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Modulating telomerase activity in tumor patients by targeting dyskerin binding site for hTR

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ABSTRACT

Telomeres shortening, which leads to apoptosis, is prevented by telomerase adding small repeated segments of DNA to the telomeres. The telomerase level has been correlated with progression of several cancer types, including acute leukemia, breast, prostate, lung cancer and melanoma. Suppression of telomerase activity was found to reduce metastatic potential but could have serious side effects in normal proliferative cells. One of the proteins stabilizing the telomerase complex called dyskerin reduces the maximum telomerase activity. We suggest a possible therapeutic agent which would disable the interaction of dyskerin and telomerase, but would not completely inhibit telomerase activity.

Introduction

Ends of eukaryotic chromosomes called telomeres have a tendency to shorten during every division which leads to chromosome instability and apoptosis after about 50 divisions. When active, telomerase slows down the shortening by adding small repeated segments of DNA to the telomeres during the cell cycle [1]. In most types of somatic cells, telomerase is either undetectable or active at very low levels. However, telomerase is active in cells with high replicative demands, such as hematopoietic cells, lymphocytes and gastrointestinal and lung epithelium.

The telomerase level has been correlated with progression of several cancer types, including acute leukemia, breast, prostate, lung and melanoma [2]. It was also found that the suppression of telomerase activity in tumor-bearing mice significantly reduced metastatic progression [3].

Hypothesis

Telomerase consists of two copies of telomerase reverse transcriptase (TERT) and two copies of its integral RNA template (TERC), and other proteins that stabilize the complex [4]. TERC gene provides a template (human telomerase RNA component, hTR) for creating the repeated sequence of DNA that telomerase adds to the ends of the chromosomes. One of the proteins found to stabilize the telomerase complex is called dyskerin. It was clearly found in a *Arabidopsis* in vivo model that mutated dyskerin homologue At-NAP57 reduced telomerase activity but did not shut it down completely [5]. It was also found that dyskerin had an active site for modifying specific uridine particles in rRNA by converting them to pseudouridine [6]. Our hypotheses is that a small chemical compound would serve as a potential therapeutic agent to target the dyskerin-hTR binding site Fig. 1 [7]. Thus, it would block their interaction and eliminate the possibility of telomerase maximum activity and metastatic progression.

Discussion

Currently, there is a number of potential therapeutic agents that target telomerase directly [8,9]. However, it is found that TERT mutations induce severe aplastic anemias in patients [4]. There are numerous other potential side effects of untargeted complete inhibition of telomerase. In vivo mouse model suggests that some mutations in a dyskerin possibly active site decreases effectiveness in pseudourilation pathways [10]. We suggest there should be a chemical compound that would target the dyskerin binding site for hTR. Following the Flory scaling law [11] the compound would need to be 15–30 Å in radius mimicking the size of a couple of RNA nucleotides. The compound would compete with hTR to bind to dyskerin and consequently reduce the telomerase complex stability. Instable telomerase complex would reduce the telomerase maximum activity and directly decrease the malignancy potential induced by it. However, the active sites of dyskerin and telomerase would be unaffected, and thus minimize the interruption of normal proliferative cells function.

Conflict of interest statement

None declared.

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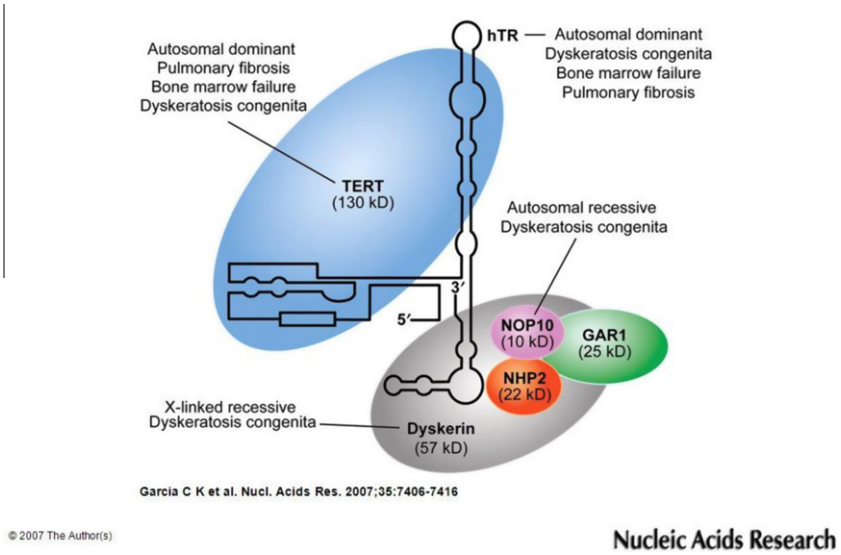

Fig. 1. Schematic structure of the telomerase complex and diseases associated with mutations in the genes encoding each protein within the complex. Reproduced by the kind permission of C.K. Garcia et al. from Nucleid Acid Research (2007) [7].

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