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A REVIEW ON TELOMERIC DYSFUNCTION

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ABSTRACT

Telomeres are specialized DNA-protein structures located at the ends of eukaryotic chromosomes whose length is progressively reduced in most somatic cells during ageing. Over the past decade, emerging evidence has shown that the telomeres are essential regulators of cellular life span and chromosome integrity in a dynamic fashion. By inducing genomic instability, replicative senescence and apoptosis, shortening of telomeres is thought to contribute to organismal ageing.In this review aims the role of telomerase of oncogenisis and the diseases associated with telomeric dysfunction.

KEYWORDS: Telomeres, Telomerase, Dyskeratosis congenita, Telomeropathies.

INTRODUCTION

Telomeres are the specialized DNA protein structures located at the ends of the eukaryotic chromosomes. The essential function of telomeres is to ensure genome stability by preventing chromosome end attrition and end-to end fusions. Telomere protection depends upon several factors such as its precise protein composition, telomere length and telomerase activity level.[1]

The existence of a capping structure at the extremities of chromosomes was first deduced in the 1930s by Herman Mueller (Mueller, 1938), who showed that X-irradiation of Drosophila rarely resulted in terminal deletions or inversions of chromosomes, suggesting that chromosome ends have protective structures that distinguish them from broken chromosomes, which he named telomeres.[2]

Telomericdysfunction and telomerase activation play major role in tumorigenesis. Telomerase activity is expressed in cancer cells but not in most normal somatic cells, suggesting that telomerase may be an important target for chemotherapy. Thus, telomere dysfunction may represent a physiological trigger of the DNA damage or apoptotic response in an analogus fashion to other genotoxic results that introduce chromosome breaks. [3]

Telomeres can be maintained by a specialized ribonucleoprotein reverse transcriptase called telomerase. It is the natural enzyme that promotes telomere repair that is minimally composed of a functional 'template' RNA and a catalytic protein that contains conserved reverse transcriptase motifs. Telomerase synthesizes telomeres de novo, hence preventing telomere shortening in those cells where it is expressed at sufficiently high levels. Dysfunctional telomeres lead to the generation of genomic aberrations, such as amplifications and deletions.[4]

Telomeres consist of tandem arrays of short, repetitive G-rich sequence bound by a variety of telomere-associated proteins that together form a dynamic terminal structure that "caps" the ends of linear chromosomes, that influence both chromosomal radiosensitivity and preservation of genomic stability and providing protection from illegitimate recombination, exonucleolytic attack and degradation.[5]

STRUCTURE AND COMPONENTS OF MAMMALIAN TELOMERE

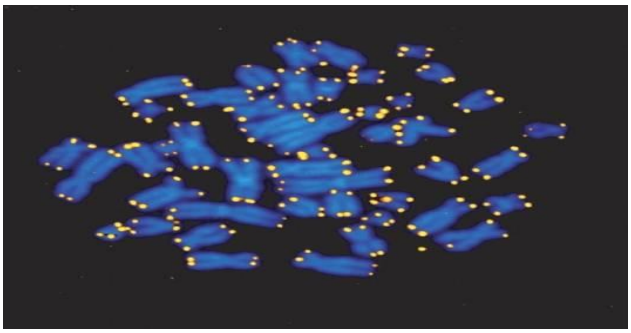

Fig. No. 1: Structure of telomeres.

TELOMERE STRUCTURE

The telomere is a large nucleoprotein complex with a structure which is different to that of the bulk of the chromatin. Mammalian telomeric DNA is composed of G-rich tandem repeats of the sequence TTAGGG, which

in humans extend 10±15 Kb at each chromosome end. The strands overhangs are likely to be a direct consequence of the end replication problem. Importantly, the G-strand overhang can fold back and invade the duplex telomeric repeats, displacing one strand and hybridizing to its complementary sequence. This higher-order telomere structure has been named the `T-loop'. The T-loop model provides a mechanism for the sequestering of the G-strand overhang which could otherwise activate DNA damage checkpoints and DNA repair enzymes. An additional function of the T-loop could be to prevent the access of telomerase to the telomere.[6]

T-LOOPS

A specialized telomere structure, the t-loop, has also been implicated in the maintenance of telomere function in humans. It has been shown by electron microscopy and, termed t loops. It involves a single-stranded 3' overhang invading proximal duplex telomeric DNA, causing a displacement (D)-loop that is 75 to 200 nucleotides long. Telomeres may also form loops in trypanosomes and hypotrichous ciliates. T-loops have been postulated to be a mechanism for hiding the telomere ends from various proteins, but also provide a structure that could result in elongation or shortening of the telomere.[7]

Telomere biology is intimately linked to the genetic/environmental aetiology of cardiovascular and metabolic diseases and telomere shortening is emerging as an important biomarker at the interface of cardiometabolic diseases. Telomere fusion, as well as other chromosomal defects, can lead to the formation of anaphase bridges.

In human subjects telomere maintenance leads to dyskeratosis congentia (DC) a rare genetic disorder characterized by progressive bone marrow failure accelerated aging and cancer predisposition. Maintenance of functional telomeres at chromosome ends is required for the prolonged survival of most organisms with linear chromosomes.Telomerase inhibitors function by reducing telomeres to a critical length. While telomerase inhibition may decrease the growth of late stage tumors, it may also select for more malignantsubclones from the tumors by enhancing genomic instability. [8]

An important area of future research will be to establish how frequently short telomeres trigger genomic instability versus apoptosis during tumor initiation.[9]

PROTECTIVE FUNCTIONS OF TELOMERES

Maintenance of functional telomeres at chromosome ends is required for the prolonged survival of most organisms with linear chromosomes. Telomeres serve to limit the loss of genetic material from chromosome ends that is thought to occur due to incomplete DNA replication, thus protecting chromosome ends from recombination and fusion. In most eukaryotes, the replenishment of telomereDNA is carried out by a ribonucleo protein reversetranscriptase called telomerase.[10]

In addition to telomere attrition, telomere deprotection can also be induced by the loss of function of double stranded telomere binding proteins at the telomere. Telomere induced by telomere attrition or generated through disruption oftelomere structure, the loss of telomere protection is commonly referred to as telomere dysfunction. The requirement for a functional telomere is thought to be particularly relevant in cancer. [10]

TELOMERE DYSFUNCTION IN CANCER AND SKIN DISEASE

Genetic instability associated with telomere dysfunction (i.e, short telomers) is an early event in tumorigenesis.. In most somatic cells, telomeres gradually become shortened because of the end replication problem during cell division. Dysfunctional telomeres lead to the generation of genomic aberrations, such as amplifications and deletions. Telomere maintenance mechanisms, such as telomerase activity and alternative telomere lengthening, provide the basis of malignant cell expansion independent of telomere shortening-induced apoptosis or senescence, ensuring tumor survival. [11]

Telomerase activation in cancer adds another level of complexity. Telomerase is activated in 90% of tumors and this activation is thought to confer immortal growth properties on the tumor cells. Telomere shortening and telomerase activation appear to have both tumor suppressive and oncogenic roles the apparent tumor suppressive role of telomere shortening may help to initiate genetic instability, and the apparent oncogenic role of telomerase activation may help to stabilize genetic instability. Telomerase expression and activity and telomere length are regulated in a tissue specific and developmental manner in several species, including humans.[11]

Xerodermapigmentosum (XP) is an ultravioletlight-sensitivity syndrome caused by nucleotide excision repair (NER) defects, resulting in hyperpigmentation and an increased incidence of skin cancer. These symptoms also characterize the skin ‘telopathies’, which result from accelerated shortening and exhaustion of the regenerative capacity of stem cells and lead to premature death. The pathways that connect stem cell dysfunction with telomere uncapping using a mouse model of telomere dysfunction which phenocopies the symptoms of XP patients. They demonstrate that both the absence of NER and the abrogation of p53activity restore stem cell functionality. This work highlights the relationship between telomeres and stem cell renewal with the pathobiology cancer.

Telomere dysfunction impairs chromosomal stability and is associated with an increased risk of various cancers.

Telomere length was statistically significantly shorter in lymphocytes from case patients with head and neck cancer, bladder, lung, or renal cell carcinoma than in control subjects. An increasing risk for head and neck, lung, and renal cancer associated with progressively shorter telomeres, indicating that telomere dysfunction may be a risk factor for cancer at these sites and possibly for cancer in general.[11]

TELOMERE AND HEPATOCELLULAR CARCINOMA

Natural history of cirrhosis is often complicated with the occurrence of hepatocellular carcinoma (HCC). The observation that telomere shortening is an established feature of chronic liver disease has led to suggest that it may play a role in the pathophysiology of HCC. The telomeres were shorter in HCC hepatocyte as compared to those in regenerative nodules and normal liver tissue and that, within group of HCC, hepatocyte telomere length of aneuploid was shorter than that of diploid tumors the telomere dysfunction plays an opposite role in the initiation versus the progression of HCC. On the other hand progression of neoplastic growth needs an efficient telomere signaling. There is a slight increase of telomere length in poorly differentiated as compared to better differentiated HCC, suggesting a reactivation of telomerase and restored chromosomal stability to a level compatible with tumor cell viability. [12]

The telomerase activity was detected in nearly 90% of HCC as compared to only 21% of non-tumor tissue and was paralleled by the increase of TERT mRNA levels implying the possibility that TERT mRNA expression could predict or be a marker of HCC. Mechanism of telomerase activation may be diverse in some way depending on the etiology of chronic liver diseases. This is the occurrence of the integration of hepatitis B virus into the human telomerase gene in HCC. Moreover the list of recurrent HBV target genes is expanding suggesting the possible mechanisms by which HBV may cause telomere dysfunction leading to initiation as well progression of HCC. The therapeutic approaches, such as combined immune-chemotherapy and gene therapy, for its cure.[13]

DYSKERATOSIS CONGENTIA

Dyskeratosiscongenita (DKC) was the first disorder linked to impaired telomere maintenance. Aside from the diagnostic triad, it is associated with a host of other symptoms that appear less frequently. Most prominently, individuals with DKC display organ failure, usually in the bone marrow and present with aplastic anemia or specific lymphopenias. In these patients, pulmonary toxicity due to bone marrow transplant conditioning (ablation of the existing stem cell compartment) can induce pulmonary fibrosis, and a subset of individuals with DKC will encounter pulmonary fibrosis before bone marrow failure. Less commonly, DKC involves failure of a variety of endothelial and epithelial compartments, including enterocolitis, emphysema, livercirrhosis, premature hair graying, short stature, dental caries,osteoporosis, and esophageal structure.[14]

TELOMEROPATHIES AN EMERGING SPECTRUM DISORDER

A constellation of related genetic diseases are caused by defects in the telomere maintenance machinery. These disorders often referred to as telomeropathies, share symptoms and molecular mechanisms, and mounting evidence indicates they are points along a spectrum of disease. Several new causes of these disorders have been recently discovered, and a number of related syndromes may be unrecognized telomeropathies.

New syndromes characterized by impaired telomere maintenance, referred to as “telomeropathies,” “telomere disorders,” or “telomere syndromes” are increasingly being identified. Telomere length measurement or telomere dysfunction (measured by colocalization of shelterin components and DNA damage signals) are often used to identify a disorder of telomere maintenance. fluorescent in situ hybridization (FISH).
The only curative therapy for the life-threatening symptomsof telomeropathies at the present time is tissue or organ transplant; bone marrow transplant in the case of bone marrow failure or via lung transplant in IPF patient. However, many patients with bone marrow failure will show improvement when treated with androgen therapy, such as danazol or oxymetholone .In the future, it may be possible to perform autologous stem cell transplantation after in vitro transient lengthening of telomeres, either through gene therapy or by as-yet undiscovered small-molecule telomerase activators.[15]

CONCLUSION

This review is an overview of the causes and symptoms of the disorders caused by the defects in telomere dysfunction. The symptoms of these disorders are extensive. The age of onset is highly variable with genetic anticipation being involved. However, the disorders share a similar underlying molecular mechanism, premature telomere shortening, leading to a spectrum of diseases that are only recently being recognized.We expect new human syndromes will be revealed in the future that correlate with telomere syndromes, which will be informative in terms of the basic science of telomere biology but also in correctly describing the spectrum disorder that these diseases represent.

The molecular cloning of telomerase and telomere components has enabled the analysis and precise manipulation of processes that regulate telomere length maintenance. In mammalian cells and in other organisms,we now recognize that disruption of telomere integrity via any one of a number of perturbations induces chromosome instability and the activation of DNA damage responses.Thus, telomere dysfunction may represent a physiological trigger of the DNA damage or

apoptotic response in an analogous fashion to other genotoxic insults that introduce chromosome breaks.Telomere shortening and telomerase regulation play an important role on tissue regeneration during aging, chronic diseases and on cancer promotion and progression.

From the future studies there are two general strategies to inhibit telomerase activity in cancer cells. One is direct i.e. compounds directly causing telomerase inhibition by inhibiting the activity of the catalytic subunit (hTERT), theRNA template (hTR) or the telomere structureIndirect strategies involve blocking telomerase access to telomeres by using G-quadruplex stabilizers, or by inhibiting binding of telomerase-associated proteins leading to telomere uncapping and cell apoptosis.

G-quadruplex structure must first be unfolded before the telomerase can initiate extension of the telomere. Therefore if telomeres could be stabilized using a G-quadruplex structure, the cells could be prevented from infinite proliferation characteristic of cancer. Small molecules that stabilize these structures and mimic their effect have been designed and found to inhibit telomerase activity. Most of the G-quadruplex stabilizing ligands contain a polycyclic heteroaromatic structure, though it is not an essential requirement for quadruplex binding. Three with commonly studied G-quadruplex stabilizing agents are Telomestatin.

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