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T Cell Costimulation Blockade and Organ Transplantation: A Change of Philosophy for Transplant Immunologists?

Daniel R. Goldstein

One of the most remarkable achievements of medicine during the 20th century has been the development of solid organ transplantation as a therapy for a variety of end-stage diseases. The pioneering efforts of many investigators now allow surgeons to routinely harvest and implant organs into recipients, whose rejection response to the allograft is dampened by the administration of generalized immune suppressants. The use of these immunosuppressive agents, coupled with careful patient monitoring, has resulted in 1-y survival rates of >80–90% for most transplanted organs. Yet despite this success, many recipients of solid organ transplants suffer from chronic transplant vasculopathy, the main reason for long-term graft loss. Furthermore, currently administered immune suppressants induce a wide variety of side effects, which lead to significant patient morbidity. Such outcomes have fueled the desire of transplant immunologists to develop clinically relevant protocols that induce immune tolerance to the transplanted organ. Since Medawar (1) demonstrated that immunological tolerance of allografts was experimentally feasible, transplant biologists have sought the elusive goal of developing therapies that allow recipients to accept their allografts and avoid long-term use of generalized immune suppression. This philosophy has driven much of the experimental transplant field since the 1960s.

By the 1990s, it was appreciated that T cells were key cellular mediators of allograft rejection. We had learned that effective T cell activation required more than one signal between the T cell and the APC (2). By the mid 1990s, two signaling pathways of T cell costimulation had been discovered (3): the CD28–B7 (CD80/86) pathway of the Ig superfamily and the CD40–CD40L pathway of the TNF–TNFR family. At this time, reagents had been developed to inhibit each pathway: CTLA4-Ig, a fusion protein that inhibits CD28 activating signals on T cells, and anti-CD40L, a hamster anti-mouse mAb that impairs CD40L activation on T cells. These reagents had been employed in several experimental rodent transplant models (e.g., heterotopic heart allografts and islet allografts) and although each reagent delayed the onset of allograft rejection, long-term survival failed to be achieved (4–6).

The study by Larsen and colleagues (7), which is this issue’s Pillars of Immunology article, assessed the impact of the combination of CTLA4-Ig and anti-CD40L on allograft rejection, using experimental rodent models. The most remarkable finding of this paper was the reported phenotype. Whereas therapy with either perioperative treatment of CTLA4-Ig or anti-CD40L failed to induce long-term acceptance of fully MHC-mismatched cardiac allografts, the combination treatment led to long-term allograft survival up to 80 d post-transplant, without chronic vasculopathy. Furthermore, in a highly immunogenic skin allograft model, the authors reported that the combined perioperative treatment with CTLA4-Ig and anti-CD40L induced acceptance of allografts up to 50 d post-transplantation, whereas neither therapy alone delayed the tempo of graft rejection compared with that in controls. Donor specificity of allograft acceptance was not demonstrated in either the cardiac or the skin allograft model.

The study by Larsen and colleagues did not discern the immunological mechanisms responsible for graft acceptance mediated by costimulatory blockade. Subsequent studies by many investigators shed light by showing that T cell costimulatory blockade induces a variety of immune regulatory pathways, including enhancement of immune suppression by regulatory T cells, T cell anergy, and skewing of T cell phenotypes (8). Furthermore, the markedly delayed skin allograft survival described by Larsen and colleagues (9) was strain specific. However, the finding that mice of different genetic backgrounds resisted the allograft-prolonging effects of dual T cell costimulatory blockade initiated studies to understand this phenomenon. This led to the appreciation that memory T cells pose a formidable barrier to transplant tolerance, which may explain the difficulty in transferring experimental transplant tolerance regimens into the clinic (10).

Impressively, within 10 y of the report of Larsen and colleagues, clinical trials were conducted to investigate costimulatory blockade and organ transplantation. However, studies examining the impact of anti-CD40L failed owing to the unforeseen development of thromboembolic phenomena (11). Yet this was an important result, as it revealed that CD40L stimulation induces platelet activation in humans. As a consequence, therapeutics to target CD40 rather than CD40L are currently under investigation as alternatives to alter immune responses to transplantation. The results of CTLA4-Ig treatment...
in nonhuman primates indicated that this agent induced prolongation of allograft survival in only a minority of recipients (12). Second-generation agents that inhibited T cell activation more potently than CTLA4-Ig were consequently developed. One such medication is belatacept, which has been compared with cyclosporine in clinical trials of kidney transplant recipients who were receiving other immune suppression (e.g., mycophenolate mofetil). After 1 year post-transplantation, patients who received belatacept had better kidney function, compared with those that received cyclosporine, with a trend to less chronic vasculopathy in the belatacept-treated group (13, 14). In addition, the belatacept-treated group, compared with the cyclosporine group, exhibited less hyperlipidemia, hypertension, and post-transplant–induced diabetes mellitus. Intriguingly, the study reported by Larsen and colleagues in this Pillars of Immunology article found that cyclosporine abrogated graft acceptance mediated by CTLA4-Ig and anti-CD40L.

It is a testament to the field of transplantation that immune modulatory agents employed in experimental studies have been swiftly examined in clinical trials. Has the success of modern organ transplantation, with high patient survival rates, however, changed the philosophy of transplant immunologists? Is the elusive goal of clinical organ transplant tolerance still obtainable? Or has thinking shifted to a paradigm in which novel therapeutic strategies, such as immune modulation blockade with belatacept in renal transplantation have been adopted in order to achieve clinical end points, including the diminution of patient morbidity and mortality? It is significant to note that the pathway for the development and testing of belatacept was governed by significant investigative efforts that focused on modulation of immune responses, the development of such an agent, and the successful clinical trials that demonstrated its immunosuppressive properties.

Disclosures
The author has no financial conflicts of interest.

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