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Review article

Immune surveillance of the central nervous system in multiple sclerosis — Relevance for therapy and experimental models

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ABSTRACT

Treatment of central nervous system (CNS) autoimmune disorders frequently involves the reduction, or depletion of immune-competent cells. Alternatively, immune cells are being sequestered away from the target organ by interfering with their movement from secondary lymphoid organs, or their migration into tissues. These therapeutic strategies have been successful in multiple sclerosis (MS), the most prevalent autoimmune inflammatory disorder of the CNS. However, many of the agents that are currently approved or in clinical development also have severe potential adverse effects that stem from the very mechanisms that mediate their beneficial effects by interfering with CNS immune surveillance.

This review will outline the main cellular components of the innate and adaptive immune system that participate in host defense and maintain immune surveillance of the CNS. Their pathogenic role in MS and its animal model experimental autoimmune encephalomyelitis (EAE) is also discussed. Furthermore, an experimental model is introduced that may assist in evaluating the effect of therapeutic interventions on leukocyte homeostasis and function within the CNS. This model or similar models may become a useful tool in the repertoire of preclinical tests of pharmacological agents to better explore their potential for adverse events.

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1. Introduction

The presentation of foreign antigen constitutes a key event in immune surveillance and host defense. Antigen presenting cells (APCs) of the innate immune system recognize, capture, and present antigen to T lymphocytes, which subsequently initiate the cellular adaptive immune response.

Within the central nervous system (CNS), three compartments, the parenchyma, the cerebral perivascular spaces (CPVSs), and the subarachnoid spaces play a critical role in antigen presentation. In the parenchyma, astrocytes are the most abundant CNS glial cell population, but their role as APCs remains controversial (Sedgwick et al., 1991; Weber et al., 1994; Shrikant and Benveniste, 1996; Aloisi et al., 1998; Stuve et al., 2002). The most potent intrinsic APCs within the CNS parenchyma are microglial cells, and recent findings appear to suggest an important role for microglia cells in the pathogenesis of experimental autoimmune encephalomyelitis (EAE), an animal model of the human inflammatory disorder multiple sclerosis (MS) (Heppner et al., 2005). Thus, microglia cells are likely to participate in CNS immune surveillance.

The second CNS compartment that plays a crucial role in CNS antigen presentation are CPVSs, or "Virchow-Robin spaces". There is now abundant evidence that hematopoetically-derived APCs, including monocyte-derived macrophages (Hickey and Kimura, 1988; Huitinga et al., 1990), and dendritic cells (DCs) (Greter et al., 2005) reside and present antigen in CPVSs, and that cells in this compartment play an essential part in the initiation and perpetuation of CNS autoimmune disease. B cells, which together with T cells provide an antigen-specific adaptive immune response, are also competent APCs that are abundantly present in the CPVSs during inflammation (Anthoons et al., 1989).

A third compartment where antigen presentation occurs, and which would therefore be critical for CNS immune surveillance is the subarachnoid space. Kivisakk et al. demonstrated in the EAE model that $CD4^+$ T cells that were polarized to produce T helper (Th) cell 1 or Th 17 cytokines accumulate within the subarachnoid space early in the disease course (Kivisakk et al., 2009). Specifically, $CD4^+$ T cells could be detected in the subarachnoid space before they entered the spinal cord parenchyma. Within the subarachnoid space, $CD4^+$ T cells proliferated, and time-lapse microscopy indicated that these cells actively scanned the tissue and interacted with local major histocompatibility (MHC) class II^+ APC.

Disruption of the innate or adaptive immune response within the CNS is likely beneficial in CNS autoimmunity. Not surprisingly, most pharmacological agents that are currently approved for the therapy of MS were specifically designed to either diminish the absolute number of immune-competent leukocytes and their function in the periphery and subsequently in the CNS, or to reduce the ability of leukocytes to enter the brain and the spinal cord. These strategies have resulted in a meaningful decrease in clinical and paraclinical disease activities, which are in turn relevant readouts of the immune system's ability to present and process antigen in CNS autoimmunity. There is, however, a downside. As stated above, the primary biological role of leukocytes is not to cause autoimmunity, but to recognize and eliminate pathogens. Thus, the occurrence of opportunistic infections or neoplastic growth is perhaps the most meaningful biological readout of impairment of CNS immune surveillance. Not surprisingly, some of the more potent pharmacological agents that have been utilized in MS carry with them side effects of CNS virus reactivation and in some extreme cases the development of progressive multifocal leukoencephalopathy (PML).

This article will outline the main cellular components of CNS immune surveillance, including its innate and adaptive components. It will also conceptualize experimental models that may allow the preclinical measurement of an impact that pharmacological interventions may have on host defense. These models are urgently required to estimate an acceptable risk–benefit ratio of individual therapies.

2. The innate immune system in CNS immune surveillance

2.1. Monocytes–macrophages

In most tissues, the initial recognition of a pathogen is followed by activation of resident macrophages, and other tissue-resident cells, including DCs and mast cells. Tissue macrophages express numerous surface receptors that identify the so-called pathogen-associated molecular patterns (PAMPs), as well as danger-associated molecular patterns (DAMPs). These receptors include lectins, scavenger receptors, Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors, and retinoic acid-inducible gene (RIG)-I family receptors (Akira et al., 2001; Inohara and Nunez, 2003; Taylor et al., 2005). Following the initial microbe challenge, tissue macrophages attract and stimulate the extravasation of neutrophils and monocytes (Ajuebor et al., 1999; Maus et al., 2002; Cailhier et al., 2005). Monocyte-derived macrophages subsequently become the majority of myeloid cells within an inflammatory site. Experimental depletion of resident macrophages results in reduced host protection to infection, reduced expression of soluble inflammatory mediators, and diminished chemoattraction (Ajuebor et al., 1999; Cailhier et al., 2005; Kolaczkowska et al., 2007, 2009).

There is considerable heterogeneity with regard to the cellular composition and receptor usage between tissues. The central nervous system (CNS) constitutes a unique organ system in that it is confined entirely within a bony space. A robust inflammatory response and the ensuing edema could easily result in severe CNS damage or even a fatal outcome. Thus, the innate immune response within the CNS appears to be somewhat attenuated in most situations that present a threat to the host. Microglia are the tissue-intrinsic macrophages within the brain and spinal cord, and they are considered one of the key players in an initial immune response (Kreutzberg, 1996; Ransohoff and Perry, 2009; Kettenmann et al., 2011). It is currently thought that microglia are a long-lived population of tissue macrophages, but it is unknown how cell populations of brain macrophages are maintained in homeostasis and during disease (Ransohoff and Perry, 2009). The somewhat immune-restrained basic phenotype of microglia may be explained at least partly by the fact that, in contrast to other tissue macrophages, these cells are shielded from serum proteins that can selectively and potently activate macrophages (Adams et al., 2007). In addition, the cytokine composition within the healthy adult CNS is relatively anti-inflammatory with detectable levels of transforming growth factor(TGF)-β2 and TGF-β3 (Unsicker et al., 1991; Flanders et al., 1993), and prostaglandin E2 (PGE2) (Ransohoff and Perry, 2009).

The pathogenic role of microglia in CNS autoimmunity has been established in the EAE animal model of the human inflammatory disorder MS. In the EAE model, several investigators demonstrated the capability of microglia to initiate an adaptive (auto)immune response against target CNS antigens. It has been known that the induction of EAE after adoptive transfer of $CD4^+$ antigen-specific T cells requires restimulation with the cognate autoantigen within the CNS compartment (Slavin et al., 2001). Experiments with radiation bone marrow chimeras, in which bone marrow-derived donor cells expressed a MHC II haplotype distinct from that present on recipient parenchymal microglia have provided clarity with respect to their role as APCs. Adoptive transfer of myelin-specific $CD4^+$ T cells restricted by the MHC II haplotype of the recipient parenchymal cells did not cause EAE. In contrast, myelin-specific $CD4^+$ T cells that were restricted by the MHC II haplotype of perivascular macrophages derived from the donor bone marrow inoculum led to clinical disease (Hickey and Kimura, 1988). Other investigators demonstrated that the elimination of all potential APCs except for $CD11c^+$ perivascular macrophages did not affect disease susceptibility in experimental animals (Greter et al., 2005). Another set of experiments, in which EAE was actively induced with one myelin epitope, followed by adoptive transfer of unprimed T cell receptor (TCR) transgenic T cells specific for a different antigenic determinant, showed