

Experimental autoimmune encephalomyelitis (EAE) is a T cell-mediated autoimmune disorder widely used as a model for human multiple sclerosis (MS). In this issue of *The Journal*, Cross et al. (1) describe the successful treatment of murine EAE using a soluble form of the T cell activation molecule, CTLA-4. Together with two other recent studies (2, 3), this demonstrates a crucial role of the CD28/CTLA-4:B7 receptor system in EAE and suggests potential therapies for human MS.

Role of CD28 in T cell activation

The interactions of T lymphocytes with antigen-presenting cells (APC) lead to T cell activation crucial for immunity to foreign pathogens, transplanted organs, or to self tissue during autoimmune disease. T lymphocyte activation by interaction with APC is consistent with a two signal model (4). The specificity of T cell/APC interactions (signal one) is provided by the recognition of antigenic peptide/MHC complexes by T cell antigen receptors (TCR). Improper TCR engagement (5) or engagement in the absence of other T cell/APC interactions leads to T cell anergy rather than activation. A successful immune response thus requires additional costimulatory interactions (second signals) between the T cell and the APC. A key T cell costimulatory signal is provided by interaction of CD28 and CTLA-4 receptors on T cells with B7 counterreceptors on APC (6). A soluble form of CTLA-4, CTLA4Ig, binds B7 molecules with high avidity and blocks T lymphocyte activation *in vitro* (7), *in vivo* immune responses to model antigens (8), organ graft rejection (9), and development of spontaneous lupus-like autoimmune disease (10). CTLA4Ig thus represents a new type of immunosuppressive drug which functions by blocking T cell costimulation (second signals) rather than TCR signals (signal one).

CD28/CTLA-4:B7 system in the pathogenesis of EAE

The study by Cross et al. (1) shows that CTLA4Ig can be used to treat murine EAE induced by immunization with central nervous system myelin. Treatment with CTLA4Ig (human CTLA-4/murine Ig) was begun the day before immunization and continued three times per week for a total of 10 doses. Clinical and histologic manifestations of EAE were inhibited, even after cessation of treatment. T cells capable of inducing EAE were not depleted from these animals, since these could induce disease in normal recipient mice after *in vitro* culture with encephalitogenic peptide. Furthermore, cultured spleen cells from CTLA4Ig-treated animals produced IL-2 in response to encephalitogenic peptide, although at lower levels than spleen cells from control animals. Thus, CTLA4Ig treatment resulted in long-term immunosuppression but did not induce T cell tolerance, in agreement with other studies (8–10).

Perrin et al. (2) reported blocking by CTLA4Ig treatment of EAE induced by T cell adoptive transfer. Addition of CTLA4Ig during *in vitro* activation of myelin basic protein-specific T cells reduced the severity of clinical disease after their transfer

in vivo. Further treatment with CTLA4Ig *in vivo* after T cell transfer was even more effective at preventing signs of disease, but *in vivo* treatment alone was ineffective. Thus, CTLA4Ig was more effective at preventing expansion of disease-causing T cells than at blocking established disease.

Instead of CTLA4Ig, which binds both B7-1 (CD80) and B7-2 (CD86), Kuchroo et al. (3) used specific mAbs for CD80 and CD86 to treat EAE. They found that anti-CD80 mAb administered at the time of disease induction reduced the severity of disease, whereas anti-CD86 mAb increased disease severity. The beneficial effects of anti-CD80 mAb were associated with recovery of predominantly Th2 clones from treated animals, which upon transfer could abrogate disease in other animals. The beneficial effects of anti-CD80 mAb were blocked by coadministration of anti-IL-4 mAb. These results suggested that interaction of CD80 and CD86 with their shared CD28 and CTLA-4 counterreceptors differentially affected generation of distinct T cell subsets, with CD86 being primarily involved in the generation of Th2 (IL-4-producing) cells which may protect against disease in this model.

Taken together, these three studies firmly establish a role for CD28/CTLA-4:B7 interactions in the pathogenesis of EAE. These interactions are crucial for the expansion of disease-inducing T cells, which is most susceptible to blocking with CTLA4Ig. Established disease is more refractory to treatment, possibly because of inability of CTLA4Ig to cross the blood-brain barrier. Protection from disease does not require tolerization of disease-inducing T cells, but can occur because of deviation of the immune response from one involving Th1 cells (IL-2- and IFN- γ -producing), which are pathogenic, to one involving Th2 cells (IL-4- and IL-10-producing), which are protective.

Therapeutic prospects

What does this mean for therapy of human MS? It is tempting to hope that CTLA4Ig might be useful for treatment of MS. However, this optimism should be tempered by the realization that other promising biological therapies for murine EAE have been described (11), but to date, none are widely used as therapies for MS. A disadvantage of previous biological therapies is that they rely on blocking signal one, and hence require knowledge of the target antigens, MHC molecules, and TCRs involved in human MS. CTLA4Ig therapy offers the advantage of being independent of these variables. Determination of the clinical usefulness of CTLA4Ig therapy for MS will require further experimentation. To be most useful, a therapy for MS should be effective on established disease; at present, CTLA4Ig has only been shown effective upon development of disease. CTLA4Ig treatment might mitigate relapses in mild MS or, if begun early enough, could reduce the severity of progressive MS. Also, CTLA4Ig treatment begun after disease initiation might still prevent disease progression by preventing activation of T cells to new central nervous system determinants (epitope spreading, reference 12). What seems certain is that these new studies (1–3) signify the beginning of a new area of investigation. We can only hope that they will culminate in new therapies for MS.

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