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Brief Commentary

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 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., 2011; 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 (Derecki et al., 2010a,b; Schwartz and Schechter, 2010), 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,b; 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, 2010a). 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

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