Adaptive immune resistance: How cancer protects from immune attack

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Abstract

Adaptive immune resistance is a process where the cancer changes its phenotype in response to a cytotoxic or pro-inflammatory 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.

Keywords

Checkpoint inhibitors; programed death-1; adaptive resistance

Introduction

There is clear evidence that the human immune system can mount cytotoxic immune responses that can eradicate cancers. This incriminates that cancers that grow progressively are either not recognized by the immune system or have developed mechanisms to avoid the immune system. Evidence from mouse models of carcinogen-induced cancers led Robert Schreiber and colleagues to postulate the concept of immunoediting, which explains how an otherwise immunogenic cancer can grow progressively (1–4). The demonstration that non-silent point mutations (which lead to antigenic neoepitopes) are more frequently lost in cancers compared to 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 the cytotoxic T lymphocyte-associated antigen 4 (CTLA4) or the programmed cell death-1 (PD-1) can lead to durable tumor responses in mice and patients (6, 7), incriminating that there are T cells still capable of recognizing and killing cancer cells when adequately

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activated. Therefore, there have to exist mechanisms that limit immune responses to cancer by actively inhibiting the cytotoxic effects of T cells. But 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 then 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 turning off the 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 a protective changes. Evidence is available for adaptive cancer cell changes induced by the exposure to interferons and tumor necrosis factor alpha (TNF-alpha) as well as other inflammatory cytokines, which are discussed below. The concept of adaptive resistance used here is different from adaptive resistance when used to describe resistance to targeted therapies for cancer. Adaptive immune resistance is a natural process resultant from the cross-talk between immune cells and cancer cells within the tumor microenviroment, while adaptive resistance to targeted therapies refers to the bypass signaling once a constitutive driver oncogene is blocked by treating with the drug.

Mechanisms of Adaptive Immune Resistance

1. Interferon-induced adaptive immune resistance

When tumor antigen-specific T cells recognize their cognate antigen expressed by cancer cells, then 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 (Figure 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 in 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, Figure 1B) (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 recognized the cancer cells, but these cancer cells (or other tumor microenviroment cells) adapted 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 microenviroment 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 trigger PD-L1 also on T cells. Therefore, the tumor uses the physiological induction of PD-L1, which normally occurs to protect tissues from infection-induced cytotoxic responses, in order to protect itself from an anti-tumor immune response (13, 20).

An alternate hypothesis is that any PD-L1 expression by cancer cells, regardless if 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 of PD-L1, PD-L2 and the interferon receptor adapter JAK2 (21, 22), which has been termed the PDJ amplicon. Hodgkin disease is notorious for triggering a large lymphocytic infiltrate surrounding the few malignant Reed-Stenberg cells. Therefore, it is possible that the PD-L1 upregulation by gene amplification may also include an adaptive immune resistance mechanism associated with the brisk T cell infiltrate (23). It is interesting that the same PDJ amplicon has been noted in other cancers (head and neck, lung, cervical, stomach, colon) and when it is present it is positively associated with an immune cytolytic activity signature (5). If these other cancers with the PDJ amplicon also respond to PD-1 blockade therapy, then interferon-inducible expression of PD-L1 reflective of adaptive immune resistance may not be the only mechanism that explains cancer responses to anti-PD-1 or anti-PD-L1 antibodies.

It has been recognized that some cancers have a signature of T cell inflammation mediated by interferons that not only leads to the expression of PD-1 and PD-L1, but also to other immune suppressive factors such as IDO and even the active presence of FoxP3+ regulatory T cells (T_{regs}) (9, 24). The negative feedback through these inhibitory pathways is an adaptive process that follows the T cell infiltration. Data in mice correctly anticipated that checkpoint inhibition might be preferentially beneficial for patients with a preexisting T cell–inflamed tumor microenvironment (8, 9). As IDO is expressed through the same interferon-inducible mechanism, it is possible that the clinical development of specific IDO inhibitors may be able to follow a similar path where the pre-existence of T cells inducing IDO expression could be used to select patients for therapy. Another interferon-inducible checkpoint is the carcinoembryonic antigen cell adhesion molecule-1 (CEACAM1) (25), which has been reported to be a partner of the T-cell immunoglobulin domain and mucin domain-3 (TIM-3) and can be blocked therapeutically using antibodies to result in antitumor activity (26). It is also possible that other interferon-inducible genes that are part of negative immune regulatory loops may be limiting T cell responses to cancer and could provide novel targets for immunotherapy.

2. Inflammatory cytokine-induced adaptive immune resistance

The production of pro-inflammatory 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 model, during the process of cancer cell killing, the tumor-infiltrating cells released the inflammatory cytokine TNF-alpha, which lead the melanoma cells to adapt by decreasing expression of gp100 and switching to a less differentiated neural crest phenotype (Figure 1C). The melanosomal antigen gp100 is a protein from the pigmentation pathway expressed by normal melanocytes and highly expressed by many melanomas. It is a well-recognized tumor rejection antigen shared by melanomas (28, 29). As with interferon-induced PD-L1 adaptive expression, the exact signaling pathway from TNF-alpha to decreased melanosomal antigen expression has also not been fully characterized. Gp100 is not required for the cancer phenotype, so adaptation by decreasing the expression of this and other lineage-specific immunogenic proteins may be a mechanism of immune evasion. In this model, TNF-alpha produced by tumor-specific T cells triggered a process of de-differentiation of melanoma cells moving back through their embryological development path arising from the neural crest, evidenced by the expression of the nerve growth factor receptor (NGFR, CD271) while losing the expression of several melanosomal antigens (30).

Phenotype switching from a differentiated melanosomal state to a more undifferentiated state by melanoma cells can be induced not only by inflammatory cytokines but also by other stress-related changes (31, 32). This process is akin to epithelial-to-mesenchymal (EMT) transition in epithelial cancers (33), where cells switch from a more differentiated and proliferative state to a less differentiated and invasive state allowing the process of metastases (34, 35). It is possible that a similar process may mediate the neuroendocrine differentiation of several cancers, such as lung and prostate, and may be related to immune escape. The EMT de-differentiation changes in several cancers have been related to inflammatory cytokines like TNF-a, interleukin-6 (IL-6) and transforming growth factor beta (TGF-b) produced by an antitumor immune response (27, 36, 37). Therefore, it is likely that adaptive immune resistance induced by inflammatory cytokines may be an immune escape and even cancer-promoting mechanism in several cancers (38).

Clinical Decision Making Based on Diagnosing Adaptive Immune Resistance

The recognition of the specific mechanism through which cancer adapts to evade an antitumor immune response may lead to rational immunoncology 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 (Figure 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-CTLA4 combined with anti-PD-1 therapy (40, 41). CTLA4 blockade has a preferential effect in the activation step of an antitumor immune responses, 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 microenviroment by direct injection of interferon-inducing molecules such as toll-like receptor agonists or oncolytic viruses, blocking T cell-excluding proteins like IDO or arginase, or inhibiting immune suppressive cells like Treg 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 adoptive cell transfer (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 where 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. 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, de-differentiation 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 if there is an ongoing adaptive process limiting an immune response or if this one is absent within the tumor.

Acknowledgments

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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.

Key Concepts and Relevance

- Adaptive immune resistance is a process through which cancer reactively 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.

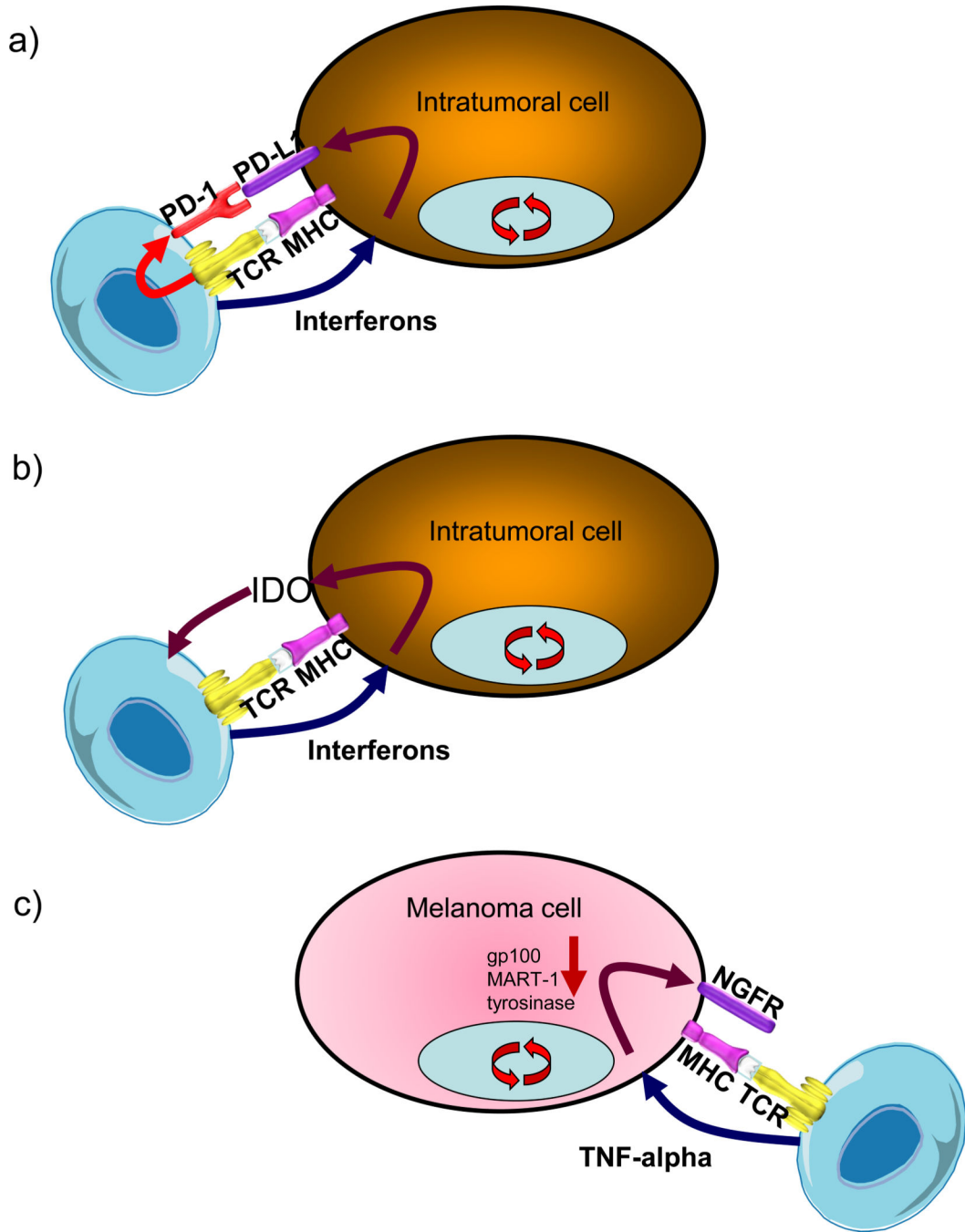- Recognizing adaptive immune resistance in baseline biopsies may lead to precision immunotherapy.

Figure 1. Examples of adaptive immune resistance

a) Specific recognition of tumor antigen by T cells leads to the production of interferons but also the expression of immune-inhibitory receptors like the programmed cell death-1 (PD-1). Cells within the tumor, including cancer cells and macrophages, react to the presence of interferons by expressing the ligand to PD-1 (PD-L1), which functionally inactivates the tumor-infiltrating T cells. b) T cells producing interferons lead to the expression of immune-suppressive molecules beyond PD-L1, including indolaimine-2,3-deoxygenase (IDO), which is a rate-limiting enzyme in the tryptophan metabolism and

essential for adequate T cell functionality. c) The production of tumor-necrosis factor alpha (TNF-alpha) by tumor-specific T cells can result in the de-differentiation of melanoma cells to stop expressing melanosomal antigens such as gp100, and instead express neural crest antigens such as the nerve growth factor receptor (NGFR or CD271).
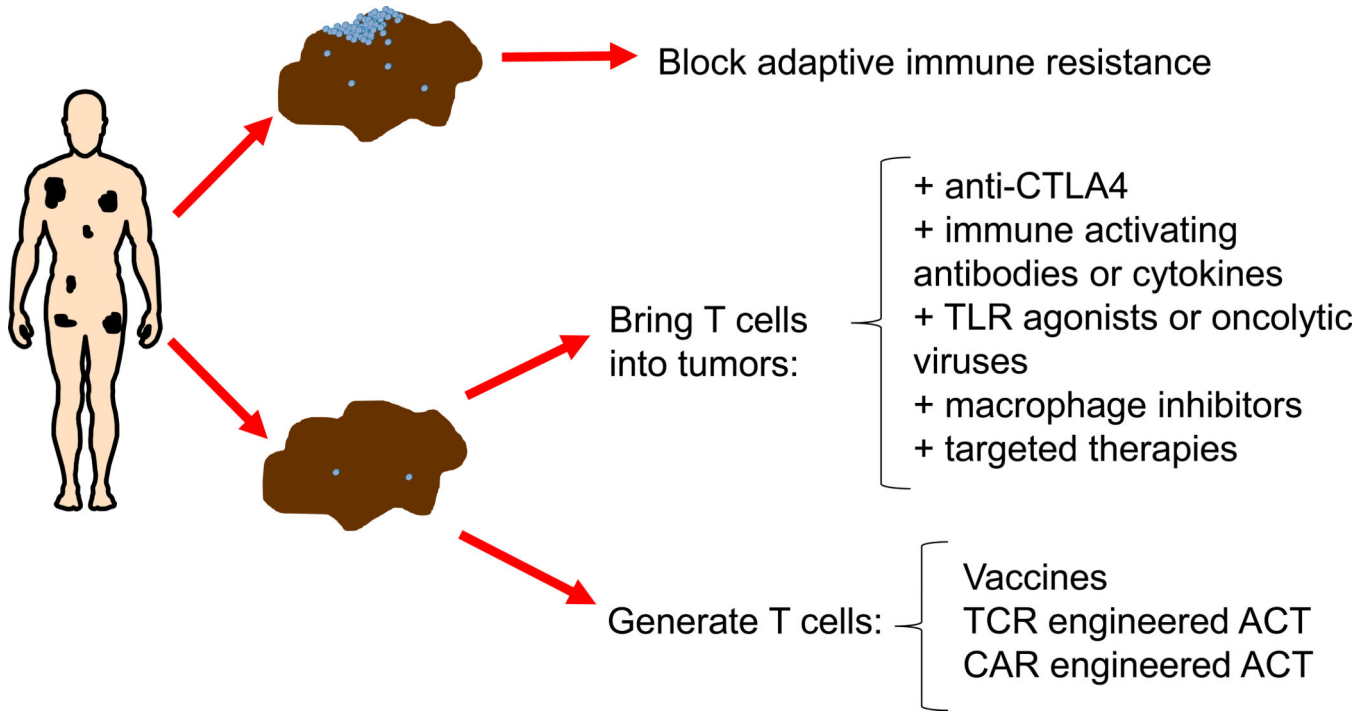

Figure 2. Treatment selection based on detecting adaptive immune resistance

Tumor biopsies from patients with advanced cancers may contain T cell infiltrates that trigger an adaptive immune resistant response. Defining the specific mechanism of this reactive tumor protection would allow tailoring the treatment of the patient to block that particular escape mechanism. For example, if T cells in tumors are turned off by PD-1:PD-L1 interactions then single agent anti-PD-1 or anti-PD-L1 would be the most appropriate therapy with high likelihood of success and avoiding additional toxicities from combinations. But if there are no T cells in tumor biopsies, then combination immunotherapies could be designed to bring T cells into tumors, or the immune system would need to be turned on by vaccination or genetically engineered using an adoptive cell transfer (ACT) approach with T cell receptors (TCR) or chimeric antigen receptors (CAR).