Chapter 6
Psychoneuromicrobiology: Cytomegalovirus Infection as a Putative Link Between Stress, Aging, and Immunity

Jos A. Bosch, Jerrald L. Rector, James E. Turner, Natalie E. Riddell, Briain o'Hartaigh and Vikki E. Burns

6.1 Introduction

Epidemiological evidence demonstrates increased morbidity and mortality in populations exposed to adverse psychosocial factors such as low socio-economic status (SES) and protracted psychological distress (Cohen and Herbert 1996; House et al. 1988; Marmot 2005; Schneiderman et al. 2005). While the data are clear, the precise mechanisms underlying these associations are yet to be determined (Antoni et al. 2006; Cacioppo and Hawkley 2003; Glaser and Kiecolt-Glaser 2005; McEwen 1998; Uchino et al. 1996). We, and others, have argued that since increasing age is a major risk factor for a wide range of chronic diseases, the aging process itself may be an important target for such mechanistic research (Bosch et al. 2009; Nilsson 1996).

This chapter discusses immunosenescence as a possible biological pathway linking psychosocial stress and health (Bosch et al. 2009; Pawelec et al. 2012). Immunosenescence refers to a decline in immune competence seen in old age, and it is associated with a dramatic rise in morbidity and mortality from infectious disease (Akbar et al. 2004; Larbi et al. 2008). For example, the elderly exhibit a many-fold higher mortality from otherwise common infections such as gastrointestinal infections, urinary tract infections and influenza (Thompson et al. 2003; Yoshikawa 2000).

J. A. Bosch (✉)
Department of Clinical Psychology, University of Amsterdam, Weesperplein 4, 1018 XA Amsterdam, The Netherlands
e-mail: j.a.bosch@uva.nl

Mannheim Institute of Public Health, Social and Preventive Medicine (MIPH), University of Heidelberg, Mannheim, Germany

J. A. Bosch · J. L. Rector · B. o'Hartaigh · V. E. Burns
School of Sport and Exercise Sciences, University of Birmingham, Birmingham, UK

J. E. Turner
CRUK Institute of Cancer Studies, University of Birmingham, Birmingham, UK

N. E. Riddell
School of Infection and Immunity, University College London, London, UK

J. A. Bosch et al. (eds.), *Immunosenescence,*
DOI 10.1007/978-1-4614-4776-4_6,

This susceptibility also promotes physical frailty and cognitive decline, further increasing mortality risk and reducing quality of life (High et al. 2005; Yoshikawa 2000). Although less well established, immunosenescence may also be a factor in the age-related increase in autoimmune and inflammatory disorders (Franceschi et al. 2000; Prelog 2006).

These clinical complications of immunosenescence mark the terminal phase of a process that already starts in adolescence (Akbar and Fletcher 2005; Nikolich-Zugich 2008a). Around that time the thymus, an organ essential for the maturation of T lymphocytes, reduces in size and function with a concomitant decline in the generation naïve T cells. This process causes immunity to become progressively dependent on the existing pool of memory T cells (Woodland and Blackman 2006). This pool of memory T cells gradually expands compensating for the diminishing influx of naïve T cells via cytokine-induced cell division (denoted 'homeostatic proliferation') and repeated antigen exposure. In particular latent herpes viruses, like cytomegalovirus (CMV) are a major source of continuous antigenic stimulation (Khan et al. 2002; Nikolich-Zugich 2008a). As a consequence the expanding pool of memory cells tends to be oligoclonal, that is, exhibit an inflated antigen receptor diversity that is skewed toward a few immunodominant viral antigens. With an increasing number of cell divisions the memory T cells gradually change their appearance; first losing the surface marker CD28 ('intermediate differentiation') and later also the surface marker CD27 ('late differentiation') (Akbar and Fletcher 2005; Appay et al. 2002). These phenotypic changes are particularly prominent in CD8+ T lymphocytes (CTLs), and the accumulation of CTLs with a late differentiation phenotype is considered a hallmark of immunosenescence (Akbar and Fletcher 2005; Hadrup et al. 2006; Pawelec 2006; Derhovanessian et al. 2011).

Other markers of an aging adaptive immune system include weakened responses to vaccination, a diminished proliferative response to mitogens, reduced IL-2 production, shortening of leukocyte telomeres (a DNA marker of cellular aging), increased serum levels of inflammatory cytokines like IL-6, persistent reactivation of latent herpes viruses (e.g., Epstein–Barr Virus, CMV), and a reduced CD4:CD8 ratio (Effros 2007; Larbi et al. 2008; Pawelec 2006; Moro-Garcia et al. 2012). (See Chaps. 1 and 2 in this book for a comprehensive review.) A reduced CD4:CD8 ratio has been found to be a strong predictor of mortality in very old age (Ferguson et al. 1995; Huppert et al. 2003; Wikby et al. 1998). Significantly, all of the aforementioned immune changes that characterize aging are, in part, a result of the accumulation of T cells with a differentiated phenotype (i.e., CD28−CD27−); that is, these T cells poorly proliferate in response to mitogens, produce little IL-2 but abundant INF-γ, have very short telomeres, expand in response to repeated latent viral reactivation, and the number of these cells correlates with weaker vaccination responses.

Those who are familiar with the psychoneuroimmunology literature may immediately note a striking similarity between the immune changes summarized in the previous paragraph and the immune effects of chronic stress (Bosch et al. 2009). Indeed, meta-analysis has shown that protracted psychosocial stressors are associated with much the same pattern of weakened responses to immunization, diminished T cell proliferation to mitogens, reduced IL-2 production, and reactivation of latent herpes viruses (Segerstrom and Miller 2004). Other distinctive features of immunesenescence, such as elevated serum levels of inflammatory markers and shortened

leukocyte telomeres, have also consistently been associated with psychosocial stress (Damjanovic et al. 2007; Epel et al. 2004; Glaser and Kiecolt-Glaser 2005; Simon et al. 2006). (See Chaps. 7 and 11 for extensive reviews on this topic.) The remarkable parallels between the aging and stress literature lead us to hypothesize that psychosocial stress contributes to the process of immunological aging (Bosch et al. 2009). This hypothesis is the topic of the current chapter. Thus, what we propose is that the effects of stress and aging on immunity not only just look the same, but may also share similar pathways. We will argue that one of these shared pathways may be the effect of CMV infection on immunity (for a comparable point of view regarding the link between exercise and immunosenescence, see (Simpson 2010) and Chap. 5 in this volume).

In the sections that follow, we will explain that CMV infection dramatically alters the composition of the blood, causing an accumulation of late-differentiated CD8 T cells (CD27−CD28−); the hallmark of an aging immune system. It is thought that this CMV-driven accumulation of differentiated cells is due to incessant low-grade viral reactivation. Viral reactivation activates CMV-specific T cells, which as a population will both expand (i.e., contributing to a larger part of the total pool of memory T cells) and differentiate (i.e., express surface molecules associated with effector function and T cell senescence) (also see Chap. 2 in this volume). Significantly, there is evidence that physiological and psychosocial stressors, via neuro-endocrine and immunological pathways, may contribute to this viral reactivation, implying that stress exposure may promote this aspect of immunosenescence.

6.2 Cytomegalovirus Infection and the Immunity

6.2.1 Herpes Infections and Latency

Viruses are microscopic pathogens, consisting of a nucleic acid genome inside a protein coat, which can only replicate once inside a living cell. While the immune system is able to eradicate most viral infections, some viruses have developed ways to escape this fate. The herpes viruses are particularly well-known for this ability to evade immune destruction and persist within their human host (Cohrs and Gilden 2001; Croen 1991). A characteristic of herpes viruses is that they remain dormant in the cellular genome, a state denoted as latency, which is interrupted by brief periods of reactivation whereby the virus replicates and infects other cells. Herpes viruses have been extremely successful in colonizing humans. Their typical infection rates range between 30 % and 90 %, depending on the virus, and are in part related to factors such as age, SES, topographical location, sexual experience, and early life exposures (e.g., higher infection rates in children that attended day care) (Arvin et al. 2007). In healthy individuals these viruses typically elicit mild (e.g., cold sores, fatigue) or no disease symptoms at all. However, in immune-suppressed patients (e.g., those with AIDS or taking immune suppressive drugs), these viruses can elicit very severe complications (Nester et al. 2008).

Eight herpes viruses have thus far been identified; herpes simplex virus 1 (HSV-1), which predominantly causes oral lesions (or cold sores); herpes simplex 2 (HSV-2), which predominantly causes genital lesions; *Varizella zoster* virus (VZV), which causes chicken pox and shingles; Epstein–Barr virus (EBV), which causes glandular fever; human herpes virus (HHV)-6 and -7, both T cell-infecting viruses and jointly referred to as 'Roseolovirus' due to the association with the common childhood rash; Karposi's sarcoma-associated herpes virus—a cause of tumors and lymphoma—and finally CMV, which in most individuals does not cause symptoms. Although more often than not the cause of mild infectious symptoms, several of these viruses have also been associated with more serious long-term effects, although these effects are rare. For example, EBV is a primary cause of Burkits lymphoma, a form of leukemia. Research has also implicated CMV in a number of severe maladies and with a reduced life expectancy (see section further below).

6.2.2 CMV: Epidemiology and Pathology

CMV is a highly prevalent herpes virus; approximately 35 % of young children and 90 % of the elderly are seropositive (Staras et al. 2006). Overall sero-prevalence in western societies approaches 60 % (Staras et al. 2006). Individuals free from infection at birth will likely become infected early in life: post-natal or childhood CMV infection is common, and caused by exchange of bodily fluids, including breast-milk (Kenneson and Cannon 2007; van der Meer et al. 1996). An inverse relationship exists between SES and CMV seropositivity. Individuals with less education, lower income, and of non-white race are more likely to become infected, and at an earlier age, than individuals of a higher SES (Dowd and Aiello 2009; Dowd et al. 2009). Studies have also reported differences in human CMV infection between various regions within the United States and Europe. (See Chap. 9 in this book.)

As a seemingly innocent and common infection, CMV infection has consequently not received much public health attention (Wreghitt et al. 2003; Zanghellini et al. 1999). This may be unwarranted. CMV infection during pregnancy, for example, is now recognized as a main cause of infant death and long-term disabilities in the United States, and well exceeds that of other, better known, congenital conditions such as Down syndrome, fetal alcohol syndrome, and spina bifida. Further, immune-compromised individuals, such as HIV patients and transplant recipients, can develop life-threatening complications due to CMV reactivation (Freeman 2009; Sutherland et al. 1992). In aging populations a positive CMV serotatus has been associated with cognitive decline, and is implicated in the pathogenesis and severity of cardiovascular diseases (Aiello et al. 2006; Michaelis et al. 2009; Soderberg-Naucler 2006). In addition, the extent of CMV infection, measured by the concentration of immunoglobulin G (IgG) antibodies to CMV, independently predicts mortality in older adults (Roberts et al. 2010; Strandberg et al. 2009; Pawelec et al. 2012). Thus, this once assumed inconsequential virus has a range of deleterious effects, particularly within the immune system. The next section will outline these effects, which are particularly prominent in CD8+ T lymphocytes.

6.2.3 The Effects of CMV-infection on Immunity

As discussed in Sect. 6.1, one of the hallmarks of an aged immune system is a decline in naïve (CD45RA + CD27 + CD28+) CD8+ T cells and an accumulation of differentiated (CD27−CD28−) CD8+ T cells. These effects are partly caused by the age-associated involution of the thymus. For example, individuals thymectomised in the first few years of life exhibit reduced numbers of naïve T lymphocytes and increased numbers of late-differentiated cells (Eysteinsdottir et al. 2004; Sauce et al. 2009; Torfadottir et al. 2006). However, it is now clear that CMV is the major driving force behind the accumulation of differentiated T cells (Moss 2010; Pawelec et al. 2004; Pawelec and Derhovanessian 2011; Pawelec et al. 2009). In particular, the combination of little or no thymic output, a hallmark of aging (see Chap 2), and a selective expansion of late-differentiated T cell populations leads to a gradual overcrowding by CD8+ T cells that have a limited ('oligoclonal') T cell repertoire, a process denoted as memory inflation (Akbar and Fletcher 2005; Brunner et al. 2010; Sauce et al. 2009; van Lier et al. 2003). Stunningly, in some older adults it has been observed that up to 70 % of the CD8+ T cell memory pool has become specific for CMV epitopes (Appay et al. 2002; Khan et al. 2002), and thus only 30 % of the memory pool of those individuals is available to combat other antigens. The relation between CMV infection and CD8+ T cell differentiation occurs independent of calendar age: young adults infected with CMV similarly exhibit skewing of the T cell repertoire as seen in older adults (Chidrawar et al. 2009; Pita-Lopez et al. 2009; Weinberger et al. 2007). Thus, it seems that infection with this common microorganism accelerates the immunological aging process.

6.2.4 T Cell Phenotypes, Their Development, and Functional Characteristics

Immunologists utilize various analytical strategies based on staining of cell-surface molecules to identify different variants of CD8+ T cell 'subsets'. A commonly used procedure is examining the expression of the cell surface co-stimulatory molecules CD27 and CD28; this approach yields three main sub-populations that represent a continuum of differentiation reflecting early (CD27 + CD28+), intermediate (CD27+CD28−), and late differentiated cells (CD27−CD28−) (Appay et al. 2002; Appay et al. 2008). Other research groups have used different combinations of surface molecules to identify the same or overlapping subsets. For example, CD45RA (an isoform of the pan-lymphocyte marker CD45) has been used in combination with the surface molecules CD27, CCR7, or CD62 L (Appay et al. 2008; Hamann et al. 1997; Sallusto et al. 2004; Sallusto et al. 1999; van Lier et al. 2003). This approach can be used to discern antigen-inexperienced or naïve cells (CD27+CD45RA+), and three additional subsets of antigen-experienced ('memory') cells; central memory (CD27 + CD45RA−), effector memory (CD27−CD45RA−), and effector memory

cells which have re-expressed CD45RA (CD27−CD45RA+). Irrespective of the identification strategy used, the general observation is that repeated contact with the same antigen moves memory cells along a differentiation continuum whereby they gradually change their phenotype and acquire so-called "effector" functions, such as increased cytotoxicity (as determined by granzyme and perforin expression) and attain a preference to migrate to peripheral tissue (e.g., the skin and lungs) rather than the lymphoid tissue. Differentiated CD8+ T cells are also efficient producers of inflammatory cytokines (e.g., TNF-α and IFN-γ,) (Clerici et al. 2001; Sansoni et al. 2008; Zanni et al. 2003), which may explain why CMV infection and the accumulation of late-differentiated T cells has been found to be associated with increased low-grade inflammation in some studies (Markovic-Plese et al. 2001; Schmidt et al. 1996; Sun et al. 2008; Wikby et al. 2006; Zanni et al. 2003). The reason these differentiated CD8+ T cells have been referred to as 'senescent' is related to other characteristics, such as having shorter telomeres, a low production of interleukin-2 (IL-2; which stimulates the growth, differentiation and survival of cytotoxic T cells), and the concomitant reduced ability to proliferate response to mitogenic stimulants (Monteiro et al. 1996; Nikolich-Zugich 2008b; van de Berg et al. 2010). Together, this CMV-induced accumulation of T cells displaying the cluster of senescent characteristics listed above, may underlie the heightened inflammation, increased risk for infection, and a reduced ability to respond to novel antigens, as well as accelerated cognitive decline observed in CMV infected adults (Larbi et al. 2009; Saurwein-Teissl et al. 2002; Trzonkowski et al. 2009; Wikby et al. 2005; Moro-Garcia et al. 2012). It is perhaps relevant to reiterate here that this cluster of immunological features is also characteristically found in response to protracted psychological stress (Segerstrom and Miller 2004).

6.2.5 The Number of Late-differentiated T Cells is Related to Viral Activity

One key assumption of the model presented here is that repeated viral reactivation, for example, as a result of stress-induced immune suppression, will promote the accumulation of late-differentiated cells and hereby promote related features of ïmmunosenescence. Virus specific T cells, such as those targeting CMV, are responsible for preventing reactivation and it would therefore be reasonable to assume a direct correlation between the number of those cells and viral load (Ogg et al. 1998; van Baarle et al. 2002). What is the evidence supporting that assumption? Research shows that immune-suppressed individuals (e.g., as a result of medical treatment or immunodeficiency diseases) are unable to maintain CMV in latency, and show larger expansions of late-differentiated T cells relative to and compared to immune-competent individuals (Gamadia et al. 2001). Less data is available for healthy free-living individuals, and recipients of organ transplants have frequently used as a model to study the kinetic effects of infection and reactivation on T cell repertoire. CMV-seronegative patients receiving CMV-infected renal transplants develop primary CMV infections and can therefore be studied longitudinally to examine the

effects of CMV infection and incessant viral reactivation. Generally, an increase in viral activity (as assessed by viral load in plasma, or IgG antibodies to CMV) promotes a compensatory increase in the number of CMV-specific T cells which do not express CD27 or CD28 (Cantisan et al. 2009; Gamadia et al. 2003, 2004). Thus, frequent reactivation of CMV, possibly by psychological stress (Coskun et al. 2010; Prösch et al. 2000; Sarid et al. 2001), might further exacerbate immunosenescence. The next section will address the evidence that psychological stressors may promote CMV reactivation.

6.3 Psychosocial Factors and CMV

6.3.1 Stress and CMV Reactivation

Although the literature on stress and CMV reactivation has examined a a wide variety of stressors, including academic exams, caring for spouses with Alzheimer's disease, space flight, and selfreported depressive symptoms, the results of these studies paint a fairly consistent picture whereby higher levels of distress are associated with higher CMV-specific IgG antibodies (used as a marker of viral reactivation). Overall, this literature replicates what has been found for other herpes viruses such as EBV and herpes simplex virus type 1 (HSV-1), which likewise show increased virus-specific IgG antibody titres with higher stress (Esterling et al. 1993; McDade et al. 2000; Shirtcliff et al. 2009).

Most studies that investigated the association between elevated distress and markers of CMV reactivity used plasma levels of virus-specific IgG antibodies as an outcome. This measurement approach is based on the assumption that increased viral load will activate the immune system, thereby stimulating B cells to increase the output of specific antibodies. While there is support for the validity this assumption, mainly from clinical data, it may be relevant to point out that other factors may also determine antibody levels. For example, exposure to different strains of the same virus, denoted as 'super-infection', may generate a more extensive polyclonal antibody response and concomitantly higher virus-specific antibody levels (Novak et al. 2008; Ross et al. 2010). The validity of the studies using antibody levels as an outcome measure are corroborated, by research that used other analytical techniques. CMV-specific IgG antibodies are found to increase in line with the increase in viral load, measured by real-time PCR in leukocytes (Kuo et al. 2008), and viral load in multiple tissues coincide with CMV-attributable clinical symptoms and disease (Boeckh and Boivin 1998). For example, Toro and Ossa assessed CMV viral load bi-weekly by quantitative PCR (qPCR) in blood, throat washings and urine. CMV viral load was then correlated with stressful psychological (e.g., academic tasks, work overload, insomnia) and physical events (e.g., trauma, surgery, X-ray or UV radiation exposure). The results revealed a positive association between CMV viral load and stress-producing events in the workplace (Toro and Ossa 1996).

Academic examinations are commonly employed as a model for acute and protracted stress (Bosch et al. 2001, 2003), and several studies have reported that

academic stress causes reactivation of herpes viruses such as EBV, HSV-1, and CMV. Glaser et al. (1985) investigated the effects of academic stress on CMV specific IgG antibody in 20 medical students and found a significant increase in antibody levels of during the first day of exams as compared to a non-stress baseline (the end of summer vacation) (Glaser et al. 1985). Changes in salivary IgG antibodies to CMV were observed in a cohort of 54 first-year nursing and physiotherapy students undergoing two exams, 2 weeks apart. This academic stressor was found to cause an approximate 65 % increase in CMV-specific salivary IgG and a 46 % increase in CMV-specific salivary IgA, as compared to baseline measurements performed at the beginning of the semester (Sarid et al. 2004). Matalka et al. (2000) investigated the effect of examination stress on CMV and EBV reactivation, defined as a 30 % increase in virus-specific IgG levels in 56 female nursing students. In both the summer and winter semester, blood samples were collected during a non-stressful period (start of semester) and a stressful-period of study (immediately after exams). Analysis of sera revealed reactivation in 26 % ($N = 12$) of all CMV-seropositive students during exams in both semesters (Matalka et al. 2000). The results of this study also suggested that there is a seasonal difference (summer vs. fall-winter) in CMV-reactivation due to academic stress, with larger effects during the winter season.

Appels et al. (2000) studied the link between depressive symptoms, vital exhaustion (a constellation of symptoms characterized by listlessness and fatigue), and CMV antibody titers in 30 patients with coronary artery disease. The patients classified as exhausted ($N = 15$) showed higher levels of inflammatory cytokines (i.e., IL-1β, IL-6 and TNF-α) in addition to elevated CMV titers compared to non-exhausted patients. After adjustment for depression the IL-1β and CMV IgM titers differences were still significant (Appels et al. 2000). However, this cross-sectional study was unable to determine if inflammation and viral reactivation caused, or were caused by, symptoms of fatigue. Inflammation might act as a pathway linking feelings of exhaustion and CMV reactivation (see the section below). In a follow-up, van der Ven et al. (2003) did not find associations between inflammatory cytokines (i.e. IL-6, IL-10, and IL-1Ra) and CMV antibody levels in 59 healthy individuals (van der Ven et al. 2003).

Phillips et al. (2008) found no association between CMV serostatus and psychological morbidity (depression and anxiety) in 137 older adults. However, in CMV seropositive individuals higher IgG antibody titers were positively correlated with symptoms of depression and anxiety (Phillips et al. 2008). The cross-sectional nature of this study did not allow for a determination of causality although the findings appear consistent with those of longitudinal studies showing that distress can trigger a reactivation of CMV (Mehta et al. 2000; Miller et al. 2002).

Miller et al. (2002) investigated the association between depression and inflammatory markers (CRP, IL-1β, IL-6, TNF-α and MCP-1) and infectious load (CMV and *Chlamydia pneumoniae*) in a group of 100 adults, of which 50 were clinically depressed. This study showed significant differences in CMV serostatus between depressed (42 % positive) and control (52 % positive) individuals. In a subsequent study, this group of researchers investigated the association between CMV serostatus and depressive symptoms in a sample of 65 patients recovering from an acute coronary syndrome (Miller et al. 2005). After splitting the subjects into three equal-sized

groups based on depression scores (using the Beck Depression Inventory), cardiac patients in the highest depression tertile were more likely to be CMV seropositive than the middle and lower tertiles. CMV+ patients also showed higher CRP levels compared to CMV-negative patients (Miller et al. 2005). The authors did not report data on antibody levels. Taken together, these results suggest that CMV seropositivity is related to a higher severity of depressive symptoms and inflammatory activity in patients with acute coronary.

Mehta et al. (2000) studied the effect of spaceflight on CMV reactivation, which was quantified by assessing the number of viral particles in urine (using qPCR) and by measuring CMV specific IgG antibody. It was observed that 10 % of the astronauts showed evidence of viral shedding (i.e., release of viral particles) in urine samples around the time of their mission, whereas this was only observed in 1 % of controls. Also serum CMV IgG levels increased from pre- to post-flight in astronauts, but only in astronauts who showed evidence of shedding (Mehta et al. 2000), suggesting that IgG titres are valid measures of reactivation. Viral shedding did not show a relation with endocrine measures (24 h urinary cortisol, adrenaline and noradrenaline). The authors also did not present any self-report data that could have corroborated a role for psychological stress, and thus a major role of physical factors (e.g., micro-gravity) cannot be excluded.

Uddin et al. (2010) assessed CMV-specific IgG antibody titers as a marker of immune function in 100 individuals, of whom 23 had lifetime post-traumatic stress disorder (PTSD). PTSD is a severe anxiety disorder that can develop after exposure to a psychologically impactful event, like being a victim of crime, accident, or a disaster or being a close witness to such events. Symptoms of PTSD typically include re-experiencing the original trauma(s) through flashbacks or nightmares, avoidance of situations and other stimuli that one associates with the events, and an elevated state of arousal and hypervigilance. PTSD is a chronic stressor that has inflammatory and immunological consequences (Gill et al. 2009). The results of Uddin et al. (2010) showed an approximately 45 % higher level of CMV-specific IgG antibody in those with PTSD versus unaffected individuals (Uddin et al. 2010).

6.3.2 Mechanisms of Stress-induced CMV Reactivation

The dominant hypothesis in psychoneuroimmunology is that latent viral reactivation is due to temporary or persistent stress-induced immune suppression. This immune suppression, in turn, may be related to dysregulation (typically hyperactivity) of various neuroendocrine stress systems (Bauer 2005; Bauer et al. 2000). Best studied in this regard are the hypothalamic–pituitary–adrenal cortex system, which regulates the release of glucocorticoids, and the sympathetic nervous system, which regulates the release of the catecholamines epinephrine and norepinephrine (Glaser and Kiecolt-Glaser 2005). While there is little doubt that this prototypical psycho-neuro-immunological pathway plays a role in viral reactivation, more direct pathways may be involved as well. One example, which we discuss in more detail here, is direct activation of the CMV promoter in the host genome. The CMV promoter is a gene

segment that regulates the expression of downstream major immediate-early (IE) genes. Expression of these genes plays an important role in the initial steps leading to reactivation of CMV from latency (Hermiston et al. 1987; Stenberg et al. 1984; Stinski and Isomura 2008). The CMV promoter region contains binding sites for transcription factors that are increased during inflammation and β-adrenergic stimulation, such Activator Protein 1 (AP-1) and cAMP Response Element Binding (CREB). This fact presents a potential pathway which may explain why systemic inflammation has been associated with CMV reactivation in various patient groups, including cardiovascular, transplant patients (Humar et al. 1999; Tong et al. 2001; Widmann et al. 2008) and intensive care unit (ICU) patients (Chilet et al. 2010; Limaye and Boeckh 2010; Limaye et al. 2008). For example, Docke et al. (1994) investigated the in vivo role of TNF-α on the reactivation of CMV in 60 septic patients in intensive care and observed CMV reactivation in 33 (75 %) of the 44 CMV-seropositive septic patients. The authors attributed the high frequency of CMV reactivation in the septic state to enhanced TNF-α levels. In addition, there is good experimental evidence that elevated sympathetic activation, and the concomitant release of the catecholamines epinephrine and norepinephrine, may likewise play a role (Docke et al. 1994; Prosch et al. 1999; Stein et al. 1993).

Stimulation of β-adrenergic receptors by catecholamines lead to a cascade of signaling that increases transcription factors (e.g., CREB/ATF-1) that directly affects CMV transcriptional activity (Montminy 1997). Prosch et al. (2000) studied myocardial infarction patients, who showed strongly elevated catecholamine but normal TNF-α plasma levels and observed viremia in a majority of patients, which peaked 7 days post-infarction. In vitro studies confirmed that stimulation of CMV-infected monocytes with epinephrine, as well as the beta2-adrenergic agonist propanolol, is capable of inducing CMV reactivation in these cells, as measured by expression of the Immediate/Early gene (I/E gene). The authors found little evidence of concomitant immunosuppression, and therefore concluded that catecholamines most likely induce reactivation directly via activation of the CMV IE enhancer/promoter and viral gene expression (Prosch et al. 2000). These experiments thus present an important non-immunological pathway by which stress may cause CMV reaction. A footnote is that although expression of the I/E genes are a first and essential step in reactivation, it is not sufficient for full viral replication, and therefore the definitive evidence for this mechanism still needs to be established.

6.4 CMV Infection Alters Immune System Responses to Acute Stress

The section above reviewed the evidence suggesting that psychosocial stressors may affect reactivation of CMV, which, we propose, may form a mechanism linking stress with accelerated immunological aging. Recent research from our laboratory has also shown that CMV may, in turn, alter psychobiological responses to stress, in particular stress-induced lymphocytosis. Lymphocytosis is probably one of the best documented effects of stress on the immune system: It involves a rapid (within minutes) increase in the absolute number of lymphocytes in the peripheral blood

(Benschop et al. 1996; Bosch et al. 2005; Dhabhar and McEwen 1999). It has been proposed that this stress-induced redeployment of immune cells enhances immunosurveillance in the face of potential threat, that is, when injury and concomitant infection are more likely (Benschop et al. 1996; Bosch et al. 2005; Dhabhar and McEwen 1997; Dopp et al. 2000). Lymphocytosis is driven by activation of β_2-adrenergic receptors (β_2AR) that are expressed by lymphocytes which become activated during the swift upsurge of catecholamines (epinephrine and norepinephrine) during psychological and physical stress. It is not surprising, then, that the strongest mobilisation is observed with lymphocyte subsets that exhibit the highest β2AR density, such as Natural Killer (NK) cells and CD8+ T cells. Via mechanisms that have not been well-characterized yet, these lymphocytes detach from endothelial cells and possibly other reservoirs, and become released into the blood (Benschop et al. 1996; Bosch et al. 2005; Dhabhar 2002; Dimitrov et al. 2010; Kuhlwein et al. 2001; Mills et al. 1995, 1997; Segerstrom and Miller 2004; Zorrilla et al. 2001).

Taking a closer look at the lymphocyte types (or 'subsets') that become mobilized during stress, it appears that this response is largely confined to cells that have a cytotoxic ability, such as the aforementioned NK cells and CD8+ T lymphocytes (CTLs), but also gamma-delta ($\gamma\delta$) T cells and the small subset of cytotoxic CD4+ T cells (Anane et al. 2009; Campbell et al. 2009; Elenkov et al. 2000). Further, even among these lymphocyte subtypes there is a response heterogeneity whereby phenotypes that show an enhanced effector potential (e.g., the ability for cytotoxicity, and inflammatory cytokine production) and exhibit a high-tissue migrating ability (e.g., as evidenced by the elevated expression adhesion molecules such as CD11a+), show the strongest mobilisation during stress (Anane et al. 2010; Bosch et al. 2005; Campbell et al. 2009; Dimitrov et al. 2010). Coincidentally, these cytotoxic T cell subsets are the same types that become strongly enriched in peripheral blood as a result of CMV infection. Thus, acute psychological stress and exercise have been demonstrated to evoke a strong and robust mobilization of the "effector-like" EMRA (CD45RA+ $CD27^-/CD28^-$) and EM ($CD45RA^-CD27^-/CD28^-$) phenotypes. In contrast, the naïve and CM subsets, which have little or no cytotoxic effector functions, are not mobilized by acute stress. The selectivity of the response is likely explained by increased expression of the β_2AR by the stress sensitive EM and, in particular, the EMRA populations (Dimitrov et al. 2009, 2010).

As previously discussed, infection with CMV can dramatically alter the CTL compartment by inducing the accumulation of these β_2AR expressing, stress sensitive, EM and EMRA cells. This enrichment would suggest that CMV infection is associated with an elevated lymphocytosis response to stress and exercise. This is indeed what we found; we observed an increase in lymphocytosis? (how was reactivity measured?) in CMV-seropositive hosts, when compared to CMV-seronegative individuals. Subsequent analyses further showed that CMV-specific CTLs had a greater propensity to mobilize than total CTLs and contained a larger proportion of EM and EMRA cells (Riddell, manuscript in preparation). Further, the same correlation between CMV seropositivity and a greater CTL mobilization is also apparent during exercise (Turner et al. 2010).

While a fascinating physiological phenomenon, it is still unclear if the enhanced stress-induced recruitment of cytotoxic cells in CMV-seropositive individuals has any immunological or clinical impact. However, the inflammatory potential of these effector-like CTLs is consistent with the idea that acute stress may cause exacerbation of inflammatory conditions, such as atherosclerosis, via promoting cell migration into the inflamed tissues (Bosch et al. 2003a, 2003b; Marsland et al. 2002; Nyklicek et al. 2005). Moreover, the enhanced adrenergic sensitivity of CMV-specific CTLs may directly impact viral control as adrenergic stimulation of T cells can alter a variety of effector functions including proliferation, lytic activity, and cytokine production (Bartik et al. 1993; Borger et al. 1998; Glaser and Kiecolt-Glaser 2005; Gratama et al. 2008; Hatfield et al. 1986; Kalinichenko et al. 1999; Leo and Bonneau 2000; Lilleri et al. 2008; Morita-Hoshi et al. 2008; Ozdemir et al. 2002; Sarid et al. 2001, 2004; Sekut et al. 1995).

In summary, while research in psychoneuroimmunology traditionally emphasizes the role of genotype and psychological experiences as key determinants of immune system responses to stress, infection history may be another and thus far underexplored determinant. One may speculate that amplification of cytotoxic lymphocyte mobilization during stressful events in CMV+ individuals may be conducive to systemic inflammation while also decreasing antigen-specific immunity, both of which are hallmarks of immunosenescence.

6.5 Summary and Conclusion

While much research effort has been dedicated to identifying the biological determinants of immune senescence, the potential role of psychosocial and behavioral factors remains ill-considered. This neglect seems unwarranted considering the remarkable similarities between the functional and phenotypical immune changes observed during immunosenescence and those seen in response to protracted stress. These changes include increases in circulating effector memory CTLs, impaired proliferation in response to mitogens, shortening of telomeres, diminished response to vaccination, and a skewed CD4/CD8 ratio. These parallels beg the question of whether the overlapping age- and stress-related immune effects involve similar pathways. This chapter presented a hypothesis whereby infection history is a proposed as a shared mechanism linking psychosocial stress with aging of the immune system. Specifically, we proposed that latent infection with and subsequent reactivation of CMV may act as a mediator linking stress and age-related decline in immunity.

In recent years, it has become increasingly clear that incessant antigenic stimulation by herpes viruses, in particular CMV, is a major driving force in senescence within the T-cell compartment. This aspect of immunosenescence is characterized by a dramatic expansion of CD8+ T lymphocytes that have an effector-memory phenotype (e.g., CD57+/CD27−/CD28−/CCR7−/CD62 L−). The extent of this expansion predicts reduced immune competence and increased morbidity and mortality in epidemiological and experimental studies. The observations from this literature

seem to dovetail remarkably well with evidence from human and animal studies showing that stress is associated with reactivation of latent herpes viruses, including CMV. The processes and mechanisms involved in this reactivation have been well-characterized, and include the impairment of cellular immunity by stress hormones such as catecholamines and glucocorticoids, as well as direct genomic viral activation by these hormones. Hence, here we presented a model that combines these different strands of evidence. In brief, what we propose is that psychological and physical stressors facilitate CMV reactivation and thereby accelerate T cell immunosenescence. A limitation of this model is that although its subcomponents have been confirmed (i.e., stress and latent herpes reactivation, and the role of CMV infection in development of immunosenescence), the full model still awaits empirical scrutiny. This scrutiny seems worthwhile as confirmation will have significant implications for our understanding of the links between stress and immunity. One of its main implications would perhaps be that the host's infection history is an important, and thus far overlooked, mediator of these links.

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