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The Immunology of Behavior—Exploring the Role of the Immune System in Brain Health and Illness

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INTRODUCTION

Advances in our understanding of immunology especially cellular immunology and cytokine biology have led to monumental changes in the practice of medicine. Indeed, elucidation of the pathways involved in T-cell regulation have led to a series of therapeutic agents referred to as 'checkpoint inhibitors' that are revolutionizing the treatment of cancer. Similarly, the development of biological therapies that target cytokines and other mediators of the inflammatory response have changed the landscape of the treatment of autoimmune and inflammatory disorders. These developments have impacted millions of lives and represent some of the most important achievements of modern medicine. Not surprisingly, the revolution in immunology has made its way to the basic and clinical neurosciences with a growing appreciation of the role of the immune system in brain health and illness. From its participation in brain development to its contributions to adulthood disorders and neurodegeneration, the immune system as a major regulator of neuronal function throughout the life cycle has attracted significant attention, enough so to warrant its own special issue of *Neuropsychopharmacology* reviews. In this issue, we have attempted to give a sample of the important research being conducted in this area with an emphasis on (1) the fundamental mechanisms by which the immune system supports neuronal integrity, (2) the pathways by which the peripheral and central immune compartments become activated and communicate—especially in the context of stress, (3) the factors that represent risk and resilience for both immune dysregulation and behavioral change, (4) the impact of the immune system on neurotransmitter systems and neurocircuits that regulate behavior, and (5) the immunological contributions to developmental disorders and neurodegeneration. It should be noted, however, that throughout the issue it is emphasized that no mental disorder is fundamentally an immunological disorder, rather the point is repeatedly made that the immune system potentially participates in a subgroup of symptoms that cut across multiple psychiatric diseases. The therapeutic promise of targeting different facets of the immune system is also addressed in every review, and each review outlines the many gaps in our knowledge and what steps need to be taken to move the field forward.

EVOLUTIONARY LEGACIES AND IMMUNE REGULATION OF BRAIN FUNCTION

In the first review, we are introduced to the concept that the immune system and the brain are intimately intertwined by virtue of an evolutionary past that included a marked selection pressure for synergy between immune and behavioral responses to microbial challenges that jeopardized reproductive success. These brain–immune interactions and their association with aggressive innate immune responses and related behaviors of avoidance and alarm, whereas essential for dealing with the threats of infection and wounding in ancestral times, are poorly designed for dealing with threats from the social environments that humans confront in the modern world. Raison and Miller, (2017) further examine the legacy of this evolutionary past in attempts to address fundamental questions regarding the role of the interconnectedness of the brain and immune system in understanding the genetics, bioregional differences, and female preponderance in certain mental illnesses, notably mood disorders. Further supporting evolutionary notions of synergistic interactions between the brain and immune system is the increasing elaboration of the network of communication of the peripheral immune system and the brain. Indeed, the long-held view that the brain is isolated from the peripheral immune system due to the lack of circulating immune cells infiltrating the brain during homeostatic conditions is rapidly changing. In the review by Marin and Kipnis, (2017), multiple layers of immune surveillance of the central nervous system (CNS) are described, including an immune presence in the brain (microglia) and compartmentalization of a full complement of immune cells in the meninges and choroid plexus, the responses of which can be communicated to the brain parenchyma. The CNS benefits of this extensive support from immune surveillance during homeostasis is elaborated, as is a role for these processes in protection of the CNS from the destructive effects of inflammation. These results highlight the essential collaboration of the immune system and the brain, and its relevance for brain health and illness.

STRESS-INDUCED IMMUNE ACTIVATION AND COMMUNICATION WITH THE BRAIN

Given the well-known impact of stress on psychiatric disease, there is a rich basic science literature using a variety of

animal models to understand the immunological mechanisms by which stress contributes to the development of neuropsychiatric disorders, especially mood and anxiety disorders. In their review, Fleshner *et al.* (2017) discuss the importance of sterile (pathogen-free) activation of inflammatory processes in both the periphery and CNS through stress-induced release of danger-associated molecular patterns that stimulate the inflammasome, a molecular complex that leads to the release of inflammatory cytokines. They argue that the inflammasome serves as an important point of integration in translating stress signals into inflammation. Preclinical and clinical evidence is described regarding the role of sterile inflammation and inflammasome-dependent signaling in behavioral changes, and the inflammasome is presented as an intriguing novel target for blocking inflammation in the treatment of neuropsychiatric disorders. Weber *et al*, (2017) elaborate on how stress can also disrupt homeostatic or 'healthy' bi-directional immune cell communication between the peripheral immune system and CNS. They present elegant data demonstrating that stress-induced increases in sympathetic nervous system outflow can bias hematopoietic stem cells to differentiate into glucocorticoid-resistant, primed myeloid lineage cells that can then be recruited to the brain by microglia and endothelial cells. Once in the brain, these cells can reinforce and maintain stress-related behavioral pathology (Weber *et al*, 2017). Menard *et al.* (2017 discuss the nuances of the immunological response to stress by detailing the cellular and molecular mechanisms of risk and resilience that shape stress-induced behavioral vulnerabilities. Special attention is paid to individual and sex-specific differences in immunological and neuroendocrine responses that drive peripheral and central immune cell activation (Menard *et al*, 2017). Specifically, they discuss cytokine signaling, peripheral monocyte infiltration, microglial activation, and hypothalamic-pituitary-adrenal axis hyperactivity in stress vulnerability and coping, while highlighting the potential for adaptive immune responses and immune modulators to decrease depressive symptoms.

GENETIC AND OTHER MEDIATORS OF RISK FOR IMMUNE DYSREGULATION AND PSYCHIATRIC DISEASE

Complementing animal models of risk and resilience to stress-induced, immune-based behavioral changes, numerous studies have demonstrated genetic and other risk factors for increased inflammation and changes in immune function that are believed to contribute to both the development and treatment responsiveness of neuropsychiatric disorders. For example, in a systematic review of the literature, Barnes *et al.* (2017) report that common genetic variants, including polymorphisms in genes for interleukin (IL)-1beta, IL-6, IL-10, monocyte chemoattractant protein-1, tumor necrosis factor, C-reactive protein, and phospholipase A2, are associated with increased risk for depression. Moreover, these authors found that protein and mRNA levels of inflammatory markers can predict the response to conventional antidepressants. In addition to genetic vulnerability, childhood maltreatment can also affect the immune response, predisposing individuals to heightened inflammatory states later in life that have long-term consequences on the brain and behavior. Danese and Lewis, (2017) propose that these early-life stress effects on the immune response offer an innovative framework to understanding psychopathology linked to childhood trauma, and that remediating the effect of trauma on inflammation before the onset of clinical symptoms represents a novel prevention strategy.

Metabolic disorders and obesity are also highly associated with psychiatric illnesses, such as depression, and may involve adiposity-related, chronic low-grade inflammatory processes that affect brain function and behavior. Capuron *et al.* (2017) review converging clinical and preclinical evidence for a bi-directional relationship between depression and adiposity, the immunological and metabolic mechanisms of which may provide identification of preventive and/or therapeutic strategies. Sleep disturbances including insomnia are another risk factor that may independently contribute to inflammatory disorders and other medical illnesses as well as neuropsychiatric disorders including depression. Irwin and Opp, (2017) provide an integrated understanding of reciprocal relationships between sleep and the innate immune response, including the effects of inflammatory mediators on homeostatic regulation of sleep continuity and macrostructure and the potential for interventions that target insomnia and other sleep disturbances to reverse inflammation. In a review addressing the role of the immune system in substance abuse, Lacagnina *et al.* (2017) describe mechanisms by which microglia and astrocytes perform critical functions in synapse formation, refinement, and remodeling, and how these processes are modified by drugs of abuse to contribute to the liability to addictive disorders. Indeed, drugs of abuse can activate microglia through signaling at innate immune receptors (toll-like receptors), in turn influencing neuronal function and synapse integrity which predisposes to later vulnerability to substance abuse. Finally, there is increasing appreciation that the microbiome and its regulation of the immune response may also have a role in the risk and resilience for neuropsychiatric disease. Indeed, the growth of 'friendly' probiotic microbes in the gut creates a positive host immune environment, while dampening the effects of chronic, non-resolving inflammatory responses. In their far-reaching review, Dinan and Cryan, (2017) propose that depletion of 'friendly' commensal populations in the gut contributes to the harmful effects of stress and inflammation, and can be replenished by the use of prebiotics, probiotics, and/or fecal microbiota transplantation to benefit patients with psychiatric and medical illnesses.

IMPACT OF THE IMMUNE SYSTEM ON NEUROTRANSMITTERS, NEUROCIRCUITS AND BEHAVIOR

Activation of the innate immune response and release of inflammatory cytokines can influence monoaminergic and glutamatergic pathways that regulate motivation and motor activity as well as threat sensitivity, to contribute to behavioral symptoms that cut across a number of psychiatric disorders. For example, a wealth of clinical and preclinical data suggest mechanisms by which inflammation can impact glutamate, including failed clearance and exaggerated release of glutamate by glial cells, aberrant extrasynaptic signaling through ionotropic and metabotropic glutamate receptors, and loss of synaptic fidelity via glutamate diffusion outside of the synapse. As proposed by Haroon *et al.* (2017), these changes in glutamate during innate immune activation may ultimately result in synaptic and circuit dysfunction that is relevant to behavioral pathology and its treatment in mood disorders. Numerous laboratories have also found that peripheral inflammatory stimuli can affect reward and other basal ganglia circuits to contribute to motivational and motor deficits that are common in patients with depression and other psychiatric disorders. Felger and Treadway, (2017) highlight recent clinical and translational data regarding the role of inflammation effects on dopamine in these alterations in corticostriatal circuit function, reduced motivation, and motor slowing, in relation to novel therapeutic strategies to treat these symptoms in patients with high inflammation. In terms of inflammation effects on threat-relevant circuitry, Eisenberger *et al.* (2017) discuss evidence of and implications for the co-regulation of inflammation and social behavior via neural circuitry that promotes adaptation to social environments during times of stress or sickness. Specifically, acute inflammation increases threat-related neural sensitivity to negative social experiences, presumably to promote avoiding challenge to well-being or safety, while increasing reward-related neural sensitivity and approach motivation toward positive social experiences that might provide support or care during sickness. Conversely, social behavior may also regulate aspects of inflammatory activity, preparing the body for situations in which wounding and infection are more likely. Related to these considerations, Michopoulos *et al,* (2017) describe a growing interest in the role of inflammation and immune activation in fear and/or anxiety disorders, including posttraumatic stress disorder, generalized anxiety disorder, panic disorder, and phobias. Exposure to stress or trauma and associated dysregulation of the neuroendocrine and autonomic systems that characterize these disorders may precipitate inflammatory states and the release of cytokines that then contribute to increased symptom severity via effects on brain circuits critical for the regulation of fear and anxiety (eg, prefrontal cortex, insula, amygdale, and hippocampus). These effects of inflammation on neurotransmitters and neurocircuits are further extended in the review by Brundin *et al.* (2017) who report a consistent association between increased inflammatory activation and suicidal behavior seen across psychiatric disorders. On the basis of this association, they propose that biomarkers of inflammation and its downstream mediators including metabolites of the kynurenine pathway, which relate to both serotonin and glutamate, may provide not only a mechanism by which suicidal behavior occurs, but also a biological estimate of suicide risk. Taken together, these findings suggest that the immune system can affect fundamental pathways that regulate behavior and thereby represents a critical pathway to pathology in neuropsychiatric diseases.

IMMUNE CONTRIBUTIONS TO DEVELOPMENTAL DISORDERS AND NEURODEGENERATION

As indicated above, many of the details regarding the basic and clinical mechanisms by which the immune system can affect the brain have been elaborated. Therefore, the opportunity exists to apply this knowledge to the role of the immune system in the development and neuroprogression of a variety of mental disorders. Much of the attention of the impact of the immune system on psychiatric disease has occurred within the context of mood disorders. However, there is a growing literature regarding a number of other metal illnesses. Both schizophrenia and autism spectrum disorders are diseases with an important developmental component, and data suggest that shared genetic risk interacting with prenatal immune activation resulting from maternal infection may be involved in both disorders. Variations in the clinical and phenotypic presentation might be attributed to distinct contributions from maternal and fetal immune responses. For example, as suggested by Meltzer and Van de Water, (2017), autism spectrum disorders may result from maternal and/or host autoantibodies that selectively disrupt neural circuits regulating social behavior. On the other hand, as discussed by Miller and Goldsmith, (2017), schizophrenia might represent excessive pruning of large-scale networks by over-active innate and adaptive immune responses leading to neurotransmitter dysregulation. On the basis of these hypotheses, common treatment/prevention for both disorders might include some overlapping components of screening/testing for prenatal infections and autoantibodies and preventative immunomodulatory therapies in at-risk populations. Divergent approaches might include treatments targeting autoimmunity in autism spectrum disorders *vs* a broader, anti-inflammatory, and neuroprotective strategy in schizophrenia, which reflects the potential impact of the immune system on both developmental and degenerative processes in the disorder. Of note, consistent with the impact of inflammation on neurocircuits involved in reward, special consideration is given to the role of inflammation in negative symptoms as well as cognition in schizophrenia. Finally, the effects of stress-induced immune activation on aging immune cells (including microglia) is reviewed by Niraula

et al, (2017) who describe age-related generation of a hyper-responsive and pro-inflammatory 'primed' phenotype that has been consistently associated with neurodegeneration and accelerated aging.

TRANSLATIONAL IMPLICATIONS

In the final review of this series, the editors of this issue address the question of whether the extant literature has reached the tipping point whereby immune-based therapies are ready for prime time (Miller *et al*, 2017). The general consensus is that the time has come for the rubber to meet the road, and a series of guidelines are set forth for intelligent clinical trial design. In addition, a series of relevant targets and treatments are described. The reader is left with a sense of excitement regarding the future success of immune-based therapies titrated by the burden of proof. Indeed, the question remains unanswered whether the clinical neurosciences will benefit from the revolution in immunology as have so many other fields of medicine. The editors of this issue believe the answer to this question is resoundingly yes.

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