Review

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Exploring the Role of PD-1 in the Autoimmune Response: Insights into Its Implication in Systemic Lupus Erythematosus

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Abstract: Despite advances in our knowledge of systemic lupus erythematosus (SLE) has increased over time, there are still many challenges in deciphering the precise mechanisms involved in the development and progression of the disease. Recent evidence has raised questions about the effectiveness of the programmed cell death protein 1 (PD-1) in suppressing autoreactive $CD4^+$ T cells during the autoimmune response. Research has ventured into investigate the potential impact of PD-1 on various $CD4^+$ T cell subpopulations, including T follicular helper (Tfh) cells, circulating Tfh (cTfh) cells, and T peripheral helper (Tph) cells, all of which exhibit substantial PD-1 expression and have been closely related with several autoimmune disorders including SLE. This review aims to highlight the complex role of PD-1 in autoimmunity and emphasizes the imperative for further research to elucidate its functions during autoreactive T-cell response. Additionally, we address the potential of PD-1 or its ligands as a possible therapeutic target in SLE.

Keywords: PD-1; PD-L1/PD-L2; Systemic lupus erythematosus; T follicular helper (Tfh) cells; T peripheral helper (Tph) cells.

1. Introduction

Autoimmune diseases are reported to affect 5–8% of the world population [1]. They have garnered significant attention in research due to the multitude of immunopathological pathways characterized by aberrant innate and adaptive responses and the absence of effective therapeutic interventions.

Systemic lupus erythematosus (SLE) is considered the prototype of autoimmune diseases due to the complexity of the molecular and immunological pathways involved in its development and progression [2]. Although the production of autoantibodies targeting nuclear antigens is characteristic of the disease, this process involves a wide range of mechanisms. One of the most important is the differentiation and maturation of T cell-dependent B cells. During this process, $CD4^+$ T cells that have evaded central and peripheral tolerance mechanisms collaborate with B cells, providing them with the necessary signals for their complete differentiation into antibody-producing plasma cells or long-lived memory cells [3].

During this interaction, T cells also require co-stimulatory signals for their optimal activation, differentiation, and function. However, ultimately, they also require inhibitory signals to maintain immune balance, limit auto-reactivity, and prevent tissue injury. These signals, known as immune checkpoints, are added to co-stimulatory signals to inhibit T cell receptor (TCR) pathway signaling, thus counteracting cellular overactivation and contributing to immune response control.

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Nevertheless, it has been reported that dysregulation in the function or expression of these checkpoints leads to a failure in controlling T cell exhaustion, favoring autoimmunity [4].

One of the most important is the programmed cell death protein 1 (PD-1) receptor, which has been reported to prevent autoimmunity since its deficiency or the blockade of the PD-1 signaling pathway exacerbates disease progression in several autoimmune mouse models [5–9], as well as observations in which mutations in the *PDCD1* gene are associated with susceptibility to several human autoimmune disorders [10–13]. PD-1 controls central and peripheral self-tolerance and prevents autoimmunity by suppressing autoreactive T cells. However, it has been reported that effector PD-1$^{+/high}$CD4^{+} T cells are increased in patients with several autoimmune diseases associated with disease activity (reviewed in [14]), like SLE. This suggests that those cells are not functionally restricted by their high expression of PD-1.

This review provides a comprehensive overview of our current understanding of PD-1 and its association with the mechanisms involved in autoimmune responses with a special focus on SLE. We aim to provide potential explanations for why PD-1 may not effectively carry out its suppressive functions, even when overexpressed on CD4^{+} T cells, and raise important questions about PD-1's function for future research in this area.

2. PD-1 Expression and Function. What Do We know?

Our understanding of the PD-1 molecule began with identifying its cDNA in 1991 [15], followed by the discovery that PD-1 transcript expression occurred in T cells just before their activation and that its function was associated with inducing cell death. Interestingly, it also was observed that mice lacking PD-1 expression exhibited abnormal activation of both B and T cells [16]. It was further demonstrated that these PD-1-deficient mice developed some diseases such as cardiomyopathy, arthritis, and nephritis, highlighting its importance not only as a negative regulator of the immune response but also in developing autoimmune-related diseases [17–19].

PD-1 (CD279) is a signal-transducing type I protein composed of 260 amino acids, that is expressed on the cell surface of activated T cells, B cells, thymocytes, natural killer (NK) cells, natural killer T (NKT) cells, macrophages, and dendritic cells (DC) [20–22]. Structurally, PD-1 is composed of an extracellular immunoglobulin variable region (called (IgV)-like domain), followed by a constant region (called (IgC)-like domain) a transmembrane domain, and an intracellular domain. The (IgV)-like domain of PD-1 contains the binding site for its ligands, while the intracellular domain contains two tyrosine residues: an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM) [23,24]. PD-1 has two major ligands known as PD-L1 (CD274) [25] and PD-L2 (CD273) [26], that share the extracellular structure with PD-1 (Figure 1). PD-1 belongs to the CD28/CTLA-4 superfamily with 21–33% sequence identity with other family members like CTLA-4, CD28, and ICOS [27].

The PD-1 pathway plays a pivotal role in maintaining immune balance, serving as a negative regulator of T cell receptor (TCR) signaling and suppressing T cell activation triggered by auto-antigens, thus PD-1 prevents excessive activation following an adaptive immune response [28]. It has also been shown that PD-1 negatively regulates B cell responses by inhibiting B cell receptor (BCR) signaling [29].

During chronic infections, PD-1 signaling plays a central role in perpetuating T cell exhaustion, a state in which T cells progressively lose their effector functions after their activation [20,30–32]. Furthermore, it has been well-documented that tumor cells exploit the PD-1 signaling pathway to evade immune responses, indeed the use of antibodies that blockade the activation of this pathway has been widely used in cancer immuno-therapies [33]. However, despite the extensive knowledge regarding PD-1's involvement in cancer responses, its role in autoimmunity, particularly in the pathogenesis of diseases like SLE, is still largely unexplored.

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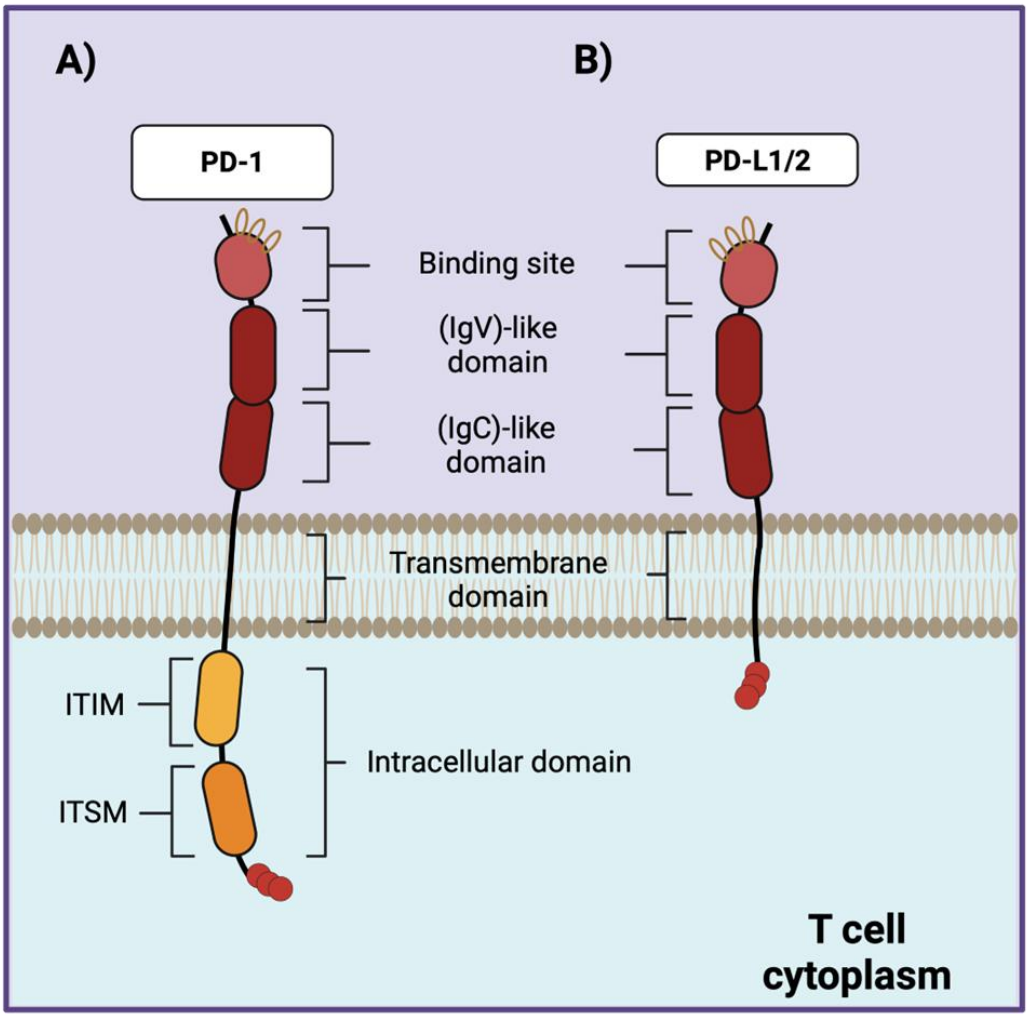

Figure 1. Structure of PD-1 and its ligands PD-L1 and PD-L2. A) The structure of PD-1 is composed of an (IgV)-like domain and (IgC)-like domain in the extracellular region, followed by a transmembrane domain, and the intracellular region is composed of an ITIM and ITSM domains. B) The structure of its ligands PD-1 and PD-L2 shared the extracellular structure with PD-1. PD-1: Programmed death 1; PD-L1: Programmed cell death-ligand 1; PD-L2: Programmed cell death-ligand 2; ITIM: Immunoreceptor Tyrosine-based Inhibitory Motif; ITSM: Immunoreceptor Tyrosine-based Switch Motif.

3. PD-1/PD-L1/PD-L2 in Central and Peripheral Tolerance

The most widely accepted role for PD-1 in autoimmunity is during the mechanisms of autoreactive T cell deletion during central and peripheral cell tolerance [34]. The initial observations regarding the significance of PD-1 in thymic selection mechanisms were conducted by Hiroyuki Nishimura et al. in 2000. They investigated the impact of PD-1 deficiency on thymocyte differentiation, finding that PD-1 negatively regulates beta selection, while modulating positive selection, thus, PD-1 significantly altered the mature T cell repertoire [35]. These findings were subsequently corroborated by others that also indicated a role for PD-1 during thymic selection [36,37]. More recently, it was reported that mice lacking the expression of both PD-1 and the autoimmune regulator (AIRE) genes developed fatal adulthood autoimmunity. This phenomenon was not observed in mice lacking other combinations of tolerance mediators, suggesting that the cooperation between PD-1 and AIRE plays a pivotal role in mediating central tolerance and autoimmune development [38].

Peripheral tolerance of T cells in the context of PD-1 is mediated by the expression of PD-L1 and PD-L2 on antigen-presenting cells (APCs), such as dendritic cells, which through this expression determine T cell inhibition [39]. However, a decrease in the expression of PD-1 or its ligands, which

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activate the inhibitory pathway, could be closely linked with the development of autoimmune diseases including SLE (as discussed below). This is due to the lack of inhibition of autoreactive T cells.

In line with this, recent research has focused on studying two subpopulations of T helper (Th) cells whose frequencies appear to be increased and associated with the pathogenesis of some autoimmune conditions. T follicular helper (Tfh) cells are usually identified by a $CD4^+CXCR5^+PD\text{-}1^+$ phenotype. These cells represent a specialized subpopulation primarily located within germinal centers (GC) of secondary lymphoid organs, which play a crucial role in mediating the differentiation of B cells into autoantibody-producing cells, a function that is primarily achieved through the expression of IL-21 [40]. IL-21 is a key regulator of various processes within the immune system and autoimmunity. It is the main cytokine required to enable mechanisms of germinal center formation, affinity maturation, and generation of plasma cells and memory B cells [41]. Furthermore, IL-21 is also required for the complete generation of Tfh cells [42,43]. A small proportion of Tfh cells called circulating Tfh (cTfh) cells can be found in the peripheral blood, and they have been extensively associated with autoimmune diseases such as systemic lupus erythematosus (SLE) [44–48], (RA) [49–51], Sjögren's syndrome (pSS) [52–56] and multiple sclerosis (MS) [57,58]. Although Tfh cells had been the main $CD4^+$ T cell subpopulation involved in maintaining the generation of autoantibodies, recent research has focused on a novel cell subpopulation that appears to be more closely associated with the pathogenesis of autoimmune diseases.

T peripheral helper (Tph) cells are characterized by a $CD4^+CXCR5^-PD\text{-}1^{+/high}$ phenotype. The absence of CXCR5 leads them to exit germinal centers and position themselves within inflamed tissues by expressing other chemokine receptors such as CCR2 and CCR5, where Tph cells induce B cell differentiation through the production of IL-21 [14]. Increased numbers of Tph cells have also been observed in SLE (59–62), RA [58–61], and pSS [54,67,68].

A shared characteristic between Tfh, cTfh, and Tph cells is the high expression of PD-1 on their cell surface, which is in some cases associated with the disease activity. Because the frequencies of cTfh and Tph cells are increased in these autoimmune diseases, it is reasonably suggested that PD-1 may not be exerting its suppressive functions on these cellular subpopulations, this potentially indicated a break in the peripheral tolerance mediated by an aberrant function of PD-1.

Another important subpopulation of T cells responsible for mediating peripheral tolerance and tissue damage are regulatory T cells (Treg), which are identified by presenting a $CD4^+CD25^+Foxp3^+$ phenotype. In addition, they express activation markers and immunomodulatory molecules such as CTLA-4, PD-1, and PD-L1 [69]. Treg cells are divided into two groups: those that express Foxp3 and differentiate in the thymus known as natural Tregs (nTreg), while those that differentiate from naïve $CD4^+$ T cells in the periphery or through *in vitro* stimulation known as peripheral (pTreg) or induced (iTreg) Treg cells [70]. Increasing evidence has shown that the PD-1 pathway is associated with the differentiation of pTreg cells. Francisco, Loise M, et al, demonstrated that PD-L1-deficient antigen-presenting cells failed to induce the polarization of naïve $CD4^+$ T cells into pTreg cells. When $CD4^+$ T cells were primed with PD-L1 *in vitro,* iTregs were induced, demonstrating that PD-L1 maintained Foxp3 expression and the suppressive function of iTreg cells [71]. This could contribute to our understanding of how the deficiency in PD-L1 expression by APC is associated with the development of autoimmune diseases. Similar observations have been made for Th1 cells, which, in a PD-L1 manner, polarized to Treg cells [72].

Recently it was demonstrated higher expression of PD-1 but lower expression of PD-L1 on $CD4^+CD25^+FOXP3^+$ Treg cells after stimulation in cell culture, which was negatively associated with the SLEDAI index in SLE patients [73]. Furthermore, it has been shown that the stimulation of PD-1 with specific agonists can inhibit autoreactive T cells and restore Treg cell homeostasis [74], highlighting the importance of the PD-1 pathway Treg cells and peripheral tolerance (Figure 2).

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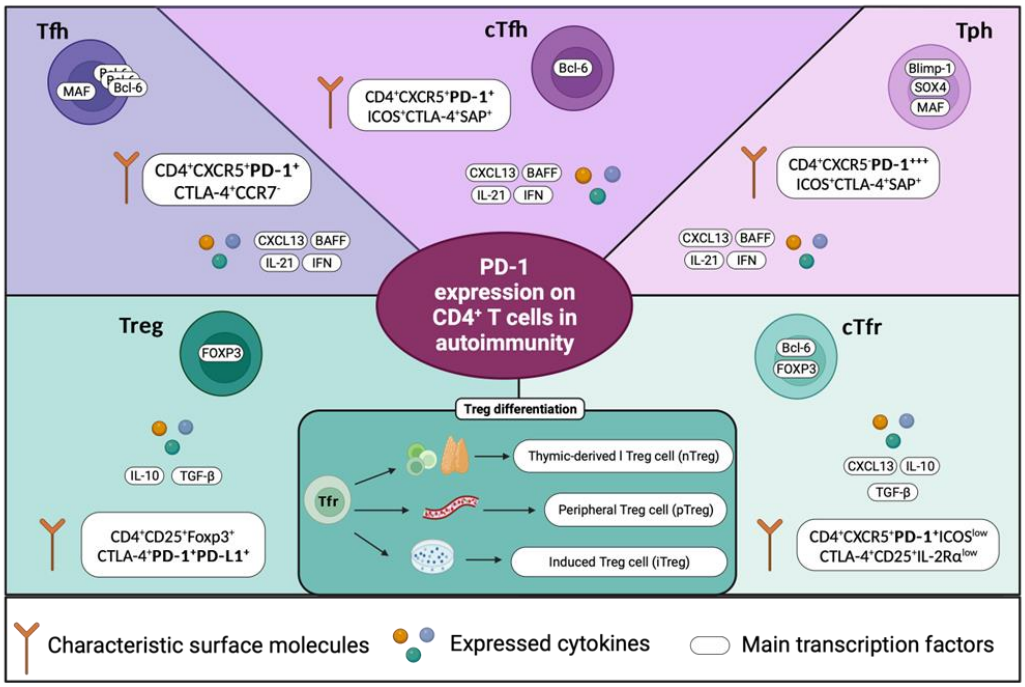

Figure 2. PD-1 expression on the surface of different CD4⁺ T cells in autoimmunity. PD-1 expression has been studied in different subpopulations of CD4+ T cells like Tfh, cTfh, Tph, Treg, and Tfr cells. Tfh: T follicular helper cells, cTfh: circulating T follicular helper cells; Tph: T peripheral helper cells; Treg: regulatory T cells; Tfr: follicular regulatory T cells.

4. Regulation of PD-1 Expression and Its Relationship with the Autoimmune Response in SLE

To understand the role of PD-1 in the autoimmune response in SLE and other autoimmune disorders it is important to consider how the expression of PD-1, its ligands, and the downstream signaling pathways are regulated.

4.1. Stimulation of PD-1 Expression

PDCD1 located in chromosome 2 is the gene encoding PD-1 in humans, whereas *Pdcd1* located in chromosome 1 is their counterpart in mice. PD-1 transcription initiates with the TCR activation and cytokine stimulation that activate various transcription factors including NFATc1 (activated by TCR signaling) [75], STAT3, STAT4, and STAT5 (activated by IL-6, IL-12, IL-2, IL-21) [76,77], the ISGF3 complex (activated by IFNα) [78], and FOXO1, AP-1, NF-κB (activated by other various cytokines) [79,80]. These transcription factors directly bind to specific enhancers and promoters located in cis-regulatory elements comprising two conserved regions: Conserved Region B (CR-B) and Conserved Region C (CR-C), of the PD-1 gene in both humans and mice [81] (Figure 3A).

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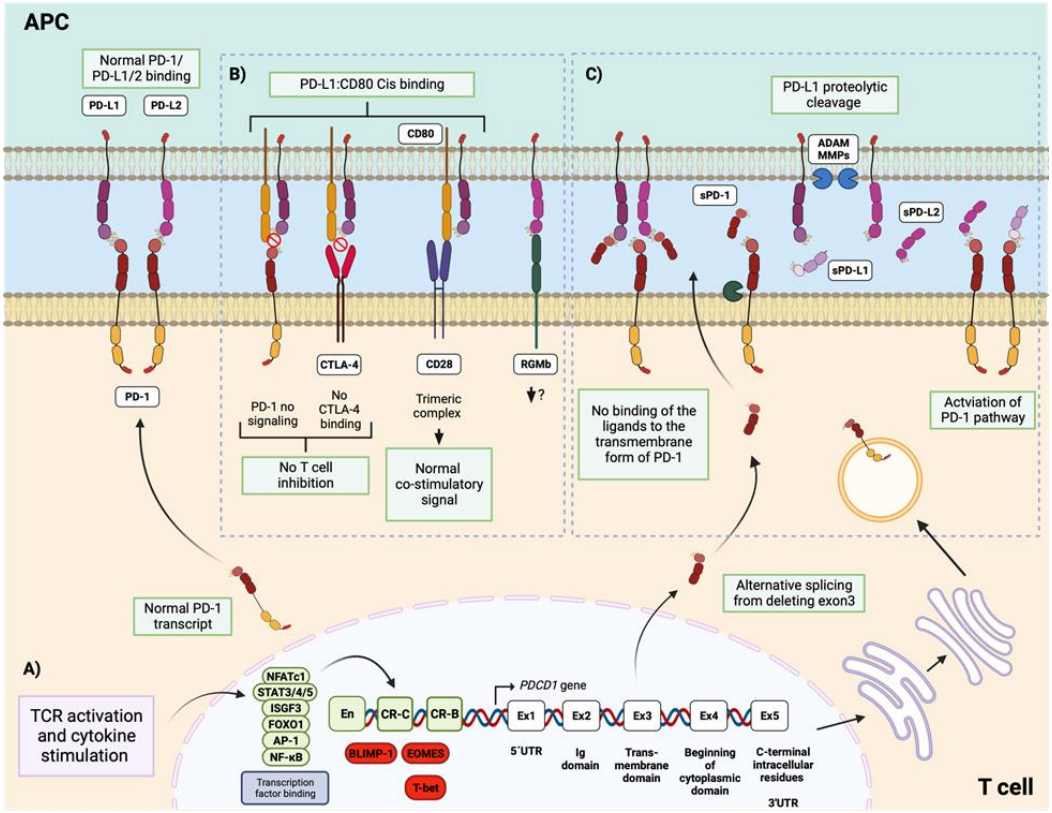

Figure 3. Expression of PD-1 and its ligands PD-L1 and PD-L2. A) The expression of PD-1 is stimulated by various transcription factors generated after TCR activation and cytokine stimulation. B) PD-L1 can also bind to CD80, and PD-L2 can also bind to RGMb molecule. C) PD-1 and its ligands can also be found in a soluble form generated by alternative splicing or proteolytic cleavage. PD-1: Programmed death 1; PD-L1: Programmed cell death-ligand 1; PD-L2: Programmed cell death-ligand 2; TCR: T-cell receptor; RGMb: Repulsive Guidance Molecule b.

This could offer an initial explanation for the overexpression of PD-1 on the surface of $CD4^+$ T cells, like cTfh and Tph cells, especially in autoimmune diseases such as SLE, where there is constant and repetitive stimulation of T cells by self-antigens and proinflammatory cytokines like IL-6, IL-21, and IFNα [82]. After translation, PD-1 is stabilized by fucosylation in the endoplasmic reticulum and Golgi apparatus [83]. The presence of PD-1 has been identified in vesicles proximal to the Golgi and trans-Golgi network, hinting at the potential role of these vesicles as reservoirs for PD-1 awaiting activation through TCR [84].

4.2. Repression of PD-1 Expression

Other transcription factor-binding sites near CR-B and CR-C serve for repression of the PD-1 expression. These include an RBP-Jκ-binding site upstream of CR-C [85], a Blimp-1-binding site downstream of CR-C [86], and a T-bet-binding site at -0.5 kb of Pdcd1 [87].

Regarding this, it has demonstrated that increased expression of the transcription factor Blimp-1 was correlated with the overexpression of PD-1 in $CD8^+$ T cells during chronic viral infection, in the same work was found that upon the conditional deletion of Blimp-1, there was also a reduction in the expression of this inhibitory receptor [88]. However, a couple of years later, it was demonstrated that PD-1 can be repressed by Blimp-1 in $CD8^+$ T cells by the suppression of the expression of NFATc1, which acts as a transcriptional activator of *Pdcd1* in acute viral infection [86]. Despite these contradictory initial results in response to the infection state, it is important to highlight that there is an association between Blimp-1 and PD-1 expression in $CD8^+$ T cells. Despite Blimp-1 could play a different role in $CD8^+$ and $CD4^+$ T cells, there has not been explored the possible association between this transcription factor and the PD-1 regulation in $CD4^+$ T cells during normal and autoimmune responses, even though Blimp-1 has been linked to exhausted protein markers such as PD-1 [89,90].

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Tph cells are characterized by expressing the Blimp-1 transcription factor which serves as a mediator of its differentiation. As Tph cells overexpress PD-1 on their surface, could be interesting to study the mechanisms involved in the regulation of the *PDCD1* gene by Blimp-1.

5. PD-1 Ligands Emerged as a New and Important Focus of Study in the Field of SLE

PD-L1 is coded by the *Cd274* gene situated on chromosome 9 in humans and chromosome 19 in mice. Similarly, PD-L2 is encoded by the *Pdcd1lg2* gene, which is found on chromosome 9 in humans and chromosome 19 in mice [91]. PD-L1 and PD-L2 belong to B7 superfamily members. Both are type I transmembrane glycoproteins composed of (IgV)- and (IgC)-like domains. Despite PD-L1 and PD-L2 sharing 30–40% of amino acid homology in humans, it has been reported that PD-L1 is the main ligan though PD-1 activates its downstream pathway [92].

PD-L1 and PD-L2 have distinct expression patterns by various components of the immune system as well as other tissue cells [93]. Both are expressed in activated T cells, B cells, dendritic cells, macrophages, and bone marrow-derived mast cells [94]. Additionally, PD-L1 is also expressed by NK cells, and non-immunological cells like endothelial, epithelial, and keratinocytes [95,96].

The PD-1/PD-L1/2 ligation is not restrictive, as PD-L1 can also bind to CD80, while PD-L2 can also bind to the repulsive guidance molecule b (RGMb) [97–99]. The binding between PD-L1 and CD80 occurs in cis (on the same cell surface) [100,101]. As the activation of the pathway needs the binding of PD-1 with any of PD-L1 or PD-L2, the availability of the ligands is necessary for the successful inhibitory function of PD-1 in T cells. Therefore, PD-L1/CD80 cis-binding on antigen-presenting cells (APCs) can reduce the number of PD-L1 available for trans-binding interaction (cell to cell) with PD-1 expressed on T cells. This not only leads to diminished PD-1 inhibitory signaling [102] but also reduced CTLA4-CD80 immune regulatory axes [103]. However, the PD-L1/CD80 interaction does not obstruct the binding of CD80 to CD28, consequently, they can form a trimeric complex that engages CD28 and thereby conveys a normal co-stimulatory signal [102] (Figure 3B).

Exploring the availability of PD-L1/L2 to PD-1 in SLE could yield valuable insights, potentially positioning the interaction as a promising therapeutic target in autoimmune responses, as it has been demonstrated in a recent study that the interaction between astrocytic PD-L1 with microglial PD-1 is necessary for the attenuation of autoimmune central nervous system inflammation in acute and progressive stages of a mouse model of multiple sclerosis [104]. Also, T cells from the synovial fluid of active rheumatoid arthritis patients exhibited decreased PD-1-mediated inhibition of their proliferation, especially at suboptimal concentrations of PD-L1. The treatment of those cells with PDL-1.Fc antibodies demonstrate an improvement in the reduction of their T cell response and ameliorate the severity of collagen-induced arthritis (CIA) [105]. In line with this, it has been demonstrated that the disruption of PD-L1/CD80 cis-binding by CD80 antibodies can alleviate autoimmunity due to the accessibility of PD-1/PD-L1 interaction [106].

The inhibitory PD-1/PD-L1/2 pathway can also be restricted by the soluble form of PD-1 (sPD-1). sPD-1 is generated from an alternative splicing event where the exon3, which contains the coding sequence for the transmembrane domain of PD-1 is deleted from the mRNA transcript. The expression of this transcript is upregulated following T-cell activation, leading to the release of sPD-1 into the plasma [107]. It has been reported that sPD-1 can interfere with PD-L1 or PD-L2, preventing the binding of the ligands to the transmembrane form of PD-1, and consequently blocking the negative signal [108] (Figure 3C). In this regard, it has been found elevated levels of sPD-1 in patients with autoimmune diseases such as SLE [109–111], RA [112–114], pSS [115,116], and the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) [117], that could be promoting the lack of cellular inhibition by blocked the inhibitory effect of membrane-bound PD-1 on T-cell activation.

PD-L1 and PD-L2 can also be found in a soluble form (sPD-L1 and sPD-L2, respectively), which are generated through proteolytic cleavage of membrane-bound protein by metalloproteases like ADAM or metalloproteinases (MMPs) [118], or by alternative splicing that induces a protein product that lacks the transmembrane domain and is secreted in a soluble form [119,120]. In the context of cancer, it has been reported that sPD-L1 influences the activation of the inhibitory function of PD-1 expressed in T cells by binding to PD-1 and leading to the activation of the downstream pathway

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[121]. However, the role of sPD-L2 in the activation of the inhibitory pathway remains unclear. Understanding the mechanisms of how sPD-L1 and sPD-L2 influence the pathogenesis of SLE and other autoimmune disorders could be challenging at this moment due to varying reports. While some authors indicated elevated levels of these ligands compared to healthy controls, others reported decreased levels, and in some autoimmune disorders, there is a lack of sufficient information. In Table 1 we summarize some of the findings of PD-1 and its ligands as well as the soluble forms in SLE and other autoimmune diseases.

Table 1. PD-1, PD-L1, and PD-L2 tissue, cell, and serum expression in systemic lupus erythematosus and other autoimmune diseases.

Disease	Evaluation	Finding	Reference
SLE	Tissue expression	PD-1 and PD-L1 were identified in the kidney of lupus nephritis patients.	Bertsias, George K et al. 2009 [122]
	Cell expression	Increased percentages of PD-1-expressing $CD3^+$ T cells and PD-1-expressing $CD19^+$ B cells in SLE. High expression of PD-L1-expressing $CD19^+$B cells and PD-L2-expressing $CD14^+$ monocytes.	Liu, Ming-Fei et al. 2009 [123]
		Elevated frequency of PD-L1-expressing neutrophils in SLE. This percentage decreased after receiving a 15-day regular treatment with corticosteroids and immunosuppressive drugs.	Luo, Qing et al. 2016 [124]
		PD-L1 was significantly higher in $CD19^+$ cells of SLE patients with active disease and LN. The expression of PD-L1 was increased in double-negative B cells (DN) and plasma cells (PC). The percentage of $CD19^+PD\text{-}L1^+$ cells correlated with the disease activity index and the T follicular helper cells (Tfh) frequency.	Jia, Xiao-Yun et al. 2019 [125]
		Higher frequency of PD-1, PD-L1, PD-L2, and CD86 in $CD19^+CD20^-$ B than in $CD19^+CD20^+$ B cells.	Zhu, Qingqing et al. 2021 [126]
		Higher expression of PD-1 and PD-L1 in $CD11c^+$ B cells.	Rincon-Arevalo, Hector et al. 2021 [127]
	Soluble levels	Increased serum levels of anti-PD-1 IgG in new-onset SLE patients.	Shi, Hui et al. 2017 [128]
		Higher serum levels of sPD-1 and sPD-L1.	Du, Yan et al. 2020 [111]
		Higher serum levels of sPD-1 and sPD-L2 in SLE patients with high disease activity. sPD-L1 was not elevated in SLE patients.	Hirahara, Shinya et al. 2020 [110]
		Higher expression of membrane-bound PD-L2 on monocytes. Lower serum levels of sPD-L2.	Tong, Min et al. 2020 [129]
RA	Tissue expression	PD-L2 was highly expressed on macrophages in the synovial tissue.	Xiong, Jian et al. 2023 [130]
		Low PD-L1 expression in RA synovial tissue	Guo, Yanxia et al. 2018 [131]
		PD-1 expression on synovium infiltrating lymphocytes.	Matsuda, Kotaro et al. 2018 [132]

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		PD-L1 expression on synovial lining cells.	
	Cell expression	Increased percentages of PD-L2-expressing CD14⁺ monocytes.	Xiong, Jian et al. 2023 [130]
		Increased PD-L1 expression on synovial fluid mDCs compared with peripheral blood mDCs	Moret, Frederique M et al. 2014 [133]
	Soluble levels	Lower sPD-L2 in the serum of RA patients.	Xiong, Jian et al. 2023 [130]
		sPD-1 levels are increased in ACPA⁺ but not ACPA⁻ early RA	Guo, Yanxia et al. 2018 [131]
		Elevated sPD-1 and sPD-L1 levels in serum and synovial fluid of RA	Wan, Bing et al. 2006 [134]
		Higher sPD-1 in early and chronic RA	Greisen, S R et al. 2014 [135]
		Elevated sPD-1 in RA serum	Bommarito, D et al. 2017 [136]
pSS	Tissue expression	PD-1 expression on infiltrating lymphocytes in the salivary gland from 52% of SS patients. PD-L1 expression on ductal and acinar epithelial cells from 68% of SS patients.	Kobayashi, Masaya et al. 2005 [137]
		PD-1 and PD-L1 expression in labial glands were higher than in non-pSS controls	Qian, Sirui et al. 2022 [116]
	Cell expression	Increased expression of PD-L1 in CD11c⁺ B cells of pSS patients	Rincon-Arevalo, Hector et al. 2021 [127]
	Serum levels	Lower sPD-L2 serum levels in pSS patients	Loureiro-Amigo, Jose et al. 2021 [138]
		Elevated sPD-L2 serum levels in pSS patients	Nishikawa, Ayumi et al. 2016 [139]
		Elevated sPD-1 and sPD-L1 serum levels in pSS patients	Qian, Sirui et al. 2022 [116]
MS	Tissue expression	Astrocytes in white matter lesions from MS patients upregulate PD-L1 in response to aryl hydrocarbon receptor and interferon signaling	Linnerbauer, Mathias et al. 2023 [140]
	Cell expression	Frequency of PD-L1-expressing CD19⁺ B cells, and PD-L1⁺/IL-10+CD14⁺ monocytes are higher in stable multiple sclerosis patients compared to acute MS (AMS) patients	Trabattoni, Daria et al. 2009 [141]
	Serum levels	No information	

Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), Primary Sjögren's Syndrome (pSS), and Primary Sjögren's Syndrome (MS).

6. Regulation of PD-L1 and PD-L2 Expression and Its Association with the Autoimmune Response

It is well known that the major inducers for PD-L1 and PD-L2 expression are interferon (IFN) cytokines including type I (IFNα, IFNβ) and type II (IFNγ) interferons. IFN-pathway through a JAK/STAT signaling promotes the activation and expression of the interferon regulatory transcription factor 1 (IRF1) that induces the amplification of the PD-L1/2 gene by direct binding to the PD-L1 promoter [142]. After PD-L1 (and probably PD-L2) translation, the protein can be modified by post-translational modifications such as glycosylation, acetylation, tyrosine phosphorylation, and mono-ubiquitination upon epidermal growth factor (EGF) stimulation [143]. The knowledge about post-translational modifications in PD-L1 has primarily stemmed from studies focused on cancer. However, there are currently no works evaluating the effect of these modifications in the context of autoimmunity. Therefore, it would be important to understand the regulatory mechanisms of both PD-L1 and PD-L2, as they could serve as potential therapeutic targets.

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PD-L1 protein can be stabilized by glycosylation in N35, N192, N200, and N219 residues increasing the half-life of the protein and regulating the PD-1/PD-L1 interaction [144]. PD-L1 has an extra glycosylation site at N64 (91). PD-L1 palmitoylation in the C272 site of cysteine residues [145,146], and phosphorylation in Try112 [147] have also been implicated in stabilizing the protein and cell surface distribution in some cancer cells. In contrast, some modifications like ubiquitination mediated by the CDK4 cyclin and phosphorylation in S195 of PD-L1 induce its degradation [147].

Recent findings have also demonstrated the association of two proteins members of the chemokine-like factor (CKLF)-like MARVEL (CMTM) family with the stability of PD-L1 expression in cancer and normal myeloid cells of both humans and mice [148,149]. CMTM6 is a type 3 transmembrane protein that binds to PD-L1, maintaining its expression on the cell surface without modifying the constitutive IFN-induced mRNA expression. CMTM6 is also found in recycling endosomes with PD-L1, preventing its ubiquitination and degradation by lysosomes. Consequently, the depletion of CMTM6 leads to a reduction in PD-L1 expression on the cell surface [148,149]. CMTM4 is another member of this family that shares 55% sequence similarity to CMTM6 but has received less attention in research, despite also demonstrating similar functions to CMTM6 in the regulation of PD-L1 [149].

CMTM6 and CMTM4 are just being explored in autoimmune diseases. Using a genetic association network model, Davis et al. conducted a resequencing analysis of exomes from SLE patients and healthy individuals, identifying CMTM4 as a new strong candidate for study in SLE as it emerged as an implicated susceptibility gene [150], this discovery suggests that CMTM4 may play a role in the pathogenesis of SLE, potentially contributing to our understanding of the disease's genetic basis and offering new avenues for research into its mechanisms and therapeutic interventions.

Another study performed in pSS disease that analyzed the serum levels of CMTM6, found increased concentrations of the molecule in pSS patients compared with non-pSS and healthy controls and found up-regulated expression of CMTM6 in labial glands of those pSS patients. In this study, CMTM6 also positively correlates with sPD-1 and sPD-L1 [116]. Recently, it was reported that lower PD-L1 expression in monocytes of patients with AVV was associated with increased lysosomal degradation of PD-L1 because of reduced expression of CMTM6 [151]. Further studies of CMTM6 and CMTM4 are needed to understand their implication in PD-L1 or PD-L2 in the autoimmune context (Figure 4).

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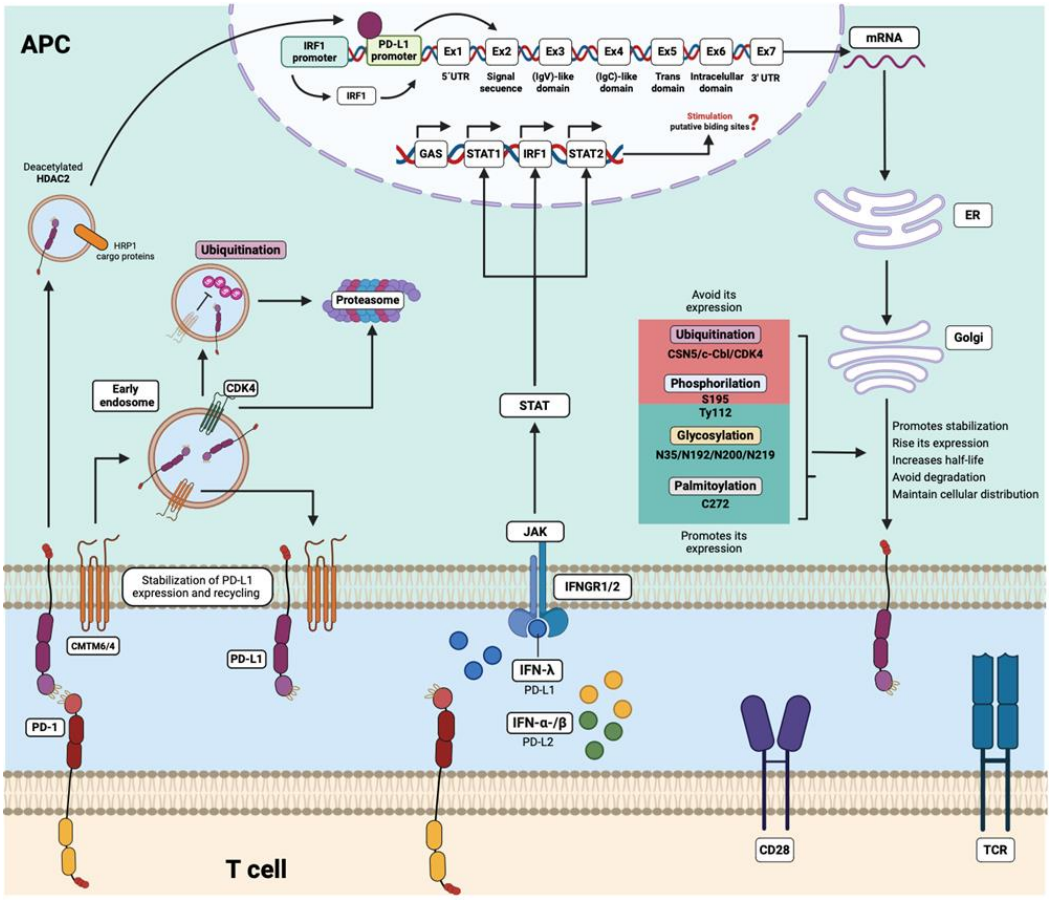

Figure 4. Regulation of PD-L1 expression. CMTM6/4 can bind to PD-L1 on the plasma membrane, maintaining its expression on the cell surface as well as in early endosomes. This interaction favors recycling, thereby preventing ubiquitination and degradation by the proteasome. In contrast, CDK4 promotes the ubiquitination of PD-L1. HDAC2 deacetylates PD-L1, facilitating its translocation to the nucleus where PD-L1 can activate genes involved in the regulation of its own expression. Post-translational modifications, such as glycosylation (N35, N192, N200, N219), phosphorylation (Try112), and palmitoylation (C272), contribute to the stabilization, increased expression, extended half-life, and maintenance of cellular distribution of PD-L1. Conversely, ubiquitination (CSN5, c-Cbl, and CDK4) and phosphorylation (S195) promote lysosomal and proteasomal degradation. HDAC2: histone deacetylase; CDK4: Cyclin D/cyclin-dependent kinase 4; PD-1: Programmed death 1; PD-L1: Programmed cell death-ligand 1; CMTM6: CKLF-like MARVEL transmembrane domain-containing protein 6; IFN-y/a/B: interferon-gamma/alpha/betha; IRF1: Interferon-gamma receptor; GAS: Gamma interferon Activated Sites; STAT: Signal Transducer and Activator of Transcription; JAK: janus kinase mRNA: messenger RNA; ER: endoplasmic reticulum.

7. Is It Possible that PD-1/PD-L1/2 Has also Another Important Role beyond Inhibition?

The binding of PD-1 with its ligands initiates a cascade of signals that results in the inhibition of T-cell signaling. When PD-1 binds to PD-L1/2, the ITIM, and ITSM domains are phosphorylated. This phosphorylation leads to the activation of the phosphatase Src homology region domain-containing phosphatase 2 (SHP2) and its requirement to the ITSM domain. SHP2 then dephosphorylates the kinases ZAP70, PI3K, and Ras, resulting in the restriction of the downstream TCR signaling pathway [21,22]. PD-1 can also inhibit the CD28 co-stimulatory signaling by limiting the PI3K/AKT, resulting in a strong inhibition of T cell activation [152]. In B cells, the PD-1-PD-L1/2 interaction also results in the phosphorylation of the tyrosine residue in ITIM/ITSM domains that recruits SHP1/SHP2. SHP1/SHP2 further dephosphorylates B-cell receptor (BCR) proximal signaling molecules that attenuate the activation of the downstream pathway, leading to the loss of B-cell functions [153].

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However, despite the well-defined signaling pathway downstream of PD-1, the question remains open: is it possible that PD-1 may exert other functions beyond the inhibition of the cellular response?

In this context, a phosphoproteomic analysis revealed that not all the pathways downstream of PD-1 are inhibitory. Instead, PD-1 ligation resulted in increased phosphorylation at several tyrosine sites, some of which were associated with the activation of cellular functions [154]. This notion was further supported by studies in which it was observed that following PD-1 ligation, the transcriptional signature of proliferating $CD4^+$ T cells was enrichment in genes associated with an activated state. Furthermore, they observed that the genes induced after PD-1 ligation significantly differed between PD-L1 and PD-L2 stimulation [155,156]. These observations are consistent with the idea that PD-1 may be involved in regulating specific cellular functions beyond its inhibitory role.

Given that PD-1 is a marker for GC-resident Tfh cells [157], and that cTfh, as well as Tph cells, express high levels of PD-1 on their cell surface as discussed above, it could be interesting to assess whether or not is it a role played by this protein in the differentiation or function of these cells, that have been mainly implicated with the pathogenesis of SLE and other autoimmune disorders.

The idea that PD-1 is important in germinal center responses potentially leading to antibody production has been increasing over the years. In 2010, Good-Jaboson et al. [158] demonstrated that PD-1 regulated the survival of germinal center B cells and the development of long-lived plasma cells. They observed that PD-1 was upregulated in Tfh cells, while PD-L1 and PD-L2 were upregulated in germinal center B cells. In their study, they also found that mice deficient in PD-1, PD-L2, or both PD-L1/L2 exhibited reduced numbers of long-lived plasma cells [158]. However, how the does the deficiency of PD-1 or its ligands is related to impaired humoral responses remains a question. They proposed that the loss of PD-1 signaling resulted in an increased number of Tfh cells but reduced synthesis of IL-4 and IL-21 mRNA by these cells. This, in turn, leads to a deficient cooperative response, as is well known that IL-21 is required for optimal differentiation and maturation of long-lived plasma cells and antibody production [159]. This notion was supported using *Pdcd1*$^{-/-}$ mice and demonstrating that the deficiency of PD-1 led to an increased expression of BCL6 in Tfh cells, and increased numbers of these cells within the germinal center. However, the expression of interferon regulatory factor 4 (IRF4), which is essential to produce IL-21, was diminished in these cells. Consequently, Tfh cells from *Pdcd1*$^{-/-}$ mice produced less IL-21 than those from wild-type (WT) mice [160]. More recently, a study conducted in bone marrow chimeras, where both PD-L1-sufficient and -deficient B cells were evaluated, also demonstrated that interactions between PD-1 on Tfh cells and PD-L1 on B cells optimized the competitiveness and affinity maturation of the B cells by controlling Tfh cells positioning and function [161]. They propose that PD-1 has a bystander signaling mode for the recruitment of Tfh cells into the follicle. This function is carried out in synergy with ICOS, another member of the B7-family of co-stimulatory molecules that is important for Tfh cell development [162]. Furthermore, it is discussed that both ICOS and PD-1 are required for optimal IL-21 production by Tfh cells, which could be a possible explanation for why these cells express high levels of PD-1 on their surface. However, it also has been demonstrated that IL-21 is essential to produce PD-1 [163], which suggests a positive feedback loop.

Most of the information available about the functions performed by PD-1 and its ligands has been obtained from studies involving $CD8^+$ T cells in cancer, where $CD8^+$ T cells expressing PD-1 have been considered as an exhausted T cell subpopulation [164]. However, it appears that the functions of PD-1 may vary depending on the context of the disease and the T cell subpopulation expressing it. In this sense, Tfh, cTfh, and Tph cells are distinguished by their high expression of IL-21 [50,54,165], the cytokine through which they perform their primary helper functions, along with the expression of other cytokines during the humoral response. Therefore, it is suggested to evaluate whether these cells can be considered as an exhausted T cell subpopulation and new studies are necessary to elucidate the role of PD-1 beyond inhibition in $CD4^+$ T cells in the context of autoimmune response.

8. PD-1 as a Possible Therapeutic Target in SLE

The proposal to develop biological agents targeting co-inhibitory pathways to treat patients with autoimmune diseases is not new [166]. Based on the discussion above, it is clear that a better

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understanding of the PD-1/PD-L1/L2 axes in SLE and other autoimmune diseases could lead to the design of new therapeutic strategies that can exclusively target the PD-1 pathway or be combined with other treatments. From our perspective, two therapeutic approaches could be followed: facilitating PD-1's accessibility to its ligands and administering PD-1 agonists.

8.1. Accessibility between PD-1 and Its Ligands

Daisuke Sugiura et al. generated anti-CD80 antibodies that dissociate the cis-PD-L1-CD80 complex. This dissociation allows PD-L1 interaction with PD-1 leading to the activation and potentiation of the inhibition of T cells, resulting in the attenuation of autoimmune symptoms [106].

8.2. PD-1 Agonists

Previously, a study was conducted using a murine model to evaluate the impact of systemically activating PD-1 through the administration of PD-L1-Ig in SLE-prone mice. The results demonstrated that PD-L1-Ig activated the PD-1 pathway, leading to the suppression of Th17 cell generation, a decrease in cytokine levels, including IFN-γ, IL-17, and IL-10, as well as reduced production of anti-dsDNA autoantibodies. These effects collectively contributed to the mitigation of kidney disease and an extension of the survival of these SLE-prone mice [167]. Using computational design, a small molecule named PD-MP1 was created to specifically bind to both human and murine PD-1 at the PD-L1 interface. The trimerization of PD-MP1 acts as a PD-1 agonist leading to significantly inhibiting the activation of murine T cells, this suggests that PD-MP1 holds potential as a PD-1 agonist for the treatment of autoimmune diseases and inflammatory conditions [168]. Also, it has developed PD-1 agonist molecules called ImmTAAI. These molecules can bind to target cells and imitate PD-L1 function, leading to highly effective activation of the PD-1 receptor on interacting T cells, and therefore achieve immune suppression [169]. The development of nanoparticles coated with dexamethasone has shown therapeutic efficacy in improving lupus nephritis (LN) in MRL/lpr mice. They specifically target $CD4^+$ T, activating the PD-1 and TIGIT (T cell immunoglobulin and ITIM domain) signaling, leading to the inhibition of effector T cells, and enhancing the immunosuppressive activities of Treg [170]. More recently, natural autoantibodies that downregulate specific autoimmune disorders have been discovered. These autoantibodies are called regulatory rheumatoid factor (regRF). regRF specifically binds to PD-1 on activated T cells, and it has been reported that serum containing regRF reduces the number of $PD\text{-}1^+CD4^+$ lymphocytes. Therefore, RegRF utilizes the PD-1 pathway to regulate activated $CD4^+$ T lymphocytes [171].

Although the potential of activating the PD-1 co-inhibitory pathway to alleviate autoimmunity is still being explored, it appears to be a promising therapeutic approach. In fact, there are PD-1 agonists ongoing in phase I and II in clinical trials, and researchers are collecting information to propose novel strategies such as combining low doses of IL-2 with PD-1 agonists [172]. Certainly, this has the potential to revolutionize conventional strategies and bring us closer to the era of precision medicine.

9. Conclusions

PD-1 is a molecule whose function appears to largely depend on the environment and context in which it is found. Most of the studies about PD-1 and PD-L1/2 expression, regulation, and function, have been made mainly on $CD8^+$ T cells in the pathogenesis of cancer. However, this review emphasized the importance of directing new assays to elucidate the mechanisms operating PD-1's function on $CD4^+$ T cells during the autoimmune response, as it has been suggested that PD-1 could play a role in the differentiation and function of various T cell subpopulations such as Tfh, cTfh, and Tph cells, that are associated with some autoimmune disorders, which suggest a more complex regulation of this molecule.

We highlighted some of the most recent findings about PD-1 and PD-L1/L2 axis in systemic lupus erythematosus to demonstrate both their inhibitory and non-inhibitory functions and their association with disease activity. We suggest that a deeper understanding of the interaction between

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B and T cells in a PD-1-dependent manner could have potential value in identifying new therapeutic targets for the disease.

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