

Immune Checkpoint Blockade in Cancer Therapy

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While there are exciting examples of successful clinical strategies to mobilize the immune system to attack cancer cells, overall the results have been disappointing. One reason for less than optimal results is that until recently insufficient attention has been paid to multiple inhibitory mechanisms that serve to shape the immune response and minimize harm to normal tissues and can frustrate generation of effective anti-tumor responses. The prototype of these inhibitory pathways is CTLA-4, which upon engaging its ligands B7-1 and B7-2 limits T cell proliferation. We have shown that blockade of CTLA-4 can greatly enhance anti-tumor responses in a number of experimental tumors in mice. Recent studies of the mechanisms involved suggest that CTLA-4 blockade enhances anti-tumor responses by blocking a cell intrinsic inhibitory pathway in effector T cell, thus rendering them resistant to inhibition by Treg cells.

Anti-CTLA-4 (MDX-010, Ipilimumab) is being co-developed by Medarex, Inc. and Bristol Meyers Squibb. The results of clinical trials in over 1700 patients have demonstrated objective, durable responses with manageable in a high fraction of melanoma, renal prostate, ovarian, and pancreatic cancer.

More recently we and others have shown that there are additional B7 family members that limit T cell responses at distinct stages, and that at least three of these are also expressed by tumor cells. Thus the extended B7 family offers a number of targets for immune checkpoint blockade in the treatment of cancer. Finally, recent studies have shown that tumors multiple coding mutations which should result in generation of multiple neoantigens. I will discuss the implications for this to immunologically based as well as conventional cancer therapy.

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