Tale of Tail Wins Nobel

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Three US Scientists Elizabeth Blackburn, Carol Greider and Jack Szostak have won this year’s Nobel Prize for Medicine for research into the genetic operation of cells, an insight that has inspired new lines of research into cancer. The trio solved the mystery of how chromosomes protect themselves from degrading when cells divide. They discovered how chromosomal tails are protected by telomeres and the role of telomerase in maintaining or stripping away this vital shield. It is for the first time that two women have received a Nobel Prize in Medicine.

Each chromosome consists of two specialized structures namely a centromere and two telomeres. Telomeres are like the caps of the p and q arms of the chromosomal ends and are important for allowing DNA replication at the chromosomal ends. Telomeres are often compared to the plastic tips at the end of shoe laces that keep those laces from unravelling. They play a minute yet vital role in aging. In a research study conducted by Njajou et al, it has been shown that telomere length is paternally inherited and is associated with parental life-span. Telomere length is thus emerging as a biomarker for aging and survival.1

In 1982, Blackburn and Szostak discovered the unique DNA sequence consisting of six nucleotide sequence (TTAGGG) in the telomeres that protects the chromosomes from degradation when the cells divide. DNA polymerase cannot replicate chromosomal ends during each replication cycle resulting in the loss of DNA at the chromosomal ends. At birth, human telomeres are 15 to 20 kb pairs long. They consist of tandem repeats of a six nucleotide sequence (TTAGGG) that are associated with specialized telomere-binding proteins forming T-loop structure. This protects the chromosomal ends from being wrongly recognized as damaged. The loss of telomeric repeats during each cell division cycle causes gradual shortening of telomeres leading to growth arrest. This is called as “replicative senescence”. This growth arrest can be bypassed if pRB and p53 are nonfunctional. However, cell death can occur when the unprotected chromosomal ends precipitate chromosomal fusions or other catastrophic DNA rearrangements. This is called as “crisis”. The ability to bypass telomere-based growth limitations is considered to be a crucial step in the evolution of most cancers. This can occur by reactivation of telomerase expression in cancer cells. Overexpression of telomerase alone, cannot induce a tumor in normal cells, but it can contribute to tumor formation in the presence of additional oncogenes and/or the disruption of tumor suppressors.2 Human tumor viruses are able to promote telomerase activity and maintain telomere length. Many of the tumor virus proteins act as transcription factors or by increasing telomerase expression or by post transcriptional regulation of telomerase or by negative regulation of telomerase.

With Greider, Blackburn also identified telomerase, the enzyme that adds TTAGGG repeats onto the 3’ ends of the chromosomes thereby making up the telomere DNA. This enzyme consists of several subunits like a catalytic subunit with reverse transcriptase activity (hTERT), hTR (human telomerase RNA) an RNA component which provides the template for telomere extension, TEP (telomerase associated protein 1), hsp 90 (heat shock protein 90), p23 and dyskerin.3 Normally all the somatic cells do not express sufficient telomerase to prevent telomere attrition which takes place with each cell division.

However, adequate amounts of telomerase are expressed by the stem cells of hematopoietic tissues, gastrointestinal epithelium, skin epithelium and germ cells which require extensive cell division to maintain tissue homeostasis.

If telomere levels are high, the telomere length is maintained and cellular ageing is kept in check. More than 90% of human cancers express high levels of telomerase. This prevents telomeric exhaustion and allows indefinite and endless replication of cancer cells. This is called as “cellular immortality” by the research scientists working in this field.

The protein component of telomerase (hTERT) acts as a tumor-associated antigen recognized by antigen-specific cytotoxic T lymphocytes (CTL) that lyse human melanoma, prostate, lung, breast and colon cancer cells in vitro. Various in vitro experiments have shown that inhibition of telomerase activity can cause tumor cell apoptosis. Finding ways to block this machinery through “telomerase inhibitors” is one of the most eagerly explored areas of cancer research. The reverse transcriptase activity of telomerase is a prime and attractive immunological target for cancer immunotherapy and vaccination research.2 Vaccination, using hTERT peptides or adoptive transfer of hTERT-specific cytotoxic T lymphocytes, induces augmented tumor regression.2 Recently Kyte has reviewed GV1001, a peptide vaccine representing a 16-amino acid hTERT sequence. Phase I/II clinical trials in advanced pancreatic and pulmonary cancer patients have demonstrated GV1001-specific T-cell responses in more than 50% of subjects, without clinically important toxicity. There is a correlation between development of GV1001-specific responses and prolonged survival. However, a large proportion of immune responders may not clinically benefit.2 Second generation vaccines are now being evaluated to enhance cellular immunity against hTERT without toxicity. The results of these clinical trials will tell us the possibility of broad-spectrum cancer immunotherapy or even immunoprotection.2

Genetic mutations in the components of telomerase (hTR, hTERT, and Dyskerin DKC1) have recently been implicated in a variety of bone marrow failure syndromes, idiopathic pulmonary fibrosis, and more recently, acute myeloid leukemia (AML) and rheumatoid arthritis.9

References