

Telomeres and Immunodeficiencies

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Abstract

The function of the immune system is highly dependent on cellular differentiation and clonal expansion of antigen-specific lymphocytes. Telomeres are conserved DNA-protein structures of linear chromosome termini. Telomere length has been investigated to be different in various lymphocyte subpopulations depending on their function and to change with aging. Association of accelerated telomere loss compared to matched controls has already been confirmed in many syndromes with immune dysregulation. Immunodeficiencies connected with dysfunction of telomeres are dyskeratosis congenita, genetic disorders involving DNA repair and disorders involving the VDJ recombination.

Keywords: *Telomeres; Dyskeratosis Congenital; Chromosome; DNA*

Introduction

Telomeres are conserved DNA-protein structures of linear chromosome termini. In mammals, the telomere DNA component consists of hexanucleotide repeats that have the sequence TTAGGG. The length of the repeats varies among species, with an average of 5 - 15 kb in humans and a notably greater in mice [1]. Whereas most of the telomeric DNA is double stranded, a G-rich single strand forms a terminal 3' overhang at the very ends of chromosomes [2]. Evidence indicate that the structure of telomeric end consists of a 'T loop', which is formed by the invasion of the single strand terminus into the double strand telomeric DNA [2]. Several telomere DNA binding proteins, collectively named Shelterins protect the structure. These include telomeric repeat-binding factor 1 and 2 (TRF 1, 2) and TPP1 proteins, which bind to the double-stranded, while POT1 (protection of telomeres 1) binds the single strand telomeric DNA. In particular, TRF1 regulates telomeric length by inhibiting telomerase, protects telomeric ends and suppresses checkpoint points [3]. Proteins TIN2, RAP1 complete the shelterin complex [4].

Estimates show that a loss of 50 - 200 bp happens with each cell division in humans caused by the inability of DNA polymerase to replicate the terminal portion of chromosome. This could attribute to the end of replication [5]. However, a compensatory mechanism prevents telomere length from shortening. The ribonucleoprotein enzyme telomerase, a specialized reverse transcriptase binds to the 3' ends of the chromosome and extends telomeres. Telomerase consists of two components: telomerase RNA template (TERC) that provides a template for synthesis of telomeric DNA repeats and a telomerase reverse transcriptase (TERT), which is important for the catalytic activity of the enzyme [1]. While TERC exists in all cell types, TERT is strictly regulated and is considered as a rate limiting factor for telomerase activity [6]. Telomerase and the regulation of telomere length have recently drawn considerable attention for their potential roles in critical biological functions. It is not expressed in most somatic cells except the ones with self-renewal capacity, such as hematopoietic stem cells, lymphocytes and skin epithelial cells [7]. The established role of telomerase in cancer and its potential role in aging underscore the relevance in immunity [1]. Its expression is found increased in 80 - 90% of cancers and has become an attractive target for treatment of neoplastic tumors [8].

The progressive shortening of telomeres to a critical limit either reaches a state termed 'replicative senescence' in which they are incapable of further cell division (Hayflick limit) or they can provoke apoptosis [9]. The life span of a cell is predictable in connection of telomere length that is the so called mitotic clock [1]. The telomere hypothesis suggests that telomere length could serve as a biological indicator for previous cell divisions in the history of the cell as well as for the residual replicative capacity [2]. The presence of telomeres maintains the integrity of chromosomes, prevents illegitimate recombination and fusion, ensures complete replication in cell divisions and is implicated in localization of chromosomes in the nucleus, separation of sister chromatids during replication, regulation of gene expression and cellular senescence [6].

The methods to investigate the length of telomeres in different tissues are flow cytometry, quantitative fluorescent hybridization and Western Blot with terminal restriction fragment analysis.

The purpose of this study is to review the current knowledge according the telomeres of cell populations responsible for immunity and present immunodeficiencies associated with telomere length.

Telomeres in Hematopoietic cells

Immunity is the capacity of the immune system to respond effectively to the constant antigenic changing of the environment. T and B cells are capable to recognize antigens by receptors on their surface (TCR and BCR receptors, respectively). The function of the immune system is highly dependent on cellular differentiation and clonal expansion of antigen-specific lymphocytes. Telomere length has been investigated to be different in various lymphocyte subpopulations depending on their function and to changes with aging [10].

Hematopoietic stem cells have longer telomeres than descendant lineages. The prurient hematopoietic stem cell is characterized by a high replicative capacity, but is difficult to investigate it, because of its rarity and lack of a defined phenotype. Telomerase is unregulated in these cells and expression levels are higher in more committed progenitors [11]. The number of cell divisions required for differentiation of a mature peripheral blood cell from multipotential cell might be different in each lineage and it is constant over the lifetime of an individual [11]. Telomere length is comparable in most leucocyte populations such as granulocytes, mononuclear, T cells, it is slightly larger in B cells and slightly lower in natural killer cells [12].

Lymphoid cell lineages have a complicated telomerase activity and telomere length dynamic. It has been estimated that a typical immune response involves 15 - 20 cell divisions, from a single naïve cell to approximately a million of its activated clones. Once the antigen is cleared the majority of these cells undergo apoptosis and a small number survives to become memory cells. Memory cells are long lived and are capable of rapid further expansion upon re-encountering with the same antigen. The overall number of cells produced during lifetime is enormous and this is achieved by the up regulation of telomerase [10]. Telomerase activity is constitutive and not actively regulated [6]. The ability of a stimulus to induce telomerase up regulation is correlated with proliferation and the cell cycle of T cells [6]. Telomerase activity exhibits different regulation during the development of T cells, being elevated in the thymus and lower in peripheral blood lymphocytes [11]. During acute infection, transient telomerase activation prevents significant shortening in antigen-specific T cells up to one year thereafter, but shortening is only postponed and not completely prevented [11].

Telomere shortening occurs along with differentiation from naïve to memory T cells in both helper (CD4) and cytotoxic (CD8) subgroups [13]. Naïve T cells are capable of 128-fold extensive division than memory. Telomere length in naïve CD4+ T cells decreases with age implying that cell division is an ongoing process through life in naïve cells and/or their precursors [8]. The rate of telomere shortening during T cell differentiation in vivo is unknown, but in cultured cells it appears minimal at the beginning of the process and is more evident at the end stage of the culture. Both naïve and memory cells are capable of up regulating telomerase activity when they are stimulated by mitogen SAC or by engagement of the BCR receptor in combination with other signals [6]. Ectopic TERT expression not only prevents aging of T cells, but may also confer a growth or survival advantage without affecting the cytokine production in vitro and their specificity for antigen [14].

During differentiation of B cells from naïve to germinal center (GC) B cells and then to memory cells occur at least 10 cell divisions without significant telomere loss. Separation of naïve and memory B cells revealed that telomere length was almost 2 kb longer in the former [12]. An increase of 3 - 4 kb in telomere length is noted in germinal center B cells compared to naïve B cells. At last no obvious difference exists between naïve and memory B cells in the peripheral blood and tonsils [6]. Telomerase activity has been found increased in GC cells and has been possibly associated with increased telomere length at this point of B cell maturation. Memory B cells down regulate telomerase, returning the lineage to proliferation-dependent telomere loss [12]. Longevity of memory B cells is maintained by up regulation of telomerase [5]. In all individuals, B cells have longer telomeres than T and NK cells and show the least decline in telomere length with age [14].

As far as NK population is concerned, telomere length is shorter in mature CD56^{dim}CD16⁺ NK cells compared to immature D56^{bright}CD16⁻ cells. Furthermore, NK cells expressing NKG2D, LFA-1 markers have significantly shorter telomeres [15]. At advanced age NK telomere attrition results in disappearance of long lived, mature cytotoxic cells and compromise immunity against foreign cells, virally infected cells and tumor cells [15].

Today, it remains unclear whether continuously increased telomere shortening after transplantation connected with myeloablative conditioning could potentially lead to hematopoietic insufficiency and finally stem cell exhaustion [7,11]. However, it is demonstrated that initial shortening of telomere length in the bone marrow is followed by a subsequent restoration [11].

Telomere length shortening occurs in somatic cells in vivo and is associated with aging. The set point for telomere length of an individual appears to be controlled at the genetic level and possibly displays a paternal inheritance [2]. During normal aging, the gradual loss of telomeric DNA in dividing somatic cells can contribute to 'replicative senescence', apoptosis and neoplastic transformation [1]. The immune system undergoes characteristic changes. T cell function is depressed in elderly individuals and this deterioration is believed to contribute to morbidity and mortality. Age-associated changes in T cell subpopulations include greater proportion of memory-phenotype CD4⁺CD45RO⁺ T cells, fewer naïve CD4⁺CD45RA⁺ cells and lower expression of the costimulatory CD28⁺ marker [16]. The important costimulatory receptor CD28 is the closest biomarker of ageing for human lymphocytes. Th2 pathway is activated during early life, Th1 phenotype predominates later and in elderly Th2 phenotype may again emerge [16]. This phenotype concerns blood cells, while fibroblasts have an immortality profile [16]. With age, telomere loss is 33 bp/year for CD4 T cells and 26bp for CD8 cells and 15 - 19 bp/year for B cells. B cells have a lower degree of shortening [12]. Rates of telomere shortening were found to be more rapid from birth to 4 years of age, with gradual shortening between 4 - 39 years and relatively stable between 40 - 95 years [2].

Immunodeficiencies related to telomere length

The immune system is a biological system in which constant self-renewal is of utmost importance and which consequently is dependent on efficient telomere maintenance. Association of accelerated telomere loss compared to matched controls has already been confirmed in many syndromes with immune dysregulation, such as Down syndrome. Immunodeficiencies connected with dysfunction of telomeres are dyskeratosis congenita, genetic disorders involving DNA repair and disorders involving the VDJ recombination [3]. The X-linked lymphoproliferative syndrome is also described.

Dyskeratosis congenita

Dyskeratosis congenita is a rare premature aging syndrome with short telomeres. The disease is characterized by functional failure of tissues with rapidly dividing cells, as those of the skin, mucosa and hematopoietic system. The diagnostic triad of mucocutaneous abnormalities, bone marrow failure due to chromosome instability and predisposition to certain types of malignancies is typical of the disease. Suggestive of the diagnosis are reticulated atrophic telangiectatic hyper and hypopigmented skin, oral leukoplakia and darker than usual palms and soles [17]. Lacrimal stenosis is investigated in 80% of cases (OMIM). Dyskeratosis congenital is clinically very heterogeneous and may manifest with a variable other somatic abnormalities such as dental, gastrointestinal, genitourinary, neurological, ophthalmic,

pulmonary and skeletal [18]. The clinical spectrum varies from severely affected individuals in the 1st decade of life to asymptomatic patients with only a few changes in blood cell counts [11]. Aplastic anaemia occurs in > 90% of cases and it is the principal cause of mortality [18]. Increased cell cycle and chromosome breaks to bleomycin resembling Fanconi anaemia are found. Cancer is an important feature described in leukoplakia lesions, blood cells, pulmonary and gastrointestinal tract.

The etiology of the syndrome is the inherited defects of the telomerase complex [19]. It has two genetic forms: the X-linked and autosomal dominant and recessive [20]. The X-linked form is caused by mutations in the gene encoding dyskerin (DKC1, Xq28), a protein implicated in both ribosomal RNA processing, which reduces the levels of TA repeats of telomeres and leads to premature telomere shortening due to telomerase dysfunction [21,22]. The autosomal form is caused by mutations of the RNA component of telomerase, TERC (3q26.2) and TERT (5p15.33) [21]. Missense mutations are identified in the TERT gene and deletions in the TERC gene [11]. The null allele is lethal in humans. Altogether these aberrations are found in 50% of patients [11]. These syndromes represent the 1, 5% of patients with aplastic anaemia. They strongly point out the strong association between bone marrow failure syndromes and telomere biology [11]. After bone marrow transplantation for aplastic anaemia, patients usually develop many complications, such as fatal vascular allograft rejection and radio- and chemotherapy complications due their sensitization. The disease is regarded as good candidate for gene therapy, because it is a single gene disorder; mortality is caused by bone marrow failure and hematopoietic cells are good targets with selective advantage (OMIM).

A variant form of dyskeratosis congenital is Hoyeraal-Hreidarsson syndrome, with usually missense mutations in DKC1 gene. The syndrome is characterized by prenatal onset of growth retardation, cerebellar hypoplasia, microcephaly, mental retardation, progressive bone marrow failure and immunodeficiency [23]. It resembles infants with TORCH syndrome. Progressive combined immunodeficiency is a recognizable feature of the syndrome and hypogammaglobulinemia and lymphocyte abnormalities are found, including lymphopenia, B-cell depletion, and T cell dysfunction [23].

Genetic disorders involving DNA repair

DNA repair diseases are caused by defects in genes, members of the RecQ family of DNA helicases and they are associated with increased genomic instability and predisposition to cancer. Werner syndrome is a human premature aging disorder displaying cellular defects associated with telomere maintenance, including genomic stability, premature senescence and accelerated telomere erosion [9]. It is an autosomal recessive disease characterized by early onset and increased frequency of age-related features, including greying and loss of hair, atherosclerosis, cataracts, diabetes mellitus and cancer. The etiology of this phenotype is loss of function of the WRN gene (8p12) having a helicase and exonuclease function [9]. In human cells, WRN protein co-localizes and physically interacts with the telomere TRF2 protein [9]. This protein is implicated in alternative telomere elongation [9]. Loss of WRN function increases occurrence of free telomeric ends that could either join to form chromosomal fusions or activate checkpoint pathways and trigger senescence or apoptosis [3]. Cells of the patients show elevated levels of DNA deletions, translocations, chromosomal breaks and display replicative defects including an extended S-phase and premature senescence [9]. During long term culture of Epstein Barr virus infected cells, some Werner cell lines showed rapid telomere shortening, while others showed telomere lengthening. Further, these B-cell lines reached replicative senescence at a wide range of telomere lengths [2]. This suggests that different mechanisms derive Werner cells to senescence or apoptosis [2].

Bloom syndrome is associated with intrauterine retardation, low height, telangiectatic rash on the face and extremities, sun sensitivity and immunodeficiency. Immunodeficiency is characterized by low IgM and NK dysfunction. BLM syndrome protein has similarities with WRN protein. It has an ATPase and helicase activity.

Rothmund Thomson is characterized by hyperpigmentation, failure to thrive, skeletal abnormalities, cataracts and premature aging. Although it exists genetic heterogeneity, mutations in RECQL4 gene are found in 40 - 66% of patients.

Fanconi's anaemia is characterized by pancytopenia in early life accompanied by abnormalities of growth and development, susceptibility to cancer and skeletal, cardiac, gastrointestinal, urogenital system anomalies by a characteristic face (microphthalmus, micrognathia, and epicanthus). Approximately 50% of patients have radial abnormalities (absent or bifid radii and thumbs). Immunodeficiency is manifested by neutropenia and decreased NK cytotoxicity. Diagnosis is confirmed by examination of chromosomes in peripheral blood lymphocytes after exposure to agents such as diepoxybutane or mitomycin (OMIM). The FA/BRCA pathway is involved in the repair of DNA damage (OMIM). Raised oxidative stress sensitivity of Fanconi anaemia cells leads to an increased cell turnover and chronologically accelerated telomere shortening [23,24]. Fanconi anaemia is consistent of 15 different complementary groups.

Ataxia telangiectasia and Nijmegen syndrome are congenital disorders characterized by hypersensitivity to ionizing radiation, immunodeficiency and predisposition to certain malignancies. Both syndromes involve the pathway of DNA damage-triggered signal transduction to p53 activation and checkpoint arrest. T cells of the patients have shorter telomeres consistent with a greater rate of cell turnover due to unrepaired genome damage [1].

Ataxia-telangiectasia is an autosomal recessive disorder involving cerebellar degeneration, oculocutaneous telangiectasia and it is considered to be a progeria disease. The important characteristic features of the disease are immunodeficiency, radio sensitivity and predisposition to cancer. Recurrent Sino pulmonary infections are also common. Laboratory findings of the syndrome is the high frequency of 7, 14 aberrations after radiation, increased level of a fetoprotein and CEA and hypogammaglobulinemia, especially of IgA, IgE and IgG2. One third of patients manifest lymphopenia mainly of the T cell compartment decreased CD4/CD8 ratio and increased number of memory T cells with $\gamma\delta$ expression. Lymphocytes function tests are abnormal. The immunological manifestations are due to dysfunction of thymus and V (D) J abnormalities. ATM is a protein kinase activated in response to double strand breaks and is thought to be essential for maintaining chromosomal stability and telomere integrity [25]. It is a major caretaker of the genome. Several reports point out that ATM may have a critical role in activating defence mechanisms against oxidative stress [25]. ATM deficient cells were found to lose telomeric sequences at significant higher rates than normal cells under usual levels of free oxygen radicals [25]. ATM has a role in the repair of DNA lesions at terminal positions in telomeric DNA [2]. Recent studies have shown that ATM and p53 can function as DNA damage check points and trigger apoptotic responses [2]. Expression of telomerase increases telomere length, but does not rescue telomere dysfunction [1].

Nijmegen-breakage syndrome is associated with features overlapping with ataxia telangiectasia. Patients display a characteristic facial appearance, microcephaly and growth retardation [24]. Hypogammaglobulinemia, particularly IgA and IgG subclass deficiency and impaired specific antibody responses are found. Mild to moderate lymphopenia is present with impaired in vitro proliferation responses to mitogens [23]. Patients manifest radio sensitivity, chromosome instability and predisposition to cancer [23].

Disorders of VJD recombination

Some disorders of VJD recombination are associated with telomere dysregulation. VDJ recombination is a process by which the germ line V, D and J segments are assembled to complete Ig and TCR variable region genes. Double strand breaks (DSB) are the initial step of this complex progress. Normal DSB are repaired by one or two pathways, homologous recombination and non-homologous end joining. The second pathway is completed by the enzymes Ku70, Ku80, XRCC4, DNA ligase 4, DNA-PKcs and Artemis. Besides recombination these enzymes reveal genomic stability and they have a protective role in telomeric end-capping. Deficiency of Ku70, Ku80, XRCC4 and DNA ligase-4 leads to growth deficiency, severe combined immunodeficiency (SCID) and increased neuronal apoptosis [1,2]. The Ku70, ku80 heterodimer functions at double strand breaks and telomeres. It contributes to telomere length regulation, telomeric chromatin structure and protects from homologous recombination [23]. DNA ligase IV is involved in non-homologous recombination and the clinical phenotype is associated with growth retardation, developmental delay, cytopenia and immunodeficiency due to hypogammaglobulinemia and polysaccharide antibody deficiency [23]. Although precise function is unclear, it seems that Artemis-DNA-PKcs complex is recognized to have a significant role in DNA repair and in telomere maintenance. Defects in Artemis gene are associated with severe combined immunodeficiency, although a milder phenotype, with lymphopenia, hypogammaglobulinemia and recurrent sinopulmonary infections occurs [23]. Telomere dysfunction is reported to contribute to the characteristic radiation sensitivity of the cells with Artemis immunodeficiency.

Artemis protein is a major genomic caretaker protein, required for repair of bleomycin-induced DNA double strand breaks and for maintenance of chromosomal stability including telomeric fusions [26,27]. Knock out mice with SCID due to DNA-PK mutations exhibit longer telomeres suggesting that this protein is involved in regulation of telomere length. Mutations of the gene leads to immunodeficiency, chromosomal aberrations, and gene mutations, telomeric end capping failure and cancer predisposition [28]. Decreased levels of DNA-PK activity has been found in human cancers including breast, lung and colon cancer. The gene is a suppressor of mutagenesis and telomere dysfunction [29].

X-linked lymphoproliferative syndrome

Finally, X-linked lymphoproliferative syndrome or Duncan's disease is a combined immunodeficiency appearing after Epstein Barr infection. The healthy otherwise patients manifest fulminant mononucleosis in 60% of cases or dysgammaglobulinemia (increased IgM, subclass deficiency) and lymphoma. The responsible gene SH2B3 (Xq25) produces SH2B3 protein, which is a T cell receptor that induces B cell proliferation. Patients with the disease exhibited CD8+ T cells with limited residual proliferative capacity secondary to telomerase down regulation and also reduced capacity to expand after stimulation. This contributes to defective Epstein Barr immunosurveillance and the development of related lymphomas. Excessive proliferation due to SAP defect leads to accelerated loss of telomeres in these cells [30].

Telomere length in chronic infection and autoimmunity

Premature telomere loss has been described in cases of increased proliferative demand such the one in chronic infection (example chronic hepatitis). HIV infection, an acquired immunodeficiency, has been associated with substantial loss of telomere length in the CD8+ subset of T lymphocytes [1]. In contrast CD4+ T cells have slightly longer telomeres than HIV negative donors. These results suggest that HIV infection is associated with alteration in the dynamics of telomeres of T cells [6].

Another interesting concept recently being investigated is that chronic immune stimulation may lead to premature aging of the immune system. Higher oxidative stress, lower basal level of telomerase activity and shorter telomere length of peripheral blood cells are found in chronically stressed individuals like the ones with mood disorders [1]. *In vitro*, these persons have lower T cell proliferation and higher production of immune regulatory cytokines (TNF- α , IL-10) in response to stimulation [1].

At the present, increasing evidence indicates that autoantibody production and B cell hyperactivity characteristic of systemic lupus erythematosus (SLE) is T cell driven and has been documented that CD4+ T cells have a central role in SLE pathogenesis. Accelerated telomere shortening is seen primarily in CD4+ T cell subsets, whereas CD8+ cells exhibited increased telomerase activity [31]. It is suspected that there is an oligoclonal population of CD4+ cells that drive B cell production of autoantibodies, which is unresponsive to down regulatory mechanisms. These cells are in a state of replicative senescence, but they can produce harmful cytokines [31]. In patients with rheumatoid arthritis naïve and memory T cells have a premature shortening of telomeres that precedes physiologic age-dependent telomere erosion by approximately 25 years [31]. It is indicated that the survival and replication of hematopoietic precursors is influenced by HLA-DR polymorphisms responsible for rheumatoid arthritis. It is proposed that HLA-DR+ individuals could be particularly sensitive to certain infections that impose excessive proliferative stress on hematopoietic system and thereby they set the stage for developing rheumatoid arthritis [31]. In rheumatoid arthritis, the diversity of TCR receptor is contracted. Va24+ NKT cells have been found reduced in elderly humans and in patients with rheumatoid arthritis and systemic lupus [14]. Further studies implicating telomere length will enlighten our knowledge of immune regulation and development of autoimmunity.

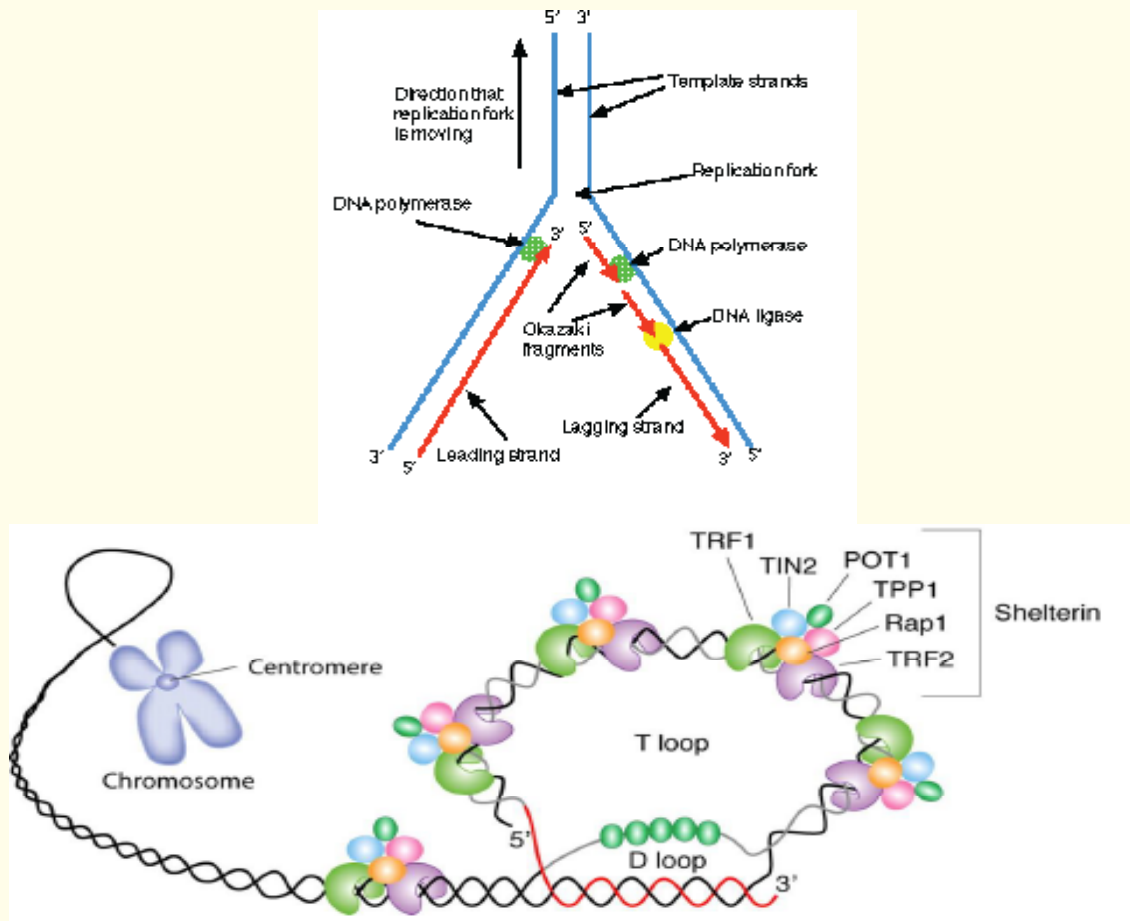


Figure 1: Structure of telomeres.

Conclusion

In conclusion, it is obvious that telomere maintenance is critical for hematopoietic cells with immune function. Although, telomere length is under aging mechanisms, it still gathers its auto replicative capacity, through telomerase up regulation. Genetic syndromes responsible for premature aging are connected with telomere dysfunction. Autoimmunity is also connected with altered telomere attrition. Further investigation will enlighten these disorders and possibly confer new therapeutic intervention.

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