

OVERVIEW

Immune responses are mediated by the activation of immune response genes that encode regulatory and effector molecules, such as cytokines, antimicrobial peptides, antibodies, and cytolytic molecules. Transcriptional activation of innate immune cells is triggered by two types of signals from the body's internal "environment" – namely, the presence of pathogen-associated molecular patterns (PAMPs) and "danger signals" derived from host cell stress or death (Matzinger, 2007). A growing body of research suggests that a third class of macro-environmental stimuli exists in the form of neural and endocrine signals and that these stimuli also play a significant role in modulating immune responses (Glaser & Kiecolt-Glaser, 2005). In addition, immune mediators such as cytokines feed back to the brain to regulate neural and endocrine activity (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). The resulting neuroimmune circuit coordinates immune responses with other physiological processes such as fight-or-flight stress responses to maximize the overall fitness of the organism within highly complex, contemporary physical and social environments that bear multiple microbial, physiological (e.g., trauma, sleep loss), and social-ecological threats (e.g., predation, conspecific violence, interpersonal loss, etc.) (McEwen, 2007). This neuroimmune circuit was initially discovered in the context of adaptive immune responses (Glaser & Kiecolt-Glaser, 2005). Recent findings, however, suggest that this circuit originates with the innate immune system (Cole, Hawkey, Arevalo, & Cacioppo, 2011b; Powell, Mays, Bailey, Hanke, & Sheridan, 2011). This review highlights emerging biological themes on the reciprocal regulation of immune response gene expression and CNS function.

Psychoneuroimmunology is the study of how psychological, neural, and immunologic processes interact and shape human health and behavior. Classic views of the immune system focused largely on how immune system processes are regulated by factors that are present inside the body, such as viruses and bacteria, and chemical signals released during host cell stress or death. It is now widely recognized, however, that characteristics of the

external physical and social environment can also strongly influence immune system activity by affecting neural and endocrine processes that regulate immune system dynamics. In addition to providing important new insights into the mechanisms underlying many mental and physical health problems, discoveries in this field have begun to inform the development of novel interventions for improving human health.

The goal of this chapter is to provide an overview of contemporary models and recent research in psychoneuroimmunology. First, we summarize the main features of the innate and adaptive immune system. Second, we describe the neural and physiologic pathways that have the ability to alter immune system dynamics. Third, we review work linking a variety of different psychoneuroimmunological processes (e.g., life stress exposure, sleep disturbance, depression) with infectious and inflammatory disease risk. Fourth, we examine the types of behavioral interventions that have been shown to alter immune system processes and impact health. Finally, we conclude with ideas for future research.

IMMUNE SYSTEM

The immune system is primarily responsible for coordinating the body's response to physical injuries and infections. It is thus critical for human health and well-being. Two interconnected branches, called *innate immunity* and *adaptive immunity*, are generally conceptualized as comprising the immune system. Innate immunity is the first and evolutionarily older branch. As the body's first line of defense against tissue damage and microbial infection (Medzhitov, 2008), innate immunity includes immune cells such as monocytes/macrophages and dendritic cells, which circulate throughout the body. By using a fixed small class of receptors to detect a wide variety of pathogens, these cells initiate a cascade of inflammatory processes that signal the occurrence of injury or infection (Medzhitov, 2008). Innate immunity is non-specific and rapid, occurring over minutes or hours, and does not confer long-lasting protection to the host.

The second branch of the immune system, called *adaptive immunity*, becomes active when innate immune system defenses are insufficient (Barton, 2008). Adaptive immunity involves the proliferation of microbial-specific white blood cells (i.e., lymphocytes) that attempt to neutralize or eliminate microbes based on an *immunological memory* of having responded to a specific pathogen in the past (Gruys, Toussaint, Niewold, & Koopmans, 2005). Compared with innate immunity, the adaptive immune response takes days to fully develop (Barton, 2008), and by virtue of the development and maintenance of immunological memory, confers lasting protection to the organism.

Innate Immune System

Highly conserved features of microbes or pathogen-associated molecular patterns (i.e., *pathogen-associated molecular patterns*, or PAMPs) are recognized by receptors of innate immune cells. This “hard-wired” recognition strategy, which uses a relatively small number of immune cell types to detect and generate a response to a wide range of microbial diversity, is termed *pattern recognition*. Hence, innate immune receptors that use this strategy are called *pattern recognition receptors*, and activation of these receptors triggers an *acute-phase response*, which leads to an increase in inflammatory activity that can occur both locally and throughout the body (Medzhitov, 2008).

Toll-like receptors (TLRs), one class of pattern recognition receptors, are found on macrophages, neutrophils, and dendritic cells (Medzhitov, 2008), and these TLRs recognize conserved components of microbes including bacteria, viruses, and fungi. Within the “family” of TLRs, there is some specificity of ligand recognition. For example, TLR4 is one type of TLR, and this receptor binds lipopolysaccharide (LPS), an endotoxin that is the major component of the outer membrane of Gram-negative bacteria. Hence LPS is a prototypical PAMP (Raetz & Whitfield, 2002). Response to TLR4 activation can be characterized by examining activation of a conserved signaling cascade, which includes key intra-cellular transcription factors such as nuclear factor- κ B (NF- κ B) and activator protein 1 (AP-1) (Karin, 2006). Activation of NF- κ B, for example, leads to the transcription of pro-inflammatory immune response genes such as tumor necrosis factor (TNF)- α and interleukin (IL)-1 and the translation and production of pro-inflammatory cytokines that help coordinate the inflammatory response (Karin, 2006). Levels of spontaneous and activated NF- κ B activity can be assayed in nuclear extracts of immune cells including peripheral blood mononuclear cells, lymphocytes, and monocytes. Additionally, the intra-cellular production of inflammatory cytokines can be assayed using flow cytometric approaches that quantify relative amounts of pro-inflammatory cytokines that are produced at the single monocytic cell level.

Because several of the leading causes of death today involve inflammation (i.e., cardiovascular disease, cancer)

(Slavich, 2015), there has recently been intense interest in understanding the mechanisms that underlie inflammation and the role inflammation plays in disease. Inflammatory cytokines are very important in this context because they are released from immune cells, such as monocytes/macrophages, dendritic cells, and neutrophils, and coordinate cell-to-cell communication; they also alter neurochemical and neuroendocrine processes with wide-ranging effects on physiology and behavior (Curfs, Meis, & Hoogkamp-Korstanje, 1997). Similar to neurotransmitters and hormones, inflammatory cytokines mediate physiological responses, rely on receptor–ligand interactions, and have self (autocrine), local (paracrine), and distal (endocrine) effects. Cytokines either increase or decrease inflammatory activity, and these cytokines are called *pro-inflammatory* and *anti-inflammatory*, respectively. A description of cytokines commonly studied in psychoneuroimmunology is presented in Table 17.1.

Among the pro-inflammatory cytokines, (IL)-1, IL-6, and TNF- α coordinate several cell functions that stimulate and enhance inflammation. These pro-inflammatory cytokines also have effects on adaptive immunity; for example, they can promote the differentiation of lymphocytes called *cytotoxic T cells* that kill pathogens. Moreover, inflammatory cytokines induce increased vascular permeability and cellular adhesion, which enable the migration of immune cells from the circulation into the tissues where they can eliminate pathogens (Dhabhar, Malarkey, Neri, & McEwen, 2012). By activating the expression of the endothelial adhesion molecule intercellular adhesion molecule-1, which then binds integrin (e.g., LFA-1) on the surface of immune cells, IL-1 promotes adhesion to endothelial cells and eventual extravasation (Smith, Marlin, Rothlein, Toman, & Anderson, 1989). Similarly, TNF- α stimulates the production of the adhesion molecule E-selectin on the endothelium, which binds to adhesion molecules on neutrophils (Hubbard & Rothlein, 2000). A family of small cytokines, called *chemokines*, are activated by TNF- α , IL-6, and IL-1 and help redistribute cells to sites of injury or infection by acting as *chemoattractants* that recruit immune cells to the site of inflammatory activity (Murphy, 2001).

Intra-cellular processes at the genomic level regulate the inflammatory response, and the specific pathway involved depends on the type of danger signal present (Amit et al., 2009). During exposure to extracellular pathogens such as bacteria, transcription factors NF- κ B and activator protein 1 (AP-1) are activated, which subsequently induce the expression of pro-inflammatory immune response genes such as *IL1B*, *IL6*, *IL8*, and *TNF*. In contrast, following exposure to an intra-cellular pathogen such as a virus, transcription factors such as interferon regulatory factors are activated, which induce anti-viral immune response genes such as type I interferon genes. In turn, translation of interferon (IFN) can activate signal transducer and activator of transcription (STAT)-1, leading to the production of pro-inflammatory cytokines (Slavich & Irwin, 2014).

Table 17.1 Inflammatory cytokines and their key characteristics

Cytokine	Family	Producer cells	Function
Pro-inflammatory cytokines			
Interleukin-1 β (IL-1 β)	Unassigned	Macrophages	Key mediator of sickness behavior; promotes fever and pain hypersensitivity; involved in HPA axis activation, lymphocyte activation, macrophage and neutrophil activation, endothelial activation, prostanoid synthesis, and IL-6 synthesis
Interleukin-2 (IL-2)	Hematopoietins	T cells	Facilitates immunoglobulin production by B cells, and differentiation and proliferation of NK cells
Interleukin-6 (IL-6) ^a	Hematopoietins	Macrophages, T cells	Key mediator of acute phase response; promotes fever, and T and B cell differentiation and activation; can down-regulate inflammation by inhibiting TNF- α and IL-1 production
Interleukin-8 (IL-8)	Chemokines	Macrophages	Key mediator of inflammation; recruits neutrophils to the site of inflammation and induces chemotaxis in target cells
Tumor necrosis factor- α (TNF- α)	TNF family	Macrophages, NK cells	Key mediator of sickness behavior; promotes fever and suppresses appetite; stimulates HPA axis, endothelial activation, and neutrophil activation; induces apoptotic cell death
Anti-inflammatory cytokines			
Interleukin-4 (IL-4)	Hematopoietins	T cells	Inhibits production of the pro-inflammatory cytokines TNF- α and IL-1; stimulates B and T cell proliferation
Interleukin-10 (IL-10)	Unassigned	Macrophages, T cells	Inhibits production of the pro-inflammatory cytokines IL-1, IL-6, and TNF- α ; enhances B cell proliferation and antibody production

NK cells = Natural killer cells; HPA axis = Hypothalamic–pituitary–adrenal axis.

^a Although IL-6 is listed as a pro-inflammatory cytokine, as described, it can also have anti-inflammatory effects. From Slavich & Irwin, 2014.

Adaptive Immune System

Based on an immunological memory of having responded to a specific pathogen or antigen in the past, adaptive immunity coordinates a specific response to an infectious challenge by a sequence of coordinated steps (Murphy, 2001). First, antigen-presenting cells (APCs) such as macrophages or dendritic cells are attracted to a site of intrusion and take up invading antigen. Upon migration to local lymph nodes, the APCs present antigen to T helper (Th) cells and release pro-inflammatory cytokines, as noted above. These inflammatory signals induce Th cells to become activated, proliferate, and then differentiate into one of two cell types. One type of Th help B cells become antibody-producing cells (i.e., plasma cells); another type leaves the lymph node to coordinate cytotoxic cell responses that act to eliminate the pathogen. When the initial adaptive immune response is complete, a fraction of antigen-specific Th cells, cytotoxic T cells, and B cells survive, forming immunological memory. Hence, with initiation of that specific infectious challenge again, a more rapid response is achieved. The memory T cell response can be assayed by evaluating the responder cell frequency, which determines the number of T cells that recognize and respond to a specific antigenic challenge.

Both co-stimulatory signals (e.g., pro-inflammatory cytokines like IL-6) and inhibitory signals (e.g., anti-inflammatory cytokines like IL-10) regulate this multi-cell response to microbial challenge. In comparison, when challenge with an intra-cellular pathogen such as a virus occurs, transcription factors such as interferon (IFN) regulatory factors are activated, which induce anti-viral immune response genes such as type I IFN genes (Slavich & Irwin, 2014). An inadequate immune response leads to immune deficiency and susceptibility to infections, whereas a response that is too robust can result in autoimmunity or septic shock.

PSYCHONEUROIMMUNOLOGY PATHWAYS OF IMMUNE REGULATION

The CNS plays a critical role in sensing external physical and social conditions (the environment, broadly speaking), assessing their implications for organismic well-being (fitness), and modulating the activity of internal physiological processes to optimally adapt to existing conditions (Irwin & Cole, 2011). When there is a perception of threat, adaptive changes in physiological function (e.g., fight-or-flight stress responses) are signaled by the CNS,

which leads to the release of neuroeffector molecules such as norepinephrine from nerves of the sympathetic nervous system (SNS) or glucocorticoids from the hypothalamus–pituitary–adrenal (HPA)-axis (Irwin & Cole, 2011). In turn, these biochemical manifestations of CNS-perceived external conditions regulate cells of the immune system (Plate 21).

The CNS gives the immune system, and specifically the innate immune system, the ability to prepare the body for physical wounding or injury prior to the exposure to pathogens resulting from an actual assault that could lead to an infection. As a preparatory “pathogen host defense,” this response coordinates an anticipatory (i.e., pre-injury) redistribution and trafficking of innate immune cells to sites of possible injury or infection. The result is enhanced post-injury wound healing and recovery, which can be critical for survival (Dhabhar et al., 2012).

At the genomic level, immune response genes “listen” for chemical signals indicating an increased risk for wound-related bacterial infection stemming from social-environmental danger. Recent research has demonstrated that exposure to adverse conditions involving social evaluation, rejection, isolation, and exclusion in the contemporary social environment activate the innate immune system (Slavich, O'Donovan, Epel, & Kemeny, 2010). The temporal features of present-day adverse social conditions, however, partly determine the type of innate immune system response that is initiated. Acute stress, for example, has been found to enhance anti-viral defenses (Edwards et al., 2006; Mays et al., 2010; Phillips, Carroll, Burns, & Drayson, 2009), whereas prolonged stress and depression have been associated with reduced anti-viral immune responses (Irwin et al., 2011, 2013). In this context, up-regulation of pro-inflammatory immune response genes – which combat bacteria and other extracellular pathogens – and a reciprocal down-regulation of anti-viral immune response genes – which target intra-cellular pathogens such as viruses – has been called a *conserved transcriptional response to adversity* (CTRA) (see Slavich & Cole, 2013). Although this response is adaptive in counteracting injuries associated with actual physical threat, activation of this ancestral host defense program by non-physical social, symbolic, anticipated, or imagined threats increases an individual's risk for both viral infection and inflammation-related disease (Slavich & Cole, 2013).

Hypothalamus–Pituitary–Adrenal Axis

Brain activation of the HPA axis, one the earliest identified CNS-mediated immunoregulatory functions of the brain, stimulates glucocorticoid release that suppresses transcription of both pro-inflammatory and anti-viral gene programs (Berkenbosch, van Oers, del Rey, Tilders, & Besedovsky, 1987; Besedovsky, del Rey, Sorkin, & Dinarello, 1986; Sapolsky, Rivier, Yamamoto, Plotsky, & Vale, 1987). By suppressive binding to gene promoter

sequences, activation of the glucocorticoid receptor inhibits the transcription of immune response genes. Additionally, activation of the glucocorticoid receptor induces transcriptional expression of anti-inflammatory genes (e.g., I κ B α -encoding NFKBIA), and also acts in the non-genomic antagonism of pro-inflammatory transcription factors such as NF- κ B and AP-1 via protein–protein interactions (Rhen & Cidlowski, 2005) (Plate 21).

When inflammation levels become high or metabolic resources need to be shifted, brain detection of peripheral inflammatory and anti-viral cytokines via multiple pathways (see below) stimulates HPA axis glucocorticoid release, which systemically inhibits immune response gene transcription (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Pace, Hu, & Miller, 2007). Hence, glucocorticoid feedback inhibition of immune response gene transcription is not only a prototype of our most effective anti-inflammatory drugs, but also a fundamental physiological mechanism for protection against hyper-inflammatory disease (Pace et al., 2007; Rhen & Cidlowski, 2005).

These dynamics typically occur when HPA axis activation is intermittent. When HPA axis activity is repeated or chronic, a different set of dynamics can emerge wherein elevated inflammation occurs despite HPA axis activity (Avitsur et al., 2007). This process, called *glucocorticoid resistance* or *glucocorticoid insensitivity*, involves a desensitization of immune cells to the anti-inflammatory effects of glucocorticoids. In such instances, excessive inflammation can occur with implications for mental and physical health (Irwin & Cole, 2011). For example, evidence of glucocorticoid resistance has been found in individuals with anxiety, depression, post-traumatic stress disorder, arthritis, cardiovascular disease, autoimmune diseases, and some cancers (Irwin & Cole, 2011; Jarcho, Slavich, Tylova-Stein, Wolkowitz, & Burke, 2013; O'Donovan, Slavich, Epel, & Neylen, 2013).

Sympathetic Nervous System

A second neural pathway mediated by the SNS allows the CNS to “steer” innate and adaptive immune responses between pro-inflammatory and anti-viral phenotypes (Cole et al., 2010; Collado-Hidalgo, Sung, & Cole, 2006). The SNS releases the neurotransmitter norepinephrine into tissue microenvironments, including all primary and secondary lymphoid organs and most visceral organs and musculoskeletal structures (Nance & Sanders, 2007). When the SNS is activated, the production and trafficking of immune cells occurs, including up-regulation of myelopoiesis and mobilization of hematopoietic stem cells, natural killer cells, and splenic neutrophils and monocytes (Nance & Sanders, 2007). In addition, norepinephrine stimulates β -adrenergic receptors associated with the adenylyl cyclase cAMP–PKA signaling cascade (Nance & Sanders, 2007). This signaling modulates adaptive immune responses by stimulating transcription of

T helper 2 (Th2)-type cytokine genes (e.g., IL4 and IL5) and suppressing Th1-type gene expression (e.g., IFNG and IL12B) (Cole, Korin, Fahey, & Zack, 1998; Lee et al., 2000; Panina-Bordignon et al., 1997), which together contribute to decreased anti-viral immune response and increased risk of infectious disease. SNS activation also steers innate immune response programs; along with suppression of type I IFN-mediated anti-viral responses (Collado-Hidalgo et al., 2006), there is up-regulated transcription of pro-inflammatory cytokines such as IL1B, TNF, and IL6 (Cole et al., 2010; Grebe et al., 2009) (Plate 21).

In addition to being regulated by these cellular and microbial microenvironments, anti-viral and inflammatory responses are influenced by the broader macroenvironment of the host body and its surrounding social ecology as perceived by the CNS (Cole et al., 2007, 2011b; Sloan et al., 2007). Hence, the discovery that the SNS could simultaneously inhibit anti-viral genes and activate pro-inflammatory genes has provided a plausible mechanistic explanation for understanding how adverse social environments increase risk of infectious disease (presumably due to insufficient immune gene expression) on the one hand, and inflammation-associated cardiovascular, autoimmune, neurodegenerative, and neoplastic diseases (presumably due to excessive immune gene expression) on the other hand (Cohen, Janicki-Deverts, & Miller, 2007; Cole et al., 2010; Kiecolt-Glaser et al., 2003; Miller, Maletic, & Raison, 2009a).

PSYCHONEUROIMMUNOLOGY INFLUENCES ON ADAPTIVE IMMUNITY AND INFECTIOUS DISEASE RISK

Adaptive Immunity

Inescapable stress, a putative animal model of depression, increases susceptibility to viral diseases such as herpes simplex, influenza, and coxsackie virus infections via alterations in immune function (Glaser & Kiecolt-Glaser, 2005). In humans, prospective epidemiologic studies and experimental viral challenge studies show that persons reporting more psychological stress, depression, and/or sleep disturbance have both a higher incidence and a greater severity of certain infectious illness, including the common cold (Cohen, Tyrrell, & Smith, 1991; Cohen, Doyle, Alper, Janicki-Deverts, & Turner, 2009; Glaser & Kiecolt-Glaser, 2005). Finally, psychological stress, depression, and sleep disturbance alter disease-specific dynamics of the immune system *in vivo*, as probed by experimental vaccinations (Cohen et al., 1991, 2009; Irwin et al., 2013; Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996; Vedhara et al., 1999).

Acute psychological stress is known to have a robust effect on immune cell distribution leading to increases in the number of lymphocytes, and especially T suppressor/cytotoxic lymphocytes and natural killer (NK) cells, which are subtypes that have the largest density of β -receptors

(Murray et al., 1992). Indeed, experimental studies have found that β -adrenergic antagonism can block the effects of acute stress on immune cell distribution (Friedman & Irwin, 1997; Murray et al., 1992). When psychological stress exposure is chronic, there appears to be minimal effect on immune cell numbers, although some studies have found that individuals with depression have increased numbers of T cells bearing T cell activation markers, including CD4+ (T helper cells) and CD8+ (T suppressor/cytotoxic cells), along with decreases in the numbers and relative percentage of NK cells (Irwin & Miller, 2007).

Psychological stress and depression have potent effects on the regulation of adaptive immunity, with meta-analyses showing a reduction in non-specific lymphocyte proliferative responses to mitogenic stimulation such as phytohemagglutinin (PHA), Concanavalin A (Con-A), or pokeweed mitogen (PWM). Major depression and major life stressors are also associated with decreases in the production of the T cell cytokine IL-2 and a shift in the relative balance of anti-viral immune responses with a decrease in the production of IFN relative to increases in IL-10, although some studies have reported increased production of interferon- γ (Irwin & Miller, 2007). Similarly, sleep loss, which is ubiquitous in psychologically stressed and depressed populations, also has robust effects with a reduction in T cell production of IL-2, which is independent of the total number of circulating T cells (see Irwin, 2015). Similarly, there is a shift in the Th1 to Th2 cytokine balance toward increased Th2 cytokine activity (Irwin, 2015), as well as a decrease in monocyte production of IL-12, a cytokine that supports Th1 responses. In contrast, sleep loss increases the production of IL-10, a cytokine that promotes Th2 responses (Irwin, 2015).

Extension of this research to viral-specific immune responses has begun to yield promising findings linking psychological stress with altered immune dynamics and increased risk of infectious disease. Specifically, data have shown a decline in specific immune responses to immunization against viral infections following stress (Miller et al., 2004; Vedhara et al., 1999). Likewise, in major depression, there is evidence of a functional decline in memory T cells that respond to varicella zoster virus (Irwin et al., 1998). Moreover, depressed patients have diminished memory T cell response to varicella zoster vaccine, which persists for two years following vaccination (Irwin et al., 2013). Because higher levels of memory T cell responses correlate with lower risk and severity of herpes zoster, untreated depression may increase the risk and severity of herpes zoster, and reduce the efficacy of zoster vaccine.

Supporting a causal association between depression and changes in adaptive immunity, treatment of major depression has been found to reverse the suppression of adaptive immune responses. In a longitudinal case-control study, depressed patients exhibited an increase in NK

activity during a six-month course of tricyclic antidepressant medication treatment and symptom resolution, in which improvements of NK activity correlated with declines of symptom severity (Irwin, Lacher, & Caldwell, 1992). Although NK cells are considered an innate immune response, these lymphocyte subtypes have a role in anti-viral immunity and their activation can shift the balance toward an adaptive, cytotoxic T cell immune response. In another longitudinal study of young adults with unipolar depression involving six weeks of treatment with nortriptyline and alprazolam (Schleifer, Keller, & Bartlett, 1999), clinical improvements in depression severity were associated with decreased numbers of circulating lymphocytes and decreased responses to PHA and Con A but not PWM. In addition, decreases in T cells, CD4+, and CD29 were found, although there were no changes in B cell numbers or CD8+ cells. Whereas none of these changes were related to nortriptyline blood levels (Schleifer et al., 1999), *in vivo* and *in vitro* treatment with fluoxetine, a selective serotonin reuptake inhibitor, resulted in enhanced NK activity along with changes in depressive symptoms, consistent with the effects of other antidepressants including nifedipine, paroxetine, sertraline, and venlafaxine (Frank, Hendricks, Johnson, & Burke, 1999). A few studies have also examined the effects of antidepressant treatment on Th1 vs. Th2 cytokine production in depression, with evidence that treatments *in vivo* and *in vitro* with imipramine, venlafaxine, or fluoxetine increased stimulated cellular production of IL-10, with a decrease in the ratio of interferon (IFN) to IL-10 (Kubera et al., 1996). Finally, treatment with selective serotonin antidepressant medications was associated with a normalization of T cell memory responses to varicella zoster vaccine, and this association was independent of improvements in depressive symptom severity (Irwin et al., 2013) (Figure 17.1).

Sleep disturbance is one of the most prominent complaints of persons undergoing psychological stress; it is also a prodromal symptom of depression risk and a common residual symptom of the disorder. Hence it is thought that sleep disturbance may be one behavioral mechanism that accounts for the association between psychological stress, depression, and suppression of adaptive immunity or anti-viral immune responses. In animals, there is evidence that sleep deprivation is associated with slowed clearing of influenza (Brown, Pang, Husband, & King, 1989), although the results are mixed (Renegar, Floyd, & Krueger, 1998). In humans, sleep loss is associated with reduced response to influenza A (Spiegel, Sheridan, & Van Cauter, 2002) and reduced response to the hepatitis A vaccine, with lower virus-specific antibody titers (Lange, Perras, Fehm, & Born, 2003), due to a reduced frequency of antigen-specific Th cells as well as reduced levels of antigen Ag-specific immunoglobulin G1 (Lange, Dimitrov, Bollinger, Diekelmann, & Born, 2011). In naturalistic studies, loneliness and poor sleep efficiency have been found to be associated with poorer antibody response to influenza vaccine (as reviewed; Irwin, 2015), with evidence that shorter sleep duration (i.e., < 6 hours per night, as confirmed by actigraphy) was strongly linked to a decreased likelihood of protection from a hepatitis B vaccination in 125 midlife adults (Prather et al., 2012). Consistent with the observations in depression, adverse effect of sleep disturbance might increase infectious disease risk by increasing susceptibility to viral pathogens or expression of symptoms, or both (Plate 22).

Infectious Disease Risk

The suppression of anti-viral immune responses in association with life stress and sleep disturbance appears to have implication for infectious disease risk and

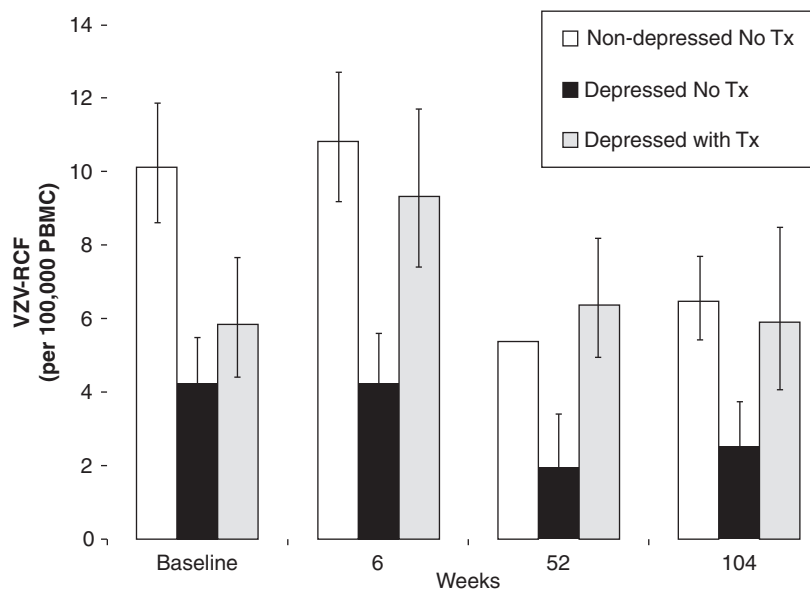


Figure 17.1 Depression study examining varicella zoster virus-specific responder cell frequency (VZV-RCF) results at baseline and 6, 52, and 104 weeks in the three groups of vaccine recipients: non-depressed controls (Non-depressed No Tx; N = 30); depressed patients who are not treated with antidepressant medications (Depressed No Tx; N = 12); and depressed patients who are being treated with antidepressant medication (Depressed with Tx; N = 12). There were significant differences at all time points between the “Depressed No Tx” and “Depressed with Tx” participants, but not between the “Depressed with Tx” and the “Non-depressed No Tx” participants ($F = 6.2$; $p < 0.005$; analysis of covariance). Abbreviations: PBMC, peripheral blood mononuclear cell; Tx, treatment; VZV-RCF, varicella zoster virus-specific responder cell frequency. From Irwin et al., 2013.

progression. For example, HIV infection shows a highly variable course with evidence that depression, bereavement, and maladaptive coping responses to stress (including the stress of HIV infection itself) all predict the rate of immune system decay in HIV patients. Indeed, decline in immune system function and increases in HIV replication are more rapid in patients living under chronic stress (e.g., gay men who conceal their homosexuality) and in patients with high levels of SNS activity (e.g., socially inhibited introverts) (Cole & Kemeny, 1997; Cole, Kemeny, & Taylor, 1997; Cole et al., 1998; Miller & Cole, 1998). Although the mechanisms of these effects are not well defined, tissue culture studies have shown that SNS neurotransmitters and glucocorticoids can accelerate HIV replication by rendering T lymphocytes more vulnerable to infection and by suppressing production of the antiviral cytokines that help cells limit viral replication (Cole et al., 1998). However, with the advent of potent and effective antiretroviral medications for the prevention and treatment of HIV, the role of SNS activity in the modulation of HIV replication and immune responses has not emerged as a prominent theme for research in HIV patients.

Whereas some research suggests that sleep disturbance may mediate or moderate the relationship between psychological stress or depression and infectious disease, other studies suggest that sleep disturbance has independent effects on infectious disease risk. This research has shown that extremes of sleep duration correlate with increased risk of pneumonia (Patel et al., 2012). Further, a study utilizing an experimental model of the common cold found that self-reported shorter sleep duration and sleep fragmentation were associated with greater susceptibility to the common cold. In experimental studies in which healthy adults are inoculated with a rhinovirus that produces symptoms of the common cold, poor sleep efficiency was associated with increased susceptibility to the common cold and greater symptom reporting (Cohen et al., 2009), similar to findings linking psychological stress to the common cold (Cohen et al., 1991).

PSYCHONEUROIMMUNOLOGY INFLUENCES ON INNATE IMMUNITY AND INFLAMMATORY DISEASE RISK

Laboratory-Based Stress and Inflammatory Responding

In animal and human studies, experimental induction of acute psychological stress increases systemic, cellular, and molecular markers of inflammation. Some of these effects are related to mobilization of specific leukocyte subsets (Richlin, Arevalo, Zack, & Cole, 2004), but there is also evidence that acute laboratory stressors increase circulating levels of IL-6 and IL-1 β (Pace et al., 2006), activate NF- κ B in peripheral blood mononuclear cells (PBMCs) (Bierhaus et al., 2003; Pace et al., 2006), and prime

leukocytes for increased *ex vivo* production of pro-inflammatory cytokines in response to stimulation by the PAMP lipopolysaccharide (LPS) and other Toll-like receptor ligands (Bower et al., 2007; Goebel, Mills, Irwin, & Ziegler, 2000; Powell et al., 2011).

What factors contribute to varying inflammatory responses to laboratory stress? Consistent with the effects of laboratory stressors on HPA axis activation and activation of the SNS efferent pathways (Dickerson & Kemeny, 2004), stressors involving social conflict, rejection, or exclusion appear to evoke the strongest inflammatory responses in the laboratory (Dickerson, Gable, Irwin, Aziz, & Kemeny, 2009; Slavich & Irwin, 2014). For example, writing about traumatic experiences involving self-blame triggers self-reported shame along with increases in a soluble receptor for TNF- α (sTNF-RII) (Dickerson, Kemeny, Aziz, Kim, & Fahey, 2004). Among married couples, those high in hostility exhibited significantly greater increases in plasma IL-6 and TNF- α following the hostile marital interaction as compared to those with low hostility (Kiecolt-Glaser et al., 2005). Finally, among participants exposed to the Trier Social Stress Test (TSST), the presence of socially rejecting raters was associated with greater *in vitro* LPS-stimulated production of TNF- α and greater glucocorticoid resistance as compared to the performance of the TSST in the absence of these raters (Dickerson et al., 2009).

In addition to differences in characteristics of the stressor manipulation, individual differences in the participants' psychological perceptions of, or emotional reactions to, a laboratory-based social stressor also appear to predict their inflammatory responses to the task. For example, experiencing more fear, greater perceived stress, or greater anxiety in response to the TSST is associated with greater increases in the pro-inflammatory marker including sTNF-RII and IL-6 (Carroll et al., 2011; Moons, Eisenberger, & Taylor, 2010). Greater difficulty in maintaining a positive cognitive-affective state during the TSST has also been associated with greater increases in circulating IL-1 β , which in turn predicted increases in depressive symptoms over time (Aschbacher et al., 2012).

Individuals' existing psychosocial characteristics also moderate the magnitude of their inflammatory response. Exposure to early life stress is one such characteristic. Persons reporting early adversity exhibit greater IL-6 responses to the TSST, despite minimal differences at baseline (see Slavich & Irwin, 2014). In addition, loneliness and social isolation are associated with greater inflammatory reactivity to the TSST and greater LPS-stimulated production of TNF- α , IL-6, and IL-1 β (Slavich & Irwin, 2014). Differences in inflammatory responding have also been linked to past and present depression status. Depressed participants exhibit greater stress-induced increases in plasma levels of TNF- α and IL-6, and the inflammatory marker C-reactive protein (CRP), as well as greater LPS-stimulated production of TNF- α and IL-6 (Slavich & Irwin, 2014). Finally, there is evidence that

exposure to early life stress among depressed individuals exaggerates their IL-6 and NF- κ B reactivity to the TSST and predicts higher post-TSST levels of IL-6 (Pace et al., 2006). Further research is needed to evaluate the independent contribution of depression versus factors commonly associated with depression, including having a sedentary lifestyle, high body mass index, and being female (O'Connor et al., 2009).

Chronic Social Adversity and Inflammation

Chronic social adversities, such as low socioeconomic status, long-term social isolation, and having a partner with a terminal illness are associated with elevated circulating pro-inflammatory cytokine levels and increased expression of pro-inflammatory immune response genes (Chen et al., 2009; Cole et al., 2007, 2011a; Miller et al. 2008b, 2009b; Slavich & Irwin, 2014). As with laboratory-based stressors, social stress appears to have a salient role. Indeed, in a large community-based case-cohort study, socially isolated individuals were 2.0–2.5 times more likely to have clinically high levels of CRP than socially integrated individuals; other data have shown that socially isolated depressed men have levels of CRP and IL-6 that are 2.0 and 3.8 times higher than socially integrated non-depressed men (see Slavich & Irwin, 2014). As previously described, these effects may be due to an up-regulated expression of pro-inflammatory immune response genes and a reciprocal down-regulation of genes involved in antibody production.

Disruptions in social connection also appear to increase inflammation. Older adults who experienced the recent death of their spouse have higher levels of IL-1 and IL-6 compared to their non-bereaved counterparts (Schultze-Florey et al., 2012). Interestingly, a gene \times environment interaction was demonstrated in which a variant in the IL-6 gene (IL-6 –174) modified individuals' likelihood of having elevated inflammation following bereavement. It is thought that bereavement leads to increases in the SNS that activates GATA1 transcription factor to up-regulate IL-6 production, but only for individuals with two GATA1-sensitive –174G alleles who showed high levels of inflammation (Schultze-Florey et al., 2012). Finally, increases in inflammatory activity have been associated with daily negative social interactions (Fuligni et al., 2009a, 2009b) and even following the experience of one major life event involving targeted rejection (Murphy, Slavich, Rohleder, & Miller, 2013; Murphy, Slavich, Chen, & Miller, 2015).

Transcriptional profiling of circulating leukocytes in human populations (Cole et al., 2007, 2011b; Miller et al., 2008b, 2009b) and experimental analyses of repeated social threat in animal models (e.g., encountering an aggressive intruder) (Engler, Bailey, Engler, & Sheridan, 2004; Powell et al., 2011; Wohleb et al., 2011) have provided additional insight into the immunological effects of long-term social adversity. Low socioeconomic

status, post-traumatic stress disorder, long-term social isolation, and having a spouse with a terminal illness have repeatedly been associated with increased expression of pro-inflammatory immune response genes despite the presence of stable or elevated glucocorticoid levels (Chen et al., 2009; Cole et al., 2007, 2011b; Miller et al., 2008b, 2009b). This may result from reduced glucocorticoid-mediated feedback inhibition or functional desensitization of the glucocorticoid receptor, which shifts gene transcription toward increased NF- κ B- and AP-1-mediated inflammatory gene expression both under basal conditions and in response to PAMP stimulation (Miller et al., 2008b). Again, even a single major life event involving targeted rejection is sufficient to shift transcriptome dynamics, as indexed by NF- κ B and I- κ B activity, and precipitate depression (Murphy et al., 2013; Slavich, Thornton, Torres, Monroe, & Gotlib, 2009).

There is also evidence that the effects of adverse social-environmental conditions on inflammatory processes, health, and mortality are modified by genetic factors, including single-nucleotide polymorphisms (SNPs), such as the functionally active regulatory SNP in the human IL-6 promoter (rs1800795). Cole and colleagues (Cole et al., 2010) examined this question, and tested whether high levels of social-environmental stress were associated with increased mortality risk for rs1800795 G homozygotes as compared to C allele carriers. Individuals who were rs1800795 G homozygotes exhibited increases in mortality risk under high levels of stress, with a 2.8-year shorter average lifespan as compared to those who were C allele carriers. Interestingly, these differential mortality rates by genotype were specific to inflammation-related causes of death (e.g., cardiovascular, neurodegenerative diseases).

Early Life Stress and Inflammation

In adolescents and young adults, exposure to early life stress characterized by a childhood environment with unpredictability and interpersonal stress is associated with increased stimulated production of IL-6 (Miller & Chen, 2010) and elevated circulating levels of CRP and IL-6 (see Slavich & Irwin, 2014). Research has also shown that early life stress *prospectively* predicts elevated inflammatory activity, and that greater cumulative stress exposure before age 8 predicts higher levels of IL-6 and CRP at age 10, and higher levels of CRP at age 15 (see Slavich & Irwin, 2014). Given that tumultuous childhood environment often co-occurs with low socioeconomic status in childhood, reports show that low socioeconomic status is also related to higher levels of circulating IL-6 and CRP in adults, as well as a shift of the leukocyte basal transcriptome toward a more pro-inflammatory phenotype (Miller et al., 2008b).

Early life stress increases risk for subsequent depression, and it appears that these effects may occur in part by elevating inflammation and sensitizing individuals to subsequent interpersonal stressors (Slavich et al., 2010,

Slavich, Monroe, & Gotlib, 2011). Depressed adults who experienced severe forms of early life stress (e.g., maternal rejection, harsh discipline, physical or sexual abuse) are 1.48 times more likely to have clinically high levels of CRP (> 3 mg/L) than depressed adults not experiencing such stress (see Slavich & Irwin, 2014). Further, the association between depression and elevated CRP appears to be mediated by early life stress (Danese et al., 2008). There is also evidence that adolescents with a history of more common forms of early life stress (e.g., low socioeconomic status, parental separation) exhibit greater increases in IL-6 and CRP when becoming depressed, and greater residual elevations in post-depression inflammation, compared to adolescents without a history of these early life stressors (see Slavich & Irwin 2014).

Depression and Inflammation

In addition to the research described above linking stress and inflammation, there is growing evidence that depression is associated with increases in multiple measures of cellular inflammation in at least some subgroups of depressed individuals. At least six meta-analytic reviews have interrogated the many studies on this topic and they have concluded that depressed individuals exhibit higher circulating levels of several pro-inflammatory cytokines including IL-1, IL-6, and TNF- α , as well as higher levels of CRP (Howren, Lamkin, & Suls, 2009; Irwin & Miller, 2007). Further, there is some evidence that severity of depressive symptoms, especially somatic and physical symptoms of depression, are related to increases in inflammation (Irwin & Miller, 2007).

Presently, evidence exists demonstrating that inflammatory cytokines may be causally implicated in the development of some types of depression. Prospective data show that increases in IL-6 and CRP predict the development of depressive symptoms (Gimeno et al., 2009), although the reverse may also be true (Matthews et al., 2010). Second, along with improvements in depressive symptoms, antidepressant medication treatments have been associated with decreases in pro-inflammatory cytokine levels in some studies (see Slavich & Irwin, 2014). Finally, serotonin is involved in the regulation of mood, and inflammatory activation depletes the availability of the serotonin precursor tryptophan, which has led to the hypothesis that cytokine-related tryptophan depletion is involved in the pathogenesis of at least some depression (Miller et al., 2009a).

Sleep Disturbance and Inflammation

Sleep disturbance, common in depressed and psychologically stressed persons, may mediate or moderate the associations between depression, psychological stress, and inflammation. Indeed, wake-sleep cycles have emerged as strong regulators of inflammatory biology, and sleep disturbance may be a common behavioral mechanism

that links psychological stress and depression to increases in inflammation, given that sleep complaints are ubiquitous in persons undergoing life adversity. Alternatively, sleep disturbance may have independent effect on inflammation, and have feed-forward effects to increase inflammation and also risk of inflammatory disorders including depression. Below, the effects of sleep loss and sustained sleep disturbance on daytime activity of the innate immune system are described (Plate 23).

Partial night sleep deprivation experimentally mimics the kind of sleep loss often reported in persons experiencing stress. When experimentally administered repeatedly for ten nights, partial night sleep loss induces robust increases in CRP (Meier-Ewert et al., 2004) and IL-6 (Haack, Sanchez, & Mullington, 2007), with even shorter periods found to increase IL-6 in men and women, or TNF in men only, and increases in inflammatory transcripts of IL-1 β , IL-6, and IL-17 (see Irwin, 2015). Yet, when sleep restriction or sleep fragmentation is limited to only one or two nights, including total sleep restriction, inflammatory markers do not appear to change, with the exception of a reduction of NK activity that parallels the suppressive effects of sleep loss on adaptive immunity (Irwin et al., 1996; Irwin, 2015). Nevertheless, when upstream mechanisms of cellular and molecular mechanisms are examined, modest sleep loss for part of the night increases the production of pro-inflammatory cytokines by monocytes following ligation of TLR-4 with lipopolysaccharide (Irwin, Wang, Campomayor, Collado-Hidalgo, & Cole, 2006), activates NF- κ B, and up-regulates a gene set that includes the master circadian regulator, several immediate early genes marking cellular signal transduction, and multiple inflammatory response genes. These effects are stronger in females (Irwin et al., 2008; Irwin, Carrillo, & Olmstead, 2010), possibly due to sex difference in SNS up-regulation of IL-6 production (O'Connor, Motivala, Valladares, Olmstead, & Irwin, 2007), which together might contribute to sex differences in the incidence of inflammation-related behavioral and autoimmune diseases.

Naturalistic, observational studies have also demonstrated associations between sleep disturbances and inflammation. As reviewed in a recent meta-analysis including nearly 34,000 participants for CRP and over 3,000 participants for IL-6, sleep disturbance was associated with increases in these two markers of systemic inflammation, with some heterogeneity among studies, no presence of publication bias, and high statistical power (Irwin, Olmstead, & Carroll, 2016). Because sleep disturbance is thought to have proximal effects on IL-6 and because IL-6 induces CRP, the effect sizes linking sleep disturbance with IL-6 were larger than those found for CRP, which raises the possibility that increases of CRP might be due to more severe sleep disturbance (as reviewed, Irwin 2015). Importantly, these effects were strongest in studies that assessed sleep disturbance using validated questionnaires that comprehensively measure sleep disturbance (Irwin et al., 2016) (Plate 24).

In contrast, sleep duration showed no significant association with IL-6, although a small effect was found for CRP (Irwin et al., 2016). Interestingly, long (but not short) sleep duration was associated with increases in CRP and IL-6, consistent with experimental evidence that short sleep duration has mixed effects on inflammation (Irwin et al., 2016). Nevertheless, the associations between sleep duration and inflammation parallel the findings on sleep and mortality in which long sleepers (> 8 hours per night) have a 30 percent greater risk of dying and short sleepers (< 7 hours per night) have a 12 percent greater risk of dying than persons who sleep 7 to 8 hours per night (Cappuccio, D'Elia, Strazzullo, & Miller, 2010).

As shown in Plate 23, sleep influences two primary effector systems, the HPA axis and SNS, which together shift the basal gene expression profile toward an increased pro-inflammatory state (Irwin & Cole, 2011; Slavich & Irwin, 2014). During normal nocturnal sleep, there is a drop in sympathetic outflow (Irwin, Thompson, Miller, Gillin, & Ziegler, 1999), which does not occur in persons who have insomnia or clinically significant sleep disturbance. Hence, sympathetic activation may be one biologically plausible mechanism underlying these effects, as activation of β -adrenergic signaling induces increases in markers of inflammation, increases in NF- κ activation, and increases in inflammatory gene expression (Irwin & Cole, 2011).

Inflammatory Disease

Adverse social-environmental conditions such as low socioeconomic status, social isolation, and death of a spouse increase risk for inflammation-associated cardiovascular, autoimmune (e.g., rheumatoid arthritis), and neoplastic diseases (Cohen et al., 2007; Cole et al., 2010; Kiecolt-Glaser et al., 2003; Miller et al., 2008b). This raises the interesting possibility that at least some comorbidity with depression may be explained by the fact that these medical disorders, depression, and related sleep disturbance share a common biological basis that involves the activation of inflammation. A detailed review of links between psychological stress, depression, sleep disturbance, and inflammatory disease risk is beyond the scope of this chapter, but several relevant examples are considered here.

Cardiovascular Disease

Sleep disturbance is approximately twice as likely to occur in individuals with coronary heart disease and three times as likely in persons with congestive heart failure compared to prevalence rates in the general population (see Irwin, 2015). In addition, depression is a well-known risk factor for cardiovascular disease, with recent findings indicating that sleep disturbance also has a critical role in mediating the association between depressive symptoms and hypertension incidence as well as all-cause and cardiovascular disease mortality. Sleep complaints, possibly through

induction of inflammation, also independently contribute to cardiovascular disease risk (Irwin, 2015). Atherosclerosis is an inflammatory process that involves a series of steps, each of which can be impacted by psychological stress and sleep disturbance. Within the vasculature, activated macrophages secrete pro-inflammatory cytokines that lead to expression of cellular adhesion molecules. In turn, endothelial activation facilitates recruitment of immune cells to the vascular endothelium, which release additional inflammatory cytokines. There is evidence that depression, as well as sleep disturbance, induces inflammation along with expression of adhesion molecules that tether and bind immune cells to the vascular endothelium. Among acute coronary patients who are depressed, for example, there is increased expression of an adhesion molecule, *soluble intra-cellular adhesion molecule*, which is a marker of activation of the vascular endothelium. Depressed acute coronary patients show greater increases in CRP than non-depressed acute coronary patients, raising the possibility that depression-related increases in inflammation may explain the increased risk of major adverse cardiac events in patients exhibiting comorbid depression. However, no study has systematically evaluated whether elevated levels of inflammation mediate the association between depression, sleep disturbance, and cardiovascular disease.

Rheumatoid Arthritis

Individuals with rheumatoid arthritis are two to three times more likely to have major depression than the general population. Chronic stress, particularly of an interpersonal nature, provokes increased production of the pro-inflammatory cytokine IL-6, which correlates with symptoms of disease including fatigue, pain, and functional limitations. Moreover, the presence of depression in rheumatoid arthritis patients undergoing stress is associated with exaggerated increases in IL-6 (Davis et al., 2008; Zautra et al., 2004), a biomarker predictive of disease progression. Finally, sleep disturbance induces increases in independent, clinician-rated measures of joint tenderness and self-reported measures of pain compared to self-reported pain in comparison controls (Irwin et al., 2012). Conversely, administration of a psychological intervention that decreases emotional distress produces improvements in clinician-rated disease activity in rheumatoid arthritis patients, along with decreases in markers of inflammation (Zautra et al., 2008).

Cancer

Depression is reported to have median point prevalence between 15 percent and 29 percent in cancer patients, which is approximately three to five times greater than the general population (Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008a; Raison & Miller, 2003; Rooney et al., 2011). Furthermore, the relative risk of depression in patients with cancer possibly exceeds that of patients who have a stroke, diabetes, and heart disease (Patten et al.,

2008; Polsky et al., 2005). Prospective data further suggest that cancer diagnosis and treatment actually provokes the occurrence of depression during the first two years after diagnosis compared with those who remain medically healthy, leading to a rate of depression occurrence that is higher than what has been found in other chronic diseases (Polsky et al., 2005).

To explain these effects, we and others have hypothesized that cancer diagnosis and treatment initiates increases in inflammatory signaling that contribute to increased risk of fatigue and depression in cancer survivors. Consistent with this possibility, acute treatment with chemotherapy activates NF- κ B and inflammation, and is associated with depression in the six-month period following treatment in breast cancer patients (Torres et al., 2013); and, as noted above, pro-inflammatory cytokines can induce increases in depressed mood (Eisenberger, Inagaki, Rameson, Mashal, & Irwin, 2009). Because wake-sleep cycles have emerged as homeostatic regulators of inflammatory biology, in which sleep loss induces activation of NF- κ B to coordinate the production of inflammatory mediators and systemic inflammation, sleep disturbance in cancer survivors may play a role in perpetuating inflammation, leading to depression and possibly cancer recurrence. Indeed, chronic inflammation is reported to be associated with recurrence of breast cancer (Cole, 2009), and epidemiological studies have shown that chronic inflammation predisposes individuals to various types of cancer including breast cancer, and underlying inflammatory responses are linked to 15–20 percent of all deaths from cancer worldwide (Mantovani, Allavena, Sica, & Balkwill, 2008). Moreover, sleep disturbance may contribute to the occurrence of cancer in the first place. Some epidemiologic research studies have found that self-reported sleep disturbance or short sleep duration contributes to cancer risk (see Irwin, 2015). To our knowledge, no research has examined prospective relations between sleep disturbance and inflammation to determine whether these behavioral comorbidities contribute to increases in inflammation with implications for predicting cancer and non-cancer outcomes.

Inflammatory Regulation of Behavior

As described above, innate immune responses are regulated by both external influences (through neural activity) and internal factors (such as pathogens and cell damage) (see Plate 25). In addition, immune response genes are involved in the reciprocal regulation of neural activity. We have previously suggested such reciprocal regulation provides exactly the feedback required by dynamic systems theory to stabilize the circuit as a whole, particularly given the fact that CNS function is itself regulated by both the internal (inflammatory) and external (ecological) environments simultaneously (Irwin & Cole, 2011) (Plate 25).

The hypothesis that inflammation might alter behavior and signal the brain to induce depressive symptoms was possibly first suggested by Neal Miller (Miller, 1964), who argued that feeling sick during times of infection helps organisms conserve energy and prioritize behaviors that are critical for survival. In the last two decades, sickness behaviors are now considered to be an organized, highly adaptive response to infection that are mediated by activation of inflammatory mechanisms (Dantzer et al., 2008; Miller et al., 2009a; Slavich & Irwin, 2014).

It is now known that several molecular signaling pathways convey peripheral pro-inflammatory and anti-viral signals into the brain (Dantzer et al., 2008; Watkins & Maier, 1999). In turn, pro-inflammatory cytokines decrease the activity of key behavior-modulating neurotransmitter systems including norepinephrine, dopamine, and serotonin (Miller et al., 2009a), which activate physiological and behavioral responses such as fever and social withdrawal. (Dantzer et al., 2008; Hart, 1988). Below, we consider the diverse effects of inflammation on a variety of behaviors, many of which are associated with depression.

Sickness behaviors including emotional alterations (e.g., anhedonia, fatigue, and dysphoria), reductions in exploratory and reward-seeking motivation, altered cognitive and motor function, sleep alterations, and reduced social and reproductive motivation (Dantzer et al., 2008; Hart, 1988) are triggered by pro-inflammatory cytokines. For example, in mouse studies, when IL-1 receptors in the hypothalamus and hippocampus (Dantzer et al., 2008; Hart, 1988) are activated by type I IFNs and pro-inflammatory cytokines, a sickness behavior syndrome occurs (Dantzer et al., 2008; Hart, 1988), wherein different cytokines trigger different behaviors.

As described above, dysregulated activation of cytokine-mediated sickness behaviors plays a role in at least some forms of depression, in addition to fatigue and sleep disturbance (Miller et al., 2009a). It is well known that depression rates are higher in clinical conditions that involve high levels of inflammation (e.g., in patients with cancer, cardiovascular disease, or rheumatoid arthritis) (Miller et al., 2008a, 2009a), that elevated levels of IL-6 and TNF increase risk for depression (Gimeno et al., 2009; Slavich & Irwin 2014), and that clinical response to antidepressant medications is poorer when circulating levels of inflammatory biomarkers are elevated (Benedetti, Lucca, Brambilla, Colombo, & Smeraldi, 2002; Miller et al., 2009a). Pro-inflammatory gene expression is also associated with fatigue, a symptom of major depression (Thomas, Motivala, Olmstead, & Irwin, 2011). For example, cancer survivors show substantial increases in NF- κ B inflammatory signaling from tumor-derived cytokines as well as cancer treatment (e.g., radiation, chemotherapy), and this inflammation is associated with fatigue, particularly among patients with high-expression polymorphisms in IL1B, IL6, and TNF (Collado-Hidalgo, Bower, Ganz, Irwin, & Cole, 2008).

Research has also shown that pro-inflammatory cytokines and type I IFNs are involved in the homeostatic regulation of sleep (Imeri & Opp, 2009). For example, elevated daytime levels of TNF have been linked with sleepiness and altered sleep architecture, including reductions in slow-wave sleep and increases in rapid eye movement (REM) sleep. Given epidemiological links between abnormally high REM sleep and mortality (Dew et al., 2003), and the substantial fraction of time we spend asleep, the regulation of sleep architecture by the innate immune system may play an important role in structuring overall inflammatory homeostasis (Imeri & Opp, 2009; Motivala & Irwin, 2007).

To probe the causal link between inflammation and depression, researchers have characterized the symptom development and severity profiles of individuals undergoing pharmacological administration of IFN α for the treatment of cancer and hepatitis C. In these quasi-experimental studies, IFN- α administration induces symptoms of depressed mood, anhedonia, fatigue, cognitive impairment, sleep disturbance, loss of appetite, and suicidal ideation, which reaches clinically significant levels in up to 50 percent of individuals (see Miller et al., 2009a). When vegetative-depressive symptoms develop early on during the course of IFN- α administration, onset of depression appears more likely. Similar to findings involving laboratory-induced inflammation, persons with a history of depression show a greater response, and in the case of IFN- α treatment are more likely to develop cognitive and affective symptoms of depression, than persons without a history of depression (Slavich & Irwin, 2014).

Researchers have also examined genetic factors that may moderate these effects. For example, functional SNPs in the μ -opioid receptor gene (OPRM1) and serotonin transporter gene (5-HTTLPR) have been associated with increased risk for depression following stress (Lotrich, El-Gabalawi, Guenther, & Ware, 2011; Slavich, Tartter, Brennan, & Hammen, 2014). In addition, there is evidence that functional SNPs in the promoter regions of the genes encoding both IDO (rs9657182) and IL-6 (rs1800795) moderate risk of IFN- α induced depression (Bull et al., 2009). Animal genetic studies and LPS administration studies in humans (Imeri & Opp, 2009; Mullington et al., 2000) have linked changes in non-rapid eye movement (NREM) sleep to elevated levels of circulating type I IFN, and pro-inflammatory cytokines and pharmacological administration of IL-6 and IFN α in humans induce complementary decreases in NREM and slow-wave sleep, and increases in REM sleep (Imeri & Opp, 2009; Raison et al., 2010), although animal studies show that other cytokines such as TNF α increase NREM and decrease REM sleep (Imeri & Opp, 2009). Finally, TNF antagonism has been found to normalize REM sleep levels (e.g., in abstinent alcohol-dependent patients who have elevated amounts of REM sleep) (Irwin, Olmstead, Valladares, Breen, & Ehlers, 2009).

To evaluate whether an inflammatory challenge that elicits physiologic (as opposed to pharmacologic) increases in inflammation might trigger depressive symptoms in humans, administration of typhoid vaccine or low dose endotoxin have been used. Typhoid vaccination induces a modest increase in circulating cytokines, but nevertheless induces significant increases in negative mood, confusion, and fatigue, which correlate with increases in IL-6 (Harrison et al., 2009). Similarly, administration of bacterial endotoxin, which leads to about ten-fold increases in IL-6 levels and fivefold increases in TNF- α levels corresponding to real-world clinical settings such as HIV infection (Breen et al., 1990) and rheumatoid arthritis (Mangge et al., 1995), elicits several symptoms of depression including sad mood, anhedonia, cognitive impairment, fatigue, reduced food intake, altered sleep (e.g., disrupted sleep continuity, increased REM latency, and REM suppression), and social-behavioral withdrawal (DellaGioia & Hannestad, 2010; Eisenberger et al., 2009; Eisenberger, Inagaki, Mashal, & Irwin, 2010b; Eisenberger et al., 2010a; for a review, see Slavich & Irwin, 2014). The relevance of this experimental paradigm for understanding mechanisms linking inflammation and depression is further supported by the fact that some antidepressant medications blunt or abate increases in depressive symptoms following an inflammatory challenge (DellaGioia & Hannestad, 2010). As shown in Plate 26, these challenges have also been shown to alter the activity and connectivity of neural circuits implicated in risk for depression, including the anterior cingulate cortex, amygdala, medial prefrontal cortex, and ventral striatum (Eisenberger et al., 2009, 2010a; Harrison et al., 2009).

Conversely, blockade of inflammatory cytokines has been shown to reduce individuals' risk for depression while improving their sleep architecture and antidepressant treatment response (see Slavich & Irwin, 2014). For example, treatment with the antidepressant medication reboxetine, in combination with the anti-inflammatory medication celecoxib, led to reductions in depression severity that was nearly twice as great as the gains achieved with reboxetine alone. Similarly, by combining an antidepressant medication (i.e., selective reuptake inhibitor) with acetylsalicylic acid (i.e., aspirin), over 52 percent of depressed patients showed a response after having not responded to the SSRI treatment alone. Use of a TNF- α antagonist etanercept, singly without combination with an antidepressant medication, resulted in a greater rate of depression remission response as compared to placebo in a group of psoriasis patients (Tyring et al., 2006). In outpatients with treatment-resistant depression, treatment with TNF- α antagonist (compared to placebo) reduced depressive symptoms in patients with high levels of CRP at entry (> 5 mg/L) (Raison et al., 2013). These findings provide additional evidence that anti-inflammatory medications may have antidepressant properties, but also raise the question of whether they are efficacious for all depressed individuals or only for

a subgroup of patients (e.g., those with elevated inflammation). Finally, pharmacological antagonism of TNF improves REM sleep, which is often disrupted in depressed and substance-dependent populations (Irwin et al., 2009). In sum, peripheral innate immune responses can influence CNS functions including neurotransmitter metabolism, regional brain activity, sleep–wake cycles, and behavioral processes including depression, sleep, and fatigue, with implications for neuropsychiatric disease.

Behavioral Regulation of Immunity

Behavioral interventions have been applied to target psychological stress, depressive symptoms, fatigue, and insomnia, and have also been found to influence anti-viral immune responding and inflammatory activity. Many of these behavioral interventions are either mind–body therapies, such as Tai Chi, Qigong, meditation, or yoga, or components of these practices that have been integrated into behavioral interventions, such as mindfulness-based cognitive behavioral therapy. The efficacy of these various mind–body treatments has been subjected to empirical scrutiny through randomized controlled trials conducted in clinical and non-clinical populations, and together there is evidence that these treatments offer many psychological and health functioning benefits, including reductions in disease symptoms, improvements in coping, behavior regulation, quality of life, and well-being (Wang, Collet, & Lau, 2004). In light of these benefits, recent investigations have sought to better understand how these effects occur, with a focus on the immune system as a possible mediating mechanism.

As noted above, psychological stress and depression impair anti-viral immune responses. Hence, behavioral interventions aimed at alleviating stress, promoting relaxation, and encouraging moderate physical activity have been shown to bolster anti-viral immune responses, particularly among older adults or adults experiencing high levels of psychological stress (Antoni, 2013; Miller & Cohen, 2001; Wang et al., 2010). A recent meta-analytic review identified seven studies that examined the effects of mind–body therapies on several anti-viral outcomes, including IFN- γ production, lymphocyte proliferation including viral-specific, cell-mediated immune responses (i.e., varicella zoster virus responder cell frequency) (VZV-RCF), and NK cytotoxicity. This review found significant effects for non-specific and viral-specific lymphocyte proliferation and vaccination responses, but not stimulated production of IFN- γ (Morgan, Irwin, Chung, & Wang, 2014). For example, the administration of Tai Chi versus health education on varicella zoster immunity found robust increases in anti-viral immune responses at rest and in response to vaccination in 148 healthy older adults (Irwin, Olmstead, & Oxman, 2007).

Alterations in inflammatory processes are thought to play a role in inducing symptoms of fatigue, sleep

disturbance, and depression, and there is increasing interest in the impact of mind–body therapies on inflammation in various populations, such as those with disabling fatigue or insomnia. In a recent review, a total of 26 trials were identified that examined effects of Tai Chi, Qigong, meditation, and yoga interventions on inflammatory outcomes (Morgan et al., 2014). The majority of studies focused on circulating markers, particularly CRP, and revealed only mixed evidence that mind–body therapies altered these inflammatory outcomes. For example, half of the studies showed decreases (or attenuated increases) of CRP in the intervention group and the other half showed no changes in CRP. The majority of studies found no effects for IL-6. This absence of change in inflammatory markers stands in contrast with many of the trials showing effects on symptoms and other outcomes. These mixed results might be due to the selection of subjects who had low levels of inflammation at baseline, use of an intervention that was too short in duration, or absence of a follow-up period to detect changes in inflammation that would follow administration of the intervention. More sustained practice may be required to alter circulating markers, such as CRP, with evidence that decreases in inflammation may be evident only when the symptom remitted. Physical activity interventions have also been found to reduce circulating levels of CRP (Nicklas et al., 2008), although this literature is beyond the scope of this chapter.

In contrast, studies that evaluated cellular markers of inflammation, assessed by the production of pro-inflammatory cytokines after *ex vivo* stimulation, were more promising. Fifty percent of the trials examined showed that production of inflammatory cytokines was reduced following Tai Chi or yoga administration (Morgan et al., 2014). The duration of follow-up after treatment may have accounted for variable findings, as it may take several months for the effects of mind–body therapies to become evident. For example, Kiecolt-Glaser and colleagues (2014) found no differences in LPS-stimulated production of IL-6, TNF, and IL-1 in 200 breast cancer survivors after 12 weeks of treatment, but significant group differences were identified at three months follow-up. Additionally, approaches that characterize the cellular source of inflammation may be more sensitive for detecting the effects of mind–body therapies on inflammation. Irwin and colleagues examined the effects of Tai Chi on monocyte production of IL-6 and TNF in two independent samples of insomnia patients (Irwin et al., 2014b, 2015). Compared to prior studies that had used mixed mononuclear cell cultures or whole blood, cellular inflammation was measured by LPS or Toll-like receptor (TLR)-4 stimulated production of IL-6 and TNF in monocytic populations. Both studies found that Tai Chi administration over 12 or 16 weeks reversed the insomnia-related increases in the percentage of monocytes expressing IL-6 alone, expressing TNF alone, and co-expressing IL-6 and TNF, with significant decreases for each of these measures (Irwin et al., 2014b, 2015) (Figure 17.2). Interestingly, Tai

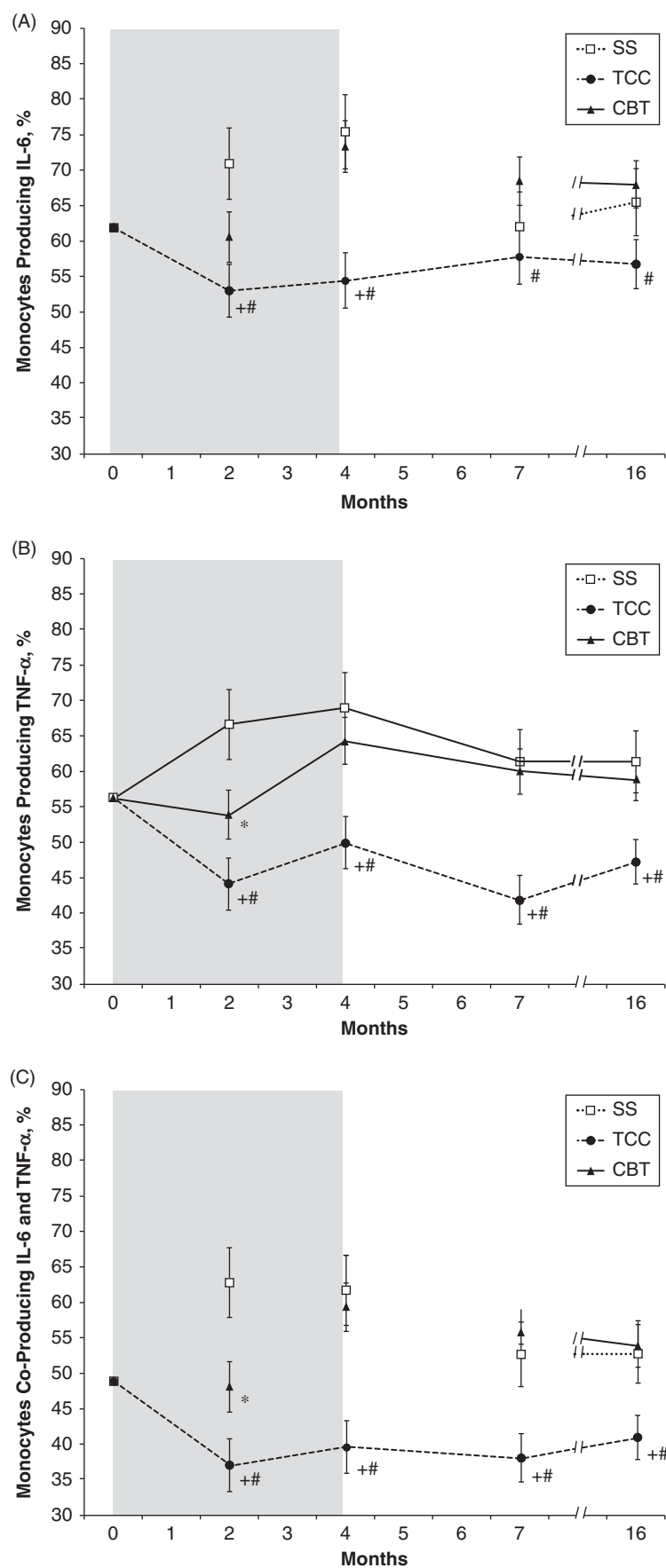


Figure 17.2 Toll-like 4 receptor stimulated monocytic production from baseline to month 16 by treatment group. Values are mean (SEM) percentage of monocytes producing interleukin-6 (IL-6) (A), tumor necrosis factor- α (TNF) (B), or both IL-6 and TNF (C). Shaded area indicates period of administration of intervention following baseline assessment. Significant pairwise comparisons: *cognitive-behavioral therapy (CBT) vs. sleep seminar (SS), $p < 0.05$; # Tai Chi Chih (TCC) vs. SS, $p < 0.05$; + CBT vs. TCC, $p < 0.05$. From Irwin et al., 2015.

Chi administration induced decreases as early as two months, with effects maintained over the course of a one year follow-up.

In mind–body trials that examined genomic indicators of inflammatory markers, consistent decreases in inflammatory gene expression profiles have been identified. Indeed, each of the seven trials that used yoga, Tai Chi, or meditation, and assessed genomic markers of inflammation, showed treatment-related effects on inflammatory signaling pathways, specifically reductions in NF- κ B activity (Bower & Irwin, 2016). These effects were seen in diverse populations. Moreover, the effects on genomic markers were evident even when the concurrent assessment of circulating markers of inflammation did not reveal decreases. As such, alterations in molecular signaling pathways may be more sensitive to these interventions, at least in the short term.

Several mechanisms likely play an important role in structuring intervention-related changes in inflammatory activity, with some attention focused on alterations in the autonomic nervous system (ANS) and HPA axis, because systems are key regulators of inflammatory gene expression and mediators of the stress response (Bower & Irwin, 2016). Indeed, mind–body therapies are associated with decreases in sympathetic activity and increases in parasympathetic activity (Bower & Irwin, 2016), reflecting greater sympathovagal balance. Irwin and colleagues found that Tai Chi led to reduced activity of cAMP response element binding protein (CREB) family transcription factors, which is consistent with reduced sympathetic nervous system signaling through β -adrenergic receptors, in tandem with decreases in NF- κ B activity (Irwin et al., 2015). Likewise, several trials have shown that mind–body therapies lead to changes in glucocorticoid receptor signaling, with evidence that Tai Chi, mindfulness, and yoga all increase anti-inflammatory GR signaling and decrease NF- κ B signaling (see Bower & Irwin, 2016).

Precisely how these effects occur remains unclear, but mind–body therapies are thought to influence activity in brain regions that regulate threat-related neural circuits. Mindfulness may also influence activity in reward-related regions, such as the ventromedial prefrontal cortex (VMPFC), ventral striatum, and septal area, which also have inhibitory effects on threat-related physiologic responding. To date, no study has concurrently evaluated changes in neural activity and inflammation in the context of a mind–body intervention (see Bower & Irwin, 2016).

Mind–body therapies may also lead to decreases in perceived stress, depression, and anxiety, along with increases in control, self-efficacy, emotion regulation, and peace and meaning in life. In a study of lonely older adults, decreases in loneliness were associated with decreases in inflammation (Creswell et al., 2012). Likewise, decreases in circulating markers of inflammation such as CRP were found only in association with

remission of insomnia or improvement in sleep disturbance in older adults with insomnia (Irwin et al., 2014a). Together, these results suggest that improvements in inflammation may be more robustly identified when clinical symptoms abate.

CONCLUSIONS

In conclusion, an abundance of research has shown that immunological processes that are relevant for health are influenced not just by internal factors, but also by the perceptions of individuals about their external social and physical environment. Research has begun to identify the immune system mediators that are most responsive to social-environmental input; the psychological, neural, physiologic, molecular, and genomic processes linking the external environment with changes in immune system dynamics; the specific psychoneuroimmunological factors that most strongly shape infectious and inflammatory disease risk; and the types of behavioral interventions that may mitigate this risk. Given that the immune system is implicated in a majority of the major causes of death in the United States today (Slavich, 2015), additional discoveries along each of these lines is highly warranted.

Looking forward, there are several promising avenues for future research. First, since studies in psychoneuroimmunology presently only concurrently examine one to two levels of analysis, future research should incorporate additional methods so that phenomena can be examined across multiple systems in the same experimental or clinical context. Second, there is a pressing need to understand not just common pathways that promote disease (e.g., inflammation, sleep disturbance), but also moderating factors that help explain why individuals experiencing similar types of environmental or physiological challenges develop different health problems. Third, because a majority of studies in psychoneuroimmunology to date have focused on person-level processes, additional research is needed to better understand how collective factors (e.g., relationship dynamics, social structures) impact immunity and health. Finally, despite overwhelming evidence that immunological processes are implicated in many different mental and physical health problems, very little is presently known about how we can alter these processes to have beneficial effects. Therefore, more attention should be paid to identifying interventions that influence immune system dynamics and the mechanisms underlying these effects. Work on these topics is challenging because it requires either advanced knowledge of several psychological and biological systems or ongoing collaborations between knowledgeable investigators. Yet the likely substantial advance in terms of better understanding the psychobiological basis of human health and behavior is clearly worth the continued effort.

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