

# PD-1, PD-L1 and their ligands: Regulating the balance between T cell activation and tolerance

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## Abstract

Pathways in the B7:CD28 family provide signals that regulate the activation, inhibition, and fine-tuning of T cell responses. The B7-1/B7-2:CD28/CD152(CTLA-4) pathway is the best-characterized T cell costimulatory pathway. The B7/CD28 family has expanded to include other costimulatory and inhibitory pathways. One of the newer co-inhibitory receptors is PD-1, which is inducibly expressed on the surface of T cells. PD-1 interacts with two B7 family members, PD-L1 [B7-H1; CD274] and PD-L2 [B7-DC; CD273], which have distinct expression patterns. PD-L1 is constitutively expressed on murine antigen presenting cells (including dendritic cells, macrophages and B cells) and T cells, and is further upregulated upon activation. PD-L1 is also expressed on a wide variety of non-hematopoietic cell types, including vascular endothelial cells, pancreatic islet cells, and at sites of immune privilege including the placenta and eye. In contrast, PD-L2 is inducibly expressed on DCs, macrophages and B1 B cells.

PD-1 and its ligands deliver signals that regulate T cell activation, tolerance and immune-mediated tissue damage. Our studies and those of others indicate that PD-1 and its ligands regulate peripheral CD4 and CD8 T cell tolerance. We will present our studies showing that PD-1 and its ligands regulate peripheral T cell tolerance at multiple checkpoints. PD-1:PD-L interactions are important during the initial phase of activation and expansion of self-reactive T cells. Interactions between PD-1 and PD-L1 also inhibit self-reactive T cell effector function during antigen re-encounter. Our bone marrow chimera studies have shown that PD-L1 on non-hematopoietic cells mediates tissue tolerance, controlling the intensity of T cell effector responses in non-lymphoid organs and shielding tissues from potentially pathogenic self-reactive T cells and immune-mediated tissue damage.

A number of microorganisms and tumors appear to have exploited PD-1 and PD-L1 to evade eradication by the immune system. Studies in the lymphocytic choriomeningitis (LCMV) model were the first to demonstrate a role for the PD-1:PD-L pathway during chronic viral infection. Viruses that cause chronic infections can render virus-specific T cells nonfunctional ("exhausted") and thereby impair antiviral T cell responses. PD-1 expression is high on "exhausted" LCMV-specific T cells, and blockade of PD-1:PD-L1 interactions can reinvigorate T cell functions and reduce viral burden *in vivo* during chronic LCMV infection. Similarly, PD-1 expression is high on Human immunodeficiency virus (HIV)-specific, Hepatitis B virus (HBV)-specific and Hepatitis C virus (HCV) specific T cells in humans. The level of PD-1 expression may serve as a useful marker on virus-specific T cells to indicate the degree of T cell exhaustion and disease severity. Blockade of PD-1:PD-L1 interactions *in vitro* can restore proliferation and cytokine production to exhausted HIV-specific, HBV-specific and HCV-specific T cells. Taken together, these findings

indicate that the PD-1:PD-L pathway contributes to T cell dysfunction and lack of viral control in chronic infection, and suggest PD-1 or PD-L1 blockade may serve as a novel therapeutic approach for chronic viral infections.

PD-1 and PD-L1 also may contribute to the immunosuppressive tumor microenvironment. PD-1 expression is upregulated on tumor infiltrating lymphocytes, and PD-L1 is expressed on a wide variety of tumors. Studies relating the level of PD-L1 expression on tumors with disease outcome suggest that high levels of PD-L1 expression on tumor cells strongly correlate with poor prognosis in human kidney, ovarian, and bladder, breast, gastric, and pancreatic cancers. Studies in animal models demonstrate that PD-L1 on tumors can inhibit T cell activation and lysis of tumor cells and in some cases leads to increased death of tumor-specific T cells. These results identify PD-1 and PD-L1 as attractive therapeutic targets for tumor immunotherapy.

A number of studies have suggested additional receptors for PD-L1. We have found that PD-L1 and B7-1 bind to each other with an affinity greater than the affinity of B7-1 for CD28, but less than the affinity of B7-1 for CTLA-4. This interaction is restricted to B7-1 and PD-L1. B7-2 does not interact with PD-L1, nor does PD-L2 interaction with B7-1. Both biophysical and cell based assays demonstrate that this interaction is functionally significant. Our studies indicate that PD-L1:B7-1 interactions can induce bidirectional inhibitory signals in T cells *in vitro*. The identification of the PD-L1:B7-1 interaction gives increased significance to B7-1 and PD-L1 on T cells. Further work is needed to investigate whether PD-L1:PD-1 and PD-L1:B7-1 interactions have unique or overlapping roles in controlling T cell activation and tolerance.