T cells and microglia as drivers of multiple sclerosis pathology

One of the many open questions in multiple sclerosis research is whether inflammation in the CNS is initiated by an autoimmune attack, triggered by unidentified environmental factors, or represents a response to axonal degeneration and myelin degradation secondary to processes that are intrinsic to the CNS.

The autoimmune hypothesis is supported by the recently well-established disease association with genes in the HLA region which encode proteins that are functionally relevant for initiating immune responses by presenting peptides to CD4+ and CD8+ T cells (Lincoln et al., 2005; Oksenberg et al., 2004). Functional evidence was provided initially by the animal model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE), which showed that the minimal requirement to trigger disease is activated T cells (Ben-Nun et al., 1981; Madsen et al., 1999). More recently, clinical trials of immune modifying drugs have also provided evidence that T cells play a role in the pathogenesis of multiple sclerosis (McFarland and Martin, 2007). In this context, the universal importance of T cells has, however, been questioned in at least one study, in which almost no T cells in plaques from patients studied early in the course were detected, but with microglial activation and apoptosis of oligodendrocytes (Barnett and Prineas, 2004).

New genetic studies have provided further support for the role of autoimmune mechanisms in the pathogenesis of multiple sclerosis. Genome wide association studies have identified several new susceptibility genes, each of which is involved in controlling immune responses. In contrast, no genes have yet been found that are directly relevant for oligodendroglial or neuronal functions (Gregory et al., 2007; International Multiple Sclerosis Genetics Consortium, 2007; Lundmark et al., 2007). It is therefore very timely that three papers in this issue of Brain further address the role of the immune system in the pathophysiology leading to the lesions of multiple sclerosis.

Junker et al. (2007) apply an elegant approach to address whether infiltrating T cells in multiple sclerosis are there as a result of non-specific bystander mechanisms or through having actively migrated to the CNS and then expanded clonally. The idea is that, if T cells arrive randomly in the CNS, a Gaussian distribution of T cell receptor recombination length would be expected. But the new data show that this is not the case. Rather, they suggest that T cells migrate actively to the CNS and expand clonally. Whilst these findings complement previous observations (Babbe et al., 2000; Junker et al., 2007), they further show, by sequencing the DNA of the dominant T cell clones in the CNS, that some are enriched and even identical in several different anatomical sites, in one instance displaying markedly different degrees of disease activity between lesions. This clearly shows that T cell expansion of certain clones is not only focused on active lesions but also ongoing throughout the CNS, suggesting that this is globally under attack in multiple sclerosis. Even more interesting is the observation that T cell receptors in different regions of the brain have slightly different nucleotide sequences in the CDR3 region, which is crucial for the recognition of peptide–HLA complexes. However, the resulting amino acid sequence is identical between these CDR3 regions, illustrating—since there is no further receptor revision after the T cells leave the thymus—that these T cells must have independently developed and homed into the CNS, where they found identical antigens and expanded clonally. It is also of interest that no T cell receptors were found which are identical in amino acid sequence between patients. This may merely be the result of a very small sample size (4 patients), with no one sharing identical-HLA haplotypes, but it may also illustrate that these so-called ‘private clones’ contribute to the disease within each individual, while the long searched for ‘public clones’ (shared between individuals and recognizing the same auto-antigen with an identical T cell receptor) are not prominent. Therefore, antigen-specific therapies may need to be individualized.

It follows that patients with multiple sclerosis have common susceptibility genes predisposing to the disease, while additional private polymorphisms, mutations, stochastic events and environmental factors (such as infections) must occur in order to spark the autoimmune T cell response (Goodnow, 2007). Accordingly, this response is likely to be shaped differently between patients and may explain some of the clinical and pathological heterogeneity in multiple sclerosis.

Another point of discussion in the field of research in multiple sclerosis is the separate role of the T-cell subtypes (CD4+ and CD8+) (Friese and Fugger, 2005) and their contribution to disease initiation and perpetuation. Here Junker et al. (2007) show by single-cell analysis that a good
The predominance of CD8+ T cells in MS lesions is further documented in the paper by Marik et al. (2007). These authors analyse a subtype of brain lesions from patients with multiple sclerosis, exhibiting hypoxia-like lesions and microglial activation (the so-called Pattern III lesion to use a term coined by Lucchinetti et al., 2000). By comparing lesions, that are characterized by the absence of demyelination, mild oedema, microglial activation and axonal injury with those showing demyelination, increased T cell infiltration and higher expression of microglial/macrophage activation markers, the authors suggest a sequence of events in which microglial activation precedes the more abundant T-cell infiltration and demyelination. By injecting lipopolysaccharide into the spinal cord of rats, the authors observe a sequence similar to Pattern III lesion formation. These findings suggest that microglial cells/macrophages play a vital role in lesion formation in some subtypes of tissue pathology in multiple sclerosis with toxic products from these myeloid cells possibly mediating a deleterious effect on mitochondria in axons and neurons leading to energy failure and expression of stress-proteins. However, although, T-cell infiltrations are rare in pre-demyelinating Pattern III lesions, they are still present and likely to activate microglial cells.

Thirdly, a very thoroughly conducted mouse study also concludes that microglial cells are instrumental in exerting damage in inflammatory CNS lesions—here, the formation of cortical lesions, axonal damage and axonal malfunction. Rasmussen et al. (2007) describe mice with EAE that show T-cell infiltrates at the peak of the acute disease, whereas microglial activation is sustained during the chronic phases. This activation correlates well with the presence of cortical lesions, alteration of synaptic function and axonal transport, each indicative of neuronal dysfunction. Together, these three studies provide further evidence that helps us to understand the initiation and perpetuation of events that underlie lesion formation in multiple sclerosis. T cells are scattered throughout the CNS possibly driving the disease by recognizing specific auto (or foreign)-antigens. As CD8+ T cells predominate in different lesions, they should be increasingly appreciated as primary targets for anti-inflammatory interventions. Lesions characterized by microglial activation and hypoxia-like characteristics, as well as cortical lesions and the slowly progressive chronic phase of the disease, are likely driven by activated myeloid cells. However, at present it is not clear what keeps the microglial cells activated. It is possible that the T cells found throughout the CNS of patients with multiple sclerosis provide constant stimuli, i.e. by pro-inflammatory cytokines, which activate microglia. Similarly, activated microglial cells are important in the pathogenesis of neurodegenerative disorders, such as Alzheimer’s disease (Block et al., 2007). So-called innate stimuli, which represent pathogen products (such as lipopolysaccharide) recognized by specialized receptors on myeloid cells, could also contribute to bouts of activation (Perry et al., 2007), but it is unlikely that they can keep up a constant level of microglial activation. Therefore, targeting the interaction between T cells and microglial cells might dampen the progressive activation and halt the neurodegenerative phase of the disease.

References


