Cancer Immunotherapy Scores Again

The use of antibodies to block pathways inhibiting the endogenous immune response to cancer, known as checkpoint blockade therapy, has stirred up a great deal of excitement among scientists, physicians, and patients alike. Clinical trials evaluating the safety and efficacy of antibodies that block the T cell inhibitory molecules CTLA-4 and PD-1 have reported success in treating subsets of patients with metastatic melanoma and renal cell carcinoma. Antibodies targeting these pathways have been approved for clinical use, and patients once unresponsive to any sort of conventional treatment have shown good and stable clinical responses-some remaining free of disease progression for many years. What types of cancer can benefit of immunotherapy and the factors that determine whether a patient will respond to treatment are now pressing questions. In the past month, seven new studies have begun to point toward the answers.



Checkpoint blockade therapy targets inhibitory pathways that keep T cells (shown in blue) from responding to tumor cells (represented in yellow). Upon release of such inhibition, the endogenous immune response can limit cancer growth (image from iStockphoto).

The first three reports expand the list of cancers that can be treated with checkpoint blockade therapy. Herbst et al. find that treatment with MPDL3280A, a monoclonal antibody specific for the PD-1 ligand (PD-L1), promotes therapeutic responses in patients with advanced non-small-cell lung cancer, renal cell cancer, and melanoma (Herbst et al. 2014), while Powles et al. show that the same antibody can be used to treat urothelial bladder cancer (Powles et al. 2014). Both groups report durable responses and low toxicity of the treatment, which is particularly important as high-grade adverse effects have limited the use of immunotherapy for cancer until now. In addition, Robert et al. provide evidence that patients with metastatic melanoma without the BRAF mutation present better responses

to immunotherapy with Nivolumab, a monoclonal antibody that blocks PD-1, than to conventional chemotherapy (Robert et al. 2014).

Thus, the list of cancers that can be targeted with immunotherapy is growing. However, only a fraction of patients treated will respond. What parameters predict a good response? Identifying biomarkers has been a long-sought goal in immunotherapy. The expression of PD-L1 in cancer cells is an obvious candidate, as it can directly turn off the immune response by inhibiting the activity of cytotoxic T cells infiltrating the tumor, but PD-L1 expression in tumor cells has had little predictive power. Analyzing samples from patients with melanoma treated with another PD-1specific antibody, Pembrolizumab, Tumeh et al. establish a set of conditions that correlates with good response to therapy (Tumeh et al. 2014). These include the presence of cytotoxic T cells in the tumor, the expression of PD-L1 and PD-1 in immune cells in the tumor margin, and less complexity (in terms of antigen receptors) in the T cell population in the tumor. In support of these findings, Robert et al. and Herbst et al. also observe that PD-L1 expression in immune cells is a good biomarker of response to immunotherapy.

The finding that complexity of the T cell population in the tumor infiltrate can predict good response to checkpoint blockade therapy highlights the importance of understanding which antigens in the tumor can elicit an effective antitumor immune response. Previous studies suggested that tumors with a high load of somatic mutations are more likely to respond to immunotherapy, as in theory these tumors would have a higher diversity of neoantigens that can trigger an immune response when the CTLA-4/PD-1 inhibition is bypassed. To test this hypothesis, Snyder et al. carry out whole-exome sequencing of tumors from melanoma patients under therapy with CTLA4-specific antibodies Ipilimumab and Pembrolizumab (Snyder et al. 2014). While the data indeed show that high load of mutations correlate with responsiveness to therapy in many cases, surprisingly some tumors with a high load of somatic mutations fail to respond to checkpoint blockade. Computational analysis allows them to identify neoepitopes, antigens created by somatic mutations eliciting a T cell response, that are shared by the patients that respond to immunotherapy. It is thus possible that the nature of the mutations present in the tumor, not just the quantity, is a determining factor in responsiveness to therapy.

Identifying which mutations give rise to neoantigens that are functionally important for triggering an antitumor response has been particularly challenging. Yadav et al. attempt to facilitate the discovery of new mutant peptides by characterizing their general properties (Yadav et al. 2014). By carrying out whole-exome sequencing of two mouse tumor cell lines and comparing the data with the reference mouse exome sequences, they are able to predict candidate neoantigens in the tumor. Only a fraction of the neoantigens is predicted to bind to MHC (major histocompatibility complex) molecules, which present antigens to T cells. An even smaller fraction binds to the MHC, as determined by mass spectrometry. The predicted mutant peptides that are immunogenic in vivo have solvent-exposed mutations, which are accessible to recognition by the T cell antigen receptor, as a common feature. Interestingly, these neoantigens are derived from proteins that are unlikely to contribute to tumorigenesis, confirming that passenger mutations play a significant role in shaping the immunogenicity of cancer cells. This platform could potentially be used to identify immunogenic antigens in any cancer cell type.

It is not entirely clear why the number of functionally relevant immunogenic antigens in the tumor is so low. One possibility is that mutations that give rise to highly immunogenic neoantigens are selected against during tumor growth. Indeed, Gubin et al. report that in a mouse model of sarcoma, resistance to immune-mediated rejection arises from loss of a major immunogenic antigen in the tumor cells (Gubin et al. 2014). The good news is that checkpoint blockade therapy can rescue the endogenous immune response, despite the loss of that antigen. The endogenous T cells infiltrating the tumor, once released from the inhibitory effect of CTLA-4 and PD-1, recognize neoantigens originating from two other mutations in the Alg8 and Lama4 genes and are thus able to reject the tumor. Importantly, vaccination of the tumor-bearing mice with these antigens also elicits tumor rejection, providing evidence that cancer vaccines can be efficacious, if the right combination of antigen and adjuvant is determined.

It is tempting to ask whether immunotherapy is evolving to become standard care for cancer patients, beyond those with advanced disease. Will it prove to be more efficacious than standard chemotherapy in cancers other than BRAF-negative melanoma? Is there a place for therapeutic regimens that combine checkpoint blockade with other strategies? While we are nowhere near having all the answers, these studies provide a wealth of data supporting the idea that somatic mutations in cancer cells are an important target of endogenous anti-tumor responses. Checkpoint blockade is effective at rescuing the anti-tumor effect and it is plausible that understanding the dynamics of the response to this therapy will also help the development of alternative and personalized approaches to treat cancer.

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