BJMS
Borneo Journal of Medical Sciences

SHORT COMMUNICATION

Telomere and a Final Verdict for Cellular Senescence

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Received: 19 February 2020

Accepted: 16 July 2020

Keywords: telomere, cellular senescence, eukaryotic cells, tumourigenesis

ABSTRACT

Telomeres are specialized DNA complexes found at the end of all chromosomes. Human, as a member of eukaryotic cells, requires telomeres to maintain the length and the stability of chromosomes. Telomeres lose their non-coding DNA sequence to protect the genetic information on the chromosomes. Shortening of telomeres occurs in most somatic cells after sufficient cell division in a human lifetime. Normal haemopoietic cells or stem cells possess telomerase enzyme to restore telomeres and allow further replication. Telomere dysfunction is the origin of several degenerative disorders and also predispose to cancer. Roles of telomere in carcinogenesis and ageing related disorders are reviewed.

INTRODUCTION

Telomeres are repetitive (TTAGGG) DNA-protein complexes at the ends of chromosomes. Shortening of telomere is one of the mechanisms of replicative senescence[1]. During replication of somatic cells, a portion of telomere is not duplicated and it becomes shorter. Telomerase enzyme is a specialised RNA-protein complex which is composed of reverse transcriptase (hTERT) and an RNA subunit (hTER)[2]. Telomerase can use its RNA as templates to add nucleotides to the end of chromosome preventing the shortening. Normal somatic cells do not express it; hence have limited replication capacity resulting in replicative senescence activation.

Telomere and Cancer

Majority of cancer cells express telomerase to maintain chromosome length to become immortal. This activity is crucial for the survival of cancer cells[3]. In other instances, telomeres in cancer cells become extremely short and form *t*-stumps. Many chromosomal instability characteristics of human cancer cells result from *t*-stumps. In tumour cells positive for telomerase, these short *t*-stumps are generated, stabilized or protected from elimination by the hTERT[4]. Several methods measure telomere length (TL) namely: quantitative polymerase chain reaction, terminal restriction fragment length analysis, quantitative fluorescent in situ hybridization, telomere dysfunctional induced foci analysis, single telomere length analysis, telomere shortest length assay[5]. Telomere Restriction Fragment (TRF) analysis is the gold standard for measurement of telomere[6].

Telomere length and telomerase activity play important role in tumourigenesis and immortality of cancer cells. Studies showed short or eroded telomeres accounted for ~73% of the 125 colorectal cancers (CRCs) analysed whereas ~27% of the tumours showed unchanged or elongated telomeres. The survival rate is better in length-maintained colorectal cancers compared to those with eroded or shortened telomeres[7]. Cancer cell expresses constitutive telomerase reverse transcriptase (TERT) expression. Overexpress TERT is seen in many cancers including colorectal cancer[8], bladder cancer[9], ovarian and lung cancer[10].

Downregulation of telomere-related genes is useful in gene therapy for cancers. Knockdown of telomerase RNA (hTER) leads to rapid growth inhibition of cancer cells[11]. Efforts to target telomerase showed that the activity of tumour telomerase becomes attenuated resulting in reduced survival of cancer cells[12]. Personalised genetic therapies which modify inhibitory effects of telomerase are reliable alternatives for effective treatment of cancer in the future.

Telomere and Degenerative Diseases

Telomere attrition is responsible for degenerative or ageing disorders[13]. There is an association between short leukocyte telomere length and cardiovascular risk factors, such as smoking, obesity, and hypertension[14]. Germline mutation of TERT is associated with idiopathic pulmonary fibrosis, emphysema and dyskeratosis congenita[15, 16]. Telomere length seems to have a key role in cardiovascular disease contributed by vascular ageing[17]. Induction of telomerase gene expression benefits regeneration after cardiac injury by inhibiting the apoptosis of cardiac myocytes. Also, a similar study showed survival of vascular lining endothelial cells and smooth muscles preventing the age-related disorders[13]. Autopsy findings revealed significantly short telomere in the hippocampus of major depressive disorders suggesting the evidence of stress-mediated accelerated cellular ageing in depression[18]. Telomere attrition was seen in the beta cell of the pancreas in type 2 diabetic patients with poor glycaemic control autopsied pancreas[19]. Some factors, such as oxidative stress, result in the accelerated shortening of telomere and diminish the survival of cells leading to cardiomyopathy and atherosclerosis[20]. Defect telomerase RNA is associated with aplastic anaemia[21]. Experimental study on Tert-gene knock out mice treated with Tert-gene therapy showed an increase in peripheral blood count and bone marrow haemopoietic cells in previously aplastic marrow[22]. In advanced liver cirrhosis and idiopathic pulmonary, the fibrotic process can be reversed by transfer of telomerase gene[23]. Experimental expression of telomere maintenance genes or telomerase is helpful for diseases associated with shortening of telomere. Non-integrative expression of these genes does not promote oncogenesis[24]. However, the potential risk of carcinogenesis by upregulation of telomerase should be studied in long term basis[25].

CONCLUSION

Telomere shortening is a natural process that all somatic cells must undergo. Some exceptional cells such as marrow stem cells and haemopoietic cells have their mechanism to maintain their telomere length to sustain their function throughout life. Modification of telomere-related genes is helpful in anti-ageing, antifibrotic or anticancer therapies. Further research on the mechanism of telomere related tumour genesis and its relationship with genomic change is essential for clinical application. Modifying genes that control telomerase and its use as a therapy has a significant role in comprehensive control of tumour progression in a variety of neoplasms.

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