Reversal of T-cell exhaustion as a strategy to improve immune control of HIV-1

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AIDS 2015, 29:1911–1915

Keywords: HIV/immunology, HIV/therapy, therapies/investigational, T lymphocytes/immunology, T lymphocytes/virology

Introduction

T-cell exhaustion is a state of functional immune impairment characterized by reduced T-cell proliferation, cytokine production, cytotoxic function, and cell survival [1]. Although exhaustion generally contributes positively to immune tolerance, it also impairs tumor-specific and virus-specific T cells to allow evasion of immune surveillance [1]. Many cell surface inhibitory receptors have been implicated in T-cell exhaustion [2–7].

In the context of metastatic cancer, the most studied inhibitory receptors are cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) [8–21]. Therapeutic blockade of these receptors with monoclonal antibodies has revolutionized cancer immunotherapy [22], promoting anticancer immune responses in various solid organ cancers and lymphomas [23]. However, inhibitory receptor blockade can result in serious autoimmune-related adverse events [8–21] that may limit its application for other diseases.

The improved immune function seen with inhibitory receptor blockade in cancer trials may translate to improved virus-specific immune function in chronic viral infections, including human immunodeficiency virus (HIV)-1 infection [1]. To illustrate, a recent case study described reductions in residual plasma HIV-1 viremia after in-vivo blockade of CTLA-4 in an HIV-infected individual on suppressive antiretroviral therapy (ART) with metastatic melanoma [24]. Given the widespread interest in a cure for HIV-1, we review here the potential for blockade of inhibitory receptors to improve HIV-specific immune function toward achieving prolonged ART-free remission of HIV-1.

Programmed cell death protein-1/programmed death-ligand 1 axis

Programmed cell death protein-1 (PD-1) blockade in chronic viral infections

PD-1 and programmed death-ligand 1 (PD-L1) expression is increased on CD4+ and CD8+ T cells in chronic viral infections and preliminary evidence suggest that its blockade can improve virologic outcome [25–31]. In a woodchuck model of chronic hepatitis B virus infection, treatment with a combination of anti-PD-L1 antibody, entecavir, and a DNA plasmid vaccine expressing viral surface and core antigens led to seroconversion and sustained virus control after treatment cessation in two of three animals [32]. In chimpanzees with chronic hepatitis C virus (HCV) infection, an anti-PD-1 antibody lowered viremia in one of three treated animals and was associated with improvements in HCV-specific CD4+ and CD8+ T-cell responses [33]. In a randomized-controlled human trial of single-dose anti-PD-1 antibody in chronic HCV infection, five of 45 participants (one of five patients in the 0.1 mg/kg cohort; one of 10 patients in the treatment-experienced 10 mg/kg cohort; and three of 10 patients in the treatment-naive 10 mg/kg cohort)
developed increases in HCV-specific immune responses associated with greater than 0.5 log_{10} reductions in HCV plasma RNA, with one patient achieving undetectable HCV RNA for longer than a year [34]. These data from studies of chronic viral infections suggest that PD-1 blockade could also improve HIV-specific immune function in chronic HIV-1 infection.

**Prospects for HIV-1 infection**

PD-1 blockade has resulted in improved virologic outcomes in models of chronic HIV-1 infection. Treatment of simian immunodeficiency virus (SIV)-infected rhesus macaques with partially humanized mouse anti-PD-1 monoclonal antibody [35–38] improved the polyfunctionality of SIV-specific CD8^+ T cells and B cells, reduced viremia, and improved overall survival. PD-1 blockade has also been shown to delay viremia rebound after ART cessation in chronically SIV-infected macaques [39,40]. These studies demonstrate that PD-1/PD-L1 blockade in animal models of HIV-1 infection is capable of producing favorable and lasting immune responses, justifying careful assessment of the safety and efficacy of PD-1/PD-L1 blockade in human clinical studies. To this end, a placebo-controlled, single-dose escalating trial of anti-PD-L1 antibody in patients on long-term suppressive ART is currently underway (NCT02028403).

Interest has also been generated by preliminary studies showing that ex-vivo PD-1 blockade possibly reverses HIV-1 latency [41]. These studies, however, were performed with either CD4^+ T cells without stimulation from HIV-1-infected viremic donors or with CD4^+ T cells with allogeneic, superantigen, or cytokine stimulation from HIV-1-infected donors on suppressive ART. Our recent studies in a variety of cell types from donors on suppressive ART revealed that PD-L1 blockade without additional stimulation rarely increased virological production despite cellular expression of PD-1 and PD-L1 [42]. Cellular interactions in vivo are likely more complex, thus PD-1/PD-L1 blockade should be evaluated in clinical trials to determine both its effects on latency reversal and generation of effective HIV-1-specific immune responses.

**Cytotoxic T-lymphocyte antigen-4**

Ex-vivo blockade of CTLA-4 on cells from HIV-1-infected individuals has improved CD4^+ T-cell polyfunctionality, but only in those with detectable plasma viremia (HIV-1 RNA >50 copies/ml) [43]. The attenuated effects in aviremic individuals were likely the result of diminished CTLA-4 expression following viral suppression [43]. In contrast, CTLA-4 blockade in chronically SIV-infected ART-suppressed macaques significantly reduced viral load in lymph nodes [44]. As noted above, a recent case study of an HIV-infected man with malignant melanoma on effective ART showed that CTLA-4 blockade with ipilimumab decreased residual plasma HIV-1 RNA. However, an unexpected and unexplained increase in unspliced cell-associated HIV-1 RNA was observed without a change in cell-associated HIV-1 DNA [24]. Although the long-term implications of this case study are unclear, it provides encouraging proof-of-concept that inhibitory receptor blockade can reduce viremia in vivo. Unfortunately, CTLA-4 blockade has been associated with 40–60% grade 3 or 4 adverse events in metastatic melanoma patients [9,10]. Although this high frequency of severe adverse events may be acceptable to extend overall survival of patients with advanced cancer, the adverse event profile will likely preclude its use in otherwise healthy HIV-infected individuals on stable suppressive ART.

**Other inhibitory receptors**

CTLA-4 and PD-1 have been the most widely studied inhibitory receptors, but many other inhibitory receptors have been characterized that may inhibit anti-HIV-1 immune responses in vivo. In-vitro or ex-vivo blockade of these other inhibitory have shown potential to improve anti-HIV immune responses. For example, ex-vivo blockade of the T-cell immunoglobulin and mucin domain-containing molecule 3 (TIM-3) improved CD8^+ T-cell proliferation, cytokine production, and cytotoxicity in response to HIV antigen stimulation [45–47]. Dual blockade of the PD-1 and 2B4 pathways resulted in greater CD8^+ T-cell proliferation in response to HIV-1 gag peptides than with either treatment alone [5]. Blockade of CD160, an inhibitory receptor that is preferentially expressed on CD8^+ T cells over CD4^+ T cells, resulted in greater HIV-specific CD8^+ T-cell proliferation and cytokine production in response to HIV-1 peptides than from anti-PD-L1 antibody [6]. In addition, CD160 is not upregulated on activated T cells [48], suggesting that CD160 blockade may lead to less severe autoimmune-related adverse events than with blockade of other inhibitory receptors. These preclinical studies show that blockade of other inhibitory receptors, either alone or in combination, has potential to improve anti-HIV immunity. Proof-of-concept studies are needed in animal models of SIV/HIV infection to validate their importance.

**Gaps in knowledge**

Some uncertainties remain regarding the benefit of inhibitory receptor blockade in HIV (Table 1). Individuals on long-term effective ART may have limited benefit because of downregulation of inhibitory receptors
following suppression of viremia [5,43,49,50], but lowering of viremia may still occur in individuals on suppressive-ART, as observed in a recent case study [24]. PD-1 and CTLA-4 have also been implicated in both promoting and inhibiting regulatory T-cell (Treg) responses [51–56], and it is still unclear whether inhibitory receptor blockade will enhance or restrict Treg activity. Further studies are necessary to characterize the varying effects of inhibitory receptor blockade on Tregs and to determine whether these effects will substantially limit favorable immune responses.

The path forward

Blockade of the PD-1, TIM-3, 2B4, and CD160 pathways have consistently improved virus-specific T-cell polyfunctionality in ex-vivo human and in-vivo animal models of chronic HIV-1 infection. In addition, inhibitory receptor blockade can delay rebound viremia following treatment cessation in animal models of HIV/SIV infection. Beneficial effects may also be amplified by simultaneously blocking multiple inhibitory receptors [5,8,57] including PD-1, TIM-3, 2B4, and CD160. Despite the extensive characterization of inhibitory receptor blockade in HIV and SIV models and its success in cancer treatment, clinical trials in HIV-1 infection have been impeded likely because of uncertain or higher risk-to-benefit ratios (Table 1). HIV-positive individuals who are successfully treated with ART can have near-normal life expectancies [58]; hence, there is lower tolerance for toxicities compared with patients with cancer. Fortunately, new therapeutics targeting inhibitory pathways such as nivolumab have milder toxicity profiles. In addition, toxicities of inhibitory receptor blockade in cancer clinical trials are now well characterized and often reversible [8–17,59], opening the way for clinical trials in HIV-1 infection.

The slow evaluation of inhibitory receptor blockade for HIV-1 therapy can be attributed to initial development for cancer immunotherapy, for which the unmet medical need was greater. Now that multiple monoclonal antibodies blocking inhibitory receptors have been Food and Drug Administration-approved for cancer immunotherapy, including ipilimumab, nivolumab, and pembrolizumab, the time is right for their evaluation in HIV infection and other chronic viral diseases. It is possible that a treatment regimen involving inhibitory receptor blockade could result in durable ART-free virologic control, but the only way to test this possibility is by proceeding with carefully designed human clinical trials that assess the safety and efficacy of inhibitory receptor blockade in individuals on effective ART.

Table 1. Benefits and limitations of inhibitory receptor blockade in HIV-1 infection.

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<th>Potential benefits</th>
<th>Potential limitations</th>
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<td>Improved HIV-1 specific immune responses</td>
<td>Autoimmune-related adverse events</td>
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<td>Control of viremia and reduction of tissue viral load</td>
<td>Modest effects because of diminished inhibitory receptor expression by effective ART</td>
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<td>Blockade of multiple inhibitory receptors could further improve HIV-specific immune responses</td>
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<td>Sustained immune control of HIV-1 replication without ART</td>
<td>Blockade of multiple inhibitory receptors may increase autoimmune responses</td>
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<td>Blockade of inhibitory receptors on regulatory T cells may produce undesired immunomodulatory effects</td>
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Acknowledgements

The authors thank Elizabeth Fyne, Anthony R. Cillo, and Bernard J.C. Macatangay for helpful comments and edits.

Source of funding: J.W.M.'s work is supported by grants from the AIDS Clinical Trials Group to the Pittsburgh Virology Specialty Laboratory (NIH AI068636), National Institutes of Health grants (NIH AI069494 and NIH AI106701) and Bristol-Myers Squibb (BMS-936559).

J.K.B. is a recipient of the Howard Hughes Medical Institute (H.H.M.I.) Medical Research Fellows Program.

Conflicts of interest

J.W.M. is a consultant for Gilead Sciences and a shareholder of Cocrystal Pharma, Inc.

References


