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Telomerase as a Target for Anticancer Therapy

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Telomerase, a cellular reverse transcriptase, is upregulated/reactivated in almost all human cancers catalyzing the synthesis and extension of repetitive (TTAGGG) telomeric DNA onto the ends of chromosomes. Normal human cells either do not express telomerase or express very low levels and thus telomeres progressively shorten with each cell division due to incomplete replication of lagging strand DNA synthesis. The correlation between telomerase activity, telomere length homeostasis, and cancer suggests that long-term tumor growth requires telomerase and that telomerase inhibitors may have utility in cancer therapeutics. Promising approaches for telomerase inhibition include the use of a mutant dominant/negative versions of the catalytic telomerase subunit (hTERT) and the use of antisense oligonucleotides directed against the template RNA component of the telomerase holoenzyme. These telomerase inhibitors, but not chemically-related molecules, have been shown to reduce telomerase activity but not initially affect cell growth rates, lead to progressive shortening of telomeres with each cell division, and ultimately cause cells to undergo apoptosis in a time-frame dependent on initial telomere length. Other approaches that do not require a time delay for efficacy include the use of the hTERT promoter in front of a suicide pro-apoptotic gene such as casapase 6 and the use of immunotherapy directed against telomerase-specific peptides. Only telomerase-expressing cells should be killed using these approaches. In the future, telomerase inhibitors may be used alone, following standard treatments. as well as in combination with angiogenesis inhibitors.

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Telomerase vaccines: Targeting a "universal" cancer antigen.

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The reverse transcriptase catalytic subunit of human telomerase complex, hTERT is involved in immortalisation of cancer cells, and is expressed in high levels in 80-90% of all human tumors. Overexpression is partly due to gene amplification in the tumor cells. The gene is turned off in most normal human tissues, and hTERT is therefore an attractive target for immunotherapy, where hTERT may represent a "universal" tumor associated antigen. Most cancer vaccines tested up to now have a narrow field of application, since most tumor antigens are expressed only by subgroups of tumors. Recently several groups have identified cytotoxic T lymphocyte (CTL) epitopes derived from hTERT that are presented by HLA-A2 and A-24 molecules. Synthetic peptides representing these epitopes can be used in vitro and in HLA transgenic animals to elicit cytotoxic T cells that are capable of lysing a broad panel of human cancer cell lines representing tumors of different origin. Also in patients with cancer immunized in vitro, hTRT-specific CTL can be generated. This indicates the existence of precursor CTL for hTRT in the repertoire of both normal individuals and cancer patients. Also hTERT mRNA transfected dendritic cells have been used to trigger antitumor CTL responses. A number of T helper epitopes from hTERT have also been defined. Currently several phase I clinical trials of hTERT vaccines in patients with non operable pancreatic cancer and other forms of advanced cancer are ongoing. The main focus of these trials are the safety aspects. In particular the potential danger that hTERT specific T cells in addition to hitting the tumor also may generate a harmful response targeting haematopoietic stem cells and crypt cells in gut mucosae is addressed.