

PD-1: Dual guard for immunopathology

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Despite remarkable medical development, chronic infectious diseases caused by the infections with persistent pathogens such as hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and *mycobacterium tuberculosis* (*M.tb*), have not been conquered yet. During the chronic infection, the interaction between host and chronic pathogen often fosters immune suppressive environment. Such environment leads to the exhaustion of pathogen-specific T cells, resulting in the failure to the eradication of pathogen but the success to the protection of host from immunopathological damage. Finally, host and pathogen ensure the reduction of host immunopathology but the extension of pathogen persistence.

Under the persistence of pathogens, effector T (T_{eff}) cells lose progressively their effector function such as cytokine production and proliferative potential and finally become exhausted T (T_{exh}) cells. T-cell exhaustion can be caused by various factors including immune checkpoints, cytokines, regulatory T (T_{reg}) cells, and altered antigen presenting cells (APCs) [1]. Immune inhibitory receptors, also known as immune checkpoints, such as programmed death-1 (PD-1), T-cell immunoglobulin mucin 3 (TIM-3), cytotoxic T lymphocyte antigen-4 (CTLA-4), and lymphocyte activation gene-3 (LAG-3) are expressed on T_{eff} cells by T-cell receptor (TCR) stimulation and their expressions are maintained or even increased by repeated TCR stimulation during chronic infection. Upon ligands binding, such checkpoints are triggered to transmit inhibitory signal into T_{eff} cells by alone or their combination, which leads to the generation of T_{exh} cells and the attenuation of T-cell-mediated immunopathology. The interaction of PD-1 and its ligand, PD-L1, has been known to play a critical role in the exhaustion of T_{eff} cells. The role of PD-1 during chronic pathogen infection in suppressing T-cell function was demonstrated in the mouse model chronically infected with lymphocytic choriomeningitis virus (LCMV) [2]. This study showed that blockade of PD-1:PD-L1 interaction during chronic LCMV infection controlled viremia by restoring the function of virus-specific T_{exh} cells. More specifically, only PD-1⁺ CD8⁺ T cells, but not PD-1⁻ CD8⁺ T cells, regained their function upon PD-1:PD-L1 blockade, indicating that the effect of PD-1 on T-cell exhaustion is T-cell-intrinsic (Figure 1). Another interesting point was that PD-L1-deficient mice succumbed to chronic LCMV infection, resulting in death of mice within one week post-infection. PD-1:PD-L1 pathway seemed to be also critical in protecting mice from

persistent bacterial infection because PD-1-deficient mice were extraordinarily sensitive to tuberculosis [3]. These data strongly suggests that PD-1:PD-L1 pathway regulates immune-mediated tissue damage during persistent infection by paralyzing the pathogen-specific T cells.

The claim that PD-1 expressed by T cells is a culprit of T-cell exhaustion is now generally accepted but there can be another causing factors. One of the candidates is T_{reg} cells, which play an important role for maintaining immunological self-tolerance and controlling T-cell-mediated autoreactive T-cell attack on tissue, because a number of studies showed the increase of T_{reg} cell population during persistent viral, helminthic, and bacterial infections. Depletion of T_{reg} cells in the mice chronically infected with LCMV was reported to strikingly expand functional LCMV-specific CD8⁺ T cells,

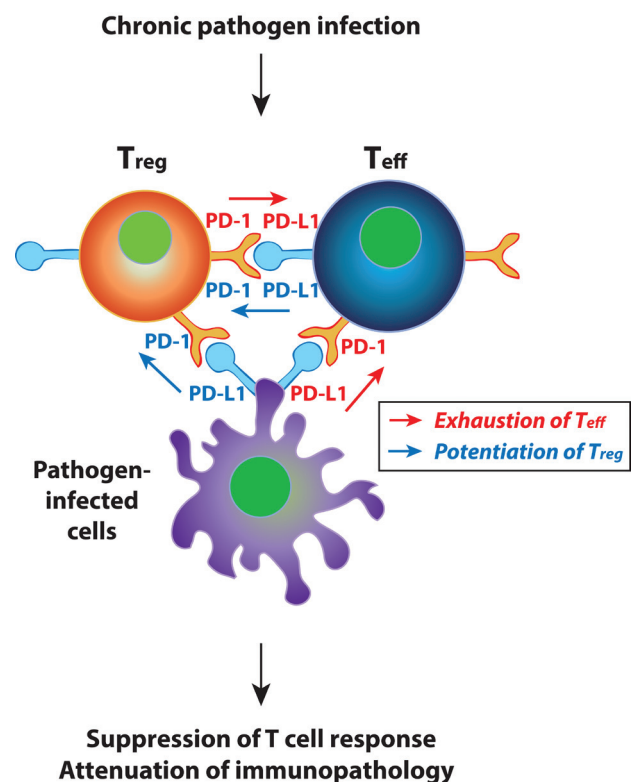


Figure 1: PD-1:PD-L1 pathway as a dual guard for the protection of immunopathological damage. PD-1 is highly upregulated on T_{reg} cells as well as T_{eff} cells during chronic pathogen infection. PD-1:PD-L1 interactions between T_{eff} cells and pathogen-infected cells or between T_{reg} cells and T_{eff} cells provide T_{eff} cell exhaustion signal or T_{reg} cell potentiation signal, thereby attenuating immunopathology.

suggesting the role of T_{reg} cells in the suppression of T-cell immune response during persistent pathogen infection [4]. However, this temporal ablation of T_{reg} cells failed to not only diminish viremia but promote immunopathology because it also triggered upregulation of PD-L1 on LCMV-infected cells, which again delivers negative signal to PD-1-expressing T cells. It has been widely known that T_{reg} cells constitutively express some immune checkpoints such as CTLA-4 and LAG-3. Of particular interest, like T_{exh} cells, T_{reg} cells during chronic pathogen infection was reported to further upregulated immune checkpoints including CTLA-4, LAG-3, PD-1, and TIM-3 [4,5,6]. However, while T_{eff} or T_{exh} cells-expressed immune checkpoints debilitate their effector function, T_{reg} cells-expressed ones, especially CTLA-4, have been reported to potentiate their suppressor function in direct or indirect way. For instance, CTLA-4 expressed by T_{reg} cells modulates dendritic cells (DCs), thereby enhancing T_{reg} cell suppressive function as positive regulator [7]. Taken together, albeit such a complexity, it is evident that T_{reg} cells can contribute to the inhibition of T-cell response and the protection of tissue from T-cell-mediated pathology.

In spite of the observation that PD-1 is upregulated on T_{reg} cells during chronic infection, it is less known about the role of PD-1 expressed by T_{reg} cells. We recently found that PD-1^{hi} T_{reg} cells generated during chronic LCMV infection displayed much stronger suppressive activity than PD-1^{lo} T_{reg} cells present in steady state [6]. Either PD-1 blockade on PD-1^{hi} T_{reg} cells or PD-L1 deficiency on T_{eff} cells dramatically ablated T_{reg} cell-mediated suppression of T_{eff} cell immune response, demonstrating the necessity of PD-1 on T_{reg} cells and PD-L1 on T_{eff} cells. These results highlight a critical role of PD-1:PD-L1 interaction between T_{reg} cells and PD-L1 on T_{eff} cells and define PD-1 upregulated on T_{reg} cells as a prerequisite for T_{reg} cell-mediated strong suppression (Figure 1). It should be further investigated for the molecular mechanism by which whether a ligation of PD-L1 in T_{eff} cells onto PD-1^{hi} T_{reg} cells triggers PD-1 signal in T_{reg} cells or a reverse signal via PD-L1 in T_{eff} cells upon a ligation of PD-1 provided by T_{reg} cells inhibits T_{eff} cell function. If the former is applied *in vivo*, PD-L1 is probably provided by pathogen-infected APCs as well as T_{eff} cells. Regarding cell-specific expression of PD-1, our results propose that

PD-1 expressed by T_{reg} cells, in addition to that by T_{exh} cells, contributes to the functional suppression of T_{eff} cells and subsequent attenuation of immunopathology (Figure 1).

Collectively, PD-1:PD-L1 interaction is a major strategy for the suppression of T_{eff} cell-mediated immune response during chronic pathogen infection. Meanwhile, in regard to the immunopathological damage, PD-1:PD-L1 interaction protects T_{eff} cell-mediated tissue damage in the host. Of importance, PD-1:PD-L1 interaction is capable to occur in between T_{reg} cells and T_{eff} cells, in addition to between T_{eff} cells and pathogen-infected cells. In both case, T_{eff} cells become exhausted via direct interaction with separate partners and eventually fail to not only eradicate pathogens but also induce immunopathology in the host. Lastly, these studies provide perspectives regarding the practical and clinical treatment strategies for chronic infectious disease. Blockade of PD-1:PD-L1 can be useful to treat efficiently chronic virus infection but its potential risk for immunopathologic damage needs to be carefully monitored.

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Keywords: Immunology and Microbiology Section, Immune response, Immunity

Received: July 02, 2015

Published: July 05, 2015

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