**Editorial**

**T-cell receptor immunotherapy in multiple sclerosis**

In the last 20 years there has been an explosion in our knowledge of the immunological events that follow the recognition of antigen by T lymphocytes. This has led to the development of promising immunomodulating reagents, many of which are currently undergoing clinical trials in multiple sclerosis patients. Ideal immunotherapy should inactivate only autoaggressive lymphocyte clones and not induce general immunosuppression. One interesting option for specific treatment comes from observations made by Cohen and co-workers nearly 20 years ago (Ben-Nun et al., 1981). They noted that rats immunized with myelin basic protein (MBP) were resistant to developing encephalomyelitis (EAE) if they had first been exposed to inactivated encephalitogenic T cells. It was suggested that this phenomenon was driven by determinants (called idiotopes) on the antigen receptors of the inactivated T cells. As soon as it was possible to deduce the amino acid sequence of the T-cell receptor (TCR), synthetic peptides were used as immunogens to show that anti-TCR peptide immunity suppressed responses to MBP and the induction of EAE (Vandenbark et al., 1989). Immunization with TCR peptides is now undergoing clinical trials in multiple sclerosis patients and pilot studies indicate that anti-TCR peptide responses are inducible and appear to reduce the frequency of MBP-specific T cells in some individuals (Vandenbark et al., 1996).

Provided that multiple sclerosis does not result from virus infection or virus-induced immunopathology, perhaps the major impediment to a successful outcome in these studies are observations indicating that responses to myelin antigens are more heterogeneous in humans than in rodents. Not only are several myelin constituents considered candidate autoantigens in multiple sclerosis, but also other animal studies indicate diversification of the immune response to subdominant and cryptic MBP regions and even to other myelin proteins as the encephalitis evolves (reviewed in Lehmann et al., 1993). This heterogeneity indicates that several TCR peptides might be required to suppress ongoing responses in multiple sclerosis. It is worth emphasizing that putative human autoantigens can only be indirectly implicated in pathogenesis by studying in vitro responses, and final proof of pathogenicity requires the demonstration of clinical efficacy after specific inactivation of the potentially autoaggressive clones in vivo (not yet achieved for any human autoimmune disease). Thus, the importance of these human clinical experiments cannot be overestimated and the methodology used should be vigorously tested, as is done in this issue of Brain by Zipp and colleagues.

But how do anti-TCR specific T cells exert their control? The central event in any antigen-specific immune response is the recognition by T cells of short peptide fragments, or epitopes, bound to major histocompatibility complex (MHC) molecules. Both CD4\(^+\) and CD8\(^+\) cells recognizing the TCR epitopes, or idiotopes, have regulatory potential in rodent EAE, and passive transfer experiments indicate that these lymphocytes are sufficient for mediating the regulatory effect. Although the evidence that T cells take up and present exogenous proteins in the context of MHC class II molecules is conflicting, some anti-TCR CD4\(^+\) lymphocytes proliferate when co-cultured with the original clone from which the TCR was derived (Broeren et al., 1993) or with T cells bearing similar receptors (Vandenbark et al., 1989), indicating that T cells can effectively present their own TCR peptides. Professional antigen presenting cells (APC) may also participate, perhaps by processing and presenting released TCR protein and by stimulating naive T cells. Whatever the mechanism, at least one study in rodents has indicated that effective regulation of autoaggressive T cells correlates with whether the TCR idiotope is naturally processed from intact or relatively unfragmented TCR protein; immunogenic subdominant regions are not suppressive (Kumar et al., 1995).

Zipp and colleagues demonstrate that the human in vitro response to artificially produced TCR antigens is quite heterogeneous, and they suggest that prior selection of TCR peptides be made on the basis of whether they contain naturally processed TCR epitopes, before their use in clinical trials. The target TCR was obtained from an autologous MBP-specific CD4\(^+\) T-cell line (HWBP-3) derived from a healthy donor. They studied T-cell responses to full-length recombinant TCR \(\alpha\) and \(\beta\) polypeptides and to homologous synthetic TCR \(\alpha\) and \(\beta\) peptides, hoping to expand in vitro anti-TCR-specific cells that might have regulatory effects in vivo. The most striking result of their study was the failure of all T-cell lines expanded in vitro with highly purified artificial antigens to recognize native TCR either on the original clone HWBP-3 or independently processed from it by APC. This was not due to an inability of the HWBP-3 line to stimulate responder T cells, since T cells with specificity for synthetic peptides could be stimulated by peptide-pulsed HWBP-3 cells. These results indicate that the
epitopes that are apparently processed from comparatively large amounts of exogenous antigen by conventional APC in vitro are not revealed on the T cell surface or after processing of native TCR by APC; at least to the T cells expanded in their cultures. Perhaps many more idiotopes are revealed at the high antigen concentrations used in vitro, or processing of the natural TCR heterodimer is different; the quaternary structure of proteins can have significant effects on natural processing (Rouas et al., 1993).

We have previously suggested that in order to demonstrate that the T cells expanded in vitro with artificially synthesized antigens have relevance in vivo, it is important to show that they also recognize native protein (Hawke et al., 1996). In characterizing responses to the human acetylcholine receptor (AChR), the target antigen in myasthenia gravis, we found that only T cells expanded with recombinant proteins cross-reacted with native AChR. Unlike Zipp and colleagues, we had little success in selecting T cells with AChR α-subunit synthetic peptides that cross-reacted with full-length recombinant proteins (Matsuo et al., 1995). Even when we used a peptide known to contain a naturally processed sequence, we were unable to select T cells responsive to native or recombinant protein in vitro. Synthetic peptides may bind surface class II MHC molecules without internalization and the arbitrarily chosen cleavage sites may produce quite a different array of peptides that can adopt alternative conformations from those naturally produced in APC. The composition of residues adjacent to the epitope core can also influence intracellular processing events (reviewed in Moudgil et al., 1998). We also found that some T cells expanded with synthetic peptides were apparently specific for synthesis artefacts (Matsuo et al., 1995).

How can the apparent efficacy of synthetic TCR peptide immunization in animal studies be reconciled with these data of Zipp and colleagues? Although any primary in vitro response to synthetic peptides is likely to contain many spuriously reactive cells, animal data indicate that synthetic peptides containing naturally processed epitopes can be expected to stimulate cells with anti-idiotypic specificity in vivo. If the frequency of T cells that respond to the naturally processed sequence is very low, we may fail to expand them from 60 ml of blood, or they may be overgrown by T cells that are more efficiently expanded in the in vitro environment. Perhaps Zipp and colleagues would have expanded cells recognizing HWBP-3 had they used multiple sclerosis patients potentially primed by MBP in their studies. In the healthy subject, the activated T cells with high enough sensitivity for the idiotopes naturally occurring on clone HWBP-3 may not have been available for expansion, indirectly implying that HWBP-3-like clones were not activated in vivo when the blood was drawn. Until it can be shown that T cells expanded in vitro recognize native TCR polypeptides either on T cells or processed by APC from fragmented T cells, doubts must exist regarding the in vitro strategy proposed by Zipp and colleagues. Perhaps the most efficient way of determining the immunodominance of TCR sequences would be to immunize patients of known HLA-type with a series of peptides and to determine whether responses were induced to recombinant TCR polypeptides or, better still, to native TCR derived from the original clone. This approach would not be without risk however; one patient developed a leucocytoclastic vasculitis after peptide immunization, although it promptly resolved with treatment (Bourdette et al., 1994).

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References


Vandenbark AA, Chou YK, Whitham R, Mass M, Buenafe A,