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Programmed Death 1 Lives Up to Its Reputation in Active Tuberculosis

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Programmed death 1 (PD-1; CD279), also known as programmed cell death protein 1 (PDCD-1), is a cell surface receptor of the immunoglobulin superfamily found on immune effector cells. It belongs to the extended CD28/CTLA-4 family of T-cell regulators and is expressed by a range of immune cells, including B cells, natural killer cells, and monocytes. Binding of PD-1 to one of its ligands, PD ligand 1 (PD-L1) or PD-L2, on antigen-presenting cells (APCs) is known to negatively regulate T-cell receptor signaling and inhibit T-cell activation [1]. In this issue of the *Journal*, Singh et al [2] demonstrate that the coinhibitory receptor PD-1 and the PD ligands are expressed on higher percentages of peripheral blood mononuclear cells (PBMCs) of patients with active tuberculosis than those of healthy controls in an area of tuberculosis endemicity. The expression of PD-1 on T cells is upregulated following in vitro stimulation with *Mycobacterium tuberculosis* antigens, and the PD-1 blockade in vitro enhances interferon γ (IFN-γ) and interleukin 2 production by specific T cells and rescues them from undergoing apoptosis. Of particular significance, the authors demonstrate during a 1-year follow-up period a significant decrease in the frequency of PD-1–expressing T cells after successful antituberculosis treatment that led to restoration of the *M. tuberculosis*–specific T-cell cytokine response in vitro. These data substantiate the role of PD-1–PD-L pathways in the inhibition of T-cell responses in patients with active tuberculosis.

Optimal T-cell activation during infection requires 2 signals. The first signal is generated by T-cell–receptor recognition of peptide–major histocompatibility complex presented by an APC, while the second signal is provided by binding of costimulatory receptor CD28 on the

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T-cell surface with one of the classic B7 family members (CD80 or CD86) on the APC. However, the persistent immune activation that is typical of chronic viral infections is marked by increased expression and signaling through the inhibitory receptors like PD-1 and results in exhaustion and dysfunction of T cells [3, 4]. Pulmonary tuberculosis is usually a chronic lung disease, and both $CD4^+$ and $CD8^+$ T-cell responses play an important part in protection against *M. tuberculosis* infection. Previously, PD-1 expression on the PBMCs, pleural fluid mononuclear cells [5], and natural killer cells [6] was shown to be upregulated following in vitro antigen stimulation in patients with tuberculosis, suggesting that this upregulation may be one of the potential mechanisms of impaired innate and adaptive immune responses in active tuberculosis. Studies performed to date using a PD-1 knockout mouse strain or passive transfer of PD-1–expressing *M. tuberculosis*–specific T cells in mice did not conclusively demonstrate the possible role of PD-1 in T-cell exhaustion or dysfunction in chronic *M. tuberculosis* infection [7–9]. It has been suggested that a number of pathogens induce immune evasion by upregulating PD-1 or its ligands, and the blockade of the PD-1/PD-L pathway in most of these models enhances immune functions for the benefit of the host. This concept led to the expectation that PD-1–deficient mice might elicit sterilizing immune response against *M. tuberculosis* after challenge. Unexpectedly, PD-1–deficient mice showed extreme sensitivity to *M. tuberculosis* aerosol infection, with reduced survival and a higher bacillary burden in the lungs [7]. This effect was associated with profoundly upregulated inflammatory responses in the lungs, with focal necrotic areas showing neutrophilic infiltrates, suggesting that the PD-1 pathway is required to control excessive inflammatory responses after *M. tuberculosis* infection. Adoptive transfer studies of *M. tuberculosis*–specific $CD4^+$ T cells from PD-1 knockout mice further demonstrated that the $CD4^+$ T cells promote *M. tuberculosis* infection in the absence of normal PD-1 inhibition [9]. The observation of increased *M. tuberculosis* susceptibility in PD-1 knockout mice led to the suggestion that PD-1 does not play an inhibitory role during *M. tuberculosis* infection but instead promotes *M. tuberculosis* clearance [8]. Next, a study evaluating the role of PD-1 in $CD4^+$ T-cell exhaustion in the mouse model of tuberculosis suggested that the PD-1 expression identifies a population of activated effector T cells, and PD-1–expressing cells transition into terminally differentiated killer cell lectin-like receptor subfamily G member 1 (KLRG1)–expressing effector cells [10]. This led to the conclusion that PD-1 and KLRG1 identify differentiating, but not exhausted, $CD4^+$ T cells in *M. tuberculosis*–infected mice during the 1-year follow-up period after infection [10].

The current study by Singh et al [2] demonstrates the numeric dominance of inhibitory PD-1 receptor– and ligand(s)–expressing T cells, $CD19^+$ B cells, and $CD14^+$ monocytes or macrophages in the PBMCs of patients with pulmonary tuberculosis, compared to that in healthy controls. The study shows that the PD-1–PD-L1/L2 pathways are actively involved in inhibiting cytokine production and proliferation of *M. tuberculosis*–specific T cells. The majority of patients with tuberculosis used in their study had moderate or far-advanced disease, and the authors show that the frequencies of $PD\text{-}1^+$ T cells and per-cell expression of PD-1 receptors significantly correlate with the bacillary load in the sputum of patients with newly diagnosed tuberculosis. Although the results of the study by Singh et al that describe the immune-inhibitory role of PD-1 in the pathogenesis of human tuberculosis appear paradoxical in the context of previously published observations describing reduced

survival of PD-1 knockout mice after *M. tuberculosis* challenge, together these results offer a more complete picture regarding the role of PD-1 in human *M. tuberculosis* infection and disease. It is possible that the *M. tuberculosis* infection may upregulate expression of PD-1 ligands on APCs, and presentation of *M. tuberculosis* antigens by APCs may lead to production of IFN-γ by T cells, which in turn may upregulate PD-1 expression on T cells. The authors propose that the basal level of PD-1 expression might play a homeostatic role in shaping T-cell responses during early *M. tuberculosis* infection in humans and help control the excessive inflammatory response. However, the persistent antigen stimulation during chronic *M. tuberculosis* infection may promote overexpression of PD-1 on T cells, leading to dysfunction or exhaustion.

Although 50% of healthy controls investigated by Singh et al were tuberculin skin test positive, *M. tuberculosis* infection in these donors was not confirmed. Therefore, it was not possible to determine the level of PD-1 expression on the T cells of infected versus noninfected BCG-vaccinated healthy controls and how it compares with that of patients with active tuberculosis in this study. It was previously shown that individuals with latent *M. tuberculosis* infection harbor high frequencies of late-stage, differentiated, antigen-specific, PD-1–expressing effector memory $CD4^+$ T cells, while uninfected BCG-vaccinated individuals have primarily early stage cells with low PD-1 expression [11], where PD-1 expression was evaluated after in vitro stimulation of PBMCs with *M. tuberculosis* antigens. In individuals with latent *M. tuberculosis* infection, PD-1–expressing antigen-specific $CD4^+$ T-cell subsets produced cytokines and were polyfunctional, suggesting that these T cells were not exhausted. The authors of the study [11] speculated that PD-1 levels on antigen-specific effector memory $CD4^+$ T cells may identify individuals whose infection is at the higher end of the proposed spectrum of latency and are at the greatest risk of developing active disease. Confirmation of this thesis would require longitudinal tracking of $CD4^+$ T-cell responses and PD-1 expression in a nonhuman-primate model of *M. tuberculosis* infection studying the transition from latent infection to active disease. Use of 4-color flow cytometry by Singh et al also limited the characterization of the different APC subsets investigated, and simultaneous expression of PD-1 and other markers of exhaustion or terminal differentiation on different T-cell subsets were not studied. In the absence of *M. tuberculosis*–specific tetramers or “touch markers,” it was not possible to investigate PD-1 expression on *M. tuberculosis*–specific T cells in patients with tuberculosis and controls. Nevertheless, this study [2] shows that the frequency of PD-1–expressing cells is increased during active tuberculosis and declines in PBMCs during successful antituberculosis therapy.

These results may form the basis of further evaluation of PD-1 as a possible biomarker to monitor the success of antituberculosis therapy in active disease, along with other markers of T-cell exhaustion. It will be interesting to evaluate PD-1 expression at the site of infection and whether PD-1 expression increases in patients with treatment failure and relapse. Targeting PD-1 pathways by using in vivo blockade has been shown to improve antiviral immune responses in animal models [12], but there have been concerns that it would also lead to increased inflammation and immunopathology. It was recently shown that PD-1 blockade actually reduces proinflammatory responses and improves immunity in simian immunodeficiency virus (SIV)–infected macaques, suggesting that this effect might have therapeutic potential in chronic infections [13]. However, caution is warranted while

considering it in cases of coinfection with *M. tuberculosis*. While PD-1 blockade may hold therapeutic potential in patients with advanced tuberculosis, it may potentially exacerbate T-cell activation in an already persistent inflammatory setting in latent tuberculosis, potentially leading to accelerated disease progression. Further studies in the nonhuman-primate model of tuberculosis may help decipher the therapeutic potential and alleviate some of these concerns. Recently, PD-1 was also found to be transiently expressed on M-72–specific $CD4^+$ T cells following vaccination of healthy adults [14], and it will be interesting to see whether it positively or adversely affects the protective efficacy of M-72/AS01 vaccine in human clinical trials. Overall, the results of Singh et al substantiate an inhibitory role of PD-1 in patients with active tuberculosis and, together with previously published studies, underscore the importance of a complex balance between proinflammatory and antiinflammatory host factors in the control of *M. tuberculosis* infection.

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