Finally, CTLA4Ig graduates to the clinic

Mohamed H. Sayegh


Commentary

It has long been known that T cells require two signals for full activation, but the mechanisms of how these signals function have been only recently elucidated (1). The first signal is provided by the T-cell receptor after interacting with the MHC/antigenic peptide complex. This so-called “signal one” confers antigen specificity to the immune response but alone is insufficient for full T-cell activation. Indeed, T cells receiving only signal one are rendered anergic (unresponsive to antigenic rechallenge, with inhibition of proliferation and cytokine production) in vitro (2). The second signal, or “costimulatory signal,” is provided by interactions between specific receptors on the T cell and their respective ligands on antigen-presenting cells (APCs). The CD28/CD152–B7-1/B7-2 T-cell costimulatory pathway is a unique and complex pathway that regulates T-cell activation (recently reviewed in refs. 3 and 4) (Figure 1). Interaction of CD28, constitutively expressed on T cells, with the B7 family of molecules (B7-1 and B7-2), expressed on APCs, provides a second “positive” signal that results in full T-cell activation, including cytokine production, clonal expansion, and prevention of anergy. In addition, CD28 signaling appears to be important in prevention of cell death and promotion of cell survival, presumably by upregulation of T-cell expression of bcl-xl genes (5). Once activated, T cells express another costimulatory molecule (CD152, or CTLA4) that is homologous to CD28, […]

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Once activated, T cells express another costimulatory molecule (CD152, or CTLA4) that is homologous to CD28, has a higher affinity to B7-1 and B7-2, and functions to provide a “negative” signal that inhibits cytokine production and arrests cell cycle progression (6–8). The importance of CTLA4 as a negative regulatory T-cell costimulatory molecule in the physiologic termination of T-cell responses (9) is highlighted by the observation that CTLA4 gene knockout mice develop massive lymphoproliferation and early death (10, 11). Furthermore, recent evidence suggests that CTLA4 negative signaling pathway may be required for the induction of acquired tolerance (12, 13). Indeed, it has been hypothesized that CTLA4 may function as a “master switch” for peripheral T-cell tolerance in vivo (14).

Several years before the regulatory function of CTLA4 was elucidated, Linsley et al. first described the creation of a new immunomodulatory agent that consists of the extracellular domain of the soluble CTLA4 receptor fused to the heavy chain of human IgG1 (6). Other similar agents have been subsequently described, including a murine form of CTLA4Ig, and several hundred articles have been published describing the immunomodulatory functions of CTLA4Ig in several experimental animal models of transplant.

Figure 1
Complexity of the CD28/CD152–B7-1/B7-2 T-cell costimulatory pathway. After antigenic stimulation (delivery of signal one through the T-cell receptor; not shown here), CD28, expressed on resting T cells, interacts with B7-2, and later with B7-1, both expressed on APCs. This results in transduction of a positive costimulatory signal to the T cell, culminating in cytokine production, clonal expansion, and prevention of anergy and cell death, thus promoting cell survival. Activated T cells then express CTLA4, a molecule that is highly homologous to CD28 but upon interaction with B7-1/B7-2 delivers a negative signal to the T cell, resulting in inhibition of cytokine production and cell cycle progression arrest, thus physiologically terminating immune responses. The use of biologic agents, such as anti-B7 monoclonal antibodies or CTLA4Ig, to block B7 binding to CD28 results in T-cell anergy in vitro, and in anergy, deletion, or induction of regulatory T cells in vivo (4).
rejection, autoimmune, infections, asthma, and others (recently reviewed in refs. 3 and 4). Although it is clear that CTLA4Ig, because of the higher affinity of the CTLA4 receptor to B7-1 and B7-2, acts as a competitive inhibitor of CD28–B7-1/B7-2 costimulation and induces T-cell anergy in vitro, its exact mechanism of action in vivo remains unclear. It has been suggested, however, that induction of tolerance by B7 blockade may be due to anergy (failure of clonal expansion), deletion, or induction of regulatory T cells in vivo (15–21) (Figure 1). Interestingly, a recent study from our group indicated that an intact CTLA4 negative signaling pathway is required for the immunosuppressive effects of CTLA4Ig in a mouse heart transplant model, adding further to the complexity of the B7-1/B7-2 costimulatory pathway in regulating immune responses (22).

After almost a decade of laboratory studies, CTLA4Ig finally “graduates” to the clinic. In this issue, Abrams et al. (23) present the results of a phase I clinical trial describing the immunosuppressive effects of CTLA4Ig in a mouse heart transplant model, adding further to the complexity of the B7-1/B7-2 costimulatory pathway in regulating immune responses (22).

Although CTLA4Ig can now celebrate its graduation to the clinic, there is still much to learn. We need to understand in which diseases it is most effective and whether it provides a clear advantage over standard therapies (Table 1). We need to study its safety and efficacy profile in randomized, controlled trials. We need to determine what doses and protocols we should use in patients with different diseases. We need to explore whether CTLA4Ig may be used safely and effectively with other immunosuppressive agents or agents that block other costimulatory pathways, such as the CD40/CD154 pathway (24–26). Indeed, there are experimental data in small animals to indicate that calcineurin inhibitors, such as cyclosporine, may abrogate the immunosuppressive or tolerogenic effects of B7 and/or CD154 blockade (24, 27, 28). Finally, we need to investigate and better understand the exact mechanisms of costimulatory blockade in vivo in humans with different diseases and to develop surrogate markers to monitor disease activity and response to therapy.

In a recent study, Guinan et al. (29) used CTLA4Ig to anergize alloreactive bone marrow T cells ex vivo to prevent graft-versus-host disease after haploidentical bone marrow transplantation. Such studies, and the pioneering work by Abrams et al. (23), pave the way for the development of new clinical trials that will further examine the immunomodulatory functions of novel agents that block T-cell costimulatory activation in several immune-mediated human diseases. A better understanding of the mechanisms of these novel agents may make the goal of achieving immunologic tolerance in humans elusive no more.

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Table 1
Human diseases in which CD28/B7 T-cell costimulatory blockade may have promise

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<th>Autoimmune diseases</th>
<th>Transplant rejection</th>
<th>Asthma</th>
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<tr>
<td>Psoriasis</td>
<td>Solid organs</td>
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<td>Rheumatoid arthritis</td>
<td>Cell transplants (slets, neural cells)</td>
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<td>Multiple sclerosis</td>
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