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Telomerase inhibition reduces cell growth

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Introduction

For cancer cells to develop, they must overcome the finite proliferative capacity associated with normal cells. Many recent studies have identified that telomeres, the protective structures found at the end of eukaryotic chromosomes, are important in this process. Telomere length is maintained by a ribonucleoprotein enzyme known as telomerase. Unlike normal cells where telomerase expression is repressed, this enzyme is found in approximately 80% of human cancers. The expression and activity of telomerase is essential for the infinite growth associated with tumour cells.

Aims

To determine the biological effects of telomerase inhibition on cellular immortality and tumourigenicity in human cell lines.

Comments

The results of this paper offer the possibility that telomerase inhibitors may be developed as novel anti-cancer agents. However, although these should be effective in limiting cancer growth, to obtain maximum benefit, it is likely these will have to be used in combination with other established therapeutic regimens.

Methods

Amphotropic retroviral vectors encoding wild type (WT)-hTERT (human telomerase reverse transcriptase) or mutant dominant negative (DN)-hTERT were introduced into a range of human cell

lines. Their effects on telomerase activity, telomere length and cell proliferation/apoptosis was monitored and tumourigenicity assays were also carried out.

Results

Expression of mutant DN-hTERT in clonal isolates of cell lines completely inhibited telomerase activity. This was accompanied by a reduction in telomere length, with a loss of approximately 3-5 kb in length from the time of infection. In contrast, those cells expressing either WT-hTERT (a control retrovirus), or which were telomerase negative, maintained stable telomere length. In metaphase cells expressing DN-hTERT, dicentric chromosomes and chromosome fusions were observed in 14/14 cells analysed. In terms of cell proliferation, expression of DN-hTERT did not have direct cytotoxic/ cytostatic effects. However, telomere shortening eventually induced apoptosis, with morphological changes and the appearance of a sub-G1 peak. Tumourigenicity studies revealed that while cells expressing a control retrovirus or WT-hTERT produced tumours in nude mice, those cells expressing DN-hTERT were non-tumourigenic.

Discussion

The results of this paper confirm amd extend previous observations indicating a role for telomerase as a prerequisite for the continued maintenance of the malignant phenotype associated with tumours. As inhibition of telomerase activity in tumour cells clearly reduces the proliferative capacity of these cells, inhibitors of hTERT could be developed as a novel therapeutic approach. The hTERT protein shares similarities with other reverse transcriptases, the inhibitors of which are already in use in indivduals infected with HIV-I.

References

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