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Telomeres and Diseases Related to Telomeres.

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Abstract

Telomeres are non-coding DNA regions present at the ends of chromosomes and help in proper sealing of chromosomes at the ends after replication. The main function that telomeres serve is to protect the coding DNA of the genome. A telomere dictates the cell's life span and whenever the length of the telomere shortens to minimal lengths, the cell senesces. Over the years various studies have reported that telomeres are linked to numerous diseases, but the exact mechanism that could explain how telomeres cause diseases still remains a mystery and further the use of medicine that could prevent telomere erosion are still up for debate. Various diseases particularly age related diseases are associated with telomeres. The molecular cause of diseases that is related to telomeres could be due to inadequate telomere repair and accelerated telomere attrition and by targeting these processes may led to the development of novel therapies.

In this review we have focused on role of telomeres in age related diseases. Further we have discussed about telomeres and telomerases as therapeutic targets for some age related diseases.

Keywords : telomeres, telomerases, therapeutic targets, telomeropathies

Introduction

Telomeres are non-coding DNA regions present at the ends of chromosomes maintaining chromosome integrity by sealing ends after every replication[1]. Telomeres prevent homologues end joining between chromosomes[1]. In telomeres thousands of TTAGGG hexanucleotides are present. Hexanucleotides are prevented from degradation by a complex made of six proteins known as sheltrin which is composed of Repressor activator protein 1 (RAP1), TIN2, TPP1, Protection of Telomere protein 1 (POT1), TRF1 and telomere repeat binding factor 2 (TRF2)[2]. Telomeres are also stabilised by formation of T-loop structure also known as T-loop lariat [3-5]. Both shelterin and lariat prevent chromosomes from DNA damage

response (DDR).With each replication telomeres shorten and telomere shortening is responsible for aging in cells[6]. When telomeres reach a critical length cells enter into a resting senescent stage[7]. Cells resist telomere shortening with the help of telomerases having an RNA template which add DNA to the ends[8]. Thus telomerases act as reverse transcriptase[8]. High telomerase activity is present in cells of embryo and pluoripotent stem cells[9, 10]. Rate of telomerase activity is always less than rate of telomere shortening so there is a progressive decrease in telomere length with age[7, 11].

Telomere shortening and aging

Telomeres shorten as we age and telomeres have been postulated as a marker of "genetic age," The length of the telomere has been marked as a simple predictor of longevity. Various studies have shown that shortening of mice telomeres occur at 100 times faster than humans which may be the reason for the shorter life span in mice i.e. 2-3 years compared to normal life span of 70 years in humans [12-14].Rate of telomere shortening annually in humans is 31-72 base pairs[15, 16]. Various laboratory experiments have shown that telomerase deficient mice age at a faster pace compared to telomerase overexpressing mice[17]. Thus telomere shortening is a main determinant of aging in organisms.

Telomeropathies

Telomeropathies are the diseases caused due to mutation or deficieny of proteins associated with telomere length maintenance as well as repair[18]. Some of the telomeropathies are aplastic anaemia characterized by low count of blood cells due to deficiency of hematopoietic cells, idiopathic pulmonary fibrosis, nodular regenerative hyperplasia, dyskeratosis congenital, hoyeraal-hreidarsson syndrome and in all these diseases regenerative capacity of tissues is lost[18, 19]. Various small molecules TA-65,danazol have been used for the treatment telomeropathies all have met with little success and have associated risk of tumourogenicity [20, 21].

Telomeres and cancer

Telomerase activity and shelterin complex proteins are altered in cancer by mutation[22, 23]. Activities of TERT1,POT1,TRF2, TERC, TIN2 is altered by mutations which eventually lead to cancer[24]. Various studies have shown that telomere crisis is an early progression of malignancy [25] . Telomerase, telomeres and progression of cancer is shown in Figure 1

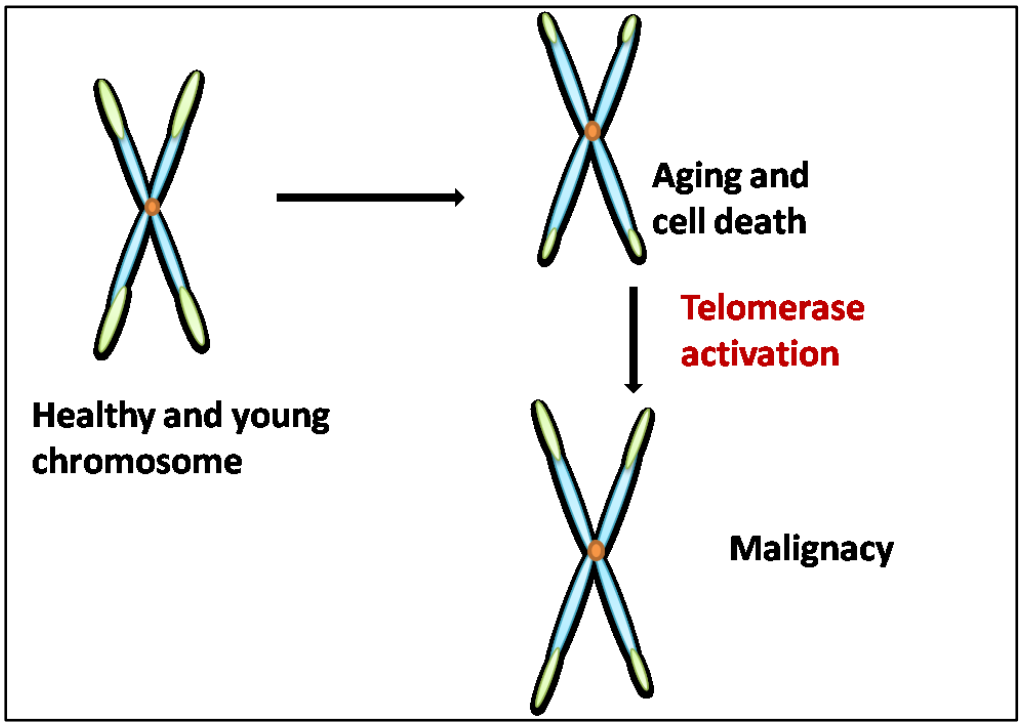

Figure: Aging leads to telomere shortening and cell arrest. Telomerases are activated and telomeres length is increased in cancer cells

When telomeres reach critically minimal lengths, most cells either stop dividing or die. The telomerase is upregulated or the ALT pathway is activated in most of the cancers thereby resulting in abnormal telomere lengthening and proliferative growth. Due to this relation between telomeres and cancer, researchers are actively studying the potential role of telomerase (TERT) as a target for cancer therapeutics, with several clinical trials ongoing.

Telomeres and telomerases as therapeutic targets against cancer and telomeropathies.

Numerous pharmaceutical companies are in research and development of drugs for the treatment of telomere related disorders[26]. Sex hormones i.e. androgens are in clinical development for aplastic anaemia and has been used as anti-ageing from long times[27, 28]. Recently TERT1 mRNA has been injected into cells which activate telomerase activity in cells [29-31]. More than 85% of cancers show telomerase positivity while majority of our somatic cells are negative for telomerase activity so telomerase is an important therapeutic target for cancer[32].

Conclusion

Treatment of telomere related diseases are in initial stages. Most of the research associated with them is restricted to in-vitro and little

research has been done on in-vivo models. There is an urgent need of new therapeutic targets for telomerases that will overcome limitations of currently available drugs and well as need of better strategies.

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