Published in final edited form as:
Exp Gerontol. 2011 ; 46(2-3): 135–140. doi:10.1016/j.exger.2010.08.027.

Telomere/telomerase dynamics within the human immune system: effect of chronic infection and stress

Rita B. Effros
Department of Pathology & Laboratory Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095-1732

Abstract

Aging of the immune system is a major factor responsible for the increased severity of infections, reduced responses to vaccines, and higher cancer incidence in the elderly. A major category of stressors that contribute to the alterations within the T lymphocyte compartment is the family of herpes viruses. These viruses, usually acquired early in life, persist for many decades and drive certain T cells to the end stage of replicative senescence, which is characterized by a variety of phenotypic and functional changes, including altered cytokine profile, resistance to apoptosis, and shortened telomeres. Indeed, high proportions of senescent CD8 (cytotoxic) T lymphocytess are associated with latent cytomegalovirus (CMV) infection in the elderly, and are part of a cluster of immune biomarkers that are associated with early mortality. Similar cells accumulate at younger ages in persons chronically infected with HIV-1. In addition to persistent viral infection, psychological stress as well as oxidative stress can also contribute to the generation of senescent dysfunctional T lymphocytes. Strategies such as cell culture manipulation of replicative senescence, as well as life-style and stress reduction techniques are discussed in terms of possible approaches to enhance immune function in older persons. This review highlights the importance of using humans in studies on immunosenescence and telomere/telomerase dynamics, since model organisms employed in other facets of aging research are not subject to the particular factors that cause the striking age-related reconfiguration of the human immune system.

Keywords

aging; T lymphocyte; immune; stress; infection; replicative senescence; telomere; telomerase

Introduction

Human aging is associated with a variety of clinical problems, the most significant ones relating to infections and cancer. Indeed, influenza and pneumonia rank as the 5th leading cause of death in adults age 65 and older within the U.S. (Panda et al., 2009). In addition to actual mortality, morbidity and prolonged periods of illness due to infections are substantially increased with age. With respect to cancer, epidemiological studies show that old age—–even more than known harmful lifestyle factors such as smoking-—is the greatest risk factor for the development of cancer. One of the major contributory factors to the age-

Address Correspondence to: Rita B. Effros, Ph.D., Department of Pathology & Laboratory Medicine, David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, Los Angeles, CA 90095-1732, reffros@mednet.ucla.edu.

related changes in severity and incidence of infections and cancer is the waning protective function of the immune system (Linton & Dorshkind, 2004).

The complex changes that occur within the immune system of aged humans are due to both intrinsic events, such as the decrease in thymic size and function (Lynch et al., 2009), as well as to environmental factors, mainly the lifelong exposure to various pathogens. The combined effects of these intrinsic and extrinsic factors lead to major alterations in immune function with age, changes that have been implicated in the deleterious effects of pathogens and cancer in the elderly (Linton et al., 2005). Ironically, vaccination, which is aimed at manipulating the immune system in ways that would prevent infection or retard cancer progression, is far less effective in the elderly (McElhaney, Upshaw, Hooton, Lechelt, & Meneilly, 1998). Even immune memory to certain pathogens that is generated early in life declines during aging.

Interestingly, although there is no change in total lymphocyte number, the proportional representation of different types of lymphocytes, particularly within the T cell compartment, is dramatically altered (Effros, Dagarag, Spaulding, & Man, 2005). The population of naïve T cells emerging from the thymus progressively declines, and the proportion of various types of memory T cells increases. Within memory T lymphocyte pool, there is a striking change in the phenotype and function of the so-called CD8, or cytotoxic T lymphocytes, with progressively increasing proportions of cells with features of replicative senescence (Boucher et al., 1998). Indeed, among the numerous cell types that have been extensively characterized with respect to the process of replicative senescence, T cells, arguably, constitute the most dramatic example of the accumulation and impact of these cells within the aging organism.

This review will summarize the effect of prolonged stress on the human immune system, with a focus on telomere/telomerase dynamics and replicative senescence in T lymphocytes. Although numerous animal models have provided novel and important insights on aging, these model systems are not relevant to the major age-related immune system changes that occur in humans, which seem to be driven by life-long stress of maintaining control over latent viral infections acquired in childhood. This decades-long “work” is reflected in the generation of large populations of T cells that are focused on one or two different viruses. The presence of these clonal populations reduces the remaining repertoire of T cells, thereby limiting the availability of T cells to combat novel antigens (Ouyang et al., 2003). Moreover, these cells also seem to exert suppressive influences on overall immune function (Suciu-Foca et al., 2005), and their abundance also correlates with many age-related pathologies (Effros, 2009; Lin et al., 2009a) in humans. In addition to the stress of viral infection, chronic psychological and oxidative stress also contribute to the generation of senescent T cells (Epel et al., 2004). Thus, studies on the immune system can provide novel insights into multiple facets of human aging and healthspan, as well as how immunological history, starting in childhood, can have late-life effects on a variety of physiological processes.

Immune system basics

The immune system is a complex and highly integrated network of cells and lymphoid organs, consisting of two interacting components that act in concert to combat invading organisms. The innate immune system is capable of dealing with certain pathogens in a rapid, albeit, somewhat non-specific manner. By contrast, the activity of the adaptive immune system takes longer to develop, but has the advantage of exquisite specificity and long-term memory. Indeed, this anamnestic response is the basis for the efficacy of vaccines.

All the cellular components of both the innate and adaptive immune systems, including B lymphocytes, T lymphocytes, monocytes and dendritic cells, are derived from primitive stem cells in the bone marrow. A significant feature of T and B lymphocytes, the main players in adaptive immunity, is the presence of antigen receptors on the surface of each cell that confer the ability to recognize a specific region of a particular pathogen. These antigen receptors are generated during the complex transition from hematopoietic stem cells to mature lymphocytes by an intricate process of cutting and splicing that leads to random joining of DNA segments from several different gene families (Janeway Jr, Travers, & Walpert, 2001). The outcome of this process is that each lymphocyte, as well as all its progeny, expresses a unique antigen receptor. If that lymphocyte encounters the appropriate antigen, it will become activated and undergo cell divison, with the identical receptor expressed on all the resulting daughter cells.

The generation of antigen receptors by this random process results in an extremely large repertoire of antigen specificities, thereby conferring the immune system with the ability to respond to multiple and varied types of pathogens. Nevertheless, the corollary of having this extremely large spectrum of different antigen receptors within each individual is that the number of lymphocytes that can respond to any single pathogen is extremely small. This feature leads to the requirement for massive cell division and clonal expansion of the few cells whose receptors recognize the invading pathogen, or , in the case of cancer, a tumor-specific antigen.

The main players within the adaptive immune system—the B and T lymphocytes—have distinct functional roles upon encounter with antigen. B cells produce soluble proteins called antibodies, which can neutralize or otherwise inactivate pathogens that are present within the blood. T cells, on the other hand, are unable to recognize “free” antigen, and can only recognize pathogens that have already infected other cells. In the case of a viral infection, for example, the infected cells become decorated with components of the virus, indicating to the immune system that the cell is no longer normal and must be eliminated. Those cytotoxic T cells whose receptors recognize the specific viral antigens on the surface of the infected cell become activated and then undergo massive cell division, migrate into the tissues, where they actually kill infected or otherwise abnormal cells, thereby controlling the infection. Once the antigen-specific T cells complete their function, most of the expanded cell population dies by apoptosis, leaving only a few memory cells to handle possible future encounters with the same antigen. Thus, proliferation and the ability to undergo repeated rounds of clonal expansion is a critical feature of effective T lymphocyte function.

The T lymphocyte replicative senescence model

In order to mimic the *in vivo* biology of age-related changes in human cytotoxic (CD8) T lymphocytes, we have developed a cell culture system that allows longitudinal analysis of the same population of cells over time. The basic protocol of our *in vitro* model is to isolate peripheral blood mononuclear cells from venous blood samples, and to stimulate the cells with either irradiated foreign (allogeneic) tumor cells, with antibodies to the T cell receptor, or with viral antigens (Dagarag, Evazyan, Rao, & Effros R.B., 2004). Irrespective of the mode of stimulation, after a period of 2-3 weeks, the vigorous cell proliferation subsides, and the cells became quiescent. The cycle of stimulation-proliferation-quiescence is repeated multiple times until the culture reaches an irreversible final stage of quiescence that cannot be overcome by further stimulation or by the addition of growth factors (Perillo, Naeim, Walford, & Effros, 1993; Perillo, Walford, Newman, & Effros, 1989). This terminal state is known as replicative senescence. The overall finding from numerous different laboratories, using a variety of modes of stimulation, is that human T cells are able to undergo a limited number of replications, after which they cease dividing (Adibzadeh, Pohla, Rehbein, &

Pawelec, 1996; Perillo et al., 1989). It is important to note that this end stage of replicative senescence does not imply loss of viability. Indeed, with appropriate feeding, senescent cells remain viable and metabolically active for several months (Wang, Lee, & Pandey, 1994; Spaulding, Guo, & Effros, 1999). Moreover, despite the emphasis on replication, the functional, genetic and phenotypic alterations associated with senescence may be at least as important to the biology of cells as the inability to proliferate (Campisi, 1997).

For CD8 T lymphocytes, one of the major changes observed in cultures that have reached replicative senescence is resistance to apoptosis, a property they share with senescent fibroblasts (Wang et al., 1994). Whereas CD8 T lymphocytes from early passage cultures undergo brisk apoptosis in response to a variety of stimuli (e.g., mild heat shock, antibodies to Fas), the descendents of these cells that have reached senescence show significantly reduced ability to undergo apoptosis, and increased expression of the anti-apoptotic protein, Bcl2 (Spaulding et al., 1999). This change in the ability to initiate timely and efficient programmed cell death is highly relevant to effective immune function *in vivo*, since elimination of the massive numbers of activated virus-specific CD8 T cells is an essential event once the infection has been resolved (Effros & Pawelec, 1997).

A variety of functional changes have been documented for cultures of senescent CD8 T cells. One prominent effect is an alteration in the pattern of cytokine production (Effros et al., 2005). Cytokine secretion by T lymphocytes is essential for cell-cell communication and efficient immune function. Our studies show that as T lymphocytes progress to senescence in cell culture, they produce increasing amounts of two pro-inflammatory cytokines. Specifically, the levels of both TNFα and IL-6 increase progressively as the cells reach senescence (Effros et al., 2005). These two cytokines are often associated with frailty in the elderly (Hubbard, O’Mahony, Savva, Calver, & Woodhouse, 2009), as well as with increased maturation and activation of bone-resorbing osteoclasts (Arron J.R. & Choi, 2000). A second important change in cytokine secretion is the anti-viral cytokine IFNγ, which CD8 T cells secrete in conjunction with their cytotoxic function. With progressive cell divisions in culture, virus-specific CD8 T cells show significantly reduced production and secretion of IFNγ, along with reduced lytic capacity and diminished production of perforin, a protein involved in cytotoxicity (Dagarag et al., 2004; Dagarag, Ng, Lubong, Effros R.B., & Yang, 2003; Yang et al., 2005). Senescent T cell cultures also produce a significantly blunted heat shock response, indicative of reduced ability to respond to stress (Effros, et al., 1994b). Finally, as cells age in culture, they show increased microsatellite instability, an indicator of reduced DNA mismatch repair capacity, which is capable of rectifying errors in DNA replication (Krichevsky et al., 2004). Thus, as T lymphocytes progress to the end stage of replicative senescence in cell culture, they are altered in a variety of processes reflecting cellular integrity and defense.

Arguably, one of the most significant changes associated with T lymphocyte replicative senescence in cell culture is the complete and irreversible loss of expression of the major signaling molecule, CD28 (Effros et al., 1994a; Vallejo, Nestel, Schirmer, Weyand, & Goronzy, 1998). This co-stimulatory receptor is an integral component of the immunological synapse, and is involved in a variety of T cell functions, including activation, proliferation, stabilization of cytokine messenger RNA levels, and glucose metabolism (Shimizu et al., 1992; Holdorf, Kanagawa, & Shaw, 2000; Sansom, 2000; Frauwirth et al., 2002). Importantly, the absence of CD28 expression is in marked contrast to the sustained expression of a variety of T lymphocyte-specific surface markers reflecting lineage, memory, and cell-cell adhesion.

In parallel with the loss of CD28 expression, CD8 T lymphocytes lose the ability to upregulate the telomere-extending enzyme, telomerase. Although robust telomerase activity

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is observed in concert with initial activation, by the third and all subsequent rounds of stimulation, CD8 T cells show no detectible telomerase activity (Valenzuela & Effros, 2002). The loss of telomerase activity parallels the loss of CD28 expression, suggesting a possible link between CD28 and upregulation of telomerase. Studies showing that blocking CD28 interaction with its ligand on antigen-presenting cells did, in fact, almost completely abrogate telomerase activity. With the loss of telomerase activity, the T lymphocytes undergo progressive telomere shortening as they continue to divide, ultimately reaching the critically short telomere length of 5-7 kb that has been associated with replicative senescence in a variety of cell types (Vaziri et al., 1993).

Thus, the extremely large T lymphocyte antigenic repertoire, which is an advantage during early life, may prove to maladaptive later in life. The low frequency of T lymphocytes specific for any particular foreign antigen necessitates extensive and rapid clonal expansion in order to reach the numbers needed for an effective response to pathogens. Although T cells can divide faster than any other vertebrate cell type, the extensive cell division is not without consequences. Indeed, some T cells can actually reach the end stage of replicative senescence, particularly by old age, but also in younger people during certain chronic infections, as will be discussed below.

In vivo observations: role of latent viral infections

The permanent loss of CD28 expression in senescent T lymphocyte cultures has been used as a biomarker to document T cell replicative senescence *in vivo*. Flow cytometry analysis of peripheral blood samples has clearly demonstrated that persons age 70-90 have high proportions of CD8 T lymphocytes that lack CD28 expression. Indeed, in some elderly persons, more than 50% of the CD8 T lymphocytes within the total peripheral blood T cell pool do not express the CD28 molecule (Effros et al., 1994a). Similar to the T lymphocytes that reach senescence in culture , CD8+CD28− T lymphocytes isolated from fresh blood samples show minimal proliferative activity, and have shorter telomeres than CD8+CD28+ T cells from the same donor (Effros et al., 1996). Moreover, recent more extensive analysis of distinct populations of peripheral blood cells has shown that CD8+CD28− T lymphocytes not only exhibit lower telomerase activity, but also have telomere lengths that are shorter than any other T and B cell subset (Lin et al., 2009b). Importantly, this extensive study on blood samples from 60 individuals shows a significant inverse correlation between the percentage of CD8+CD28− T lymphocytes and overall telomere length of the total peripheral blood mononuclear cell (PBMC) population (Lin et al., 2009b). This observation is significant, since numerous studies have shown associations between overall PBMC telomere length and various diseases (Effros, 2009), suggesting that the proportions of CD8+CD28− T lymphocytes may be increased in multiple human pathologies.

What is the driving force for the generation of senescent CD8 T lymphocytes *in vivo*? It has been suggested that latent infection with several herpes viruses, which are endemic and persist throughout life in infected individuals, are the main culprits (Pawelec et al., 2004). Clinical data on bone marrow and organ transplant recipients indicate that under conditions of immunosuppression, cytomegalovirus (CMV) and other latent herpes viruses are often reactivated. Moreover, these patients show increased incidence of EBV lymphomas. In the elderly, many of whom are also immunocompromised, another herpes virus, varicella zoster virus (VZV), is often reactivated, manifesting itself as shingles. By contrast, in healthy individuals with normal immune systems, reactivation rarely occurs, suggesting that maintaining viral latency requires active participation by the immune system. It has been proposed that the constant and prolonged CD8 T lymphocyte activity, which involves proliferation, may drive certain virus-specific T cells to senescence (Pawelec et al., 2004). This notion is confirmed by extensive studies of HIV-infected individuals, in whom the *in* *vivo* presence of CD8 T lymphocytes with markers indicative of replicative senescence is accelerated. Indeed, 40-year-olds who are HIV-positive show proportions of senescent CD8 T cells that are as high as uninfected 90-year-olds. Latent infection with Epstein-Barr Virus (EBV) is also associated with telomere shortening in antigen-specific CD8 T lymphocytes (Hathcock, Weng, Merica, Jenkins, & Hodes, 1998; Maini, Soares, Zilch, Akbar, & Beverley, 1999), presumably due to the down-regulation of telomerase activity associated with repeated antigen-driven proliferation (Valenzuela et al., 2002).

The accumulation of senescent CD8 T lymphocytes in persons chronically infected with certain viruses is due to the long-term chronic antigenic stimulation, which leads to increased rounds of proliferation. Similar antigen-driven proliferation is presumably also responsible for the presence of senescent CD8 T cells in the context of certain forms of cancer. For example, in advanced renal carcinoma, the proportion of CD8 T cells with markers of senescence has predictive value with respect to patient survival (Characiejus et al., 2002). Also, in patients with head and neck tumors, it has been shown that the CD8+CD28− T lymphocyte subset undergoes expansion during the period of tumor growth, and decreases after tumor resection, consistent with the notion that the increased antigenic burden may cause extensive proliferation in the tumor-reactive cells (Tsukishiro, Donnenberg, & Whiteside, 2003). Conversely, the maintenance of CD28 expression is associated with improved *in vitro* expansion capability of CD8 T cells that have been isolated from actual melanoma tumors (Li et al., 2010). The common theme among all of these reports of senescent CD8 T cells present *in vivo* is chronic antigenic stimulation, which leads to extensive proliferation, and finally to the end-stage of replicative senescence. Due to the apoptosis-resistance of these cells, once generated, they persist.

The *in vivo* significance of T lymphocyte replicative senescence is underscored by the prognostic value of these cells in several longitudinal studies. In the very old, T lymphocytes with markers of senescence are part of the so-called “immune-risk phenotype”, which is predictive of earlier all-cause mortality (Wikby et al., 2002). In the case of HIV disease, high proportions of CD8+CD28− T lymphocytes early in the infection is predictive of more rapid subsequent progression to AIDS (Cao, 2007). Finally, analysis of PBMC telomere length of a cohort of 60-year-old persons showed that the shortest telomere size quartile was associated with earlier mortality, with a 7-8 fold increased risk of dying from infection (Cawthon, Smith, O’Brien, Sivatchenko, & Kerber, 2003).

Additional contributory stressors to T cell replicative senescence

There are other types of stress, in addition to viral infections, that can drive T lymphocytes to senescence, and/or compromise immune function. Psychological stress, in particular, has been extensively documented as a major factor in suppressing immune function. One of the common models of chronic, long-term psychological stress is that of caregivers of a family member with dementia. Several studies suggest that these caregivers have poorer responses to vaccines than their noncaregiving, age-matched controls. Influenza vaccination is considered successful if it elicits a 4-fold increase in antibody titer, and dementia caregivers are less likely to have this level of response. Moreover, even within the population of spousal caregivers, those with greater levels of perceived stress and depression (by self-report) showed lower antibody responses to the vaccine than control group persons who differed only by levels of perceived stress. Importantly, the deleterious immune effects on vaccine responses and *in vitro* T cell responses to influenza persisted long after the death of the demented spouse (Gouin, Hantsoo, & Kiecolt-Glaser, 2008). Coincidentally, low antibody titers in response to vaccination are also associated with having high proportions of CD8+CD28− (i.e., senescent) T lymphocytes (Saurwein-Teissl et al., 2002; Goronzy et al., 2001), suggesting that future studies on emotional stress may want to include analysis of some immune cell marker changes. Interestingly, similar to psychological stress, CD8+CD28− T lymphocytes have been shown to have suppressive effects on various aspects of immune function (Cortesini et al., 2002).

Chronic psychological stress is also associated with telomere shortening and reduced telomerase activity, which are signature changes associated with T cell replicative senescence. A study on mothers of chronically ill children showed significant associations between both perceived and chronicity of stress with higher oxidative stress, lower telomerase activity, and shorter telomeres (Epel et al., 2004). Caregivers of Alzheimer's patients also showed reduced telomere length, which was associated with diminished cell proliferative capacity (Damjanovic et al., 2007). The effect of stress on latent viral infections has been observed in older family dementia caregivers, who have higher antibody titers and impaired cellular responses to herpes simplex -1 (HSV-1) and Epstein-Barr virus. These observations suggest that chronic stress can lead to reactivation of latent herpes viruses, which, in turn results in chronic stimulation of the immune cells that recognize these viruses. Pessimism has also been documented to correlate with shortened telomeres, as well as with elevated IL-6 levels, reminiscent of two changes that have been documented in senescent T cell cultures (Effros et al., 2005). Behavioral and life style influences have also been linked to altered telomere/telomere dynamics. Poor metabolic health (e.g., greater adiposity, insulin resistance) as well as chronic preoccupation with weight, manifested by dietary restraint) are all associated with premature telomere shortening. Extreme psychological stress can affect the immune system in an additional way—by causing thymic involution, thereby reducing the production of naïve T cells, a change that is already caused by aging itself.

Another modulator of the process of replicative senescence is oxidative stress, which accelerates telomere shortening in cell culture. We have recently shown that oxidative stress in the form of oxidized low-density lipoproteins (LDL, the "bad' cholesterol) also accelerates the progression of T lymphocytes to the end stage of replicative senescence in cell culture. This, in turn, hastens the accumulation of two cytokines (IL-6 and TNFα) that are known to enhance the maturation and activation of bone-resorbing osteoclasts. In addition, short term exposure of human T lymphocytes to oxidized LDL stimulates the production of another major osteoclastogenic factor, receptor activator of NFkB ligand (RANKL) (Graham et al., 2009). These observations provide a possible mechanism for the epidemiological association between atherosclerosis and osteoporosis, both of which are associated with increased oxidized LDL, and also underscore the potential contribution of senescent T lymphocytes to age-associated bone loss.

Finally, T cell telomerase activity is also subject to hormonal regulation. Consistent with the reduced telomerase activity and telomere shortening associated with a variety of mental and physical stressors, experimental exposure of human T cells in culture to physiological levels of the stress hormone, cortisol, in concert with activation stimuli, results in a significant reduction in telomerase activity. This effect persists even during the second round of stimulation (Choi et al., 2001). The dysregulated production of cortisol, a stress hormone known to have immunosuppressive effects, might have influenced the diminished vaccine responses in caregivers under stress. Indeed, spousal dementia caregivers who received an influenza immunization had higher salivary cortisol levels than noncaregiving controls over a 6-month period. In contrast to the cortisol inhibitory effect, exposure of T cells to estrogen, which is associated with increased immune reactivity, results in enhanced telomerase activity (Effros et al., 2005). Finally, we have preliminary data showing that exposure to another hormone, 25-hydroxyvitamin D, upregulates telomerase activity in human T cells (Chou, Parish & Effros, unpublished data).

Therapeutic approaches to retarding the process of T lymphocyte replicative senescence

Given the multiple deleterious effects of senescent T cells *in vivo*, researchers have focused on developing strategies to prevent or retard this process. One approach is based on the key role of telomere shortening in signaling replicative senescence. We have shown that sustained telomerase activity, via either transduction with the hTERT gene, or exposure of T cells to a chemical telomerase activator, stabilizes telomere length and delays/prevents replicative senescence (Dagarag et al., 2004; Fauce et al., 2008). Importantly, increasing telomerase activity not only affects the telomeres and proliferative potential, but also enhances a variety of anti-viral immune functions in the T cells. These include cytotoxicity and the production of anti-viral cytokines and chemokines.

A second approach involves the inhibition of one of the major cytokines produced by senescent T cells, namely, TNFα. We recently showed that inhibition of TNFα, either with a neutralizing antibody, or with a receptor inhibitor, significantly increases proliferative potential as well as telomerase activity (Parish, Wu, & Effros, 2009). Gene transduction with CD28 is yet another strategy that retards replicative senescence in cell culture (Parish & Effros, manuscript in preparation). Additional approaches that may be practical *in vivo* would be to physically remove the senescent T cells from the blood, or induce them to undergo apoptosis. Finally, since one major driver involved in the accumulation of large populations of senescent T cells by old age is CMV, developing a childhood vaccine against this virus might have long-range therapeutic effects on the ever-increasing elderly population.

Behavioral interventions that reduce stress are practical, non-invasive methods to retard telomere shortening and the accumulation of senescent T cells. Indeed, a randomized controlled trial showed that older adults who practiced relaxation had reduced antibody titers to latent HSV-1, suggesting that this life-style intervention resulted in lower levels of antigenic stimulation, which was reflected in the lower antibody levels (Gouin et al., 2008). This observation is consistent with the well-documented associations between stress and the development of “cold sores”, caused by reactivation of HSV-1. Similar results were reported for another randomized controlled trial involving 16 weeks of Tai Chi, which led to increased VZV cellular immunity following a VZV vaccine (Irwin, Olmstead, & Oxman, 2007). These studies suggest that stress-buffering strategies, including meditation and mindfulness might be practical salutary interventions for caregivers and other persons experiencing chronic mental stress (Epel, Daubenmier, Moskowitz, Folkman, & Blackburn, 2009).

Concluding remarks

The human immune system constitutes one of the prime examples of the pleiotropic effects of replicative senescence during aging. Modeling this process in cell culture has provided novel insights into the major phenotypic, genetic and functional changes associated with this final stage of T cell development. The documentation of senescent T cells in a variety of age-related pathologies demonstrates the central role of the immune system in diseases of aging. Moreover, the predictive value of these cells in all-cause mortality, and conversely, the maintenance of long telomeres in healthy centenarians (Terry, Nolan, Andersen, Perls, & Cawthon, 2008), underscores the central role of the immune system in lifespan and longevity. Finally, these studies highlight the importance of performing immunosenescence studies in *homo sapiens*, a species that is subjected to a variety of environmental stressors, particularly latent viral infections, that are absent in most laboratory models of aging.

Acknowledgments

The research described in this review has been supported by the following grants to the author (AI 060362; AG 023720), and by the Geron Corporation and TA Therapeutics, Ltd.

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