Neuroimmunology: To Sense and Protect
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Editorial

Neuroimmunology: To Sense and Protect

The influence of the CNS and peripheral nervous system (PNS) on immune health, and vice versa, has been a central theme of health, science, and folklore for centuries. People have long suspected that stress enhances our susceptibility to infections and promotes episodes of autoimmunity. On the flip side, Cox2 inhibitors ameliorate both immune-based inflammation and neural-based pain. Clinicians also noted that denervation can stem the progression of rheumatoid arthritis or psoriasis, suggesting that sensory neurons might fuel some aspects of inflammation.

However, cross-talk between the neural and immune systems, which are so central to human health and disease, was difficult to assess and, until recently, neuroimmunology was relegated to the final sessions of many conferences. This backwater status has taken a dramatic about-face in recent years because of a number of watershed discoveries. These include our realization that Alzheimer disease (AD) and other neurodegenerative conditions are propagated by inflammation, with some of the neuronal destruction occurring through actions of immune cells within the CNS.

As with many revolutions, the emergence of neuroimmunology as a prominent field came with technical advances that now permit a more holistic approach to study dialogue between the immune system and other organ systems. Breakthroughs in multiparameter cytometry, imaging, and single-cell sequencing technologies have begun to unravel, with an unprecedented resolution, the diversity of cells, their locations, and molecular functions that orchestrate the immune–neural interface.

Given the palpable excitement and the rapid proliferation of papers in the field, I felt that it would be timely for the fourth annual issue of topical reviews to focus on neuroimmunology. I am proud to introduce “Neuroimmunology: To Sense and Protect”—a collection of 11 reviews, including a Translating Immunology review and a Pillars of Immunology commentary. It is my hope that this collection will provide our readers with a broad perspective on not only the healthy dialogue between immune and neural cells, which maintains homeostasis in both systems, but also how the wrong conversations or overreaction of one system can trigger a variety of pathological conditions, ranging from chronic pain to autoimmunity to loss of neural function.

The first portion of this special collection focuses on the interplay between the immune system and the PNS. Woolf and colleagues (1) begin the collection with an overview of the plasticity present in both systems, highlighting the “sense and protect” theme. They also provide a thoughtful discussion of how to prioritize approaches that will yield a deeper understanding of receptor–ligand communication between the two systems, which they call the “neuroimmune interactome.”

Next, Kaplan and colleagues (2) delve into a more specific aspect of neuroimmune cross-talk: neuronal regulation of cutaneous immunity. As discussed in both reviews, the PNS and immune systems serve as sentinels for invading pathogens, with barrier tissues, such as the skin, being rich in immune cells and nociceptors, sensory neurons that detect noxious agents or dangerous pathogens by producing pain or itch sensations. Both the Woolf and Kaplan reviews highlight the multitude of molecules produced by neurons and immune cells to communicate danger to each other (e.g., cytokines, chemokines, and neuropeptides) and by which neurons can sense pathogens (e.g., TLRs).

Henneke and colleagues (3) next discuss how immune cells communicate with the PNS to discriminate between healthy and damaged neurons. The authors discuss the variety of embryonically derived macrophages that associate with peripheral neurons. These cells not only may contribute to axon guidance, homeostasis, and nerve regeneration but also can cause damage following an infection or trauma. The codependent mechanisms may be especially relevant to peripheral nerve diseases, including diabetic neuropathy and chronic pain.

Another emerging theme in neuroimmunology is the important role that neurons may play in in the tumor microenvironment. Shurin et al. (4) review how nerves, especially glial Schwann cells, can create tumor-friendly inflammatory microenvironments and can serve as “magnets” to promote...
tumor migration (metastasis). Once the tumor is formed and innervated, neurons can generate immunosuppressive cytokine milieus and have a profound negative impact on therapeutic responses.

The collection then shifts focus to the CNS, historically thought to be devoid of lymphoid cells under healthy conditions due to their exclusion by the blood–brain barrier. Recent breakthrough studies, however, indicate that immune cells do reside within the CNS, especially in the meninges surrounding the parenchyma, and that special mechanisms are at play to enforce “immune privilege.” Kipnis and colleagues (5) review the current understanding of CNS immune structures and how cerebral spinal fluid likely serves as a highway for the movement of CNS-derived Ags toward meningeal immune cells and into the peripheral immune system. Although our current understanding of these anatomical connections is inchoate, progress in this area will have broad implications for infectious disease, autoimmunity, and immune responses to CNS tumors.

One of the sole immune cell types to reside in the parenchyma is the microglia, a CNS-resident macrophage. In a selected Pillars of Immunology article and accompanying commentary, Antel et al. (6) describe their pioneering work in culturing adult human microglia from healthy primary tissues. This advance permitted the first characterizations of microglial signatures at the molecular level and furthered the understanding of how microglia contribute to immune responses, clear debris, and communicate with astrocytes, a specialized glial cell that helps maintain the blood–brain barrier but can also inflict encephalitic damage. Colonna and colleagues (7) provide a state-of-the-art update on brain macrophage populations, with regard to their origin, anatomic location, phenotype, and function. They place emphasis on microglia, the immune sentinels of the CNS, and how phenotypic changes in these cells during disease are major pathologic determinants, especially during inflammatory responses associated with AD.

Two additional reviews continue the discussion of the mechanisms driving AD. Tenner (8) reviews recent progress toward unraveling the role of complement in brain health and in neurodegenerative disorders, including AD, where a genetic link has been established. Indeed, the complement system is now known to be important in synaptic pruning during neural development. Complement activation by β-amyloid protein mediators of AD can also contribute to CNS damage via inflammatory mechanisms. The authors conclude with an exciting discussion on the potential for therapeutic intervention in AD at the level of complement. On a similar theme, Schwartz et al. (9) describe their 20-year journey to understand the immune–CNS axis and how this knowledge is being leveraged to innovate immunotherapies for combating AD and other tauopathies.

The collection is rounded off by two reviews focused on additional immune-based neurologic diseases. Karpus (10) examines the role of cytokines and chemokines in experimental autoimmune encephalomyelitis, the classic mouse model of multiple sclerosis. The author describes the Th1/Th17 nature of experimental autoimmune encephalomyelitis and the soluble factors that drive inflammatory responses, resulting in myelin destruction. Karpus also discusses the opportunities and challenges of targeting these cytokine culprits with a new generation of therapeutics. Pierce and colleagues (11) conclude with an update on the quest to understand cerebral malaria, a disease characterized by uncontrolled immune responses to Plasmodium infections that can result in long-term disabilities, especially in children. The authors describe exciting advances in a mouse model for cerebral malaria, and how this model will be employed in a search for therapeutic interventions.

Together, this collection will provide readers with a panoramic overview of leading-edge research on the complex conversations that transpire continuously between the nervous and immune systems. Although the field of neuroimmunology has advanced in leaps and bounds, much work yet remains. New insights are especially imperative given the advancing age of our human population, which will only escalate the prevalence of neurodegenerative disorders with immune/inflammatory origins. Once again, immunologists will play a vital role this quest, as we expand and strengthen our collaborative networks to include neuroscientists and neurologists. Only then will we understand how to control the neuroimmune dialogue, confining it to its primary role: to sense and protect us from the harsh world in which we live.

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