We thank Binder and Schreiber for their comments and suggestions on our article “Dual Blockade of PD-1 and CTLA-4 Combined with Tumor Vaccine Effectively Restores T-Cell Rejection Function in Tumors” published recently in Cancer Research (1). In this article, we demonstrated a parallel regulation of T effector cells (Teff) and regulatory T cells (Treg) by both PD-1 and CTLA-4 in subcutaneous solid tumor models, CT26 colon carcinoma, and ID8-VEGF ovarian carcinoma. Upon in vivo blockade of PD-1 and CTLA-4 on both Teffs and Tregs combined with whole tumor vaccination, we observed regression of tumors in mice. The authors Binder and Schreiber viewed this tumor rejection function as a preventative rather than a therapeutic effect (2). We agree that tumors were quite small at the time of treatment, which could justify the claim of preventive therapy at a first glance.

Many studies, in particular by the Schreiber group, elegantly reported the role of tumor stroma in further promoting tumor progression (3, 4). Their studies also pointed out that established tumors with well-organized stroma prevent effective homing or engraftment of T cells into the tumor, a phenomenon that is still not fully characterized. We also reported on the role of tumor vasculature to provide a barrier function, which we termed the blood–tumor barrier (5). This could be one of the reasons why the recent study by Binder and colleagues (6) did not observe response to PD-1 and/or CTLA-4 blockade in late-stage tumors.

In this regard, our recent article (7) describes a time-dependent response to combined immunotherapy (PD-1 blockade, 41BB costimulation, and whole tumor vaccination) in an intraperitoneal orthotopic mouse model of ovarian cancer. When tumor-bearing mice were treated at a late stage of tumor growth, only minimal effect was observed, with rejection of tumor only in 2 of 12 mice (Fig. 1A). In contrast, when mice were treated at an early stage of tumor growth, 75% of the mice (9 of 12) eradicated tumors (Fig. 1B). Interestingly, we found that CD8+ T cells infiltrated early tumors, but were almost completely absent in advanced tumors, largely replaced by rare CD4+ FoxP3+ Tregs. Thus, effective PD-1 blockade requires the prior presence of T cells in tumors, and therefore therapy of tumors lacking T cells may predict failure of PD-1 blockade, at least in the mouse. It is therefore plausible that our results argue not that PD-1 blockade is effective in early tumor settings or in prevention strategies, but rather that PD-1 blockade...
requires preexistence of T cells in tumors. Arguably, preexisting tumor-infiltrating lymphocytes may emerge as an important biomarker for the selection of patients for PD-1 pathway blockade (8). A recent observation that response to PD-1/PD-L1 blockade may in part correlate with PD-L1 expression by tumor cells (9) is perhaps also consistent with the notion that response to PD-1/PD-L1 blockade correlates with preexisting tumor-reactive T cells, because PD-L1 is also in part induced by the presence of T-cell populations in tumor.

In this context, it is fascinating to learn that Binder and colleagues showed evidence that even advanced-stage tumors can be rejected by immunotherapy (6). The authors used bacterial vaccine vector to deliver tumor-specific antigen into the established tumor. Along with the therapeutic vaccination, the checkpoint blockade enhanced rejection of tumors in 80% of mice. In this setting, antigen-loaded tumor was more immunogenic and generated (and recruited) a higher number of tumor-reactive T cells in the tumor microenvironment and, with the support of PD-1 blockade, promoted T-cell engraftment in advanced tumors. Furthermore, in their setting, the bacterial vaccine could have triggered potent activation of innate immunity through Toll-like receptors, resulting in the influx of T cells into tumor (10). Interestingly, also in our study, the only mice with advanced tumors that responded to treatment were those receiving GVAX vaccine with checkpoint blockade. It will be really exciting to further explore these questions in the laboratory and the clinic.

Disclosure of Potential Conflicts of Interest

G.J. Freeman has ownership interest (including patents) in CoStim Pharmaceuticals, Bristol-Myers Squibb, Roche, Merck, EMD Serono, Boehringer-Ingelheim, and Amgen, and is a consultant/advisory board member of CoStim Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

Received September 26, 2013; accepted October 21, 2013; published OnlineFirst January 9, 2014.

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