CTLA-4: Not All Costimulation Is Stimulatory
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To activate a T cell, it was widely accepted, even in the 1960s, that there had to be a “signal one,” namely, receptor recognition of a foreign Ag. That fact did not make it less exciting when, in the early 1980s, Abs to the TCR were generated and the genes that encode it identified (1). As a result, we learned about the TCR structure and the signal transduction pathways that turned “signal one” into action (2).

The story became more interesting when we realized that to activate a naive T cell, “signal one” had to be joined by “signal two.” This idea meshed well with theories put forward by Bretscher and Cohn (3), as well as previous work by Lafferty (4), on the need for “passenger leukocytes” to activate graft rejection. It was given additional substance with the demonstration in vitro that engagement of the TCR alone not only failed to induce effective T cell activation but also actually induced T cell anergy (5). Before long, we had learned that “signal two” could be provided by the engagement of CD28 on the T cell by its ligands on APCs, B7-1 (CD80), and/or B7-2 (CD86), thereby producing costimulation.

In a key observation, CTLA-4 soon was found to have significance (hence CTL activation gene number four, or CTLA-4) (8). In a subtractive cDNA library produced from activated CTLs by negative regulating molecules as well. Just how important these negative signals are was revealed when CTLA-4 knockout mice were found to die at an early age owing to massive lymphocyte infiltration involving visceral organs (12, 13).

Since the publication of these two Pillars of Immunology articles, the list of positive and negative costimulatory molecules has grown substantially, with the addition of ICOS, PD-1, and others expressed on T cells, along with their ligands on APCs (14). In addition, we have learned that many soluble factors can modulate T cell responses as well. Today, we appreciate that the regulation of T cell activation is finely tuned by an elaborate interaction of molecules that function at different times and sites. However, we could not begin to unravel this complexity until we understood that we were looking for negative as well as positive signaling molecules, making publication of these manuscripts a turning point in the story.

The discovery of CTLA-4 and the recognition that it provided a negative T cell signal resulted from outstanding basic research; however, an appealing part of the story is that this basic research has led directly to important clinical advances. CTLA4Ig (abatacept) has been approved by the U.S. Food and Drug Administration for treatment of rheumatoid arthritis, and a Food and Drug Administration advisory panel has...
recommended approval for use in transplantation of a mutated form of CTLA4 Ig (belatacept) that has higher ligand-binding affinity, especially for CD86. Furthermore, an anti–CTLA-4 Ab (ipilimumab), which blocks the inhibitory effect of CTLA-4 on the T cell response, including the antitumor T cell response, has been approved for treatment of advanced malignant melanoma. Thus, the story of CTLA-4 is one that taught us an important immunologic principle about T cells and that also went from the bench to the bedside.

In retrospect, the complexity of T cell costimulation seems obvious. What biological system can we think of that uses activating pathways and does not also have counterbalancing inactivating pathways? Lots of ideas are obvious in retrospect, however. These two Pillars of Immunology articles considered a set of observations from an entirely opposite point of view and in the process guided us toward an understanding that not all T cell costimulation is stimulatory.

Disclosures
H.A. has family members with a financial interest in Bristol-Meyers Squibb. L.A.T. has family members with a financial interest in Novartis.

References