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Meeting Abstract

Checkpoint blockade in tumor immunotherapy

James P. Allison

Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Abstract

While there are exciting examples of successful 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 and 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 naïve T cells, while CTLA-4 limits proliferation of the responding T cells. Over the past several years our work has provided some insight into the molecular mechanisms whereby CTLA-4 inhibits T-cell proliferation, and how blockade of this inhibition can enhance anti-tumor responses 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 shown that the anti-tumor effects of anti-CTLA-4 are not due to depletion or interference with the activity of regulatory T cells, but rather by enhancing mobilization of effector T cells in a cell autonomous manner.

CTLA-4 blockade is being developed as a cancer therapeutic by Medarex and Bristol Meyers Squibb and is currently in a large number of Phase II trials in a variety of cancers, and in pivotal Phase III trials in melanoma. To date, objective responses have been observed in melanoma, as well as renal, ovarian, and prostate cancer. While there have been significant adverse immunological breakthrough events associated with frequent dosing, recent studies by Hodi and Dranoff suggest that objective responses can be achieved in the absence of severe adverse events.

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 be 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 cytolysis. 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.