



PD-1 immunobiology in systemic lupus erythematosus

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ABSTRACT

Programmed death (PD)-1 receptors and their ligands have been identified in the pathogenesis and development of systemic lupus erythematosus (SLE). Two key pathways, toll-like receptor and type I interferon, are significant to SLE pathogenesis and modulate the expression of PD-1 and the ligands (PD-L1, PD-L2) through activation of NF- κ B and/or STAT1. These cell signals are regulated by tyrosine kinase (Tyro, Axl, Mer) receptors (TAMs) that are aberrantly activated in SLE. STAT1 and NF- κ B also exhibit crosstalk with the aryl hydrocarbon receptor (AHR). Ligands to AHR are identified in SLE etiology and pathogenesis. These ligands also regulate the activity of the Epstein-Barr virus (EBV), which is an identified factor in SLE and PD-1 immunobiology. AHR is important in the maintenance of immune tolerance and the development of distinct immune subsets, highlighting a potential role of AHR in PD-1 immunobiology. Understanding the functions of AHR ligands as well as AHR crosstalk with STAT1, NF- κ B, and EBV may provide insight into disease development, the PD-1 axis and immunotherapies that target PD-1 and its ligand, PD-L1.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder influenced by a complex etiology of both genetic and environmental factors which results in a clinically heterogeneous presentation [1]. The programmed death (PD)-1 receptor and its ligands (PD-L1, PD-L2) are immune regulatory molecules implicated in the development of SLE [2]. Targeting PD-1 receptors with antibodies to block their activation is an established therapeutic in the treatment of several cancers [3]. This antibody therapy may also lead to the development of immune-related adverse events that clinically present with symptoms similar to autoimmune diseases like SLE [1,3]. The complexities of the PD-1 axis are highlighted by the expression of PD-1 on myeloid and lymphoid subsets and the expression of PD-1 ligands on both immune and non-immune cells in the microenvironment. Understanding the regulatory signals involved in PD-1 receptor expression and function may be pivotal to the pathogenesis of disease and mechanisms of action for anti-PD-1 therapies and their adverse events and is therefore the purpose of this review.

2. The PD-1 axis

PD-1 and its ligands (PD-L1, PD-L2) provide negative signals that

terminate and/or attenuate the immune response [4]. The most common interaction described involves CD4 T cell PD-1 with PD-L1 or PD-L2 on an antigen presenting cell. Ligation of these receptors induces the activation of an immunoreceptor tyrosine-based inhibitory motif (ITIM) in the PD-1 cytoplasmic tail which inhibits activation sequences contained in the immunological synapse [5]. However, PD-1 is also identified on B cells [6] and myeloid cells [7,8] and the ligands are identified on neutrophils [9], lymphocytes [10,11] and additional non-immune cells including tumors [12], epithelial cells [13], endothelial cells [14], and stromal cells [12]. PD-L1 and PD-L2 cross-compete for binding to PD-1 whereas PD-L1 also binds CD80 [4]. This latter interaction involves antigen presenting cell CD80 binding to CD4 T cell PD-L1 which reduces CD4 T cell activation [10]. Thus, cell signals from PD-1 or its ligands regulate the adaptive immune response. This highlights the rationale for PD-1 immunotherapies. However, immune-related adverse events, similar to various autoimmune diseases [1,3], are known to occur in response to PD-1 immunotherapies. Dysregulated cell signals in SLE may therefore identify pathways involved in controlling the PD-1 response. Two pathways of interest include the toll-like receptor (TLR) pathway and the type I interferon (IFN) pathway, which are highly active in the pathophysiology of SLE [15,16] and the regulation of the PD-1 axis [17–19]. TLR cell signals induce the activation of NF- κ B and production of type I IFNs that subsequently

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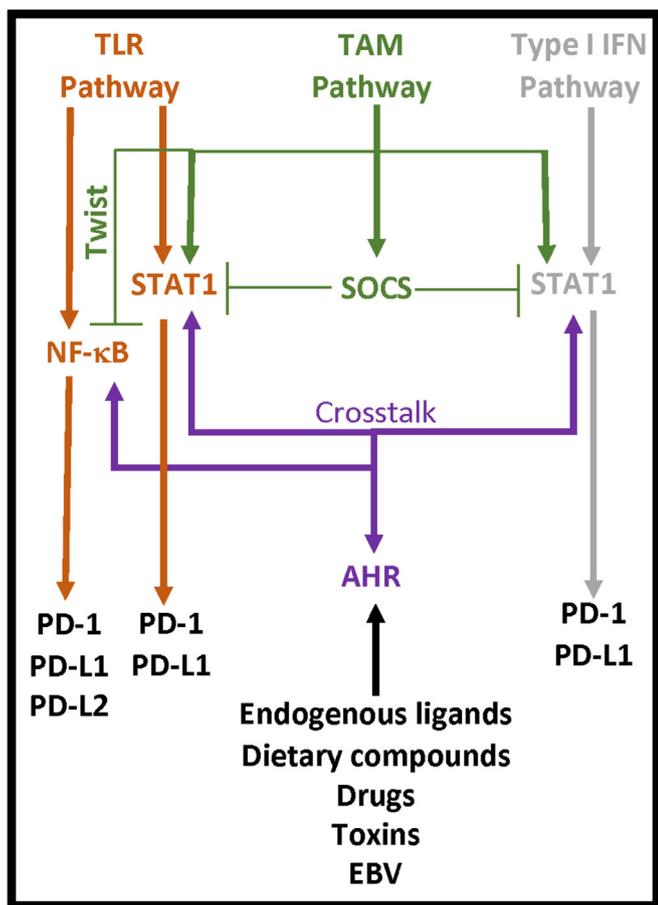


Fig. 1. Common SLE cell signals that modulate the PD-1 axis. PD-1 receptors are activated by TLR- and Type I IFN-induced NF-κB and/or STAT1 activation. TLR and Type I IFN cell signals are regulated by TAM receptor activity and the functions of suppressor of cytokine signaling (SOCS) and Twist transcriptional repressors. AHR is activated by ligands involved in the etiology, pathogenesis, and treatment of SLE. AHR also exhibits crosstalk with NF-κB and STAT1.

activate STAT1 [20] and these transcription factors (NF-κB, STAT1) regulate the expression of PD-1 [21], PD-L1 [19,22] and PD-L2 [23]. Elevated expression levels of NF-κB [24] and STAT1 [25,26] in SLE indicate that regulatory signals, possibly associated with the activity of Tyro3, Axl and Mer (TAM) receptor tyrosine kinases or the aryl hydrocarbon receptor (AHR), are reduced or absent which may influence the PD-1 axis (Fig. 1).

3. Systemic lupus erythematosus (SLE)

In the United States, the incidence and prevalence of SLE is approximately 5.5 and 73 per 100,000 people respectively [27]. The disease predominantly affects women of child-bearing age, with an increased prevalence in individuals with an African ancestry [27,28]. The etiology is a multifactorial process involving disruptions in innate and adaptive immunity that culminate into pronounced chronic immune dysregulation. Genetic, epigenetic and environmental factors are implicated in the initiation of the disease [29]. Genetic factors may include polymorphisms within TLR-7,8, and 9 [30], DNase I [31], and within the major histocompatibility (MHC) locus, including human leukocyte antigen (HLA) class I genes (MHCI), class II genes (MHCII), and class III genes encoding tumor necrosis factor (TNF)-α, complement C2 and C4 [32]. Identified environmental factors include agents that are infectious (e.g.: Epstein-Barr virus (EBV) [33–35], endogenous retroviruses [36]) and non-infectious (e.g.: ultraviolet light [37],

smoking [38], drugs [39], stress [40], diet [41]). The exact combination of genetic and environmental factors that elicits the initiation of disease is yet to be determined. Disease heterogeneity coupled with a prolonged subclinical phase complicates and delays the diagnosis of SLE [42]. Diagnosis and classification is based on a combination of multiple clinical (butterfly rash, oral ulcers, non-scarring alopecia, synovitis, serositis, leukopenia, thrombocytopenia, renal and neurological functional deficits) and immunological (elevated anti-nuclear, phospholipid, dsDNA, β2 glycoprotein I, cardiolipin, or Smith antibodies; low levels of C3 and C4 complement) manifestations [1]. Treatment is dependent upon disease severity and may target TLR signaling (anti-malarials), cell proliferation (methotrexate, cyclophosphamide), NF-κB activity (corticosteroids), B cells (rituximab) or cytokines such as B cell activating factor/BAFF (belimumab) [43].

Two key pathways in SLE immunogenesis are the TLR pathway [15] and the type I IFN pathway [16]. The TLR pathway is most commonly activated by components of pathogens, but in SLE, increased cell death, due to apoptosis, neutrophil extracellular trap (NET) activity and/or lack of clearance of the dying cells, results in the increased presence of nucleic autoantigens that activate TLRs (e.g. TLR3:dsRNA, TLR7/8:ssRNA, TLR9:DNA) and contribute to the pathology [44]. The TLR pathway can also induce the production of type I IFNs. Activation of dendritic cell (DC) TLR7 or TLR9 induces the extracellular release of the type I IFN, IFN-α [45], which is a cytokine elevated in SLE patients sera [46] (Fig. 2). In SLE patient peripheral blood B cells, another type I IFN, IFN-β, is elevated intracellularly compared to healthy controls, enhanced by TLR3 ligands, and strongly associated with increased autoantibody production and renal disease [47]. TLR ligands also regulate myeloid production of complement proteins [48], which are notably reduced in SLE patients [1]. Lack of complement protein C3 also enhances TLR-induced type I IFN production [47,49], highlighting the strong association between the TLR and type I IFN pathways in SLE.

TAMs are identified in the etiopathogenesis of SLE [50–52] and are

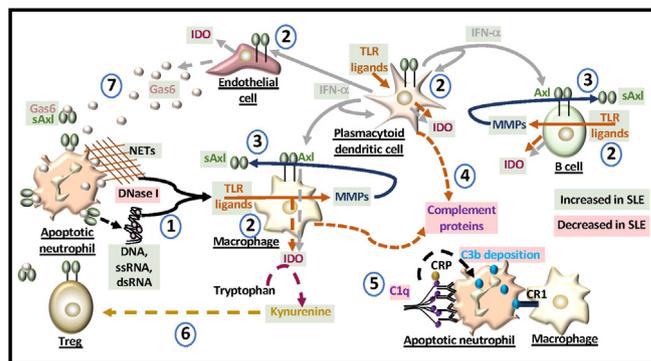


Fig. 2. Molecules dysregulated in SLE. (1) Mutations in DNase I can limit the degradation of DNA from apoptotic cells and/or from neutrophil extracellular traps (NETs) and induce the release of nucleic acids that can act as TLR ligands. (2) IFN-α and IDO production are elevated in SLE. TLR ligands induce the production of IFN-α and IDO from antigen presenting cells and endothelial cells. IFN-α also induces the production of IDO and cell surface expression of Axl. (3) TLRs can generate matrix metalloproteinases (MMPs) that cleave Axl from the cell surface. In SLE, soluble Axl (sAxl) is elevated and generated mainly from macrophages and B cells. (4) The production of complement proteins is modulated by TLR ligands. (5) C1q binds antibodies that opsonize the apoptotic cell. C reactive protein (CRP) binds to C1q in activating the complement cascade involving C3b deposition which binds to macrophage complement receptor 1 (CR1). Reduced levels of C1q alter macrophage uptake of apoptotic cells. (6) IDO generates kynurenine from tryptophan that can enhance the formation of Tregs. Kynurenine production is elevated in SLE but the levels of Tregs do not increase. Ligation of Treg Axl with Gas6 enhances their suppressor activity which may be blocked by sAxl. (7) Gas6 sourced from activated endothelial cells is elevated in SLE and binds apoptotic cells and Axl. In SLE, the levels of sAxl may block immune cell recognition of apoptotic cells and alter the function of immune and non-immune cells in the microenvironment.

Table 1
Clinical PD-1 phenotypes identified in SLE.

Cell type	Patients	Source	PD-1 marker
Neutrophils [9] (CD15 ⁺ CD3 ⁻)	Chinese patients diagnosed according to the revised criteria for SLE from the American College of Rheumatology (ACR) 1997	Whole blood	PD-L1^{hi} is compared to healthy controls, correlated with the SLEDAI score, and can be reduced with immunosuppressive drugs
DCs (CD14 ^{lo}) and monocytes (CD14 ^{hi}) [75]	U.S. pediatric patients diagnosed according to ACR 1997	Peripheral blood mononuclear cells (PBMC)	PD-L1^{reduced} is compared to healthy controls
Mucosal-Associated Invariant T (MAIT) cells [84] (CD3 ⁺ TCR $\gamma\delta$ ⁻ V α 7.2 ⁺ CD161 ^{high})	Korean SLE patients diagnosed according to ACR 1997	PBMC	PD-1^{elevated} is identified on MAIT cells that are reduced in percentages compared to healthy controls
CD4 T follicular helper (Tfh) [85] (CD4 ⁺ CXCR5 ⁺)	Chinese SLE patients diagnosed according to ACR 1997	PBMC	PD-1 + Tfh cell expansion is positively associated with SLEDAI score and B regulatory cell (CD19 ⁺ CD5 ⁺ CD1d ^{high}) expansion
CD4 Tfh cell [86] (CXCR5 ^{+/−} CXCR3 ⁻)	Chinese SLE patients diagnosed according to ACR 1997	PBMC	PD-1⁺ Tfh cell percentages are positively associated with SLEDAI score
CD4 T cell [87] (CD25 ⁺)	Icelandic and Swedish patients with at least 4 of ACR 1982 classification criteria for SLE	Anti-CD3/anti-CD28 treated PBMCs	PD-1^{reduced} is compared to controls and associated with PD-1.3A polymorphism
CD8 T cell [88] (IL-7 receptor ^{lo})	United Kingdom SLE patients presenting with untreated, active (at least 4 ACR 1982 criteria) disease	PBMC	PD-1^{reduced} is compared to PD-1 on characterized “exhausted” CD8 T cells highlighting a defect in these cells that is also linked to poor SLE patient outcomes
B cell [89] (IgG antibodies)	Chinese SLE patients diagnosed according to ACR 1997	Sera	Anti-PD-1 antibodies are elevated and positively associated with SLEDAI score
B cell [90] (CD11c ^{hi} T-bet ⁺ CD27 ^{lo} CD38 ^{lo})	U.S. SLE patients	PBMC	PD-1 and PD-L1 transcripts are elevated compared to healthy controls and the frequency of these cells is associated with SLEDAI score
DN2 effector B cell [91] (CD27 ⁻ IgD ⁻ CXCR5 ⁻ CD11c ⁺ T-bet ⁺)	U.S. African American SLE patients diagnosed according to ACR 1997	PBMC	PD-1 transcripts are elevated compared to healthy controls and the frequency of these cells is associated with SLEDAI score
Unknown [92]	Chinese SLE patients	Sera	Soluble PD-L1 is elevated compared to healthy controls

known to regulate the activation of TLR and Type I IFN pathways [53] (Fig. 1). In SLE patients, soluble Axl (sAxl) production is elevated [54]. This may occur in response to IFN- α -induced Axl expression [55,56] that is cleaved by TLR-induced matrix metalloproteinases (e.g. ADAM 10, ADAM 17) [54,57] (Fig. 2). Because expression of PD-L1 can be similarly induced by IFN- α [58], TLR-induced sheddases may also be responsible for the production of soluble PD-L1 (sPD-L1) in some cases of SLE (Table 1). TAM ligation is pivotal to cell migration, survival, and efferocytosis [53]. The ligands alone or bound to an apoptotic cell interact with TAMs and include vitamin K-dependent growth arrest-specific protein 6 (GAS6), which has the highest affinity for Axl yet binds all three receptors, or protein S, which only binds Tyro3 and Mer [53,59]. Elevated levels of Gas6 in active SLE [52,60] would be anticipated to bind Axl on T regulatory cells (Tregs) for enhanced suppressor activity [61] and inhibit antigen presenting cell type I IFN and TLR signals through the activation of suppressor of cytokine signaling (SOCS) and Twist transcriptional repressors [59] (Figs. 1 and 2). Dysregulation of TAMs or production of sAxl, which are known to occur in SLE [50–52,54], may thwart these responses and the downstream activation of PD-1 and the PD-1 ligands.

AHR regulates the type I IFN and TLR pathways by blocking cell signals involved in type I IFN production [62] and exhibiting crosstalk with the transcription factors NF- κ B [63] and STAT1 [64] (Fig. 1). This nuclear receptor responds to EBV activity, endogenous ligands in tryptophan catabolism (e.g. kynurenine, 6-formylindolo[3,2-b]carbazole (FICZ)), exogenous ligands found in the diet (e.g. flavonoids, indoles), cigarette smoke (e.g. benzo(a)pyrene), and certain drugs (e.g. omeprazole) [65–67]. Type I IFN or TLR cell signals induce the production of indoleamine 2,3-dioxygenase (IDO) [63,68], which is responsible for the catabolism of tryptophan into the AHR ligand kynurenine [69]. In SLE patients, lower serum levels of tryptophan and higher levels of kynurenine compared to healthy controls, identify increased IDO activity [70]. In myeloid cells, AHR is required for IDO production [71] but IDO is not a relevant factor in myeloid AHR-mediated IL-10 production involving apoptotic thymic cell co-cultures

[72]. Moreover, the absence of AHR in myeloid cells promotes TLR-induced hypersensitivity [73] and the development of SLE [72], suggesting that AHR activation is required for myeloid immune tolerance. This is supported by experiments with human DCs that demonstrate increased TLR4-induced AHR, PD-L1, and PD-L2 expression in association with enhanced IDO and IL-10 production upon secondary TLR4 stimulation [63]. These immune-tolerant DCs are immunotherapeutic targets in cancer [74] that could also be targeted in SLE. The lack of identified PD-L1 expression on SLE patient DCs [75] may indicate a disruption in AHR cell signals or cleavage of PD-1 ligands from the cell surface. Because B cells are also able to produce IDO and express PD-L1 and PD-L2 [11,76] that bind PD-1⁺ follicular T helper cells (Tfh) [77], AHR expression in B cells may be a therapeutic target in regulating germinal center reactions in SLE.

Moreover, endothelial cells are another source of IDO and these cells also express PD-L1 and PD-L2 [14,78], possibly via AHR, type I IFN, and/or TLR signals [71,79,80]. Endothelial dysfunction is a characteristic feature of SLE that increases the risk of atherosclerosis and cardiovascular diseases in these patients [81]. Aberrant endothelial activity may alter PD-L1 and PD-L2 expression on these cells that are known to suppress CD8 T cell activation by binding CD8 T cell PD-1 [14]. Endothelial Gas6 and AHR ligands such as the uremic toxin indoxyl sulfate can each independently promote leukocyte adhesion to the endothelium [82,83]. Because ligation of TAMs and AHR regulate signals involved in the expression of PD-L1 and PD-L2 (Fig. 1), elevated production of Gas6 [52,60] and/or kynurenine [71] in SLE may alter endothelial PD-L1 and PD-L2 expression. Additional examination of the regulatory cell signals in the PD-1 axis is needed to understand the relevance of the various cell types and biomarkers in SLE (e.g. PD-1 antibodies, sPD-L1) (Table 1).

4. The PD-1 axis and SLE

In SLE, the number of PD-1⁺Tfh cells increase with disease severity and their development is regulated by B cell PD-L1 ligation [77,85,86].

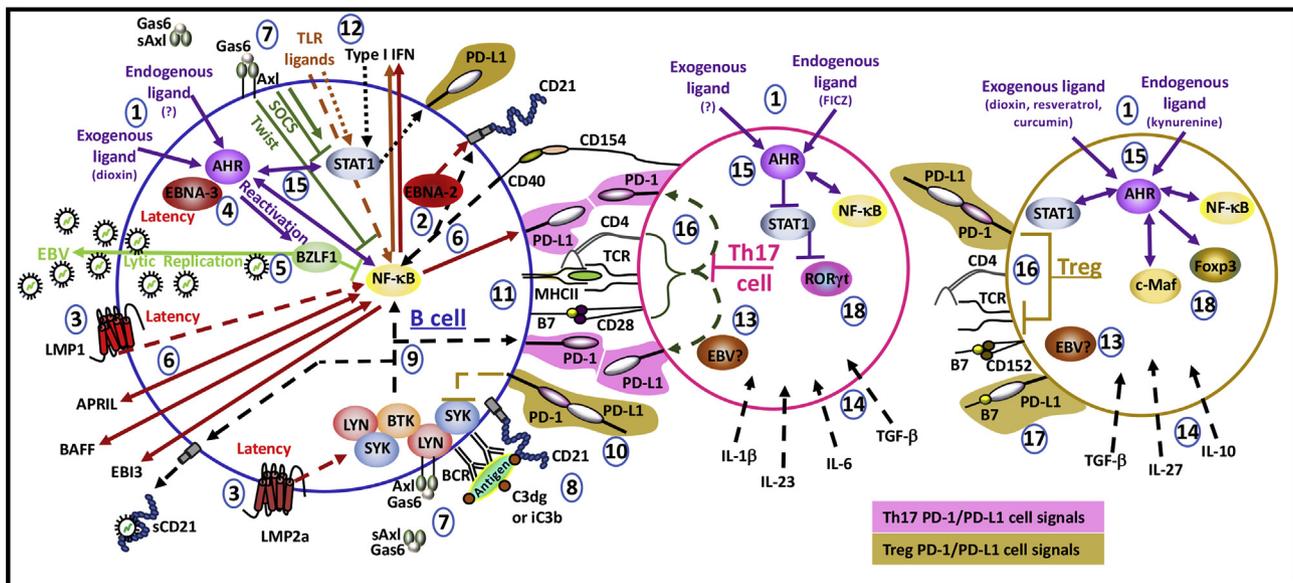


Fig. 3. Possible cell signals in lymphocytes. (1) Distinct endogenous and exogenous AHR ligands regulate the differentiation of lymphocytes. (2) Latent EBV protein EBNA-2 and CD40 ligation induce cell surface expression of CD21. (3) Latent EBV proteins LMP1 and LMP2a mimic respective cell signals induced by CD40 and the BCR. (4) Latent EBV protein EBNA-3 enhances dioxin-induced AHR transcriptional activity. (5) Dioxin-induced AHR activates EBV protein BZLF1 involved in lytic replication and antagonizing NF-κB. (6) LMP1 induces the production of APRIL and the NF-κB-induced expression of PD-L1 and production of BAFF and EB13. APRIL and BAFF activate NF-κB. (7) Axl, activated by Gas6, can complex with kinases (LYN, SYK), activate the PI3K/AKT pathway, or in the presence of type I IFN, activate JAK/STAT signals. In SLE, soluble Axl (sAxl) is produced. (8) CD21 is an EBV receptor that also assists the BCR in the recognition of complement (C3dg, iC3b) bound to antigens. (9) BCR activation induces NF-κB cell signals, CD21 shedding, and the expression of PD-1. (10) B cell PD-1 ligation to PD-L1 inhibits SYK activity. (11) The immunological synapse involves CD40 and B7 ligation associated with MHC:peptide interaction with the TCR for full activation of the B and T cell. (12) LMP1 and TLR NF-κB-induced production of type I IFN activates STAT1. (13) The functions of EBV in T cells are not clearly known. (14) Distinct cytokines regulate the development of T cell subsets. (15) AHR regulates the activity of NF-κB and STAT1 in lymphocytes. (16) In Th17 cells, PD-1 and PD-L1 are repressed whereas in Tregs, these receptors are expressed. T cell PD-1 ligation inhibits activation sequences contained in the immunological synapse. (17) T cell PD-L1 ligation with the B7 molecule, CD80, also suppresses T cell activation. (18) STAT1 antagonizes RORγt which is a transcription factor required for Th17 cell differentiation. Foxp3 and c-Maf are associated with subsets of Tregs. AHR induces the expression of Foxp3 and c-Maf exhibits crosstalk with AHR.

B cell PD-1 ligation inhibits tyrosine phosphorylation of effector molecules (e.g. SYK, SHP-2) effectively blocking B cell receptor signaling [6] (Fig. 3). The expansion of B cells in SLE [90] may suggest that B cell PD-1 is not effectively expressed or ligated in SLE despite increases in transcript levels [90,91]. The lack of significant PD-1 expression on SLE patient CD8 T cells is an identified defect in regulatory cell signals for this cell type [88]. In tumor models, macrophage PD-1 expression correlates negatively with their phagocytic potency [7]. Possibly, macrophages in SLE also express PD-1 as a biomarker of their reduced ability to clear apoptotic cells.

PD-1 polymorphisms have been identified in SLE. The susceptibility to lupus nephritis and SLE is associated with PD1.3 and PD1.5 polymorphisms, respectively [2,93]. PD1.6 polymorphisms may be a protective factor to SLE [94]. Both TLR ligands and IFN-α induce PD-1 expression on myeloid [17,95] and lymphoid subsets [96,97]. TAM cell signals, which are disrupted in SLE [50–52] and regulate TLR and IFN-α pathways [53], likely influence PD-1 activation in SLE immune subsets. This is supported by independent models that display glomerulonephritis in PD-1-deficient [98] and the Mer-deficient mice [99]. However, Axl deficiency or blockade exhibits a protective effect against glomerulonephritis [99,100] and in tumor models, Axl blockade improves PD-1 immunotherapy [101]. This suggests that Axl exhibits a distinct mechanism in regulating the PD-1 axis. Identified links in tumor cells between Axl and PD-L1 expression [102] indicate that Axl inhibitors could block B cell PD-L1 interactions with proliferating PD-1⁺Tfh cells in SLE [77] (Table 1).

The production of PD-1 antibodies in SLE [89] may break immune tolerance established by the expression of PD-L1 and PD-L2 on epithelial and endothelial cells [13,14], resulting in nephritis, similar to cases identified with PD-1 therapies [103]. Polymorphisms in PD-L1 or PD-L2 have not revealed associated risks in developing SLE [104]. PD-

L1 expression is upregulated on SLE patient peripheral blood neutrophils but reduced on DCs and monocytes (Table 1). These responses may be partly explained by a lack of C3 and C1q complement proteins in SLE [28] since neutrophil PD-L1 expression is negatively correlated with C3 [9] and C1q opsonized apoptotic cells induce PD-L1 and PD-L2 expression on human macrophages and DCs [105]. The complexity is further displayed in lupus-prone murine models that demonstrate improved kidney function in response to PD-1 activation [106] or blockade [107].

5. AHR and the PD-1 axis

The transcription factor and nuclear receptor, AHR, is integral to hematopoiesis, xenobiotic metabolism, adhesion, and migration [108,109]. The expression of AHR is induced by TLR cell signals that activate the NF-κB p65(ReIa)/p50 heterodimer in the AHR promoter [110,111]. AHR ligands are highly linked to the amino acid tryptophan. FICZ, which is a product of UV-B irradiated tryptophan [112], is an AHR ligand that may mediate SLE patient sunlight-induced flares [112]. IDO oxidation of tryptophan forms the AHR ligand kynurenine, which is elevated in SLE patient sera [70]. FICZ and newly identified trace derivatives of kynurenine exhibit greater affinity to AHR compared to kynurenine [108,113]. Full degradation of kynurenine generates nicotinamide adenine dinucleotide (NAD) [114], which is a molecule essential for life that is reduced in cells treated with another high affinity AHR ligand, dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD) [115]. Thus, the type of ligand may affect AHR activation and downstream cell signals in immunity.

5.1. AHR in T cells

The AHR ligands dioxin and kynurenine induce the formation of T regulatory cells (Tregs) [112] and the expression of PD-1 on CD8 T cells [116]. FICZ, which has higher binding affinity to AHR than kynurenine, induces the formation of the proinflammatory interleukin-17 producing T cells (Th17) [108]. Despite elevated levels of kynurenine in SLE patients [70] the ratio of Tregs to Th17 cells is reduced in SLE patient peripheral blood compared to healthy controls [117] and the levels of PD-1 on SLE patient CD8 T cells is also reduced compared to healthy controls [88]. The expression of PD-1 on CD4 and CD8 T cells is mediated by the NF- κ B p50 homodimer [118]. Because AHR is able to form a complex with NF- κ B p50 [64], the activity of AHR in these cells may direct PD-1 function. NF- κ B and AHR activity are involved in the generation of both Treg and Th17 cells [119,120]. AHR is also characterized in regulating STAT1 activity during Th17 differentiation [121]. STAT1 promotes Foxp3 [122] but represses IL-17 [123] transcriptional activity. The ability of AHR to complex with NF- κ B p50 and STAT1 in myeloid cells [64] suggests that similar interactions occur in Th17 cells to promote their activity and suppress PD-1 receptors. A lack of STAT1 activation in T cells may also explain the increased levels of STAT1 protein in SLE patient CD4 T cells compared to healthy controls [26]. Dietary compounds (e.g. curcumin and resveratrol) can bind AHR, ameliorate SLE symptoms [124,125], and regulate the activation of NF- κ B [126,127] and STAT1 [128,129]. These compounds antagonize the AHR ligand FICZ, inhibit the formation of Th17 cells and enhance the generation of Foxp3⁺Tregs [130–132]. AHR-induced repression of STAT1 [123] may promote the activation of the nuclear receptor retinoic acid receptor-related orphan receptor (ROR)- γ t, which is required for the differentiation of Th17 cells [123,133]. Exogenous synthetic ROR γ t ligands but not currently known endogenous ROR γ t ligands reduce PD-1 expression on T cell lines and murine primary T cells [134] (Fig. 3). Whether certain ROR γ t ligands, additional dietary ligands or rapidly metabolized ligands, which do not accumulate in the same manner as toxins, regulate PD-1 expression and tolerance continues to be explored [135,136].

5.2. AHR in B cells

Similar properties of AHR exist in B cells. STAT1 and TLR7 signaling are required for the formation of germinal centers that are common in SLE [137]. This process is regulated by TLR9 signals [137] and the various heterodimers or homodimers of NF- κ B [138]. Distinct findings of AHR activity in B cells suggests that AHR may interact with STAT1 and NF- κ B signals in these cells. For example, cross-linking the B cell receptor significantly induces the expression of AHR and activation of AHR with dioxin negatively affects the processes of class-switch recombination and plasma cell differentiation [139]. Dioxin, like kynurenine, encourages the production of Tregs via AHR activation [140] which suggests that ligands such as FICZ, which induce Th17 formation [108], may also distinctly affect the activity of B cells. AHR is an identified as a factor required for murine B cell proliferation [141]. Because B cells exhibit increased proliferation in the absence of PD-1 [142], AHR may potentially modulate PD-1 expression in B cells as well as BAFF cell signals, which have established functions in B cell survival, class-switch recombination, and plasma cell differentiation [143].

5.3. AHR in myeloid cells

In myeloid cells, AHR is established in the regulation of immune tolerance and the expression of PD-1 ligands [63,72], which may be in response to AHR complexing with STAT1 and NF- κ B p50 [64]. Tolerance and the formation of M2 alternative macrophages is dependent upon NF- κ B p50 in myeloid cells [144], further implicating AHR ligands and cell signals in the SLE response. In mouse embryonic fibroblasts, viral induced IFN- β is regulated by AHR activation of 2,3,7,8-

tetrachlorodibenzo p-dioxin-inducible poly(ADP-ribose)polymerase (TIPARP), which antagonizes cell signals involved in type I IFN production [62]. Whether this cell signaling mechanism in response to various AHR ligands also exists in DCs that generate IFN- α in SLE is not known.

6. EBV and the PD-1 axis

EBV infection and reactivation are associated with SLE etiology [33–35]. The seroprevalence of EBV progressively increases during childhood with greater than 90% of U.S. adults exhibiting antibody positive titers by the age of 35 [145]. EBV can infect neutrophils [146], T cells [147], epithelial cells [148], but preferentially infects B cells [149]. Two common EBV proteins are latent membrane protein 1 (LMP1) and LMP2a which mimic cell signals induced by CD40 ligation and BCR activation respectively [149]. LMP1-induced NF- κ B activation generates various cytokines in B cells (e.g. the IL-27 subunit EBV-induced gene 3 (EBI3), A proliferation-inducing ligand (APRIL), BAFF, IFN- α , IFN- γ) that are elevated in SLE [150–152]. The production of IFNs by LMP1 subsequently induces STAT1 activity [152] and these cell signals may play role in LMP1-induced PD-L1 expression in infected cell lines [153]. Possibly, these same signals regulate peripheral blood neutrophil PD-L1 over-expression in SLE [9].

In various cell lines, the EBV immediate early viral transactivator, BRLF1, has been shown to induce the expression of Mer [154], indicating that TAM receptors are regulated by EBV activity. Either BRLF1 or another EBV immediate early viral transactivator, BZLF1, is sufficient to induce lytic replication in both latently infected epithelial cells and B cells [155]. Research has identified AHR complexed with the latent protein, EBV nuclear antigen-3 (EBNA-3) [66], and dioxin-induced AHR is directly involved in the reactivation of the EBV immediate early viral transactivator, BZLF1 [67]. This initiating factor in lytic viral replication antagonizes latent viral signals, in part, by blocking NF- κ B activity [156] (Fig. 3).

T cell AHR and PD-L1 expression are also induced by the EBV cytokine IL-27. In these cells, AHR interacts with c-Maf, a transcription factor identified in a subset of Tregs [157,158]. These CD4⁺CD25⁺Foxp3⁻c-Maf⁺ Treg cells, termed Treg-of-B cells, are formed in response to repeated interactions with B cells [159]. Treg-of-B cells express PD-1 and additional checkpoints in regulating Th2, Th1, and Th17 responses under physiological cues that have yet to be fully elucidated (Fig. 3).

Moreover, EBV binds to B cells via complement receptor-2 (CR2, CD21) and the levels of soluble CD21 (sCD21), released subsequent to BCR activation, are indicated to block EBV infection [160–162]. CD40 ligation and the latent EBV molecule, EBNA-2, induce CD21 expression [163,164] which then cooperates with the BCR to recognize and respond to complement (C3dg or iC3b)-bound antigens [165] (Fig. 3). In SLE patients, low levels of CD21 are identified on activated naïve and memory B cell subsets and the levels of serum sCD21 are reduced compared to healthy controls [166,167]. In mice deficient of CD21 and the complement receptor 1 (CR1, CD35), B cells express increased levels of PD-1 [168] and increased levels of PD-1 transcripts are expressed by activated B cells in human SLE [90,91]. Interestingly, the expansion of PD-1⁺ B cell subsets similar to the ones expanded in active SLE have been reported in association with the development of autoimmune complications of checkpoint inhibitors in melanoma patients [169]. Because PD-1 ligation antagonizes TCR and BCR cell signals [5,6], the presence of sPD-L1 in SLE [92] may directly affect the activity of lymphocytes. The production of sPD-L1 is also linked to an SLE associated disease, non-Hodgkin lymphoma (NHL) [170,171].

7. SLE and non-Hodgkin lymphoma (NHL)

The diagnosis of SLE is independently and significantly associated with higher proportions of blood cancers compared to age and sex-

matched controls [171]. NHL is the most common SLE associated blood cancer, which accounts for 4.3% of all cancers, affects both men and women, and originates from oncogenic B- or T-cells [171,172]. The highest NHL incidence occurs in diffuse large-B-cell lymphoma (DLBCL) and B-cell chronic lymphoid leukemia (B-CLL) affecting 4–7 and 4–8 per 100,000 people respectively [172]. DLBCL is the most common type of NHL in SLE patients whereas B-CLL is a rare occurrence [172–174]. In DLBCL, sPD-L1 is a marker of poor prognosis [170], which may indicate that sPD-L1 in SLE is a risk factor for this disease. In B-CLL, membrane Axl is a contributing factor in disease progression [175] by complexing with kinases, such as LYN and SYK [176]. The lower risk of B-CLL may reflect the increased levels of sAxl in SLE that potentially block membrane Axl cell signals. Similar to SLE, DLBCL and B-CLL are driven by EBV infection [177], polymorphisms in complement [178] and TLR [179,180] genes. Continued evaluation of the cell signal similarities and differences between SLE and NHL may allow for the identification of biomarkers for SLE patients at risk of developing NHL and possibly better therapies for both diseases.

8. Summary

SLE is the result of complex genetic and environmental factors that alter innate and adaptive immunity. The PD-1 axis is involved in the regulation of innate and adaptive immune subsets in SLE and certain cancers. This axis is also a target in the treatment of various diseases where the mechanisms that regulate immune checkpoints have yet to be fully revealed. The complexities of PD-1 immunity are embedded in the multiple cell signaling pathways that regulate the expression and activation of the receptors on both immune and parenchymal cells in the microenvironment.

Dysregulation of SLE TAMs, such as Axl, may affect TAM-induced regulation of type I IFN and TLR cell signals and their downstream responses involving the PD-1 axis. These cell signal networks are also influenced by AHR (Figs. 1 and 3). The ability of AHR to induce PD-1 coupled with noted deficits in the phagocytic potency of PD-1⁺ or TAM deficient macrophages in various models may indicate that AHR ligands are involved in TAM expression and/or the clearance of apoptotic cells. Because STAT1 and NF- κ B are integral to myeloid, B cell, Treg and Th17 development, further exploration of these transcription factors in the AHR response is needed. The involvement of AHR in the generation of Tregs, that can express PD-1 receptors, and Th17 cells, that lack these checkpoints, suggests that AHR cell signals participate in PD-1 immunity, highlighting AHR as a therapeutic target. Mechanisms to block FICZ interactions with AHR but promote AHR ligation with kynurenine or kynurenine trace derivatives may promote tolerance. Moreover, because kynurenine is a precursory step in the production of NAD, metabolic enzymes and metabolites in kynurenine catabolism may be pivotal to the PD-1 axis and the function of immune subsets in SLE.

Endogenous or exogenous AHR ligands can also regulate EBV latent or lytic activity, suggesting that EBV-induced TAM receptor expression or LMP1-induced PD-L1 expression may involve AHR. Evidence that the EBV receptor, CD21, regulates PD-1 expression needs further exploration. The involvement of the EBV associated cytokine, IL-27, in the expression of AHR and PD-L1 further highlights the complex interactions involved in the PD-1 response. These integrated functions of AHR in SLE and the PD-1 axis in various cell types suggest that interventions that prevent or induce PD-1 ligation modulate AHR expression and/or responses. The identification of sPD-L1, PD-1 antibodies, and kynurenine in SLE highlights possible dysfunction between AHR and the PD-1 axis. Understanding how AHR or additional AHR associated transcription factors influence the development and activation of distinct cell types in a multi-cellular microenvironment may aid in identifying factors in the progression and treatment of SLE and NHL. Identification of AHR ligands that enhance or inhibit cell surface PD-1 and PD-L1 may also be beneficial in immunotherapies that target these receptors.

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