

# Telomeres in cancer therapy

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Finding new targets to improve current cancer therapies is one of the areas of Biomedicine and Biotechnology that generates greater expectations. The telomeres, special protective structures at the end of eukaryotic chromosomes have been metaphorically proposed to be cancer's Achilles heel, since they are essential to stabilize linear chromosomes [1]. There is mounting evidence that loss of telomere function, either by altering telomere-binding proteins or by loss of telomeric sequences, is associated with loss of cell viability through induction of apoptosis [1]. Most of the attempts to impair telomere function have consisted in the inhibition of the enzyme telomerase, a ribonucleoprotein DNA polymerase that synthesizes telomeres, *de novo* [2]. The characterization of mice that lack the RNA component of telomerase showed that telomerase inhibition in a mammal leads to telomere shortening, increased chromosomal instability, and loss of viability [3]. Furthermore, inhibition of telomerase in various cancer cell lines, either using dominant versions of the enzyme or antisense oligonucleotides against the RNA component, also lead to telomere shortening and cell death or differentiation [4–6]. All these studies suggested that telomerase inhibition might compromise tumor growth by leading to an accelerated telomere shortening and cell death, hence, anticancer therapies based in telomerase inhibition could be a promising approach. Some data suggest, however, that the situation may be more complex. The first doubt thrown on the efficacy of an anticancer therapy based on telomerase inhibition came from the fact that telomeres can be maintained by means other than telomerase itself [7, 8]. Such telomere maintenance mechanisms seem to be selected when telomeres reach a critical short length, chromosomal abnormalities have occurred and cell viability has been compromised [9]. In other words, even though telomerase inhibition in a tumor might result in short telomeres and cell death, there is a possibility that resistant clones might arise that would be refractory to the treatment and would bear a higher chromosomal instability. This is supported by evidence from the mouse model without telomerase: even though these mice show loss of viability associated with telomere shortening, a fraction of telomerase-deficient mice appear to develop lymphomas at a higher frequency than the wild-type counterparts [10]. These tumors are possibly the consequence of loss of check-

points associated with telomere loss, this allowing the growth of cells bearing high chromosomal instability and maintaining telomeres without telomerase [11]. An analogous situation could happen in human cancers where the proliferative pressure is very high. Such telomerase-independent telomere maintenance mechanisms should be targeted if we want to assure an efficient telomere-based therapy. We have learned from studies in yeast that these mechanisms might involve homologous recombination and DNA repair proteins [12, 13]. More recently, it has been proposed that a special structure at human telomeres, known as the telomeric loop, could also account for telomerase-independent telomere elongation [14]. It is possible, however, that different tissues have different sensitivities to telomere loss. In this regard, the skin of telomerase-deficient mice is resistant to chemical tumorigenesis [15]. This supporting that telomerase inhibition in skin tumors might cease their growth.

A second possible problem of a tumor therapy based on telomerase inhibition is that tumor cells may divide without telomerase before reaching critically short telomeres. In other words, telomerase inhibition is not expected to have an immediate effect on tumor growth.

In summary, there is strong evidence that telomeres may be a very good target for new anticancer therapies. To date, most of the efforts to compromise telomere function in cancer cells have involved telomerase inhibition. The fact that telomeres can also be maintained in a telomerase-independent way and that telomeres have to reach a critical length before effects on viability are seen, might result in a low efficiency of a treatment based on telomerase inhibition. This should encourage researchers to focus future studies not only on development of telomerase inhibitors but also on inhibitors of telomeric proteins, disruption of telomere structure, or disruption of alternative telomere maintenance pathways.

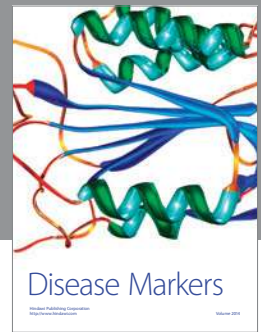
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