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Meeting Abstract

Immune checkpoint blockade in tumor therapy: new mechanisms and strategies

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Abstract

One reason for less than optimal success of clinical strategies to mobilize the immune system to attack cancer cells is that the immune system has multiple cell intrinsic and extrinsic regulatory circuits that serve to limit autoimmunity but can also frustrate anti-tumor responses. The prototype of cell intrinsic circuits is 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. CTLA-4 blockade is being developed as a cancer therapeutic by Medarex and Bristol-Myers Squibb and is currently in a large number of trials in a variety of cancers. To date, objective responses have been observed in many melanoma patients, and anecdotal reports have been obtained in renal, ovarian, and prostate cancer.

FoxP3+ regulatory T cells (Treg) provide a cell extrinsic mechanism for limiting effector T-cell responses, and are associated with poor anti-tumor responses. Data will be presented concerning the interaction of CTLA-4 blockade and Treg cells in tumor rejection in experimental mouse models. We will also present data suggesting that depletion of Treg after establishment of tumors may not be effective in enhancing anti-tumor responses elicited by anti-CTLA-4 and a GM-CSF expressing tumor cell vaccine, as well as a means by which to overcome Treg induced refractoriness.

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. The two newest members, B7-H3 and B7x, bind an as yet unidentified receptor and appear to be capable of inhibiting effector T-cell function. It is thus of considerable interest that many mouse and human tumor cells express B7x. We have recently found that high levels of expression of these inhibitory B7 molecules on human prostate cancer cells correlates with a higher rate of clinical failure. These might represent another checkpoint whose blockade would be of value in tumor immunotherapy.