The Impact of Everyday Stressors on the Immune System and Health

6

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6.1 Stress, Immunity, and Health

The central nervous system (CNS), endocrine system, and immune system are complex systems that interact with each other. Stressful life events and the negative emotions they generate can dysregulate the immune response by disturbing the sensitive interplay among these systems (Glaser and Kiecolt-Glaser 2005). Psychoneuroimmunology (PNI) is a field of investigation concerned with the interactions of psychological factors with the neuroendocrine and immune system and consequences for higher brain function and human behavior (Dantzer 2010).

A stressor can be defined as an event that exceeds an individual's perceived ability to cope (Lazarus and Folkman 1984) and can result in an allostatic load and overload (see Chap. 4). Individual differences exist in the extent to which people mount a physiological stress response. Individual differences in stress physiology are, among other things, related to the brain, which plays a critical role in appraising stressors, as well as in modulating immune system reactivity to physical and

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social threats (Slavich and Irwin 2014). Additionally, certain characteristics of a situation are associated with greater stress responses, including the intensity, severity, controllability, and predictability of the stressor. Physiological reactivity to stressors are commonly observed even after repeated exposure to the same stressor (Dhabhar 2014).

The autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis are two major stress-signaling pathways that contribute to immune dysregulation (Glaser and Kiecolt-Glaser 2005). Experiencing a stressful situation, as perceived by the brain, activates the HPA axis and the sympathetic-adrenal medullary axis (SAM), which provokes the release of hormones which modulate immune function including adrenocorticotropic hormone (ACTH), cortisol, growth hormone, prolactin, epinephrine, and norepinephrine (Glaser and Kiecolt-Glaser 2005) (see Chap. 7).

Immunity is the natural or acquired resistance of an organism to bacterial or viral invaders, diseases, or infections, while having adequate tolerance to avoid allergy, and autoimmune diseases. Lymphocytes, including T and B cells are the main type of cells of the immune system. T cells orchestrate the immune response via the production of cytokines and stimulate B cells to produce antibodies and signal killer cells to destroy the antigen-displaying cell (Sompayrac 2016). Helper T cells (Th) can be separated into Th1 cells, which primarily produce IL-2, IFN-γ and TNF, and Th2 cells, which produce IL-4, IL-5, IL-6, IL-10, and IL-13. Typically, type 1 cytokines favor the development of a strong cellular immune response, whereas type 2 cytokines favor a strong humoral immune response (Spellberg and Edwards Jr. 2001). Chronic stress can suppress or dysregulate innate and adaptive immune responses by altering the type 1/type 2 cytokine balance, thereby inducing low-grade inflammation and suppressing the function of immuno-protective cells (Dhabhar 2014).

A primary focus of the field of psychoneuroimmunology has been to understanding the link between stress and inflammatory responses. Although acute inflammation is an adaptive response to physical injury or infection, exaggerated and/or prolonged inflammatory responses are detrimental to health (Dhabhar 2014). Chronic inflammation secondary to long-term stress has been causally linked with risk for numerous diseases, including infectious illnesses, cardiovascular disease, diabetes, certain cancers, and autoimmune disease, as well as general frailty and mortality (Glaser and Kiecolt-Glaser 2005; Dhabhar 2014; Padro and Sanders 2014; Webster Marketon and Glaser 2008). One potential explanation for the mechanism linking chronic stress and inflammation in the onset of a wide range of diseases is that prolonged stressors result in glucocorticoid receptor resistance, which, in turn, causes dysregulated HPA axis function and interferes with the appropriate regulation of inflammation (Cohen et al. 2012).

Animal models have provided compelling evidence that biobehavioral stress mechanisms and their molecular and cellular pathways can cause illness behavior and illness itself. These experimental studies have conclusively demonstrated that exposure to restraint stress triggers exaggerated inflammatory responses (Korte et al. 1992; Ahlers et al. 1980; Bartolomucci et al. 2003). In addition, pharmacological

experiments have amply demonstrated that mice injected with proinflammatory cytokines, including IL-1β or TNF, have decreased motor activity, social withdrawal, reduced food and water intake, increased slow-wave sleep, altered cognition, and increased pain sensitivity (Bluthe et al. 2000; Dantzer 2009). These experiments highlight how conditions of chronic inflammation can induce sickness and depressive-like behaviors in response to chronic stress (Dantzer et al. 2008).

6.2 Stress and Wound Healing

Wound healing is a vitally important process during recovery from either injury or surgery. Poor healing is associated with increased risks for wound infections and other complications, patient discomfort, prolonged hospital stays, and delays in one's return to normal activities (Tevis and Kennedy 2013). Converging evidence from observational, experimental, and interventional studies implies that stress and other behavioral factors can impede wound healing processes and compromise immunity via multiple physiological pathways (Kiecolt-Glaser et al. 1998; Gouin et al. 2008; Ebrecht et al. 2004; Pinto et al. 2016; Walburn et al. 2009).

Wound healing progresses through several sequential and overlapping phases, including inflammation, proliferation, and regeneration. Cellular immunity plays an important role in the regulation of wound healing through the production of proinflammatory cytokines and chemokines (e.g., platelet derived growth factor [PDG]; transforming growth factor [TGF]; vascular endothelial growth factor [VEGF]; TNF; IFN-γ; IL-1β; IL-8), which mediate many of the complex interactions involved in wound healing. These factors act as chemo-attractants for the migration of phagocytes and other cells to the wound site, starting the proliferative phase which involves the recruitment and replication of cells necessary for tissue regeneration and capillary regrowth (Gethin 2012). Inflammation is a prerequisite to healing. Proinflammatory cytokines help to protect against infection and prepare injured tissue for repair by enhancing the recruitment and activation of phagocytes. Unfortunately, stress disrupts the production of proinflammatory cytokines that are essential for wound healing and, when dysregulated, impose a considerable delay in wound repair (Gouin and Kiecolt-Glaser 2011).

The clinical relevance of the relationship between stress and impaired wound healing has been demonstrated in several studies. In one experiment, individuals with a "slow healing" speed had higher stress and higher cortisol levels at awakening, implicating a key role of elevated cortisol levels in the process of cutaneous wound healing (Ebrecht et al. 2004). A meta-analysis (Walburn et al. 2009) corroborated these findings, synthesizing 17 articles that documented how stress is significantly associated with impaired healing and dysregulation of biomarkers crucial to wound healing. In addition to this meta-analysis, a statistically significant and moderately strong inverse correlation of $r = -0.42$ (95% CI = −0.51 to −0.32; $p < 0.01$) was calculated between the level of stress and speed of wound healing. These results confirm earlier findings by Kiecolt-Glaser et al. (1995), who observed that women experiencing the long-term stress of caring for a relative with Alzheimer's disease,

took 24% longer than controls to heal a small, standardized dermal wound. In addition, the peripheral blood leukocytes of caregivers produced less IL-1β in response to lipopolysaccharide (LPS) stimulation.

Surgical complications (e.g., postoperative pain; permanent disfigurement) pose significant challenges to surgical patients and may contribute to psychological distress, anxiety, and depression (Pinto et al. 2016). In an observational study involving patients undergoing coronary artery bypass graft (CABG) surgery, individuals with more depressive symptoms at discharge had more infections and poorer wound healing over the first six weeks following surgery than individuals who reported less distress (Doering et al. 2005). In addition, the pain associated with surgery can itself generate psychological distress, which has been shown to further influence wound healing. A prospective study involving 17 women who underwent elective gastric bypass surgery revealed that greater acute pain immediately after surgery and persistent pain in the four weeks following surgery both were associated with slower healing (McGuire et al. 2006).

In summary, acute and chronic stressors can negatively impact the wound healing process, by interrupting the inflammatory cascade that is fundamental for wound repair. These findings highlight the importance of addressing patients' psychological needs in a timely manner, if possible both before and immediately after surgery, so as to prevent stress-related immune disruption.

6.3 Stress and Infectious Agents

Stress can also dysregulate humoral and cellular immune responses to pathogens, increasing risk for infectious illnesses including influenza and the common cold (Glaser and Kiecolt-Glaser 2005). The association between psychological stress and susceptibility to the common cold has long been recognized; stress suppresses the host resistance to infection and increases rates of infection (Cohen et al. 1991). Loneliness is another well-established risk factor for poor physical health. In a study of our own, we were able to demonstrate that loneliness predicts self-reported cold symptoms after a viral challenge, suggesting that cold symptoms are more severe among those who feel lonely (LeRoy et al. 2017).

Vaccination against influenza virus reduces both risk and severity of infection, thus decreasing risk for hospitalization and death. Vaccine effectiveness is of particular importance among high-risk groups, including pregnant women and older adults. However, the protective efficacy of antiviral vaccines depends upon their ability to induce both humoral and cell-mediated immune responses (Lambert et al. 2012).

A meta-analysis of 13 studies concluded that the effect of stress on antibody responses to influenza virus vaccination corresponded to adequate antibody responses among 41% of stressed individuals versus 59% of less-stressed individuals with similar effects among older and younger adults (Pedersen et al. 2009). Furthermore, psychological distress and biobehavioral vulnerabilities, which arise from being older or sedentary, have independently been found to alter immune responses to influenza vaccination (Segerstrom et al. 2012). In addition, studies in

adults and adolescence have confirmed that negative emotions, including anxiety and depression, can modulate the antibody and T-cell responses to antiviral vaccinations, resulting in suppressed immune responses (O'Connor et al. 2014; Coughlin 2012). Interestingly, a 4-week massage intervention in students embarking on academic examinations was associated with reduced distress and enhanced antibody responses after a hepatitis B vaccine (Loft et al. 2012). Positive effects of other mind-body therapies, including Tai Chi, Qi Gong, meditation, and Yoga, on the immune system and virus-specific antibody responses to vaccines have also been documented in a meta-analysis of 34 studies (Morgan et al. 2014).

Herpes viruses, including herpes simplex virus (HSV) I and II, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV), assume a latent state after the initial infection (Grinde 2013). After primary infection, the herpes virus continues to reside in B lymphocytes and white blood cells for the life of the individual. Under normal health conditions, reactivation and replication of the EBV virus is prevented by the cellular immune system, largely orchestrated through specific-memory cytotoxic T cells and natural killer (NK); thus, individuals with herpesvirus infections generally remain asymptomatic (Glaser et al. 1993). However, under stressful conditions, suppressive immune activity may be reduced, permitting reactivation of the virus.

The relationships between neuroendocrine activity, immune function, and latent HSV type 1 reactivation were initially documented in animal studies. Among mice infected with HSV type 1, those exposed to a stressor exhibited reactivation of the latent virus, whereas nonstressed mice did not (Padgett et al. 1998). Today, a body of literature in humans confirms that psychosocial stressors predict reactivation of latent viruses (see Chap. 19). For instance, higher self-reported health was associated with lower reactivation of latent herpesviruses and inflammation (Murdock et al. 2016). Meanwhile, increased antibody titers against EBV viral capsid antigen (VCA) have been observed in the context of depression (Bennett et al. 2012), perceived stress (Brook et al. 2017), childhood adversity (Fagundes et al. 2013a), bereavement or divorce (Derry et al. 2012), exam stress (Matalka et al. 2000), attachment anxiety (Fagundes et al. 2014), and perceived discrimination (Christian et al. 2012). Together, these human and animal studies show that stress can modulate the steady-state expression of latent herpesviruses, downregulating specific T-cell responses to the virus to an extent that is sufficient to result in viral activation.

Human immunodeficiency virus (HIV) is similar to herpes viruses, in that the virus remains in a latent state in the body after primary infection. As individuals infected with HIV may have lowered levels of T cells, cells that are important to fight infections, much interest exists in whether chronic stress and depression—that also are known to suppress the human immune system—may affect HIV disease progression. Indeed, there is a substantial body of evidence pointing at a relationship between chronic stress and the rate of HIV disease progression. In particular, stressful life events are considered to exert important impacts on certain biological markers of the disease: viral load and CD4 cell count (Kołodziej 2016). For instance, HIV-infected persons with posttraumatic stress disorders (PTSD) after Hurricane

Katrina were more likely than those without PTSD to have detectable plasma viral loads and CD4 cell counts <200 mm^{-3} at 12 and 14 months, as well as two years post disaster (Reilly et al. 2009).

Major depression is highly prevalent among HIV-positive patients. Depression is associated with, among other factors, increased inflammatory markers (e.g., CRP; IL-1β; IL-6, TNF) (Slavich and Irwin 2014), which may alter the function of lymphocytes and decrease NK activity, contributing to HIV disease progression and mortality in these patients (Arseniou et al. 2014). These findings are corroborated by a study that investigated norepinephrine, cortisol, depression, hopelessness, coping, and life event stress as predictors of HIV progression in a diverse subject sample every 6 months over a period of 4 years. The authors found that norepinephrine, depression, hopelessness, and avoidant coping significantly predicted a greater rate of decrease in CD4 and increase in viral load, demonstrating a robust effect of chronic stress on HIV disease progression (Ironson et al. 2015).

In summary, stress can not only increase susceptibility to illness after exposure to infectious agents but also can inhibit antibody and virus-specific T cell responses to vaccines, permit reactivation of latent herpesviruses, and influence the progression of HIV-related disease.

6.4 Stress and Cardiovascular Disease

Cardiovascular disease (CVD) is a major cause of morbidity and mortality. Chronic low-grade inflammation is implicated in the link between stress and CVD via contributions to the early emergence, progression, and thrombotic complications of atherosclerosis (Liu et al. 2017). IL-6 and CRP, two important biomarkers of inflammation, are thought to be indicative and potentially predictive of atherosclerosis (Nadrowski et al. 2016). Of clinical importance, the biological effects of stress do not exist in isolation, and are often aggravated by unhealthy behaviors including poor diet, inadequate physical activity, tobacco use, and poor adherence to medication (Lagraauw et al. 2015).

Epidemiological research over the last half-century has conclusively linked chronic stress and other psychosocial factors to the increased incidence of coronary artery disease (von Kanel 2012). For instance, individuals exposed to work-related stressors including shiftwork, workplace conflict, and positions typified by high demands combined with low control, exhibit risk for elevations in serum CRP and IL-6 (von Kanel et al. 2008), as well as CVD (Kivimaki and Kawachi 2015). Furthermore, evidence suggests that childhood adversity, particularly severe physical and sexual abuse, confers risk for cardiovascular events, particularly among women (Garad et al. 2017). Similarly, among adults with greater childhood adversity/trauma, elevated risk for depressive symptoms, higher serum CRP, reduced methylation of the IL-6 promoter, and higher serum IL-6 have been observed (Janusek et al. 2017). These results shed light on potential epigenetic mechanisms that could link childhood adversity to disproportionally elevated risks of inflammatory disease in adulthood.

6.5 Stress and Metabolic Disease

Type-2 diabetes mellitus (T2DM) is a chronic metabolic disorder that results from defects in insulin secretion and insulin action (Hackett and Steptoe 2017). Though limited, an emerging body of literature suggests that stress plays a role in the etiology of T2DM, both as a predictor of new-onset T2DM and as a prognostic factor in individuals with existing T2DM (Hackett and Steptoe 2017). Stress-related biological pathways, including chronic activation of the HPA axis, which can lead to dysregulated cortisol output and neuroendocrine dysfunction, have been conjectured to contribute to the pathogenesis of T2DM (Hackett and Steptoe 2017). For instance, insulin resistance frequently develops during acute or chronic stress (Tsuneki et al. 2013). Moreover, obesity commonly co-occurs in patients with T2DM, and visceral adipose tissue (e.g., adipokines) is a major source of inflammation, including CRP, IL-1β and IL-6 (Donath and Shoelson 2011), supporting a link between T2DM and inflammation.

Results from meta-analyses suggest that depression further contributes to an increased risk of diabetes mellitus (Bădescu et al. 2016; Yu et al. 2015). Stress exposure during childhood has also been found to constitute a risk factor for obesity and diabetes. Experiencing an adverse childhood experience increases a child's risk of type 1 diabetes during childhood (Nygren et al. 2015). Likewise, a review of literature revealed a significant association between exposure to childhood adversity and an increased risk of T2DM in adulthood (Huffhines et al. 2016; Hughes et al. 2017), with the effects of neglect and sexual abuse most prominent (Huang et al. 2015). Of particular note, stress can perinatally impair metabolic health in later life. Fetal exposure to high concentrations of maternal glucocorticoids, as well as obesity, have been associated with low birth weight, which in turn is associated with increased risk for hypertension, diabetes, and cardiometabolic diseases during adulthood (Zöller et al. 2015; Capra et al. 2013). However, the mechanisms for this effect are not yet fully understood. One novel potential pathway linking maternal and child weight is the transmission of obesogenic microbes from mother to child (Galley et al. 2014).

6.6 Stress and Cancer

Research over the past 30 years in the field of psychoneuroimmunology has contributed to considerable understanding of the effect of stress on cancer biology, and has identified psychosocial factors including stress, depression, and the lack of social support as risk factors for tumor progression (Moreno-Smith et al. 2010). Stress hormones (e.g., glucocorticoids, norepinephrine, epinephrine) have multiple effects on human tumor biology. Thus, via adrenergic- and glucocorticoid-mediated mechanisms, sympathetic nervous system (SNS)-activation may alter immune defenses mechanisms and anti-tumor immune capabilities with implications for tumor progression (Antoni et al. 2006; Lutgendorf and Andersen 2015; Armaiz-Pena et al. 2013). For instance, exposure to chronic stress (Lamkin et al. 2012) as well as the

pharmacological stimulation of SNS pathways with a β-adrenergic agonist (e.g., isoproterenol) (Sloan et al. 2010) in tumor-bearing animals, significantly enhances tumor progression and metastasis, implying a fundamental role of stress hormones and β-adrenergic receptor signaling in both processes. Furthermore, both animal and human studies have consistently revealed that the negative effects of stress on tumor cell dissemination can be abrogated using a β2-adrenergic receptor antagonist (e.g., propranolol), supporting the use of β-blockers to modulate cancer metastasis (Sloan et al. 2010; Shaashua et al. 2017).

Chronic stress can increase inflammation and alter protective immune responses, and thereby may increase susceptibility to certain types of cancer by suppressing type 1 cytokines and protective T cells, and increasing regulatory/suppressor T-cell function (Dhabhar 2014). Correspondingly, increased catecholamine levels have been linked to T lymphocyte apoptosis (Radojevic et al. 2014), altered distribution of NK (see also Chap. 13) and granulocytes, and suppressed NK activity (Elenkov and Chrousos 2002), all important defense mechanisms against tumors and their metastasis (see also Chap. 13). It has become clear that cancer-related systemic inflammation is associated with poor outcomes, independent of tumor stage (Dolan et al. 2017). Several inflammatory mediators including IL-6, IL-12, IFN-γ, and TNF are implicated in tumor growth and progression (Cash et al. 2015; Landskron et al. 2014).

The immune system plays a critical role in the occurrence and progression of immunogenic tumors, including skin cancer (Song et al. 2016). For instance, an increased immune response reflected by enhanced expression of intercellular adhesion molecule (ICAM) 1 and infiltration of CD68+ cells (macrophages) surrounding, or within the tumor, have been observed during basal cell carcinoma (BCC) tumor regression following treatment (De Giorgi et al. 2009; Urosevic et al. 2003). Furthermore, immunosuppression, such as in solid-organ transplant recipients and patients with human immunodeficiency virus (HIV) or hematologic malignant neoplasms, has been clearly linked with increased incidence of non-melanoma skin cancer, including BCC, and squamous cell carcinoma (Song et al. 2016; Jensen et al. 2009).

Importantly, chronic stress can alter the anti-tumor-specific immune response to immunogenic tumors. Our own data demonstrate that emotional maltreatment in childhood and occurrence of a major life event in adulthood, showed poorer immune responses to BCC as indexed by suppressed expression of messenger RNA (mRNA) immune markers (CD25, CD3ε, ICAM-1, and CD68) to BCC (Fagundes et al. 2012). Animal models support these findings; mice under restraint stress developed ultraviolet-light (Illi et al. 2012) -induced squamous cell carcinoma more rapidly and showed a poorer immune response [as assessed by messenger RNA (mRNA) in their tumors] relative to nonstressed control mice (Saul et al. 2005). Taken together, these preclinical and clinical studies provide evidence that behavioral stressors can influence the tumor microenvironment.

While much initial work focused on direct effects of catecholamines and other stress mediators on cancer progression, subsequent work identified that the tumor microenvironment is a critical regulator of cancer progression and metastasis (Landskron et al. 2014; Wang et al. 2017; Berghoff and Preusser 2015). The tumor

microenvironment has a pivotal role in regulating tumor cell growth, invasion, and metastasis, specifically through reciprocal cross-talk with infiltrating immune cells (lymphocytes, neutrophils, and macrophages), endothelial cells, mesenchymal stromal cells (fibroblasts and myofibroblasts), and their secretory products, all of which can modulate gene expression and alter the behavior of tumor cells (Mostofa et al. 2017).

6.7 Contextual Factors and Immune-Dysregulation

6.7.1 Stressful Life Events

Many investigators have studied pathways between major life events and inflammation. Caring for a loved one with a chronic medical condition, such as a spouse with dementia, is commonly characterized by significant life changes and social isolation (Holmes and Rahe 1967). The chronic stress of caregiving has been linked with exacerbation of typical age-related increases in serum levels of IL-6 and CRP (Gouin et al. 2012), providing a plausible physiological pathway via which chronic stress may lead to poor health. Analogously, the loss of a spouse is considered one of the most stressful life events one may encounter (Holmes and Rahe 1967). Indeed, bereavement has been associated with increased inflammation (Buckley et al. 2012; Cohen et al. 2015) as well as elevated rates of chronic inflammatory conditions, including type 2 diabetes, cardiovascular disease, and cancer within the first three years following the death (Stahl et al. 2016).

Particularly strong evidence indicates that trauma exposure during adulthood increases risks for psychiatric morbidity and poor health outcomes, and there is emerging evidence that inflammation contributes to this link (Flory and Yehuda 2015). Trauma exposure and posttraumatic stress disorder (PTSD, see Chap. 7) have been linked to increased risks of both depression (Dunn et al. 2017) and cardiovascular disorders (Edmondson and von Kanel 2017). The prevalence of trauma-related inflammation was addressed in a review paper, providing evidence for elevated systemic inflammation in individuals with PTSD, with this effect especially strong among those with comorbid PTSD and depression (Baker et al. 2012). In another study involving survivors of the World Trade Center attacks on September 11, 2001, altered salivary cortisol responses to trauma activation (induced by trauma recollections through a standardized interview) were observed, with stronger effects documented in those with comorbid PTSD and depression (Dekel et al. 2017).

6.7.2 Adverse Childhood Experiences

Early adversity confers risk for physical and mental illness (e.g., depression, cardiovascular disease, type 2 diabetes, cancer) in adulthood (Ziol-Guest et al. 2012; Ehrlich et al. 2016) with more robust effects amongst those experiencing multiple adversities (Hughes et al. 2017). Inflammatory pathways are implicated in these

links; meta-analyses of 25 studies concluded that early life adversity contributes to significantly elevated peripheral CRP, IL-6, and TNF in adulthood (Baumeister et al. 2016). Most interestingly, different types of trauma exposure impacted inflammatory markers differentially: physical and sexual abuse were associated with significantly increased TNF and IL-6, but not CRP (Baumeister et al. 2016). Similar results were reported by Lin et al. (2016), who found that adults who had experienced childhood adversity had elevated levels of CRP and were almost three times as likely to have experienced trauma as an adult, relative to those without adverse childhood experiences.

Health behaviors (e.g., smoking and obesity) appear to partially mediate this relationship. For instance, in one study it was shown that early adversity predicted increased smoking and BMI through ongoing chronic stress in young adulthood (Raposa et al. 2014). In the same study, higher BMI predicted higher levels of soluble TNF receptor type II (sTNF-RII) and CRP, suggesting that early adversity contributes to inflammation, in part through ongoing stress and maladaptive health behaviors. In accordance with this, several previous studies provide evidence that specific early adversity, including low socioeconomic status in childhood (Brummett et al. 2013; Hagger-Johnson et al. 2012) and childhood abuse (Matthews et al. 2014), affects CRP through unhealthy behaviors and increased BMI.

Evidence also supports a role for heightened emotional and physiological reactivity to stress, which in turn drives the expression of an increasingly proinflammatory phenotype (Slavich and Irwin 2014). In accordance with this assumption, Shapero et al. (2014) reported that individuals with more severe childhood emotional abuse experienced greater increases in depressive symptoms when confronted with a stressor, implying the importance of emotional abuse as an indicator of reactivity to stressful life events. In addition, individuals who have experienced childhood adversities may have fewer social and psychological resources available to them for coping with stress (Fagundes et al. 2013b).

Taken together, intense and chronic stress experienced during one's developmental years appears to have long-lasting neurobiological effects and increases one's risk of later morbidity (e.g., anxiety, depression, and physical disorders) and mortality (Raposa et al. 2014; Fagundes et al. 2013b). Another important effect is that stress exposure during childhood might alter behavioral and physiological responses to acute and chronic stress in adulthood, which may determine one's later risk of disease.

6.7.3 Pregnancy

The prenatal period is a critical time for neurodevelopment and, as such, represents a period of vulnerability during which a wide range of exposures has been found to exert long-term effects on brain development and behaviors (Christian 2012). Maternal psychosocial stress during pregnancy is associated with risks to maternal health and birth outcomes, as well as to various adverse health and behavioral outcomes in the offspring (Christian 2015). During pregnancy, the immune system

undergoes substantial adaptations. Under normal circumstances, pregnancy is characterized by elevations in circulating inflammatory mediators relative to nonpregnancy (Christian and Porter 2014). However, excessive inflammation or deviations in inflammatory trajectories of change across pregnancy have been associated with gestational hypertension, miscarriages, preterm births, and adverse influences on fetal development (Christian 2012).

Stress, anxiety, and depression in pregnancy are considerable risk factors for adverse outcomes for both mothers and babies, and are associated with shorter gestation and impaired fetal neurodevelopment and child outcomes (Christian 2012). Inflammation is a likely mechanism by which stress may promote these negative health outcomes (Christian et al. 2009).

Inflammatory responses to influenza virus vaccine have been shown to be mild, transient, and generally similar in pregnant and nonpregnant women (Christian et al. 2013a). Since it is considered safe and recommended for pregnant women, seasonal influenza vaccination provides a useful model with which to study individual differences in inflammatory responses during pregnancy. In one influenza-virus vaccine study in pregnant women, Christian et al. (2013a) demonstrated that women in the highest percentile of depressive symptoms had markedly higher inflammatory responses, as indicated by elevated serum levels of macrophage migration inhibitory factor (MIF) one week post-vaccination, indicating that women with depressive symptoms may be more vulnerable to negative sequelae of infectious illness during pregnancy. Similarly, in pregnant women, greater EBV reactivation has been reported in association with maternal depression, perceived distress, and perceived racial discrimination. Notably, this effect was significantly stronger among African American women who reported greater racial discrimination (Christian et al. 2012).

Other risk factors can mediate the association between chronic stress and inflammation in pregnant women. Obesity, conceptualized as a physiological stress, has been linked to considerable increases in circulatory inflammatory markers, particularly IL-6, throughout pregnancy and postpartum. Moreover, psychological stress and obesity may interact synergistically, resulting in more pronounced effects among women with both risk factors (Mitchell and Christian 2018). In addition, obesity has been observed to increase the risks of gestational hypertension and gestational diabetes via inflammatory pathways. Most importantly, obesity-induced inflammation is transmitted to the child, and can potentially affect their immune function, metabolism, and cognitive development (Christian 2015). In addition, it is well established that poor sleep triggers inflammation. Accordingly, sleep-induced immune dysregulation has been found to be predictive of preterm birth. This effect, again, was especially pronounced in African American women (Blair et al. 2015). Indeed, the relationship between stress-induced inflammatory responses has been found to be more robust in racial minorities, placing these women at greater risk of delivering their infants preterm (Christian et al. 2013b).

Self-rated health is a reliable predictor of health outcomes including morbidity and mortality (Idler and Benyamini 1997; Nielsen et al. 2008). Indeed, poorer self-rated health has been shown to be associated with significantly higher serum IL-1β

and MIF in pregnant women during the second trimester, suggesting an influential role of inflammation on self-rated health prior to the emergence of objective and quantifiable signs of disease (Christian et al. 2013c).

These studies suggest that pregnant women with psychosocial risk factors may experience higher daily exposure to inflammatory mediators. It is critical to identify biological markers, symptoms, and diagnostic thresholds that warrant prenatal intervention, and to develop efficient and valid screening and intervention strategies to prevent stress-related adverse health outcomes in mothers and their offspring.

6.7.4 Aging

Chronic stress has been shown to suppress and dysregulate immune function by affecting immunosenescence (Mathur et al. 2016). The term *immunosenescence* refers to a loss of immune function that typically occurs in elderly individuals. Declining T-cell function is a very well-characterized feature of immunosenescence, which contributes to chronic low-grade inflammation (Wu and Meydani 2008). Typically, elderly individuals (aged 65 years and older) compared with other age groups have two- to fourfold elevations in circulating levels of proinflammatory cytokines, such as IL-6, TNF, CRP, and serum amyloid A (SAA) (Michaud et al. 2013), which in turn suppresses the function of immune-protective cells and disrupts the body's ability to defend itself against bacteria, viruses, and parasites. As a result, age-associated deterioration in immune function contributes to many illnesses and renders older individuals more vulnerable to further assaults on their immune system (e.g., stress, immunocompromising medications, infectious diseases) (Burleson et al. 2002). Dysregulation of the inflammatory pathway may also affect the central nervous system and the pathophysiological mechanisms of neurodegenerative disorders including Alzheimer's disease (McCaulley and Grush 2015).

Epel et al. (2004) demonstrated that chronic stress in healthy premenopausal women was significantly associated with higher oxidative stress, lower telomerase activity, and shorter telomere length. Telomere length shortens with age (Rizvi et al. 2014). Extensive research has revealed that progressive shortening of telomeres leads to senescence, apoptosis, and carcinogenesis, which has been associated with the increased incidence of various diseases and poor survival (Shammas 2011). Moreover, adverse life experiences and lifestyle factors appear to affect the rate of telomere shortening over one's lifespan (Rizvi et al. 2014). In accordance with these findings, in one of their studies Kiecolt-Glaser et al. (2011) demonstrated that childhood adversities have considerable consequences for cell aging in later life, and that the presence of multiple childhood adversities is linked to shorter telomeres, which underlines how adverse childhood experiences can generate continued vulnerability through to older adulthood. These findings have implications for understanding, at a cellular level, how stress gets "under the skin" and may promote the precocious onset of age-related diseases.

6.8 From Daily Life to Space Travel

Spaceflight conditions reflect an extreme and complex environmental challenge, with the potential for multiple aversive consequences for human health. Spaceflight, even when short in duration, can induce a wide range of adverse effects by reason of adaptations to the physical stressors of gravitational changes, radiation, malnutrition, disrupted sleep, and psychological stress (Choukèr 2012). As such, space travel presents an exceptional and intense combination of physical and psychological challenges that also provides a unique opportunity for investigators to examine the susceptibility of the human body to stress and explore interventions to promote psychological and physiological resilience.

In a study investigating spaceflight effects on the immune system in 30 cosmonauts, striking alterations in immune responses during and after space flight were observed, including a reduced percentage of NK, as well as suppressed NK activity by up to 85% relative to pre-flight (Rykova et al. 2008). Similar findings were reported in a study on long-duration spaceflight by 12 Russian cosmonauts, which included significantly suppressed T-cell immunity and exaggerated cytokine production after landing relative to before launch (Morukov et al. 2011). Moreover, alterations in the endocannabinoid system (ECS), which is known to play an important role in the regulation of various physiological functions, including stress regulation, behavior, mood, memory, vegetative control, and immunity, were observed following time on board of the International Space Station (ISS), resulting in an increase in circulating endocannabinoids (Strewe et al. 2012).

Despite the many improvements that have been made to living conditions aboard the ISS and during space travel, the clinical health risk of time in space remains high, as demonstrated by a remarkably compromised immune system and disease-fighting capabilities following exploration missions, placing cosmonauts at a greater risk for disease development, including bacterial and viral infections. In light of these results, full characterization of the shifts in the innate and adaptive immune system after space travel (see Chaps. 11–15) is critical to understand the relationship between microgravity and the stress effects of space flight in human space explorers (Morukov et al. 2011). In turn, studies of stressors encountered in space travel might also advance our understanding of stress in our daily lives.

6.9 Interventions

Given the clear negative impact of stress on immune function and health, interventions addressing stress from a psychosocial, physical, nutritional/dietary, and pharmacological perspective are of clinical importance. To appropriately manage stress in both healthy and ill individuals, comprehensive and multidisciplinary approaches that include psychopharmacological treatment, education, cognitive behavioral therapy, mindfulness-based approaches, and relaxation techniques should be provided at an early stage, particularly in physically ill patients.

A variety of stress-reduction techniques have demonstrated beneficial effects for reducing stress and improving mental health and quality of life, including cognitive behavioral therapy (Antoni et al. 2009), mindfulness-based stress reduction interventions (Gallegos et al. 2015), meditation (Rosenkranz et al. 2016), and yoga (Kiecolt-Glaser et al. 2010). Moreover, psychological interventions including cognitive behavioral stress management (Antoni et al. 2009; Gallegos et al. 2015), meditation (Rosenkranz et al. 2016), and yoga (Kiecolt-Glaser et al. 2010) have been demonstrated to improve immune function in diverse populations, including healthy individuals, women exposed to trauma, and cancer patients. These stress-reduction interventions seem to result in a healthy balance between sympathetic and parasympathetic arousal (Chaoul et al. 2014).

Exercise presents a promising intervention to counteract the deleterious effects of chronic stress (see also Chap. 32). A body of research has already examined the ability of physical/aerobic exercise to enhance immune responses when performed regularly and in moderation (Simpson et al. 2015). Beneficial effects of exercise and lifestyle interventions on stress reduction, inflammation, and overall well-being have been found for healthy working adults group (Kettunen et al. 2015), elderly individuals (Emery et al. 2005), patients with T2DM (Chen et al. 2015), and cancer patients (Zhu et al. 2016).

Undoubtedly, exercise is a powerful behavioral intervention with the potential to improve immune function and health outcomes in the healthy, the obese, and the elderly, as well as in patients specifically having CVD, diabetes, or cancer. Improvements in immunity, resulting from regular exercise of moderate intensity, may be due to reduced inflammation, maintained thymic mass, enhanced immunosurveillance, reduced psychological distress, and improved overall well-being (Simpson et al. 2015).

In summary, a variety of interventions show promise for counteracting the negative effects of psychological stress. The particular intervention (i.e., stress management, physical activity, meditation), which is most beneficial, likely depends upon the outcome of interest and the type of stressors experienced, as well as on the individual's personality characteristics and preexisting primary illness and comorbidities.

6.10 Conclusions

The findings synthesized above highlight the complex interactions that underlie the relationships among stress, neuroendocrine activity, immunity, and health outcomes. Chronic stress and its correlates affect a variety of clinically meaningful immune parameters, including wound healing, antibody responses to vaccines, susceptibility to infectious illnesses, the ability of the immune system to suppress latent viruses, and various inflammatory processes. These effects, in turn, can increase one's risk a variety of physical and mental disorders, including cardiovascular disease, diabetes, certain cancers, and autoimmune disease, as well as general frailty and mortality. Together, these findings provide a robust pathway through which

chronic stress and immune dysregulation may contribute to serious adverse health outcomes. Past research provides support for several promising avenues for interventions to prevent stress-induced immune dysfunction. However, further research is warranted to provide individualized intervention strategies.

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