Editors' Viewpoint—Response

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Exciting clinical studies of antibody therapies that target so-called immune checkpoint molecules like CTLA4 and PD1 have re-fired longstanding hopes in cancer immunotherapy. Recently, PD1 blockade has shown unexpected efficacy in the setting of non-small cell lung cancer (NSCLC), and its study in combination therapy is now proceeding rapidly with due caution. Currently, not all tumors respond to immune checkpoint blockade, so not all patients can benefit from treatment. Thus, determining the criteria for patient selection is a top priority. Preclinical studies may be able to offer insights into this crucial clinical issue. In the Letter to the Editor and its Reply (1, 2), the authors confront an extremely timely and important question: what conditions in the tumor are required for immune checkpoint blockades to be most efficacious? In particular, they discuss the likelihood that efficacious PD-1 blockade may require the preexistence of T cells infiltrating the tumor, a condition that is not universal but can be determined readily by biopsy staining.

Understanding the spatial nature of PD1 signaling may help address this question. PD1 as expressed on immune cells must encounter its ligands PDL1 or PDL2 to prevent immune cell activation. Notably, PDL1 is expressed on tumor cells, where its expression is controlled by oncogenic activity, IFN-γ release by nearby T cells, or both. If PDL1 expression is induced by oncogenes, tumors at very early times may arise in a "cloaked" form that licenses an important route of immune escape, as tumor antigens may be essentially inert to infiltrating lymphocytes. In such settings, immunogenicity might be "unveiled" by blocking PDL1–PD1 interactions that occur in the tumor microenvironment and strengthened considerably by concomitant vaccination (if tumor antigens are known) or by delivering other modalities (if tumors antigens are not known), such as T-cell agonist antibodies, targeted drugs, or traditional cytotoxic drugs that when combined may engender a powerful immunochemothrapy. Alternately, if PDL1 expression in tumor cells is driven by IFN-γ that is released by nearby T cells, the tumor microenvironment may persist in an immunosuppressed state where PD1 blockade fails to provoke T-cell attack, based on the ability of IFN-γ to activate indoleamine 2,3-dioxygenase (IDO) in both tumor cells and antigen-presenting cells. Thus, even when T cells are present in the tumor, PD1 or PDL1 antibodies may be impotent without coordinate delivery of IDO inhibitors or other modalities to activate local T cells, including (perhaps even better) infusions of newly generated T lymphocytes at the time of PDL1 blockade. With the rapid pace of clinical and preclinical studies in this area, ongoing work to define the best strategies to use PD1 blockade will no doubt continue to be exciting.

Disclosure of Potential Conflicts of Interest

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