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The future of cancer therapy: Selecting patients who respond to PD-1/L1 blockade

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Summary

It is conceivable that, in the near future, an assay that defines the likelihood of a patient with advanced cancer to respond to immunotherapy based on PD-1/L1 blockade will be the initial decision point to select the treatment of patients with any cancer type.

Therapies blocking PD-1/L1 have shown unprecedented rates of durable tumor responses in a variety of cancer types (1-5). The identification and characterization of factors in the tumor microenvironment at baseline (immediately before starting treatment) that predict which patients are likely to respond therapy has become a top priority challenge in cancer medicine. In this issue of Clinical Cancer Research, Taube *et al*. report on the analysis of 68 tumor samples obtained from 41patients with advanced lung, renal, colorectal and prostate cancers as well as metastatic melanoma treated with the anti-PD-1 antibody nivolumab (6). Based on expression of PD-1, PD-L1, PD-L2 and lymphocytic infiltration using immunohistochemistry (IHC) techniques, they found that PD-L1 expression, as a single factor, showed the strongest association with response to anti-PD-1 blockade. The results of this study advance our knowledge about factors in the baseline tumor microenvironment that may predict response to PD-1 blockade therapy and serves as a stepping-stone for further investigation. Additional work will be needed to understand if archival tissues (obtained up to 13 years prior to start on therapy in the current report, with a mean of 3 years for the whole series) perform similarly as samples obtained immediately before starting on anti-

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PD-1 therapy, and if results are the same when using methodology-validated commercial grade PD-L1 IHC assays.

The efficacy of PD-1/L1 blocking antibodies is contingent on the presence of tumor-specific PD-1+ T cells being negatively regulated by PD-L1 expressing cells in the tumor (7). In this situation, interrupting a functionally intact PD-1/PD-L1 axis with monoclonal antibodies enables T cells to mediate cancer cell killing. Key to this interaction is the detection of PD-L1 expressed by the tumors as highlighted by the work by Taube *et al* (6). However, the *in situ* location of induced PD-L1+ cells of the tumor (i.e., PD-L1+ cells that interface with PD-1+ expressing T-cells) represents a distinct microenvironment in the tumor and is different than constitutive PDL1+ expression. Figure 1 provides several scenarios of the interaction between cells of the tumor, T cells and PD-1/L1. Expression of PD-L1 can be induced by interferon-producing T-cells, which was termed adaptive immune resistance by Drew Pardoll (8). In this scenario, tumor antigen-specific T cells infiltrate metastatic lesions and specifically recognize tumor antigens through their T cell receptor (TCR), which triggers the expression of PD-1 and other activation-induced T cell markers. These T cells also produce interferons, which in some cancer and tumor stromal cells induce the expression of PD-L1 (9). If all components of the axis are intact, it is logical that therapies blocking PD-1 or PD-L1 have the potential to mediate tumor rejection. In some cases, PD-L1 can be constitutively expressed through oncogenic processes that vary according to different cancer types (8). Evidence is scarce as to whether constitutive oncogenic expression of PD-L1, in the absence of adaptive PD-L1 expression induced by T cells, is associated with antitumor activity of PD-1 blockade therapy. In a third scenario, tumors may be associated with T cells that are dysfunctional; that is, they have no TCR specificity to tumor antigens, or they are not interferon-producing that lead to PD-L1 and PD-1 expression. The benefit of PD-1/L1 blocking therapies in this scenario remains in question.

Hence, the expression of PD-L1 in tumors is an important factor in determining the likelihood of a tumor regressing during PD-1 blockade. However, its presence must be put within the context of additional variables that make up for a more complex equation. PD-L1 expression in the absence of T cells is of unknown significance for response to PD-1 blockade therapy, as is the presence of T cells in tumors without an adaptive expression of PD-L1 (Figure 1). For PD-1/L1 blockade therapy to work, pre-existing PD-1+ T cells with tumor antigen specificity that become disabled upon PD-L1 engagement is likely required.

Significant efforts by several research groups as well as by industry are actively taking place to provide sensitive and specific assays to detect and quantify PD-L1 expression in tumors. The current challenges surrounding the cross-reactivity, specificity, and sensitivity of PD-L1 IHC antibodies will likely be resolved with these efforts. However, a PD-L1 antibody for IHC or immunofluorescence that overcomes these challenges does not have, *per se*, the capacity to fully characterize the full biology of the PD-1/PD-L1 interaction. The presence of T cells, in particular of cytotoxic CD8+ T cells, is a standard IHC protocol, but falls short of providing information about the T cell tumor specificity. Indirect measures of tumor specificity of T cells are the expression of TCR activation markers, of which PD-1 is one, as well as CD137 (4-1BB), OX40 or TIM3. A more direct measure is the clonality of TCRs that can be analyzed by deep sequencing approaches (10). Specific TCR engagement by the

recognition of tumor antigens should lead to the release of cytokines such as interferons, which can be detected directly by laser capture microscopy and PCR or *in situ* hybridization methods (9), or indirectly by analysis of gene expression profiling looking for signatures of inflammatory or immune response in cancers (11).

In conclusion, PD-1 blocking therapies have achieved unprecedented rates of durable clinical responses in several cancers. Therefore, it is envisioned that, in the near future, instead of relaying on the status of estrogen receptor or Her2/neu in breast cancer, EGFR in lung cancer or BRAF in melanoma to decide on the front line therapy, oncologists will want to know if a patient is predisposed to respond to anti-PD-1/L1 antibody therapy as the initial decision point to select oncologic therapy. Such a predictive assay will likely need to take into account PD-L1 expression as well as other variables that quantitate tumor antigen-specific T cell infiltration leading to a dominant role of PD-1/L1 negative signaling in the cancer of a particular patient.

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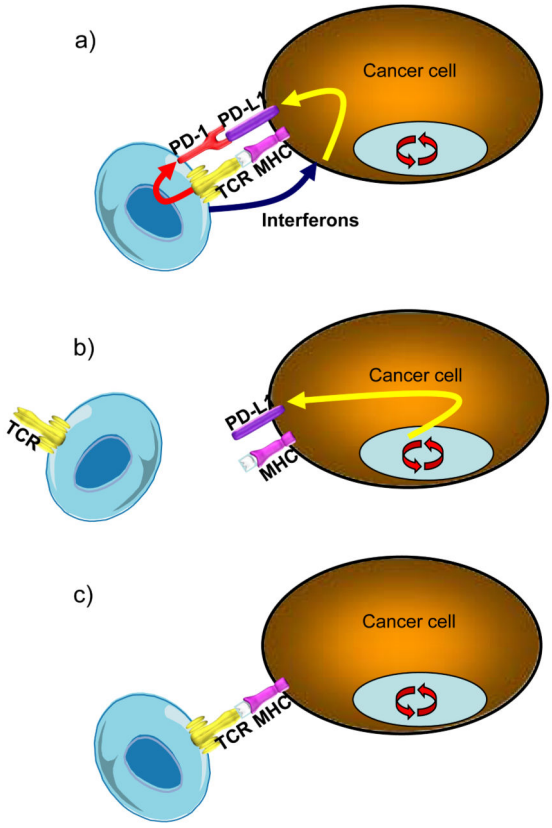

Figure 1.

Potential interactions between cancer cells and T cells limited by PD-1/PD-L1. A) Adaptive immune resistance happens when a T cell with a T cell receptor (TCR) specific for a tumor antigen is activated upon antigen recognition on the surface of a cancer cell. Upon activation, the T cell expresses PD-1 and also releases interferons. The interferons are recognized by the cancer cell and lead to the adaptive surface expression of PD-L1. In this case there is a co-localization of T cells, tumor cells and PD-1 and PD-L1. B) In some instances, oncogenic events in the cancer cells lead to constitutive PD-L1 expression, which may be independent of the presence of tumor antigen-specific T cells. C) In other scenarios, T cells may infiltrate cancers in an environment that leads to their inactivation, not triggering the production of interferons and therefore not resulting in the adaptive expression of PD-L1.