CTLA-4: From conflict to clinic

CTLA-4 was first identified in 1991 as a second receptor for the T cell costimulation ligand B7. Uncertainties about its biological function plagued the early years after its discovery until 1995, when it was confirmed to be an inhibitor of T cell responses. CTLA-4 has since scored in the clinic as a target for antitumor therapy and as a soluble inhibitor of autoimmunity.

By the late 1980s, it was clear that naive T cells require two signals through two different receptors to spark to life. Tickling the T cell receptors (TCRs) alone with antigenic ligands makes the cells anergic. But a second signal from the B7 ligand on antigen-presenting cells (APCs) to the CD28 coreceptor goads T cells into action (1). As researchers pursued the mechanism of B7-CD28–mediated T cell costimulation, another T cell surface molecule was generating interest due to its homology with CD28.

Another T cell switch...

In 1987, researchers hunting for cytotoxic cell surface molecules isolated a cDNA from activated CD8+ T cells and called it cytotoxic T cell antigen (CTLA)-4 (2). Genetic studies provided a clue that connected CTLA-4 to T cell–inhibiting soluble CTLA-4 originally defined by Linsley and Ledbetter is a negative regulator of T cell function and proliferation.

The debate arose because in vitro assays of costimulation-dependent T cell proliferation offered multiple interpretations. T cells normally proliferate in vitro when cultured with B7-expressing APCs. But when soluble CTLA-4 was added to the mix, this proliferation was strongly inhibited (5).

One interpretation of this finding was that the soluble CTLA-4 blocked the binding of B7 to the CTLA-4 on the T cells. In this model, the T cell CTLA-4 was needed for proliferation, along with CD28. This conclusion was supported when the group showed that antibodies to CTLA-4 enhanced CD28–stimulated proliferation (6).

A second interpretation, however, was that soluble CTLA-4 might block proliferation by gumming up B7’s interaction with CD28. And the CTLA-4 antibody might enhance proliferation not because it stimulates CTLA-4’s proliferative power, but because it blocks CTLA-4’s negative signal.

This alternative role for CTLA-4 was supported by the work of James Allison and his team at the University of California (Berkeley, CA), which was also published in the JEM (7). This group studied cross-talk among TCR, CD28, and CTLA-4 by cross-linking these receptors. T cells proliferated when the TCR was linked to CD28, but not with CTLA-4.

REFERENCES