Rehabilitation for Oncogene Addiction: Role of Immunity in Cellular Sobriety

David L. Bajor and Robert H. Vonderheide

Clinical responses to oncogene inhibitors result from direct effects on cell-intrinsic growth signals and disruption of downstream messages that produce a protumor immunosuppressive microenvironment. Combining oncogene-targeted and immunomodulatory therapies may result in synergistic effects, producing increased response rates and longer periods of tumor control than can be achieved with either class alone. Clin Cancer Res; 18(5); 1192–4. ©2012 AACR.

In this issue of Clinical Cancer Research, Wilmott and colleagues (1) report that the administration of selective BRAF inhibitors in patients with metastatic melanoma results in early infiltration of CD4+ and CD8+ T lymphocytes. The magnitude of CD8+ lymphocyte infiltration correlates with tumor shrinkage, but at the time of tumor progression the immune infiltrate is most often lost. These data are important because they support the hypothesis that immune activation plays a role in the antitumor activity of targeting the BRAF oncogene in patients.

Metastatic melanoma is a notoriously deadly malignancy, and until recently there were no therapies capable of extending patient survival. In 2011, 2 agents with different mechanisms of action were approved in the United States for use in melanoma, based on evidence that they each prolong overall survival in selected populations. Ipilimumab, a fully human monoclonal antibody, antagonizes cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) on T lymphocytes, thereby silencing a negative regulator of T-cell response. CTLA-4 blockade allows T-cell activation and leads to immune-mediated destruction of melanoma cells. When used as a single agent, the objective response rate for ipilimumab is <15%, but for a minority of patients, clinical response can be sustained long-term (2). The selective BRAF inhibitor vemurafenib was also approved last year, and the drug has emerged as a highly active and well-tolerated treatment that improves survival for patients whose tumors harbor a BRAF mutation. Although cancer cells possess multiple genetic abnormalities, single mutations, such as the constitutively active BRAF^{V600E} in melanoma, can be so crucial to growth and survival that their blockade results in tumor cell death, a phenomenon termed “oncogene addiction” (3). Responses to selective BRAF inhibition are often dramatic in terms of reduction of overall tumor burden; unfortunately, however, these transient responses do not typically lead to long-term disease control (4). The fundamental principles of clinical oncology suggest the utility of testing combinations of treatments that exhibit single-agent activity but have different mechanisms of action and non-overlapping toxicities. By showing that BRAF inhibition is associated with an influx of T lymphocytes, Wilmott and colleagues (1) further fuel the notion that combining targeted therapy and immunotherapy may be able to yield synergistic responses in melanoma (5).

The presence of intratumoral T cells is a positive prognostic biomarker in primary melanoma. This may also be the case in metastatic melanoma. Wilmott and colleagues (1) now report that selective BRAF inhibition in patients with metastatic melanoma results in a marked increase in tumor-infiltrating T cells. Although they are not addressed specifically in this study, at least 2 mechanisms could explain this immunological effect. First, tumor cell death in the wake of a therapy that is not itself overly immunotoxic or immunosuppressive may produce a "vaccine effect" insofar as tumor antigens that are shed after therapy may be processed and presented by host antigen-presenting cells (APC) to drive tumor-specific adaptive immune responses. Second, the influx of T cells during treatment may also occur as a direct response to changes in the tumor microenvironment caused by BRAF inhibition. For example, the production of the immunomodulatory cytokines interleukin 10 (IL-10), VEGF, and IL-6 by melanoma cell lines is controlled by the mitogen-activated protein kinase (MAPK) pathway and decreased in vitro by treatment with mitogen-activated protein–extracellular signal-regulated kinase (MEK) inhibition or BRAF^{V600E} RNA interference (6). Thus, treatment with selective BRAF inhibitors in vivo may alter this immunosuppressive cytokine milieu and permit enhanced infiltration of T cells. In addition, dying tumor cells may also release ATP (7) and other cellular contents that act as strong chemoattractants for T cells that are not otherwise present in...
the tumor microenvironment. In this case, T cells may be actively recruited to regressing melanoma, as clearly shown in this study, although it remains to be shown that tumor-infiltrating T cells following BRAF inhibition are tumor specific. The key point, however, is that vemurafenib does not appear to be immunosuppressive, and in fact may promote T-cell responses by enhancing antigen presentation by tumor cells (8, 9).

Other immunological effects of BRAF inhibition on the tumor microenvironment may be highly nuanced and intertwined. For example, macrophages are generally considered to be tumor-promoting leukocytes through their roles in angiogenesis, metastasis, and production of a T-cell–suppressive microenvironment. Melanoma cell line growth in the mouse is enhanced by tumor-associated macrophages (10), and the production of macrophage chemoattractant protein 1, the major chemokine for macrophages, is upregulated in part by the MAPK pathway (11), which suggests that its production may be decreased by selective BRAF inhibition. Understanding the role of tumor-associated macrophages in patients receiving selective BRAF inhibitors would be a valuable next step in elucidating the interplay between oncogene inhibition and the innate immune system.

The findings from Wilmott and colleagues fit nicely with the increasing body of data regarding the importance of the immune system in eradicating tumors following oncogene inactivation. Using a mouse model of T-cell acute lymphoblastic lymphoma (T-ALL) driven by the c-MYC oncogene, Rakhra and colleagues (12) showed the necessity of the immune system for eliminating tumors completely. In their study, T-ALL tumors driven by the tetracycline-sensitive c-MYC oncogene were implanted into wild-type mice or mice with various forms of lymphocyte deficiency. Tumor growth was monitored following oncogene inactivation, which was accomplished experimentally by doxycycline administration. Partial regression was seen upon c-MYC inactivation in all of the animals; however, in the absence of CD4+ T cells, tumors failed to regress completely and began to grow despite continued oncogene inactivation. The host immune system was shown to produce antitumor cytokines in the presence of c-MYC inactivation, which were necessary mediators of tumor elimination. Similar immune-mediated responses were also seen in a BCR-ABL oncogene–induced model of pro-B-cell acute lymphoblastic leukemia.

To the extent that such murine models show that an immune response is important or even required for optimal tumor regression following oncogene inactivation, strategies to add potent immunomodulatory drugs (e.g., anti-CTLA-4 mAb) to oncogene-targeted cancer therapies have merit. This is particularly true in melanoma, for which ipilimumab is clinically approved. Indeed, a phase I/II trial combining ipilimumab and vemurafenib recently began accrual. In one proposed mechanism of action (Fig. 1), selective BRAF inhibition blocks the activated MAPK pathway, resulting in tumor cell death by targeting
oncogene-addicted cells. The concomitant release of tumor-specific antigens can then be picked up by APCs, which present tumor antigen to T cells and produce cytokines and chemokines that are capable of accelerating the antitumor immune response. BRAF inactivation may also decrease production of immunosuppressive cytokines that regulate the tumor microenvironment, further driving intratumoral infiltration of CD4+ and CD8+ T cells. Ultimately, and unfortunately uncommonly, treatment resistance emerges, leading to recapitulation of an immunosuppressive microenvironment, immunological escape, and clinical relapse. Treatments such as ipilimumab may be able to fuel a more robust immunological response and potentially clinical responses as well, even perhaps preserving clinical activity in the setting of resistance to BRAF inactivation. Several immunomodulatory agents with different mechanisms of action and more muted toxicity profiles than ipilimumab are currently showing promise in clinical investigations of melanoma and other malignant diseases (Fig. 1), and many of these can be seen as potential partners with oncogene-targeted therapy. With the increasing development of targeted therapies for multiple types of tumors, the combination of these agents with immune therapy represents an exciting clinical frontier with a sound scientific rationale.

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