

# Checkpoint blockade in tumor immunotherapy

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## Abstract

While there are exciting examples of success clinical strategies to mobilize the immune system to attack cancer cells, overall the results have not met the promise hoped for in tumor immunotherapy. One reason for less than optimal results is that until recently there was insufficient knowledge of the complex regulatory pathways employed by the immune system to avoid autoimmunity, and therefore insufficient attention has been paid to strategies for avoiding the negative impact of these mechanisms on the effectiveness of immunotherapies. It has become quite clear over the past several years that while T-cell responses are initiated by engagement of the antigen receptor, they are shaped by additional signals that act in concert to shape the magnitude, quality, and location of the response to maximize target destruction minimize harm to normal tissues. The prototype of these regulatory circuits was the CD28/CTLA-4 axis, which regulates early stages of the T-cell response. CD28 provides critical costimulatory signals necessary for activation of naive T cells, while CTLA-4 limits proliferation of the responding T cells. Both CD28 and CTLA-4 bind B7-1 and B7-2 in a complex and dynamic way that can shape the early T-cell response.

Our work has provided some insight into the molecular mechanisms whereby CTLA-4 inhibits T-cell proliferation in a cell intrinsic manner and can shape the emerging immune response by differential inhibition of individual clones based on the strength of TCR signaling. We have also shown that blockade of CTLA-4 can greatly enhance anti-tumor responses in a number of experimental tumors in mice. As a single agent anti-CTLA-4 can induce the rejection of tumors with inherently high immunogenicity, and in combination with appropriate vaccines can induce rejection of poorly immunogenic tumors. We have recently found that anti-CTLA-4 does not deplete nor block the activity of regulatory T cells, but rather by enhancing mobilization of effector T cells, especially CD8 cells. Thus, CTLA-4 and Treg cells represent two distinct means of limiting anti-tumor responses, and thus can be used together to obtain synergy. We have also shown that CTLA-4 blockade can synergize with a variety of conventional therapies, including chemotherapy and local radiation. Medarex, Inc. has developed a fully human antibody to CTLA-4, MDX-010. This has been shown by the Dranoff and Rosenberg groups to have activity in melanoma and ovarian cancer. MDX-010 is now in a pivotal Phase III clinical trial in melanoma.

In the last few years, the number of B7 family members has risen to seven. These fall into four groups, and have distinct expression patterns and immunological functions. We recently identified B7x, a molecule that appears to expressed in epithelial tissues, rather than by cells in the immune system. By interacting with an as yet unidentified receptor, B7x appears to be capable of inhibiting effector T cell function, including cytotoxicity. This suggests that B7x may play a role in protecting tissues against damage by aberrantly activated auto-reactive T cells. It is of considerable interest that many mouse and human

tumor cells express B7x. We are currently seeking to determine whether B7x might represent another checkpoint whose blockade would be of value in tumor immunotherapy.