

Immune Checkpoint-Targeted Therapy: Cancer and Autoimmune Diseases Represent Two Sides of the Same Coin

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Abstract

The immune system plays a critical role in tumor surveillance and cancer prevention. However, some cancer cells can evade immune destruction by acquiring the ability to inhibit immune checkpoint regulatory pathways and suppress anti-cancer immune responses. In recent years, the immune checkpoints took center stage in cancer immunotherapy and several promising strategies, based on the intervention in immune checkpoint-regulated pathways, have been designed in order to overcome mechanisms of immunosuppression. Clinical studies, using anti-inhibitory immune checkpoint-receptor antibodies, demonstrated durable clinical responses even in patients with advanced cancer. However, the clinical benefit was limited to a subset of cancer patients. Furthermore, the immune checkpoint therapy, which unleashes the immune system in order to augment the anti-cancer immune response, also increases the incidence of autoimmune diseases and induces an array of immune-related adverse effects. Here we briefly discuss some of the pros and cons of immune checkpoint-directed immunotherapy.

Keywords: Immune checkpoint; Immunotherapy; Cancer; Autoimmune diseases; T lymphocytes

Description

One of the most promising approaches for cancer therapy involves the manipulation of immune checkpoint receptors, which consist of a number of stimulatory and inhibitory cell surface proteins that are critical for the regulation of immune cell functions.

Under normal physiological conditions, immune checkpoints are implicated in the initiation of immune responses and determination of the intensity and duration of the response. As such, they operate to limit collateral tissue damage during anti-microbial immune responses. More important, they maintain self-tolerance and are critical for the prevention of autoimmune diseases.

Recent studies indicated that cancer cells could evade immune destruction by acquiring abilities to inhibit immune

checkpoint pathways and suppression of anti-cancer T cell responses. More specifically, immune checkpoint receptor-expressing tumor infiltrating lymphocytes were found to interact with their cognate ligands on the surface of the tumor cell thereby undergoing local, selective immunosuppression at the tumor microenvironment [1]. Based on these observations, antibodies (Abs) were designed to downregulate the inhibitory immune-checkpoint receptors, and there *in vivo* administration was found to unleash effective anti-tumor immunity. Clinical studies demonstrated that such Abs could induce durable clinical responses even in patients with advanced cancer [2,3].

The cytotoxic T lymphocyte associated antigen-4 (CTLA-4; CD152) is the most studied immune-checkpoint receptor in the context of cancer immunotherapy and the first immune-checkpoint receptor to be clinically targeted [4-6]. It is a potent negative regulator of T cell responses which counteracts the activity of the costimulatory receptor CD28. CTLA-4 and CD28 share the B7.1 (CD80) and B7.2 (CD86) ligands, but a higher affinity of CTLA-4 allows it outcompete CD28 in ligand binding and delivery of inhibitory signals to the T cells [7,8]. Thus, while cytotoxic T lymphocytes (Tc) can identify and destroy a large variety of cancer cells, signal delivery via the CTLA-4 surface receptor downregulates Tc functions and their ability to eradicate cancer. Nevertheless, a monoclonal antibody (mAb), which blocks CTLA-4, termed Ipilimumab, was found to turn off this inhibitory signal and allow the cytotoxic T cells to destroy cancer cells. Ipilimumab (trade name Yervoy™, a human IgG1 mAb) was the first to demonstrate survival benefit for patients with metastatic melanoma [6]. It received U.S. Food and Drug Administration (FDA) approval for melanoma treatment in 2011, and is currently under clinical trials in various types of tumors, including lung carcinoma, bladder cancer and metastatic hormone-refractory prostate cancer.

Programmed death-1 (PD-1; CD279) is the second immune-checkpoint receptor that emerged as a promising target for immunotherapy. PD-1 is expressed on T cells and a variety of other types of immunocytes and plays a major role in down regulating inflammatory immune responses to infection and inhibition of autoimmune responses [4]. High expression of PD-1 was noted on tumor infiltrating lymphocytes [9] and regulatory T cells (Tregs) [10], and PD-1 ligands, including PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273), were found on

the surface of multiple cell types, including dendritic cells, monocytes and macrophages. The expression of PD-1 ligands on T-, B-, NK-, and dendritic-cells, as well as, epithelial cells and vascular endothelial cells is upregulated during inflammatory responses, predominantly by the effect of interferon [11,12]. The high expression of PD-1 ligands, in general, and in the tumor microenvironment in particular, suppresses Tc functions, and allows cancer cells to evade immune surveillance [13-15].

To test whether blocking of the PD-1/PD-L pathway will impact on anti-tumor immunity, PD-1-specific Abs were administered to patients with advanced melanoma. A significant overall survival improvement was observed in several independent studies. Two of the anti-PD-1 mAbs, pembrolizumab (Keytruda, a humanized mAb) and nivolumab (Opdivo a human IgG4 mAb), received FDA approval in 2014, and studies are in progress in order to test their effectiveness in different cancer diseases.

A similar strategy to target PD-L1 was tested in squamous and non-squamous non-small-cell lung cancer (NSCLC) and bladder cancer patients, and initial results of clinical trials, using durvalumab (anti-PD-L1 IgG1; MEDI4736) and atezolizumab (anti-PD-L1 IgG1; MPDL3280A) demonstrated a limited durable benefit [16,17].

Immunocytes express additional types of inhibitory immune-checkpoint receptors, such as the B- and T-lymphocyte attenuator (BTLA; CD272), lymphocyte activation gene-3 (LAG-3; CD223), T-cell immunoglobulin (Ig) domain and mucin domain 3 (TIM-3), and the killer-cell immunoglobulin-like receptor (KIR) [18,19]. Some of the inhibitory immune checkpoint receptor-ligands were found to be selectively upregulated in certain types of cancer cells. Attempts to block these receptors and their cognate ligands in order to augment anticancer immune responses are in progress.

The clinical use of Abs against negative checkpoint regulators represents a new and novel approach in cancer immunotherapy since the targets of the Abs are receptors on T cells that regulate their biological activity, rather than tumor cell-specific target molecules. In addition, the anti-immune checkpoint receptor Abs do not activate T cell responses against specific tumor antigens, but remove inhibitory pathways that block effective T cell responses against multiple types of tumors. While the immune checkpoint therapy represents an important weapon against cancer, unfortunately, it elicits long-term remission of tumors only in a fraction of the cancer patients. This is likely to reflect the large genetic and phenotypic heterogeneity existing between tumors and among cells within individual tumors, as well as the enormous genetic polymorphism prevailing among people, which determines not only the susceptibility to various diseases, but also the ability to respond to drugs and recover. In an attempt to overcome some of these difficulties, ongoing studies will be aimed to identify predictive biomarkers that will help select optimal therapies to individual cancer patients. Additional information on regulatory pathways that control T cell functions will help identify new drug targets, while a combination therapy which targets distinct immune cell types and intervenes at different

stages of the immune response is likely to provide an overall survival benefit for a greater number of patients.

Despite the proven effectiveness of immune checkpoint-based immunotherapy in a range of cancer diseases, these new treatment modalities came with a price. The intervention in the normal physiological regulation of T cells has led to immune dysfunction and an increase in the incidence of autoimmune diseases.

As indicated earlier, CTLA-4 is an important attenuator of T cell activation and an essential component of the regulatory system that controls peripheral tolerance [20,21]. Direct linkage of CTLA-4 to autoimmunity was clearly demonstrated in germline *Ctla4*-deficient mice, which developed a T cell-mediated autoimmune lymphoproliferative disorder associated with splenomegaly, lymphadenopathy, growth retardation, and early death [22,23]. In addition, a blockade of CTLA-4 in various mouse models of autoimmunity led to exacerbate autoimmune responses [24-26], while genetic evidence provided a further link between *Ctla4* and an array of human autoimmune diseases [26,27].

Mice with a restricted germline deletion of *Ctla4* in Tregs suffered from T cell-mediated autoimmune symptoms, which resembled those observed in *Ctla4*-deficient mice [28]. Although some studies support a role for CTLA-4 in Treg suppressor activity [29,30], others demonstrated that *Ctla4*-deficient Tregs are capable of suppressing certain autoimmune diseases [31,32] suggesting that CTLA-4 might be involved in selective Treg functions that predispose hosts to autoimmune diseases [33].

The entire spectrum of side effects induced by anti-CTLA-4 Abs, as well as by Abs directed against other co-inhibitory immune checkpoint receptors, is referred to as 'immune-related adverse events' (irAEs). The frequency and type of irAE symptoms varied in clinical trials, depending on the nature of the target molecule and the patient cohort, the type and amount of Ab, as well as the particular protocol, and involved a range of tissues and organs. These symptoms led to dermatitis, enterocolitis, hepatitis, and wide spread endocrinopathies (hypophysitis, thyroiditis, adrenal insufficiency), with less frequent symptoms of uveitis, nephritis, arthritis, and inflammatory myopathy [6,34,35].

These autoimmune-like side effects are likely to reflect the immune tolerance breaking by the CTLA-4 (or other co-inhibitory receptor) blockade, since these symptoms tend to resolve upon cessation of Ab treatment. Unfortunately, the development of autoimmune symptoms did not correlate with health improvement and/or tumor regression in anti-CTLA-4/anti-PD-1-treated cancer patients, indicating that they cannot serve as valid predictors of treatment outcome.

Immune checkpoint therapy has also been considered in autoimmune diseases and one of the major approaches is based on the inhibition of costimulatory immune checkpoint receptors.

It is well established that T cells require two independent signals in order to become fully activated. The first signal is

obtained by TCR interaction with a peptide antigen presented on a major histocompatibility complex (MHC) receptor on the surface of an antigen-presenting cell (APC), while the second signal is provided by interaction of the CD28 costimulatory receptor with the APC-expressed CD80 or CD86 ligand. TCR-mediated signaling in the absence of costimulation allows T cells to interpret signals as "self" and acquire a state of anergy. In contrast, simultaneous triggering of the TCR and the CD28 costimulatory receptor promotes the differentiation into potent effector T cells.

An autoregulatory mechanism that prevents the constitutive activation of the T cells is mediated by the TCR/CD28 activation-induced expression of CTLA-4, which can then interact with CD80/CD86 on the surface of APC, and deliver an inhibitory signal that terminate the response. This inhibitory signal is delivered to the fully differentiated effector T cells that have already synthesized and secreted a multitude of proinflammatory cytokines which amplified the immune response. Therefore, intervention with CTLA-4-dependent signals in autoimmune patients cannot alleviate autoimmune response.

In order to downregulate the activity of autoreactive T cells at a very early stage, scientists designed a soluble protein mimetic molecule, which binds CD80/86 and blocks T cell activation. This drug, termed abatacept (Orencia) consists of an extracellular domain of CTLA-4 fused to the Fc portion of a human IgG1 (CTLA4Ig), and since CTLA-4 exhibits a higher binding affinity to CD80/CD86, compared to CD28, the drug competes with CD28, occupies CD80/CD86, prevents the delivery of the costimulatory signal, and dampens-down autoimmune and inflammatory responses [36]. Indeed, abatacept was able to prevent antigen-presenting cells (APCs) from delivering CD28-dependent costimulatory signals to T cells [37]. Furthermore, abatacept has demonstrated long-term efficacy in various forms of rheumatoid arthritis [38,39], as well as other disease conditions [40,41].

It should be noted that besides, CD28, T cells express a number of immune-checkpoint receptors with costimulatory activity, including the CD28-family member, inducible T-cell costimulator (ICOS), members of the tumor necrosis factor (TNF) receptor superfamily, such as CD27, CD40, CD134 (OX40), CD137 (4-1BB), and the glucocorticoid-induced TNFR family related gene (GITR) [18,19,42,43]. Engagement of these receptors can potentially contribute to the T cell activation response, and therefore these costimulatory receptors and their cognate ligands can serve as putative targets for immunotherapy in various autoimmune diseases.

The progress made in immunotherapy, using immune checkpoint blocking Abs, has significantly improved the outlook for patients with a variety of malignancies. Further discoveries of novel immune-checkpoint receptors and characterization of their mechanism of action will increase the spectrum of target molecules for immunotherapy. In addition, determination of the most effective combinatorial approaches for particular diseases will enhance the rate of recovery. Since the current treatments are effective only in a fraction of cancer patients, the identification of predictive biomarkers will

help define optimal therapies for individuals and maximize the treatment benefit. The intense future studies to optimize immune checkpoint-targeted therapy must take into account the drug-induced immune-related adverse events and develop highly effective strategies to counteract the common iatrogenic effects.

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