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Review

Interfering with coinhibitory molecules: BTLA/HVEM as new targets to enhance anti-tumor immunity

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ABSTRACT

Despite the powerful aspects of immune reactions, most often tumor cells are able to evade immune recognition and destruction. Cosignaling molecules from the B7/CD28 and TNF/TNFR superfamilies emerge as novel targets in immunotherapy. Upregulation of coinhibitory molecules by the tumor cells or tumor-infiltrating lymphocytes clearly attenuates T-cell responses against cancer and appears to be a mechanism exerted by the tumor to escape immune response. Today, a variety of coinhibitory molecules, including CTLA-4 and PD1 have been implicated in immune escape of cancer cells. Antagonist antibodies are developed to overcome immune evasion and until now anti-CTLA-4 and anti-PD1 antibodies have been tested in clinical trials with encouraging results. Here we summarize the recent advances made on PD1/PD1 ligands expression in cancer and we discuss about another couple of inhibitory molecules, BTLA and its ligand HVEM and their potential role in immune escape. Such information may provide novel therapeutic targets to reverse tumor-induced T-cell dysfunction in patients with advanced cancers.

1. Introduction

The importance of the antitumor immunity in the outcome and control of cancer is now recognized. Innate and adaptive immunity maintains effector cells such as lymphocytes and natural killer cells that distinguish normal cells from "modified" cells as in the case of tumor cells. However, most often tumor cells are able to evade immune recognition and destruction. The mechanisms of tumor escape are numerous. Those exploited by tumor cells to evade the immune system include: impaired antigen presentation (mutation or downregulation of MHC molecules or tumor antigens, defects in antigen processing), secretion of immunosuppressive factors in the tumor microenvironment (cytokines: TGF-β, IL10, VEGF. . .), recruitment of inhibitory immune cells: regulatory T cells (Treg), myeloid suppressor cells (MSC) or pDC (plasmacytoid dendritic cells, which suppress tumor cell-lysis directly by inhibition of CTLs or indirectly by inhibition of DCs), but also induction of T cell apoptosis by Fas and PD1, or phenotypic alterations of NK cells that abrogate their anti-tumor cytotoxic functions [1–4]. Altogether, these immune escape mechanisms show that tumor cells leave little chance to anti-tumor immunity to efficiently exert their functions. Another immune suppressive mechanism has emerged this last decade: the immunosuppressive action of coinhibitory molecules. Activation of lymphocytes is regulated by both costimulatory and coinhibitory molecules, belonging to the B7/CD28 superfamily (also known as the Immunoglobulin (Ig) superfamily) and the TNF/TNFR superfamily. The balance between these signals determines the lymphocyte activation and consequently regulates the immune response. These costimulatory and coinhibitory molecules were called "immune checkpoints" [5]. Indeed, tumor cells can evade immune control by down-regulating co-stimulatory molecules, such as CD80 and CD86, or in contrast by upregulating coinhibitory molecules and this is now recognized as an important immune resistance mechanism. These immune checkpoints have the advantage to be soluble or membrane receptor–ligand pairs; thereby they are easily targetable using agonist antibodies (for costimulatory molecules) or antagonist antibodies (for coinhibitory molecules). In contrast to antibodies commonly used in cancer therapy that target tumor cells directly (for example *Herceptin*® (trastuzumab) in breast cancer), the antibodies directed against cosignaling molecules target lymphocyte receptors or their ligands on tumor cells to enhance immune anti-tumor response. The two

Abbreviations: *BTLA*, B- and T-lymphocyte attenuator; *CTLA-4*, CTL-associated-antigen-4; *CRD*, cystein-rich domain; *HVEM*, herpes virus entry mediator; *Ig*, immunoglobulin; *LIGHT*, homologous to lymphotoxin, exhibits inducible expression, and competes with HSV Glycoprotein D (gD) for HVEM, a receptor expressed by T lymphocytes; *mAb*, monoclonal antibody; *PD1*, programmed death-1; TA, tumor antigen; TILs, tumor-infiltrating lymphocytes; TNF, tumor necrosis factor receptor.

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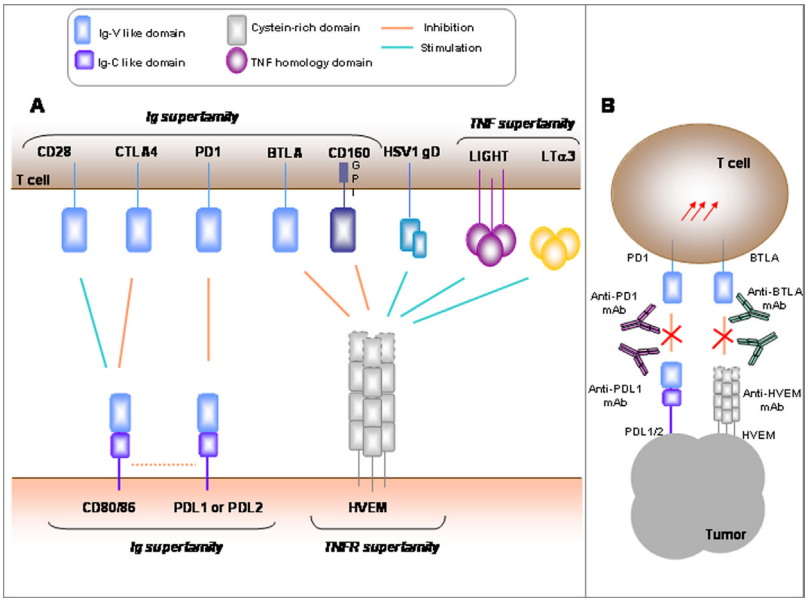

Fig. 1. (A) Interactions around PD1 and HVEM. PD1 belongs to the B7/CD28 (Immunoglobulin) superfamily and delivers negative signals upon binding to its ligands, PD-L1 and PD-L2. Recently, an unexpected interaction has been shown between PDL1 and CD80, whereby CD80 expressed on T cells can potentially behave as a receptor by delivering inhibitory signals when engaged by PDL1. CD80 and CD86 bind to the same two receptors, the stimulatory CD28 and the inhibitory CTL-associated-antigen-4 (CTLA-4) molecules. HVEM from the TNF/TNFR superfamily is clearly now a central immune molecule given the complexity of its interactions. HVEM has initially been discovered as the coreceptor for the glycoprotein D (gD) of the herpes simplex virus 1 (HSV-1), allowing the entry of the virus in the cell. HVEM interacts with LIGHT and lymphotoxin α3 to stimulate T cell responses. More recently, two novel ligands inhibiting T cell responses have been identified for HVEM: BTLA and CD160, a glycosphingolipid-linked protein, both belonging to the Ig superfamily, highlighting a crosstalk between the TNF-TNFR superfamily and the Ig superfamily. (B) Targeting coinhibitory molecules with monoclonal antibodies. Monoclonal antibodies (mAbs) are the primary immunotherapeutic modality used to promote immune function via antagonism or agonism of inhibitory or stimulatory molecular pathways, respectively. Cancer cells exploit the upregulation of coinhibitory molecules to inhibit T cell activation and to evade anti-tumor immunity. Indeed, PD1 is upregulated in TILs from many tumors and its ligands PDL1 and PDL2 are overexpressed in cancer cells. The anti-PD1 and anti-PDL1 mAbs block the interaction of PD1 with PDL1, reversing the inhibitory signaling and promoting lymphocyte activation. Similarly, high expression of BTLA was reported in tumor antigen-specific T cells from melanoma, thus BTLA would mediate inhibition of lymphocyte activation through engagement with its ligand HVEM expressed on tumors.

coinhibitory molecules that have been the most extensively studied and for which antagonist monoclonal antibodies (mAbs) already tested in clinical trials are cytotoxic T-lymphocyte-associated antigen 4 (CTLA4; also known as CD152) and programmed cell death protein 1 (PD1; also known as CD279). Here we will focus on PD1 and we will present another recent described immune checkpoint, BTLA/HVEM, and its potential in clinical immunotherapy.

1.1. Coinhibitory molecules

These past few years several coinhibitory molecules have been implicated in immune escape from cancer. The two immune checkpoints for which clinical information are now available are CTLA4 and PD1. We will discuss about PD1 and its ligands PDL1 and PDL2 which has become prime targets in monoclonal antibody-based therapies against cancer and we will present others promising candidates in our opinion which are BTLA and HVEM.

2. PD1

2.1. Expression and function

Programmed death-1 (PD-1; CD279) is an inhibitory receptor belonging to the CD28 superfamily of immune-regulatory receptors. However, while CTLA-4 expression is limited to T cells, PD-1 has a broader expression profile and is induced on other activated non-T lymphocyte subsets, including B cells and natural killer (NK) cells, which reduces their cytotoxic activity [6]. PD-1 (programmed death 1) downregulates T cell function (proliferation, cytokine secretion, and cytolysis of target cells) by delivering negative signals upon binding to its ligands, PD-L1 (also known as B7-H1 and CD274) and PD-L2 (also known as B7-DC and CD273). Recently, an unexpected interaction has been shown between PDL1 and CD80 [7], whereby CD80 expressed on T cells can potentially behave as a receptor by delivering inhibitory signals when engaged by PDL1.

The crucial role of PD1 and its ligands to control the anti-tumor response have been shown in mouse models. Indeed, PD1-deficient mice exhibit enhanced anti-tumor T cell responses toward solid and hematopoietic tumor, including melanoma; these mice survive longer and the tumors are regressed [8,9]. Blocking the PD1/PD-L1 pathway delays tumor progression [8–10].

Fig. 1

2.2. Role in immune escape and cancer therapy

Several lines of evidence support the role of inhibitory pathways in impeding effective anti-tumor T-cell immune responses.

First, PD1 is upregulated on peripheral tumor-antigen (TA)-specific CTLs and on a large proportion of tumor-infiltrating lymphocytes (TILs) from many different tumor types (melanoma, prostate. . .) [11–13]. This increased expression of PD1 may correlate with an anergic or exhausted state of CD8+ TILs and impaired effector function (decreased cytokine production) in melanoma [12]. These findings suggest that the tumor microenvironment can lead to up-regulation of PD-1 on TILs to impair anti-tumor immune responses.

Second, a highly dysfunctional subset of TA-specific T cells present at the periphery or at tumor sites, co-upregulates PD-1 and another coinhibitory molecule, T-cell immunoglobulin and mucin-domain-containing molecule 3 (Tim-3) expression. PD-1 and Tim-3 pathway blockades act in synergy to enhance TA-specific CD8 T-cell numbers and functions in patients with advanced melanoma and induce tumor regression in animals [14,15].