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31 Psychoneuroimmunology

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Introduction

The field of psychoneuroimmunology (PNI) aims to elucidate relationships between psychosocial factors, immune function and health by integrating research in psychology, immunology, physiology, neuroscience and medicine. PNI research questions have traditionally focused on the immune system as a mediator between psychosocial factors (e.g. stressful life events, depression) and health outcomes. More recently, the field has expanded to explore other pathways, such as how health-related immune changes may affect cognition and mood. Regardless of the pathway, PNI research emphasizes physiological mechanisms that link psychosocial factors and health.

The immune system is highly complex and measured by a wide array of methods (see Chapter 49). For the purposes of this chapter, a number of commonly measured immune cells and their primary functions are described in Table 31.1. For descriptive purposes, the immune system is

Table 31.1 Cells of the immune system

Cell type	Function
White blood cells (WBCs)/leukocytes	Respond to antigens such as bacteria or viruses and altered host cells such as tumor or infected cells; include phagocytes and lymphocytes
Phagocytes	Subset of WBCs that ingest and destroy antigens; include monocytes, macrophages, eosinophils, and neutrophils
Lymphocytes	Subset of WBCs that include T- and B-cells and natural killer (NK) cells
NK cells	Destroy tumor cells or virally infected host cells
T-helper (CD4) cells	Enhance immune responses by stimulating T-cell replication and activating antibody production by B-lymphocytes
T-regulatory cells	Inhibit immune responses (subset of CD4 cells)
T-cytotoxic (CD8) cells	Destroy virus-, parasite- and tumor-infected cells; reject transplanted tissue
B-cells	Produce antibodies involved in the antibody-mediated response

divided into innate and adaptive processes. The innate immune response is the second line of defense after physical barriers (e.g. skin) once pathogens have entered the body and includes the inflammatory cascade. Phagocytes in the tissue and bloodstream initiate this response by secreting proinflammatory cytokines, signaling proteins that act as immune messengers and coordinate local and systemic inflammatory responses. In recent years, PNI research has focused on the assessment of circulating levels of these cytokines as a metric of ongoing or 'systemic' inflammatory processes in the body. This shift follows increased understanding of the role of inflammatory processes in the pathophysiology of numerous diseases (e.g. cardiovascular disease (CVD), cancer) and the relative ease of cytokine measurement. Some of the most commonly assessed inflammatory markers in PNI research are the cytokines interleukin(IL)-6, IL-1β, tumor necrosis factor (TNF)-α, and the downstream inflammatory marker protein (CRP). Other cytokines serve important roles in communication between cells of the innate and adaptive immune systems.

The adaptive immune response provides a complex third line of defense that adapts to protect the body from specific invaders (e.g. viruses). Lymphocytes are the primary effector cells of this system (see Table 31.1). Adaptive immunity includes two different types of immune response: the antibody-mediated response (i.e. humoral immunity) and the cell-mediated response (cellular immunity). Antibody-mediated immunity involves activation of B-lymphocytes (B-cells) and the production of antibodies that protect against extracellular microorganisms. Cell-mediated immunity is orchestrated by T-lymphocytes (T-cells) that protect against intracellular pathogens, such as viruses (see Table 31.1).

Biological Pathways that Regulate the Immune System

Once thought to be autonomous from other body systems, the immune system is now known to interact with the brain via the autonomic nervous system (ANS), the hypothalamic–pituitary–adrenal (HPA) axis, and humoral pathways. Central nervous system (CNS) appraisals of stressful psychosocial stimuli modulate ANS responses by upregulating activity of the sympathetic nervous system (SNS) and downregulating activity of the parasympathetic nervous system (PNS) (Gianaros & Wager, 2015). Immune organs are innervated by SNS fibers and both innate and adaptive immune cells express receptors for SNS neurotransmitters (e.g. epinephrine, norepinephrine); thus there is a clear anatomical pathway by which the SNS communicates with the immune system (Nance & Sanders, 2007). SNS–immune interactions are complex, as the SNS can both inhibit and enhance different attributes of the immune system, including stress-induced immune alterations (Bachen *et al.*, 1995). Although there is less anatomical evidence for PNS innervation of immune organs, new evidence suggests that the PNS may play an important role in regulating immune function; this is thought to occur by inhibiting overproduction of proinflammatory cytokines during the inflammatory response, thus reducing the harmful effects of excessive inflammation (Tracey, 2002). Research on autonomic–immune mechanisms is ongoing, but it is clear that the ANS contributes to regulation of the immune system.

The HPA axis stress response is also initiated by activation of central pathways via stress appraisals, leading to release of adrenocorticotropic hormone (ACTH) by the pituitary gland and glucocorticoids (GCs; e.g. cortisol in humans) by the adrenal cortex. The HPA axis can both inhibit and potentiate numerous aspects of the immune response through these hormones; all immune cells have receptors for GCs, ACTH and corticotrophin-releasing hormone. GCs, in particular, can enhance monocyte and dendritic cell function (Franchimont, 2004). GCs can also have immunosuppressive effects by binding to receptors in peripheral immune cells and down-regulating a number of innate immune processes, including blocking lymphocyte activation, modulating leukocyte trafficking and down-regulating secretion of proinflammatory cytokines.

Although PNI has focused largely on central modulation of the immune system, communication between the CNS and the immune system is bidirectional. Specifically, the immune system communicates with the CNS via cytokine signaling to impact mood, cognitive function and behavior (Irwin & Cole, 2011). In the context of acute illness, these 'sickness behaviors' are thought to be adaptive and include fatigue, lethargy and decreased appetite (Watkins & Maier, 2005), which are proposed to preserve metabolic energy for fighting infection. Cytokines also act centrally to activate efferent sympathoadrenal and HPA pathways that modulate the production of peripheral cytokines by peripheral immune cells (Tracey, 2002; Watkins & Maier, 2005). These feedback loops are closely regulated to maintain homeostatic balance and protect health. For example, peripheral proinflammatory cytokines that access the CNS can activate the HPA axis, resulting in peripheral release of GCs that downregulate the inflammatory response. In this way, inflammatory responses are tightly controlled to handle acute infection, without incurring damage that may result from chronic inflammatory processes.

Stress and the Immune System

As a field, PNI has focused on understanding whether exposure to psychological stress affects susceptibility to disease by altering the function of the immune system. The term 'stress' has many operational definitions (see also Chapter 34), ranging from acute and short-term naturalistic stressors (e.g. laboratory paradigms and exam stress) to more chronic stressors (e.g. caregiving for an ill loved one, socioeconomic disadvantage or marital discord). Many of these exposures fall into multiple categories; for example, a natural disaster is often a severe but brief event that can cause a chronically taxing situation. Different types of stress can have dramatically different effects on the immune system, with

some studies showing stress-related immunosuppression and others showing immune enhancement. The following provides a brief overview of two areas in stress and PNI research.

Acute Laboratory Exposures

Laboratory studies provide one method to examine stress–immune interactions. Such investigations approximate the effects of transient daily life stressors and provide a means to investigate potential mechanisms underlying stressor-evoked immunological changes. Experimental laboratory stressors frequently include simulated public speaking, challenging computer tasks and mental arithmetic. Exposure to these stressors can evoke short-term alterations of both innate and adaptive immune processes (Kiecolt-Glaser *et al.*, 1992). For example, these tasks evoke increases in circulating levels of proinflammatory cytokines, such as IL-6 and IL-1β (Steptoe *et al.*, 2007). Notably, there are individual differences in immunological responses to stress that may have implications for susceptibility to clinically relevant outcomes (Brydon & Steptoe, 2005). In summary, exposure to acute stress has wide-ranging effects on the immune system but more work is needed to determine how such alterations affect long-term health.

Chronic Exposures

Chronic exposure to adverse life experiences has a profound impact on the immune system and, ultimately, health outcomes. Typically, chronic stress is defined as an event or situation that does not have a clear end, lasting for weeks, months or years. Some of the most commonly assessed chronic stressors in PNI research are long-term caregiving, maltreatment, socioeconomic disadvantage and job strain. Although the effects of chronic stressors are wide-ranging, exposure to chronic stress can suppress some aspects of immune function while enhancing others (Dhabhar, 2009; Segerstrom & Miller, 2004). Associations between chronic stress and numbers of circulating leukocytes are inconsistent across studies (Dhabhar, 2009; Segerstrom & Miller, 2004). However, chronic stress appears to suppress most functional immune measures, such as leukocyte function and magnitude of lymphocyte response to immune stimulants (Dhabar, 2009; Segerstrom & Miller, 2004). Additionally, chronic stressors have been linked with the upregulation of proinflammatory cytokines or systemic inflammation. Although an increase in proinflammatory cytokines can be adaptive as a short-term defense against pathogens, prolonged heightened systemic inflammation may contribute to the development of chronic diseases (Dhabar, 2014; Miller *et al.*, 2011). In summary, exposure to chronic stressors leads to both functional immunosuppression and heightened levels of systemic inflammation, possibly increasing risk for chronic inflammatory disease.

Psychopathology

Mood Disorders

Substantial evidence indicates that inflammatory processes contribute to major depressive disorder (MDD) and bipolar disorder (BPD). Compared to healthy controls, individuals with MDD show elevations in proinflammatory cytokines (Howren *et al.*, 2009). Moreover, the relationship between depression and inflammation appears to be bidirectional, with elevated proinflammatory cytokines predicting future depressive symptoms (Valkanova *et al.*, 2013) and depression also predicting subsequent levels of circulating cytokines (Copeland *et al.*, 2012). In addition, depression predicts and is often comorbid with chronic diseases with an inflammatory component, such as CVD, rheumatoid arthritis, systemic lupus erythematosus and the metabolic syndrome (Bachen *et al.*, 2009; Slavich & Irwin, 2014); these comorbidities suggest that depression and chronic diseases may share common immune mechanisms.

In bipolar disorder, heightened levels of peripheral cytokines are seen during both depressive and manic episodes (Muneer, 2016). Adding to the evidence that inflammation plays a role in BPD, anti-inflammatory pharmacological treatment paired with conventional therapy has been found to improve symptoms of BPD more effectively than conventional therapy alone (Rosenblat *et al.*, 2016). In addition, comorbid medical conditions, such as obesity, diabetes and CVD, which are themselves associated with greater systemic inflammation, predict BPD severity and treatment outcomes (Kemp *et al.*, 2010).

PTSD

Among the anxiety disorders, post-traumatic stress disorder (PTSD) has received the most attention in PNI. PTSD is associated with a cytokine imbalance, characterized by heightened levels of proinflammatory mediators (Kang *et al.*, 2015; Wang & Young, 2016) and lower levels of anti-inflammatory cytokines (Cohen *et al.*, 2011). This imbalance is also reflected in greater numbers of proinflammatory T-helper cells and lower numbers of anti-inflammatory regulatory T-cells among people with PTSD compared to controls (Wang & Young, 2016). PTSD is also associated with increased risk for medical conditions with an immune or inflammatory component, including allergies, cardiovascular disease and autoimmune diseases (e.g. rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis) (Kang *et al.*, 2015; Wang & Young, 2016). When interpreting this body of research, it is important to consider the role of other psychiatric conditions (including mood and other anxiety disorders) and alterations in health behaviors (e.g. smoking, substance use, sleep) that often accompany PTSD.

Health Behaviors

Numerous health behaviors can impact the immune system; for example, sleep and cigarette smoking affect immune function. Short-term sleep deprivation and sleep restriction in laboratory-based studies are associated with increased proinflammatory mediators (Irwin, 2015; O'Connor *et al.*, 2009). Similarly, poor sleep quality, difficulty falling asleep and sleep apnea are all associated with heightened CRP (Irwin, 2015; O'Connor *et al.*, 2009). Sleep impairments have also been linked with decreases in NK activity and function (Irwin, 2015) and clinically relevant immune outcomes, such as poorer immune response to the hepatitis B and influenza vaccines (Miller *et al.*, 2004; Prather *et al.*, 2012).

Cigarette smoking and other tobacco use is associated with both heightened systemic inflammation in disease-free populations and also greater risk for inflammatory lung diseases (Alexander *et al.*, 2015), suggesting that inflammatory processes may contribute to the relationship between smoking and lung disease. More frequent smoking is associated with higher levels of circulating proinflammatory and lower levels of anti-inflammatory cytokines (O'Connor *et al.*, 2009; Rom *et al.*, 2013). Cigarette smoking has also been linked to increased risk and

poorer outcomes for a number of autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, Crohn's disease, Graves' disease, systemic lupus erythematosis and psoriasis (Perricone *et al.*, 2016), suggesting that smoking not only exacerbates existing autoimmune conditions, but also plays a role in their pathophysiology.

Applications and Clinical Significance

Viral Challenge Studies

Viral challenge studies apply experimental PNI methods to clinically relevant outcomes. Such studies are useful because they allow researchers to examine whether psychosocial factors are prospectively related to susceptibility to infectious disease. For a more detailed description of viral challenge studies, see Chapter 49. The Pittsburgh Common Cold Studies are perhaps the best example of this approach, showing that psychosocial factors discussed in this chapter predict susceptibility to upper respiratory infections (Cohen, 2005). For example, multiple types of psychological stress (e.g. stressful life events, chronic stress, interpersonal problems) predict greater risk for developing a cold after experimental exposure to the virus, with chronic stress the strongest predictor. Social factors, such as greater social integration and support, also seem to buffer the effects of stress on cold susceptibility.

Cardiovascular Disease

Over the past two decades, it has become increasingly clear that inflammation plays a critical role in the pathophysiology of CVD, as atherosclerosis is largely a chronic inflammatory process. Damage to the blood vessels enables migration of monocytes into the arterial wall, where they mature into macrophages and secrete growth factors and cytokines that maintain the vascular inflammatory response (Libby *et al.*, 2011). These chronic processes occur over many decades, increasing the risk for future cardiac events (e.g. heart attack and stroke). Epidemiological evidence shows that heightened levels of circulating inflammatory mediators confer increased CVD risk (Danesh *et al.*, 2008). As numerous psychosocial risk factors are linked with heightened levels of inflammatory mediators, these findings set the stage for new research on how inflammatory processes may mediate the relationship between psychosocial factors and CVD risk.

Cancer

Cancer also provides an interesting model to examine immune pathways between psychosocial factors and disease risk. Although evidence for a link between stress and cancer incidence has been mixed, stress and other psychosocial factors can impact both immune function and cancer progression (Chida *et al.*, 2008). The past decade has also seen a greater focus on factors in the tumor microenvironment and tumor progression (McDonald *et al.*, 2013), with evidence indicating that stress-related activation of the ANS and HPA axis can directly facilitate tumor growth and progression (Lutgendorf *et al.*, 2010). Finally, there has been an increase in research on immune-to-brain pathways that lead to sickness symptoms, such as fatigue, that accompany cancer diagnosis and treatment (Bower *et al.*, 2011). On the whole, there have been great strides in cancer and PNI research over the past decade, with growing evidence indicating complex pathways between psychosocial factors, the immune system and certain types of cancer progression.

Psychological Interventions

A significant body of work has examined whether psychological and behavioral interventions impact the immune system. Many of these interventions specifically target stress, given demonstrated associations between stress and immune function. These interventions include cognitive behavioral stress management, yoga and mindfulness-based stress reduction (MBSR). A recent meta-analysis concluded that mind–body interventions are associated with moderate decreases in inflammation, but not with changes in anti-viral or enumerative measures of the immune system (Morgan *et al.*, 2014). Growing research on human immunodeficiency virus (HIV) indicates that MBSR may help reduce disease-related depression and anxiety (Yang *et al.*, 2015), while cognitive behavioral stress management interventions can effectively target immune biomarkers of HIV (Antoni, 2012). Importantly, psychological interventions seem to be most effective in clinical or stressed samples, as opposed to non-stressed healthy populations.

Future Directions

This chapter presents a broad overview of the diversity of research in the PNI field. While exciting new advances in PNI have occurred over the past decade, more work is needed to advance and expand the field. First, the shift toward a greater focus on bidirectional brain–immune pathways represents a promising new direction for research on biopsychosocial mechanisms that link the central nervous and immune systems. Recent advancements in human neuroimaging methods provide novel tools for studying these bidirectional pathways. Second, greater emphasis must be placed on building more direct evidence for immune mediation of associations between psychosocial factors and disease. Although this model has been proposed for decades, much of the current research continues to examine individual pieces of the model (e.g. associations between psychosocial factors and immune mediators, or immune mediators and disease outcomes), rather than the complete model with all three elements (psychosocial, immune and disease). Finally, research on psychological interventions for immune-related outcomes needs larger sample sizes and longer follow-up times to further elucidate efficacy. With a focus on these goals, the field of PNI will continue to inform current understanding of relationships between psychosocial factors, nervous and immune systems, and health.

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