

Chapter 2

Stress and Inflammation: Translational Implications in Mind–Body Medicine

2.1 Stress and Inflammation: A Systems Biology Perspective

Stress and disrupted homeostasis can be caused by environmental changes and stimulations. However, the same stressor may result in different responses in different individuals, such as behavioral alterations or pathological dysfunctions in some people but little or no effects on other people. Different coping strategies and adaptive capabilities may account for such different impacts (Leonard and Myint 2009).

Stress can be acute or chronic. Acute stress responses can be protective in the adaptive processes for potential adverse environments. Chronic and constant stress may damage the ability of adaptation with changes in the immune system and hypothalamic–pituitary–adrenal (HPA) axis. Such changes may lead to pathological problems such as hypercortisolism, hypertension, and psychiatric disorders such as anxiety and depression (Leonard and Myint 2009).

Psychoneuroimmunology (PNI) studies may help explain the complex mechanisms underlying such processes. In stress responses, the endocrine and neurotransmitter systems are closely associated with the immune system with a wide range of molecules involved such as catecholamines, glucocorticoids, endorphins, and other neuropeptides (Leonard and Myint 2009). Stress and negative emotions may cause sympathetic hyperactivity and higher oxidative stress through cytokine receptors on endocrine cells and neurons, as well as hormone and neurotransmitter receptors on immune cells (Kemeny 2009; Irwin 2008; Alford 2007).

PNI studies based on systems biology approaches would enable the systemic insights into the complex stress–inflammation–disease correlations. The understanding of such interrelationships may be critical for the practice of human-centric personalized medicine by treating the shared pathological mechanisms instead of an isolated illness (see Chap. 1).

Inflammation has a significant role in adverse stress responses and various diseases. For instance, problems including anxiety, depression, and posttraumatic stress disorder (PTSD) have been associated with the elevated proinflammatory cytokines such as interleukin-6 (IL-6) and inflammatory networks such as the NF- κ B pathway (Haroon et al. 2011; Segerstrom and Miller 2004; Carpenter et al. 2010). At the cellular and behavioral levels, relevant factors include T-cell subpopulations, dietary intake, adiposity, and the bacterial composition of the gut microbiota (Haroon et al. 2011).

The inflammatory mechanisms provide the common linkages among the leading causes of mortality (Aggarwal et al. 2006). For example, the proinflammatory cytokines including IL-6 and IL-1 β are the key factors in cardiovascular diseases, cancers, type II diabetes, arthritis, Alzheimer's disease, as well as skin disorders including psoriasis (Kiecolt-Glaser et al. 2002). Elevated proinflammatory cytokine levels triggered by stress and depression are associated with prolonged infectious periods and delayed wound healing (Glaser and Kiecolt-Glaser 2005).

In addition, various evidences have connected childhood maltreatment and adverse experiences with poor health in the adulthood. Inflammation is a pivotal mediator in such linkages as those adults with early life stress often have higher systemic inflammatory responses to acute stressors including elevated IL-6 levels (Carpenter et al. 2010). Early life stress experiences have also been related to the higher risks for adult obesity (D'Argenio et al. 2009).

2.2 The PNI Networks, Systems-Based Biomarkers, and Mind–Body Mechanisms

The integration of multiple emerging scientific disciplines including PNI, psychosocial genomics, and systems biology may pave the scientific ground for the translation and practice of mind–body medicine. The dynamical biopsychosocial models may provide the insights into the basic mechanisms at different systems levels of the human complex adaptive system (CAS) (see Chap. 1). These multiple levels expand from gene expression and neurogenesis to human experiencing, behavior, and consciousness (Rossi 2002).

Such dynamical biopsychosocial models emphasize the integrative psychoneuroendocrine-immune networks and the impacts of both stress and relaxation on the immune functions. The frameworks may help interpret the underlying mechanisms of mind–body medicine via the description of the multidirectional pathways that convey information between the central nervous system (CNS) and the peripheral systems. Such information exchanges are involved in the affective, autonomic, hormonal, and immune responses (Taylor et al. 2010).

Systemic factors can be used as the potential biomarkers for the central–peripheral communications and homeostasis in such integrative frameworks, including the

heart rate variability (HRV) and inflammatory markers. Specifically, certain fronto-temporal cortical areas are pivotal in showing and regulating adverse symptoms in chronic diseases (Taylor et al. 2010). These areas may communicate reciprocally with subcortical structures associated with stress responses and homeostasis.

At the molecular and cellular levels, many factors may be involved in the complex networks, including endocrine components corticotrophin releasing factor (CRF), adrenocorticotrophic hormone (ACTH), glucocorticoids (GC), alpha-endorphin, as well as Met-enkephalin (Mahbub-E-Sobhani et al. 2011). The immune factors include T cells; B cells; monocytes/macrophages; natural killer (NK) cells; as well as cytokines such as tumor necrosis factor- α (TNF- α), interferon- α (IFN- α), and interleukins such as IL-1, IL-2, IL-4, IL-6, IL-10, and IL-12.

In addition, stressful emotions may affect white blood cell functions by weakening their responses to viral infected cells and cancer cells (Littrell 2008). Vaccination has been found less effective and wounds may heal more slowly among the stressed people. However, stress may worsen certain types of autoimmune disease associated with some subsets of white blood cells.

At the system levels, both of the psychological and physical benefits of mind-body approaches have been explored. Emerging evidences are revealing the effects of these approaches on the immune system, especially on the inflammatory biomarkers and antiviral associated immune responses (see Chap. 13).

Different types of stress such as acute, brief naturalistic, and chronic stress may lead to different immune processes that affect the homeostasis (Mahbub-E-Sobhani et al. 2011). On the other hand, relaxation techniques may help keep the homeostasis. For instance, the PNI framework has been found especially appropriate in inflammatory bowel disease (IBD) as it involves intense immune reactions (Smith and Bryant 2002). Because of the strong mind–gut links, the behavioral interventions such as those applied by professional nurses may promote the quality of life by controlling symptoms for the IBD patients.

2.3 The Stress–Inflammation–Disease Associations: Translational Implications of PNI

The systems-based PNI studies on the stress–inflammation correlations have the translational implications in a wide range of diseases. According to the biopsychosocial models, the different ways that different individuals respond to stressors have the profound meanings to health, wellness, and illnesses (Lutgendorf and Costanzo 2003; also see Chap. 1). For example, stress and depression may have the impacts on food choices especially unhealthy choices such as the preferences for snack foods rather than fresh fruits (Kiecolt-Glaser 2010).

Stress can alter the gastroduodenal and colonic motilities (Yin et al. 2004). Experiments using a laboratory stressor showed that about 14% longer time than

normal would be needed for the clearance of a fat load (Stoney et al. 2002). The hyperactivity of the sympatho-adrenal system associated with chronic stress may disturb metabolic homeostasis and result in fat accumulation, hypertension, and diabetes.

Although depression is a psychiatric disorder, it has profound influences on the neuroendocrine-immune systems. Those with chronic stress and depression often have the higher levels of inflammatory biomarkers such as C-reactive protein (CRP) and TNF- α (Leonard and Myint 2009). As proinflammatory cytokines are associated with neurotransmitter metabolism and synaptic plasticity, they may have impacts on various pathophysiological processes (Shelton and Miller 2010).

Specifically, the changes at the molecular and cellular levels including the stimulated microglia with activated proinflammatory cytokines have been associated with neurodegeneration and Alzheimer's disease (Leonard and Myint 2009). In the meantime, decreased levels of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) can cause slower neuronal repair (see Chap. 4). Changes at the tissue and organ levels include the alterations in the regions of the hippocampus, frontal cortex, and amygdalae (Leonard and Myint 2009).

In addition, complex correlations have been identified among stress, depression, and obesity, multiple sclerosis, psoriasis, rheumatoid arthritis, cancers, as well as cardiovascular diseases (Shelton and Miller 2010). The higher incidences of obesity and metabolic syndromes have been observed among patients with posttraumatic stress disorder (PTSD), possibly mediated via the neuropeptide Y (NPY) and glucocorticoid systems (Rasmusson et al. 2010). On the other hand, weight loss interventions may lead to the lower levels of inflammatory markers with better emotional status (Capuron et al. 2010).

Psychosocial stress has been related to coronary artery disease (CAD), thrombus formation, and myocardial infarction through affecting the immune system (Ho et al. 2010). Various aspects can be influenced, including the endothelial functions, NK cells, and acute phase proteins. However, those with the relevant cardiovascular risk factors can benefit from mind–body approaches including exercises, healthy diet plans, as well as antidepressants (Irwin 2008).

Cancer also has the tight linkages with stress via the suppression of lymphocyte proliferation and NK cell activities (Tausk et al. 2008). Studies have found that stress management methods including relaxation training may benefit the survival of cancer patients probably by improving the cytotoxic and NK cell functions.

Furthermore, emotional stressors have been related to various skin disorders including acne, atopic eczema, herpes simplex infections, psoriasis, and vitiligo (Tausk et al. 2008). Psoriasis patients often have dysfunctions in the HPA axis with hypertension and higher heart rates upon stress stimulations. Mind–body techniques such as meditation and hypnosis have been found helpful for the quicker clearance of psoriasis (Tausk et al. 2008). More discussions about the clinical implications of stress, inflammation, and various diseases will be available in the following chapters.

2.4 Targeting the Stress and Inflammation-Associated Networks

The dynamical biopsychosocial models based on PNI and systems biology can be applied for drug design targeting the shared pathways of different illnesses instead of a single isolated problem. As discussed previously, such approaches will facilitate the conversion from the disease-centered drugs to human-centric medicine, the main goal of personalized medicine (see Chap. 1).

Specifically, targeting the stress and inflammation-associated networks including IL-6, NFkB, and p38 MAPK signaling cascades may benefit a broad spectrum of disorders including depression, cancer, and cardiovascular disease (Yan 2011b). Such methods would allow for the more efficient drug strategies by using conventional drugs for better clinical outcomes and reducing the drug development costs (Yan 2011a).

For instance, drugs such as etanercept, infliximab, and anakinra that are conventionally used for rheumatoid arthritis may have potential applications for mood disorders. Etanercept administration has been shown to have beneficial effects on depression in psoriasis patients (Irwin and Miller 2007).

In summary, the understanding of the stress–inflammation networks in the behavior–neuroendocrine–immune communications would enable health practitioners to achieve better therapeutic outcomes with higher quality of life among patients. For instance, in intensive care units, patients' immune dysfunctions have been correlated to the stressors including trauma, anxiety, fear, and sleep disturbance (DeKeyser 2003). The integrative PNI models can be applied by physicians and nurses for stress reduction via empathetic methods and better coping strategies (Langley et al. 2006; Starkweather et al. 2005; McCain et al. 2005).

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