Editorial

Targetting the PD-L1/PD-1 axis holds promise in the treatment of malignancy

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Tumor cells create an immunologic milieu characterized by the disruption of effective antigen presentation, loss of effector cell function and complexity, and upregulation of pathways that promote tolerance and T cell anergy (1,2). A critical element of tumor mediated immunosuppression is the presence of the negative checkpoint molecules CTLA-4 and PDL-1/PD-1 that inhibit immune activation and the expansion of antigen specific T cells (3). In health, these pathways represent an essential stopgap against hyperactivation and the generation of autoimmunity. In the setting of malignancy, upregulation results in an exhausted T cell phenotype that promotes disease growth, resistance to immunotherapy, and disruption of CTL mediated killing of tumor targets (4). Ipilumumab is a clinical grade antibody targeting CTLA-4 that was recently approved as therapy for melanoma (5,6). As a featured theme in the *New England Journal of Medicine*, Brahmer (7) *et al.* and Topolian (8) *et al.* present studies that examine the efficacy of antibody blockade of the PD-1/PDL-1 pathway.

The PD-1/PD-L pathway is an important inhibitory pathway that regulates T cell activation and mediates T cell tolerance. The programmed death (PD)-1 receptor is expressed on T cells, B cells, monocytes, and NKT cells following activation. PD-L1 (B7-H1) and PD-L2 (B7-DC), the two ligands for PD-1, are expressed on antigen presenting cells, including dendritic cells (DCs) and macrophages (4). In addition, PD-L1 is expressed on non-hematopoietic cells including pancreatic islet cells, endothelial cells, and epithelial cells, playing a role in protecting tissue from immune mediated injury (3). Binding of PD-1 to PD-L1 or PD-L2 inhibits T cell proliferation, decreases secretion of Th1 cytokines, and results in T cell apoptosis.

The critical role that PD-1 plays in blunting activated T cell responses was first demonstrated by the autoimmune phenotypes that develop in PD1 knockout mice (4,9), including cardiomyopathy, diabetes, glomerulonephritis, and arthritis (10-12). It has been shown in models of experimental autoimmune encephalitis that PD-1 blockade exacerbates disease and increases inflammatory infiltrates in the CNS (13,14). In addition, PD-L1 expression on non-hematopoeitic cells, including renal tubular epithelial cells, inhibits immune mediated tissue damage (3,15-17), indicating that the PD-1/PD-L1 pathway is a critical mediator of tissue tolerance. The PD-1/PD-L1 pathway plays an important role in modulating immune response to infection. T cell expression of PD-1 is upregulated during chronic viral infection, resulting in an "exhausted" T cell phenotype. The lymphocytic choriomeningitis virus (LCMV) model was the first to demonstrate the impact of the PD-1/PD-L1 pathway in limiting clearance of virally infected cells (3,18). Barber *et al.* demonstrate that PD-1 expression is upregulated in mice chronically infected with LCMV, and that PD-1 blockade enhanced the clearance of virus (18).

There has been increasing interest in exploring the contribution of the PD-1/PD-L1 pathway to tumor evasion of host immunity. Tumor cells secrete inhibitory cytokines, including TGF-B and IL-10, creating an immunosuppressive milieu and limiting effective anti-tumor immunity. Recent studies suggest that tumor expression of PD-L1 may play an important role in contributing to tumor-mediated immunosuppression. A variety of tumors have been shown to express PD-L1, including renal, melanoma, stomach, breast, and lung carcinoma (19-30). In addition, PD-LI expression on tumor cells has been shown to correlate with

a poor prognosis in a variety of malignancies (19-24,26). In a murine model, it was shown that transgenic expression of PD-L1 rendered a mastocytoma cell line less susceptible to CTL mediated killing and enhanced their tumorigenicity *in vivo*. These effects were reversed in the presence of PD-1 blockade (31). In a melanoma model, PD-1 expression on tumor infiltrating lymphocytes (TIL) was shown to be significantly higher than on T cell isolated from the peripheral blood or normal tissue of the same individuals (32). In this study, PD1+ TIL demonstrated impaired effector function, as measured by interferon gamma secretion, suggesting that PD-1 expression on TILs limits their capacity to mount an effective immune response. Similarly, Blank *et al.* demonstrated higher levels of PD-1 expression on TIL than on peripheral blood lymphocytes isolated from melanoma patients (12). In addition, PD-1 blockade increased interferon gamma secretion by T cell populations in response to stimulation by antigen loaded dendritic cells. In a muring model of CML, leukemia specific cytotoxic T lymphocytes (CTLs) were shown to express high levels of PD-1, and were functionally exhausted. PD-L1 blockade was shown to restore the function of CML specific CTLs, and prolong survival (32). The effect of PD-1 blockade on enhancing activated anti-tumor T cell responses makes it an ideal therapeutic target to study in the setting of malignancy.

The reports published in the *New England Journal of Medicine* by Brahmer *et al.* (7) and Topalian *et al.* (8), are the first to demonstrate the potency and promise of blocking the PD1/PD-L1 pathway in the clinical oncology setting. Brahmer *et al.* report on a multicenter phase 1 clinical trial evaluating escalating doses of anti-PD-L1 antibody administered intravenously to patients with advanced malignancies. 207 patients were treated on the study, for a median duration of 12 weeks. Treatment was well tolerated, with treatment related grade 3-4 adverse events occurring in only 9% of patients. The most common treatment related adverse events were fatigue, infusion reactions, diarrhea, arthralgia, rash, nausea, pruritis, and headache. Of note, 39% of patients experienced toxicities thought to be potentially immune mediated including rash, hypothyroidism, hepatitis, and oe case of sarcoidosis, endopthalmitis, diabetes milletus, and myasthenia gravis. These events were predominantly of mild intensity although 9 patients required transient administration of glucocorticoids. Response rates were observed in 9 out of 52 patients with melanoma, 5 of 49 patients with non-small cell lung cancer, 2 of 17 patients with renal cancer, and 1 of 17 patients with ovarian cancer. In addition, prolonged disease stabilization (>24 weeks) was observed in 12-41% of patients with these advanced malignancies.

In the same issue of the New England Journal of Medicine, Topalian *et al.* (8) report the results of a phase 1 multicenter study in which 296 patients with advanced melanoma, non-small cell lung cancer, prostate cancer, or colon cancer were treated with escalating doses of anti-PD1 antibody. 14% of patients developed grade 3-4 adverse events related to therapy. Common treatment related events include fatigue, rash, diarrhea, pruruutis, decreased appetite and nausea. Toxicities with a potential immune mechanism included pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroditis. Of particular interest was the presence of pneumonitis occurred in 9 patients that were predominantly responsive to withholding of the drug and/or institution of glucocorticoids, while 3 patients (1%) succumbed as a result of pneumonitis. Responses were seen in 26 of 94 patients with melanoma, 14 of 76 patients with non-small cell lung cancer, 9 of 33 patients with renal cell cancer. Importantly, responses were durable, with 20 of 31 responses lasting a year or greater in patients with at least one year of follow up. Notably, 9 of 25 patients with PD-L1 positive tumors, as asssessed by immunohistochemistical analysis of pre-treatment tumor samples, had disease response. In contrast, none of 17 patients with PD-L1 negative tumors had responsive disease.

The clinical response rates observed in both the Brahmer (7) and Topalian (8) studies validate the role that the PD1-PD-L1 pathway plays in mediating tumor tolerance, and demonstrates the therapeutic potency of targeting this pathway. Several findings in the studies are of particular note. Responses were observed in non-small cell lung cancer patients, a disease that was classically not thought to be sensitive to immune based treatment. This finding illustrates the potency of immune manipulation, and suggests that immunotherapy may have a role in the treatment of a wide range of tumor types. The durability of responses in both studies was striking. Responses lasting greater than a year in patients with advanced solid tumors are rarely observed in response to chemotherapy or targeted therapy. The potential for inducing durable immune responses that result in long term disease control has the ability to dramatically alter the treatment and natural history of malignancy. Assessing the whether memory T cell responses are induced, determining the optimal treatment duration, and evaluating whether clinical responses are long-lasting, will require further study and longer follow

up. Understanding tumor and host factors that contribute to response to immune based therapy is an area worthy of further study. In the study by Topalian *et al.*, response to anti-PD1 antibody was associated with tumor expression of PD-L1. Studies to assess tumor markers and host factors that will predict response to treatment are critical to selecting patients who will benefit from immune based therapy. Therapy was generally well tolerated although some significant immune mediated toxicities were observed. Pneumonitis was observed in a small subset of patients patients treated with the PD-1 antibody while inflammatory colitis which has been seen with ipilumumab therapy, was not commonly seen.

The PD-1/PD-L1 pathway is a critical mechanism by which tumors evade immune attack. The clinical studies by Brahmer *et al.* (7) and Topalian *et al.* (8) illustrate the clinical potency of blocking this pathway in the setting of advanced malignancy. The PD-1/PD-L1 pathway has also been shown to be upregulated in response to stimulation with tumor vaccines (33), and studies to evaluate the potential synerygy between tumor vaccines and PD-1 blockade are underway. For example, PD-1 blockade enhances response to the DC/tumor fusion vaccine characterized by polarization of T cells towards a Th1 phenotype, decreased levels of regulatory T cells, and increased CTL mediated killing by fusion stimulated T cells (33). A clinical trial to examining the efficacy of PD-1 blockade in the context of DC/tumor fusion vaccination has been initiated in patients with multiple myeloma undergoing immunotherapy following autologous transplantation. The use of PD-1/PD-L1 blockade alone, and in combination with tumor vaccines, chemotherapy, or targeted therapy, has the potential to dramatically improve outcomes for patients with malignancy. These two clinical trials highlight the therapeutic potency of immune based therapy, and demonstrate that immunotherapy has the potential to alter the treatment paradigm improve outcomes for patients with malignancy.

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