Expression of the full-length telomerase reverse transcriptase (hTERT) transcript in both malignant and normal gastric tissues

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Abstract

Activation of telomerase by the induction of a full-length telomerase reverse transcriptase (hTERT) transcript is a critical step during cellular immortalization and malignant transformation. Telomerase activity or hTERT expression has thus served as diagnostic and/or prognostic markers in different types of human malignancies. In the present study, we investigated the expression of the telomerase components hTERT and telomerase RNA template (hTER) in normal and malignant gastric tissues derived from 37 patients with gastric cancers. Overall hTERT mRNA was detectable in 33/37 (90%) of tumour specimens and 23/37 (62%) of the corresponding normal gastric tissues. Twenty-five of thirty-seven tumours (71%) expressed the full-length hTERT mRNA, and unexpectedly, this full-length transcript was found in 16 of 37 (43%) normal gastric tissues. Immunohistochemical analyses demonstrated a positive hTERT staining in small fractions of normal epithelial cells and in most gastric cancer cells. A close correlation between the presence of a full-length hTERT transcript and the c-MYC oncogene expression was observed in both normal and cancerous gastric specimens. Moreover, the full-length hTERT expression was positively associated with the tumour size in these patients. Similar levels of hTER expression were expressed in tumour and their corresponding normal tissues. The finding that the full-length hTERT transcript was present in both normal and malignant gastric tissues will preclude its use as a gastric cancer marker. Nevertheless, full-length hTERT mRNA expression may indicate a progressive gastric cancer, and its presence in normal gastric mucosa may have an impact on the anti-telomerase strategy for cancer therapeutic purpose.

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Abbreviations: β2-M, β2-microglobulin; hTER, human telomerase RNA template; hTERT, human telomerase reverse transcriptase; POT1, protection of telomere 1; RT-PCR, reverse transcriptase-polymerase chain reaction.

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malignant cells, the vast majority of hTERT variants are non-functional or even dominant-negative while less than 10% of them are full-length transcript \([30,40]\). Many types of normal tissues/cells only express the spliced variants of hTERT mRNA \([12,15,32]\). During the embryonic development of human kidneys, the spliced hTERT variants can remain at a relatively high level during one’s adult life period long after the disappearance of telomerase activity and full-length hTERT mRNA \([12,15]\). The absence of the full-length hTERT transcript contributes to undetectable telomerase activity in normal renal tissues. In addition, human resting T lymphocytes express only the spliced hTERT variants and lack telomerase activity whereas the full-length hTERT transcript and the enzymatic activity are induced when the cells are stimulated to enter into a proliferation pool. Based on the immunohistochemical analysis, the hTERT protein-positive cells are localized in proliferation zones of normal gastric mucosa, and these cells might thus be the source of overall and full-length hTERT mRNA variants. Because adult stem cells, epithelial progenitors and proliferating epithelial cells are known to express full-length hTERT mRNA and telomerase activity for their sustained proliferation, they should constitute hTERT-expressing cells present in normal gastric mucosa.

The oncogene c-MYC is an important activator for the transcription of the hTERT gene \([5,6,11]\). It has also been shown that c-MYC is required for the expression of a full-length hTERT mRNA in lymphoid cells \([32]\). The induction of the oncogene c-MYC was intimately associated with the expression of the full-length hTERT transcripts in renal cell carcinomas \([12]\). Consistently, we observed a close correlation between the full-length hTERT mRNA and c-MYC expression in both normal gastric mucosa and gastric cancer tissues. Thus c-MYC drives the transcription of the full-length hTERT transcript variant in various types of human cells or tissues.

hTER, one of two core components constituting the telomerase holy-enzyme, was previously observed to be up-regulated during the development of gastric cancers \([18,36,37]\). However, no significant difference in hTER expression was found between gastric cancer specimens and their corresponding normal mucosa in our cohort of patients, even with careful titration using a semi-quantitative RT-PCR (data not shown). This result, in high accordance with its ubiquitous presence in human cells/tissues \([5,6]\), suggests that the increased hTER expression does not always occur in the gastric oncogenesis.

According to our present results, there were no striking differences in either hTERT or hTER expression between malignant and normal gastric tissues. It is thus plausible that other factors regulating telomerase function and telomere biogenesis are dysregulated in gastric cancers. For instance, POT1 binds to single-strand telomeres and controls telomerase access to telomeres for their elongation \([3]\). It has recently been shown that expression of POT1 is associated with tumour stage and telomere length in gastric cancers, contributing to stomach carcinogenesis \([21]\). Likely, alterations in multiple factors, although not dramatic for each of them, are sufficient to synergistically maintain telomere stabilization in gastric cancers.

In summary, our present results demonstrate the expression of overall and full-length hTERT mRNA variants in both gastric cancer specimens and their normal counterparts, which indicate that hTERT assessment is unlikely a diagnostic marker for gastric cancers. However, the presence of the full-length hTERT mRNA suggests a higher tumour burden that may be clinically relevant. Importantly, it has been shown that even a trace amount of hTERT expression in normal fibroblasts plays a critical role in maintaining their physiological life-span and its abolishment induces premature senescence of the cells \([38]\). Therefore, our findings should be taken into consideration for potential side-effects when telomerase inhibitors are applied for cancer therapeutic purpose.

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