Telomeres and Telomerase in Lung Cancer

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Abstract: Protected telomeres ensure normal chromosomal segregation during mitosis but at the same time can endow genetically abnormal cancer cells with immortality. Telomerase has a pivotal role in telomere protection, both in normal and cancer cells. Understanding the functional interplay between telomere shortening and telomerase expression in cancer cells is of critical importance to elucidating the precise mechanisms by which these cells are able to bypass telomere crisis and become immortal.

Key Words: Cancer, Lung, Telomere, Telomerase.

(*J Thorac Oncol.* 2008;3: 1085–1088)

TELOMERES: AN ANTICANCER BARRIER

Telomeres are the ends of linear genomes. Made of multiple copies of a TTAGGG sequence, telomeres protect chromosomes from degradation, irregular recombination and end-to-end fusions.[1] Normally, a sheltering complex—*shelterin*—composed of at least six telomere associated proteins, caps the telomeres, protecting them from being recognized as double strand breaks by the DNA damage response (DDR).[2] Telomeres shorten with every cell division. Somatic primary cells in cell culture shorten their telomeres by 50 to 200 base pairs after each round of replication until they reach a critical length below which the shelterin complex becomes inefficient. This leaves the telomeres "un-capped," which in turn activates the DDR and triggers cellular senescence.[1,2] This process is known as the "mitotic clock for aging."[3] The current hypothesis of telomere involvement in cancer (Figure 1*A*) states that proliferative preneoplastic cells suffer persistent telomere shortening leading to massive senescence (mortality stage I) in all but a few positively selected cells, which are able to bypass senescence by altering their DDR by mutation or silencing of DDR-related proteins such as ataxia telangiectasia mutated, p53, and p16.[4] These cells extend their life span and continue losing telomere fragments until their telomeres become dysfunctional, causing genomic instability and subsequent apoptosis (mortality stage 2). According to this model, during this process a small subpopulation of cells is able to avoid apoptosis by maintaining their telomere length. Telomere length maintenance at this stage is related to the expression of telomerase, which adds TTAGGG fragments to the end of the telomeres, lengthening and maintaining them in the capped conformation. More rarely, telomere elongation can also be achieved through homologue recombination between telomeric sequences: the alternative lengthening mechanism. Thus, according to the current model, the progeny of the few, genetically unstable, immortal cells that escape both mortality stages may allow the progression of a preneoplastic lesion towards malignant stages.[1,3–6]

Telomerase is a large DNA polymerase ribonucleoprotein (RNP) complex containing an RNA subunit (telomerase RNA component [TERC]) and a protein component (telomerase reverse transcriptase [TERT]). Most somatic cells do not show detectable telomerase activity mainly because of lack of telomerase expression. However, stem and embryonic cells do express telomerase as a mechanism to prevent telomere attrition.[7]

TELOMERE MAINTENANCE AND TELOMERASE REGULATION

Because of its importance for cell fate, telomere length is finely regulated. Telomerase activity is the main mechanism for telomere maintenance and thus, telomerase activity itself is also carefully controlled (Figure 1*B*).

The active telomerase RNP consists of three subunits: the telomerase reverse transcriptase (TERT), the TERC, and dyskerin 1.[8] The catalytic activity of this enzyme resides in the TERT component, and thus the regulation of TERT mRNA expression seems to be the most important step for telomerase activation. In this context, many oncogenic and tumor suppressor pathways have been shown to regulate TERT mRNA transcription. C-myc, RAS, E6, STAT 3, and estrogens are activators of TERT, whereas Mad 1, p53, TGF-β, RAK, BRIT1, and MDM2 are inhibitors. TERT transcription is also regulated by epigenetic modifications of its promoter, which contains clusters of CpG islands which can be methylated, and thus silenced, by DNA methyl transferases. Besides transcriptional regulation, TERT activity may be regulated by alternative splicing and posttranslational modifications.[7] Active telomerase RNP requires that transiently expressed TERT assembles with constitutively accu-

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Disclosure: The authors declare no conflicts of interest.

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ISSN: 1556-0864/08/0310-1085

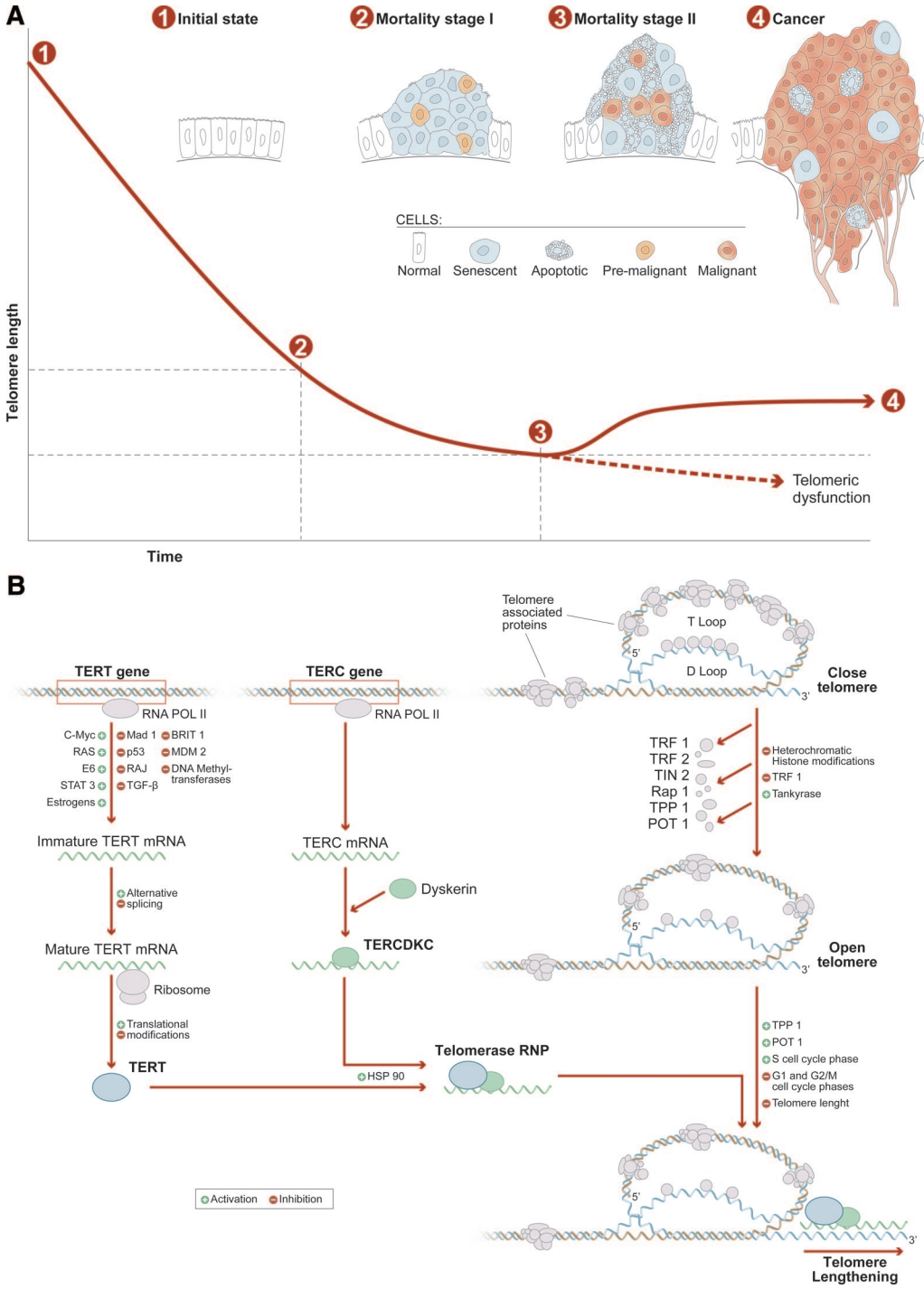

FIGURE 1. *A*, Theoretical model of the association between telomere length and the carcinogenesis process. The cells continuously proliferating in preneoplastic lesion suffer persistent telomere shortening leading to senescence (mortality stage I). Some cells are able to bypass senescence by altering their DDR and keep proliferating. These cells extend their lifespan until their telomeres become dysfunctional, entering apoptosis (mortality stage II). A small subpopulation of cells with genetic abnormalities escapes both mortality stages and progress towards malignancy. *B*. Summary of the telomerase regulation and telomere elongation pathway. Abbreviations: telomerase reverse transcriptase (TERT), telomerase RNA component (TERC), RNA polymerase II (RNA POL II), dyskerin (DKC), telomerase ribonucleoprotein (telomerase RNP), telomeric repeat-binding factor (TRFs) 1 and 2, TRF1-interacting nuclear factor 2 (TIN2), TRF2-interacting protein 1 (Rap1), adrenocortical dysplasia protein homolog (TPP1), and protection of telomeres protein 1 (POT1).