Commentary

Antigen-specific immunotherapy: Is it a real possibility to combat T-cell-mediated autoimmunity?

Roland Tisch * and *Hugh O. McDevitt*†

Departments of *Microbiology and Immunology, and* †*Medicine, Stanford University Medical Center, Stanford, CA 94305-5402*

A functional immune system is in part characterized by its ability to discriminate between myriad self antigens and those antigens expressed by foreign invaders. Lacking this ability, self tissues are attacked and autoimmunity is established. Typically, patients suffering from an autoimmune disorder are treated with anti-inflammatory drugs or drugs that block cell proliferation. These agents, however, may have serious side effects and the general immunosuppressive effect often associated with their function may compromise the patient's ability to resist opportunistic infection. Ideally, one would prefer to selectively target only those cells mediating the disease process, with few or no side effects, while maintaining the integrity of the remainder of the immune system.

In T-cell-mediated autoimmune diseases such as multiple sclerosis (MS), insulin-dependent diabetes mellitus (IDDM), and rheumatoid arthritis (RA), autoreactive T cells are an obvious target for immune intervention. One way to target these cells and block their pathogenic activity is to induce tolerance in ("tolerize") the autoreactive T cells by using the appropriate autoantigen or autoantigen-derived peptides. In this manner, the exquisite specificity associated with T-cell antigen recognition can be used to selectively eliminate the unwanted T cells. Indeed, studies have shown that treatment of young mice with the β-cell antigen glutamic acid decarboxylase (GAD) can tolerize GAD-specific T cells and, in turn, prevent spontaneous diabetes in the nonobese diabetic (NOD) mouse, a murine model for human IDDM (1, 2). Similarly, treatment with immunodominant peptides of myelin basic protein (MBP) can prevent and treat the $CD4^+$ T-cell-mediated murine model of experimental autoimmune encephalomyelitis (EAE) (3–6). In this issue, Aichele *et al.* (7) provide further evidence that this approach may be feasible by showing that an acute viral-induced diabetes in a transgenic mouse model can be prevented by tolerizing the autoreactive T cells specific for a viral neo self antigen.

In this model system, mice that selectively express the lymphocytic chori-omeningitis virus (LCMV) 120-kDa glycoprotein (GP) transgene in the insulin-producing β cells of the islets of Langerhans become diabetic after infection with LCMV. The GP-specific $CD8^+$ cytolytic T cells activated in the periphery upon encountering viral peptides home to the pancreas, where the β cells presenting GP peptides on their surface in the context of major histocompatibility complex class I molecules are lysed. However, when Aichele *et al.* (7) first give three intraperitoneal injections of a viral GP peptide-(33–41) corresponding to an immunodominant cytotoxic T-cell epitope, the effector T cells recognizing this peptide are tolerized and diabetes is prevented in LCMV-infected animals. These authors, having identified the immunodominant cytotoxic T-cell epitope recognized on LCMV GP, could selectively induce peripheral deletion/anergy in the appropriate effector $CD8^+$ T-cell population, leading to successful protection from the virally induced diabetes. This group further demonstrated that a response to the LCMV nucleocapsid protein persisted, showing that tolerance induced by injection of the GP peptide was highly specific.

In this study and others, it is apparent that peptide/antigen-specific immunotherapy, when applied to a highly defined model of autoimmunity, can be effective. However, could this approach be feasible in prevention or treatment of spontaneous autoimmune diseases such as MS, IDDM, or RA, in which the target autoantigen(s) is not known and a number of autoantigens appear to be involved in the disease process?

Various studies using different protocols to induce antigen-specific T-cell tolerance suggest (with guarded optimism) that this form of immunotherapy may be plausible in a clinical setting. However, the effectiveness of this approach hinges on several factors. The most critical factor is whether the therapy can be used to treat an ongoing autoimmune response or whether it is effective only in terms of prevention. Typically, an autoimmune disease is diagnosed at a time when significant tissue damage has already occurred. At this point, the need is for a form of therapy that can prevent further tissue damage and eliminate or block all, or nearly all, autoreactive T cells. It is possible, however, that administering an antigen/peptide after pathogenic T cells have been activated may have an immunizing effect and exacerbate the disease condition.

How the antigen is administered is also a key factor in determining whether an immunogenic or tolergenic response is induced. Aichele *et al.* (7) show that administering the GP peptide systemically leads to a tolergenic effect; locally administered, the peptide induces an immunogenic response. The duration of the tolergenic effect is an additional factor requiring consideration. Frequent treatment over a prolonged period is cumbersome and costly, and it may result in unforeseen immunological complications. Thus, the success of antigen-specific immunotherapy depends in large part on the nature of the tolerance induced by a specific treatment protocol.

In general, the experimental protocols used have induced two distinct processes of peripheral T-cell tolerance: (*i*) clonal deletion/anergy and/or (*ii*) induction of regulatory T cells. Inducing clonal deletion/anergy with whole antigen or peptide may prove to be effective in instances in which the inciting autoantigen has been identified and in which the disease-relevant determinants recognized on that autoantigen are known, as in the study of Aichele *et al.* (7).

However, the high degree of specificity required for the process of clonal deletion/anergy may be limiting when dealing with diseases such as MS, IDDM, and RA, in which there are responses to several autoantigens (as many as six to eight in IDDM) and the critical inciting autoantigen(s) is not known. An alternative approach is to consider treatment of these diseases with protocols that induce the production of regulatory T cells.

Recently, it has been shown that diabetes can be prevented in young NOD mice after intrathymic injection of GAD (1). The protective effect appears to result from the induction of regulatory T cells, which inhibit T-cell but not antibody responses to GAD and to other β-cell antigens. This protective effect was shown to be antigen specific in that

peripherin, another β-cell autoantigen, could not similarly prevent diabetes. In this study and another similar study carried out by Kaufman *et al.* (2), mice were injected with GAD at an age prior to the development of autoimmunity. Only in EAE, where defined antigens (MBP or the MBP peptide Ac1-11) have been used to induce disease, has antigen-specific immunotherapy clearly succeeded in treating an ongoing autoimmune response (5, 6). The critical tests of systemic antigen-specific immunotherapy have yet to be done. These tests should involve treatment of an ongoing, spontaneous autoimmune disease, such as IDDM in the NOD mouse, with peptides and/or proteins that are known targets of the autoimmune process.

Another antigen-specific approach to inhibit the activity of autoreactive T cells is through oral (and nasal) administration of antigen or antigenic peptides leading to down-regulation of self-reactive T cells. Studies utilizing animal models of autoimmunity such as IDDM (8), EAE (9), experimental autoimmune uveoretinitis (10), and adjuvant arthritis (11) have shown that feeding whole protein or specific peptides (or nasal inhalation of peptides) of an autoantigen can delay or suppress the pathogenic processes associated with these autoimmune disorders. In addition, a recent study has reported that oral administration of type II collagen to 28 patients suffering from severe, active RA can lead to a small decrease in the number of swollen joints and, in four cases, to complete remission of the disease (12).

It appears from some animal studies that antigen-specific CD8+ regulatory T cells are induced, an effect that is often variable and highly dose dependent (13, 14). The suppressive effect of the regulatory T cells, termed "antigen-driven bystander suppression," appears to be due to the secretion of anti-inflammatory cytokines that actively suppress the disease process in the target organ (14). It is believed that antigen-specific regulatory T cells induced in the gut home to the target organ and secrete cytokines such as transforming growth factor β and interleukins 4 and 10 (15). These cytokines then down-regulate the activity of the pathogenic T cells in a nonspecific manner. It is thus possible via this approach to treat an organ-specific autoimmune disease, despite the fact that the "initiating" autoantigen is not known. The clinical reports suggest that oral administration may allow for effective treatment of an ongoing autoimmune response. However, the orally administered protein must be a constituent of the target tissue and must be capable of inducing regulatory T cells. While oral administration of antigen appears to be nontoxic, its effects are variable and highly dose specific, which does not appear to be the case with systemically administered antigen.

It is naive to expect that one form of antigen-specific immunotherapy will be effective in the treatment of all T-cell-mediated autoimmune diseases. It is more likely that different forms of this type of immunotherapy used in concert or with other therapeutic agents may prove to be generally effective. Furthermore, as additional autoantigens are identified, protocols will begin to use a battery of antigens to target the polyclonal populations of autoreactive T cells characteristic of these diseases, thereby increasing the likelihood of successful treatment. As we continue to learn in greater detail the mechanisms involved in establishing self tolerance, we may be able to devise additional and more effective protocols for treatment. The work carried out by Aichele *et al.* (7), and others in the field, suggests that this approach may indeed be a productive means to combat T-cell-mediated autoimmunity.

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