Scientific Commentary

Multiple sclerosis and immune regulatory cells

The multiple sclerosis disease process is defined on the basis of lesions disseminated in space and time within the CNS. Immunization of humans (vaccines) and animals with neural tissue can result in multi-focal CNS inflammatory lesions with demyelination; such disorders are usually uniphasic or self-limited. They are initiated by systemically activated myelin-reactive T cells that then access the CNS. Myelin-reactive T cells can be recovered from the CNS and blood in multiple sclerosis. Such cells can also be recovered from unaffected individuals. These observations raise issues regarding the origin of such cells in non-immunized individuals and why their presence is variably associated with uniphasic disease, recurrent disease, or no disease. Most autoreactive cells may actually be generated in response to exogenous peptide antigens with which there is cross-reactivity (molecular mimicry) with myelin antigens, reflecting the degeneracy of antigen recognition by T-cell receptors (Nino-Vasquez et al., 2004).

Studies in animals showing that depletion of specific subpopulations of immune cells can unmask spontaneous or antigen-induced autoimmune disease, or conversely that such cells can transfer disease resistance, indicate that active immune-regulatory mechanisms contribute to the disconnection between the presence of autoreactive T cells and the development of autoimmune disease. As the capacity to define subsets of immune cells has evolved, an increased number of such subsets have been implicated as mediators of immune regulation with different potential mechanisms of action.

An initial ‘holy grail’ of immunology was to find a regulatory (‘suppressor’) cell with properties equivalent to the classic cytotoxic and helper cell members of the adaptive immune system, namely cells that were both antigen and major histocompatibility complex (MHC) restricted. Initial studies focused on the CD8 T-cell subset which includes both cytotoxic cells and ‘suppressor’ cells. The therapeutic approach aimed at depleting disease-relevant antigen-specific T cells by immunizing animals or multiple sclerosis patients with myelin-reactive T cells or their receptors probably is mediated via generation of CD8 cytotoxic T cells directed at the autoreactive cells (Ben Nun et al., 1981). CD8 T cells can also inhibit CD4 T-cell-dependent immunoglobulin production in a non-cytotoxic manner; such functional CD8-mediated suppression is decreased in multiple sclerosis (Antel et al., 1984). In the experimental autoimmune encephalitis (EAE) model, CD4 T-cell-mediated suppression accounts for animals being refractory to recurrent disease immediately after the initial exacerbation (Lenz and Swanborg, 1999). CD4-mediated suppression can involve production of anti-inflammatory (Th2/3) cytokines. More recently, a functional derangement in a subset of suppressor CD4 T cells, defined by the phenotype CD4⁺CD25⁺ and acting via cell–cell-dependent mechanisms, was found to correlate with disease activity in multiple sclerosis (Viglietta et al., 2004).

Takahashi et al. (Brain, this issue) focus attention on natural killer (NK) cells as suppressors of myelin basic protein (MBP)-reactive T cells in multiple sclerosis patients. Although NK cells lack the receptor diversity of T and B cells, their array of surface receptors permits them to distinguish self from non-self. NK cells are defined by their capacity to mediate cytotoxicity of cell targets lacking expression of self MHC, or additional inhibitory ligands. Activated NK cells can be cytotoxic to autologous oligodendrocytes in vitro (Morse et al., 2001), and are detected in acute inflammatory CNS lesions (Matsumoto et al., 1998). However, depletion of NK cells results in increased severity of EAE, demonstrating their role as regulatory cells (Takahashi et al., 2001). Thus NK cells, analogous to CD8 T cells, have both cytotoxic and regulatory potential. Predicting the net outcome of increasing or decreasing their numbers or function in autoimmune disease would be difficult.

Takahashi et al. initially found that peripheral blood of multiple sclerosis patients in remission had increased proportions of NK cells that expressed high levels of CD95 (Fas), a receptor that can induce apoptosis. Increased Fas/CD95 expression was not associated with uniform overexpression of other markers used as indicators of cell activation. Fas ligand is produced by activated T cells and microglia/macrophages, raising speculation that this may be a mechanism contributing to CD95 NK cell apoptosis. These NK cells also expressed a profile of non-inflammatory or Th2 (IL-5) cytokines. These features were lost during relapse. Takahashi et al. now use an in vitro approach to show the potential functional relevance of the CD95⁺ NK cell subset. Depletion of this subset from the peripheral blood unmasked the presence of MBP-reactive T cells in some but not all multiple sclerosis patients during remission.

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The study raises a number of questions regarding this and other cell populations with regulatory functions in multiple sclerosis. In the current study, patients could switch from high to low proportions of CD95 NK cells or vice versa. MBP-reactive T cells did not emerge in those who switched from high to low, although there was a suggestion that such a switch may be predictive of a pending relapse. In patients with low CD95 NK proportions but no MBP-reactive cells, other autoantigens may be involved since regulatory NK cells are not antigen specific. The current study does not show directly whether the CD95 NK high group has reduced immunoreactivity to other antigens. If, as postulated, NK cells exert their regulatory effect via Th2 cytokines, then this would represent further justification for immune deviation direction therapies such as altered peptide ligands (Kappos et al., 2000) for MS.

The MHC independence of regulatory NK cells is predicted to be opposite to that of antigen-specific regulatory T cells. Perhaps NK cells fill a particularly important regulatory niche in the CNS, a compartment in which there is relatively low MHC expression. The increased proportion of CD95 NK high cells during remission was not linked with increased cytotoxic activity. Cytotoxic NK activity is depressed in multiple sclerosis patients during relapse (Kastukoff et al., 2003). One can speculate whether NK regulation and cytotoxicity are differentially controlled by inhibitory ligands, which themselves may be differentially expressed in different tissues including the CNS.

Overall this paper addresses the important concept that multiple sclerosis disease in many patients remains potentially chronically active (‘smouldering multiple sclerosis’) but is held in check by regulatory cells. This raises the issue as to how current and future therapies impact on these control mechanisms.

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References


