Chapter 2
The Immune System and Man-Environment Interaction: A General Understanding

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Environmental factors have long been known to be able to affect immune responses from both animal and human studies (Glover-Kerkvliet 1995; Monteleone et al. 2012; Rook 2013; Tedeschi et al. 2003). Over the past few decades, many efforts have been made to understand the interaction between various environmental factors, genetic factors, and the development of immune pathologies, such as allergic/autoimmune disease (Andiappan et al. 2014; Lau et al. 2014; Barne et al. 2013; Kauffmann and Demenais 2012; Willis-Owen and Valdar 2009). The environmental factors and stressors related with missions to space include: microgravity, ecologically and environmentally closed systems, prolonged isolation, acute physical strain (such as during launch or landing), radiation, changes in blood sheer forces, as well as other variables that might have not been recognized yet (Sonnenfeld et al. 2003; Gueguinou et al. 2009; Crucian and Sams 2009). These environmental factors could each individually affect immune functions, but they could also be interactive during spaceflight to alter immunity (Gueguinou et al. 2009; Crucian and Sams 2009).

Many studies of gene-environment interaction have indicated that individuals often vary in their susceptibility to environmental influences (Hunter 2005). Among others, two specific genetic polymorphisms, the serotonin transporter gene 5-HTTLPR and the dopamine receptor gene DRD4, have been widely studied. They have long been regarded as "vulnerability genes," since carriers of particular alleles have higher risk of developing certain psychological problems or physiological disorders including inflammatory diseases in the face of adversity. However, more recent evidence indicates that they should more appropriately be treated as "plasticity genes" because carriers of the putative risk alleles seem to be especially susceptible to environmental influences either adverse influences or also favorable ones (Belsky

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and Hartman 2014). For 5-HTTLPR, it has been reported that in the case of Caucasian children under 18 years of age, short-allele carriers are more susceptible than long-allele carriers to both positive and negative developmental experiences (van Ijzendoorn et al. 2012). For DRD4, increased susceptibility has been found in the 7-repeat allele carriers with social circumstances such as maternal positivity and pro-social behavior, contextual stress and support, and several other kinds of environmental influences (Belsky and Hartman 2014).

Although genetic factor plays an important role in deciding reactions to environmental influences, interestingly, a recent systems-level analysis of 210 healthy twins has revealed that the human immune system is mainly "shaped" by environment, with a generally limited influence of genetic factors (Brodin et al. 2015). Environment, often described as combination of multiple "environmental exposures" is defined as "non-genetic" factor in the broad sense. Compared to the fast development of human genome sequencing tools for examining individual susceptibility through genome-wide association studies (GWAS), only a limited number of tools or methods are available so far for performing exposure assessments. Given that autoimmunity, chronic infection, and other chronic diseases develop predominantly from a combination of environmental exposures with restrained genetic background influences, the ability to measure and to describe environmental exposures becomes particularly demanding to understand the effects of specific environmental exposures on human health. Environmental exposures, if we only consider the external factors based on traditional understanding of environment, can be categorized as specific ones and general ones. Specific exposures may refer to radiation, infectious agents, environmental contaminants, air pollutions, diet, lifestyle factors (e.g., tobacco, alcohol), occupation, and medical interventions (Wild 2012). These factors have been the main focus of epidemiological studies seeking a link between environmental risk factors with chronic immune disease. For general exposures, they include the broader social, economic, and psychological influences on each person, for example, social status, education level, financial condition, physiological or psychological stress, geographic environment, and climate (Wild 2012). All these specific and general environmental exposures work together and may to a certain extent formulate the major causes of a large number of human disorders.

For space exploration, space travelers are exposed to many extreme environmental conditions, and for future interplanetary space exploration, such as Mars mission, astronauts can be exposed to a completely strange environment, which means new and more complex combinations of conditions of "environmental exposure." How could these "environmental exposures" affect the human immune system and the health conditions? This is a critical and challenging question waiting for illumination. The main challenge here is to identify, to understand, and to elucidate the interaction between one type of exposure and the corresponding immune responses to that exposure. Knowledge achieved from this aspect can not only imply the link between an exposure and a disorder, but also provide insights into the underlying mechanisms of how an exposure might be applying its effects, which may add to the mass of evidence in allocating causality to an exposure-disease association and shed light on prevention strategies through modulation of specific identified mechanistic

pathways. To investigate interactions between exposure, mechanism, and disease has become one of the emerging directions for biomarker discovery (Vineis and Perera 2007).

Space exploration, as mentioned in this volume, provides many extreme environmental conditions. The capability of addressing the interaction between exposure, mechanism, and health problem might yield innovative insights into how seemingly distinct risk factors, such as psychosocial stress (e.g., Yi 2015; Basner et al 2014), diet that is too salty (e.g., Yi et al. 2015) or too sweet, immune suppression, or immune hypersensitivity, act to produce similar health problems (Terry et al. 2011; Thayer and Kuzawa 2011). With an integrative systems biology approach in this regard, evaluations of psychosocial stress have been reported to be correlated with inflammation and telomere length, contributing evidence of how seemingly unrelated risk factors may act through shared biological pathways (Wild 2012).

Exposure of humans, animals, and cell cultures to spaceflight conditions has resulted in aberrance of immune responses (Gueguinou et al. 2009; Crucian and Sams 2009). Although cellular immunity has been shown to be primarily influenced, changes in humoral immune responses after spaceflight have also been observed (Gueguinou et al. 2009; Crucian and Sams 2009). Both the innate and adaptive immune systems were affected, characterized by changes in "cytokine production, leukocyte blastogenesis, NK cell and macrophage activity and production, antibody production, and enzyme functions in pathways important for immune functions" (Sonnenfeld 2013). Several recent studies have consistently indicated alterations in neutrophil, monocyte, and lymphocyte populations (cell population numbers and function), altered expression of antibody variable heavy chain genes, and others in response to spaceflight conditions (Gueguinou et al. 2009; Crucian and Sams 2009). However, the question of which of the factors are responsible for the spaceflight-induced alterations of the immune functions has to be elucidated and some of which would be discussed in more detail in the following chapters.

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