11 T Cell Receptor Peptides for the Vaccination Therapy of Multiple Sclerosis

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11.1 Introduction

Current options for treatment of diseases with a presumed autoimmune etiology such as multiple sclerosis (MS) are far from satisfactory. Most treatments are associated with undesirable side effects due to toxicity and lack of immunological specificity. For these reasons, one of the primary goals in the development of immunotherapies has been to achieve selective inactivation of disease-inducing lymphocytes in the absence of general immunosuppression. It appears that the peripheral immune system can be divided into two compartments: one in which positive responses are initiated and another one where tolerance is induced (Mitchison 1998). Augmenting of tolerance by immunoregulation ranks prominently among the various approaches studied for the treatment of autoimmune disorders. Strategies in this direction include
induction of specific immunological tolerance via anergizing, deletion, or suppression of autoreactive clones (Van Paris et al. 1998). The role of some of these mechanisms in maintaining peripheral tolerance in vivo is still very much a matter of debate.

One approach that has received much attention recently is T cell vaccination, originally proposed by Cohen and Ben-Nun (Ben-Nun and Cohen 1981; Ben-Nun et al. 1981). Their initial observation was that radiation-inactivated encephalitogenic T cells could be used as preventive vaccines against the induction of experimental autoimmune encephalomyelitis (EAE). Based on these early findings, other means of inactivating potentially autoreactive T cells, including high pressure, alkylating agents such as mitomycin C or chemical crosslinkers, were used in order to successfully attenuate myelin basic protein (MBP)-specific T cells. Upon adoptive transfer, these cells conferred resistance to subsequent active EAE induction in naïve recipients. Successful T cell vaccination therapy was subsequently demonstrated in animal models of arthritis (Lider et al. 1987; Kumar et al. 1997), lupus (Ben-Yehuda et al. 1996), and type I diabetes (Elias et al. 1999). Encouraging results in animal models using vaccines based on the pathogenic T cell have prompted the design of novel and selective immune-based experimental therapies for human autoimmune disease.

Although the protective effect of T cell vaccination in vivo has been extensively documented, the precise mechanism for this effect has remained unclear. Since initial studies, much evidence has been accumulated in support of the function of regulatory T cell antigen receptor (TCR)-specific T lymphocyte networks (Lider et al. 1988). Current concepts of the pathophysiology of autoimmune disease point to the crucial role of pathogenic Th1 T cells, autoantigenic epitopes, major histocompatibility complex (MHC) molecules, and possibly regulatory T cell populations in the disease process. It is widely accepted that Th1 cells, critical for cell-mediated immunity by their production of IL-2, IFN-γ, TNF-α, and lymphotoxin are involved in the immunopathology of organ-specific autoimmune disease (O’Garra et al. 1997). A role as regulators has been suggested for Th2 cells (O’Garra et al. 1997) and cells producing TGF-β, recently characterized as Th3 and Tr (regulatory) CD4+ T cells. Results from vaccination experiments of rats with a low, subencephalitogenic dose of a pathogenic T cell clone suggested that T cell vaccination induced resistance to autoimmune disease by