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Telomeres and immune competency

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Abstract

Telomeres are essential for the integrity of chromosomes and for cellular replication. Attrition of telomeres occurs during DNA replication due to the inability of conventional DNA polymerase to replicate chromosomal termini and the insufficient compensation for telomere loss by telomerase, an enzyme that synthesizes telomeric DNA. A number of genetic defects have been described in humans and in animal models which cause accelerated telomere attrition, in turn leading to severe phenotypes of hematopoietic and other proliferating cells. Telomere length, most frequently measured as an average value in heterogeneous peripheral blood leukocyte populations in humans, has been associated with a wide range of health conditions and diseases of immune and non-immune cells. Here, we review recent studies of telomere length dynamics with particular relevance to immune function.

Introduction

The termini of linear chromosomes are called telomeres, consisting of an array of DNA repeats [(TTAGGG)_n in mammals] and a number of telomere binding proteins [1;2]. The incomplete replication of chromosomal ends during cell division results in loss of a small fraction of telomere DNA and makes telomere length a marker of the biological age of cells, tissues/organs, and probably of humans [3]. Telomeric DNA is synthesized by telomerase which maintains telomere function via compensating the loss of telomeric DNA resulting from cell-division. Telomerase consists of two core components: telomerase reverse transcriptase (TERT) and telomerase RNA template (TERC). Telomerase activity is tightly regulated as most mature cells express very little telomerase, with the exception of germline cells, stem cells, and lymphocytes.

Telomere length attrition has been well documented during continued *in vitro* replication of cultured human cells, including fibroblasts and lymphocytes [4;5]; and in leukocytes and fibroblasts with progressive age [6–8] both in normal individuals and at an accelerated rate in the presence of some genetic abnormalities, disease states, or environmental stressors [9–11]. A large body of research has established that intact telomere function is essential for cell proliferation and that impaired telomere maintenance has a severe detrimental impact for cells such as stem cells which rely on proliferation for their function.

Blood leukocytes are composed of multiple cell types that derive from two hematopoietic lineages. Myeloid derived cells include granulocytes (neutrophils, basophils and eosinophils) and monocytes/macrophages, whereas lymphoid derived cells include T cells,

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B cells, and NK cells. The proportions of these different cell types in blood undergo changes with age, including increased monocytes, decreased lymphocytes, a decrease in naïve lymphocytes, and an increase in memory lymphocytes [12]. Because the mature myeloid lineage cells are non-dividing cells, whereas mature lymphocytes undergo extensive cell division in mediating their function, telomere length measured for leukocytes reflect sums or averages over cells with potentially very different replicative histories. Furthermore, telomeres are on average longer in naïve than in memory T cells [4;7], and are longer in CD28⁺ than in more differentiated CD28⁻ CD8⁺ T cells [13]. Therefore, measuring telomeres in defined cell populations whenever possible will facilitate a more informative interpretation of results.

Defects in telomeres cause severe problems in hematopoietic and other systems

The *in vivo* role of telomeres in cellular replication is best demonstrated from the studies of genetic disorders that impair various components of telomerase and telomeres [9;10]. The first genetic disorder reported to be associated with short telomeres is *Dyskeritosis congenita* (DC), a rare syndrome with abnormalities of the skin, nails, mucous membranes, and bone marrow [14]. A number of different genetic mutations in components of either telomerase ribonucleoprotein complex (DKC1, TERT, TERC, NOP10, and NHP2) or telomere binding protein-associated protein (TIN2) have been subsequently found in DC families [9;14]. In addition, genetic mutations of telomerase components, with consequent short telomeres, have also been found in association with idiopathic fibrosis of lung [15], fibrosis/cirrhosis of liver [16;17], and hereditary cancer risk [18]. Together, these mutations show defects in the maintenance of telomere maintenance (short telomeres), accompanied by replicative dysfunction in stem cells [19], the hematopoietic system (bone marrow failure) [20], lung (idiopathic pulmonary fibrosis) and liver (cirrhosis), and predisposition of cancer.

A striking feature of these genetic defects and diseases is the phenomenon of genetic anticipation. This is the appearance of progressively shorter telomeres in DC patients and earlier onset of disease manifestations from generation to generation within the same family. It is telomere length, in the presence of an identical genetic mutation, that appears to explain an earlier onset age and severity of the disease in later generations. Thus, genetic and clinical evidence indicates that short telomeres cause genomic instability and lead to cellular dysfunction in those highly proliferative tissues and organs [9;10].

Short telomeres of leukocytes associated with aging and immune dysfunctions

Cellular proliferation is a key component of an effective adaptive immune response. Therefore, the role of telomeres in leukocytes, particularly in lymphocytes, is of great interest [21]. A number of intriguing observations have indicated that a shortening of telomeres occurs in cells of the human immune system as a function of *in vivo* lineage differentiation and with aging, as well as during *in vitro* culture. The loss of telomeres has been observed during naïve T cell differentiation to memory T cells [4;7], during CD28⁺ to CD28⁻ CD8 T cell differentiation [13], in long-term cultured T cells [4;5], and in chronic viral infections [22]. In the cultured CD8 T cells, significantly shortened telomeres appear to be to cause senescence as the ectopic expression of telomerase is capable of rescue telomere shortening and prolong their proliferation [23]. Furthermore, cross-sectional analyses show that telomere shortening occurs in leukocytes or PBMC and in isolated granulocytes and lymphocytes (CD4, CD8 T cells and B cells) with age [6–8]. Collectively, these findings show that telomere attrition occurs in blood leukocytes of both myeloid and lymphoid

lineages, and that telomere length associates with leukocyte differentiation and age. However, the degree to which telomere attrition contributes to the overall decline of immune function with age remains to be determined.

Short telomeres of leukocytes or PBMC have also been described in association with a number of immune-related diseases [24]. Patients with some common autoimmune syndromes including rheumatoid arthritis [25], and diabetes mellitus (type 1 and type 2) [26;27] display significantly shortened telomeres in leukocytes or PBMC compared to age-matched healthy controls. In addition, patients with viral infections including HIV, EBV, and CMV undergo extensive proliferative response of T cells in response to these infections, and it has been observed that viral reactive T cells have short telomeres associated with replicative impairment [22;28]. A common pathological basis of these immune dysfunctions is the extensive proliferation of lymphocytes, leading to the exhaustion of telomeres and replicative potential.

Finally, short telomeres of leukocytes or PBMC are also found in patients with malignancies and as a risk factor for some type of tumors, whether or not the malignancies are of immune cell lineages [29] or other cell types [30]. In malignancies of immune cell origin such as leukemia, it is currently unclear whether short telomeres contribute causally to leukemia pathogenesis or are the consequence of extensive proliferation of tumor cells, or both. Even less is known about the cause of short telomeres of leukocytes or PBMC in patients with tumors of non-immune cells. Whether the burden of tumor bearing affects immune cell function, and more specifically how telomere maintenance is affected requires further study. Nevertheless, these findings suggest that telomere shortening may be a cause and/or a consequence of immune cell dysfunction.

Some known factors influencing telomere lengths in blood leukocytes

An increasing number of publications in recent years show that various physiological and/or psychological factors have an impact on overall health as well as an effect on telomere length of peripheral blood leukocytes [31–36]. Early studies showed an association of sustained stress, such as that experienced by the mothers of sick children or the caregivers of Alzheimer's diseases, with short telomere length in leukocytes or PBMC compared to healthy controls [31;32]. Individuals with major depression over a long period of time have also been reported to have shorter telomeres in leukocytes than healthy controls [33]. More recently, short telomeres have also been found in the offspring of mothers who had experienced a severe stressor in the index pregnancy, suggesting that prenatal stress exposure is linked to subsequent shorter telomere length in offspring [34]. Other studies have shown that a healthy lifestyle such as exercise, healthy weight, lower meat and higher fruit/vegetable consumption is linked to longer telomeres of leukocytes [35] whereas obesity is associated with shorter telomeres [36]. It has further been suggested that a sustained healthy lifestyle may even attenuate the effect of stressors on telomere length [37].

These epidemiological analyses of mostly case-control studies reveal a correlative link between telomere length of leukocytes and various health conditions. Considering that telomere length is highly polymorphic in the population, a large sample size and preferably a longitudinal follow-up will be needed to further test these findings. More importantly, it will be critical to understanding the underlying mechanism of these correlative findings. Do these physiological and/or psychological factors affect the length of telomeres by actual shortening/lengthening of telomeres in leukocytes, or do they alter telomere length in heterogeneous leukocyte populations by altering the relative proportions of different cell types known to differ in telomere length? A parallel analysis of telomere length and leukocyte composition, or more rigorously still, a direct analysis of telomere length in

leukocyte subsets with longitudinal follow-up may provide some answers. Only limited studies to date have carried out any longitudinal analysis of leukocyte subsets [8], and still more refined subpopulation analysis will be necessary to better define the potentially complex effects of telomere length change. It has also been suggested that the length of individual telomeres in a cell, rather than the overall average of telomere length, may be important to function [38]. It remains to be determined whether this is in fact relevant to normal and pathological human conditions. As noted in the summary of available methodologies, measurement of this parameter remains highly challenging in human population studies.

Comprehensive assessment of immune function including telomere length

Whether telomere length of leukocytes can be a useful parameter for predicting health and diseases is a subject of current debate [39;40]. Here we focus on whether telomere length of leukocyte or PBMC is a useful measure for assessing the competence of immune system function. From the study of genetic syndromes of telomere/telomerase dysfunction that were described above, there is little question that telomere length can influence bone marrow function. However, it remains to be determined whether there are measurable effects of telomere length on immune function, either with normal aging, during normal immune responses, or in defined pathologic states.

It has been shown that patients with various genetic defects in telomere maintenance have leukocyte/PBMC telomere length in the lower 10% of the age-matched normal population [41]. Therefore, telomere length equal to the lower 10% or 5% in a population of a given age could be used as an operational criterion of short telomeres (Figure 1). Considering the variation of telomere length in populations, applying this criterion requires establishing a standard telomere length range of leukocytes and/or PBMC in the normal population and its change with age. As telomere length of leukocytes and PBMC is dynamic [42;43], repeated measurements of telomere length over time (months to years) is necessary to accurately determine the rate of telomere length change, a parameter that has critical value in assessing the telomere status in addition to the absolute length.

Considering the heterogeneous nature of cell lineages, types, and proliferative history, and the heterogeneity of telomere length on individual chromosomes within a cell, the measurement of average telomere length of heterogeneous cell populations alone is likely to be insufficient for assessing immune competence. As the adaptive immune response is antigen-specific, an average telomere length does not always predict the telomere length of those antigen-reactive lymphocytes which represent a small percentage of total lymphocytes. The most specific assessment of telomere function in a specific response thus must be conducted by analysis of antigen-specific populations. A more comprehensive assessment of immune function in human must also include other measures, such as detailed analysis of composition of different cell type such as monocytes and lymphocytes, and the relative percentages of naïve, effector, and memory cells, and levels of cytokine/chemokines [44]. Integrating these measures will reveal new insight into the human immune system and its change with age (Table 1). This in turn will help to further assess how telomere length may contribute in predicting immune competency.

Potential applications of telomere length measurement in leukocytes

What is the usefulness of knowing one's telomere length of leukocytes? First, identifying individuals, children in particular, with short telomeres may reveal genetic defects of telomere maintenance and allow early diagnosis prior to development of the typical phenotype. Second, individuals with short telomeres but without any known genetic defects may need additional follow-up measurements and observation to determine if they develop

any symptoms due to currently unknown mutations or not. Third, it may be feasible to use pharmacological agents to enhance telomere length and reduce telomere attrition for those adults who have short telomeres. Recent *in vitro* studies show that telomerase activator (TAT2) modestly retards telomere shortening and increases proliferative potential of CD8 T cells [45] and that inhibition of mitogen-activated protein kinase (p38) enhances telomerase activity and survival after TCR activation [46], suggesting that enhancing telomerase activity in immune cells by a pharmacological approach could restore or improve immune function that is limited by the telomeres in genetic disorders as well as in aging.

Vaccination and immunization has been perhaps the most cost-effective intervention in modern medicine. Regardless of what type or kind of vaccine, often some individuals do not respond well to the vaccine which could be due to different possible reasons. Dysfunctional telomeres may be a contributing factor. As observed in various chronic viral infections, repeated stimulation causes extended proliferation and short telomeres of antigen-specific T cells, which eventually leads to exhaustion [22;28;47]. Since a successful immune response to a vaccine requires substantial division of naïve lymphocytes, individuals with short telomeres may be susceptible to exhaustion of these vaccine reactive lymphocytes, limiting their ability to respond to an eventual real encounter with a pathogen [47]. This is of particular relevance to the vaccination of the elderly. Older adults (over 75 years old) have diminishing numbers of naïve lymphocytes, the primary target cells for an effective vaccination, and have limited residual replicative capacity due to generally short telomeres of their lymphocytes. It has been observed that the efficacy of seasonal influenza vaccine shows an inverse correlation with age in this elderly population (the efficacy is measured by the frequency of antibody conversion in sera: 50% from 60–70 years old, 31% from 70–80, and 11% after 80 years old) [48]. Although it remains to be directly determined whether short telomere length of lymphocytes in the elderly contributes to their decline of vaccine response, these observations suggest that a comprehensive assessment of immune function including the measurement of telomere length might be informative prior to giving a vaccine to the elderly. For those elderly with immune function limited by lymphocyte exhaustion, which can be the result of telomere shortening, active immunization may be of limited efficacy, and passive immunization strategies may be more effective. Therefore, developing the protective antibodies against influenza and other viruses with broad specificity will be a useful alternative for those elderly [49].

Concluding remarks

A plethora of data has been generated in characterizing the role of telomeres in cell proliferation, in identifying factors influencing telomere length regulation, and in demonstrating an association of telomere length with various health and abnormal conditions. Studies of genetic abnormalities associated with telomere impairment demonstrate a critical role of telomeres in proliferation of stem cells. It is conceivable that shortened telomeres in lymphocytes will have a detrimental impact on their ability to combat pathogens which requires their robust proliferation. Studies of chronic viral infection show that exhausted viral reactive T cells have very short telomeres while other T cells have normal telomere length [22;28], suggesting that telomere shortening may limit T cell function in antigen-dependent and antigen-specific manner. Thus, lymphocytes with short telomeres will have reduced ability to mount a strong and sustained immune response.

Like many biological parameters, telomere length in peripheral blood is an average value of different chromosomes within a cell and of a heterogeneous population of cells. It is therefore not a precise reading with high specificity and resolution. Nevertheless, such measurements may reflect a general status, which will be useful as an initial screening test. Longitudinal monitoring of telomere length will be of particular importance in providing a

dynamic picture of telomere length change over time, which is equally important in predicting the immune cell function as the absolute telomere length. Longitudinal measurement of telomere length in combination with other immune parameters may offer valuable information in analyzing of the status of immune function across the age range, in children, adult, and elderly.

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Highlights

- Telomeres are essential for the integrity of chromosomes and for cellular replication.
- Attrition of telomeres in leukocytes occurs during DNA replication and observed with aging.
- A number of genetic defects cause accelerated telomere attrition and severe phenotypes of hematopoietic and other proliferating cells.
- Telomere length, an average value in heterogeneous peripheral blood leukocyte populations, has been associated with a wide range of health conditions and diseases of immune and non-immune cells.
- Telomere length in leukocytes in combination with other measurements can be used for evaluation of immune function, which will have clinical implications.

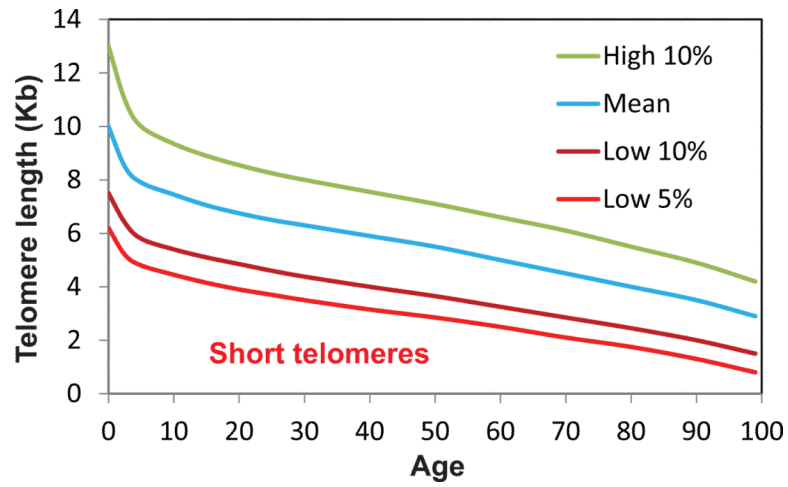


Figure 1. Distribution and attrition of telomere length in human leukocytes with age. Telomere length is highly polymorphic in the general population. The distributions of telomere length with age are presented as percentages (modified based on [41]).

Table 1

Suggested panel of tests for evaluating the status of human immune function

Test	Method
Blood cell counts of all types of leukocytes	CBC
Telomere length of leukocytes or PBMC	qPCR or Flow-FISH
Leukocyte composition including lymphocyte subsets	Multi-color flow cytometry
Serum cytokine profile	Multiplex assay