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PD-1 as an Immune Modulatory Receptor

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Abstract

Programmed cell death 1 (PD-1) is an inducible immune modulatory receptor. Upon interaction with its ligands B7 homolog 1 (PD-L1) and B7-DC (PD-L2), PD-1 plays important roles in negative regulation of T cell responses to antigen stimulation and maintaining peripheral tolerance. In addition to the inducible expression pattern on conventional T cells, PD-1 is also found on regulatory T cells, follicular T and B cells, and antigen-presenting cells including activated dendritic cells and monocytes. Therefore, PD-1 may have a much broader functionality than expected in negative regulation of multiple arms of immune responses. In addition to cancer therapy, the manipulation of PD-1 and its ligands may hold great promise for therapeutic applications also in autoimmune and infectious diseases.

Keywords

Programmed cell death 1 (PD-1); cancer therapy

In recent years, immunotherapy targeting cell surface immune modulatory molecules on host immune cells, especially the B7-H1 (B7 homolog 1)/PD-1 pathway, has emerged as a promising clinical strategy for the treatment of cancer with the potential to induce durable memory responses. Complementing other articles in this special issue, in this review we focus on the expression profile and physiological function of the PD-1/B7-H1 pathway weighted toward PD-1 receptor.

THE DISCOVERY AND IMMUNE MODULATORY FUNCTIONS OF PD-1

Programmed cell death 1 (PDCD1, PD-1), a CD28 receptor family member, was first isolated from a murine T cell hybridoma and a hematopoietic progenitor cell line undergoing classic apoptosis in 1992.[1] The expression of PD-1 was associated and suggested to play an active role in programmed cell death of lymphocytes. Subsequent study found PD-1 was upregulated on activated T and B lymphocytes, while absent or expressed at low level on the naive counterparts.

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Even before the discovery of its ligands, the critical function of PD-1 in controlling lymphocyte activation and maintaining peripheral tolerance was evident in PD-1–deficient mice.[2–4] First reported in 1999, PD-1–deficient mice in C57BL/6 background develop lupus-like proliferative arthritis and glomerulonephritis spontaneously at senior age (>14 months).[3] Accordingly, PD-1–deficient T cell has greatly enhanced proliferation against allogeneic antigen in vitro and in vivo. Programmed cell death 1–deficient mice on different strain backgrounds were later found to have different degree and divergent autoimmune conditions. In BALB/c, but not in immune-deficient BALB/c RAG2−/− background, PD-1 knockout mice develop dilated cardiomyopathy and suffer sudden death by congestive heart failure.[4] One of the major contributing causes is later identified to be the generation of high-titer autoantibodies against the heart-specific protein cardiac troponin I.[5] In NOD (nonobese diabetic) background, PD-1 deficiency leads to early onset of type I diabetes due to the accelerated islet-specific T cell expansion and infiltration into pancreas islets.[2] The molecular basis for PD-1–mediated suppression depends on its long cytoplasmic domain, which harbors an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Both ITIM and ITSM motif serve as docking sites for phosphatases upon cross-linking. Experimental data indicate that the ITSM motif, but not the ITIM domain of PD-1, recruits SHP-2 phosphatase and reverses activation-induced phosphorylations downstream of T cell receptor signaling.[6,7] Recently, casein kinase 2 was identified as another direct downstream target of PD-1 signaling, which in turn enhanced the phosphatase and tensin homolog (PTEN) phosphatase activity, and thus inhibiting phosphatidylinositol-3-kinase/Akt pathway.[8]

THE LIGANDS AND THEIR FUNCTIONS OF PD-1

A major advancement in understanding of the physiological function and regulation of PD-1 was the identification of 2 PD-1 ligands, B7-H1 and B7-DC, in 2000[9] and 2001,[10] respectively. B7 homolog 1, the third member of B7 ligand family, also known as PD-L1 and CD274, was first identified in 1999 by homology search against B7-1 and B7-2 sequences, and its immunesuppressive functions were suggested by in vitro study using human T cells.[11] As a common scene among the B7 family members, human B7-H1 shares a relatively low 20% and 15% protein sequence identity with human B7-1 and B7-2, respectively, in the extracellular domains.[11] The expression of both human and murine B7-H1 messenger RNA has broad tissue distribution, including primary and secondary lymphoid organs (thymus, bone marrow, spleen, and lymph node) and peripheral organs (heart, lung, kidney, liver skeletal muscle, placenta, etc). In contrast, constitutive surface expression of B7-H1 was restricted to antigen-presenting cells (APC) in lymphoid tissues and resident dendritic cell (DC)/macrophage-like cells in the peripheral organs and cells at immune-privileged sites, including placenta, pancreas islet, and retina.[12,13] Expression of B7-H1, however, could be induced on a variety of tissue and cell types, including T cell, B cell, natural killer cell, DC/macrophage/monocyte, mesenchymal stem cell, cultured bone marrow–derived mast cell, and peripheral epithelial and endothelial cells upon stimulation by proinflammatory cytokines, such as interferons and tumor necrosis factor (TNF).[14–17] The B7-H1 expression profile implicates a role in APC function and host response to

inflammatory stimuli. The detailed description of B7-H1 molecules and their functions in the evasion of tumor immunity could be found in this series (Sanmamed and Chen).

B7-DC, also known as PD-L2 and CD273, a B7 family ligand discovered in 2001, shares the highest sequence similarity (48%) with B7-H1.[18] However, unlike the broad inducible expression pattern of B7-H1, surface expression of B7-DC is restricted to dendritic cells and macrophages, implicating a role in APC function. More recently, B7-DC has been found to bind RGMb (repulsive guidance molecule b), which express preferentially in lung and brain, and may participate in the induction of pulmonary tolerance.[19]

The differential expression patterns of B7-DC and B7-H1 indicates B7-H1 may be the main inducible regulatory ligand for PD-1 in peripheral tissues in response to inflammation whereas B7-DC together with B7-H1 serve as ligands for PD-1 during antigen priming and T-cell activation in the secondary lymphoid organs.[20] This hypothesis of differential ligand function is supported by several animal disease models using systematic administration of specific blocking antibodies against B7-H1 or B7-DC disrupting PD-1 interaction. Antibody against B7-H1, but not B7-DC, accelerated experimental autoimmune encephalitis,[21] autoimmune diabetes,[22] autoimmune hepatitis,[23] and graft-versus-host disease.[15] Furthermore, by comparing genetic ablated mice, the suppressive function of PD-1 pathway in the periphery has been attributed largely through the engagement of B7-H1 rather than B7-DC in vivo.[24] Native islet expression of B7-H1, but not B7-DC, protects against attack from autoreactive T cells after transplantation of syngeneic islets into recipients with type 1 diabetes.[25] Furthermore, the expression and function of B7-H1 are also dominant over B7-DC in regulating graft-versus-host disease– induced lethality.[26]

Interactions of PD-1 with these ligands have been explored extensively for their roles in the regulation of immune responses in general and in organ-specific diseases. Mechanisms of T cell suppression induced by these interactions will be discussed in another article in this series (Sanmamed and Chen).

THE EXPRESSION AND FUNCTION OF PD-1 ON T FOLLICULAR HELPER CELLS AND B CELLS

The expression of PD-1 on activated B cells has long been observed,[27] and the augmentation of circulating autoantibody levels has also been reported in PD-1–deficient mice.[3] However, compared with the well-studied suppressive function of PD-1 in regulating activated T cell, the underlying mechanisms of how PD-1 modulates B cell activation and affects antibody production remain largely uncertain. The finding that T follicular helper cell (Tfh) (CXCR5+ICOS+CD4+ cells) expresses high levels of surface PD-1 indicates that PD-1 could regulate B cell activation and antibody production directly or via Tfh cell–dependent pathways.[28] Located at germinal center (GC), Tfh cells play a crucial role in B cell activation, maturation, and differentiation tomemory B cell or plasma cell (PC). Within GC, both B7-H1 and B7-DC are up-regulated on GC B cells and engage PD-1 on Tfh cells.[29] Disruption of PD-1 pathway by gene ablation leads to a prominent reduction of long-lived PC, which potentially alters the composition and balance of antibody responses.[29] In a separate study, the total number of Tfh cells is significantly elevated in PD-1–deficient mice,

which leads to altered IgA production in the intestine and profound change of commensal microbial flora.[30]

The expression of PD-1 on anti–immunoglobulin M–activated mouse B cell was first reported in 1996.[27] Subsequent study on human B cell reveals naive B cell and immunoglobulin M memory B cell, but not GC B cell, express PD-1.[31] Blockade of PD-1 pathway by antibodies in vitro enhanced B cell activation, cellular proliferation, and production of inflammatory cytokines.[31] Upon ligand engagement, PD-1 was recruited and colocalized with B cell receptor complex, indicating a potential direct impact on BCR signaling through PD-1 intracellular domain. As a result, the elevated antibody response in the absence of PD-1 is likely a combined consequence from alternations in both Tfh function and memory B cell/PC differentiation.

THE EXPRESSION AND ROLE OF PD-1 ON REGULATORY T CELL AND FOLLICULAR REGULATORY T CELL

As often observed for other T cell activation markers, PD-1 is also expressed on regulatory T cell, which plays instrumental roles in maintaining peripheral tolerance. B7-H1–deficient DC had impaired ability to promote the differentiation of native T cell to inducible Treg (iTreg) in the presence of TGF-β.[32] In contrast, B7-H1 cross-linking enhances and sustains FOXP3 expression in iTreg and maintains iTreg-suppressive function.[32] Mechanistically, B7-H1 enhances PTEN expression while attenuating phosphatidylinositol-3-kinase/Akt pathway during iTreg conversion. B7-H1/PD-1 axis could therefore inhibit T cell activation and simultaneously promote iTreg expansion and maintain iTreg-suppressive function. In addition to the traditional Tfh cell, PD-1 is also highly expressed on a recently defined CXCR5+ ICOS+ FOXP3+ CD4+ follicular regulatory T cell (TFR).[33] TFR is thought to negatively regulate Tfh cell function. In the absence of PD-1 or B7-H1, TFR cell number was significantly elevated with enhanced suppressive function, indicating PD-1 also negatively regulates TFR function.[33]

THE EXPRESSION AND SUPPRESSIVE FUNCTION OF PD-1 ON APCs

In addition to its expression on activated T and B lymphocytes, PD-1 was later found to be inducible on activated macrophages, DCs, and monocytes, while absent from the naive cells.[34,35] Activation-induced PD-1 expression on these cell types was shown to suppress both adaptive and innate immune responses.[34,35] Programmed cell death 1 can be induced on mouse splenic DC by various stimuli including Toll-like receptor ligands and suppresses the production of inflammatory cytokine by DC. Programmed cell death 1–deficient mice are more resistant to *Listeria* infection than wild-type controls, even in the absence of T and B lymphocytes in Rag1 knockout background. Rag1 PD-1 double-deficient mice produce higher level of DC-derived IL-12 and TNF-α than Rag1-deficient mice immediately after *Listeria* challenge.[34] Human immunodeficiency virus–infected patients also had elevated PD-1 expression on circulating monocytes, which correlated with the increased IL-10 level in the plasma. Importantly, monocyte-associated PD-1, when engaged by B7-H1, enhanced the production of IL-10, which in turn shut down CD4 T cell response. Activation-induced, APC-associated PD-1 thus serves as an innate immune response checkpoint, which could

directly inhibit monocytes/DC-derived inflammatory cytokines such as IL-12 and TNF-α while promoting the production immune-suppressive cytokine IL-10.

SUMMARY

The B7-H1/PD-1 pathway is the master controller of peripheral tolerance. B7-H1 is rapidly up-regulated in the peripheral tissues in response to inflammation to shut down immune responses through PD-1 expressed on lymphocytes and APCs. B7-H1/PD-1 axis is the host "peace-keeping" force to prevent immunopathology as a consequence of lymphocyte overactivation. This safeguarding mechanism is exploited by cancer and virus to promote immune evasion. In the meantime, therapeutic B7-H1/PD-1 blockade has generated unprecedented objective responses and long-lasting clinical effects in cancer therapy and holds great potential in treating infectious diseases.

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