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A conceptual revolution in the relationships between the brain and immunity

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The perception of brain-immune interactions has dramatically changed over the past decade. Current neuroimmunology has moved from classic studies focusing on how immune cells can damage the brain into a field acknowledging that the immune system plays a key role in maintaining the brain and in supporting its plasticity. Such a redefinition of this field is manifested by studies focused on understanding how innate and adaptive immune responses contribute to the brain's functionality, and how to boost or modify these activities, rather than fully suppressing them, in the treatment of multiple pathologies including Alzheimer's disease, Parkinson's disease, multiple sclerosis, age-related dementia, mental dysfunction and other neurological diseases in which local inflammation is often involved.

For decades, the central nervous system (CNS) was considered to be an autonomous unit, nourished by the blood and shielded from circulating immune cells and from pathogens and toxins originating from the circulation. In addition, it was commonly accepted that the healthy brain operates optimally when no immune cells are present. This assumption developed because of the way in which the blood-brain-barrier and the blood-cerebrospinal barriers were viewed, the concept of CNS tissue as immune privileged, and the assumed linkage between brain pathologies and inflammation. At that time, it was believed that the brain has no need for assistance from peripheral immune cells in support of its maintenance and repair, and that brain inflammation is a sign of infiltration of immune cells that should be mitigated. Based on these assumptions, attempts were made to arrest immune activity as an approach for treating all brain pathologies.

Over the years, it became clear that resident innate immune cells, known as microglia, are activated in response to acute or chronic neurodegeneration. Yet, today, the debate still rages: Is microglial activation a sign of malfunction that contributes to the disease, or are activated microglia a sign of an unsuccessful and insufficient attempt at disease resolution? Moreover, since infiltrating blood macrophages are indistinguishable from activated microglia, their activity was also viewed as detrimental. A decade of experimental evidence has shown that in contrast to these initial assumptions: (a) Circulating immune cells (CD4+ T cells) recognizing brain antigens support brain plasticity in health and disease. We introduced and named this concept, “protective autoimmunity’, proposing that T cells

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recognizing self-antigens defend against internal threats, in analogy to T cells recognizing non-self antigens that fight external threats (Moalem et al., 1999; Schwartz and Kipnis, 2002). (b) Infiltrating blood-derived macrophages in the form of 'alternatively-activated' macrophages (M-2 and myeloid-derived suppressor cells) are locally required to heal the traumatized or diseased brain (Derecki et al., 2010c; Rapalino et al., 1998; Shechter et al., 2009). (c) Most acute and chronic neurodegenerative diseases include a local inflammatory component, though systemic anti-inflammatory compounds fail to arrest neuroinflammation (Schwartz and Shechter, 2010b). Yet, in several neurodegenerative conditions, depletion of circulating immune cells exacerbates the disease process (Beers et al., 2008; Chiu et al., 2008; Kipnis et al., 2002). Finally (d) immune cells can pass the brain-cerebrospinal-barrier and gain access to the healthy brain without entering the parenchyma (Ransohoff et al., 2003). These findings and others, such as the requirement for CD4+ cells for facial motoneuron survival following injury (Jones et al., 2005), have led to a new model that suggests both the central and peripheral nervous system is critically dependent on circulating immune cells. These cells are selected to populate meningeal areas of the choroid plexus and the cerebrospinal fluid, which are integral compartments that help maintain proper functioning of the brain. Malfunction of such cells can impact cognitive performance (Brynskikh et al., 2008; Derecki et al., 2010a; Derecki et al., 2010b; Derecki et al., 2010c; Kipnis et al., 2006; Kipnis et al., 2004; Ziv et al., 2006), resilience to stress (Cardon et al., 2010; Cohen et al., 2006; Lewitus et al., 2008), emergence of developmental neuropsychological disorders (Cardon et al., 2010), and the onset and progression of neurodegenerative diseases (Schwartz and Shechter, 2010). The concept of "protective autoimmunity" unifies our perception of the role of immune cells in the healthy brain. It does so by establishing a physiological connection between these immune cells and protective immunity, on the one hand, and pathologies of the brain resulting from an overwhelming or insufficient immune response on the other.

According to this new understanding, the role of T cells is not restricted to a single T cell population. Instead, the participating T cells encompass CD4+ T cells recognizing self-antigens and are not restricted to Th1, Th2 or Treg cell population. Likewise, innate immune cells are not restricted to a single population, as they include activated microglia and infiltrating monocytes. These cells promote healing as long as their activity is appropriately regulated in terms of time, level and location. The contributions of various cell populations reflect the physiological state and stage of ongoing pathology, similar to the involvement of immune cells in any other tissue in the processes of maintenance, defense or resolution of infections.

The first (unorthodox) experiments on the role of T lymphocytes in the healthy brain, which emerged following the demonstration of their role in CNS repair, included a comparison of wild type and immune deficient mice in their performance of the spatial learning and memory tasks, such as the Morris water maze task (Kipnis et al., 2004; Ziv et al., 2006). Mice lacking adaptive immunity were shown to be cognitively impaired, and repopulation of these mice with T cells from wild type donors significantly improved their cognitive function. Moreover, wild type mice that were depleted of their own bone marrow and transplanted with the bone marrow from immune deficient (SCID) mice exhibited cognitive impairment, in contrast to the mice that were transplanted with normal bone marrow (Brynskikh et al., 2008; Derecki et al., 2010a; Ron-Harel et al., 2008). Collectively, this was the first demonstration that changes at the level of peripheral adaptive immunity could potentially affect higher brain function (Derecki et al., 2010b; Kipnis et al., 2008; Miller, 2010; Ron-Harel and Schwartz, 2009; Schwartz and Shechter, 2010a). The T cells supporting cognitive function were localized to the meningeal areas, where these cells regulate the phenotype of meningeal myeloid cells through their secreted IL-4, the major regulator of cognitive function by adaptive immunity (Derecki et al., 2010a). Such a

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dialogue was found to be relevant for coping with mental stress, and is amenable to boosting as a way of reducing the behavioral outcome of stress exposure (Lewitus et al., 2008).

While the role of T cells as active players in brain function has been clearly demonstrated in mouse models, there is a long way to go before the relevance of these discoveries to human health are understood. Fundamental questions remain to be addressed regarding mechanisms underlying the beneficial effects played by immune cells in both the healthy brain, and in the stressed or injured CNS. The topics described in this special issue range from pathologies such as multiple sclerosis and brain infections through the physiological responses of the immune system to CNS injuries to the role of immunity in learning, memory, plasticity and adult neurogenesis.

Studies in this special issue promote our understanding of the role of T cells in neuroprotection (Xin et al., 2010) and chronic neurodegenerative diseases such as ALS (Beers et al., 2010). These new data identify novel MHC and non-MHC genes that regulate the inflammation and T cell responses after injury (Al Nimer et al., 2010). The ability of the brain-resident cells to phagocytose debris of dead cells suggests the possibility of a novel process of antigen processing and presentation in the CNS. These findings might shed new light on the generation and antigen specificity of protective vs. destructive immune responses in the healthy and diseased CNS (Sokolowski et al., 2010).

One of the most extensively studied neuroinflammatory conditions in the CNS is multiple sclerosis. Most of the animal studies of this disease are based on an animal model known as experimental autoimmune encephalitis (EAE). New insight into the pathogenesis of multiple sclerosis is provided in this special issue through studies showing impaired striatal GABA transmission in experimental autoimmune encephalitis (EAE) (Rossi et al., 2010) and the role of brain-derived molecules such as docosahexaenoic acid that regulate an immune response and thus affect the progress of EAE (Kong et al., 2010). The newly discovered role of IL-23 in modulation of myelin-specific T cells (Kroenke and Segal, 2010) and the role of CXCL13 in recruitment of B cells to the inflamed CNS (Rainey-Barger et al., 2010) highlight additional aspects of the molecular mechanisms of brain inflammation outlined in this special issue.

Recently, a role of the immune system and immune-derived molecules in regulating brain plasticity and function has been proposed (Kipnis et al., 2008). Studies in this special issue further advance the field showing the effect of cytokines on neural progenitor cell proliferation (McPherson et al., 2010), the effect of physical activity on adult neurogenesis and telomerase activity in the models of schizophrenia (Wolf et al., 2010), and the role of immune responses in autism and autistic spectrum disorders (Ashwood et al., 2010; Mandal et al., 2010). The role of TGF-β on endothelial cell interaction with macrophages and T cells is shown to underlie to development of cerebrovascular amyloidosis (Weiss et al., 2010). Moreover, a novel role of superantigen-induced T cell activation and its subsequent effects on learning and memory is proposed (Woodruff et al., 2010). The role of tissue expression of steroid hormone receptors is shown to be associated with differential immune responsiveness (Butts et al., 2010).

CNS inflammation due to infection is another major challenge for future research in the interplay of brain and immunity. Studies in this special issue describe the role of toll-like receptors (TLR) and superantigens on adaptive immune responses during CNS staphylococcal infection (Vidlak et al., 2010). Another paper describes the role of CD14 and TRIF in governing different responses of mouse microglial TLR4 challenges using structural variants of LPS (Regen et al., 2010). CNS-derived CCL21 is proposed to drive homeostatic

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CD4+ T cell proliferation and migration of these cells into the CNS parenchyma following CNS infection (Ploix et al., 2010).

Glial cells are now widely accepted to serve a role beyond that of a ‘glue’ in the CNS. Not only do glia play tremendously important roles in brain function, but they also serve as an interface between the immune and the nervous systems, thus representing an important topic of research in understanding immune-brain interactions. Several novel aspects of glial cells in CNS structure and function are represented in this special issue. First, the transcriptional networks of subventricular zone microglia under different experimental conditions provide important insight into the plasticity of these cells (Starossom et al., 2010). The role of astrocyte-derived IL-1β is shown to support hippocampal-dependent memory and long-term potentiation (Ben Menachem-Zidon et al., 2010). Furthermore, angiotensin II type 1 receptor signaling in astrocytes is demonstrated to regulate synaptic degeneration-induced leukocyte entry into the CNS (Fuchtbauer et al., 2010).

The role of the immune system in regulating brain and behavior is probably one of the fastest developing fields of modern science. While this special issue on immunity and the brain will likely become outdated within a few years, it provides an important collection of studies addressing the mechanism underlying numerous modes of communication between the immune system and brain. Even if the interpretations given today are completely modified tomorrow, we are confident that the data in this volume will continue to represent contemporary aspects of psycho-neuroimmunology for generations of future scientists.

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