Targeting Unconventional T Cells for Vaccination against Tuberculosis

Tuberculosis (TB) caused 10 million cases of active disease and 1.2 million deaths among human immunodeficiency virus (HIV)-uninfected persons in 2018 (1). Although the recent success of the M72/AS01E candidate vaccine in showing 50% protective efficacy over 3 years among HIV-uninfected persons is very encouraging (2), there is an urgent need for a vaccine that is also effective in people living with HIV. Unconventional T cells bridge the innate and adaptive immune system and are not restricted by the classical major histocompatibility complex (MHC). They recognize lipids, small-molecule metabolites, and specially modified peptides that are bound and presented by diverse nonpolymorphic antigen-presenting molecules. These include CD1 (cluster of differentiation 1)-restricted T cells, MR1 (MHC-related protein 1)-restricted mucosal-associated invariant T cells, MHC class Ib–reactive T cells, and γ-δ T cells (3). The T cells that recognize antigens presented through these molecules are genotype independent and therefore termed donor-unrestricted T (DURT) cells (4). DURT cells express invariant T-cell receptors that are shared across genetically unrelated individuals. The combined features of low interdonor diversity of invariant T-cell receptors and the donor-unrestricted nature of antigen presentation makes these cells important targets for vaccine development (5).

The nonpolymorphic MHC class Ib family in humans (nonclassical HLA class I) includes HLA-E, which presents signal sequence–derived peptides of other HLA class I molecules to inhibit natural killer cell–mediated lysis via CD94/NKG2A recognition (6). However, HLA-E can also bind peptides derived from tumor cells or pathogens and present them to unconventional CD8 T cells, which can be mobilized to fight the specific tumor or infection (7). Indeed, *Mycobacterium tuberculosis* (*Mtb*) peptides presented by HLA-E are targets for human CD8 T cells that have cytolytic and immunoregulatory activities and are able to inhibit *Mtb* growth in infected human macrophages (8–10). Using HLA-E tetramers (TMs), previous studies demonstrated that the *ex vivo* frequency of HLA-E/*Mtb*-peptide-TM$^+$CD8$^+$ T cells is increased in the circulation of patients with active TB and declines after successful chemotherapy (9, 11). More recently, the crystal structure of HLA-E bound to peptide 53-61 of the *Mtb* gene Rv1484 was solved, revealing how peptides might be designed to activate HLA-E–restricted T cells for vaccination (12). An advantage of HLA-E–based vaccines over traditional vaccine strategies targeting HLA class Ia molecules (HLA-A, -B, and -C) is that HLA-E expression is not downregulated by HIV in the context of *Mtb* coinfection (7).

In this issue of the *Journal*, La Manna and colleagues (pp. 430–439) investigate the hypothesis that HIV-1 and *Mtb* coinfection differentially affects the surface expression of HLA-A and HLA-E molecules, impacting the recognition of infected targets by HLA-A2–restricted CD8$^+$ T cells, but not by HLA-E–restricted CD8$^+$ T cells (13). In their study, the authors used peripheral blood mononuclear cells (PBMCs) from patients with TB ($n = 10$), patients with TB/HIV-1 ($n = 7$), and six healthy control subjects. HLA-A2 and HLA-E surface expression was not affected by *Mtb* H37Rv infection in monocyte-derived macrophages (MDMs), but HIV-1$_{Ba-L}$ coinfection differentially downregulated HLA-A2. The authors investigated the consequences of CD8 T-cell recognition using T-cell clones: the HLA-A*0201–restricted clone NFA2-16 recognizing epitope 120-128 of *Mtb Acr* antigen (9), and the HLA-E–restricted clone MV-14E (8) recognizing epitope 53-61 of *Mtb* Rv1484 with the recently reported crystal structure (12). Both clones were able to kill MDMs from HLA-A*0201–typed individuals infected with *Mtb*, but in the presence of HIV-1 coinfection, only MV-14E remained cytotoxic, demonstrating that *Mtb*/HIV-1 coinfection-induced HLA-A2 downmodulation also results in resistance to lysis by HLA-A2–restricted CD8 T cells, whereas HLA-E surface expression and HLA-E–restricted cytolytic activity were not affected. These findings were reproduced using polyclonal CD8 T-cell lines generated from PBMCs of patients with active TB. Using TMs, the authors found that the *ex vivo* frequency of HLA-A2/*Mtb*-peptide-TM$^+$CD8$^+$ T cells was highest in patients with TB, but HLA-E/*Mtb*-peptide-TM$^+$CD8$^+$ T cells were ∼50-fold more abundant in patients with TB/HIV-1 and displayed a terminally differentiated effector memory phenotype. Interestingly, these cells were not able to expand further in culture after specific peptide stimulation and showed extensive apoptosis, as well as high levels of PD-1 (programmed cell death 1) receptor expression in the patients with TB/HIV-1, indicating an exhausted phenotype. A limitation of this study is that it did not include a control group of patients with HIV-1 infection alone; nevertheless, these findings highlight the role of HIV coinfection in T-cell exhaustion.

Immune checkpoints regulate the activation of the immune system: activated T cells expressing immune checkpoints will undergo downregulation of activation and proliferation, ultimately favoring "exhaustion" of the immune response. There has been a recent increase in applications of immune checkpoint blockade for cancer therapy. Monoclonal antibodies that block the coinhibitory receptor PD-1 and one of its known ligands, PD-L1 (programmed cell death ligand 1), result in improved T-cell function and a favorable therapeutic response. A potential role for checkpoint blockade in infectious diseases has also been suggested (14). La Manna and colleagues found that coculturing the anti–PD-1 monoclonal antibody nivolumab with PBMCs from patients with TB/HIV-1 in addition to peptide 53-61 of *Mtb* Rv1484 led to increased proliferation and reduced apoptosis of HLA-E/*Mtb*-peptide-TM$^+$CD8$^+$ T cells compared with control antibody-treated cells.

A major limitation of this *in vitro* model is that it does not consider the complex role of the different components of the immune system. PD-1 knockout (PD-1$^{-/-}$) mice are more susceptible to *Mtb* infection, likely owing to an increased *Mtb*-specific T-cell response that paradoxically leads to excessive production of IFN-γ, exacerbating TB and resulting in early mortality (15–17). So far, no study has investigated the use of PD-1/PD-1L during active TB in humans; however, it may be possible to extrapolate data from several cases of acute TB reported after their use in patients with cancer (18, 19). Barber and colleagues studied the *Mtb*-specific immune response in a patient with Merkel cell carcinoma who developed checkpoint-associated TB after anti–PD-1 administration (19). They observed an expansion of circulating *Mtb*-specific CD4 T cells producing IFN-γ, but not in *Mtb*-specific T-helper cell type 17 or CD8$^+$ T cells. These results corroborate the murine model and highlight the complex balance of the immune system in response to pathogens, which must be carefully considered before strategies to block the PD-1/PD-1L pathway can be applied for the treatment of TB. Further *in vivo* studies are needed to assess the potential benefits and risks of PD-1/PD-1L blockades in the context of TB. However, a vaccination strategy that involves boosting HLA-E–restricted T-cell subsets might be successful in people living with HIV, a population most in need. ■

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