Adaptive Immune Resistance: How Cancer Protects from Immune Attack

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**ABSTRACT**

Adaptive immune resistance is a process in which the cancer changes its phenotype in response to a cytotoxic or proinflammatory immune response, thereby evading it. This adaptive process is triggered by the specific recognition of cancer cells by T cells, which leads to the production of immune-activating cytokines. Cancers then hijack mechanisms developed to limit inflammatory and immune responses and protect themselves from the T-cell attack. Inhibiting adaptive immune resistance is the mechanistic basis of responses to PD-1 or PD-L1–blocking antibodies, and may be of relevance for the development of other cancer immunotherapy strategies.

**Significance:** Several new immunotherapy strategies to treat cancer are based on inhibiting processes through which cancer adapts and evades from an immune response. Recognizing the specific adaptive resistance mechanisms in each case is likely to allow the personalized development of immunotherapies tailored to block how a particular cancer protects itself from the immune system. Cancer Discov; 5(9); 1–5. © 2015 AACR.

**INTRODUCTION**

There is clear evidence that the human immune system can mount cytotoxic immune responses that can eradicate cancers. This indicates that cancers that grow progressively either are not recognized by the immune system or have developed mechanisms to avoid the immune system. Evidence from mouse models of carcinogen-induced cancers led Schreiber and colleagues to postulate the concept of immunoediting, which explains how an otherwise immunogenic cancer can grow progressively (1–4). The demonstration that nonsilent point mutations (which lead to antigenic neoepitopes) are more frequently lost in cancers compared with silent point mutations (not recognized by T cells) highlights the relevance of the immunoediting process in human cancers (5). Following this logic, it is reasonable to think that some cancers grow progressively because they are no longer immunogenic. However, this cannot explain the progression of all cancers, as the administration of immune-activating cytokines or the release of immune checkpoints such as cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4) or programmed cell death-1 (PD-1) can lead to durable tumor responses in mice and patients (6, 7), indicating that there are T cells still capable of recognizing and killing cancer cells when adequately activated. Therefore, there have to exist mechanisms that limit immune responses to cancer by actively inhibiting the cytotoxic effects of T cells. However, these mechanisms have to be specific for cancer antigens, as there is little evidence that most patients with cancer have a state of systemic immune suppression (patients with cancer do not usually get opportunistic infections), other than at terminal stages when the cancer has overwhelmed many body systems.

The concept of adaptive immune resistance is used to describe a process in which tumor antigen-specific T cells attempt to attack the cancer, but the cancer changes in a reactive fashion to protect itself from this immune attack. It was first used by Drew Pardoll to describe how the production of interferons by T cells upon recognition of their cognate antigen results in the reactive expression of the ligand of PD-1 (PD-L1) by cancer cells and the turning off of PD-1–positive T cells (7). This concept can explain how there can be a state of specific lack of recognition of otherwise immunogenic cancers, while the immune system continues to be able to protect the body from opportunistic infections. In addition to PD-1–PD-L1 interactions, it is possible that adaptive immune resistance can be mediated by several other mechanisms triggered by the recognition of immune-stimulating proteins by cancer cells that then result in protective changes. Evidence is available for adaptive cancer cell changes induced by the exposure to interferons and TNFα as well as other inflammatory cytokines, which are discussed below. The concept of adaptive resistance used here is different from adaptive...
Adaptive immune resistance is a process through which cancer reactivity expresses molecules that actively turn off an otherwise effective antitumor immune response. The antitumor activity of PD-1 blockade therapy is explained by blocking adaptive immune resistance through the expression of PD-L1. Recognizing adaptive immune resistance in baseline biopsies may lead to precision immunotherapy.

**MECHANISMS OF ADAPTIVE IMMUNE RESISTANCE**

**Interferon-Induced Adaptive Immune Resistance**

When tumor antigen-specific T cells recognize their cognate antigen expressed by cancer cells, signaling through the T-cell receptor (TCR) leads to the production of interferons and, at the same time, the expression of activation-induced regulatory receptors, including PD-1 (Fig. 1A). The interferons are aimed at amplifying the immune response and attracting other leukocytes, such as NK cells and macrophages. However, in both mouse models (8, 9) and humans (5), interferons also lead to the expression of a series of interferon-inducible immune suppressive factors, including PD-L1 and indolamine 2,3 dioxygenase (IDO; Fig. 1B; ref. 9). This is an adaptive process that limits immune and inflammatory responses, and cancer uses it to its advantage.

PD-L1 can be constitutively expressed through a series of currently incompletely analyzed oncogenic pathways (10–12), which likely converge in the activation of signal transducers and activators of transcription (STAT) proteins or other interferon receptor downstream effectors, or can be induced in response to both type I and II interferons produced during an active antitumor immune response (13–16). The interferon-inducible expression of PD-L1 seems to be more common than the constitutive expression in most cancer histologies and results in a restricted PD-L1 expression in T cell–rich areas of tumors, in particular at the invasive margin (17, 18). This pattern of expression suggests that PD-L1 is adaptively induced as a consequence of the presence of tumor antigen-specific T cells that recognize the cancer cells, but these cancer cells (or other tumor microenvironment cells) adapt by expressing PD-L1 and turning off the otherwise specific cytotoxic immune response (17). The signaling pathway through which interferon leads to expression of PD-L1 has not been fully characterized, but current evidence suggests that it follows the canonical type II interferon receptor signaling (16). The adaptive expression of PD-L1 has been noted on the surface of cancer cells, myeloid-lineage cells, and other tumor microenvironment stromal cells (18), as well as tumor-infiltrating T cells themselves (19), likely a reflection of the presence of tumor-specific T cells producing interferons that can also trigger PD-L1 expression on T cells. Therefore, the tumor uses the physiologic induction of PD-L1, which normally occurs to protect tissues from infection-induced cytotoxic responses, in order to protect itself from an antitumor immune response (13, 20).

An alternate hypothesis is that any PD-L1 expression by cancer cells, regardless of whether it is inducible or constitutive, results in immune evasion. The high response rate to PD-1 blockade in patients with chemotherapy-refractory Hodgkin disease has been explained by the frequent genetic amplification of chromosome 9, including the locus encoding PD-L1, PD-L2, and the interferon receptor adapter JAK2 (21, 22), which has been termed the PDJ ampiclon. Hodgkin disease is notorious for triggering a large lymphocytic inflammation (21, 22), which has been termed the PDJ ampiclon.
Adaptive Immune Resistance

The production of proinflammatory cytokines by tumor-infiltrating cells can result in changes in the cancer cells that may lead to immune escape. Conclusive evidence of this mechanism has been provided in a mouse model of adoptive cell transfer (ACT) therapy, where the infusion of T cells that specifically recognize a melanoma differentiation antigen, gp100, resulted in transient tumor responses (27). In this specific case, the recognition of the specific mechanism through which cancers may be a mechanism of immune evasion. In this model, TNFα produced by tumor-specific T cells triggered a process of dedifferentiation of melanoma cells moving back through their embryologic development path arising from the neural crest, evidenced by the expression of the nerve growth factor receptor (NGFR, also known as CD271), while losing the expression of several melanosomal antigens (30).

Inflammatory Cytokine-Induced Adaptive Immune Resistance

The recognition of the specific mechanism through which cancer adapts to evade an antitumor immune response may lead to rational immuno-oncology drug development and personalized cancer immunotherapy. Based on the detection of an ongoing adaptive immune resistance, cancers may be classified into two main groups, the ones that have active intratumoral immune responses blocked by adaptive immune resistance and the ones lacking intratumoral T cells (Fig. 2). If there is a sufficient density of T cells in tumors, in particular at the invasive margin, these are likely turned off by inducing adaptive immune resistance, and PD-1–PD-L1 may be dominant in this setting at least in some cancer histologies (17, 18, 39). If T cells have not made it into the tumor, then it may be envisioned that combination with another immunotherapy able to bring T cells into tumors would be a rational choice, such as the successful clinical development of anti-CTLA-4 combined with anti–PD-1 therapy (40, 41). CTLA-4 blockade has a preferential effect in the activation step of an antitumor immune response, broadening the diversity of the immune response and bringing T cells into peripheral tissues in mouse models and in humans (6, 42–44). Other potential approaches include means to change the tumor microenvironment by direct injection of interferon-inducing molecules such as Toll-like receptor (TLR) agonists or oncolytic viruses, blocking T cell–excluding proteins such as IDO or arginase, or inhibiting immune-suppressive cells such as Tregs or macrophages. In the remaining cases, there may not be T cells capable of differentially recognizing tumor antigens, so there would be no hope in unleashing an endogenous antitumor immune response. For these patients, immunotherapy would require...
creating an immune response by gene-engineered ACT using TCR or chimeric antigen receptors (CAR). Therefore, analysis of baseline tumor biopsies to detect adaptive immune resistance may guide treatment of cancer in the future (45).

**CONCLUSIONS**

Adaptive immune resistance may be a generalized phenomenon by which cancer cells evade otherwise functional tumor-specific T-cell responses and foster the cancer's progressive growth. It gives the advantage to the cancer to be able to specifically escape from T cells while the host’s immune system continues to function correctly for any other antigens. Recognizing this process has allowed the successful clinical development of checkpoint inhibitors, such as anti–PD-1 and anti–PD-L1 antibodies (44, 46), where intratumoral pre-existing T cells specific for the cancer are actively turned off by adaptive immune resistance, and therapeutic blocking antibodies to PD-1 or PD-L1 could reverse this situation (18, 19). Identifying similar processes that lead to the expression of other immune checkpoints, or immune-suppressive factors through which cancers protect themselves from an active T-cell cytotoxic response, may lead to the rational and personalized development of additional cancer immunotherapies. Furthermore, therapeutic interventions with small-molecule inhibitors or cytokine-blocking antibodies aimed at inhibiting cancer phenotype switching, dedifferentiation, and EMT may be rationally combined with immunotherapies for cancer. Clinical decision-making may be guided by the detailed analysis of how the immune system is interacting with cancers in tumor biopsies, which would allow defining whether there is an ongoing adaptive process limiting an immune response or if this is absent within the tumor.

**Disclosure of Potential Conflicts of Interest**

A. Ribas has ownership interest in Compugen and Kite Pharma.

**Grant Support**

A. Ribas is funded by NIH grants R35CA197633, P01 CA168585, U54 CA19347, and R01 CA170689; the Reseler Family Fund; the Grimaldi Family Fund; the Dr. Robert Vigen Memorial Fund; and Stand Up To Cancer—Cancer Research Institute (SU2C-CRI) Cancer Immunology Dream Team Translational Research Grant (SU2C-AACR-DT1012). Stand Up To Cancer is a program of the Entertainment Industry Foundation administered by the American Association for Cancer Research (AACR).

Received May 8, 2015; revised June 22, 2015; accepted June 30, 2015; published OnlineFirst August 13, 2015.

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Cancer Discovery  Published OnlineFirst August 13, 2015.

Updated version  Access the most recent version of this article at: doi:10.1158/2159-8290.CD-15-0563

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