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Mini Review

Telomeres, immune aging and autoimmunity

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Abstract

Telomere length is important in constraining the replicative potential of cells; cellular systems that are dependent on cell replenishment for renewal or on cell proliferation for functionality are highly sensitive to telomeric erosion. Cell replication invariably leads to telomere loss, which, in some cellular systems, is partially compensated for by telomerase activity. In addition to this typical telomere loss, several mechanisms of sporadic telomere loss exist. Heterogeneity in age-dependent telomere loss can be a consequence of increased cellular turnover during a lifetime, accelerated telomeric DNA damage, or defects in telomere repair. The immune system is a prime example of a highly dynamic cellular system, for which telomere maintenance is pivotal. Immune competence is strictly dependent on rapid expansions of clonal T- and B-cell populations, and telomere loss may contribute to defective immune responses in the elderly. Equally interestingly, accelerated T-cell aging combined with telomeric shortening may predispose for autoimmune responses and thereby explain the increased susceptibility for chronic inflammatory diseases in the elderly.

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Keywords: Telomere; Telomerase; T cell; B cell; Immunosenescence; Premature aging syndrome

1. Introduction

A prerequisite to successful aging is good maintenance. Nature has committed considerable resources to repair, in particular in complex multicellular organisms; the success and longevity of an organism requires balancing the resources committed to maintenance and repair with the need to provide for effector functions. On a cellular level, enzymatic machineries exist to prevent and repair damage; their sole purpose is to maintain and restore genomic integrity (Hasty et al., 2003). Even if irreparable damage has been inflicted, cells can survive and sustain some functionality while being rendered senescent. Cellular senescence limits proliferative potential, thereby preventing the propagation of detrimental errors and, depending on the cell type, is associated with shifts in gene expression that can be harmful (Krtolica et al., 2001; Vallejo et al., 2004). However, these shifts involve only a minority of the expressed genes and many effector functions are therefore maintained (Fann et al., 2005).

Complex organisms have evolved additional supracellular mechanisms, which allow self-repair and renewal. Such organisms have a pool of proliferating precursor cells that provide a source for continuous cell replacements within differentiated post-mitotic tissues. In the immune system and possibly also in other organ systems, the ability for cells to die by apoptosis and subsequently make space for replacement is central to longevity (Hsu et al., 2005). Turnover rates vary widely between different somatic tissues, with epithelial cells and bone marrow-derived cells at the extreme of the spectrum.

The option of tissue renewal by mitotic cells brings with it the risk of hyperproliferative diseases. In its more benign form, such diseases can lead to organ failure; for example, proliferation of vascular myofibroblasts can lead to intimal occlusion, or proliferation of mesenchymal cells in the lung can impair diffusion capacity. In its extreme forms, uncontrolled cell growth is characteristic for malignant diseases where cell proliferation sets the stage for acquiring and propagating somatic DNA mutations.

One important mechanism that limits the proliferative potential of individual cells is the erosion of telomeres. Telomeres are chromatin structures that cap and protect the end

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of chromosomes. In vertebrates, they are formed by tandem repeats of hexamer sequences (TTAGGG) that are associated with various specific proteins. With self-replication, telomeres lose TTAGGG repeats because conventional DNA polymerases are not able to completely replicate linear chromosomes (Lansdorp, 2005). As a result, telomere erosion has been considered a mitotic clock, with the telomere length approximately reflecting the life history of divisions of individual cells. Progressive telomere shortening has detrimental implications; chromosome caps are unprotected, which leads to chromosome instability, fusion, and cell death (Blackburn, 2001; McEachern et al., 2000). However, in normal cells, telomere erosion initiates a cell senescence program which prevents further divisions, thereby protecting cells from excessive telomere loss and cell death (Blackburn, 2001; McEachern et al., 2000).

In addition to the extent of telomere erosion, the original baseline telomere length determines the biological consequences of cell proliferation. Interestingly, the telomere length varies tremendously between various species. Mice have relatively long telomeres and therefore do not experience any biologically significant telomere erosion within their lifespan. Experiments in telomerase knockout mice have shown that it takes several generations until consequences such as infertility are being observed (Blasco et al., 1997). In contrast, humans have relatively short telomeres, and telomere erosion impacts cell function during aging. Inverse relationships between telomere length and age have been shown for several cell compartments including vascular endothelium cells (Chang and Harley, 1995) and hematopoietic cells (Hastie et al., 1990). Telomere length of human peripheral blood cells appears to be a predictive marker of age-dependent mortality (Cawthon et al., 2003).

2. Mechanisms of telomere shortening

In the conventional model, telomere loss is considered to be a consequence of the end-replication problem and is, accordingly, strictly linked to cell replication (Olovnikov, 1973). DNA polymerase fails to replicate the 3' end of the chromosome; newly formed DNA strands have a small gap where the RNA primer used for the initiation of DNA replication was formerly bound. Telomere loss is counteracted by the activity of telomerase, a multimolecular complex that is able to extend telomeric DNA (McEachern et al., 2000). Telomerase activity is particularly evident in cell types that heavily depend on successful replication and that function in self-renewal, such as sperm cells (Wright et al., 1996), stem cells (Elwood, 2004), or activated lymphocytes (Hodes et al., 2002); some telomerase activity is transiently expressed during the S-phase in most somatic cells (Masutomi et al., 2003) and is critical for cell cycle transit and for preventing or delaying cellular senescence. With the exceptions of sperm cells and tumors, telomerase is only able to slow down but not fully compensate telomere loss even in those cells that have a high expression level of the enzyme complex (Elwood, 2004; Hodes et al., 2002).

Estimates in several organisms have suggested a loss of about 10 bp with each cell cycle that can be attributed to the end replication problem in the absence of telomerase activity (Lansdorp, 2005). This is much less than the 50–200 bp telomere attrition that has been measured in various human cells with each division. Also, end-replication-dependent telomere erosion should equally affect all chromosomes. However, single telomere length analysis of individual chromosomes have demonstrated a high degree of heterogeneity, which was partially explained by inter-allelic differences imposed by maintaining zygotic telomere length differences (Baird et al., 2003). Superimposed on this, however, were occasional substantive changes in length, suggesting that additional mechanisms are influencing telomere length. These telomere attrition pathways, globally labeled as sporadic losses to distinguish them from the more general or typical loss associated with cell division, have attracted increasing interest and may be of particular importance for the aging process. Some of these mechanisms are closely related to cell replication, such as variable exonucleolytic processing of the C-rich template strand of the telomere or higher structures in the chromosome that interfere with DNA replication and hinder access for telomerase activity. A typical example is the deletion of G-rich sequences during replication that has been observed in both *Caenarhabditis elegans* and mice (Lansdorp, 2005).

Telomeres are also regions of the genome that are particularly sensitive to DNA damage. G-rich sequences are highly sensitive to oxidative damage, while the repair of oxidative damage by nucleotide excision is known to be less efficient in non-coding DNA regions (Lansdorp, 2005). It is conceivable that repair by homologous recombination is more complicated in telomeres because of the repeat nature of the sequences. Sister chromatid exchange, which is frequently found in telomeres, may be a convenient way of repair, consistent with the observation that telomeres are hot spots for recombination events. Age-dependent telomere shortening may therefore be significantly accelerated by DNA damage, replication errors, and failure to repair properly (Fig. 1). Accordingly, telomere length would not simply be a numerical measure of replicative history, but would be the complex result of numerous deterministic and stochastic events.

3. Telomere loss in the immune system

The immune system is a biological system in which constant self-renewal is of utmost importance and which is, consequently, highly dependent on efficient telomere maintenance. All cells of the immune system are derived from hematopoietic stem cells that can divide and differentiate throughout life. Hematopoietic stem cells have a high level of telomerase activity; however, they are not immune to telomere loss (Elwood, 2004). Serial adoptive transfer and passage studies of hematopoietic stem cells in mice have documented significant telomere shortening (Allsopp et al., 2003). Also, studies in humans have shown that the telomere length in neutrophils declines with age, with a loss of about 1000–2000 bp during

adulthood (Robertson et al., 2000). Neutrophils undergo few divisions during differentiation from hematopoietic stem cells and do not divide as mature cells, thereby providing a valid estimate of the telomere length in stem cells.

It is reasonable to expect that telomere shortening in stem cells has a negative impact on the renewal potential of hematopoietic lineages with age, although direct proof for this assumption is still lacking.

Renewal of T-lymphocytes is unique and distinct from other hematopoietic cell lineages because it includes the bottleneck of thymic activity controlling T-cell development. Thymic function progressively declines with age, is already low during early adulthood, and is likely to be completely insignificant in most individuals after the age of 40 years. Thymic function depends on the presence of hematopoietic stem cell-derived precursor cells and the functional activity of thymic epithelial cells. Thymic degeneration is a complex process, and it is unclear which, if any, role the availability of precursor cells has. It is of interest to note that the thymus has a high degree of telomerase activity (Weng et al., 1996). Telomere lengths of newly generated T cells are, correspondingly, not only determined by the telomere length of the hematopoietic stem cells, but also by the efficacy of telomere elongation mechanisms in thymocytes. It is currently unclear whether there is any evolutionary benefit associated with the age-dependent demise of thymic function and why nature has introduced this additional control mechanism in the renewal of naïve T cells.

T-cell renewal during adult life therefore largely depends on the homeostatic proliferation of naïve T-cells. Irrespective of whether homeostatic proliferation is associated with any telomere elongation mechanism, the net effect is clearly that telomere loss and telomere lengths in naïve T cells progressively decline with age (Fig. 1) (Weng et al., 1995).

The T- and B-lymphocyte systems are unique in that proliferation is not only part of their self-renewal, but is also essentially incorporated in their biological function. The efficacy of an immunological response highly depends on the rapid clonal expansion of single antigen-specific T- and B-cell precursors. Antigen-specific CD4 and CD8 T cells undergo at least 10–15 population doublings within a few days after antigen stimulation. During infections, frequencies of antigen-specific T cells in the peripheral blood can increase from 1 in 50,000 cells to more than 1 in 100 cells of peripheral blood lymphocytes. This rapid expansion is followed by clonal contraction to generate a population of long-lived memory cells. To allow for the desired extent of clonal expansion, T cells, and also B cells have the ability to express telomerase (Hodes et al., 2002). In vitro studies have shown that naïve and memory T cells after T cell receptor-mediated stimulation have high levels of telomerase activity. In both populations, telomerase activity is rapidly lost in vitro with repeated restimulation (Weng et al., 1997). Several studies have shown that these findings hold up in vivo, and that CD4 (Hathcock et al., 1998), as well as CD8 (Maini et al., 1999), T cells expanded in antigen-specific responses express telomerase activity. Nevertheless, the clonal expansion takes its toll. Memory T cells generally have shorter telomere lengths (Weng et al., 1995), and senescent T cells that have been repeatedly stimulated in vivo and that are characterized by the loss of the CD28 molecule, have the shortest telomeres (Monteiro et al., 1996).

Peripheral blood mononuclear cells are a convenient tissue source for cross-sectional studies, and telomere length studies have been done in several human populations. Interestingly, telomere shortening has been described in a number of chronic inflammatory diseases (Fig. 2). Studies in patients with rheumatoid arthritis (Koetz et al., 2000; Schonland et al., 2003), scleroderma (Artlett et al., 1996), systemic lupus erythematosus (Honda et al., 2001), Wegener's granulomatosus (Vogt et al., 2003), insulin-dependent diabetes mellitus (Jeanclos et al., 1998), psoriasis (Wu et al., 2000), and atopic dermatitis (Wu et al., 2000) have shown telomeric erosion in peripheral blood mononuclear cells from patients compared to controls. The major cellular component of peripheral blood mononuclear cells is T cells, and the reduction in average

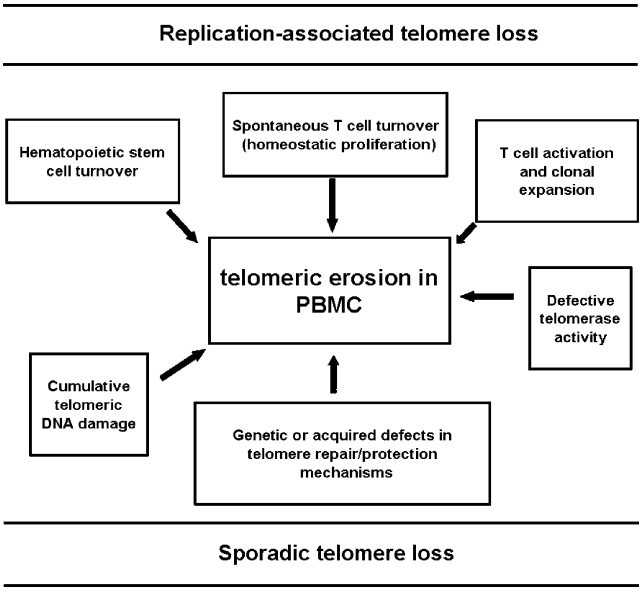

Fig. 1. Variables determining telomere loss in PBMC with age.

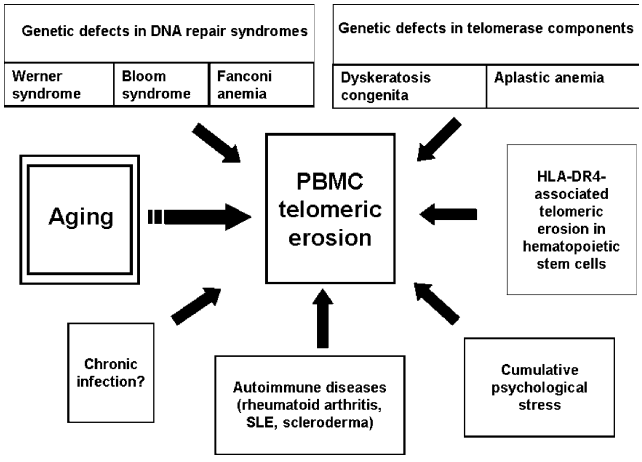

Fig. 2. Conditions and diseases associated with telomere erosion.

telomere length likely reflects this population. These findings have generally been interpreted as evidence of accelerated T-cell proliferation in the autoimmune process. Studies in scleroderma patients have, however, suggested that, while this mechanism may contribute to telomeric erosion in some diseases, this is certainly not the sole mechanism. Telomere loss was not limited only to patients with scleroderma, but was also found in their healthy family members. Accordingly, the authors have proposed that telomere loss is a genetically imposed risk factor leading to chromosomal instability and scleroderma (Artlett et al., 1996).

Studies in patients with rheumatoid arthritis have provided further evidence that the model of increased proliferation of autoreactive T cells is not the likely explanation for the observed telomere shortening. These studies have shown that telomere shortening is not only found in memory T cells, but also in naïve T cells. Moreover, patients with rheumatoid arthritis have decreased frequencies of T cell receptor excision circle-carrying T cells, indicating reduced T-cell output. One possible explanation for these findings is that increased homeostatic proliferation compensates for defective thymic output and that accelerated telomeric erosion is not a consequence of a chronic inflammatory process but of compensatory cell renewal. Subsequent studies have also shown that other hematopoietic stem cell-derived lineages have shortened telomeres in rheumatoid arthritis, suggesting that accelerated telomeric erosion occurs at least in part at the level of the stem cell. This phenomenon appears to be genetically determined and is inherited with the HLA-DR4 haplotype, one of the major disease-risk haplotypes of rheumatoid arthritis, as well as of some other autoimmune diseases, such as diabetes mellitus. The mechanisms responsible for the shorter telomeres appear to be confined to hematopoietic stem cell-derived cells and are not seen in other tissues, such as sperm. Telomere attrition in hematopoietic stem cells occurs between birth and young adulthood (Koetz et al., 2000; Schonland et al., 2003; Weyand and Goronzy, 2004). These examples show that common genetic factors and diseases lead to accelerated telomere erosion and consequently immune aging.

4. Insights from genetic models

Early studies have shown that age-dependent telomere shortening is highly variable. Various environmental stresses clearly can accelerate telomere shortening; obvious examples are chronic viral infection, but even chronic emotional stresses accelerate telomere shortening (Epel et al., 2004). As discussed earlier, it is debated whether telomere shortening in various autoimmune diseases is a primary defect or secondary to the activation of autoreactive immune responses. In addition to these environmental stressors, genetic factors are in part responsible for this heterogeneity. Twins have higher concordance in telomere length in peripheral blood mononuclear cells than do age-matched controls (Slagboom et al., 1994). Obviously and as already referred to above, genetic factors such as HLA-DR4 could influence telomere length by regulating hematopoietic stem cell turnover or could directly be involved in telomere maintenance and elongation. Given this complexity with common diseases or common genetic risk factors, genetic diseases that are associated with telomere shortening and have a monogenetic trait, have been insightful.

As one might have expected, several genetic diseases of premature aging have been correlated with telomerase defects (Fig. 2) (Blasco, 2005). The classical example is dyskeratosis congenita. These patients carry either mutation in the TERC gene (Mitchell et al., 1999) or in the dyskerin gene (Heiss et al., 1998). The TERC gene encodes for the telomerase RNA template that, together with the telomerase reverse transcriptase or TERT, forms the telomerase complex (McEachern et al., 2000), while dyskerin belongs to the group of proteins that stabilize the enzyme complex (Comolli et al., 2002). Patients with aplastic anemia have been found to have mutations in both the TERT (Yamaguchi et al., 2005) and TERC (Vulliamy et al., 2002) genes. Knockout mice have confirmed the importance of each of these three genes, although, as one would expect because of the longer telomere length in mice, several generations were needed before clinical manifestations were evident. A second group of genes that has been found to be abnormal in genetic diseases characterized by telomere shortening are DNA repair proteins. Examples of such diseases include Bloom syndrome and Werner syndrome, where genes involved in cross-link repair are mutated; and Fanconi anemia and ataxia telangiectasia (Blasco, 2005), both also caused by mutations in DNA repair proteins.

In addition to these genetic disorders, a number of mutations in molecules that are involved in DNA repair or in telomere regulation have been associated with telomere shortening in tumors. Studies of natural variants of all of these gene families in healthy populations have the potential of identifying genetic risk factors that predispose to accelerated telomere loss and aging and that are, in part, responsible for the huge variability of telomere length in cross-sectional studies.

5. Telomere loss—a direct instigator in age-related disease?

How much the length of telomeres directly determines the predisposition for age-dependent disease is a matter of debate. Experiments in the TERC and TERT knockout mice have clearly shown that telomere shortening acts as a tumor suppressor mechanism by inducing a senescent state with the up-regulation of p53 and several cell cycle inhibitors, such as p16 or p19ARF, consistent with the idea that short telomeres trigger a DNA damage response. The most striking finding in telomerase-deficient mice is a reduced incidence of cancer. Infertility after several generations is also a common phenomenon in those genetically modified mice, while other aging-related pathologies are variable and depend on additional alterations in the genetic background. An organ system in which telomere erosion should have direct clinical implications is the immune system. Obviously, telomere shortening in hematopoietic stem cells should reduce the hematopoietic reserve and limit regenerative capacity. Moreover, the adaptive immune system is highly dependent on the

rapid clonal expansion of antigen-specific T- and B-cells to maintain its functionality. In vitro studies have clearly shown that reduced telomere length correlates with limited expansion and reduction in maximal clonal size that can be reached during in vitro stimulation, supporting the concept that telomeric erosion affects the kinetics of primary and memory T-cell responses. This may be particularly relevant for the response of memory cells where telomeres already tend to be shorter. Also, virus-specific T cells that have been chronically stimulated in patients with persistent infection and that have lost replicative potential tend to have shorter telomeres. Such senescent cells show many phenotypic changes, and it remains to be determined whether the shorter telomeres or other changes are involved in limiting proliferative capacity (Vallejo et al., 2004). However, transfection experiments with telomerase genes could at least, in part, restore their proliferative ability (Rufer et al., 2001). Thus, critical telomere shortening could be partially responsible for the defective T-cell memory responses in elderly individuals (Akbar et al., 2004). Such critical telomere shortening could also explain the sudden contraction of the T-cell receptor repertoire that occurs between the ages of 65 and 75 and that may be caused by the accelerated apoptosis of aging lymphocytes (Goronzy and Weyand, 2005b; Naylor et al., 2005).

While a causative role of lymphocyte telomere shortening in defective immunocompetence is intuitive, it is more difficult to reconcile telomere shortening with susceptibility to autoimmune disease in a pathogenetic model. Epidemiological studies certainly support the notion that aging is a risk factor for autoimmunity; many of the autoimmune diseases are diseases of the post-menopausal adult and the elderly and, therefore, occur at a time when the immune system is functionally declining (Goronzy and Weyand, 2003; Goronzy and Weyand, 2005a). In general, the pathogenetic immune responses in such elderly patients with chronic inflammatory diseases are smoldering, and activation markers and T cell-derived cytokines by far do not reach the levels that are seen in infections or vaccinations of young adults. In fact, patient-derived T cells are less responsive to in vitro restimulation. It is possible that such autoimmune responses reach pathogenetic significance because they stay below the recognition threshold for triggering regulatory mechanisms. Response kinetics typical of the aging immune system could dodge control and tolerance mechanisms and be directly responsible for the chronic inflammatory response. In this model, telomere shortening, as well as other senescence mechanisms, would contribute to the pathogenesis of autoimmune disease.

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