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Commentary

Centrality of telomerase in cellular life

Nagapoosanam and colleagues[1] in this issue have reported that the silencing of human telomerase reverse transcriptase (hTERT) leads to Bax/caspase-3 dependent apoptosis in HeLa cells. They used siRNA-loaded chitosan-coated polylactic-co-glycolic acid (PLGA) nanoparticles for the stable delivery of small interfering RNA (siRNA) against hTERT. Centrality of telomerase in cell cycle progression makes it a particularly important point of convergence of several signalling pathways. Here we summarize the significance of silencing of the catalytic component of telomerase (or hTERT) on different signalling pathways associated with apoptosis and its relevance in cancer therapeutics.

hTERT is the catalytic entity of telomerase complex. Its expression is indispensable for the genetic integrity of stem cells and cancer cells. However, very few molecules of hTERT are expressed in cells; therefore, most of the studies have considered its function specifically for telomere maintenance. The other functions of telomerase had not been duly appreciated initially. However, in subsequent years many research groups have reported increasing number of functions associated with hTERT expression. Knocking down telomerase RNA (hTR) or hTERT leads to resetting of expression of several genes involved in ribosome function, metaphase to anaphase transition, tissue-type plasminogen activator, urokinase-type plasminogen activator and Kruppel-like factor[2,3]. These functions of telomerase relate to repair of DNA damage, inhibition of apoptosis, stress responses and invasion and metastasis and have been referred to as extracurricular functions of telomerase[4,5]. Telomerase activity is required for maintenance of telomere length which is necessary if the cells were to continue dividing as in normal stem cells and in cancerous cells. This gives telomerase a pivotal position in terms of monitoring cells fitness to grow and divide. The cellular processes influenced by telomerase have culmination in tumour progression and assume greater significance in malignant tumour[4]. During malignant transformation, cells adopt new signalling pathways to avert the apoptotic signals. One of these is activation of anti-apoptotic proteins such as Bcl-2 and MCl-1 to pre-empt pro-apoptotic molecules from causing cytochrome release and effecting activation of executive caspases[4]. Targeting anti-apoptotic proteins is an emerging therapeutic strategy against cancer. hTERT is an important pro-survival factor that is differentially overexpressed in 90 per cent of cancer cells[4]. Therefore, it is considered as a significant target in cancer therapy. Past studies suggest that diminishing hTERT expression in cells have both early and late consequences. Varshney *et al*[6] showed that an RNA aptamer selected for binding with hTERT-inhibited telomerase activity *in vitro*.

Cells with diminished expression of hTERT become senescent after a few divisions due to genetic instability. In the absence of hTERT, the telomere undergoes shortening successively through each cell division cycle. The shortened telomere finds it increasingly difficult to fold into its conformation complexed with dozens of proteins required to safeguard the telomere and to ensure functioning of these proteins and after a certain stage, the telomere in its unfolded form is recognized as double-strand break by dsDNA damage sensors[4]. These activate ATM/ATR (ataxia-telangiectasia-mutated/ataxia-telangiectasia and Rad-3-related) pathway of DNA damage repair and steer cells towards senescence. However, this phenotype appears in later stages and it depends on the length of telomere in the cells. Cells with lowering of hTERT also develop a propensity to undergo early apoptosis. This is primarily attributed to p53-dependent pathway of apoptosis. The multi-faceted molecule p53 acts as the master regulator of several cell cycle-related functions particularly in the G1-S phase of cell cycle, arresting unfit cells and causing apoptosis. Thus, p53

acts upstream to several pro-apoptotic factors. It is not surprising that p53 is mutated in almost 50 per cent of all cancers[4]. In cells with wild-type p53, loss of hTERT shows drastic morphological changes. It has been observed that p53 is reciprocal to hTERT expression[4]. The advanced stages of cancer have enhanced telomerase expression that may antagonize the p53 dependent apoptosis. In other words, telomerase acts as a pro-survival and an anti-apoptotic factor during cancer progression. It reduces the downstream molecules of p53-like p16 (INK4) and enhances the expression of cyclin D1 in cancer patients[4]. The sudden reduction of hTERT from the cells enhances the p53 expression that unfolds the accumulation of p16INK and initial senescence followed by programmed cell death.

The extracurricular activity of telomerase is still an emerging area of investigation. Results from our group[7] have shown that translationally controlled tumour protein (TCTP), the major tumour reversion target, is a downstream molecule of the hTERT telomerase-positive cells. TCTP is a multi-functional protein that has implication in anti-apoptosis, DNA damage sensing and stress response. It is a growth factor responsive protein that participates in early stages of cancer progression primarily during the epithelial to mesenchymal transition and its downregulation by knocking down with interfering shRNA (short hairpin RNA) results in reduced invasive potential of the cells[7]. The cross-talk of these two major determinants of cancer progression substantiates the significance of this pathway. However, these observations need a thorough investigation *in vivo*.

The therapeutic potential of hTERT is based on the differential expression of hTERT in cancer cells and actively dividing normal cells. The above-mentioned differential extracurricular activities of hTERT in cancer cells strengthen the idea of using this molecule as a probable therapeutic target. Moreover, the association of hTERT with major tumour determinants such as p53 and TCTP makes it a unique target that has a broad range of function and suitability as a target. A challenge while targeting a molecule as pivotal as hTERT will be to selectively target cancer cells sparing the actively dividing normal cells.

***Conflicts of Interest*:** None.

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