Telomerase and Cancer: Where and When?

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Several lines of evidence now support the notion that the maintenance of telomeres plays an essential role during malignant transformation. Mammalian telomeres, specialized nucleoprotein structures composed of large concatamers of the guanine-rich sequence 5′-TTAGGG-3′, constitute the ends of eukaryotic chromosomes and serve to protect linear chromosomes from damage, thus promoting genomic stability (1). In addition to this protective function, recent evidence implicates the regulation of telomere length as an important factor in regulating cellular life span (2). The roles of telomeres in regulating both genomic stability and replicative immortality appear to contribute in essential ways to cancer initiation and progression.

Several laboratories have shown that normal human cells progressively lose telomeric DNA with passage in culture, whereas telomere length is stable in neoplastic cells (2). Telomeres are maintained by telomerase, a multisubunit enzyme comprised of an RNA component, hTR,2 which provides the template for the synthesis of telomeric repeats and a protein reverse transcriptase component, hTERT, which catalyzes the synthesis reaction (3). In humans, telomerase enzyme activity is absent in most normal cells but present in the majority of tumors (4). Recent work has confirmed these observations in both solid and hematopoietic cancers (5), leading to the proposal that telomerase expression may prove to be an important diagnostic tool as well as a novel target for cancer therapy.

Although active telomerase requires the coexpression of both hTR and hTERT components, the RNA component is ubiquitously expressed (6), and expression of hTERT correlates most closely with telomerase activity in most tumor cell lines, which suggests that it is the regulation of hTERT expression that permits telomerase activation (7, 8). Consistent with these observations, experimental introduction of hTERT into normal human cells that lack telomerase activity reconstitutes readily detectable telomerase enzyme activity and stabilizes telomere length (9). Furthermore, the expression of hTERT in many mortal cells permits immortalization (9), and inhibition of telomerase in tumor cell lines leads to telomere shortening and apoptotic cell death (10, 11). Coexpression of telomerase with oncogenes converts normal human cells into cells capable of tumorigenic growth (12, 13). Taken together, these observations confirm that the acquisition of telomerase activity is not only a crucial step in attaining replicative immortality but also plays an important role in human cell transformation.

A simple model that emerges from these observations predicts that the limited life span of normal cells is tightly regulated by hTERT repression and that cancer cells surmount this replicative barrier through the illegitimate expression of hTERT. Although almost certainly correct in its broad outlines, several disparate observations require further investigation. For example, although most somatic cells lack telomerase activity, some normal, differentiated cell types such as lymphocytes, basal keratinocytes, and germ cells, exhibit telomerase activity and express hTERT (4, 14). Furthermore, in lymphocytes, the regulation of hTERT, and therefore telomerase, may also involve posttranscriptional modifications (15). In addition, still unanswered are the questions of how tight repression of hTERT is accomplished and when during cancer initiation and progression do hTERT and telomerase become activated?

In this issue, Kim et al. (16) provide important initial steps toward a deeper understanding of the role of hTERT in the development of human cancer. Using real-time RT-PCR, Kim and colleagues found that although total RNA from the majority of samples derived from both normal human oral (11 of 13) and squamous cell carcinomas (SCC, 11 of 12) showed detectable hTERT transcripts, that the levels of hTERT expression were significantly higher in SCC. When they analyzed tissue sections using in situ RT-PCR, they found that sections derived from tissues with normal or mild dysplasia lacked hTERT transcripts, whereas sections taken from tissues with moderate or severe dysplasia or SCC expressed hTERT. Although these two techniques clearly differ in their sensitivity, these observations raise a note of caution in interpreting the results of telomerase assays, hTERT RT-PCR, and immunohistochemistry in tissue sections.

In particular, these findings are in consonance with those previously reported that showed the presence of hTERT transcripts in RNA derived from tissues previously described as lacking telomerase enzyme activity (14, 17). Although these observations may suggest that hTERT is not the rate-limiting component of the telomerase holoenzyme, several groups have reported alternatively spliced, catalytically inactive forms of hTERT that may be detected by RT-PCR or in situ hybridization (18). Alternatively, because some normal cells such as lymphocytes and some basal epithelial cells have also been shown to express active telomerase (4), a small population of telomerase-expressing cells may contribute to the observed expression of hTERT in RNA taken from tissues reported to lack telomerase activity. These alternative possibilities make it essential for future studies to analyze which cells within a given tissue express hTERT. Taken together, these observations add signifi-
icant complexity to the use and interpretation of hTERT expression as a surrogate for telomerase activity in a diagnostic setting.

Despite the above considerations, the observation that hTERT was expressed in squamous epithelial cells at a specific histological stage (from mild to moderate dysplasia) begins to address the biological question of when during the stepwise progression of normal cells into cancer cells does hTERT become activated. Some have argued that telomere shortening and the subsequent chromosomal instability that occur in the absence of telomerase activity not only drive the characteristic karyotypic abnormalities seen in human epithelial cancers but also select the further mutations that program the malignant state (19). In this model, telomerase activation occurs after the selection of mutations that stimulate abnormal cell proliferation, and, thus, telomerase activation may be a relatively late event in tumor initiation that allows for genome stability after the acquisition of cancer-associated mutations. Alternatively, others have argued that because hTERT expression can be observed at relatively early stages of dysplasia, telomere shortening and selection for telomerase activation may occur before the selection of the complete set of critical mutations that are needed to program malignant growth (14). The present observations appear to place hTERT activation relatively early during the development of squamous cell cancers. These findings are similar to what has been observed in breast and colon tissues using in situ hybridization in which hTERT activation was seen in lobular and ductal carcinoma in situ and in adenomas (14). Additional studies using methods that permit histological localization will help determine whether a specific neoplastic transition correlates with telomerase expression or whether telomerase activation occurs at distinct times in different types of cancers. Because some have argued that telomerase expression curtails further genomic instability (20), determining the temporal frame of telomerase activation has important implications for our understanding of the role of telomerase activation during oncogenesis.

Moreover, as effective telomerase inhibitors are developed, knowing where and when telomerase is activated during malignant transformation will influence the design of clinical trials. By understanding which normal, premalignant, and malignant cells express hTERT and telomerase, we will be better able to make rational decisions regarding what types of patients and what stage of disease might benefit from telomerase inhibition and what side effects might be anticipated.

References
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