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Bugs and Brain: How Infection Makes You Feel Blue

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In this issue of *Immunity*, Prinz and colleagues (2016) describe an unexpected mechanism underlying the role of type I interferon in the initiation of cognitive impairment and sickness behavior during viral infection through induction of chemokine CXCL10 in central nervous system epithelial and endothelial cells.

Social avoidance, fatigue, reduced appetite, and inactivity are common side effects that are considered an uncomfortable part of the experience that affects sick individuals. Behavioral changes during disease, in all likelihood, happen in light of the need to contain an individual infection and the body's decision to prioritize rest and healing. Within the last four decades, mechanisms that mediate the profound effects of increased systemic inflammation on brain and behavior have been elucidated (Dantzer et al., 2008). A vast literature in humans and laboratory animals describing peripheral pro-inflammatory mediators such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), IL-1α, and IL-1β produced by innate immune cells to act on the brain and induce sickness. Several pathways are proposed to facilitate immune-to-brain communication by incorporating direct activation of afferent nerves in the periphery and/or transmission of cytokine message from outside the blood-brain-barrier into the brain parenchyma either through direct access or secondary cellular mediators.

Motivated by identifying the behavioral disturbances caused by systemic viral infection and the notion that in humans, major depressive disorders develop in metastatic cancer, hepatitis C, and multiple sclerosis patients treated with the cytokines IL-2 and interferon-α (IFN-α) (Raison et al., 2006). Blank et al. (2016) set out to focus on type I IFN signaling and its potential role in sickness behavior. To prove a role for type I IFNs in the etiology of sickness behavior or motor activity in an inevitable situation, the authors tested vesicular stomatitis virus (VSV)-infected mice via forced-swim tests. Interestingly, dramatic elevation on circulating levels of IFN-β induced depression-like behavior through alterations in IFN-stimulated genes (such as ISG15) in brain endothelial cells. This effect was independent of any direct action of VSV on the brain but rather the net result of plasmacytoid dendritic cells (DCs)—potent type I IFN producers in spleen and lymph nodes. Indeed, lack of IPS-1, an inducer of interferon I and adaptor molecule for the viral sensors RIG-I and MDA5, addressed selected symptoms of sickness behavior (immobility and spatial learning), while leaving motor function and vision unaffected. Moreover, administration of recombinant IFN-β appears to have depressant-effects, even in the absence of IPS-1. These findings indicate that IFN-β might modulate behavior changes by signaling in brain endothelial cells. The authors tested this hypothesis by genetically eliminating IFN-α receptor 1 (IFNAR1) in specific cell types such as neurons, myeloid cells (including microglia), and endothelial and epithelial cells.

Although the obvious candidates such as microglia led to no results, mice deficient in IFNAR1 on epithelial and endothelial cells in the central nervous system (CNS) were protected from virus induced sickness behavior. Specifically, the authors used *Slco1c1-CreERT2* mice (Ridder et al., 2011) to deplete IFNAR1 in endothelial and epithelial barriers within the CNS. In future studies, it would be interesting to understand what dictates the specificity of this gene to CNS endothelial and epithelial cells. The authors demonstrate that type I interferon stimulates endothelial cells of the blood-brain-barrier, which then transiently produce the chemokine CXCL10 and chemokine receptor, CXCR3. Remarkably, deficiency in *Cxcl10* and *Cxcr3* prevented IFN-β or VSV induced sickness behavior (Figure 1). These results not only revealed a novel pathway responsible for development of infection-associated sickness behavior but also identified a new potential therapeutic target, for intervention, which might ameliorate behavior alterations associated with infection.

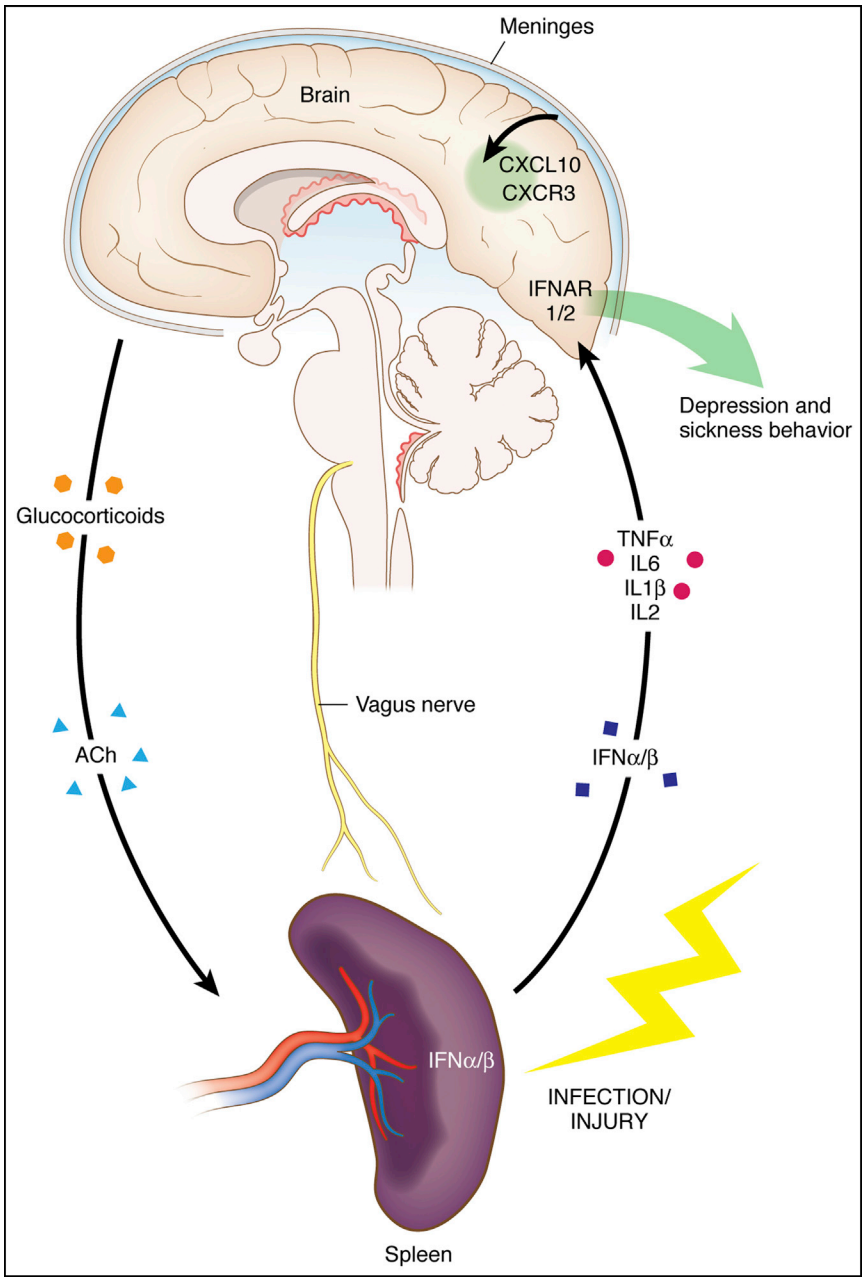

Figure 1. Pathways that Facilitate Immune-to-Brain Communication and Vice Versa

(Right) Immune-to-brain interactions: Infection or injury lead to an inflammatory response and the release of pro-inflammatory mediators such as TNF-α, IL-6, IL-1β, and IL-2 in the periphery. These cytokines access the brain via active transporters or through areas lacking the blood-brain barrier. However, in response to IFN-α/β, epithelial and endothelial cells of the meninges can convey inflammatory signals into the brain parenchyma through IFNAR1. Subsequent induction of robust local CXCL10 secretion and activation of neuronal CXCR3 signaling is critical in inducing decreased synaptic activity, thereby facilitating depression and sickness behavior.

(Left) Brain-to-immune communication: The brain connects with the immune system via the secretion of hormones such as glucocorticoids or vagus nerve endings. Complex brain activity and message is translated into direct secretion of the neurotransmitter acetylcholine (ACh) into the spleen, which inhibits inflammation due to suppression of cytokine release from tissue-residing innate immune cells.

The results presented in this study vividly demonstrate that endothelial cells initially recognize type I IFNs through surveillance of systemic inflammation. Intriguingly, within the meninges immune recognition of circulating inflammatory mediators by endothelial cells highlight the need to understand the immune apparatus that resides within the meninges (Kipnis et al., 2012) and supports the notion of infection and induce control.

The exciting findings presented here by Blank et al. document new routes to the development of sickness behavior. The authors show that meningeal inflammation can signal inward to the brain parenchyma via activating endothelial and epithelial cells. We and others have been addressing the role of meningeal cytokines on brain function (Kipnis et al., 2012). It has been proposed that meningeal T cells, through their secreted cytokines, such as IL-4 (Derecki et al., 2010), could regulate cognitive behavior. This effect is supposedly mediated via meningeal myeloid cells and in part via astrocytes lining the surface of the brain (through their glia limitants). Interestingly, however, in CNS injury IL-4 is mediating its neuroprotective effect via neuronal IL-4 receptors, where its signaling potentiates the neuroprotective signaling of neurotrophins (Walsh et al., 2015). Cytokines have also been shown to affect neurogenesis and rejuvenate aged mouse brains (Villeda et al., 2011). Although the possibility of peripheral cytokines affecting the brain via epithelial and endothelial cells has been previously entertained, a direct demonstration and a mechanism as are shown in this study have not been demonstrated.

This sort of neuroimmune communication is not unilateral. It has been shown in the past that the nervous system communicates and to some extent controls the immune response through an alternative mechanism of inflammatory control (Valentin and Tracey, 2015). Beside the secretion of hormones such as glucocorticoids, the CNS connects with the immune system via efferent vagus nerve endings to the intestines, liver, and spleen. Complex brain activity and message is translated into direct secretion of the neurotransmitter acetylcholine (ACh) into the specific organ with the objective to inhibit inflammation due to suppression of TNF release and other cytokines in innate immune cells (Figure 1). Macrophages express receptors for ACh that via vagus nerve stimulation significantly inhibit cytokine synthesis (e.g., TNF,

IL-1, IL-6). Exciting developments in the field suggest that it might be possible to directly stimulate the vagus nerve to suppress cytokine production and reduce damage during chronic inflammatory diseases such as rheumatic arthritis.

In summary, sickness behavior is part of a healthy immune reaction, through complex interactions with innate immune responses involving the type I interferon system. This ancient pathway is present in fruit fly, birds, and vertebrates. Even, viral inhibitors of higher plants show major structural and functional similarities to interferons in mammals. Communication between the two entities, allow to alert the central nervous system and immune system to the fact that pathogen invasion has begun. This mechanism is extremely important from an evolutionary perspective since social and exploratory behaviors increase exposure to infectious agents. As humans, we might have experienced an increase in coping mechanisms (such as social avoidance) in response to disease, which might have marked our recent evolutionary history.

Further investigation into dual functions of ancient signaling pathways, such as the Toll-like receptor pathway, MHCI molecules (Lee et al., 2014), or interferons, and their involvement in neuronal function and behavioral constrains remain to be tested to broaden our understanding of the co-evolution of cognition and immunity.

As therapeutic application is concerned, these findings would pose the opportunity to treat short courses of depressive-like symptoms or sickness behavior, however, would also alter immune function and increase vulnerability of infection. The overall effects of type I IFNs are very crucial for an effective T cell and B cell response, especially in viral infections. Based on this study, other possible approaches at the onset of disease include potent and selective small-molecule antagonists of CXCR3 that have been shown efficacy in preclinical models of inflammatory diseases. But how the risk would compare in targeting the management of behavioral changes during viral infection or type I IFN therapy to failure of limiting viral infection needs to be carefully evaluated.

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CD5: A New Partner for IL-6

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IL-6-STAT3 axis is known as a key factor of tumor progression. In this issue of *Immunity*, Yu and colleagues (2016) show that IL-6-binding CD5, rather than IL-6 receptor-α in B cells, amplifies STAT3 activation via JAK-STAT signaling to promote cancer.

Enormous evidence supports the proposal that hyper-activation of STAT3 is associated with tumor growth and progression. Indeed, constitutive activation of STAT3 has been demonstrated in a large number of human tumors including lung, brain, glioma, breast, ovarian, colon, gastric, pancreatic, prostate, melanoma, lymphoma, multiple myeloma, and leukemias. Interleukin-6 (IL-6) is a potent inducer of STAT3 activation in multi-types of tumor cells. STAT3 is also activated in immune cells in tumor microenvironment, where IL-6 is abundant (Yu et al., 2014). Recently, the efficacy of a humanized anti-IL-6 receptor monoclonal antibody, tocilizumab, has been implicated on tumor cells such as chronic lymphocytic leukemia (CLL), in which blocking of IL-6 signaling has a significant effect on STAT3-mediated survival and growth signals (Liu et al., 2015). Thus, although IL-6-STAT3 axis in tumor microenvironment appears to