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Research Article

The Role of Telomerase Activity in Virus- Induced Infections

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Abstract:

Structures called telomeres located at the linear ends of chromosomes play an important role in maintaining chromosome integrity. Short telomeres produce signals similar to those produced by DNA damage, leading to both ageing and programmed cell death. The enzyme telomerase repairs shortened telomeres so that the telomere chains remain long. Studies aimed at understanding the activation of the telomerase enzyme on telomeres, have shown that this enzyme will have a positive effect on cellular rejuvenation on living cells, prolong the life span of living cells, thus preventing age-related diseases before they occur, and also making it impossible for many types of cancer that may develop due to old age to occur in the first place. This increases the cell's ability to divide. Studies investigating the relationship between telomerase activity and animal and human tumoral viruses are being conducted to determine the function of telomerase in cellular transformation and carcinogenesis. It has been suggested that although there is little or no telomerase activity in human and animal somatic cells, telomerase activity persists in cells infected with oncogenic viruses and may prevent cellular senescence. Interestingly, human and animal oncogenic viruses can reactivate the telomerase enzyme through mechanisms they have developed. This review is compiled from studies investigating the relationship between viral infection and telomerase activity.

1. Introduction

Telomere can be defined as the structure that protects the last part of a chromosome and ensures the maintenance of chromosome integrity and stability against conditions such as recombination, destruction and fusion [1]. The first studies on chromosomes showed that deletions and inversions in the terminal region were rare, and later studies showed that chromosome integrity was provided by telomeres [2]. There is a large loop at the end of the telomere. These are called loops. The formation of T-loop is not random, primarily the D-loop region and D-loop region is also homologous to the homologous region. This occurs when a single strand rich in guanine (G-tail) penetrates the double-stranded telomere and replaces one of the telomere strands [3].

Six proteins formed in response to telomere T-loop structures protect telomere ends by ensuring telomere stability and prevent their recognition as DNA damage. These proteins are called TRF1 (Telomeric Repeat Factor 1), TRF2 (Telomeric Repeat Factor 2), POT1 (telomere protector 1), TIN2, TPP1 (tripeptidyl peptidase 1) and Rap1 (repressor activator protein). Together they form a structure called "Shelterin" (Figure 1) [4]. TRF1, TRF2 and TIN2 proteins are known as telomere negative regulators because they inhibit telomerase binding and cause telomere shortening. On the other hand, POT1 and TTP1 proteins are positive regulators of telomeres [5]. Recent studies have identified the presence of G-quadruplex (G4-DNA or G-tetrad) compounds in

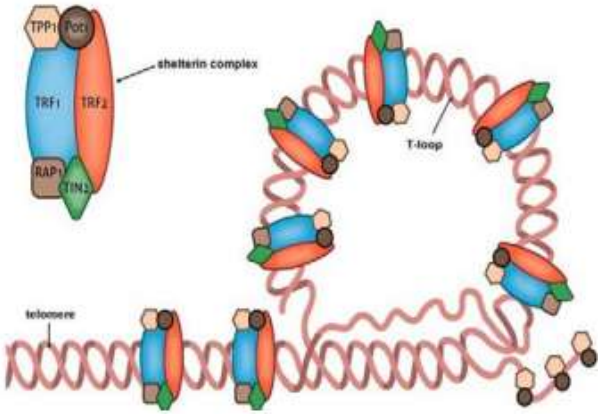

Figure 1. *"Shelterin" complex at telomeres.*

telomeres. These structures suggest that structures that stabilise G-4 DNA and stop the activity of telomerase can be used in cancer treatment [6].

2. Telomerase and Telomer Size

It has been reported that telomere shortening observed in tissue culture studies causes changes in somatic cells, restricts proliferation, leads to cellular senescence and even death. In laboratory studies, this leads to research difficulties because cells lose a large amount of telomere nucleotides after multiple divisions [7]. This limited number of divisions recognised within the cell is called the "Hayflick limit" [8].

Short telomeres have also been found to cause both ageing and programmed cell death by producing signals similar to DNA damage, where the time of death is determined by a biological biological clock known as telomere length [9].

This organism contains the enzyme telomerase, which is responsible for repairing shortened telomeres and keeping telomere chains long. Telomerase (telomere deoxynucleotidyl transferase or telomere terminal transferase) is a specialised DNA polymerase of ribonucleoprotein structure, secreted by the telomeres at the ends of chromosomes and involved in the synthesis of "TTAGGG" repeats at the ends of chromosomes. Telomerase reverse transcriptase (TERT), a protein subunit of the telomerase enzyme, determines telomerase activity. The more telomerase is activated in a cell, the longer the telomeres become and the length of telomeres increases the cell's ability to divide [10].

3. Telomerase Activity in Virus-Induced Infections:

In order to determine the function of telomerase in cellular transformation and carcinogenesis, studies have been conducted to investigate the relationship between telomerase activity and animal and human tumoural viruses. In these studies, viral changes in non-coding viral RNAs (ncRNAs) and host cell ncRNAs have been found to increase telomerase activity [11].

Viruses such as Epstein-Barr virus (EBV), herpes virus (seen in Kaposi sarcoma), papilloma virus (HPV), hepatitis B and C viruses (HBV-HCV), T-cell leukaemia/lymphoma virus type 1 (HTLV-1) have been observed to cause an increase in telomerase transcription [12]. In addition, tissue biopsies taken from hepatitis B and hepatitis C positive patients were found to have increased telomerase activity compared to non-patient liver tissue [13]. Analysis of samples from people with nasopharyngeal carcinoma concluded that EBV positivity rate was ±5 and telomerase positivity rate was ±9 [14].

Another study showed high telomerase activity after analysing EBV-infected B lymphoblastoid cell lines [12]. Endothelial cells infected with human Kaposi's sarcoma-associated herpes virus 8 (KSHV/HHV-8) were found to have increased telomerase activity compared to uninfected cells [15].

It has been proven in chicken studies that Marek's disease virus (MDV), one of the animal viruses, has very low levels of telomerase ribonucleoprotein complex, reverse transcriptase activity (TERT) and RNA subunits (TR) [16]. In addition, viral RNA subunit (vTR) has been shown to cause T cell immortalisation by increasing telomerase activity during MDV infection. Thus, MDV increased telomerase activity like other oncogenic viruses [17].

In another study, it was reported that telomerase activity increased in animals infected with bovine leukaemia virus (BLV) [18]. It was also found that telomerase activity increased during the ongoing lymphocytosis phase of BLV infection or during the detection of visible tumours and this increase was statistically significant [19]. In addition, while some tumour viruses effectively control telomerase and telomere length, some viruses develop additional mechanisms that are negative regulators of telomerase, and viruses and their hosts have been found to increase the complex relationship between many tumours. It has also been found to function as a transcription factor that increases the expression of cellular telomerase [12].

For example, HBV (hepatitis B virus), HBV X (transactivator oncoprotein) may cause an increase in telomerase expression and telomerase activity in hepatocytes [20]. Latent membrane protein 1 (LMP1), encoded by Epstein-Barr virus (EBV), prevents apoptosis and promotes carcinogenesis by using essential nuclear factor kappa B (NF-kB) and JAK/STAT intracellular signalling pathways and may cause tumour activation [21]. Studies have shown that the increase in telomerase activity of tissues and organs infected with EBV virus contributes to the establishment of EBV infection of epithelial cells [22]. LMP1 was found to play a role in increased telomerase activity in EBV-infected nasopharyngeal epithelial cells and B-cell lymphoma, and LMP1 expression also increased hTERT protein expression in EBV-negative nasopharyngeal carcinoma cells [23].

EBV latent membrane protein 2A (LMP2A) has been shown to function as an hTERT negatively regulated promoter [24]. Another study reported that TERT expression and telomerase activation play an important role in EBV tumour formation [25].

Although telomerase activity is present in the foetal and developing organs of birds and humans, this activity is largely absent in somatic tissues. Studies have also found that the viral LTR (long terminal repeat) of avian leukaemia virus (ALV) specifically enhances the activity of the telomerase promoter in the opposite direction and thus directly regulates TERT transcription [26]. MDV was also found to be the first known virus encoding a functional telomerase RNA subunit [16].

Such different activities of telomerase play a role in important cycles such as cellular ageing and cancer. Based on these data, researchers studying telomerase and cellular senescence have shown that cellular senescence occurs after transformation of DNA by tumour viruses such as simian virus 40 (SV 40), human papillomavirus (HPV) and adenovirus and discovered that this can be prevented. They also observed that tumour viruses contain proteins that can bind to and inactivate cellular tumour suppressor proteins such as p53 and p110 RB in cells. This inactivation also explains the long life cycle of cells transformed by the virus. It has even been observed that p53 and p110 RB proteins are absent in many immortal cells due to mutations or genetic deletions [27].

Among environmental factors, exposure to cigarette smoke has been identified as the greatest risk factor for the development of idiopathic interstitial pneumonia (IPP). Numerous clinical and epidemiological studies show that both sporadic and familial IPF are more common in smokers and that exposure to cigarette smoke is associated with short telomeres [28,29].

The first clinical link between telomerase and lung diseases was discovered in dyskeratosis congenita [28]. In 2005, Armanios and colleagues identified a mutation in hTERT, a telomerase-related enzyme, that causes telomere shortening in a family with autosomal dominant dyskeratosis congenita. Lung fibrosis was observed in half (3/6) of the family members with this mutation [30]. In 2007, mutations in telomerase genes were found to cause familial IPF in some families [31-34].

Mutations in telomere-associated genes often result in shortened telomeres. However, in cases where there are mutations in TERT, TERC, PARN, and RTEL1, telomeres can shorten from one generation to the next even without the transmission of the mutation itself. This means that the disease onset can occur earlier in subsequent generations. This type of inheritance, called epigenetic-like inheritance, can explain why individuals without familial mutations can still be affected by the disease. The length of telomeres is not solely determined by inherited telomere length or telomere repair proteins, but also influenced by environmental factors. For example, exposure to cigarette smoke has been associated with shorter telomeres in blood, which suggests that environmental factors can contribute to telomere length. Generally, organs or tissues that require frequent renewal throughout life, like the lungs, tend to have shorter telomeres [28].

4. Conclusions

With reference to previous studies, it is concluded that telomere length and telomerase activity are closely linked to cancer, cell senescence and death in humans and animals. Short telomeres can cause both aging and programmed cell death (apoptosis) by producing signals similar to DNA damage. Telomere length, the body clock, also plays a crucial role in this biological process.

Although there is little or no telomerase activity in human and animal somatic cells, it has been suggested that telomerase activity persists in cells infected with oncogenic viruses and can prevent cellular senescence. However, research on carcinogenic animal viruses on this subject is scarce. Further studies on the effects of these viral factors, which are mostly not considered pathogenic for human beings, on telomerase activity, cellular senescence and cancer eradication are needed.

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