Cancer Immunity, Vol. 5 Suppl. 1, p. 9 (6 April 2005)

CANCER
IMMUNITY
Meeting Abstract

Blockade of T cell inhibitory signals: a new paradigm in tumor immunotherapy?

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It has become clear over the past several years that many receptor/counterreceptor pathways orchestrate the elaboration of T-cell responses to ensure that the magnitude, type, and location of the responses are appropriate to deal with the problem (virus, bacteria, tumor) without causing autoimmunity. The prototype of these co-stimulatory circuits was CD28, which upon engaging its ligands B7-1 and B7-2 provides a critical signal that allows the proliferation and differentiation of naive T cells following antigen receptor engagement. CTLA-4, which also binds B7-1/2, has opposing effects and is essential for down-regulation of T-cell responses: ctla-4$^{-/-}$ mice suffer from a lethal lymphoproliferative response that is initiated by uncontrolled T-cell expansion. Thus, CD28 and CTLA-4 play critical roles in regulating early stages of the T-cell response. There are now at least 7 known members of the extended B7 family, which can be divided into four groups based on phylogeny and receptor usage. These include both stimulatory and inhibitory molecules that may have overlapping functions, but play distinct roles in shaping T-cell responses.

For the past several years my lab has been studying the biological roles of CD28 and CTLA-4. Our work suggests that there is a dynamic integration of TCR, CD28, and CTLA-4 signals during T-cell activation. CTLA-4 seems to attenuate T-cell responses, inhibiting strong T-cell signals more than weak ones. We have also found that CTLA-4 can regulate both the occurrence and severity of experimental autoimmune disease in mice. This led us to determine whether blockade of the inhibitory signals mediated by CLTA-4 might be effective in enhancing T-cell responses to tumors. Our work has shown that CTLA-4 blockade as a single agent can result in rejection and long-lived immunity to strongly immunogenic tumors, and in combination with appropriate vaccines can result in rejection and immunity to even poorly immunogenic tumors. These effects can be attributed to the enhancement of CD8 cytotoxic T-cell responses. We have also shown that prior depletion of CD25+ CD4+ Treg cells can enhance the effectiveness of CTLA-4 blockade, suggesting that CTLA-4 and Treg cells provide independent regulation of T-cell responses.

Medarex, Inc., has developed a fully human monoclonal antibody to human CTLA-4 that has shown anti-tumor activity in Phase I/II and II trials. The results of trials in melanoma and ovarian cancer patients previously vaccinated with tumor cells expressing GM-CSF (Steve Hodi and Glenn Dranoff) and in melanoma patients in combination with gp100 peptides (Steven Rosenberg, NCI) are particularly exciting and will be discussed.

The clinical data seem to confirm the potential of blockade of the inhibitory signals of CTLA-4 in the immunotherapy of human cancer. There are, of course, other inhibitory circuits known. Last year we identified a new B7 family member, B7x. Unlike B7-1 and -2, whose expression is limited to professional antigen presenting cells (dendritic cells, etc.), B7x is expressed in a variety of epithelial tissues. Our preliminary data indicate that B7x can also inhibit T-cell responses, and we have suggested that it may play a role in the prevention or amelioration of autoimmunity. Interestingly, it is also expressed on tumor cells. Thus B7x may offer an additional target for blockade of inhibitory signals that play a role in late stages of T-cell responses that will complement CTLA-4 blockade in tumor immunotherapy.