Nature Reviews Immunology | AOP, published online 3 April 2009; doi:10.1038/nri2549

NEUROIMMUNOLOGY

Finding a way into the brain

Experimental autoimmune encephalitis (EAE) is an inflammatory demyelinating disease that is used as a model for multiple sclerosis. Both interleukin-17 (IL-17)-producing T helper 17 (T_H17) cells and interferon-γ (IFNγ)-producing T_H1 cells are thought to be involved in the initiation and development of EAE. The process of T cell migration into the central nervous system (CNS) in inflammatory conditions is fairly well understood — α4β1 integrin expressed by migrating T cells interacts with vascular cell adhesion molecule 1 expressed by the endothelial cells of activated blood vessels in the CNS parenchyma — but the molecular mechanisms of T cell entry during the initiation phase of the disease are not clear. Now, Reboldi and colleagues show that the initiation of EAE is controlled by the CC-chemokine receptor 6 (CCR6)-dependent entry of T_H17 cells through the choroid plexus.

The idea that chemokines and their receptors are important in controlling T cell trafficking at different locations in the body is a well-established principle in immunology. Because CCR6 is expressed by IL-17-producing T cells, the authors studied the role of CCR6 in the development of EAE. Both wild-type and CCR6-deficient mice were immunized subcutaneously with peptide 33–55 from myelin oligodendrocyte glycoprotein ($MOG_{33–55}$) in complete Freund's adjuvant to induce EAE, but the CCR6-deficient mice were resistant to the development of EAE despite the detection of IL-17- and IFNγ-producing T cells in their spleens.

When naive $MOG_{33–55}$-specific T cells from wild-type mice were transferred into wild-type and CCR6-deficient mice that were then immunized with $MOG_{33–55}$, the transferred T cells developed into IL-17-producing cells, and both sets of mice developed EAE. So, CCR6 expression by the transferred T cells was necessary and sufficient to reconstitute the disease. Unexpectedly, however, in the CNS of CCR6-deficient mice, the transferred wild-type CCR6-expressing T cells predominated only during the initial phase of disease development, whereas the active phase of the disease was dominated by endogenous CCR6-deficient T cells (both T_H1 and T_H17 cells).

The authors next looked at the expression of CC-chemokine ligand 20 (CCL20; the ligand for CCR6) in brain tissue. CCL20 was expressed by epithelial cells of the choroid plexus in both wild-type and CCR6-deficient mice. In human tissue, CCL20 expression was similarly detected in the choroid plexus in normal brain and was also expressed by activated astrocytes in inflamed tissue from the brains of patients with multiple sclerosis.

These results support a two-stage model for the development of EAE in which CCR6-expressing autoreactive T cells enter the CNS through the choroid plexus and disseminate via the cerebrospinal fluid into the subarachnoid space. These cells are locally activated by recognizing self antigens that are displayed on resident antigen-presenting cells and trigger the recruitment of a second wave of T cells that enter the inflamed brain in a CCR6-independent manner. On the basis of these findings, the authors propose that CCR6 is important for controlling the brain-specific trafficking of lymphocytes for surveillance of the CNS.

Elaine Bell

ORIGINAL RESEARCH PAPER Reboldi, A. *et al.* C-C chemokine receptor 6-regulated entry of T_H-17 cells into the CNS through the choroid plexus is required for the initiation of EAE. *Nature Immunol.* 22 Mar 2009 (doi:10.1038/ni.1716)