Structure of PD1 and its Mechanism in the Treatment of autoimmune diseases

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Abstract

PD-1 and CTLA-4 can play an important role in addressing the issue of autoimmune diseases. PD-1 is a transmembrane glycoprotein expressed on T, B, and Dentric cells. This molecule functions as a checkpoint in T cell proliferation. Ligation of PD-1 with its ligands stimulates the production of IL-2, IL-7, IL-10, and IL-12 as well as other cytokines, which can inhibit cell proliferation and inflammation. Today, scientists attempt to protect against autoimmune diseases by PD-1 inhibitory signals. In this review, we discuss the structure, expression, and signaling pathway of PD-1. In addition, we discuss the importance of PD-1 in regulating several autoimmune diseases, reflecting how manipulating this molecule can be an effective method in the immunotherapy of some autoimmune diseases.

Structure of PD1 and its Mechanism in the Treatment of autoimmune diseases

Running title: PD1 acts as a potential target in the treatment of autoimmune diseases. Given the importance of PD-1 in regulating several autoimmune diseases, manipulating this molecule can be an effective method in the immunotherapy of some autoimmune diseases

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in T cell proliferation. Ligation of PD-1 with its ligands stimulates the production of IL-2, IL-7, IL-10, and IL-12 as well as other cytokines, which can inhibit cell proliferation and inflammation. Today, scientists attempt to protect against autoimmune diseases by PD-1 inhibitory signals. In this review, we discuss the structure, expression, and signaling pathway of PD-1. In addition, we discuss the importance of PD-1 in regulating several autoimmune diseases, reflecting how manipulating this molecule can be an effective method in the immunotherapy of some autoimmune diseases.

Keywords : Autoimmunity; Programmed cell death-1; T cells; Anti-PD-1 therapy; Type 1 diabetes; Rheumatoid Arthritis; systemic lupus erythematosus

Significance paragraph:

1. The structure, expression, and signaling pathway of PD-1 were discussed in this article.

2. The importance of PD-1 in regulating several autoimmune diseases reflects how manipulating this molecule can effectively treat some autoimmune diseases.

Introduction

Two mechanisms adjust the activation of T-cells, peptide and MHC linkage to the T cell receptor (TCR) and co-stimulatory signals (1). Several co-stimulatory receptors are responsible for the regulation of positive and negative T cell responses. CTLA 4 and PD-1 (which are also called PDCD1 and CD279 are the negative regulators of immune responses (2). PD1 confronts positive signals through the T cell receptor (TCR) and CD28 by emitting its ligands: PDL-1 and PDL-2 (3). PD1 and PDL1 are found on B cells, T cells, macrophages, and several dendritic cell (DCs) types.

The bondage of PD-1 to its ligand, PD-L1, results in the control of self-reactivity, induction of tolerance, and prevention of autoimmunity (4). Therefore, disruption in this pathway can hugely impact host physiology, and PDCD1-deficient mice showed precipitated autoimmunity. This supports the critical role of PD-1 in controlling T cell responses (5).

In this review, our main focus is on the physiological role of PD1 and its ligands in immunotherapy. To provide a context for these studies, we first explain the structure and expression of PD-1, then briefly review PD-1-mediated signaling and its role in autoimmunity. Preclinical and clinical findings indicate that modulation of PD-1 is a promising strategy for the treatment of autoimmune diseases such as rheumatoid arthritis, type 1 diabetes, and lupus erythematous.

Structure, expression, and ligands of programmed cell death 1 (PD-1)

Two signals activate T cells: The primary signal is provided by TCR, which is an incomplete one, and the second one is provided by a costimulatory receptor, that strengthens the responses. An important group of these costimulatory receptors is provided by ligation between the T cell membrane proteins CD28 and its ligands B7.1 (CD 80) and B7.2 (CD86) which plays a major role in T lymphocyte stimulation (6). This family contains an increasing number of diverse proteins classified by the single-chain glycoprotein, which gives rise to two extracellular Ig-like domains, along with a transmembrane section and an intracytoplasmic region (7). Among B7 members, PD1 has been assuming importance recently.

PD-1 is categorized in the extended CD28/CTLA-4 family of T cell regulators; however, Its domain has 21-23 % sequence similarity with CTLA-4 (8). PD1 is a type I transmembrane glycoprotein and consists of an IgV-type extracellular domain, a trans-membrane region, and an intracellular tail (9). The extracellular domain stands for an immunoglobulin variable region and the tail includes an immunoreceptor tyrosine-based inhibitory motif (ITIM) and several individual phosphorylation sites in immunoreceptor tyrosine-based switch motif (ITSM) (10). PD-1(CD279) consists of 268 amino acids encoded by the PDCD1 gene.

In humans, the PD-1 gene is located on chromosome 2 and has approximately 9 Kb size, and consists of 5 exons. Exon 1 encodes a short signal sequence, exon 2 encodes an Ig domain, the third exon contains stalk and transmembrane domains, and the fourth exon encodes a short 12 aa sequence, which marks the beginning of the cytoplasmic domain. The C-terminal intracellular residues and a long 3 UTR are contained in exon five (11). Nielsen et al. cloned four variants of PD-1 mRNA transcripts, including PD-1[?]ex2, PD-1[?]ex3, PD-1[?]ex2,3, and PD-1[?]ex2,3,4, and the full-length isoform (12). upon activation of T cells with anti-CD28 and anti-CD3, all variants are expressed (12).

PD-1 is expressed on myeloid cells, NK cells, T, and B cells (13). NK cells with a more stimulated phenotype express larger amounts of PD1 in comparison to NK cells with a fatigued phenotype (14). Stimulated T cells express PD-1 on their surface and emit interferons that encourage the expression of PD-L1 in several tissues In a mouse model of cytomegalovirus infection (MCMV), endogenous glucocorticoids have been confirmed to join microenvironmental signals to trigger PD-1 expression, including tissue-specific cytokines and neuroendocrine (15). PD-1 expression is regulated by multiple mechanisms.

Several factors are involved in the regulation of PD-1 expression. Cytokine-induced STAT family of proteins and insulators (CTCF) bind to DNA on the PDCD-1 gene (16, 17). At least 8 - cis-regulatory elements regulate PDCD-1 expression, and two conserved regions (CR-B and CR-C) are involved in PDCD-1 activation (18, 19). In the regulation of expression, CR-C is more important than CR-B. These regulatory sites are located at the upstream region of the transcription start site (TSS), and multiple transcription factors bind to these sites and regulate the PDCD1 gene expression (20, 21). A CR-B contains an AP-1 binding site, while CR-C has a binding region for the nuclear factor of activated T cells (NFAT)c1, interferon-stimulated response element (ISRE), NF-ϰB, and FoxO1 (19). The immune activation of PD-1 is dependent on its gene strains, for example, Pdcd1 gene polymorphisms are associated with the induction of autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis (AS), type 1 diabetes mellitus (T1DM), and multiple sclerosis (MS) (22).

Central and peripheral tolerance are two main procedures to control the progression of autoimmune diseases via regulating self-reactive T cells (23). The balance between stimulatory and inhibitory signals is critical for defensive immune responses, self-tolerance, and promotion of T cell homeostasis (24, 25). PD-1 reduces the interfaces between dendritic cells with self-reactive T cells and stimulation and development of auto-reactive T cells. Therefore, PD-1 induces tissue tolerance via suppression of self-reactive T cell activation in conjunction and protects against immune-mediated tissue injury (26).

Regulatory T (Treg) cells are an important subtype of T cells that have a key role in maintaining tolerance by regulating insufficient responses and immune cell activation (27). PD-1 and PD-L1 are highly expressed on Tregs, and unlike other subtypes of T cells, engagement of PD-1 on Tregs increases the number of these cells. That is the reason why this pathway is important in maintaining development and immune responses, and is in charge of functional responses of Treg cells (28).

On the other side, continuous and persistent formation of PD-1 and its ligands are common during long-time infections and malignancy (29). Although PD-1 is critical in the maintenance of peripheral T-cell tolerance, it can limit anti-tumor and anti-viral responses. Indeed, the blockage of the PD1 pathway in these disorders causes an increase of T cells and a reduction in tumor and virus load burden (30). As an example, malignant tumors mainly express PD-L1 on their surface, and the bondage of PD-L1 to PD-1 inhibits the expansion of active T cells and causes a drop in anti-tumor immunity (25, 31). PD-1 is likely to disrupt protective immune responses; therefore, in severe viral infections and malignant T cells are more dysfunctional (32, 33)

Ligands of PD1

PD-L1, a type 1 transmembrane protein of 290 aa, is encoded by the Cd274 gene on chromosome 9 and consists of seven exons (34). The first exon encodes the second, third and fourth, fifth, and sixth exons contain the 5' untranslated regions (5'-UTR), signal sequence, an IgV-like domain, IgC-like domains, the transmembrane and the intracellular domains, respectively. The intracellular domain residues plus the 3' UTR are encoded by the last exon (34). In brief, the intracellular domain PD-L1 is short and conserved

with no known function (35). A spliced isoform of PD-L1 was reported in humans, lacking an IgV-like exon that cannot bind PD1 (36). Whereas, spliced variants of murine PD-L1 have not been reported.

PD-L1 is mainly expressed on antigen-presenting cells (APC) by interferon γ (IFN-γ), and non-immune cells such as epithelial cells (37). Various processes can regulate the expression of PD-L1, such as gene transcription, post-transcriptional and post-translational modifications, and exosomal transport. Therefore, we should expand our knowledge about the regulation process of PD-L1 expression to introduce immune checkpoint blockers with high efficacy and advance immunotherapy strategies (38). PD-L1 or CD274 is located on chromosome 9p24.1, which amplification and translocation in this region upregulate PD-L1 expression, resulting in increased immune escape as demonstrated for gastric adenocarcinoma, primary mediastinal large B cell lymphoma, classical Hodgkin lymphoma, squamous cell carcinoma, and NSCLC (38, 39). Interestingly, Janus kinase 2 (JAK2) is also located on chromosome 9p and can regulate the expression of PD-L1 that mutation and amplification of the JAK lead to upregulation of PD-L1 (40). Elevated activity of the JAK2/STAT (signal transducers and activators of the transcription) signaling pathway increases PD-L1 expression (41). A DNA double-strand breaks (DSBs) activates STAT1 and STAT3 signaling which requires ataxia-ATM (telangiectasia mutated)/(ATR) ATM- and Rad3-related/(Chk1) checkpoint kinase 1 kinases, resulting in PD-L1 upregulation (42, 43). On the other hand, PD-L1 3'-UTR disruption involves in various human cancers through cancer-immune evasion (44). The CD274 3' UTR disruption by CRISPR (clustered regularly interspaced short palindromic repeats)/Cas9 increase PD-L1 expression and leads to immune (44, 45). Together, these results demonstrated that genomic alterations have an essential role in elevated PD-L1 levels in the number of cancers, and these alterations can be used as targeting biomarkers to improve the therapeutic efficacy of anti-PD-1/PD-L1 (46). chromatin modifiers, such as epigenetic regulations, have a critical role in the expression of PD-L1. Recently, blocking PD-L1 signaling using BET inhibitors reduced PD-L1 expression and showed high therapeutic potential in cancer (37,38). Histone deacetylase 3 (HDAC3) is also another repressor of PD-L1 and HDAC inhibitors can upregulate the PD-L1 expression (47, 48). Therefore, a combination of PD-1/PD-L1 blockade with HDAC inhibition may augment immunotherapies. Similarly, Lu et al. showed that tri-methylation of histone H3 on lysine 4 (H3K4me3) also induces the expression of PD-L1 cancer cells such as pancreatic cancer (49, 50). Another possible epigenetic regulator of PD-L1 is zeste homolog 2 (EZH2), which catalyzes H3K4me3 and is positively related to PD-L1 in breast cancer (51, 52). The inhibition of the (ADP-ribose) polymerase 1 (PARP1) can upregulate PD-L1 levels via negative regulation of EZH2 (53, 54). These findings prove that the expression of PD-L1 is epigenetically regulated by several mechanisms (55).

PD-L2 or CD273 encoded by the Pdcd1 Ig2 gene is a type I transmembrane protein and is next to Cd274 with seven exons. Three PD-L2 splicing variants are identified, including the first form eliminating the exon 3 encoding IgV-like domain with no potential to bind PD-1, the second one is created without the IgC-like domain, and the third form loses the IgC-like domain (56). The expression of PD-L2 is more restricted than PD-L1 expression and is expressed on antigen-presenting cells (APCs), including monocytes, macrophages, dendritic cells, and some B cells (57). PD-L2^{-} and PD-L2^{+} B1 cells have similar proliferative patterns and immunoglobulin production, but PD-L2^{+} B1 cells are enriched for the expression of VH1/VH12 genes (58). The expression of PD-L1 depends on TLR4 and STAT1 and PD-L2 up-regulation can induce by IL-4Rα and STAT6 (59). Interestingly, T helper (Th) 1 cell up-regulate PD-L1 expression, whereas up-regulates PD-L2 (59). Little is known about the transcriptional regulation of PD-L2 and more studies are needed.

Both CD28 and IL-2, though indirectly, encourage initial activation signals. PD1 induces a delay in this pathway; hence, T-cell proliferation and existence get disturbed reliably (60). After CD28 binding to CD80/CD86 enhances IL-2 production by induction of T cell responses (60, 61). CD28 receptor activates the Src family tyrosine kinases, Fyn and Lck, in lymphocytes (62). Tyrosine motifs of CD28 are phosphorylated by Fyn and Lck and lead to the activation of phosphatidylinositol 3-kinase (PI3K) and Akt protein kinase, which induce glycolytic metabolism (63). In contrast, IL-2 promotes the PIM1 or PIM2 expression, through the JAK/STAT signaling pathway with the same effect on glycolytic metabolism (63). In brief, costimulation of CD28 can induce the activation of various intracellular pathways, which lead to T cell responses, including cell survival, cell proliferation, and cytokine production (64).

CTLA-4 and PD-1 can suppress the activation of T cells by distinct but synergistic mechanisms. Both of these inhibitory receptors suppress glucose metabolism and Akt phosphorylation (65). Akt increases thymocyte survival, cell growth, and proliferation in T lymphocytes (66). Despite the similar inhibitory mechanism, the cytoplasmic domain of CTLA-4 and PD-1 have significant differences. The cytoplasmic domain of CTLA-4 interacts with protein phosphatase 2A (PP2A) and tyrosine phosphatase SHP-2 (64, 67). PD-1 encodes both of immunoreceptor tyrosine-based switch motif (ITSM) and immunoreceptor tyrosine-based inhibitory motif (ITIM) (68, 69). The inhibitory function of PD-1 is mainly depending on ITSM which recruits tyrosine phosphatases SHP-1 and SHP-2 for signal transduction (60, 70). The expression of SHP-1 is mainly related to hematopoietic lineage, whereas the exact role of SHP-2 is not fully clear (71, 72). Both SH-2 domains of SHP-2 are necessary for SHP-2 interaction and enzymatic activation and the absence of even one of the SH2 domains prevents interaction with PD-1 (73). PD-1 phosphorylation by TCR-proximal Src family tyrosine kinases enables SHP-2 to form a linkage with two phosphorylated ITSM-Y248 residues via its N-SH2 and C-SH2 domains (74).

PTEN (Phosphatase and tensin homolog) is the main negative controlling mechanism of the PI3K/Akt (75). PTEN via its phosphatase activity converts PIP3 to inactive PIP2 which PIP3 is essential for the AKT phosphorylation (76). the phosphorylation of T382, S380, and T383 within the tail of PTEN regulates stability and activity (77). The cytoplasmic domain of PTEN is phosphorylated by CK2 (Casein Kinase 2) which leads to inhibiting PTPN phosphatase activity (76). PD-1 inhibits TCR activation signals by inhibiting the CK2 function and dephosphorylation and activation of the PTEN (78).

PD-1 not only suppresses the induction of Bcl-xL, but also brings an end to the proliferation of transcription factors correlated with effector cells, such as GATA-3, T-bet, and Eomesodermin (79). Stimulation of Foxp3 expression in T cells and induction of inhibitory function of Treg cells is the main pathway by which tolerance is encouraged by PD1 (80).

During chronic viral infections, the up-regulation of PD-1 on exhausted CD8+ T cells is associated with decreased TNF-α, IL-2, IFN-γ, and perforin production (81). It is shown that PD-1 ligation makes T lymphocytes much less sensitive to TCR-mediated signals (82). Given that PD-1 regulate T cell exhaustion, blocking the PD-1/PD-Ls ligation can reduce apoptosis, reinvigorate exhausted CD8 T cells, and reprogram exhausted CD8 T cells into durable memory T cells (83, 84). Coexpression of T-cell Ig- and mucin-domain-containing molecule–3 (Tim-3) 3 and PD-1 is related to more CD8 T-cell exhaustion (85, 86).

PD-1/PD-L1 pathway is associated with various diseases, such as cancer, stroke, neurological disorders, and autoimmunity (87). For example, the development of lupus diseases has been shown in C57BL/6(B6)-PD-$1^{-/-}$ congenic mice (88). For autoimmune diseases immunotherapy to be successful, the PD-1/PD-L1 pathway can be considered an effective target. Recently, several studies have been done on specific molecules and pathways that have vital roles in triggering immunological tolerance. Nevertheless, the death toll of autoimmune diseases associated with PD1 is still high. The PD-1 signaling pathway is briefly shown in figure 1.

The PD1 pathway and autoimmune diseases

1. PD-1 in Type 1 diabetes

Type-1 diabetes (T1D) is an outcome of severe β-cell damage in pancreatic islets. Type-1 diabetes leads to hyperglycemia accompanied by similar issues of clinical diabetes (89). PD1 sustains tolerance by mechanisms that are separate from those of CTLA-4. First of all, PD-1 deficiency leads to tissue-specific injury slowly, dependent on the genetic background, whereas CTLA-4 deficit culminates in rapid multi-organ inflammation and death, disregarding genetic (90). Secondly, while CTLA-4 blockade ameliorates the antitumor immune responses associated with the creation of autoimmune responses, the blockade of the PD-L1/PD-1 pathway is distinct from that (91). Thirdly, a lower T-cell motility is brought about in PD-1/PD-L1 blockade; however, in CTLA-4 blockade is not (25). Finally, PD-1/PD-L1 blockade swiftly accelerates diabetes regardless of age. By stark contrast, CTLA-4 blockade stimulates diabetes in neonates (92).

PD-L1 is expressed on β-cells of islets that produce insulin. It may also act as an inhibitory factor for regulating self-reactive T cells in the marked tissue (89, 93). Deficiency or blockade of PD-1/PDL1 lead to the development of autoimmune diabetes in NOD mice (94). T1DM is initiated in NOD mice by MHC class I-dependent T cell responses and subsequent pancreatic β cell destruction (95). NOD islets showed a decreased capacity to upregulate B7-H1 expression, which is induced by inflammatory cytokines (96). These results suggested that NOD islets cannot upregulate the expression of B7-H1 immunoregulatory molecules in response to pro-inflammatory cytokines (96). In NOD mice, PDL1-mediated regulation of diabetogenic CD4+ and CD8+ T cells is necessary for the development of diabetes (97). This was approved by CD4+ and CD8+ TCR–transgenic mice; a study showed an elevated number of T cells following the blockade of PD-L1 (98, 99). Th1 and Th2 imbalance is also associated with developing autoimmune diabetes in NOD mice, but the protective effect of PD-1 is not related to inducing IL-4 and suppressing IFN-γ producing cells (99).

As previously mentioned, PD-L1 induces tolerance and controls pathogenic self-reactive effector T cells using two binding partners, PD-1 and B7-1 (100). Two anti–PD-L1 Abs with different blocking activities, anti–PD-L1 mAb 10F.9G2 blocking both PD-1/PD-L1 and PD-L1/B7-1 interactions and anti–PD-L1 mAb 10F.2H11 blocking only PD-L1/B7-1 interactions, can accelerate diabetes in NOD mice, but single-blocker 10F.2H11 mAb is more important at promoting diabetes in older (101). Therefore, PD-1 pathway blockage in NOD mice can both improve the disease-related breakdown of tolerance causing T1D in a particular organ and limit T cell numbers and functions (102).

Anti-PD-1 and anti-PD-L1 monoclonal antibodies can also cause T1D in human subjects, and diabetes can be an adverse effect of anti-PD-1/PD-L1 immunotherapy (103, 104). For example, treatment with pembrolizumab, a humanized IgG4 anti-PD-1 Ab, lead to the induction of autoimmune diabetes in the Chinese population (105). Onset diabetes is also reported following the treatment with nivolumab or pembrolizumab, which monitoring glycemia was not predictive of autoimmune diabetes occurrence (106). One of the reasons for the rapid onset of diabetes is possibly because of the uncontrolled activation of T cells (107). T cell infiltration with the low expression level of PD-1 into pancreatic islets initiates β-cell injury and T1D in the patients (108). The fulminant onset of diabetes in the affected subjects is partially related to Human leukocyte antigen (HLA) DR4 and T1D-related autoantibodies (109). HLA-DRB1*09:01–HLA-DQB1*03:03 also showed a significant and strong association with T1DM (110). In contrast, HLA-DRB1*15:02 is mainly protective for type 1 diabetes (111). Sun et al. showed that the progression of T2D is related to the expression of PD-1 on NK cells and that more investigation into this is needed (112). Another important reason for the induction of diabetes after anti-PD-1 therapy is the increase in C-reactive protein (CRP) levels (113). These results show the importance management of immune-related adverse events (irAEs) in subjects during the treatment with immune checkpoint inhibitors to reduce mortality and morbidity rate (114). Hickmott et al. suggested HbA1c (hemoglobin A1C) and plasma glucose level monitoring before and during PD-1/PD-L1 therapy (115).

MicroRNAs, a small non-coding RNA, have critical roles in various cell functions such as development, differentiation, cell cycle, and apoptosis (116). Some microRNAs are related to the expression of PD-L1 in HSPCs (hematopoietic stem cells) and T1D pathogenesis, which PD-L1 expression can be used as an effective and safe immunotherapy option (117). Ben Nasr et al. revealed that PD-L1 pharmacological restoration or genetic overexpression in progenitor cells and HSPC can reverse T1D (117).

The PD-1 pathway in systemic lupus erythematosus

Systematic lupus erythematosus (SLE) is the most common type of lupus and mainly affects women of child-bearing age (118). In this autoimmune disease, self-tissues are targeted and destroyed by the immune responses that cause serious inflammation (119, 120). Type I interferon (IFN) and Toll-like receptor (TLR) signaling are involved pathogenic factors in SLE (121).

T follicular helper (Tfh) and regulatory B (Breg) cells are associated with SLE pathogenesis, in which Breg cells are the negative regulator of immune responses during autoimmune diseases (122). In SLE, The

frequency of Breg cells and the production of IL-10 increase in SLE flares, whereas decrease during disease remission. CXCR5+ PD-1+ Tfh cells produce IL-21 and expand in SLE. Yang et al. demonstrated that IL-21 can induce IL-10 production during the development of Breg cells (122). IL-21 in the presence of lipopolysaccharide (LPS) and PIB can also promote the development of CD19+ IL-10+ B cells (122). IL-21 can also potently promote the differentiation of CD11chiT-bet+ B cells into Ig-secreting autoreactive plasma cells (123). CXCR3- PD-1 +CD4+ T cells associate with SLE disease severity through B-cell-help for the production of autoantibodies (124). B cells migrate to target tissues that correlate with SLE clinical manifestations. The high serum level of autoantibodies against PD-1 in SLE patients is related to disease activity that can break tolerance (125). TIM-3 (T cell immunoglobulin mucin-3) binds to Galectin-9 and is a negative regulator of T cell-mediated immune responses. Interestingly, the co-expression of PD-1 and TIM-3 on NK cells in SLE patients is related to disease severity and activity and has a role in SLE pathogenesis (126).

The number of CD4+CD25+ T cells decreases in clinically active SLE patients (127). Decreased frequency of CD4+CD25+T cells in patients with active SLE is inversely associated with disease activity and serum anti-double-stranded DNA levels (128). The suppressive capacity of Treg cells also decreases in SLE patients, in which PD-1 expression is required for the regulatory function of CD4+ CD25+ Foxp3+ Treg cells to control autoimmune responses (129). Low PD-1 expression on Treg cells is shown in SLE patients. Kristjansdottir et al. suggested that low PD-1 expression is related to the PD-1.3A allele (130). Polymorphisms in PD-1 have revealed associated risks in SLE development, whereas PD-L1 or PD-L2 have not been showing associated risks (131). PD1.5 polymorphisms are significantly related to SLE susceptibility, while PD1.6 is protective (132, 133).

In vivo treatment with anti–PD-1 mAb decreased the frequency of f CD4+ PD-1+ T cells in the kidney of NZB/W (New Zealand Black 3 New Zealand White) F1 mice and accelerated lupus-like nephritis and mortality rate (134). These results suggest that the expression of PD-1 is critical for the induction of immune tolerance mediated by CD8+ Foxp3+ T cells that inhibit both pathogenic T and B cells (135).

The Programmed Cell Death 1 pathway in Rheumatoid Arthritis

Rheumatoid arthritis (RA), an immune-mediated inflammatory disorder of the synovium, is characterized by hyperplasia and mononuclear cells infiltration to the synovial membrane, and secretion of proteases resulting in adjacent bone and destruction of articular cartilage (136). Macrophages, synovial fibroblasts, and autoreactive CD4+ T cells are involved in RA pathogenesis (137). there is no doubt that Treg cells maintain self-tolerance by controlling the activation of autoreactive T cells (136). An aberrant proportion of CTLA-4 and PD-1 have been related to the persistent activation of autoreactive T cells in RA (138). The low expression level of PD-1 on CD4+ and CD8+ T cells is related to the disease activity score of RA (139). The emergence of inflammatory arthritis irAEs in patients treated with PD-1/PD-L1 immunotherapy highlight the important role of this pathway in the regulation of immune responses (140).

The high concentration of soluble PD-1 seen in SF and serum specimens is correlated with TNF-α and rheumatoid factor (RF) in SF and the clinical relevance of RA (138). Wan et al. suggested the expression of an alternative splice variant (PD-1[?]ex3) that has an extracellular domain of PD-1 without the membrane-spanning domain can affect the regulatory effect of full-length PD-1 on T cell activation (138). Therefore, overexpression of these soluble factors can block the inhibitory effect of costimulatory molecules (CTLA-4 and PD-1). Therefore, agonistic PD1 antibody-based therapeutic options can show efficacy in the treatment of RA (120). Besides CTLA-4 and PD-1, TIM-3 is also involved in the immune dysregulation of RA (141).

Studies in Collagen II (CII)-induced arthritis (CIA), a murine experimental model of RA, approved the protective effect of PD1 or PD-L1 in RA (142, 143). The protective role of PD-1 in RA was shown by inducing CIA in PD-1–deficient mice (144). In this way, B7-H1-/- (PD-L1) mice showed exacerbated arthritis and elevated CD4+ T-cell responses. In B7-H1-/- mice the number of $CD4^{+}PD\text{-}1^{hi}$ $CXCR5^{hi}ICOS^{hi}$ $CD62L^{lo}$ Tfh cells with elevated expression of IL-21, Bcl6, the apoptosis-inducer molecule FasL increase, whereas the frequency of $CD38^{+}CD138^{+}$ plasma cells and antibody responses decrease (145). Hamel et al. suggested B7-

H1 expression on non-T and non-B cell signals through PD-1 on T cells required B-cell antibody responses and development of arthritis (145). It is also demonstrated that B7-H1 expression is essential for B-cell survival by regulating the activation of Tfh cells (145). PD-1+TOX+BHLHE40+ population of T cells expressed genes supporting B cells activation and driving inflammation by the production of CXCL13 and IL-21, and activation of myeloid cells by production of GM-CSF and TNF (145). A PD-1+TOX+EOMES+ population of CD4+ T cells expressed attracting genes for myeloid cells (145). Extracellular Vesicles (EVs) are present in RA patients and transfer both the PD-1 receptor and microRNAs associated with T cell inhibition (TIM-3, CTLA-4, and IRF9) to cells in the microenvironment (146). Greisen et al. suggested EVs are involved in the development of RA chronicity, favoring the progression of T cell inhibition and T cell exhaustion (146).

Therefore, the administration of PDL-Ig could significantly reduce the CIA severity through the inhibition of cell proliferation and anti-inflammatory actions (147).

The Programmed Cell Death 1 pathway in Multiple Sclerosis

Multiple sclerosis is an autoimmune chronic demyelinating disease of the central nervous system (CNS) (148). MS is an immune-mediated disorder that autoreactive T cells that play an important role in the immunopathological process (148). Experimental autoimmune encephalomyelitis (EAE), an animal model of MS, is also a T cell-mediated autoimmune disease of the CNS that has pathological and clinical features with MS (149). PD-1/PD-L1 pathway maintains immune tolerance and inhibits autoimmunity by delivering a negative regulatory signal (150, 151). The elevated severity of EAE e in PDL-1-/- and PD-1-/- mice is related to a high production level of pro-inflammatory cytokines TNF, IL-6, IL-17, and IFN-γ (152). PD-1 down-modulation in Tregs alters Treg-mediated immune suppression, induces the activation of T cells, and promotes the EAE (153). It is demonstrated that signals delivered by the B7-H1-Ig fusion protein could control Th17 differentiation and CNS autoimmunity (154).

Astrocytes and microglia cells can control brain-infiltrating antiviral T-lymphocytes through the upregulation of PD-L1 (155). Brain endothelial cells control immune responses and T cell migration into the CNS via PD-L2 expression (156). Downregulation or absence of the endothelium PD-L2 in MS lesions is correlated with infiltrating T cells (156, 157). PD-1 polymorphism is related to defect inhibition of T cell activation and progression of MS (158). The presence of the PD-1.5 T allele is associated with the initial manifestations of MS, such as pyramidal signs and diplopia (159). Decreased number and functionally exhausted Treg cells in MS are due to the high expression level of PD-1 (129,135). Targeting the PD-1/PD-L1 has therapeutic potential in a variety of cancers, but PD1/PD-L1 axis blockade in the brain remains controversial (139). Krakauer et al. suggested low expression levels of CCR4, PD-1, and L-selectin in MS can be normalized by treatment with interferon-β (138).

Inflammatory bowel disease

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are inflammatory, chronic disorders with similar features like abdominal pain, weight loss, and diarrhea (141). Treg cells prevent both innate immune and T cell-mediated responses in the intestinal lamina propria through IL-10 production and CTLA-4 and PD-1 expression (142,143). Totsuka et al. suggested that the CD4+CD25–PD-1+ T cells represent a substantial amount of Treg cells and inhibit the development of colitis (144). It is demonstrated that $CD44^{high}CD62L^{-}CD4^{+}IL\text{-}7Ra^{high}$ effector-memory (TEM)-like cells in colitic mice are exhausted and convert into cytokine-non-producing Treg cells (145). Blockade of the PD-1/PD-L1 can restore exhausted T cells ability to undergo proliferation, kill infected cells, secrete cytokines, and reduce viral load (146). Interestingly, blockade of the CTLA-4 has no beneficial effect on either T-cell function or infection control (146).

Colitis is the most frequent irAEs related to immune checkpoint inhibitors. Features of anti-CTLA-4 colitis are similar to anti-PD-1 colitis, with increased crypt atrophy/dropout and apoptosis (152). After anti-PD-1 therapy, colitis generally occurs later and is widely variable, but anti-PD-1 irAE is different and less common than anti-CTLA-4 (147,148,150). For example, severe colitis after PD-1 blockade with nivolumab is related

to Th1 responses, CRP, and IL-6 production (149). Park et al. suggested that PD-1 deficiency alters gut microbiota and protects the development of experimentally induced colitis (151). Therefore, it is critical to understand the other treatment options to minimize toxicity and mortality rate.

Anti-PD1 therapy and autoimmune diseases

The popularity of anti-PD1 therapy has been increasing in recent years. Immune checkpoint monoclonal antibodies (mAb) target PD-1 and improve antitumor immune responses (160). There are two IgG4 monoclonal antibodies named Pembrolizumab (Kytruda) and nivolumab (Opdivo) that target the PD-1 molecule (161). According to recent studies, T1DM patients have a considerable reduction in PD-1 expression on CD4+ T cells, this is subject to the progression of T1DM by T cell activation (162). Therapy pembrolizumab precipitates type 1 diabetes since it reactivates CD8+ T cell clone and blocks the PD-1 pathway (163). In the aftermath of PD-1 pathway blockade, PD-L1 molecules lose the ability to bind to the PD-1 receptors on autoreactive T cells since pembrolizumab has blocked them (164). Anti-PD1 therapy has also similar results. With PD-1 reduction, autoreactive T-cells get stimulated and a wide range of autoimmune responses appear (165).

On the other hand, since malignant cells circumvent the immune system by either expressing PD-L1 or PD-L2, anti-PD-L1 and anti-PD-L2 checkpoint suppressors are invented (166). These anti-checkpoints obstruct the pathway of PD-1 and thus restore the role of T-cells (167). Blockage of this pathway leads to both survival of cancer-sensitive T cells and autoreactive T cells. For instance, T cells that fight against pancreatic islet cells are survived. These cells cause T1DM (168).

Immune therapy has a range of immune-related adverse events (irAEs) (169). Pneumonitis, colitis, hepatitis, dermatitis, nephritis, pancreatitis, vitiligo, rash, pruritus, and endocrinopathies are all common side effects of anti-PD1 therapy. As well, diabetes mellitus type 1 is induced by targeting PD-1, though it happens less commonly (170). Tumors are prone to evade the immune system by building an immunosuppressive tumor microenvironment or activating the inhibitory pathways that suppress tumor-specific T cell responses (171). IrAEs are more probable in patients who are sensitive or predisposed to the progression of autoimmunity. IrAEs occur before, after, or during PD-1 inhibitor therapy (172). Moreover, patients who have one autoimmune disease are more susceptible to developing a second one (173). Whether immune checkpoint inhibitor therapy in patients with autoimmune disease is efficient or not goes beyond discussion since the benefits derived from this method far outweigh the disadvantages of irAEs (174). Additionally, Addison's disease is reported to develop in 0 % - 8% of patients undergoing anti-PD-1 therapy (175). Nevertheless, there are several future perspectives. Although PD-1 antibodies rose to popularity after they intervened in cancer therapy, their treatment efficacy varies in each cancer and each patient. Generally, there are many unsolved challenges in anti-PD-1 therapy: First, clarification of how PD-1 antibodies cause anti-tumor impacts, second, biomarker progression to have a clear prediction of the side effects, and third, further developments in combination therapy.

Discussion

Immunotherapy is a method of treating autoimmune diseases which recently has assumed importance. Two main molecules have been utilized in confronting autoimmune diseases: CTLA-4 and PD-1. PD-1 is a type I membrane protein composed of 288 amino acids. It is a member of the CD28/CTLA-4 family of T cell regulators. Programmed Cell Death 1 construction contains an extracellular IgV domain, a transmembrane region, and an intracellular tail. It is mainly found on B cells, T cells, macrophages, and some types of Dendritic cells. Programmed Cell Death-1 hinders T cell responses by activating PPA2 (inhibitory phosphatase 2) which culminates in an augmented migration of T cells from tissues. The two ligands of Programmed Cell Death 1 are PD-L1 and PD-L2. PD1/ PD-L1 interaction leads to the secretion of IL-10 and the subsequent decrease in T cell multiplying. This pathway plays an important role in tolerating and abolishing self-AG-specific cells. One of the principal mechanisms by which PD-1 induces tolerance is the promotion of

Foxp3+ Treg cells, which depends on the engagement of PDL-1-expressing APCs. The strength of the TCR signal is a major factor in the extent of PD1-mediated inhibition. The lower levels of TCR stimulation are, the more PD1-mediated inhibition occurs. It has been approved that PD1 is of vitality in control of Type 1 diabetes since it blocks Ab treatment and leads to rapid precipitation of the disease. PDL1 blockade triggers diabetes by a straight impact on pathogenic T cells owing to the assumption that the PD-L1 pathway blocks the responses of CD4+ and CD8+ T cells. CD4+ and CD8+ are vital throughout the late phases of diabetogenesis. In lupus erythematosus, B cells expand. This puts forward the theory that B-cell PD-1 is not sufficiently expressed or ligate in SLE. Moreover, PD-1+Tfh cells have a direct relation with the severity of the disease. Although expression of PDL1 is unregulated on SLE patients peripheral blood neutrophils, it dwindles on DCs and monocytes. These alterations are explicable solely based on a shortage in C3 and C1 q complement proteins. Standing on the other side of the continuum, Rheumatoid arthritis is another autoimmune disease that is mainly induced by Collagen II (CII). Indeed, owing to the impact of grown T-cell proliferation and increased emission of IFN-c and IL-17, the severity and incidence of RA increase. However, IL-10 and Anti-CII IgG do not undergo any significant alterations. Hence, it has been shown that RA PD1 has a more considerable impact on the Th1/ Th12 pathway in preference to Th2 or humoral responses. Therefore, it is deduced that by blocking PD-1 pathways, SLE can be treated. Additionally, blockage of Th1 CD4+T cell responses, which is a definite result of PD-1 emission, leads to a subsequent reduction in the severity of rheumatoid arthritis. Treatment of diverse cancers is facilitated by the intervention of Anti-CTLA-4 and anti-PD-1 antibodies. Nevertheless, these drugs have distinct mechanisms to place their effect. CTLA-4 blockade confronts the co-stimulation required to reactivate the T cells. On the other hand, PD-1 blockade obstructs the signaling from the TCR complex abundant on T cells. The TCR complex is a very elaborate set of proteins that cooperates with antigens emitted by APCs, such as MHC molecules expressed on APCs. Subsequently, T cells are allowed to accomplish their functions owing to the downstream signaling brought about by the cooperation of TCR and APCs antigens. Modifications in the TCR signaling cascade lays the fundamentals of interrupted T cell performance. Since the PD1 blockade switches the downstream signaling from the TCR and interrupts signals of T cell inhibition, T cells are left free to stay activated; and therefore, distinguish and destroy tumor cells. In other words, the anti-PD1 ought to maintain T cells active whereas CTLA-4 tries to reactivate them. Concerning the fact that each molecule has its mechanisms in treatment, a combination of both would be a worthwhile therapy method to achieve the maximum anti-autoimmune effects. Taking all of the above-mentioned into consideration, it is still necessary to remember manipulation of PD-1 may bring about indelible damages. Still much is unclear about the Programmed cell death-1. However, evidence is that its pathways have the potential to be utilized in novel treatments of autoimmune disease.

Conclusion

Despite several progressions made in the treatment of autoimmune diseases, the death toll of autoimmunities linked to PD-1 is still high. Bondage of PD-1 to its ligands culminates in a wide range of stimulations and responses, specifically in T cells and NK cells; which in turn triggers or obstructs autoimmune diseases. PD-1 is a transmembrane glycoprotein with an extracellular IgV domain. In T1DM, PDL-1 triggers the secretion of IL-10 and T cells. On the other hand, PDL-2 costimulates naïve T cells and Th1 cytokine production. by controlling these pathways, it is presumed that T1DM can be treated. In SLE, two key factors exist to gain control over the disease: First, the TLR pathway which is associated with the emission of IFN-α. Second, B cell ligation leads to IFN secretion.

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Conflict of Interest

There is no conflict of interest.

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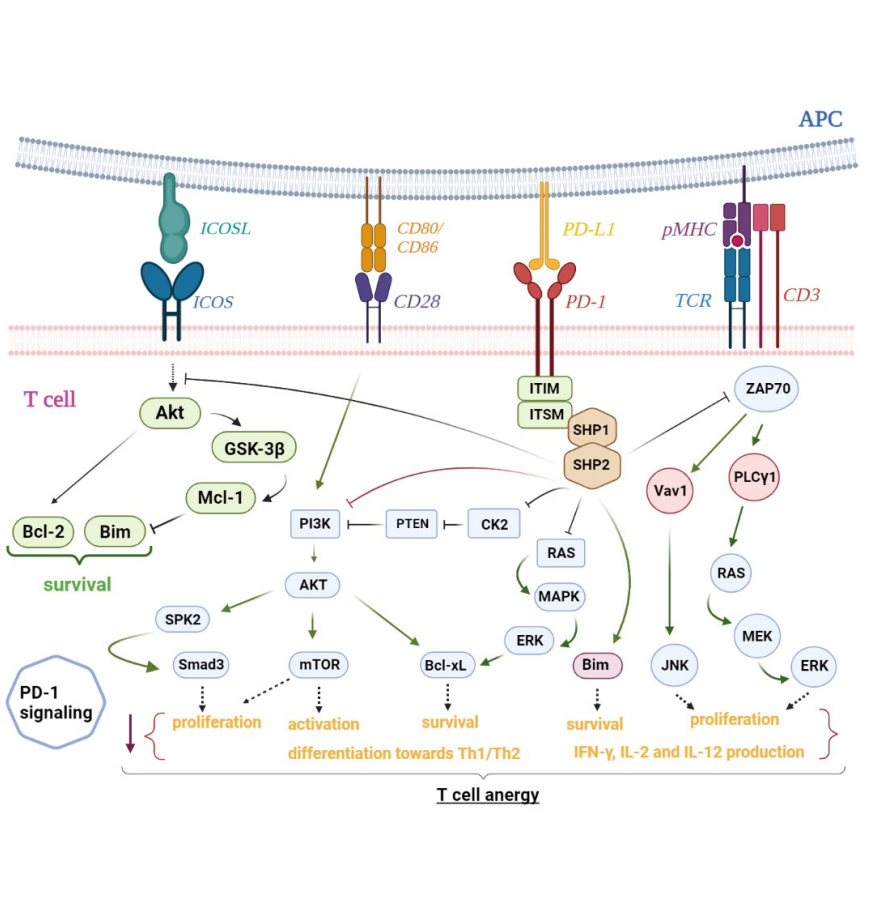

Figure1 . Ligation of PD-1 to PD-L1 leads to the inhibition of C3G, LAT, and PI3K pathways. Subsequently, IL-2 emission is blocked. Also, the proliferation and adhesion of T cells decrease. This attachment also leads to overexpression of IL-10 and the resultant decrease of T cells reproduction. As a result, T cell activity, cytokine release, and cytotoxicity of T cells decrease.