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The Role of Telomerase in Cellular Aging, cancer, and Developmental Disorders: Mechanisms and Regulation

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ABSTRACT

Telomeres are a structure found at the end of chromosomes that act as a cap to protect the genetic code. Every time cells divide; the length of telomeres decreases. This initiates the aging process, as when telomeres reach critical length cells perform apoptosis (programmed cell death). Telomerase is the enzyme responsible for preserving telomere length, however, it has not been found active in somatic cells; its levels of detection are limited to certain types of stem cells and are prevalent in most cancers. This review will address the potential effects the deregulation of telomerase may have in a human organism. To do so, the role and regulatory mechanisms involved in controlling telomerase expression including histone deacetylation and DNA methylation will be described. Additionally, the effects of various genes implicated in these regulatory processes are discussed as well.

Keywords: Telomerase, Telomeres, Stem Cells, Regulation, Acute Myeloid Leukemia, Dyskeratosis Congenital, Expression

INTRODUCTION

Telomeres are repetitive non-coding DNA sequences found at the end sections of all chromosomes; they act as a cap to protect the genetic material from being lost or tangled. (Chadwick. 2024). During each cellular division, a section of each telomere is lost resulting in continual shortening. Telomeres that are too short in length are interpreted as DNA damage by the cell. This response activates checkpoint mechanisms that stop cell cycle applications leading to apoptosis. (Paull *et al.* 2000). The shortening process increases as an organism ages, and eventually, the reduction of cells contributes to tissue degradation and health problems in an individual. Therefore, telomere loss is the explanation for the aging and death of an organism and has often been compared to a biological clock since it acts as one of the main factors in controlling eukaryote lifespan (Masood, 2011). Moreover, telomere shortening happens because DNA polymerase, the enzyme responsible for replicating DNA.

before a cellular division takes place has a unidirectional nature. This means that it can only replicate one strand continuously (the leading strand) while the other one (the lagging strand) is synthesized in small RNA primers called Okazaki fragments. When the primer is removed, and the fragments join the end part is not replicated and therefore is lost. (Broccoli *et al*. 1997).

Telomeres consist of a repetitive sequence of TTAGGG for the lagging strand and AATCCC for the leading that has a high affinity for certain DNA binding proteins including TRF1 and TRF2. At the end of the telomere is a base pair overhang which coils up forming a T loop (figure 1). The binding proteins attach in groups of six and form the sheltering complex which helps in telomere maintenance and function. (Chan and Elizabeth, 2004).

Despite the natural shortening of telomeres with each division, an enzyme called telomerase plays a crucial role in their maintenance. It functions by adding guanine-rich repetitive sequences to telomeres counteracting the shortening process (Zvereba *et al*. 2010). Since its discovery telomerase activity has not been observed in most human somatic cells. Nevertheless, it has been found highly active in over 90% of cancer cells as well as some types of stem cells. (Greider and Blackburn, 1996) Furthermore, research has demonstrated that when telomerase is expressed, cells can become immortalized since it preserves telomeres enabling them to evade senescence and maintain an unlimited ability to proliferate. Additionally, it has been found that telomerase improves the capability of the DNA repair mechanism preventing cells from accumulating DNA damage and stress.

Telomerase works as a reverse transcriptase meaning that it copies RNA into DNA, and it synthesizes it in a 3' to 5' direction. (Greider and Blackburn, 1996). It is a ribonucleic protein that consists of two components, the first one is the RNA component (hTR) which acts as a template for telomeric DNA synthesis, and the second one is a catalytic protein called (hTert) that has the reverse transcript activity. (Harrington *et al*.1997). Telomerase is responsible for fixing the end replication problem of telomeres. By identifying the termination point of a current repeat sequence, it utilizes an RNA template to extend the leading strand, ensuring the complete replication of chromosome information. This review discusses the mechanisms of telomerase regulation in different human cells as well as the effects of its abnormal expression.

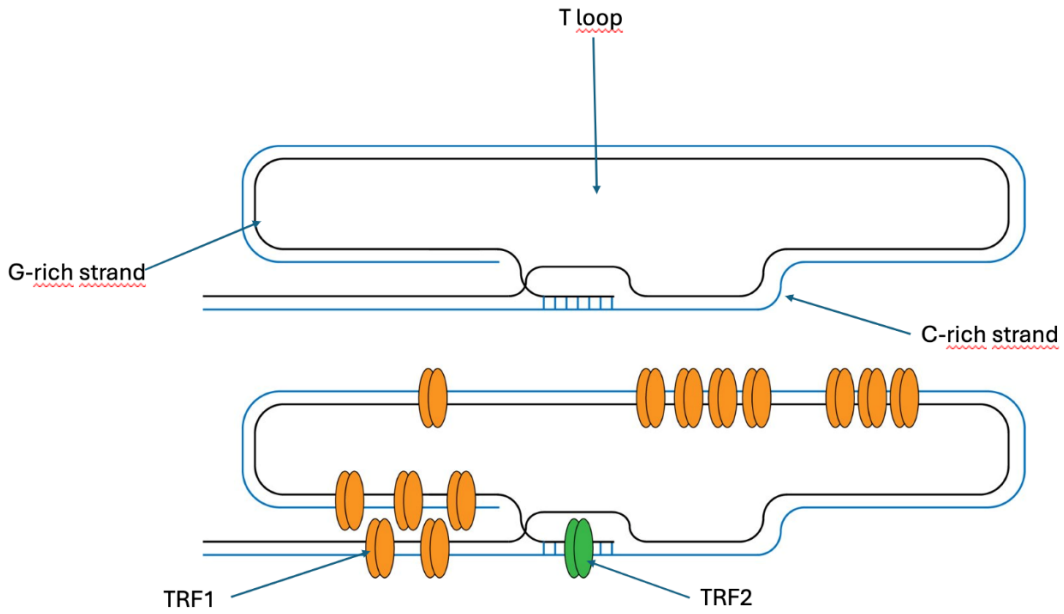

Fig. 1 : proposed structure of T loop and arrangement of TRF1 and TRF2 telomere binding proteins and components of the shelterin complex.

Epigenetic Regulation of Telomerase Expression During Development

The regulation of telomerase varies across cell types to serve its function in genomic stability. Some mechanisms act during development to ensure the appropriate expression of telomerase in embryonic stem cells and its downregulation as cells differentiate. For instance, Histone deacetylation and DNA methylation have a significant role in this process.

Histone deacetylation consists of the removal of acetyl groups from histones, proteins to which DNA in the form of chromatid wraps resulting in a more compact structure known as chromosomes. Removing the acetyl groups, affects how tightly histones grip the DNA, making it tighter and therefore limiting the access of factors and enzymes involved in transcription, the process of making RNA from DNA to code for proteins (Park and Kim, 2020). A second modification, DNA methylation is a process in which methyl groups are added to DNA specifically to the base's adenine and guanine. Because methyl groups are positively charged, they are attracted and bind to negative DNA resulting also in it getting more tightly coiled around the histones preventing the attachment of transcription factors. (Jin *et al.* 2011). DNA methylation is a fundamental process during embryonic development by directing and regulating cellular differentiation, thereby preventing regression to an undifferentiated state. Its levels vary during development significantly influencing the activation and suppression of genes. (Bergman, 2012). By compressing DNA both mechanisms are related to the silencing of genes as they prevent them from being transcribed and translated. Their presence during development represses the TERT gene from being transcribed contributing to the decrement of telomerase levels in differentiated cells.

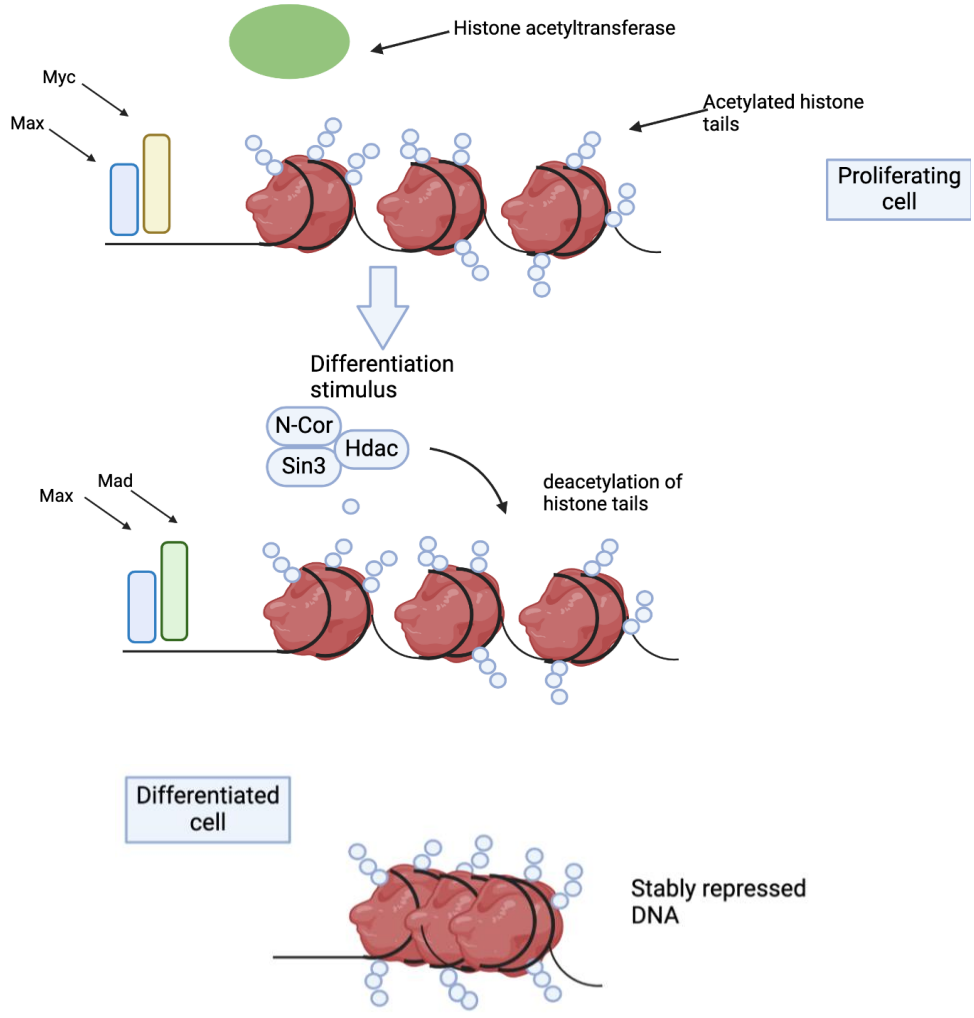

Fig 2: A switch in heterodimers from Myc- max to mad- max repress gene expression in differentiating cells.

Levels of Telomerase and its Regulation in Stem Cells

Because of their role in repressing telomerase expression in differentiated cells these two processes are essential in modulating the level of the enzyme in different types of stem cells.

Stem cells have the potential to develop into a wide variety of body cells. Given the heightened proliferative capacity of these cells, there exists a necessity for a mechanism to preserve telomeres throughout divisions. Consequently, stem cells exhibit higher levels of telomerase activity compared to typical somatic cells. (Hiyama and Hiyama. 2007). Different types of stem cells express different amounts of telomerase due to the activity of silencing mechanisms like DNA methylation and histone deacetylation. For instance, there is a significant contrast in the activity of the enzyme between embryonic stem cells and hemopoietic stem cells.

Embryonic stem cells (ES) are a pluripotent type of cell as they lack specialization so they can differentiate into all types of somatic cells of an organism. Because of this, no repressing mechanisms are acting on them since they appear as cells differentiate. As a result, this allows a high activity of telomerase to maintain telomere length which is essential to sustain their infinite proliferation.

Hemopoietic cells (HCS) are a multipotent type of stem cell that can be differentiated into all blood cells (Till and Mcculloch, 1980.). Because of their constant need for self-renewal and replacement, hemopoietic stem cells have detectable activity of telomerase which helps them maintain telomere length allowing a high proliferating capacity. However, as HCS are more differentiated than ECS they contain silencing mechanisms that restrict the amount of telomerase being expressed. This limits their expanding capacity and does not allow them to be infinitely preserved. (Sean *et al*. 1996). Additionally, several experimental studies have shown how hemopoietic stem cells suffer from stem cell exhaustion. This term is used to describe the gradual functional decline of adult, tissue-specific stem cells to maintain homeostasis of the tissue in which they reside (Peter *et al*. 1993), in other words, a limit in their self-renewal capability. Experiments involving stem cell transplantation in mice have proved this, since after its transplantation HCS never returned to their original amount. Likewise, it was evident how HCS harvested from an older mouse had a lower and more limited proliferating and self-renewal capacity than when collected from younger recipients. (Sykes *et al*. 2013). This suggests that although HCS has a detectable level of telomerase, it does not prevent them from progressively losing telomere length.

Consequences of Abnormal Levels of Telomerase in Human Somatic Cells

The regulation of telomerase is essential for the proper function of an organism, and as such there are different genes responsible for coding for mechanisms to control its activity. For instance, the gene MYC has been found to play a significant role in the expression of the TERT gene which encodes one of the subunits of telomerase. MYC is responsible for regulating different cellular processes including cell differentiation through the production of transcription factors. (Ahmadi *et al*. 2021). In human cells, RNA polymerase, the enzyme responsible for this process must attach to a specific site known as the gene's promoter to initiate transcription. Transcription factors, proteins that bind to DNA at precise sequences, play a crucial role in this process by either facilitating or impeding the binding of RNA polymerase, thereby regulating the transcription of genes. (David, 1993)

Specifically, MYC recruits a complex of transcription factors called histone acetyltransferases (HATs) which acetyls histones allowing the transcription of genes (Frank *et al*. 2003). As previously stated, the process of cellular differentiation and the suppression of TERT are tightly correlated. During this process, there is a transition in binding proteins from MYC to MAD1 leading to a decrease in acetylation which represses TERT. These two proteins compete against each other to bind to a DNA target site known as E box in a gene promoter zone. They form heterodimers, which are complex molecules formed by a protein the with MAX gene. This rearrangement of binders provides a system for transcriptional regulation. Additionally, A recent study on the differentiation of HL60 cells revealed that the MYC transcription factor was found to be bound during cell proliferation, but not during differentiation. On the other hand, the MAD 1 protein was induced and bound to the TERT promoter only in completely differentiated HL60 cells as well as contributing to histone deacetylation. This data suggests that changing the binder from MYC-MAX to MAD1-MAX is an

important factor in repressing telomerase in differentiated cells. (Xu *et al*. 2001)

Acute Myeloid Leukemia

Defects in mechanisms repressing telomerase can cause an upregulation of the enzyme triggering numerous consequences. In particular, it can give rise to Acute Myeloid Leukemia (AML) a type of blood cancer. It has been established that cancer cells are able to achieve immortality by having an increased amount of telomerase levels. These high levels allow them to indefinitely proliferate without suffering from telomere shortening and therefore escape the activation of DNA damage response which ultimately makes them commit apoptosis.

In AML the bone marrow produces a large number of abnormal cells called myeloid blasts. These cells fail to meet checkpoints in cell division multiplying uncontrollably and not dying. The accumulation of these defective cells in the bone marrow makes less room for healthy blood cells causing the marrow to halt the production of new, healthy cells. (Vakiti and Mewawalla, 2023) The lack of functioning blood cells can have many health complications such as the development of illnesses like anemia, thrombocytopenia, pancytopenia, etc. Additionally, as AML cells keep multiplying they travel through the bloodstream and spread through the whole body.

Moreover, several studies have shown that AML cells contain shorter telomeres than normal leukocytes due to constant division. This short length can have consequences due to the loss of the capping end of chromosomes causing a fusion between them. This, in turn, may lead to genomic instability and cytogenetic abnormalities such as non-reciprocal translocations and a gain or loss of chromosomes which can be an important factor for the initiation of AML. (Kumar, 2011) These abnormalities have been identified as contributing factors in the mutation of genes, such as FLT3, which lead to the development of this illness.

FLT3 codes for the protein tyrosine kinase 3, a protein that is responsible for stimulating signaling pathways that control processes such as growth, division, and cell survival. One of the most significant mutations that can lead to a deregulation of this protein involves internal tandem duplications. These mutations, occur in approximately 23% of AML patients and consist of the insertion of duplicated sequences into a specific sector of the receptor. The result is an over-activation of FLT3. A number of findings support that these receptor sends signals that promote proliferation and inhibit apoptosis leading to the multiplication of AML cells. (Kiyoi *et al*. 2019) Additionally, the mutation of the FLT3 gene deregulates the expression of MYC and therefore has a significant role in the upregulation of telomerase. Studies involving the comparison of healthy mice with AML-affected ones revealed that in the AML mice, there was significant overexpression of the MYC gene due to the signaling of FLT3 increasing MYC activity and suppressing MAD expression. (Mori *et al*. 2017) The overexpression of MYC and downregulation of MAD might deregulate the expression of the TERT gene allowing the reactivation of telomerase in AML cells.

Dyskeratosis Congenital

A downregulation of telomerase can also have detrimental effects on an individual. Dyskeratosis Congenital (DC) is an uncommon inherited disorder caused by germline mutations that result in irregular telomere biology. Patients of DC have excessively short telomeres, resulting in an inability of the bone marrow to produce sufficient blood cells. They often present abnormal nails, skin pigmentation, and oral Leukoplakia (a white patch in the oral cavity). (Savage and Alter, 2009) and are predisposed to cancer, anemia, and premature aging. (Michael and Dokal. 2009) The mutations related to DC have been found to happen in genes responsible for the function and maintenance of the telomerase complex.

One of the most important mutations associated with the disorder involves the gene DKC1. This gene codes for the enzyme Dyskerin which regulates the accumulation of hTERC one of the subunits of telomerase. (Liu *et al*. 2023). Dyskerin associates with H/ACA small nucleolar RNAs (snoRNAs), targeting RNA-specific sites to catalyze a process called pseudouridylation, the most common post-transcriptional RNA modification (Federico *et al*., 2022). In this process, uridine—a molecule with uracil bonded to ribose—is converted into pseudouridine by rotating it 180 degrees, resulting in an extra hydrogen bond (Borchardt *et al*., 2020). Pseudouridine is found in various RNA types but is crucial for the processing of rRNA, contributing to its folding and stability, which are essential for proper protein production.

A mutation on the catalytic subunit of Dyskerin has been shown to reduce rRNA pseudouridylation leading

to deregulations in gene expression. (Penzo and Lorenzo, 2018).

Additionally, pseudouridylation is also present in mRNA by altering mRNA splicing, the mechanism that removes introns (non-coding sections) to the transcribed mRNA and joins exons (coding sections). This is a fundamental process since the introns must be removed for the mRNA to be able to encode the protein with the right sequence. (Suzanne Clancy. 2008) Small nuclear RNAs (snRNA) are molecules that bind to proteins to form RNA complexes such as a spliceosome. They are a critical component of RNA splicing as they are responsible for removing the introns in the pre-mRNA. It has been found that pseudouridylation enhances the interaction between spliceosomal RNA and mRNA to facilitate the regulation of this process. (Jhon Karijolich and Yi-Tao Yu. 2014). Moreover, mutations in the catalytic subunit of dyskerin reduce the presence of pseudorines in mRNA which may contribute to aberrant mRNA splicing. Furthermore, in mRNA splicing an exon junction complex is produced by the bonding of two exons during the process. This complex has a significant role in translation by helping in the binding of ribosomal polysomes (multiple ribosomes translating a single mRNA) to mRNA for the synthesis of proteins. (Herve Le Hir et al 2016). A deregulation in mRNA splicing may lead to a decreased exon junction formation causing a reduction in gene expression.

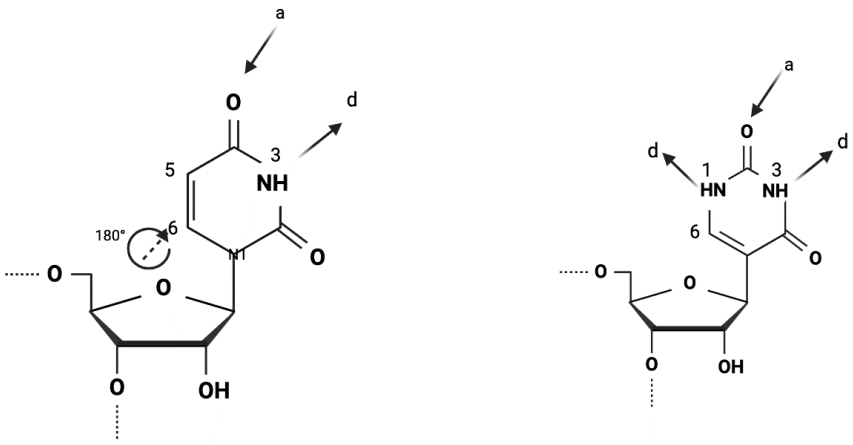

Fig 3: Pseudorlylation of uridine, uridine (u), and pseudorine() are indicated. 180 rotation of uridine, a: hydrogen bond acceptor d: hydrogen bond donor.

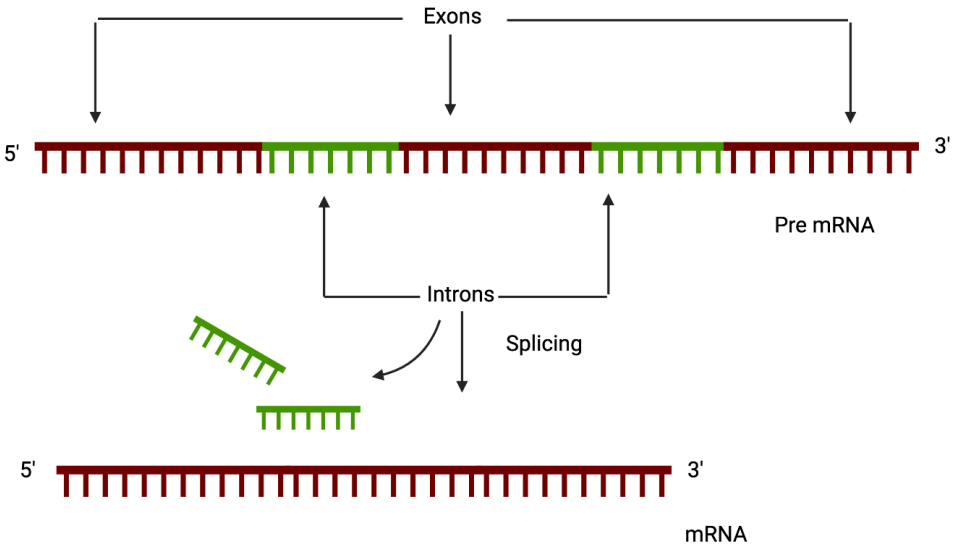

Fig 4: Pre mRNA splicing noncoding introns between coding exons are removed to join them and form mature mRNA.

Mutations in dyskerin resulting in abnormal pseudouridylation of both mRNA and rRNA could potentially lead to a reduced accumulation of TERC thereby contributing to dysklerosis congenital. As TERC provides the template for telomere elongation and it is one of the main subunits of telomerase a reduced expression of this gene overall decreases the accumulation and function of telomerase. Since there is not enough accumulation of telomerase to preserve telomeres, they shorten at a faster level triggering DNA damage response. (Micheal et al. 2011) This mechanism is activated as telomeres get to a critical length and cells no longer have the protection that this structure provides them. As DNA damage increases cells commit senescence which ultimately reduces the number of functional body cells directly affecting essential processes and leading to bone marrow-related disorders.

DISCUSSION

Telomerase is the enzyme responsible for maintaining telomere length in human cells. By preserving telomeres, this protein has a significant role in regulating the proliferating capacity of all cells. Telomerase was found to be tightly downregulated in somatic cells, while highly active in some types of stem cells and cancer cells. During embryonic differentiation, telomerase is repressed as cells become specialized, which explains why pluripotent cell types such as embryonic stem cells contain more telomerase than completely specialized ones. Haemopoietic stem cells are multipotent meaning that they are not completely differentiated but are more specialized than embryonic cells. They contain a detectable amount of telomerase which enables them to self-renew and become all types of blood cells. The levels of telomerase present, however, are not enough to allow them to divide without a limit leading to accumulation of DNA damage and apoptosis. It has been found that both histone deacetylation and DNA methylation are processes that contribute suppressing telomerase activity in differentiated cells. In the first process, enzymes remove acetyl groups from histones, similarly in DNA methylation methyl groups are added. This leads to DNA wrapping tighter around histones. As a result, transcription factors cannot access the modified genes, and gene expression is reduced.

Another system that has been found to have a significant role in the repression of telomerase during development is the Myc/Max/Mad network. When Myc binds to Max histones are acetylated enhancing telomerase expression and allowing cell proliferation. A switch from Myc to Mad binding, instead removes acetyl groups repressing the enzyme expression. This is an essential mechanism since an abnormal regulation of the telomerase is associated with leading to different life-threatening disorders. For instance, Acute Myeloid Leukemia, a type of blood cancer is related to an overexpression of telomerase in defective cells which allows them to infinitely proliferate taking away resources from healthy cells. Furthermore, the short telomeres presented cause cytogenetic abnormalities leading to the mutation of the FTL3 one of the causes of AML. This is because the deregulation of FTL3 causes an overexpression of the Myc oncogene leading to an enhanced telomerase transcription, however, the exact mechanism by which it does it is still being researched.

Another illness, dyskeratosis congenital features abnormally short telomeres due to a lack of telomerase leading to a faster shortening and senescence. The lack of functional blood cells in the body causes bone marrow failure and premature death. A mutation on the catalytic subunit of DKC1 gene has been found to be one of the causes of the illness. The reduced expression of Dyskerin leads to a decrement in the pseudorylation of rRNA which may lead to an abnormal function of this structure causing a reduced gene expression, although a deeper understanding of this process is still under research. Moreover, a decreased pseudorylation due to Dyskerin mutations lessens mRNA splicing which may contribute to reducing the formation of Exon junctions that may cause a malfunction in the translation process resulting in a lower expression of telomerase-related genes. All these processes mentioned could potentially cause an effect in telomerase regulation leading to a significant impact in an organism.

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