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Contributions of the adaptive immune system to mood regulation: Mechanisms and pathways of neuroimmune interactions

Miles Herkenham *, Stacey L. Kigar

Section on Functional Neuroanatomy, Intramural Research Program, National Institute of Mental Health, NIH, Bethesda, MD, USA

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ABSTRACT

Clinical and basic studies of functional interactions between adaptive immunity, affective states, and brain function are reviewed, and the neural, humoral, and cellular routes of bidirectional communication between the brain and the adaptive immune system are evaluated. In clinical studies of depressed populations, lymphocytes—the principal cells of the adaptive immune system—exhibit altered T cell subtype ratios and $CD4^+$ helper T cell polarization profiles. In basic studies using psychological stress to model depression, T cell profiles are altered as well, consistent with stress effects conveyed by the hypothalamic-pituitary-adrenal axis and sympathetic nervous system. Lymphocytes in turn have effects on behavior and CNS structure and function. $CD4^+$ T cells in particular appear to modify affective behavior and rates of hippocampal dentate gyrus neurogenesis. These observations force the question of how such actions are carried out. CNS effects may occur via cellular and molecular mechanisms whereby effector memory T cells and the cytokine profiles they produce in the blood interact with the blood-brain barrier in ways that remain to be clarified. Understanding the mechanisms by which T cells polarize and interact with the brain to alter mood states is key to advances in the field, and may permit development of therapies that target cells in the periphery, thus bypassing problems associated with bioavailability of drugs within the brain.

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1. Introduction

Converging evidence from multiple clinical and experimental lines of research supports a role for the peripheral immune system in the etiology and maintenance of depressive disorders. Support for this role is based on the following: 1) recent evidence from genome-wide association studies show prominent links between immune gene variants and mood disorders (Bufalino et al., 2013; Network and Pathway Analysis Subgroup of Psychiatric Genomics, 2015; Wong et al., 2008); 2) autoimmune diseases, infections, and other inflammatory diseases are comorbid with depression (Benros et al., 2013; Maes, 2011); 3) immune system molecules such as cytokines are elevated in depressed patients (Baumeister et al., 2014; Capuron and Dantzer, 2003; Dowlati et al., 2010; Dunn et al., 2005; Felger and Lotrich, 2013; Liu et al., 2012; Zunszain et al., 2013); 4) depression symptoms are induced following therapeutic administration of the cytokines interleukin-2 (IL-2) or interferon α (Raison et al., 2009); and 5) proinflammatory cytokines produce sickness behavior in animals that is reminiscent of depression by several criteria such as fatigue, anhedonia, changes in appetite, and sleep disturbances (Dantzer, 2012; Dantzer et al., 2008).

While there are excellent reviews on the subject of brain-immune interactions underlying psychiatric disorders (Haapakoski et al., 2016; Maier and Watkins, 1998; Najjar et al., 2013), we will focus more specifically on interactions between the brain and the adaptive immune system, which has only recently received attention in relation to mental health. The adaptive immune system is one of two functionally distinct arms of what is collectively called the peripheral immune system (Fig. 1). The first arm is the innate immune system, including monocytes and other cells of the myeloid lineage that rapidly respond to pathogenic challenges. The second arm is the adaptive immune system, comprising lymphocytes that exhibit a delayed response in the face of inflammatory challenge during which adaptation and commitment (polarization) of lymphocytes occur to generate cellular memory for pathogens.

2. Organization of pathways connecting the brain and the immune system

2.1. Brain-to-immune signaling

Appreciation of a functional link between the immune system and the central nervous system (CNS) requires some knowledge of how

Abbreviations: PCs, antigen presenting cells; BBB, blood-brain barrier; BDNF, brain derived neurotropic factor; CNS, central nervous system; CSF, cerebrospinal fluid; CRH, corticotropin releasing hormone; DG, dentate gyrus; HPA, hypothalamic pituitary adrenal; IFNγ, interferon γ; IL, interleukin; MBP, myelin basic protein; PVN, paraventricular nucleus; SCID, severe combined immunodeficiency; SNS, sympathetic nervous system; Tcm, T cells, central memory; Treg, T regulatory cell; TGFβ, transforming growth factor β.

* Corresponding author at: Bldg. 35, Rm. 1C913, Bethesda, MD 20892-3724, USA.
E-mail address: herkenh@mail.nih.gov (M. Herkenham).

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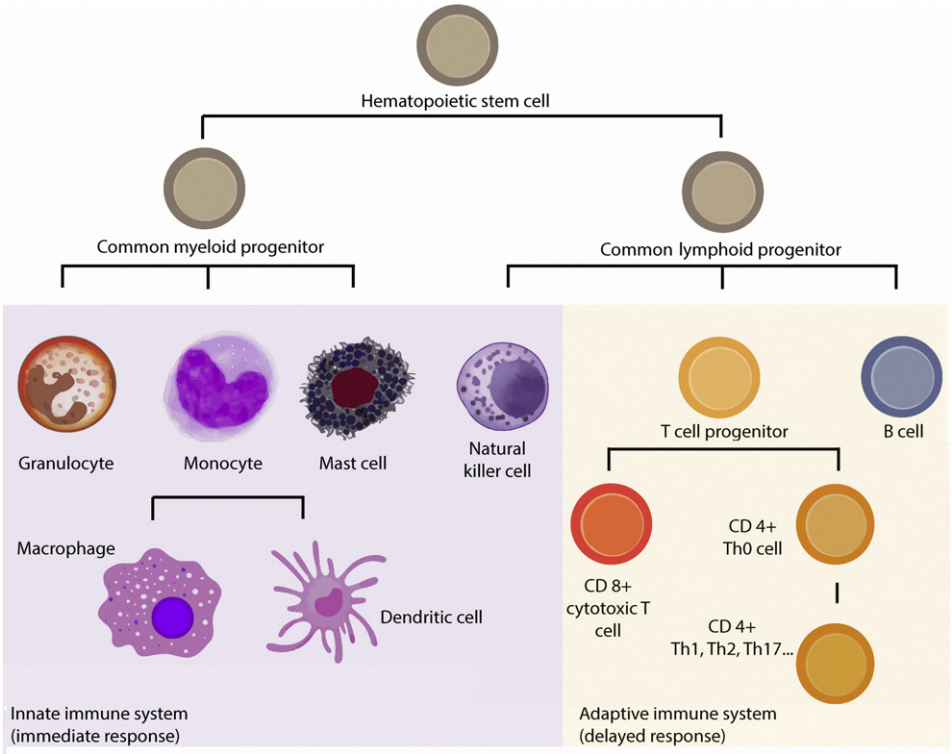

Fig. 1. Innate and adaptive immune cells, derived from myeloid and lymphoid progenitors, which themselves originate from hematopoietic stem cells, facilitate the body's reaction to infection or damage. The innate immune system acts as a 'first-responder' to immediately curb a peripheral threat. It consists of granulocytes (i.e., basophils, neutrophils, and eosinophils), mast cells, lymphoid-derived natural killer cells, and monocytes which when activated primarily become macrophages. Antigen presenting dendritic cells can also form from monocytes, though multiple cell types appear to contribute to the dendritic cell population. The adaptive immune system acts more slowly, over the course of days or weeks, by developing cellular memory for pathogens. It consists of $CD3^+$ T cells, which upon activation differentiate into $CD8^+$ cytotoxic T cells or $CD4^+$ T helper cells, and antibody-producing B cells. $CD4^+$ T cells further subdivide into various T helper cell subtypes, including Th1, Th2, Th17, Treg, and others; they are primarily classified based on the prototypical cytokines they produce.

they are physically linked to achieve bidirectional communication. We begin with the brain, which communicates to immune organs such as the spleen, thymus, and lymph nodes via neural, humoral, and cellular pathways. Neural and humoral signaling mechanisms are fairly well characterized (Glaser and Kiecolt-Glaser, 2005; Irwin and Cole, 2011); briefly, efferent neural and humoral control of immune organs originates in the brain's stress circuits, which converge on autonomic control centers at the level of the hypothalamic paraventricular nucleus (PVN). Higher order neural circuits, largely limbic in nature, drive stress-related changes in PVN activity (Ulrich-Lai and Herman, 2009; Wrona, 2006). Some PVN neurons project to the spinal cord intermediolateral cell column to control the sympathetic preganglionic neurons. Other PVN neurons project to the median eminence and are the origin of the hypothalamic-pituitary-adrenal (HPA) axis, which—when activated—culminates in the release of glucocorticoid hormones into the blood. These efferent systems notify the periphery of threat (Ulrich-Lai and Herman, 2009). Prolonged HPA signaling is thought to be a key manifestation of life stress and depression (McEwen, 2004) and plays a major role in mediating effects on the immune axis (Pariante and Lightman, 2008).

Neural efferent signaling to the lymphoid organs is accomplished via noradrenergic innervation by the sympathetic nervous system (SNS). The other arm of the efferent peripheral autonomic nervous system, the parasympathetic system, does not innervate these organs (Nance and Sanders, 2007; Schafer et al., 1998), although a vagal "anti-inflammatory reflex" has been proposed wherein cholinergic parasympathetic efferent fibers end in the sympathetic celiac ganglion just proximal to lymphoid organs (Andersson and Tracey, 2012; Pavlov and Tracey, 2015). Norepinephrine is therefore the dominant neurotransmitter for brain-to-immune system neural communication. In addition, co-released neuropeptide Y (NPY), corticotropin releasing hormone (CRH), substance P, vasoactive intestinal polypeptide (VIP), and calcitonin gene-related peptide (CGRP) can all modulate the activity of immune cells (Elenkov et al., 2000; Miller et al., 1998; Steinman, 2004).

Within the immune organs, notably lymph nodes and spleen, neurotransmitters are released onto the two major lymphocyte cell types—T and B cells. Activated B cells generate the humoral immune response to extracellular pathogens by producing circulating antibodies that recognize specific epitopes. Activated T cells differentiate into either $CD8^+$ T cytotoxic (killer) cells, which induce the death of infected cells, or one of several forms of $CD4^+$ T helper cells, which "manage" the immune response by directing other cells to perform specific tasks. These $CD4^+$ subtypes include T helper 1 (Th1), Th2, Th17, or Treg, each designed to eliminate different types of pathogens or promote self-recognition (Fig. 1). They are best identified by the prototypic cytokines they produce—proinflammatory interferon γ (IFNγ), anti-inflammatory IL-4, proinflammatory IL-17, and regulatory TGFβ, respectively (Luckheeram et al., 2012).

Evidence shows that adrenergic stimulation of this milieu of lymphoid cells is largely immunosuppressive, with other complex actions. One notable consequence is an altered balance between lymphocytic $CD4^+$ Th1 versus Th2 cell phenotypes. SNS activity inhibits Th1 and drives Th2 cytokine responses, though this is a simplified picture and depends on the duration of stimulation (Elenkov et al., 2000; Nance and Sanders, 2007). We later return to this concept, as an altered balance of Th1 to Th2 cell types is seen in some clinical studies of depression.

Humoral input to lymphoid organs primarily occurs via glucocorticoid secretion from the adrenal glands in response to activation by the HPA axis. Glucocorticoids such as cortisol in humans and corticosterone in rodents reach all immune organs and cells via the blood. They also reduce the Th1/Th2 ratio in $CD4^+$ T cells (Calcagni and Elenkov, 2006) and