. Many telomerase inhibition strategies targeting cancer therapy have been developed in the last decades, but paradoxically it is believed that telomerase inactivation caused by transcriptase reverse inhibitors, as the one used in the treatment of some retroviruses, may contribute to accelerated aging and other collateral effects observed in the treatment of HIV-infected individuals. One alternative to solve this paradox would be a directed cell-type specific delivery. Today it is known that beyond telomere maintenance, telomerase plays many other important roles at cellular environment and its comprehension can bring new breakthroughs in cancer research and other areas of the scientific knowledge.

Keywords: Telomerase activity; Ribonucleoprotein complex; Carcinogenesis; Telomestatin; Mitochondrial dysfunctions

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Introduction

Human telomerase is a ribonucleoprotein complex, constituted by a catalytic subunit (hTERT), responsible to regulate the enzymatic activity as a reverse transcriptase, a RNA chain (hTER) that provides the template to add the telomeric sequence to the chromosome ends (TTAGGG in humans) and other accessory proteins. This enzyme was first described by Carol W. Greider and Elizabeth Blackburn in 1985 [1]. Due to its ability to add telomeric sequences in the end of eukaryote chromosomes overcoming Hayflick's limit, since its discovery telomerase has been the subject of scientific research in different areas of knowledge.

The initial features exhibited by telomerase made many scientists think that telomerase could be target of an anti-ageing therapy. In adult tissues, the enzyme is expressed just in some specific cell types, like hematopoietic and stem cells, whereas embryonic and germ cells show high levels of telomerase expression. The ectopic expression of telomerase catalytic subunit hTERT restores telomerase expression of human cells and is able to immortalize most of human cell types, being used as an in vitro protocol to

produce established cell lines. It is also suggested that telomere dysfunction plays an important role in the cellular decline of patients with progeria disease and telomerase expression ameliorate the phenotype [2]. Altogether, these facts indicated this fabulous enzyme as a cure to senescence.

This first optimistic wave was broken down when many papers started to associate telomerase expression with the indefinite proliferation observed in tumors. Today it is known that telomerase is reactivated in 96% of human tumors and it is believed that the overexpression of this gene is one important step on carcinogenesis. We believe that normal cells in which telomerase is not activated start a chromosome instability process due to a fault in the replicative mechanism, acquiring a chromosome imbalance. This genetic modification provides adaptive and proliferative advantages until a crisis state, in which telomere disruption leads to many chromosomal structural alterations. This state is overcome by variant insurgent cells that activated telomerase gene [3]. Currently it is known that telomerase also plays other important roles at cellular environment, which are not associated to telomere maintenance and are also involved with tumorigenesis.

Telomerase plays diverse non-canonical or non-telomeric roles, in different cell compartments. At the nucleus it works in the regulation of chromatin structure and gene expression, regulates DNA damage responses, enhance DNA repair, protects cell against apoptosis and hTER promotes suppression of DNA damage checkpoints. At cytoplasm, TERT binds to stress particles under non-stress conditions and interact with many signaling pathways. At mitochondria, TERT increases membrane potential, protecting cells against reactive oxygen production and mtDNA against damage, avoiding apoptosis. Decreasing ROS generation at mitochondria TERT also prevents nuclear DNA damage. Telomerase also is essential for the beneficial effects of physical exercise [4-6].

Faced to this essential enzyme that has multifaceted functions, many research groups converged efforts to develop many strategies to inactivate it. Today we have a huge range of bioactive molecules that act on the suppression of telomerase function targeting two components of telomerase, hTERT and hTER. Imetelstat sodium (GRN163L) is a lipid modified 13-mer oligonucleotide that binds in the active site of telomerase to hTER, acting as a competitive inhibitor and this molecule is being assessed in multiple phase II clinical trials. Another studied drug is BIBR1532, a small synthetic non-nucleic molecule that inhibits telomerase in a noncompetitive that links to hTERT in its active site and reduces the number of added TTAGGG repeats [7,8].

Another tested drug is the telomestatin, a natural telomerase inhibitor isolated from streptomyces bacteria. It has been shown to be a powerful anticancer agent and is selective for cancer cells. It belongs to a class of molecules called G-quadruplex stabilizers, due to its ability to sterically block the binding of telomerase to the

telomere, forming a stable complex in the end of DNA molecule [9]. Telomerase also can be a target to immunotherapy, once that their epitopes are expressed in tumor cells and are not find in the normal cells. Multiple peptides as GV1001, Vx-001 and I540, are known to stimulate the immune system and induce hTERT-specific immune responses [8]. Telomerase also can be attacked at pre-translational level using RNA interference technology and antisense oligonucleotides. The other non-canonical functions of telomerase can be a target of therapeutic approaches too, and more studies are essential to better understand the importance of these non-telomeric associated functions.

As can be seen, there are many attempts to inactivate telomerase, but these therapies can induce some side effects once that normal cells that express telomerase, as the stem cells, can be harmed too. These side effects of telomerase inactivation are observed in AIDS treatment with anti-retroviral nucleosides. These drugs inhibit viral reverse transcriptase and consequently attacks telomerase, causing accelerated aging and mitochondrial dysfunctions.

An alternative to solve this problem could be the development of directed cell-type delivery, carrying these therapeutic biomolecules specifically to tumor cells. In this context, the use of antibodies or ligand peptides directly coupled to drugs or associated with liposomes or nanoparticles is a promising strategy. Finally, the knowledge about telomerase and the functions performed by this enzyme in the cellular environment has improved drastically in the last decades and a huge range of applications can be glimpsed, but scientists still have much to learn about this promising field of study.

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