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PD-1$^+$ T cells: exhausted and premature?

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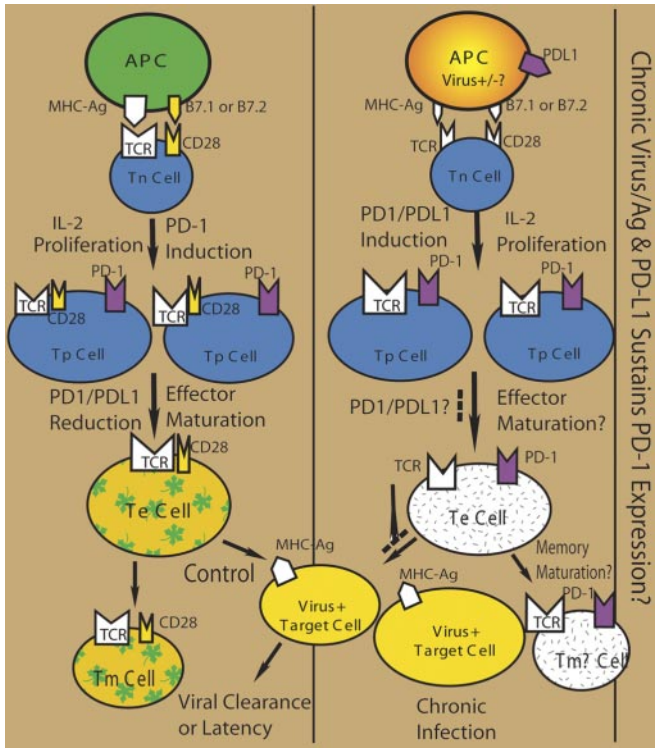
PD-1 up-regulation is correlated with the exhaustion of virus-specific CD8 T cells in people chronically infected with HIV-1. Zhang and colleagues report that PD-1 is up-regulated on HIV-specific CD8 T cells in typical disease progressors (TPs) but not in long-term nonprogressor (LTNP) patients, and PD-1 expression is down-regulated in HIV-1 patients with successful response to HAART therapy.

Zhang and colleagues report that PD-1 is up-regulated on human immunodeficiency virus (HIV)–specific CD8 T cells in typical disease progressors (TPs) but not in long-term nonprogressor (LTNP) patients. PD-1 up-regulation is associated with reduced expression of CD8 effectors perforin and IFN-γ, and decreased T-cell proliferation. Of interest, as blockade of PD-1 with anti–PD-L1 mAb in vitro restores effector functions of CD8 T cells, HIV-1 patients with successful response to highly active antiretroviral therapy (HAART) appear to also restore HIV-specific CD8 T cells in vivo. These findings suggest that sustained PD-1 expression on HIV-specific CD8 T cells depends on active HIV-1 viremia, and reducing viremia with HAART can reverse the defects associated with PD-1 expression in HIV-specific CD8 T cells.

In the seminal report on the role of PD-1 in the exhaustion of virus-specific CD8 T cells,[1] PD-1 is up-regulated on "exhausted" CD8 T cells in mice chronically infected with lymphocytic choriomeningitis virus (LCMV). Of importance, blockade of PD-1 with anti–PD-L1 mAb in chronically infected mice enhances proliferation and effector functions of the exhausted T cells, correlated with reduced LCMV infection. Several groups have since reported similar up-regulation of PD-1 on HIV-specific T cells in HIV-1–infected people.[2-4] The level of PD-1 on HIV-specific T cells is correlated with HIV-1 viral loads and inversely with CD4 T-cell counts. Treatment of PD-1$^+$ "exhausted" HIV-specific T cells with anti–PD-L1 in vitro also increases their effector functions.[2,4] Of interest, PD-1$^+$ HIV-specific CD8$^+$ T cells show a poorly differentiated phenotype ($CD27^{hi}CD28^{lo}CD57^{lo}CD127^{lo}$ $CCR7^-CD45RA^-$ or $CD27^+CD45RO^+$) that is correlated with dysfunctional CD8$^+$ T cells.[3,4] In the current report, PD-1 up-regulation is also associated with reduced expression of CD8 effectors perforin and IFN-γ. Therefore, "exhausted" HIV-specific CD8 T cells are also impaired in phenotypic and functional maturation, correlated with sustained expression of PD-1 (see the figure).



Tn/Tp/Te/Tm cells: naive/primed/effector/memory T cells.

The inhibitory receptor PD-1 is rapidly up-regulated on activated T cells (reviewed in Sharpe et al[5]). Its expression is decreased on effector T cells and diminished on memory T cells after antigen clearance. Upon antigen restimulation, effector T cells also up-regulate expression of PD-1. Therefore, sustained stimulation of naive and/or effector T cells during chronic virus infection will lead to accumulation of PD-1$^+$ T cells. Antigen-presenting cells (APCs) in HIV-1–infected patients express high levels of PD-L1 or B7-H1.[6] It is likely that impaired APCs with PD-L1 may help sustain PD-1 expression on T cells and impair their effector maturation, and allow chronic viral infection (see figure).

The current report further demonstrates that PD-1 up-regulation and the associated defects in HIV-specific CD8 T cells are correlated with HIV-1 disease progression, and the defects are reversible because inhibition of HIV-1 viremia by HAART restores virus-specific CD8 T cells with reduced PD-1 expression. This highlights PD-1/PD-L1 interaction as a potential therapeutic target for chronic HIV-1 infection. It is possible to recover HIV-specific T-cell functions either by reducing viremia or by blockading PD-1/PD-L1 interaction. However, it is important to point out that blockading PD-1 and PD-L1 interaction may have serious autoimmune implications, as PD-L1 mutant mice succumb quickly to chronic LCMV infection with severe tissue damage.[1] It also highlights the importance to elucidate the mechanism of PD-1 in virus-specific T-cell exhaustion and in impairing T-effector maturation.

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REFERENCES

1. Barber DL, Wherry EJ, Masopust D, et al. Restoring function in exhausted CD8 T cells during chronic viral infection. Nature. 2006;439:682-687.

2. Day CL, Kaufmann DE, Kiepiela P, et al. PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. Nature. 2006;443:350-354.

3. Petrovas C, Casazza JP, Brenchley JM, et al. PD-1 is a regulator of virus-specific CD8+ T cell survival in HIV infection. J Exp Med. 2006;203:2281-2292.

4. Trautmann L, Janbazian L, Chomont N, et al. Upregulation of PD-1 expression on HIV-specific CD8+ T cells leads to reversible immune dysfunction. Nat Med. 2006;12:1198-1202.

5. Sharpe AH, Wherry EJ, Ahmed R, Freeman GJ. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nat Immunol. 2007;8:239-245.

6. Trabattoni D, Saresella M, Biasin M, et al. B7-H1 is up-regulated in HIV infection and is a novel surrogate marker of disease progression. Blood. 2003;101:2514-2520.

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How low can you go: quality effects of an anti-CD4 antibody

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In this issue of *Blood*, Kim and colleagues demonstrate that zanolimumab offers promise for treating refractory early- and advanced-stage mycosis fungoides and Sézary syndrome.

Cutaneous T-cell lymphomas (CTCLs) are malignancies of skin-homing T cells with the most common subtype, mycosis fungoides (MF)/Sézary syndrome (SS), characterized by the $CLA^+/CD4^+/CD45RO^+/CCR4^+/CCR10^+/CD7^-/CD26^-$ phenotype. The malignant T cell has increased glutamate acetyl transferase 3 (GATA-3) expression, enhanced IL-4/IL-5/IL-10 production, and decreased interferon gamma production. This immunologic imbalance, as well as the decreased normal T-cell repertoire observed in MF/SS patients, results in intrinsic immunosuppression.[1] While numerous biologic (bexarotene), immunomodulatory (interferons), and targeted therapies (denileukin diftitox, histone deacetylase inhibitors) have been developed for CTCL, the "perfect" targeted single agent that results in durable clinical responses has been elusive and, thus, current therapies are most effective in combination.

CD4 has long been one of the more attractive targets: it is highly and reliably expressed in most CTCLs throughout the disease course and less strongly expressed in bystander cells such as monocytes and dendritic cells (DCs). This is in contrast to CD3 (the target of anti-CD3 Abs), which can be lost with more advanced disease, or CD25/IL-2Rα (the target of the IL-2/diphtheria toxin fusion protein known as denileukin diftitox, and of radioactive anti-CD25), which has variable expression in CTCL.[2] Alemtuzumab (anti-CD52) treatment is associated with a 20% rate of serious infections due to the fact that CD52 is expressed not only by malignant T cells but also by B cells, natural killer (NK) cells, and monocytes.[3]

In this issue of *Blood*, Kim and colleagues assess the efficacy and safety of weekly infusions of zanolimumab, the first humanized monoclonal anti-CD4 antibody to be developed, in a pair of phase 2, multicenter, prospective, open-label clinical trials of refractory early- and advanced-stage MF (38) and SS (9) patients. Dosing was initially at 280 mg ("low dose"), but was subsequently increased to "high dose" (560 mg in the early-stage group, 980 mg in the advanced-stage group) because of inadequate trough levels. Zanolimumab had previously been shown to exert its effects by interfering with CD4-mediated T-cell activation as well as depleting CD4 T cells through antibody-dependent cellular cytotoxicity (ADCC).

For their primary end point, the overall objective response (OR) rate in the high-dose groups of this refractory population was 56%, which was comparable if not better than that seen in other recently FDA-approved CTCL therapies. ORs were dose dependent and correlated with maximum trough concentrations. Peripheral blood $CD4^+$ T-cell counts rapidly decreased at the 280-mg dose; by the end of the study, the 980-mg dose cohort had a median CD4 count of 42/mm^3. Despite this highly efficient peripheral blood CD4 T-cell depletion, leukemic SS patients had lower ORs than patch/plaque/tumor stage MF patients (raising the questions of whether the degree of leukemic tumor burden correlated with response in SS patients and whether the optimal dose was achieved in this group).

Particularly impressive was the median duration of response of 81 weeks in the high-dose groups, which significantly exceeds that seen with other single agents. Probably contributing to this durability, the peripheral blood $CD4^+$ T-cell depletion persisted for at least a year after the end of the study and recovered slowly, on average increasing by 137 cells/mm^3 per year. Surprisingly, despite the human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS)–like low CD4 counts, the infections reported were predominately low-grade skin and respiratory infections, and serious infections (grade 3 or higher) were reassuringly not common, though longer follow-up is naturally needed. The authors appropriately note that CTCL patients are intrinsically predisposed to skin/soft tissue infections due to their underlying immune and skin barrier defects; however, it would have been interesting to know whether skin infections were increased even in patients without a specific prior history of such. While the authors report that peripheral blood monocyte counts were not depleted during treatment, future detailed characterization of immune function would be desirable (cytolytic T-cell responses, NK and DC function).

Eczematous dermatitis was also observed in a proportion of treated patients and appeared to correlate with response. This is surprising as atopic dermatitis is also a CD4/Th2-driven disease[4]; however, similar eczematous dermatitis reactions have been seen in other patient populations treated with anti-CD4 mAbs (rheumatoid arthritis). Furthermore, other T-cell–targeted therapies have also been associated with dermatitis development. One potential mechanism includes the disruption of CD4-expressing inhibitory T regulatory cells and their negative modulation of inflammatory responses.

A pivotal phase 2 trial is ongoing, and issues that remain to be addressed include long-term T-cell recovery and infectious/secondary malignancy rates, role of prophylactic antimicrobial regimens, management of the eczematous dermatitis side effect (possibly with combination therapy with skin-directed agents such as phototherapy), and optimizing doses for treatment of SS patients, particularly those with lower peripheral blood tumor burden. Nonetheless, the zanolimumab data presented by Kim et al demonstrate promising efficacy, tolerability, minimal immunogenicity, and surprisingly few infectious complications thus far.

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