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Review Article

The Effect of Telomerase Enzyme on Cell Aging and Cancer Formation-Treatment

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Abstract:

Research has made the effects of the telomerase enzyme on both cellular ageing and cancer even more important. Measurement of telomerase activity appears to be a unique marker in addition to known methods for cancer diagnosis and treatment. In addition, numerous studies have shown that the reduction of telomeres shortens the life span of living cells. It is a known fact that cells with shortened lifespan age earlier and predispose to many diseases, especially cancer types. The fact that old cells are the basis for many diseases and young cells are resistant to many diseases has revealed the reality of keeping the cells young in order to prevent diseases. 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. Predictions such as preventing and stopping cellular senescence in human cells, providing cellular rejuvenation by reversing cellular senescence and extending human life span as much as desired are also worthy of further emphasis with the studies carried out.

1. Introduction

1.1 Telomere Region at Chromosome Ends

What is Telomere?

Telomeres are the terminal regions of chromosomes that differ both structurally and functionally from chromosomal DNA sequences. The enzyme telomerase (telomere terminal transferase or reverse transcriptase) is responsible for telomere synthesis and this enzyme also maintains the length of telomeres. Telomeres shorten during cell division and this is associated with the aging process [1].

After 1930, Hermann J. Müller, Barbara McClintock and Drosophila melanogaster and Zea mays chromosomes were studied to elucidate the concept of telomeres. Müller analysed the structural changes after exposure to X-rays and investigated the frequency of these changes. At the end of his studies, he observed that deletions and inversions in the terminal regions were less than expected. In later studies, it was found that if the ends of chromosomes were broken, coalescence was easy, whereas in unbroken chromosomes, telomere formation was stable. Chromosomes with broken ends did not fuse either with their own ends or with other telomeres. In the light of the findings, it has been proved that there are certain end structures that cause the integrity of chromosomes [1-4].

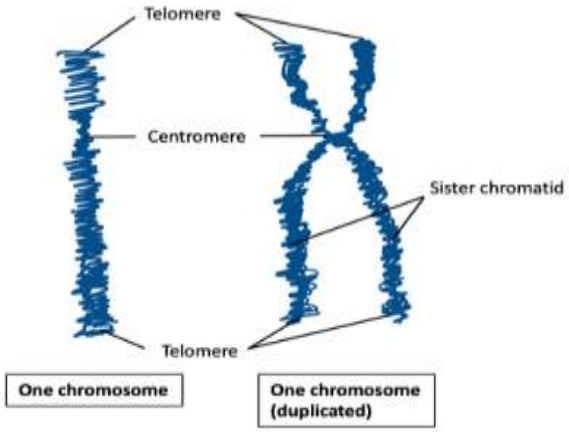

Figure 1. *A typical chromosome with its structures. (Often, the centromere has a three layered covering known as Kinetochore.)*

Two important properties of telomeres are, firstly, that they ensure the completion of replication at the ends of chromosomes and, secondly, that they prevent chromosome ends from interfering with each other or reacting with the inner parts of chromosomes (Figure 1). Telomeres shorten during cell division and are associated with the ageing process. These structures prevent the loss of genetic information by maintaining the stability of chromosomes [1, 2].

G4-DNA structures in telomeres contain guanine-rich nucleic acid sequences and are called G-quadruplex (G-tetrad or G4-DNA). This structure refers to a four-chain structure composed of guanines. Compounds that stabilise G-4 DNA play an important role in cancer therapy. These compounds stabilise the G-4 quadruplex structure so that the enzyme telomerase cannot reach the telomeres. Stopping the activity of telomerase can affect cell senescence and limit the uncontrolled division of cancer cells [5].

Functions of Telomeres

Telomeres are specialised structures at the ends of eukaryotic chromosomes that do not encode any genes. These structures maintain the integrity of the chromosomes, avoiding DNA breaks and the joining of chromosome ends. Telomeres are also important in cellular functions, such as organising chromatin, regulating the replication of chromosomes and playing a role in cell proliferation. The human telomere consists of a double-stranded sequence of repeated 3' TTAGGG hexanucleotides, present in the terminal regions of chromosomes. These sequences terminate in a 3' single-stranded TTAGGG sequence with a G-rich (G-tail) overhang of 100-200 nucleotides forming a lasso loop (T-loop). The unique T-loop pattern of telomeres is formed by folding the telomeres backwards. A single protruding guanine-rich strand (G strand) passes 'through' the double-stranded telomere. This structure replaces one of the telomere strands and forms the second loop, the D-loop. These D-loop and T-loop structures protect telomeres from end-to-end connections with other chromosomes and from checkpoints in the cell cycle that recognise telomeres as chromosome breaks and initiate repair of telomeres.

TRF1 is important for its function in the folds within telomeres and for regulating the length of telomeres. Overproduction of TRF1 results in telomere shortening and its inhibition results in telomere lengthening.

Although TRF2 binds along the telomere length, it is abundant near the T-loop and is important for the formation and stabilisation of the T-loop. The co-operation between these two proteins is similar to a two-handed knot; the first hand (TRF1) forms the loop while the other hand (TRF2) tightens and protects the thread. In each cell cycle, telomeres shorten by an average of 50 to 150 base pairs. This shortening of telomeres ultimately limits the number of cell divisions. Reaching critical telomere limits can also lead to genomic instability and tumour formation. It has been proven that many cancer cells have very short telomeres compared to normal cells. The enzyme telomerase is responsible for telomere synthesis and is a ribonucleoprotein. Telomerase was first found in Tetrahymena and then in human HeLa cells.

Telomerase enzyme was found to be active in embryonic cells, stem cells and cancer cells. However, telomerase enzyme activity was not found in somatic cells.

Many factors such as smoking, lack of physical activity, stressful lifestyle, obesity, bad weather conditions can accelerate the shortening of telomeres and cause aging and the formation or development of many other diseases, especially cancers [1, 2, 4].

Telomere nuclei are known as structures located close to the cell membrane and forming a 180° angle with centromeres. These nuclei allow telomeres to pass between homologous and non-homologous chromosomes. Telomeres are repetitive nucleotide sequences of DNA at the ends of chromosomes. These structures help to maintain the stability and integrity of chromosomes. In addition, telomeres shorten during cell division, which leads to the ageing and death of cells. The effect of telomeres on the ageing process, cancer occurrence, treatment or diagnosis is considered important. Targeting of telomeres is being investigated along with medical treatment methods in cancer treatment and diagnosis. The functions of telomeres are a complex part of the cellular life cycle and are critical to ensure genetic stability. [4]. The structure, function and synthesis mechanisms of telomeres have only recently been understood because they constitute as little as 0.003% of total DNA in organisms. These studies have been particularly abundant in ciliated protozoa with linear and short DNA. Today, the structure, function and synthesis mechanism of telomeres are still being investigated in protozoa, mould fungi, plant and animal cells. These studies contribute to our understanding that telomeres play a critical role

in ensuring genetic stability and are associated with ageing processes [1, 2].

Telomeres, which have a specialised heterochromatin structure, are located at the ends of eukaryotic chromosomes and do not encode any genes. These structures protect chromosome integrity and avoid random double strand DNA breaks and unwanted chromosome end joining [2, 4].

Telomere Structural Proteins

The enzyme telomerase and telomere structural proteins are proteins that interact with the telomere regions of chromosomes. This specialised amino acid sequence protein binds to the telomeric DNA repeat and acts to ensure telomere stability and regulate the length of telomeres. The part of the telomere consisting of TTAGGG sequence repeats and telomere binding proteins is called 'telesome'. These structures protect the chromosome ends, ensuring the integrity of the genetic material and may affect cell ageing. [4].

1.2. Telomeric Sequences and Their Regulation

Telomere Sequences

In eukaryotes, telomere regions are the end regions of chromosomes containing DNA and proteins. The telomeres of chromosomes contain certain simple repeat sequences. One of the DNA strands is rich in guanine. It runs in the 5' direction and is longer than the cytosine-rich strand.
This single strand extends outwards and folds to form a guanosine-guanosine pair structure that does not show Watson-Crick bonds, forming a hairpin-like structure [1, 2, 4].

There are structures in the telomere regions that can be said to be a regular disorder in a sense that can cause single-strand breaks. This means that ligase enzymes acting on open sites in DNA cannot bind and these sites are not recognised by nucleases. Truncated chromosomes, which have hairpin-like structures and lack telomere sequences, can fuse with free DNA ends.

These structures lacking telomere sequences are also susceptible to exonucleotic degradation. Telomeres are not known to be destroyed by telomere proteins. The unique structure of the telomere prevents the formation of dyscentric chromosomes, chromosome fusion and loss of genetic information from subtelomeric regions of chromosomes [4-6].

Telomere regions are structures located at the ends of eukaryotic chromosomes that protect the ends of chromosomal DNA. These regions ensure the integrity of chromosomes, avoiding random double-stranded DNA breaks and unwanted chromosome end joining. Telomeres are also important in cellular functions. For example, telomeric proteins work at these sites and regulate the stability and length of telomeres or carry out telomere repair. Telomeres contain specialised sequences that repeat. In humans, telomeres usually consist of TTAGGG sequence repeats. These sequences are a double-stranded sequence of repeated hexanucleotides found in the end regions of chromosomes. The unique structure of telomeres regulates the function of telomeric proteins. For example, telomere binding proteins such as TRF1 and TRF2 regulate the length of telomeres and ensure the stability of telomeres. Telomeres are known to be associated with the ageing process and cancer development. Telomeres shorten by an average of 50-150 base pairs in each cell division. This telomere shortening limits the number of cell divisions and is associated with the aging process. Furthermore, the enzyme telomerase regulates the length of telomeres and enables telomere synthesis. Telomerase has been found to be active in stem cells, embryonic cells and cancer developing cells. No telomerase activity was detected in somatic cells. In conclusion, telomeres protect the ends of chromosomes, ensuring genetic stability and influencing cell ageing. These specialised structures play a critical role in cellular functions and prevent the loss of genetic information [4, 6].
Telomerler, tek iplikli kırılmalara neden olabilen düzensiz yapılar içerir. Telomerin bulunuşu ilk olarak 1970'li yıllarda Ciliat kromozomlarında tesbit edilmiş, daha sonra mayalar ve diğer organizmalarda da bulunmuştur. Telomerler, sentetik telomeraz enzimi tarafından tekrarlayan dizilerle uzatılır. Bu telomer bölgeleri, dışarıya doğru uzantı yapar ve saç tokası şeklinde kıvrılıp Watson-Crick eşleşmesi göstermeyen, guanozin-guanozin eşleşmesi yapan bir yapı oluşturur. Sonuç olarak, telomerler, genetik stabiliteyi sağlayarak hücre yaşlanmasını etkiler ve yaşam süresini belirler [2, 4, 6].

Telomere Loss Affecting Telomere Length

There are many genetic and physiological factors that influence telomere length. This is a telomere length maintenance mechanism and prevents the progressive shortening of chromosome ends at the

end of semi-conservative DNA replication. Telomeres of dead cells in cultured cells were found to shorten by 65 base pairs (bp) in each first generation. Human germline chromosome ends contain 10 kb of telomeric AGGGTT repeats. Studies have been conducted on human cells of various ages, precultures of human fibroblasts and many cancer cells. It has been observed that the length of telomeres decreases with multiple cell divisions and increasing age. Telomerase activity was detected in HeLa immortal tissue culture cells, Tetrahymena cells and human germ cells. When human somatic cells were examined, telomerase enzyme activity was not found and it was noticed that the telomeres in these cells were shorter. The only exception to this was observed in mouse telomeres. Mouse telomeres are 5 to 10 times longer than human telomeres. There was no significant difference between the telomere lengths of old and young mice. Orobnikov first discovered in 1973 that telomere shortening leads to death, limits the proliferation of somatic cells and causes cellular senescence. [7]. Subsequent research also confirmed Orobnikov's findings.

Telomere repeats are lost in every cell cycle. However, these losses are compensated by the addition of telomere repeats at the 3' end. In some cases, repeats can be copied from the telomeres of one chromosome to the telomeres of another chromosome through a recombinant replication mechanism. In the absence of telomerase, it is important that the TnGn chain at the 3' end of the chromosome provides an excellent template for the DNA polymerase enzyme, minimising telomere loss. This increases the likelihood that repetitive telomere sequences will be recognised primarily by DNA polymerases. [6].

Telomeres are the ends of chromosomes and shorten during DNA replication. This shortening can be corrected by the enzyme telomerase. However, if telomerase activity is not corrected, the protective function of the telomere region decreases. Recent studies have shown that the structure of telomere regions and telomerase activity play an important role in cellular aging and cancer development. [4, 6].

Telomeres are the terminal regions of chromosomes containing DNA and proteins. These regions are structurally and functionally different from other DNA sequences on the chromosome. Telomeres protect the terminal parts of chromosomes from abnormal effects such as fusion, recombination and breakage. It has also been shown through molecular analysis that telomeres allow the replication of linear chromosomal DNA ends without losing the 5' terminus of each DNA strand. Such losses are thought to be a feature of traditional semi-protective replication mechanisms [4].

Loss of telomere strands with cell division can cause abnormalities in chromosomes. For example, the ‘est1’ mutation in yeast causes shortening of telomere length, which leads to chromosome loss and thus cell death [2, 6].

Sex cells have to pass on all chromosomes to their offspring. However, the telomere hypothesis suggests that the length of telomeres in somatic tissues decreases with age. The telomere sequences of sperm are long and this length is stable. On the other hand, it has been observed that the telomere length of blood cells decreases with age. These results prove that germ cells, not somatic tissue, maintain telomere integrity [8].

Structure of Telomerase

Telomerase is a specialised DNA polymerase structure responsible for the repetitive synthesis of the TTAGGG sequence in the terminal regions of chromosomes. The enzyme telomerase was first identified in the organism Tetrahymena and was later observed in human HeLa cells. This enzyme is active in embryonic and adult stem cells, undetectable in normal somatic cells and reactivated in cancer cells [8].

Function of Telomerase

DNA replication in eukaryotic cells is the process of copying double-stranded DNA. In this process, synthesis occurs continuously on the leading strand, but synthesis occurs on the interrupted strand using short RNA primers called okazaki fragments.

However, if the 3' end of the mould DNA is not copied by the normal copying mechanism, this is called an end-of-replication problem. This results in a loss of approximately 50 to 200 nucleotides at the 3' end of the chromosomal DNA during each cell division and accelerates cellular senescence. Telomeres are repetitive DNA sequences located at the ends of chromosomes. At the 3' ends of telomeres, there is an extension of 12 to 16 nucleotides, rich in guanine and thymine. These extensions serve as templates during the telomere lengthening step. In humans, the enzyme telomerase uses a short segment complementary to

the telomeric DNA sequence as a template to extend the 3' end of the strand. In this way, telomere length is maintained and cellular ageing is delayed. [2,9].

2. Discussions

2.1 Telomeres and Aging

In normal tissues, the systems involved in telomere elongation do not continue their activities during cell division. Therefore, telomeres shorten with each division of the cell. Telomere length determines the replicative lifespan of a cell. When telomeres shorten to a critical length, the aging process is activated. Cell division then stops, but the cell continues to live and function. Telomeres are actively maintained in germ cells. This is because chromosomes have to be passed on to the next generation. This occurs through the activity of the enzyme telomerase, which is responsible for telomere replication [1].

Telomere Hypothesis in Cell Ageing

Olovkinov first discovered in 1973 that telomere shortening can control and time replicative lifespan [7]. However, information on the structure and function of telomeres was published by Harley in the 1990s [10].

Human cell senescence and death occur in two stages. The first stage is called death stage 1 (M1). In this stage, telomeres shorten and chromosomes reach a critical length. This point, called the Hayflick limit (proliferation limit), stops the cell cycle and starts the ageing programme. After the cell passes this point, telomeres shorten to the M2 point, especially due to oncogenic transformation. The M2 point is called the crisis point and leads to massive cell death. Telomerase activity is required to overcome this crisis. This repairs telomere length and structure, allowing cells to divide indefinitely. Normal body tissues can only reach an aged state, but only germ cells or cells capable of transformation are capable of unlimited cell division. Telomeres are considered to be an important and valid model for the mechanisms of ageing and cancer [11].

DNA tumour viruses such as monkey virus 40 (SV 40) can be used to overcome cellular senescence. Transforming cell cultures can extend their life cycle. Tumour viruses bind to tumour suppressor proteins in cells, inactivating them. This is good evidence that the long life cycle of cells transformed by viruses occurs through inactivation of these molecules. Some immortal cells lack p110RB and p53 due to mutation and gene deletion [12].

Banszerus and colleagues analysed the relationship between the length of telomeres and the epigenetic clock in a study with a group of humans. The epigenetic clock uses the DNA methylation fraction as an indicator of chronological age. The researchers estimated the epigenetic age of an average of one thousand people participating in the study and compared it with telomere length measured in blood cells. It was determined that telomere length was insufficient to predict epigenetic age, but the epigenetic methylation model better described the chronological age of the participants. Thus, it was proved that both of the two parameters represented different aspects of cell ageing [13].

Shekhidem et al. conducted a study examining telomeres on cell senescence and longevity. In this context, they analysed age-related telomere shortening between short- and long-lived rodents. At the end of the study, they found that the naked mole rat, one of the two long-lived species, showed no measurable telomere shortening during its lifetime, while the other species, the blind mole Spalax, had the same age-related telomere shortening rate as short-lived mice [14].

2.2 Telomere- Cancer Relationship

Studies on cancer cases have revealed the relationship between telomere length and cellular telomerase activity. In vivo studies have shown that tumour formation and telomerase activity are related. There are important findings on this subject.

Benign tumours: Benign tumours have low telomerase activity and when telomeres shorten, these tumours revert to their initial stages. This limits the growth of cancer cells.

Metastatic tumours: High telomerase activity was observed in more aggressive metastatic tumours. Telomerase contributes to the rapid growth of these tumours.

In this context, telomerase inhibitors are proposed as potentially effective drugs in cancer treatment. These drugs targeting telomerase may help control tumour growth by preventing cancer cell proliferation [1].

Telomerase Activity in Cancer Diagnosis

In 1994, Kim and colleagues developed the TRAP (telomere repeat amplification protocol) method to measure telomerase activity in cells and tissues. This study investigated 24 different types of cancer and reported that cancer was associated with telomerase expression. To date, telomerase activity has been detected in more than 50% of the various tumour types tested. These results showed that telomerase activation is renewed in immortal cells [15].

The development of the TRAP method has enabled the measurement of telomerase activity in tissues, enabling the investigation of telomerase expression in many types of cancer. Today, research on telomerase expression in many tumour types continues. From these results, it is understood that telomerase is the best known marker for cancer diagnosis. A study conducted by Shay and Wright in 1996 found that 50% of malignant tumours have telomerase activity. This telomerase activity in malignant tissue shows that telomerase enzyme has a very different importance in cancer diagnosis [16].

Traditional cancer diagnostic methods include biopsy using standard histopathological techniques. However, these methods do not always give accurate results. Telomerase activity can be used as a more sensitive marker in cancer diagnosis.

Detection in body fluids: The main clinical advantage of telomerase is that it can be found in body fluids such as urine, saliva, blood, etc. For example, different leukaemia diagnoses may not give clear results. Therefore, more sensitive markers will provide important information in the detection of blood cancers. Telomerase activity can be measured in the urine or blood cells of blood cancer patients.

Brain tumours and telomerase: The relationship between brain tumours and telomerase is being investigated. Telomerase activity has not been detected in healthy brain tissues. While 81% activity was detected in malignant tumours, 100% telomerase activity was detected in metastatic cancer tumours. Patients with telomerase activity were found to have a poor prognosis and short life expectancy compared to those without telomerase activity. Therefore, telomerase activity is an important indicator that can be used in the diagnosis and prognosis of brain tumours. This information will help us better understand the role of telomerase in cancer research [17].

The study by Nakatani et al. examined the association of brain tumours with telomerase. Here is a broader view on this topic:

Telomerase and Activity in Normal Brain Tissue: While telomerase activity was not detected in brain tissues with normal cells, 81% telomerase activity was detected in malignant tumours and 100% telomerase activity was detected in tumours with metastatic properties. This shows that telomerase is associated with brain tumours.

Prognosis and Telomerase Relationship:

The prognosis of telomerase (+) subjects is worse than telomerase (-) subjects and their life span is shorter. Therefore, telomerase activity is an important indicator that can be used in the diagnosis and prognosis of brain tumours [18].

In the study by Bednarek et al. telomerase activity was detected in 95% (99/104) of breast cancer cells and 20% (1/5) of fibroadenoma cells. However, no statistically significant correlation was found between telomerase activity and tumour size, metastasis status, stage and estrogen-progesterone receptor level. Therefore, it is thought that telomerase activity is not an accurate marker for prognosis.

This study shows that breast lesions such as breast cancer and fibroadenoma were analysed in terms of telomerase activity. Telomerase activity is an important mechanism that contributes to the unlimited division ability of cancer cells. However, no clear relationship between telomerase activity and tumour characteristics was found in this study. Therefore, it was concluded that it cannot be used alone as a reliable indicator for determining breast cancer prognosis. The researchers hope that more studies on the discovery of genes regulating telomerase activity will be conducted in the future [19].

In the study by Yoshida et al. enzyme activity was detected in 86% of the samples taken from bladder cells. However, no clear correlation was found between tumour stage and telomerase enzyme activity [20]. Furthermore, RT-PCR of tumour and adjacent normal tissues revealed a significant correlation between telomerase activity and hTERT mRNA expression and suggested that hTERT expression is one of the factors regulating telomerase activity. These findings suggest that telomerase activity can be used as a potential

indicator in the diagnosis and prognosis prediction of bladder cancer[21].

In the USA, endometrial cancer is a type of cancer known to reach the highest frequency in the postmenopausal period. The study by Kyo et al. showed that there is a relationship between telomerase activity in the endometrium and the proliferation capacity of cells. In addition, hTERT mRNA expression was found to change characteristically according to menstrual cycle phases [22]. Therefore, it is thought that telomerase activity may be a determinant in the early diagnosis of endometrial cancer in postmenopausal patients. In a study conducted by Akbay et al. in 2008, it was also determined that there was a relationship between breast cancer and shortening of telomeres. This study examines the relationship between endometrial cancer and telomerase activity and demonstrates a link between the ability of cells to proliferate and telomerase activity. Telomerase is an enzyme that contributes to the unlimited division ability of cancer cells. This study suggests that telomerase activity may be a potential indicator in the diagnosis of early endometrial cancer in postmenopausal patients [23].

When we look at ovarian cancers, it is seen that it is one of the tumours with a worse prognosis among the tumours belonging to the reproductive system. Effective differential diagnosis of epithelial ovarian tumours plays a critical role in the planning of treatments. Early diagnosis and correct treatment methods are important to improve the quality of life and prognosis of patients.

The Role of Telomerase Activity in Cancer Therapy

It is thought that the enzyme telomerase may have important effects in treating cancer. Cancer is a disease characterised by the uncontrolled growth of certain cell populations in the body. Research to date has aimed to understand the growth of cancer cells and the control of cell proliferation. These studies have led to the discovery of many oncogenes and revealed that cell division is controlled by dysregulated mechanisms. Cancer research focuses on the infinite proliferation capacity and immortality of malignant cells.

Telomerase is an enzyme that contributes to the unlimited division ability of cancer cells. Research has been conducted to understand the mechanisms that control the growth of cancer cells. These studies are important for the discovery of oncogenes and the determination that cell division control occurs by dysregulated mechanisms. The potential of telomerase in cancer therapy can be better understood and translated into clinical applications with future studies[17].

The limited ability to divide in somatic cells is associated with telomeres. This can be seen as a tumour suppressor mechanism. By limiting cell division, eukaryotes can control out-of-control cell growth. However, cancer cells have discovered a crucial way to overcome this barrier and initiate cell immortalisation: activation of the enzyme telomerase. Therapeutic and diagnostic developments targeting the immortalised structures of malignant cells have the potential to be more effective methods in cancer diagnosis and treatment than other applications.

Telomerase is an enzyme that contributes to the ability of cancer cells to divide without limit. Research has been conducted to understand the mechanisms that control the growth of cancer cells. Telomerase is considered as a potential target in cancer diagnosis and treatment [16,17].

Telomerase enzyme may have therapeutic effects in cancer treatment. Cancer is a disease characterised by the uncontrolled growth of certain cell populations in the body. Research to date aims to understand the growth of cancer cells and the control of cell proliferation. These studies have led to the discovery of many oncogenes and revealed that cell division is controlled by dysregulated mechanisms. Telomerase is an enzyme that ensures the immortality of cancer cells. Inhibition of telomerase leads to significant shortening of telomeres. Shortened chromosomes cause instability and cell death. Telomerase expression is closely associated with cell immortality and early stages of cell differentiation, but is independent of the proliferation rate. In other words, immortalised cells regulate the expression of telomerase. This fact emphasises the importance of the relationship between telomerase enzyme activation and cell division [2].

Telomerase is an important enzyme that affects the ageing of cells and their ability to divide. Telomerase slows the ageing of cells by synthesising and protecting the repeat sequences at the ends of DNA called telomeres. In normal cells, telomerase activity is low and the length of telomeres shortens by 100 base pairs with each division. This shortening causes cell division to stop over time. However, telomerase activity is preserved in cancer cells and stem cells. Therefore,

cancer cells and stem cells are considered immortal and retain the ability to divide continuously [17].

Telomeres are known as DNA and protein-containing structures located at the end regions of chromosomes. These telomeres shorten during cell divisions and contribute to the aging process. In recent studies, the presence of structures called G4-DNA in telomeres has been found. G4-DNA are guanine-rich nucleic acid sequences and refer to a four-chain structure formed by guanines. These structures can help stabilise telomeres and may constitute a promising area for cancer treatment.
Telomerase is an enzyme that synthesises and protects telomeres. While telomeres shorten during each cell division, the enzyme telomerase can prevent this shortening. Telomerase plays a promising role in cancer treatment and the aging process. In the light of this information, the importance of telomeres and G4-DNA structures is better understood. Their effects on cancer treatment and the aging process constitute a promising area for future research [5].

In a study, Veverka and colleagues examined how the telomeric shelterin complex affects telomerase's access to telomeres. Shelterin is a protein complex that protects telomeric DNA and regulates the length of telomeres. The researchers determined that the protein TPP1 is a critical component for the formation of the shelterin complex and for telomerase access to telomeres. Therefore, they found that TPP1 could be a potential target for blocking telomerase from reaching telomeres, reducing the proliferation of tumour cells [24].

Wen and colleagues examined the results of disrupting the hTERT gene in cancer cells with CRISPR/Cas9 technology. In the study, this genetic disruption caused a significant decrease in telomerase activity and cancer cell proliferation in HeLa cells. This decrease was associated with the apoptosis mechanism. However, since the researchers did not analyse telomere length, they could not conclude whether these effects targeted conventional or unconventional pathways of TERT/telomerase.

An important finding of the study was that tumour cells partially lacking the TERT gene failed to form tumours after transplantation into mice. Therefore, inactivation of the TERT gene by gene editing in this way may be an important new treatment option for cancer therapy in the future [25].

Role of Telomerase Inhibitors in Cancer Treatment

Blocking the part that binds telomerase to DNA is considered a promising approach in cancer treatment. Although specific inhibitors are not yet available, research in this field shows that it may offer new treatment options in the future.
Telomerase inhibitors can be used in combination with conventional cancer therapy to prevent the proliferation of cancer cells or to prevent their recurrence after treatment. These inhibitors may be effective against the tumour by affecting the life cycle of cancer cells. However, side effects may also occur in cells with telomerase activity (e.g. blood cells, genital cells, activated B and T lymphocytes, proliferating cells). Therefore, it should be considered as a tumour-specific treatment.

Studies in this field show that it may be a new source of hope in cancer treatment. Developing more specific and effective telomerase inhibitors in the future may improve the quality of life of cancer patients and support treatment success[16,17].

3. Conclusions

3.1. Effect of Telomerase Enzyme on Cell Ageing Process

The telomere-cell ageing relationship is still a poorly understood topic and more research is needed. However, studies in this field offer promising clues for future treatment modalities. There are several items that should be emphasised on this subject:

1. Can We Prevent Cell Ageing by Telomerase Expression in Transplanted Tissues: Can external expression of telomerase prevent or delay senescence in transplanted tissues and organs? This is an important question for future therapeutic strategies.

2. Telomerase Expression and Oncogenic Changes: Does telomerase expression affect the likelihood of oncogenic changes in transplanted tissues and organs? This is important in terms of cancer risk.

3. Effect of Artificial Telomere Increase: Can telomere increase be achieved artificially and does it work? Experiments in human primary cells have shown that cells with telomerase (+) eliminate the aging property and continue to divide. Studies in cell types such as retinal epithelial cells and

fibroblasts have shown the same results. Shortening of telomeres reduces the lifespan of human cells, which has also been demonstrated by studies. It is thought that the expression of hTERT, which is the functional subunit of the telomerase enzyme, which undertakes the task of lengthening telomeres, may enable human cells to proliferate in large numbers. In the light of this information, further research on the role of telomerase and potential treatment methods is required [2, 6, 16].

The question 'Is it possible to have immortality and eternal youth by increasing the length of telomeres?' has been a subject of great curiosity in the scientific world. Recent studies show that the aging process can be reversed by artificially increasing the telomerase enzyme in the cell. Telomeres are structures located at the ends of the chromosomes of cells and shorten during cell division. This shortening is a marker of the ageing process.

By cloning the telomerase gene in cultured human cells, scientists have proven that cells continue to divide past the senescence point and lengthen telomeres by 1000 base pairs. This means that we could theoretically reverse the effects of ageing. However, it is important to note that this carries a risk of cancer. Overactivation of telomerase can lead to uncontrolled division of cells and increase the risk of cancer.

Therefore, it is important to investigate safer and balanced methods to increase telomere length and achieve eternal youth. Scientists continue to work in this field and strive to understand the aging process and develop healthy aging strategies [1,2].

3.2. Effect of Telomerase Enzyme on Cancer

Studies in many types of cancer have shown that telomerase activity can be important in diagnosis. This method is valuable in analysing small samples and body fluids (e.g. urine, pleural samples, ascites fluid, pelvic/peritoneal material). The use of telomerase as a marker may enable more sensitive and early diagnosis in such samples.

Telomerase inhibition shortens the lifespan of tumour cells, especially those with short telomeres, supporting the role of telomerase reactivation in immortalisation and carcinogenesis. Nevertheless, several tumour types and immortalised cell lines have long telomeres even though they do not show telomerase enzyme activity. This suggests the existence of another mechanism involved in telomere elongation.

The cloning of human telomerase subunits, the discovery of genes that regulate telomerase activity and the elucidation of other mechanisms that cause immortalisation other than telomerase holoenzyme are opening the door to surprising developments in the fields of gerontology and cancer treatment. It is hoped that research in this field may lead to more effective and personalised cancer treatments in the future (26,27).

In light of all this information and research, it should be said that telomeres, which form the terminal ends of chromosomes, have the potential to contribute to a more hopeful future for humanity. Chromosomes are the basic building blocks of life and carry genetic material. Telomeres are known as structures located at the ends of chromosomes that shorten during cell division. A better understanding and regulation of these structures is important for understanding the aging process and developing healthy aging strategies. Scientists aim to reach more effective and personalized cancer treatments in the future by continuing their studies in this area.

Author Statements:

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- **Data availability statement:** The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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