Available online at www.sciencedirect.com
ScienceDirect
Mechanisms of Ageing and Development 129 (2008) 60–66
Mechanisms of Ageing and Development
www.elsevier.com/locate/mechagedev

Review

Telomere and adaptive immunity

Nan-ping Weng *

Laboratory of Immunology, National Institute on Aging, National Institutes of Health, 5600 Nathan Shock Drive, Baltimore, MD 21224, United States

Available online 8 December 2007

Abstract

The adaptive immune response relies on the ability of lymphocytes to undergo periodic massive expansion. It is an enigma how lymphocytes are able to undergo this seemingly unlimited number of cell divisions. Telomeres and telomerase play a critical role in regulation of the replicative lifespan of cells, providing a potential mechanism which lymphocytes may employ. Here I will review the recent progress of the role of telomeres and telomerase in lymphocyte differentiation, function, and aging.
Published by Elsevier Ireland Ltd.

Keywords: Human; Telomere; Telomerase; Aging; T cells; B cells

1. Introduction

A typical adaptive immune response starts with the selection of the best antigen-binding naïve T and B lymphocyte(s) and ends with an enormous expansion of this selected lymphocyte to combat an antigen/pathogen. It has been estimated that a typical immune response involves in 15–20 cell divisions, from a single naïve cell to approximately a million of its activated clones, namely effector cells. Once the antigen/pathogen is cleared, the majority of these effector cells undergo apoptosis and a small number of them survive to become memory cells. Memory cells are long-lived and are capable of further rapid expansion upon re-encounter with the same antigen (Dutton et al., 1998; Kaech et al., 2002). For a common pathogen, such as influenza, the periodic expansion of the influenza-recognizing lymphocytes occurs through the entire life of a person. Thus, the cumulative numbers of cell divisions of these antigen-specific lymphocytes that occur over a lifetime could be an astronomical figure. The question is what mechanism(s) lymphocytes employ to allow them to achieve this.

The telomere is a specialized structure at the end of a chromosome. As the cap of the chromosome, telomeres protect the integrity of chromosomes and ensure the complete replication of chromosomes (Cech, 1994; Blackburn, 2001). Telomeres consists of tandem hexanucleotide repeats ($5'$-T_2AG_3-$3'$ over 1000 copies in human) and several telomere DNA binding proteins including telomere repeat binding factors 1 and 2 (TRF1 and TRF2), protection of telomere 1 (POT1), etc. and collectively called Shelterins (de Lange, 2005). Due to the inability of conventional DNA polymerase to completely replicate the $3'$ ends of chromosomes, loss of a portion of telomere repeats occurs after each round of genome replication. Without an adequate compensatory mechanism, telomere lengths are substantially shortened after substantial cell divisions. Once telomeres are critically shortened, whether it occurs to a single chromosome end or to the ends of multiple chromosomes, cells cease to divide and become senescent or undergo apoptosis (Allsopp et al., 1992; Hao et al., 2005). This function of telomeres as a means for counting the number of cell division provides a mechanism for limiting cell divisions by normal somatic cells.

Telomerase is a unique reverse transcriptase that equips with an RNA template containing a complementary sequence to synthesize telomeric DNA repeats. Telomerase binds to the $3'$ ends of the chromosome and extends telomeres, and thus could compensate for the telomere loss that results from chromosomal replication. Two core components of telomerase have been identified: (1) the telomerase RNA template (TR, TERC) and (2) telomerase reverse transcriptase (TERT) (Blasco et al., 1995; Nakamura et al., 1997; Meyerson et al., 1997; Hahn et al., 1999). While TERC is ubiquitously present in all human cells, the expression of TERT appears to be strictly regulated and thus is considered as a rate limiting factor for telomerase activity. Telomerase activity is detected in germ

* Tel.: +1 410 558 8341; fax: +1 410 558 8284.
E-mail address: Wengn@mail.nih.gov.

0047-6374/$ – see front matter. Published by Elsevier Ireland Ltd.
doi:10.1016/j.mad.2007.11.005

cells and in some stem or progenitor cell types but is low to undetectable in most somatic cells (Kim et al., 1994; Wright et al., 1996; Morrison et al., 1996). Most normal somatic cells exhibit capacity for only a finite number of divisions in vitro before reaching replicative senescence, a well-known phenomenon called the Hayflick limit. Recent studies demonstrate that these senescent cells have significantly shortened of telomeres as compared to their young countparts. This is partly cumulative telomere loss from cell divisions is due partly to the absence or insufficient levels of telomerase activity, suggesting that telomeres play an essential role in determining the replicative lifespan of these cells. Although lymphocytes are normal somatic cells, they exhibit a capacity for expression of telomerase that differs from many somatic cells and resembles the ability of stem cells to express telomerase.

This review will focus on the role of telomeres and telomerase in human adaptive immune responses. In particular, it will describe what is known about the telomere and telomerase during T and B cell differentiation and about telomere function under normal conditions as well as abnormal situations. The review will conclude with a discussion of the in vivo role of telomeres in the alterations of the adaptive immune response that occurs with aging.

2. Telomeres and telomerase in lymphocyte differentiation and function

The adaptive immune response relies on the functions of two types of lymphocytes: T and B cells. T cells can be further divided into CD4 (''helper'') and CD8 (cytotoxic) T cells. CD4 T cells are responsible for facilitating the ability of CD8 T cells to kill target cells and the ability of B cells to produce antibodies. CD8 T cells are responsible for killing cells infected with intracellular pathogens, while B cells are responsible for secreting pathogen-recognizing antibodies and facilitating the subsequent destruction of these pathogens. Both CD4 and CD8 T cells are derived from bone marrow progenitors that home to the thymus where they differentiate. New thymic migrants from the thymus, are mature CD4 and CD8 T cells which have not yet encountered foreign antigens, are called naïve T cells and are found circulating in peripheral blood and lymphoid organs (Spits, 2002). Upon encounter with antigen, naïve T cells are activated and expanded to become effector cells. After clearance of the antigen, the majority of these effector cells undergo apoptosis, while some survive to become memory T cells that are long-lived. Memory T cells can be subsequently activated by the same antigen and go through similar phases of effector and memory stages with a much rapid expansion phase.

In contrast, B cells derive from bone marrow progenitor cells and mature in the bone marrow. B cells also undergo an ordered sequence of differentiation during lineage development and during activation of an immune response. In a T cell-dependent immune responses, mature antigen-naïve B cells differentiate in a unique germinal center (GC) environment into GC B cells, then to memory B cells or plasma cells (Heyzer-Williams and Heyzer-Williams, 2005). In the GC, substantial cell division occurs during a differentiation process which comprises several important events including somatic hypermutation of variable domains of immunoglobulin (Ig) genes, clonal selection of mutated antibody-producing B cells with high antigen-binding affinity, and Ig isotype switching. Only those B cells with the best affinity/avidity are selected for further expansion and differentiation to become plasma cells (professional antibody producers) and memory B cells. Like memory T cells, memory B cells are long-lived and are capable of re-activation by the same antigen.

2.1. Telomeres in T cell functions

As described above, T cells undergo numerous cell divisions during the differentiation from naïve to memory cells. The first evidence of shorter telomeres in memory CD4 T cells than in naïve CD4 T cells was reported over a decade ago (Weng et al., 1995). Human naïve and memory CD4 T cells isolated from the peripheral blood of normal adult donors (aged from 25 to 70, n = 20) based on their surface phenotype show different length of telomeres: naïve CD4 T cells have consistently longer telomeres than do memory CD4 T cells. Subsequently, Rufer et al. analyzed a larger cohort (over 500 donors aged from 0 to 90) and confirmed that naïve CD4 T cells have consistently longer mean telomere lengths than memory CD4 T cells (Rufer et al., 1999). In addition, Rufer et al. also show that naïve CD8 T cells have longer telomere than do memory CD8 T cells. As both naïve and memory T cells are heterogeneous in nature, a more precise analysis of telomere attrition during clonal expansion can be accomplished by examining antigen-specific T cells. Burns et al. reported that antigen-expanded memory T cells specific for tetanus toxoid and *Candida Albicans* have significantly shorter telomeres than those of the naïve T cell populations (Burns et al., 2000). Together, these findings confirm that clonal expansion of T cells during the differentiation of naïve to memory T cells in vivo results in the loss of telomere repeats. However, it is unclear to if cumulative loss of telomere would eventually affect memory T cell function.

The rate of telomere attrition during T cell differentiation and division in vivo is unknown. Culture of primary T cells in vitro allows the recording of the number of cell divisions and therefore provides a means to directly assess the relationship between telomere attrition and cell divisions. Under culture systems using either cross-linking of TCR and co-stimulatory receptor with antibodies or mitogen (PHA) plus Interleukin 2 (IL-2), T cells at the end of culture have shorter telomere length than in the beginning of culture for both CD4 and CD8 T cells and naïve and memory T cells (Weng et al., 1995; Effros and Pawelec, 1997). A close look at telomere length during these long-term cultures suggests that loss of telomere length is not a linear function of cell division. At the beginning of culture, telomere shortening appears to be minimal, while shortening of telomere length is more evident at the late stage of culture. Furthermore, under culture systems using homeostatic cytokines such as IL-7 and IL-15, the cell division rates are slower than those cross-linking TCR or mitogen and there is little loss of telomere repeats of T cells (Li et al., 2005; Wallace et al., 2006). This raises the question of how telomere length is regulated and maintained in T cells.