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Immune checkpoint molecules. Possible future therapeutic implications in autoimmune diseases

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A B S T R A C T

During host immune response, an initial and sufficient activation is required to avoid infection and cancer, yet an excessive activation bears the risk of autoimmune reactivity and disease development. This fastidious balance of the immune system is regulated by co-stimulatory and co-inhibitory molecules, also known as immune checkpoints. Both excessive co-stimulation and insufficient co-inhibition can induce the activation and proliferation of autoreactive cells that may lead to the development of autoimmune diseases. During the last decade, a growing number of new immune checkpoint receptors and ligands have been discovered, providing an attractive approach to investigate their implication in the pathogenesis of autoimmune diseases and their potential role as targets for effective therapeutic interventions. In this review, we focus on the roles and underlying mechanisms of co-stimulatory and co-inhibitory receptors and other molecules that function as immune checkpoints in autoimmune diseases such as systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, Sjögren's syndrome, type I diabetes and inflammatory bowel disease. We also summarize previous and current clinical trials targeting these checkpoint pathways in autoimmune diseases and discuss further therapeutic implications and possible risks and challenges.

1. Introduction

The immune system is well-orchestrated and can be mobilized against infection or cancer while maintaining homeostasis through negative regulation of cell activation. Aberrant immune regulation often leads to a breakdown of self-tolerance and the development of autoimmune diseases; understanding the underlying mechanisms may offer potentially new targets for more effective therapeutic interventions [1].

Genome-wide association studies (GWAS) have revealed that mutations of the HLA locus are the most significant known genetic factor for many human autoimmune diseases, implicating T cells as major players mediating autoimmunity [2]. However, potential autoreactive T cells are tightly regulated by several control mechanisms [3]. The first one is central tolerance, induced when T cells expressing T cell receptors (TCRs) with high affinity for self-peptides are eliminated by

Abbreviations: APC, antigen presenting cell; AS, ankylosing spondylitis; BTLA, B and T lymphocyte attenuator; CD, Crohn's disease; CIA, collagen induced arthritis; Con A, concanavalin A; CTLA-4, cytotoxic T-lymphocyte associated antigen 4; DC, dendritic cell; EAE, experimental autoimmune encephalomyelitis; Fgl2, fibrinogen like 2; GITR, glucocorticoid induced TNF receptor; GWAS, Genome-wide association study; HLA, human leukocyte antigen; IBD, inflammatory bowel disease; ICOS, inducible T-cell co-stimulator; IDO, indoleamine 2, 3-dioxygenase; ILCs, innate lymphoid cells; IMQ, Imiquimod; iNOS, inducible Nitric oxide synthase; ITP, immune thrombocytopenia; LAG-3, lymphocyte-activation gene 3; mAb, monoclonal antibody; MG, myasthenia gravis; MHC, major histocompatibility class; MS, multiple sclerosis; PBC, primary biliary cholangitis; PD-1, programmed cell death protein 1; pDC, plasmacytoid dendritic cell; SS, sjögren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1D, type 1 diabetes; TCR, T cell receptors; Tfh, follicular helper T cells; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; TLR, Toll-like receptors; Treg, regulatory T cells; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; TNFRSF, tumor necrosis factor receptor superfamily; VISTA, V domain-containing Ig suppressor of T-cell activation

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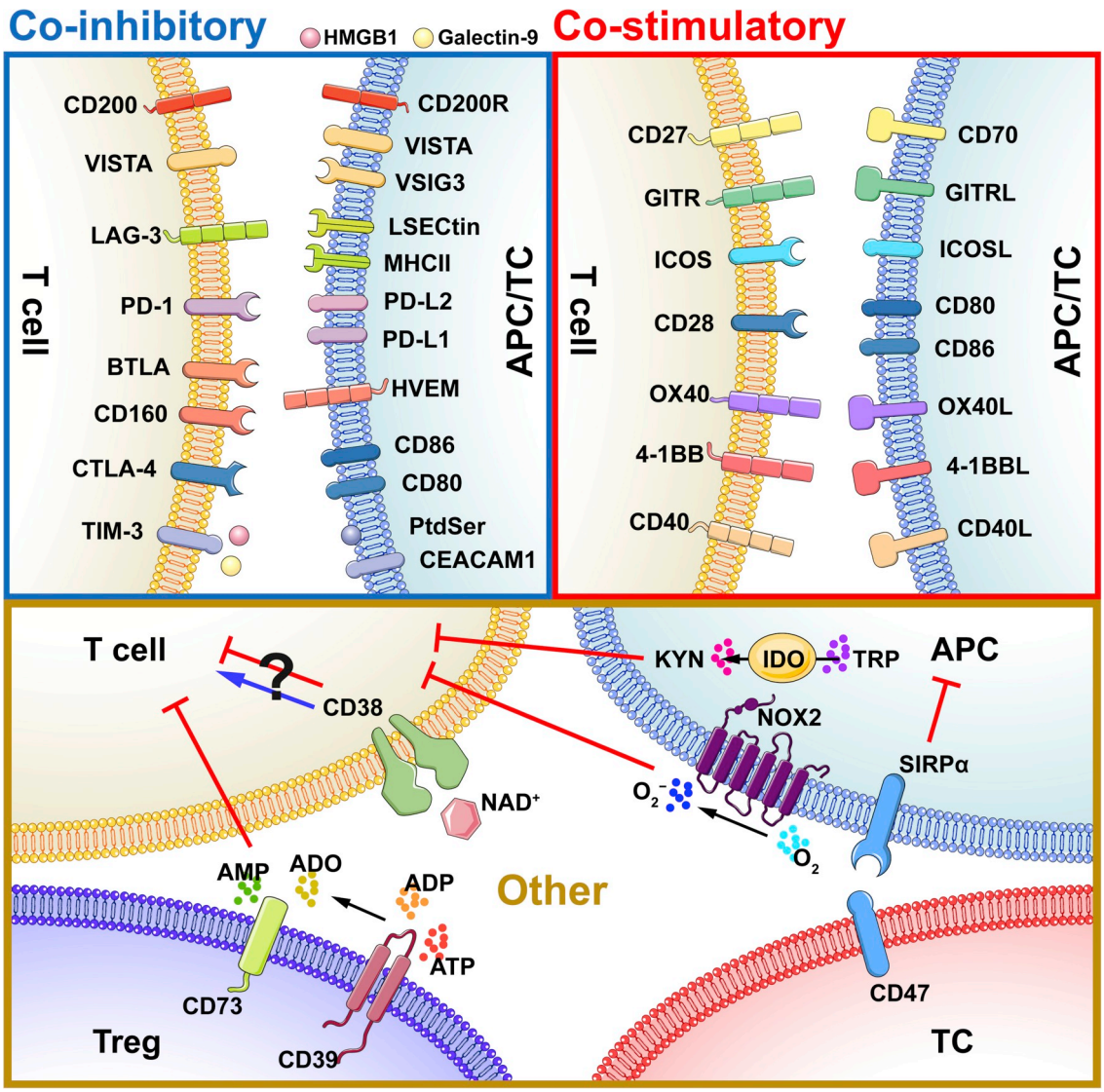

Fig. 1. Immune Checkpoint Pathways. Summary of immune checkpoint pathways that are reported or may be associated with autoimmune diseases. Co-stimulatory receptors (right up with red frame) can induce the activation and proliferation of autoreactive T cells, while co-inhibitory receptors (left up with blue frame) prevents autoimmunity. Their ligands are expressed on APCs or tissue cells (TC). Other immune checkpoint molecules (down with golden frame) regulate either T cell or myeloid cell function with different mechanisms. Interaction of ligands and receptors are showed in the same color.

negative selection in the thymus. The second one is peripheral tolerance which is primarily induced by immunoregulatory cells such as regulatory T cells, regulatory B cells and tolerogenic dendritic cells (DCs) [4]. Autoreactive T cells must be activated by antigen presenting cells (APCs) to become pathogenic. Activation of T cells requires three signals, the engagement of TCR with self-peptide bond major histocompatibility class molecules, co-stimulation signals and cytokines from APCs [5,6]. Co-inhibitory receptors are induced to control excessive T cell activation and arrest immune response against self [6]. Thus, co-stimulatory and co-inhibitory molecules act in coordination to modulate the immune response of autoreactive T cells.

There are many co-stimulatory and co-inhibitory molecules, termed immune checkpoint molecules (Fig. 1). To date only a minority of them has been well characterized. Nonetheless, as their number is growing, it becomes evident that the expression of inhibitory receptors and their ligands displays variation in different tissues, cell types and cell subsets, also changing with the status of cell activation. Except for T cells, immune checkpoint molecules are also involved in regulating immune response of natural killer (NK) cells, innate lymphoid cells (ILCs) and myeloid cells [7–9]. Cancer immunotherapy by immune checkpoint blockade has been proven to be effective in the treatment of many tumors such as melanoma and non-small cell lung carcinoma [10–12]. However, implications of immune checkpoint molecules in autoimmunity to date has been demonstrated only in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS) and type 1 diabetes (T1D) [6]. Thus so far very few drugs targeting these molecules have been developed to combat autoimmune diseases.

In this review we summarize the studies demonstrating the involvement of immune checkpoint molecules in different autoimmune diseases either in animal models or in human (Fig. 2), and we describe how these pathways may be utilized to identify new therapeutic targets.

2. CO-INHIBITORY SIGNALING

2.1. CTLA-4

CTLA-4 (Cytotoxic T-lymphocyte antigen 4, CD152) is structural homologue of the co-stimulatory CD28 receptor binding with higher affinity to the homologue of B7 family ligands (CD80, CD86), which is expressed on activated T cells, B cells, and monocyte derived DCs [13].

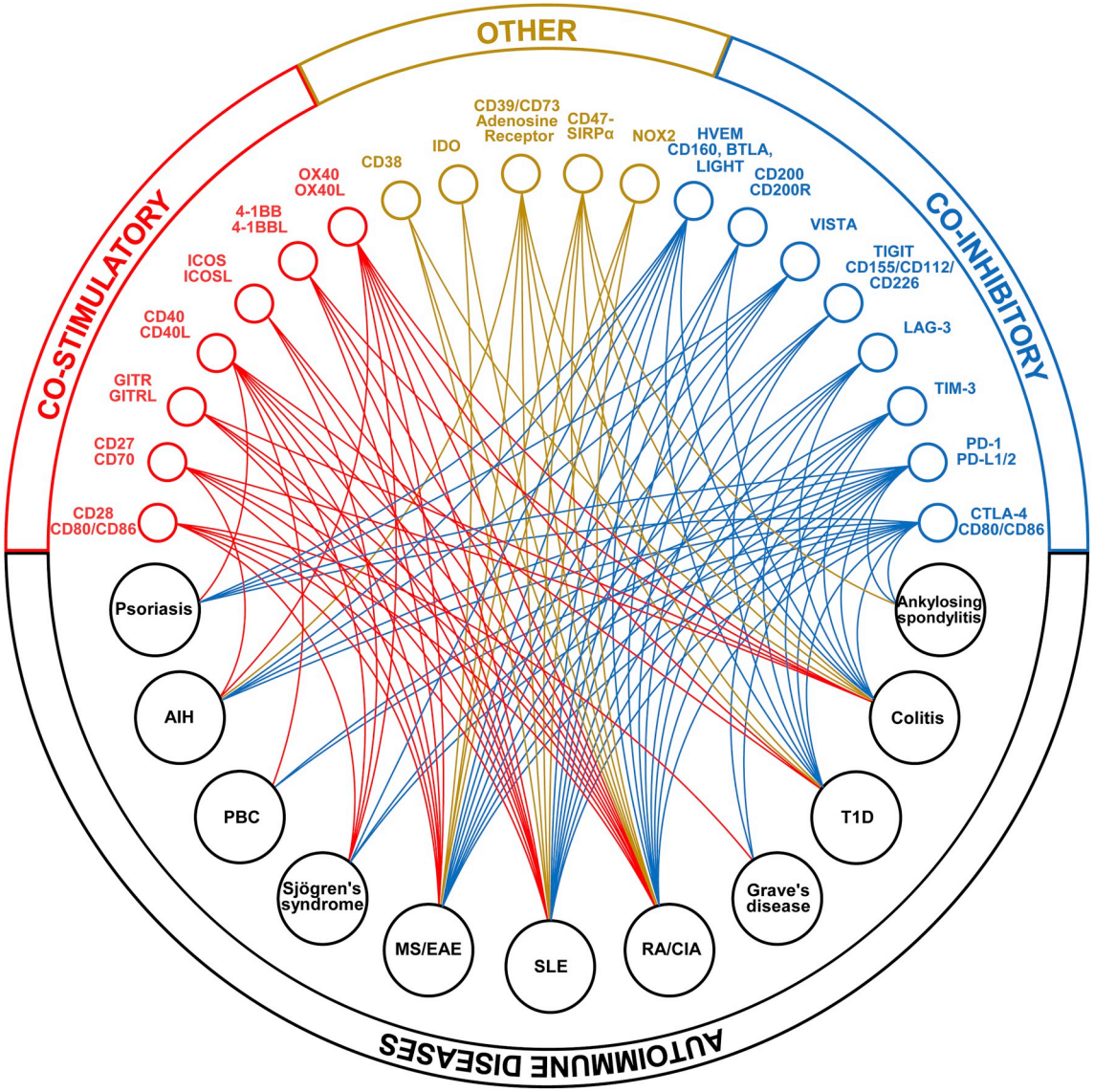

Fig. 2. Association of Immune Checkpoint Pathways with Autoimmune Diseases. It is reported that many immune checkpoint molecules play important roles in autoimmune diseases. Line connection means the association of a certain immune checkpoint pathway with an autoimmune disease, with different colors. Gene mutations, altered protein expression, disease feature changes in knockout mice, therapies with antibodies or fusion proteins against immune checkpoint pathways are considered to describe the association.

It binds to CD80/CD86 to compete with CD28 and functions as a negative regulator of T cell activation. Thus, CTLA-4 is a critical inhibitor of autoimmunity, as it stops potential autoreactive T cells at the initial stage of their activation. GWAS have identified the association of CTLA4 gene polymorphisms with various autoimmune diseases, including SLE, RA, Grave's disease, autoimmune hypothyroidism and T1D [14]. CTLA-4 deficient mice develop lethal autoimmune disease with lymphoproliferation and skewed CD4/CD8 ratio toward CD4 at the age of 3 weeks [15]. CTLA-4 deletion in adult mice also induces lymphoproliferation and autoimmune disease [16]. In addition, blockade of CTLA-4 using antibodies leads to exacerbation of disease in various mouse models of autoimmunity [17,18]. Furthermore, CTLA-4 pathway has been reported to play a negative role in many autoimmune diseases, including T1D [19], MS [16,20], inflammatory bowel disease (IBD) [21], RA [16], autoimmune hepatitis (AIH) [22], primary biliary cholangitis (PBC) [22–24], psoriasis [25], Sjögren's syndrome (SS) [16,26], SLE [27] and Grave's disease [28]. CTLA-4-Ig fusion proteins (abatacept and Belatacept) are used or being tested in clinical trials in various autoimmune diseases (Table 4) [29,30].

CTLA-4 is also highly expressed on regulatory T (Treg) cells, which are important regulators of immune homeostasis. The role of CTLA-4 on Treg cells remains controversial. It has been reported that CTLA-4 plays an important role in Treg cell mediated suppression [31]. However, in other cases, CTLA-4 deficient Treg cells retain suppressive function [32]. Deletion of CTLA-4 on Treg cells in adult mice leads to failure to ensue spontaneous autoimmunity and resistance to develop experimental autoimmune encephalitis (EAE) [20]. This may be due to the overlapping role of CTLA-4 and Treg cells in immune regulation [31]. Although CTLA-4 is initially described as a transmembrane protein, soluble form of CTLA-4 (sCTLA-4) can also be generated by mRNA splicing [33]. Serum levels of sCTLA-4 are increased in several autoimmune diseases, including Graves's disease, SLE, T1D and PBC [14]. sCTLA-4 can inhibit early T cell activation. However, higher levels of sCTLA-4 may compete with membrane-bound CTLA-4, causing a reduction in inhibitory signaling. Thus, the role of sCTLA-4 in autoimmune diseases needs further clarification.

Table 1
Role of co-inhibitory molecules in autoimmune diseases.

	SLE	RA/CIA	MS/EAE	Sjogren's syndrome	AIH	colitis	T1D	PBC	Psoriasis	Grave's disease
CTLA-4	CTLA-4–deficient mice spontaneously develop SLE [25]	CTLA-4–deficient mice have more severe CIA [16]	Deletion of CTLA-4 on Treg cells during adulthood leads to resistance to EAE [20]; CTLA-4 deficient mice are protected against EAE [16]	Deletion of CTLA-4 on Treg cells develop Sjögren's syndrome [16]		CTLA4-Ig suppresses T cell transfer induced colitis [21]		CTLA4-Ig treatment protected mice against cholangitis [23,24]	CTLA4-Ig suppresses T cell transfer induced psoriasis [21]	CTLA4 inhibits Grave's disease [28]
PD-1	PD-1 knockout mice spontaneously develop lupus-like disease [35]; Anti-PD-1 mAb alleviates while anti-PD-L1 mAb accelerates lupus in NZB/W F1 mice [25]	PD-1 knockout mice are more sensitive to CIA; PD-L1-Fc ameliorates CIA [41]	PD-1 knockout mice have accelerated EAE [38]; Depletion of PD-1 + cells ameliorates EAE [49]	Blockade of PD-L1 accelerates SS-like pathologies in NOD/ShiLtJ mice [45]		PD-1 knockout mice are resistant to DSS-induced colitis [39]; PD-L1-Fc ameliorates colitis in mice [40]	Depletion of PD-1 + cells ameliorates T1D in NOD mice [49]		PD-L1–Fc reduces psoriatic inflammation in IMQ treated mice [44]	
TIM-3	Administration of Gal-9 reduces lupus in mice [62]	Galectin-9 knockout mice are susceptible to CIA [60]	TIM-3 antibody or TIM-3 deficiency enhances EAE, and galectin-9 administration ameliorates EAE [64,65]			Tim-3 blockade exacerbates DSS induced colitis [67]	Galectin-9 inhibits autoimmune diabetes in NOD mice [66]			
LAG-3	LAG-3 + regulatory T cells suppress lupus-like disease in MRL/lpr mice [79]	The frequency of IL-10 producing LAG-3 + Treg cells is lower in RA and increases after abatacept treatment [75]	LAG-3 participates in the suppression of EAE by 2D2-IEL-THIGH cells [83]			Treg cells suppress ILC3 mediated colitis through LAG-3 [74]	LAG-3 knockout mice develop accelerated autoimmune diabetes [81,82]			
TIGIT-CD155/CD112/CD226	In vivo administration of CD155 delays SLE development in MRL/lpr mice [93]	Soluble TIGIT inhibits while anti-Vstm3 blocking mAb accelerates CIA [90]	TIGIT knockout mice are resistant to EAE and TIGIT transgenic mice are more sensitive to EAE [90]							
VISTA (PD-1H)	VISTA deficiency or blockade accelerates lupus in mice [102,103]	Deficiency of VISTA or anti-VISTA antibody treatment attenuates CIA [104]	Deficiency of VISTA or anti-VISTA antibody exacerbates EAE [101,106]		VISTA knockout mice are more susceptible to Con A–induced hepatitis, and VISTA.COMP suppresses T cell activation [98,100]				VISTA deficiency exacerbates murine psoriasiform inflammation [105]	
CD200-CD200R	Increased CD200/CD200R1 expression promotes Th17 cells from SLE patients [109]	CD200-Fc in vitro inhibits Th17 cells from RA patients [107]; CD200-Fc suppresses collagen-induced arthritis in mice [116]	CD200 knockout mice show greater sensitivity to EAE, and CD200-Fc ameliorates EAE [110,111]			CD200 knockout and CD200R1 knockout mice show greater sensitivity to acute colitis, while CD200 overexpression protects mice from colitis [113]				

(*continued on next page*)

Table 1 (*continued*)

	SLE	RA/CIA	MS/EAE	Sjogren's syndrome	AIH	colitis	T1D	PBC	Psoriasis	Grave's disease
HVEM-CD160, BTLA, LIGHT	BTLA plays a protective role in MRL-lpr mice [125]	HVEM-Ig in CIA mice results in augmented disease activity [128]	HVEM knockout mice are more sensitive to EAE [122]	BTLA knockout mice spontaneously develop Sjögren's syndrome [124]	BTLA knockout mice spontaneously develop autoimmune hepatitis-like disease [124]; CD160 knockout mice are more susceptible to Con A or α-GalCer induced hepatitis [123]; HVEM knockout mice are more sensitive to ConA-induced hepatitis [122]	In T cell transfer induced colitis model, absence of HVEM on donor T cells leads to decreased colitis, while absence of HVEM in recipients leads to acceleration of colitis [121]; Blocking LIGHT/HVEM signaling ameliorates TNBS-induced colitis [119]	Anti-BTLA antibody delays the onset of diabetes in NOD mice [127]		BTLA knockout mice are susceptible to IMQ induced psoriasis [126]	

2.2. PD-1

PD-1 (Programmed cell death 1, CD279) is an inhibitory receptor expressed on activated and exhausted T cells in acute and chronic infection, cancer and autoimmunity [34]. PD-L1 and PD-L2 are the ligands of PD-1. PD-L1 is widely expressed on both hematopoietic and non-hematopoietic cells (including vascular and stromal endothelial cells, pancreatic islet cells, placental syncytiotrophoblasts and keratinocytes), while PD-L2 expression is restricted on APCs [34]. PD-L1 and PD-L2 can be induced upon inflammatory signals. PD-1 and PD-L1 blocking antibodies can boost anti-tumor immunity cells and are used in current clinical practice for cancer immunotherapy [10]. PD-1 is an immune inhibitory molecule; PD-1 knockout mice spontaneously develop lupus-like proliferative arthritis and glomerulonephritis [35]. Single nucleotide polymorphisms of PD-1, PD-L1 and PD-L2 are reported to be associated with SLE, ankylosing spondylitis (AS), RA and T1D [36]. Data from both human samples and mouse models have shown a negative role of PD-1 pathway in autoimmune diseases, including T1D [37], MS [38], IBD [39,40], RA [41], AIH [42], PBC [42], psoriasis [43,44], SS [45] and SLE [25,35]. Based on the significance of the PD-1/PD-L1 interaction in regulating autoimmunity, several methods targeting this pathway for the treatment of autoimmune diseases have been developed in murine models [46]. One method is to transfer PD-L1 expressing DCs in the treatment of EAE [47]. Another method is overexpressing PD-L1 using adenovirus for the treatment of lupus-like syndrome in BXSB mice [48]. Depletion of PD-1^+ cells can lead to the amelioration of autoimmune diseases including T1D and EAE [49]. Thus, targeting PD-1 is a promising strategy for treating autoimmune diseases.

2.3. TIM-3

TIM-3 (T cell immunoglobulin and mucin-domain containing protein-3) is a type I transmembrane protein that is expressed on T helper 1 (Th1) and T cytotoxic 1 (Tc1) cells, Treg cells, NK cells, monocytes, macrophages, and DCs. Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), galectin-9, high mobility group box 1 (HMGB1) and phosphatidylserine (PtdSer) are ligands of TIM-3. CEACAM1 co-expressed with TIM-3 forms a heterodimer with TIM-3 promoting T cell exhaustion [50]. Galectin-9 binds to TIM-3 and suppresses Th1 immunity [51]. HMGB1 is a damage-associated molecular pattern from dying cells, and can mediate immune suppression through TIM-3 [52,53]. PtdSer expressed by apoptotic cells is a non-protein ligand for TIM-3 and mediates phagocytosis of apoptotic cells [54]. TIM-3^+PD-1^+ $CD8^+$ T cells represent a “deeply” exhausted T cell population compared to PD-1 single positive $CD8^+$ T cells in tumor, and synergistic blockade of TIM-3 and PD-1 can restore their effector function and promote antitumor immunity [53]. TIM-3 not only suppresses effector T cell function, but TIM-3^+ Treg cells demonstrate enhanced suppressive capacity [55]. TIM-3 can also regulate NK cell function although this is controversial. TIM-3 expression on DCs and macrophages suppresses their function and can expand the population of myeloid-derived suppressor cells (MDSCs) [56].

Several studies have demonstrated that TIM-3 polymorphism is associated with MS, Graves' disease, Hashimoto's disease, AS, idiopathic thrombocytopenic purpura (ITP), SLE and RA [57]. TIM-3 expression is reduced on T cells from peripheral blood cells of MS, RA and psoriasis patients [58]. TIM-3 expression on T cells and NKT cells inversely correlates with disease activity in RA [59]. Galectin-9 knockout mice are more susceptible to CIA with increased number of $CD4^+$TIM-3^+ T cells and decreased number of Treg cells [60]. In SLE patients, TIM-3 on $CD14^+$ cells promotes while soluble TIM-3 inhibits phagocytosis of apoptotic cells [61]. Administration of galectin-9 also reduces lupus in BXSB/MpJ and NZB/W F1 mice [62]. In MS patients, decreased TIM-3 may lead to higher level of IFN-γ secretion by $CD4^+$ T cells, and TIM-3 antibody results in increased severity of EAE accompanied by

Table 2
Role of co-stimulatory molecules in autoimmune diseases.

	SLE	RA/CIA	MS/EAE	Sjogren's syndrome	AIH	colitis	T1D	PBC	Psoriasis	Grave's disease
CD28-CD80/CD86	CD28 blockade or deficiency delays and diminishes symptoms in SLE mouse model [129,130]	CD28 is indispensable for the development of CIA [128]	The CD28:B7 co-stimulatory pathway promotes autoreactive T cell priming during the development of EAE [6]	Local delivery of CTLA4-IgG decreases sialadenitis and improves gland function in SS mouse model[299]						
CD27-CD70	Blockade of $CD27^{-}CD70$ decreases B-cell proliferation and IgG secretion in SLE [140]	Blockade of $CD27^{-}CD70$ signaling ameliorates CIA [142]	Anti-CD70 mAb can prevent EAE, but CD27 co-stimulation ameliorates the development of EAE [145,146]			blockade of $CD27^{-}CD70$ signaling ameliorates murine experimental colitis [143]				
GITR-GITRL		Blockade of GITR signaling ameliorates CIA, in which increased Treg function and decreased Tfh [163,164]	In the EAE model, GITR overexpression expands Treg cells and delays EAE development [160]			Lack of GITRL reduces macrophage infiltration in the colon and ameliorates colitis [159]				
CD40-CD40L	blockade of $CD40^{-}CD40L$ axis alleviates and prolongs survival in SLE mouse mode [171]	stimulatory anti-CD40 mAb resulted in earlier onset of CIA and more severe disease [172]	Treatment with CD40L Ab completely prevented the development of EAE, and reduced clinical manifests [173]	CD40 can upregulate the adhesion molecules upon CD40L stimulation, anti-CD40L can prevent the development of SS in mice [177,178]			In T1D patients, CD40L may help to form a prothrombotic and proinflammatory milieu [182]; and CD40L blockade prevents the development [183]	Anti-CD40 ligand mAb delays the progression of murine autoimmune cholangitis [174]	CD40L-triggered signals could be involved in the early stage of psoriatic lesion formation [175]	
ICOS-ICOSL	promoting spontaneous Tfh cell induction, GC formation, and autoantibody production in SLE progression [300]	ICOS:ICOSL promote Tfh cell generation, GC formation and auto-Ab production in CIA [301]		Salivary gland epithelial cells promote CD4 + naive T cells into Tfh cells via upregulation of ICOS-L [179]						
4-1BB-4-1BBL	Protect from SLE by agonist anti-CD137 mAb treatment and deletion results in progression in mouse [201,204]	4-1BB agonist Ab ameliorated established arthritis by induction of tolerogenic DCs and induction of regulatory $CD8^{+}$ cells [202]	agonistic 4-1BB Abs ameliorated disease severity EAE mice by promoting activation-induced cell death of autoreactive T cells and inhibiting Th17 cell differentiation [203]			Agonistic anti-4-1BB mAb can improve experimental colitis by reduction of IL-2 and augmentation of Treg [205]				
OX40-OX40L	OX40L-OX40 axis promotes human lupus by promoting Tfh response and impairing Treg and Tfr function [217,218]	Lack of OX40:OX40L signaling resulted in decreased IFNγ and auto-Ab production, and increased tissue integrity in CIA [6]			In concanavalin A-induced hepatitis, OX40 triggers invariant NKT cell pyroptosis and liver injury [219]	Blockade of OX40–OX40L interactions inhibits colitis in various mouse models [302]	interruption of OX40:OX40L interactions exhibited significant delay in diabetes onset in NOD mice at 12 week-of-age [303]			

Table 3
Role of other checkpoint molecules in autoimmune diseases.

	SLE	RA/CIA	MS/EAE	AIH	colitis	T1D
CD39/CD73 & Adenosine Receptor	CD39 or CD73 deficiency promotes lupus in mice [235]	CD73 deficient mice are susceptive to CIA [236]; Gingival tissue-derived MSCs attenuate CIA via CD39-adenosine pathway [238]	Deficiency of CD39 promotes EAE [232]; CD73-deficient mice are resistant to EAE [233]	CD39 deletion is protective in Con A induced hepatitis [226]	Deletion of CD39 exacerbates experimental colitis; CD73 knockout mice are more susceptible to experimental colitis [239,240]	Knockout of CD39 accelerates diabetes development while overexpressing CD39 suppresses disease [241]
CD38	Knockout of CD38 have diverse function in different lupus models [249]	CD38 knockout mice develop attenuated CIA [250]			CD38 knockout decreased disease development in colitis [251]	Deficiency of CD38 leads to accelerated development of T1D in NOD mice [252]
IDO		The induction of IDO suppresses CIA [260]	IDO down-regulates autoimmune inflammation [259]			IDO protects from diabetes [257,258]
NOX2	NOX2 inhibits the pathogenesis of SLE [270]	Deficiency in NOX2 subunit Ncf1 results in aggravated CIA [267]	NOX-deficient NOD mice are susceptible to EAE [269]			NOX-deficient NOD mice show resistance to T1D [269]
CD47-SIRPα	Knockout of CD47 in Faslpr mice ameliorates autoimmune nephritis284	Resistance to CIA in SIRPα mutant mice [276]	SIRPα mutant mice are resistant to EAE [275]; function of CD47 deficiency vary in different EAE models [281,283]		CD47 deficient mice show decreased pro-inflammatory cytokine in colitis [282]	SIRPα with higher binding affinity to CD47 exacerbates diabetes [279]; CD47 deficient mice have increased incidence in another diabetes model [280]

uncontrolled macrophage activation [63,64]. TIM-3 deficiency regulates Th1 but not Th17 driven EAE, and galectin-9 administration ameliorates EAE [51,65]. Galectin-9 inhibits also autoimmune diabetes in NOD mice [66]. Tim-3 blockade exacerbates dextran sulfate sodium (DSS) induced colitis by enhancing M1 macrophage responses, while overexpression of Tim-3 promotes M2 macrophage polarization and attenuates colitis [67]. Reduced levels of Tim-3 on $CD4^+$ effector cells and of galectin-9 in Treg cells contribute to impaired immunoregulation in AIH patients [68]. Besides, the ligands of TIM-3 are often highly expressed in specific organs and TIM-3 is specifically upregulated on tissue Treg cells [58,69]. Thus TIM-3 pathway regulates organ-specific autoimmunity and can possibly be a key point in the treatment of organ specific autoimmune diseases.

2.4. LAG-3

LAG-3 (Lymphocyte-activation gene 3, CD223) is an inhibitory immunoglobulin superfamily member expressed on activated T cells and subsets of NK cells. LAG-3 structurally resembles the CD4 co-receptor and binds to MHC class II [58]. Galectin-3 and LSECtin can also bind to LAG-3 and suppress T cell response [70]. Recently, liver secreted fibrinogen-like protein 1 has been identified as a ligand of LAG-3, which can promote immune suppression in cancer [71]. LAG-3 is induced by T cell activation and is highly expressed on T cells with regulatory function such as Treg cells and IL-10-producing T cells. Loss of LAG-3 reduces their suppressive function [72]. LAG-3 ligation to MHC-II can induce tolerance in DCs and suppress the priming of effector T cell responses [73].

Investigation of the role of LAG-3 in autoimmunity has been focused on Treg cells. Treg cells suppress ILC3-mediated colitis in mice by restraining inflammatory macrophages via LAG-3/MHCII engagement [74]. The frequency of IL-10 producing $LAG3^+$ Treg cells was lower in RA and increased after abatacept treatment [75]. $LAG\text{-}3^+$ Treg cells specifically express transcriptional factor Egr2 (early growth response gene 2), which plays a vital role in their suppressive activity [76]. Polymorphisms in the Egr2 gene influence susceptibility to SLE and Crohn's disease [77,78]. Egr2 is important in the induction of TGF-β3 in Treg cells and adoptive transfer of $LAG\text{-}3^+$ Treg cells suppresses the progression of lupus and colitis in mice [79,80]. LAG-3 deficiency alone does not induce autoimmunity in non-autoimmune-prone mice strains, while LAG-3 deficiency accelerates T1D mellitus in non-obese diabetic mice [81,82]. In MS model 2D2 mice, LAG-3 participates in the suppression of EAE by 2D2-IEL-T_{HIGH} cells, a subset of gut intraepithelial T cells with higher expression of TCR [83]. The therapeutic potential associated with LAG-3 is also related to Treg cells. Direct transfer of $LAG\text{-}3^+$ Treg cells may suppress the development of autoimmune diseases. Egr2 expressing $LAG\text{-}3^+$ Treg cells may exert antigen-specific suppressive function which is of great importance in suppressing autoreactive T cells without disturbing conventional T cell response [76].

2.5. TIGIT-CD155/CD112/CD226

TIGIT (T cell immunoreceptor with Ig and ITIM domains) is an inhibitory receptor that belongs to the CD28 family and is expressed on exhausted T cells, Treg cells, follicular helper T (Tfh) cells and NK cells. It can interact with CD155 (PVR) and CD112 (PVRL2) to compete with CD226 to inhibit the activation of T and NK cells [84,85]. $TIGIT^+$ Treg cells inhibit pro-inflammatory responses but not Th2-like response through fibrinogen like 2 (Fgl2) [86].

Blockade of TIGIT elicits potent anti-tumor immunity [7,87,88]. TIGIT is also involved in autoimmune diseases. In non-European populations, the coding variant rs763361 CD226 correlates with autoimmune diseases such as SLE, T1D and RA [89]. Although TIGIT deficiency does not induce autoimmunity, TIGIT deficient mice are more susceptible to CIA [90] and EAE [90,91]. Mice treated with soluble TIGIT develop less severe CIA while blocking TIGIT antibody

Table 4
Clinical trials targeting immune checkpoint molecules in different autoimmune diseases.

	MS	SLE	RA	Psoriastic arthritis	T1D	IBD	PBC	Ankylosing Spondylitis	Sjogren's syndrome	Psoriasis	Lupus Nephritis
CTLA-4	CTLA4-IgG4m (RG2077) NCT00076934 CTLA-4-Ig (Abatacept) NCT01116427	CTLA4-IgG4m (RG2077) NCT00094380 CTLA-4-Ig (Abatacept) NCT02429934	CTLA-4-Ig (Abatacept) NCT03457792 CTLA-4-IgG1 (Belatacept) NCT00279760	CTLA-4-Ig (Abatacept) NCT01860976	CTLA-4-Ig (Abatacept) NCT00505375 CTLA-4-IgG1 (Belatacept) NCT00501709	CTLA-4-Ig (Abatacept) NCT00410410	CTLA-4-Ig (Abatacept) NCT02078882	CTLA-4-Ig (Abatacept) NCT00558506	CTLA-4-Ig (Abatacept) NCT02067910	CTLA-4-Ig (Abatacept) NCT01999868	CTLA-4-Ig (Abatacept) NCT00430677
CD160, BTLA, LIGHT-HVEM			Human LTβR–Ig fusion protein (Baminercept/ BG9924) NCT00664716			Human LIGHT-specific antibody (SAR252067)			Human LTβR–Ig fusion protein (Baminercept/ BG9924) NCT01552681		
$CD28^{--}$ CD80/ CD86		A domain antibody conjugated with PEG (BMS-931699/ lulizumab) NCT02265744	Humanized monovalent Fab' antibody targeting CD28 (FR104) NCT02800811						A domain antibody conjugated with PEG (BMS-931699/ lulizumab) NCT02843659		
$CD40^{--}$CD40L	Humanized anti-CD40L IgG1 mAb (IDEC-131)	Fc modified human anti-CD40 IgG1 mAb (CFZ533) NCT03656562 CD40L Fab' fragment (Dapirolizumab pegol) NCT02804763 Humanized anti-CD40L IgG1 mAb (IDEC-131)	Human CD40-specific antibody (ASKP1240/4D11) Antagonistic Anti-CD40 Monoclonal Antibody (BI 655064) NCT01751776 Fc modified human anti-CD40 IgG1 mAb (CFZ533) NCT02089087 CD40L Tn3 Fusion protein (MEDI4920) NCT02780388	Chimeric CD40-specific antibody (PG102) NCT00787137		Human IgG4 anti-CD40 mAb (ch5D12) Anti-CD40 Monoclonal Antibody (FFP104) NCT02465944 Humanized anti-CD40L IgG1 mAb (IDEC-131)	Anti-CD40 Monoclonal Antibody (FFP104) NCT02193360		Fc modified Human anti-CD40 IgG1 mAb (CFZ533) NCT02291029	Human IgG4 anti-CD40 mAb (ASKP1240) NCT01585233	Antagonistic Anti-CD40 Monoclonal Antibody (BI 655064) NCT03385564 Humanized anti-CD40L IgG1 mAb (BG9588) NCT00001789
ICOS-ICOSL									Human anti-ICOSL antibody (AMG 557/MEDI5872) NCT02334306		
OX40-OX40L						Anti-OX40 Monoclonal Antibody (KHK4083) NCT02647866					
CD39/CD73 & Adenosine Receptor			Adenosine A3 receptor agonist (CF101) NCT02647762							Adenosine A1/A3 receptor antagonist (PBF-1650) NCT03798236	
CD38		CD38 depleting antibody (TAK-079) NCT03724916									
LAG-3										LAG-3 depleting antibody (GSK2831781) NCT02195349	

aggravates disease [90]. Agonistic anti-TIGIT antibody inhibits EAE development [88], and stimulation of TIGIT pathway restores the deletion of functional Treg cells in relapsing-remitting MS patients [92]. CD155 stimulation down-regulates the activities of $CD4^+$ T cells from SLE patients, and in vivo administration of CD155 delays SLE development in MRL/lpr mice [93]. Activation of TIGIT with CD155-Fc inhibits proliferation of $CD4^+$ T cells from patients with psoriasis [94]. Therefore, TIGIT specifically inhibits pro-inflammatory immune responses that drive organ-specific autoimmunity, and soluble TIGIT or agonistic anti-TIGIT antibody may have therapeutic potential for these disorders.

2.6. VISTA (PD-1H)

VISTA (V domain-containing Ig suppressor of T-cell activation) is a unique inhibitory checkpoint of B7 family widely expressed on $CD4^+$ T cells, $CD8^+$ T cells, monocytes, neutrophils and DCs, with highest expression in the myeloid lineage [95,96]. Recently, VSIG3 (V-Set and Immunoglobulin domain containing 3) has been identified as a VISTA ligand that suppresses human T cell activation [97]. VISTA on both $CD4^+$ T cells and APCs contributes to the inhibition of T cell response, and agonistic anti-VISTA antibody can directly inhibit T cells [98].

Several studies have demonstrated a role of VISTA in regulating the function of diverse immune cell types in autoimmunity. VISTA deficient mice develop an autoimmune phenotype [99]. They are more susceptible to concanavalin A (Con A) induced hepatitis with increased production of inflammatory cytokines [98]. A designed stable pentameric VISTA construct by genetically fusing its IgV domain to the pentamerization domain from the cartilage oligomeric matrix protein inhibits Con A induced hepatitis [100]. Knockout of VISTA accelerates autoimmune diseases in PD-1 knockout mice [101], and lupus development in *Sle1.Sle3* mice [102]. VISTA blockade enhances murine arthritis and lupus disease progression [103]. Deficiency of VISTA or anti-VISTA antibody treatment attenuates collagen antibody-induced arthritis in experimental models [104]. In murine model of psoriasis, VISTA deficiency exacerbates psoriasis, enhances the production of inflammatory cytokines and chemokines in DCs and promotes the development of Th17 cells [105]. A combined genetic deficiency of VISTA and PD-1 exacerbates EAE in 2D2 mice [101], and anti-VISTA treatment exacerbates development of EAE [106]. Thus, VISTA is important in regulating both innate and adaptive immune responses and act as a key regulator of several types of autoimmune diseases.

2.7. CD200-CD200R

CD200 (OX2) belongs to the immunoglobulin superfamily, is expressed by a variety of cells and is a non-signaling molecule. Its ligand, CD200R (OX2R) is mainly expressed by myeloid cells and microglia, in some cases by T cells and NK cells. The ligands of CD200 include CD200R1-4, while CD200R1 has the highest binding affinity in humans [107]. Upon CD200 stimulation, the NPXY motif of CD200R interacts with signaling adaptor molecules PTB/PID binding domains, which inhibit the activation of myeloid cells and reduce their production of inflammatory cytokines [107,108].

CD200-CD200R signaling is involved in human autoimmune diseases. Increased CD200/CD200R1 expression reduces Th17 cells and diminishes phagocytosis of apoptotic cells by DCs from SLE patients [109]. CD200R is down-regulated in the initial phases of MS, which may lead to damage of the nervous system. Up-regulation of CD200R in EAE models may be a compensatory way to control inflammation [110]. CD200 knockout mice show more severe clinical signs of EAE than control mice, and CD200-Fc can ameliorate EAE by suppressing the accumulation of $CD11b^+$ cells in the CNS [111,112]. CD200(−/−) and CD200R1(−/−) mice show greater sensitivity to acute colitis than WT mice, while CD200 over-expression protects mice from colitis [113]. In experimental autoimmune uveoretinitis, agonist CD200R antibody suppresses macrophage activation and tissue damage [114], while CD200R blocking antibody augments inducible nitric oxide synthase (iNOS) expression and aggravates disease [115]. CD200-Fc also inhibits $CD4^+$ T cell proliferation, promotes necrosis, and inhibits Th17 differentiation in RA patients and CIA in rodents [107,116].

2.8. HVEM-CD160, BTLA, LIGHT

HVEM (Herpesvirus entry mediator, TNFRSF14, CD270) is a membrane-bound receptor that is broadly expressed on hematopoietic cells including lymphocytes and myeloid cells [117]. LIGHT (TNFSF14), BTLA (B and T lymphocyte attenuator, CD272) and CD160 are ligands of HVEM. Upon binding to LIGHT, downstream NF-κB signaling of HVEM is activated to induce proinflammatory cytokine production and promote cell survival [117]. In the meantime, HVEM can induce negative signal in T cells that express its ligands CD160 and BTLA [117]. Thus, HVEM works as a bidirectional switch with both co-stimulatory and co-inhibitory functions. HVEM can also work in *cis* with BTLA which blocks the *trans* binding and conveys inhibitory signal [118].

Bidirectional signaling, multiple ligands and *cis* interaction make the HVEM-mediated network complicated and important in the regulation of autoimmune diseases. HVEM interaction with LIGHT or BTLA has been reported to participate in the development of colitis [119]. T cells with transgenic LIGHT expression have enhanced Th1 response and can induce colitis upon transfer into $RAG1^{-/-}$ mice; anti-BTLA antibody which triggers BTLA inhibitory signaling can ameliorate colon inflammation [120,121]. HVEM or BTLA knockout mice are more susceptible to EAE [122]. CD160 knockout mice are more susceptible to Con A or α-galactosylceramide induced hepatitis, implicating CD160 as a co-inhibitory receptor for NKT cells [123]. BTLA knockout mice spontaneously develop autoimmune hepatitis-like disease and SS and their survival decreases to 7 months [124]; the same is also observed in a mouse model of SLE [124,125]. BTLA knockout mice are susceptible to Imiquimod (IMQ) induced psoriasis, and an agonistic, anti-BTLA antibody, inhibits γδ T cells to restrict psoriasis [126]. Anti-BTLA antibody delays the onset of T1D in NOD mice [127]. HVEM is also involved in RA, as treatment of HVEM-Ig in CIA mice results in augmented disease activity [128].

Thus, blockade of HVEM/LIGHT co-stimulation or enhancement of the HVEM/BTLA/CD160 pathway with antibodies or recombinant proteins may present alternative ways for the treatment of autoimmune diseases. Clearly, further studies on the predominance of HVEM/BTLA/CD160 co-inhibitory axis and the HVEM/LIGHT costimulatory axis are needed.

3. CO-STIMULATORY SIGNALING

3.1. $CD28^{-}$-CD80/CD86

CD28 is the most important co-stimulatory molecule expressed on T cells and is essential for full T cell activation and for the development and homeostasis of Treg cells [129]. CD28 competes with CTLA-4 to bind CD80 (B7.1) and CD86 (B7.2) on APCs, and regulates T cell activation by multiple processes, including participation in the formation of the immunological synapse, the posttranslational modification of many signal proteins and remodeling of actin cytoskeleton, driving a complex transcriptional program in T cells [129].

As the most important receptor that provides second signal to T cells, and a regulator of Treg cells, uncontrolled expression or signaling of CD28 is associated with many human diseases. GWAS have identified single nucleotide polymorphisms in CD28 closely related to RA and Grave's disease [130,131]. Deficiency of CTLA-4 which induces enhanced CD28 signaling results in autoimmune diseases as described above [132]. CD28 blockade or deficiency delays and diminishes symptoms in SLE mouse model [133,134]. CTLA-4-Ig fusion proteins are the first biologics to antagonize with CD28 signaling [29,30].

However, most anti-CD28 antibodies have both antagonistic and agonistic properties, limiting their applications in human diseases [135]. On the other hand, antagonist-only anti-CD28 antibodies that have modulated Fc or conjugated with polyethylene glycol have been developed. These antibodies have been tested in animal models of psoriasis, EAE, arthritis, autoimmune uveitis and SLE nephritis [135]. Thus, selective CD28 targeting may have clinical benefit for many autoimmune diseases.

3.2. CD27⁻⁻CD70

CD27 belongs to the TNF receptor superfamily and is constitutively expressed on subsets of T cells, B cells and NK cells [136]. Its ligand, CD70, is primarily expressed on APCs, and is regulated by the stimulation of CD40, BCR, TCR and Toll-like receptors (TLRs) [136]. The interaction of CD27/CD70 provides a positive signal for the expansion and cytokine production of effective T cells [137], and $CD8^+$ T cells can be activated by CD27 signaling independent of $CD4^+$ T cells [138]. CD27 signaling facilitates memory B cells to differentiate into plasma cells and promotes the production of immunoglobulin [139]. However, CD70 signaling shows distinct functional consequences on B cells depending on different CD70 ligands [140].

Activating the CD27 co-stimulation by agonistic CD27 antibodies, soluble CD70 or CD70-bearing DCs promote the anti-tumor effector response and are in clinical trials for cancer immunotherapy [141]. In SLE, serum level of soluble CD27 is increased and correlates with disease activity in patients [142]. The rate of the peripheral activated $CD70^+CD4^+$ T cells is also increased [143]. Blockade of $CD27^-CD70$ decreases B-cell proliferation and IgG secretion by CpG-stimulated pDCs, reflecting that $CD27^-CD70$ axis plays a non-negligible role in SLE [144]. Like SLE, the number of $CD70^+CD4^+$ T cells is increased in RA patients, which produce high levels of IFN-γ and IL-17 [145]. Blockade of $CD27^-CD70$ signaling ameliorates CIA [146]. APCs in the lamina propria constitutively express CD70, and blockade of $CD27^-CD70$ signaling ameliorates murine experimental colitis [147]. Gene sequencing has identified CD27 as a susceptibility locus for psoriasis in Chinese patients [148], but the role of CD27 in psoriasis needs further investigation. However, there is evidence that the $CD27^-CD70$ pathway may also suppress autoimmunity. Anti-CD70 monoclonal antibody (mAb) can prevent EAE through inhibiting the production of TNF-α, but CD27 co-stimulation suppresses Th17 cell response and ameliorates development of EAE [149,150]. CD27 co-stimulation can rescue Treg cells from apoptosis and thus promote the generation of Treg cells in the thymus [151]. CD70 signaling can regulate the function of T cells and B cells [140]. CD27/CD70 pathway might be a target for the treatment of autoimmune diseases.

3.3. GITR-GITRL

Glucocorticoid induced TNF receptor (GITR, CD357) is a member of the TNF receptor superfamily, and is expressed at high levels on Treg cells and at low levels on conventional T cells, while its ligand GITRL is predominantly expressed on activated APCs [152,153]. GITR works as a co-stimulatory molecule of T cells and can decrease the threshold of $CD8^+$ T cell activation by influencing their response to CD28 [154]. Stimulation of GITR can abrogate Treg mediated suppression of T cells, which involves increased resistance of effector T cells and decreased suppressive activity of Treg cells [155,156]. Thus, agonistic anti-GITR antibody or recombinant GITRL can enhance T cell responses and inhibit Treg cell infiltration and are used for cancer immunotherapy [157,158].

GITR seems to be an important signal in the pathogenesis of many autoimmune diseases. GITR expression is increased on T cells with expansion of $CD4^+CD25^{low/-}GITR^+$ cells in SLE patients, which may regulate the abnormal immune response in SLE [159,160]. Th1 and Th2 responses are enhanced by GITR co-stimulation in colitis, and agonistic anti-GITR antibody promotes disease development [161,162]. Lack of GITRL reduces macrophage infiltration in the colon and ameliorates colitis [163]. In the EAE model, GITR overexpression expands Treg cells and delays EAE development [164]. Anti-GITR mAb treatment during the disease onset enhances autoreactive $CD4^+$ T cell activation and aggravates EAE [165]. GITRL expressed on B cells promotes resolution of EAE [166]. Blockade of GITR signaling through either GITR knockout or GITR fusion protein ameliorates CIA, through increased Treg and decreased follicular helper T (Tfh) cell function [167,168]. Thus GITR plays an important role in Treg cell function, and in vitro or in vivo expansion of $GITR^+$ Treg cells may be a promising strategy to combat autoimmune diseases [169].

3.4. CD40⁻⁻CD40L

CD40 is a member of the TNFR superfamily and is constitutively or inducibly expressed on a variety of cells including B cells, DCs, macrophages and non-immune cells such as endothelial and epithelial cells [170]. CD40 ligand (CD40L, CD154) is expressed on activated $CD4^+$ T cells, principally on Tfh cells to sustain germinal center responses, but it can also be expressed on other cell types upon induction [171,172]. CD40 signaling also activate DCs and macrophages to form a pro-inflammatory milieu [173].

$CD40^-CD40L$ has been reported to participate in autoimmune thyroiditis, T1D, IBD, psoriasis, MS, RA, SS, SLE, PBC [174–179]. The principle role of CD40 is to stimulate B cell activation, proliferation and antibody production. Thus it plays an important role in diseases that are driven by autoantibodies [173]. Meanwhile, CD40 can function beyond germinal center and B cells. In RA, CD40L engagement stimulates the production of rheumatoid factors by plasmablasts and pro-inflammatory mediators by synovial fibroblasts, which promotes disease progression [180]. CD40 is constitutively expressed on salivary gland ductal epithelial cells and endothelial cells. It upregulates the expression of adhesion molecules upon CD40L stimulation and induce Tfh cell differentiation, anti-CD40L can prevent the development of SS in mice [181–183]. Increased expression of CD40L and CD40 is also observed in SLE [184] and IBD [185]. In T1D patients, CD40L and platelet monocyte interactions are increased, which may help to form a prothrombotic and proinflammatory milieu [186]; and CD40L blockade prevents the development of autoimmune diabetes [187].

There are several clinical trials targeting $CD40^-CD40L$ pathway to treat autoimmune diseases [173]. Antibodies (IDEC-131, BG9588, Dapirolizumab pegol) and fusion proteins (BMS-986004, MEDI4920) targeting CD40L are blind tested in Crohn's disease (CD), MS, SLE, ITP and RA patients; antibodies (CFZ533, ASKP1240, BI655064, ch5D12, FFP104) targeting CD40 are blindly tested in SS, RA, SLE, myasthenia gravis (MG), ITP, CD, PBC and psoriasis patients [173].

Thus, targeting the $CD40^-CD40L$ pathway has the potential to modulate both antibody mediated and cellular immune processes in several autoimmune diseases. Future work is needed in better defining the roles of $CD40^-CD40L$ in health and disease, developing new proteins targeting this pathway and expanding treatment to orphan autoimmune diseases.

3.5. ICOS-ICOSL

Inducible T-cell co-stimulator (ICOS, CD278) is a member of CD28 family, which is induced after TCR and/or CD28 co-stimulation and promotes T cell activation and proliferation. The ligand of ICOS, ICOSL, is expressed on APCs including macrophages, DCs and B cells, and can be induced in nonlymphoid tissues under inflammatory conditions [188]. ICOS signaling plays a controversial role in Th1 immunity and promotes Th2 immunity [189]. Importantly, ICOS is highly expressed on Tfh cells and is required for generation, maintenance and follicular homing of Tfh cells, which drive antibody affinity maturation in the germinal center formation [188,190]. Therefore, ICOS plays important

roles in regulating the disease state of many human diseases.

In RA patients, ICOS is highly expressed on activated T cells and ICOS gene polymorphism is associated with RA susceptibility [191]. In mice, ICOS signaling is essential to induce CIA, and anti-ICOSL antibody inhibits Tfh cells and germinal center B cells in CIA [192]. ICOS is also upregulated in SLE patients, with the expansion of circulating Tfh-like cells, which have enhanced IFN-γ expression and can promote autoantibody production [193]. In lupus-prone MRL.*Fas*^{lpr} mice, ICOSL expressed by DCs promotes kidney and lung inflammation by protecting invading T cells from apoptosis [194]. Knockout of ICOS or anti-ICOSL antibody in murine SLE can suppress Tfh cells, germinal center formation and autoantibody production [192,195]. A clinical trial using human anti-ICOSL antibody AMG557 in SLE treatment demonstrates that ICOSL blockade reduces the anti-KLH IgG response in SLE patients [196]. Thus ICOS/ICOSL axis may become a key point in therapies of autoimmune diseases, especially those with autoantibodies.

3.6. 4-1BB-4-1BBL

4-1BB (CD137, TNFRSF9) is expressed on activated T cells (a larger extent on CD8$^+$ T than on CD4$^+$ T cells), exhausted T cells, Treg cells and NK cells, and some activated neutrophils and DCs [197]. Its ligand, 4-1BBL, is mainly expressed on activated APCs such as DCs, macrophages and B cells [198,199]. 4-1BB signaling promotes activation and suppresses activation-induced cell death of T cells, especially CD8$^+$ T cells [200]. However, 4-1BB co-stimulation can either expand functionally suppressive Treg cells, or inhibit the suppressive function of Treg cells in different conditions [201,202]. Thus, 4-1BB emerges as an important candidate against many diseases, although the biology of 4-1BB is more complicated than positive regulation of T cell activation.

Serum levels of 4-1BB and soluble 4-1BBL are increased in RA, MS, systemic sclerosis and correlate with disease activity [170]. Murine model 4-1BB promotes autoimmunity, i.e. SLE, T1D and colitis [203–205]. These results suggest that blocking 4-1BB-4-1BBL interaction may have applications in the treatment of autoimmune diseases, but it has received little clinical attention so far. Interestingly, agonistic anti-4-1BB antibody can suppress several autoimmune diseases in mice, including RA [206], EAE [207], SLE [208], colitis [209,210] and experimental autoimmune uveoretinitis [211]. The capacity of 4-1BB to suppress autoimmune diseases may be due to its ability to inhibit Th17 responses by promoting Th1 and Treg cells, or the induction of a subset of regulatory CD8$^+$ T cells [170,212]. Agonistic anti-4-1BB antibody or soluble 4-1BBL are also used in cancer immunotherapy [199], with side effects of autoimmune liver inflammation mediated by excessive activation of CD8$^+$ T cells and NK cells [197,213]. Although intriguing, this contradiction may hinder the use of agonist 4-1BB antibody.

3.7. OX40-OX40L

OX40 (CD134, TNFRSF4) is a co-stimulatory molecule that is predominantly expressed on activated lymphocytes, especially CD4$^+$ T cells. The expression of OX40 on T cells is induced by TCR stimulation, and augmented by co-stimulation of CD28 and CD40 L [214,215]. CD40L is mainly expressed on APCs and is upregulated in response to antigen presentation and some inflammatory cytokine stimulation. Ligation of OX40 on T cells expands effector T cells as well as Treg cells, and promotes the generation of Treg cells and memory T cells [214,216,217]. It can also facilitate the adhesion and migration of activated T cells [214]. Thus OX40-OX40L interaction has the capacity to enhance immunity and participate in the development of autoimmune diseases.

OX40 expression is upregulated at sites of autoimmune inflammation and on peripheral circulating lymphocytes in autoimmunity [214]. Polymorphisms in the *TNFSF4* gene are associated with SLE [214], systemic sclerosis [218] and SS [219]. OX40L-transgenic (OX40L-Tg) mice that overexpress OX40L spontaneously develop interstitial pneumonia and IBD with significant production of anti-DNA autoantibodies [220]. Adoptive transfer of increased memory CD4$^+$ T cells from OX40L-Tg mice to Rag2$^{-/-}$ mice also leads to inflammatory diseases [220]. Several other studies have reported altered expression and function of OX40 or OX40L in human or mouse models of autoimmune diseases, including SLE, colitis, RA, celiac disease, uveitis, T1D, MS, myasthenia gravis, systemic sclerosis, hepatitis and inflammatory myositis [214,221]. For example, naive and memory T cells can be induced to differentiate into Tfh cells by OX40/OX40L in SLE patients, while the suppressive functions of Treg and Tfh cells are inhibited [222]. In Con A induced hepatitis, OX40 triggers invariant NKT cell pyroptosis and liver injury [223]. Several studies have also tried to manipulate OX40-OX40L to treat autoimmune diseases. Anti-OX40 blocking antibody or OX40-IgG fusion protein can ameliorate CIA and colitis, while anti-OX40 agonist either exacerbates or delays disease development in mouse models of MS, T1D and SLE [203,224,225]. Thus in most cases of autoimmunity, OX40-OX40L inhibition can ameliorate disease which can be a promising therapeutic target, while OX40 agonism shows a temporal effect with differential expansion of effector and regulatory T cells.

4. OTHER CHECKPOINT MOLECULES

Some molecules are not co-stimulatory/inhibitory receptors or ligands, but they function as immune checkpoint molecules in tumor immunology. These molecules also participate in the development of autoimmune diseases and may be used as therapeutic targets (Table 3).

4.1. CD39/CD73 & adenosine receptor

CD39 (ectonucleoside triphosphate diphosphohydrolase-1, ENTPD1) and CD73 (ecto-5′-nucleotidase, 5′-NT) are ectonucleotidases expressed on cell membrane of cancer cells, regulatory immune cells, and the vasculature [226]. Adenosine triphosphate (ATP) is released from activated, stressed or damaged cells [227]. CD39 catalyzes extracellular ATP and ADP into AMP, then CD73 hydrolyzes AMP into adenosine [226]. Adenosine plays an anti-inflammatory role by binding to adenosine receptors (A1, A2A, A2B and A3) expressed by Treg cells and effector T cells [227]. Small molecule drugs inhibiting CD39, CD73 and A2AR have been used in preclinical tumor models [228].

Adenosine related signaling also participates in autoimmune diseases [229,230]. In MS, IFN-β treatment up-regulates the expression of CD73, which may result in the increase of adenosine within the CNS and contribute to a beneficial effect [231]. Deficiency of CD39 abrogates accumulation of Treg cells and elevates Th1/Th17 signals during EAE [232], while A2AR antagonist protects mice from EAE [233,234]. CD39 deficiency promotes expansion of Th17 cells in lupus mouse model [235]. CD73 deficient mice are susceptive to CIA, while A2AR antagonist protects mice from disease [236]. CD39 is highly expressed on T cells from the joint of juvenile arthritis patients while CD73 is decreased, suggesting that ATP could not be broken down to adenosine completely at the chronic inflammatory site [237]. Recently it is found that gingival tissue-derived mesenchymal stem cells attenuate the disease severity and bone erosion via CD39-adenosine signal pathway in CIA [238]. CD73$^{-/-}$ mice are more susceptible to DSS-induced colitis than WT mice, and deletion of CD39 exacerbates experimental murine colitis [239,240]. In T1D, knockout of CD39 accelerates diabetes development while overexpressing CD39 suppresses disease [241]. Besides, activation of the A2AR attenuates experimental autoimmune myasthenia gravis severity [230,242]. Clinically, adenosine A3 receptor agonist has been tested in RA (Table 4), indicating that manipulating adenosine pathway may be a strategy in treating autoimmune diseases.

3.10. CD38

CD38 (ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase 1) is an

ecto-enzyme that metabolizes nicotinamide dinucleotide (NAD^+) and mediates NAD^+ and extracellular nucleotide as well as intracellular calcium homeostasis [243,244]. It is expressed by T and B cells, monocytes/macrophages, granulocytes and DCs in response to stimulation and can promote activation. It is also expressed by non-hematopoietic cells such as tumor cells. CD38 mediates immunosuppression in tumor models by inhibiting NAD^+ signaling and inducing T cell exhaustion, and antagonist or depleting anti-CD38 antibody mediates broad-spectrum anti-tumor activity [245,246].

CD38 has multiple expression patterns and enzymatic activities with broad biological roles. Data from previous studies indicate contradictory roles of CD38 in autoimmune diseases. Older CD38 knockout mice have decreased lifespan and increased levels of ANA and anti-dsDNA autoantibodies [247]. CD38 is a candidate gene for lupus susceptibility loci in humans and CD38 expression is increased in SLE patients [248]. However, knockout of CD38 accelerates the development of SLE in Fas^{lpr} mice, while it decreases disease activity in pristane-induced lupus model [249]. This may be interpreted by different clearance of apoptotic cells in different models. CD38 knockout mice develop an attenuated form of CIA through decreasing the activation of NF-kB [250]. Knockout of CD38 leads to decreased disease severity of DSS-induced colitis [251]. However, deficiency of CD38 leads to accelerated development of T1D in NOD mice, possibly due to selective death of Treg cells [252]. Although the function of CD38 in many autoimmune diseases remain unknown, regulating autoreactive T cells using antibodies and small inhibitory molecules targeting CD38 may have immunomodulatory potential.

3.11. IDO

Indoleamine 2, 3-dioxygenase (IDO) is a mammalian cytosolic enzyme expressed in DCs, monocytes and macrophages, catalyzing the initial step in tryptophan catabolism via the kynurenine degradation pathway [253]. Kynurenine pathway metabolites have immunosuppressive roles involving the suppression of $CD8^+$ T cells and NK cells as well as the increased activity of $CD4^+$ Treg cells and myeloid-derived suppressor cells, making IDO a checkpoint controller [254]. IDO inhibitors are used in clinical cancer therapy, usually in combination with anti-CTLA-4/anti-PD-1 antibodies [254,255].

As a negative immune regulator, IDO suppresses disease progression in various models of autoimmune diseases including T1D, MS, RA and SLE [256]. Forced IDO expression in DCs restores immunosuppressive effects of TGF-β and inhibits the development of autoimmune diabetes in NOD mice [257]. IDO activity is increased in EAE and CIA, and administration of IDO inhibitors exacerbates diseases such as autoimmune diabetes, EAE and CIA [258–260]. A number of strategies to boost IDO activity have been tried to enhance the functions of sCTLA4, TLR4/9 ligands, Stimulator of IFN Genes (STING) Agonists and Interferons [261]. However, it will take some time to translate these strategies into clinical applications, as many IDO inducing drugs can elicit tissue-damaging responses as well as tissue-protective tolerogenic responses.

3.12. NOX2

NADPH oxidase isoform 2 (NOX2) is an enzyme expressed on myeloid cells which is critical for the generation of reactive oxygen species (ROS) and host defense against microbial pathogens [262]. In tumor cells, NOX2 exerts immunosuppression to promote tumor development and metastasis by generating ROS [263]. The NOX2 inhibitor histamine dihydrochloride shows anti-cancer efficacy in experimental tumor models, indicating that NOX2 is a targetable immune checkpoint [264].

NOX2 is also involved in autoimmunity. Mutations in any of the components of NOX2 cause chronic granulomatous disease (CGD) in humans, characterized by recurrent infections associated with hyper-inflammatory and autoimmune manifestations [265,266]. Mice deficient in the function of NOX2 subunit Ncf1 exhibit aggravated CIA and mannan induced psoriasis [267,268]. NOX-deficient NOD mice show resistance to T1D but are more susceptible to EAE, with T cells exhibiting increased Th17 but deficient Th1 response [269]. On the other hand, NOX2-deficient lupus-prone mice have markedly exacerbated disease [270]. However, the mechanisms linking deficits in the NOX2 complex with autoimmunity are incompletely understood.

3.13. CD47-SIRPα

CD47 is the ubiquitous marker of self [271]. Signal regulatory protein α (SIRPα) as the receptor of CD47, is expressed on phagocytes [272]. SIRPα contains immune-receptor tyrosine-based inhibition motifs that can be phosphorylated and recruit inhibitory molecules [9]. Engagement of CD47 triggers SIRPα signaling, which prevent cell activation and provides a “don't eat me” signal [9]. Tumor cells often overexpress CD47 for immune evasion, while anti-CD47 antibody blockade facilitates macrophage phagocytosis of tumor cells and T cell mediated anti-tumor response [272–274].

CD47-SIRPα axis has been proposed to be involved in the development of autoimmune diseases, but the data is disputed by others. Animals lacking the intracellular domain of SIRPα are resistant to EAE and CIA [275,276], while SIRPα and CD47 deficiency promotes the progression of autoimmune hemolytic anemia in mice under inflammatory conditions, due to enhanced phagocytosis of self-red blood cells [271,277]. A GWAS identified the association of *SIRP* gene cluster with susceptibility to T1D [278], and polymorphism of *Sirpa* gene in NOD mice, which encodes a SIRPα with higher binding affinity to CD47, exacerbating diabetes development [279]. However, in a pre-diabetes mouse model, CD47 deficiency induces diabetes [280]. CD47 deficient mice are refractory to EAE and experimental colitis [281,282]. However, blockade of CD47 with CD47-Fc fusion protein, or CD47 deficiency on hematopoietic cells, suppresses EAE development by inhibiting Th17 cell infiltration through decreasing IL-1β production in macrophages [283]. Knockout of CD47 in Fas^{lpr} mice ameliorates autoimmune nephritis with reduced IgG autoantibody [284].

3.14. Concluding remarks

Treatment of autoimmune diseases has primarily focused on immunosuppression [285]. Researchers are seeking new targets for autoimmune disease therapy, including small molecules targeting the TCR downstream signaling pathway to reduce the activation of T cells [286]. With the remarkable progress in understanding immune checkpoint molecules in autoimmune diseases (Tables 1–3), modulating T cell over-activation via co-stimulatory and co-inhibitory pathways may provide a novel therapeutic strategy [287]. There are also several clinical trials targeting immune checkpoint molecules in different autoimmune diseases (Table 4). However, many questions and challenges remain to define the mechanisms of action of these molecules and understand their toxicity.

One issue is the complexity of immune checkpoint regulation in autoimmune diseases. The expression of immune checkpoint molecules can be spatially and temporally different, as seen on different cell subsets and activation stages [288,289]. While CD28 and CTLA-4 function as primary co-stimulatory and co-inhibitory molecules, other molecules may participate in different conditions and stages of T cell activation. On the other hand, expression of the same molecule may have different effects on different immune cell types. For instance, TIGIT expression on Th1 cells inhibits their activation but promotes Th2 response [290]. Co-stimulation can promote autoimmunity but also impact Treg cells which can limit autoimmunity. Engagement of 4-1BB with its ligand provides a co-stimulatory signal. However, in multiple autoimmune settings agonist 4-1BB antibody promotes activation-induced cell death, generation of tolerogenic DCs and Treg cells

[197,213]. There may be compensatory or synergistic effects of different co-stimulatory or co-inhibitory pathways. For instance, CD86 can compensate the function of CD80 when interacting with CD28 after CD80 is blocked, while co-stimulation through ICOS and OX40 can partially compensate the function of CD28. On the other hand, CD80 expressed on APCs can interact with PD-L1 to stop suppression of T cell activation initiation [291].

Another issue is how to control the level of co-stimulation and co-inhibition to improve efficiency while avoiding side effects. This can be seen in cancer immunotherapy where immune checkpoint inhibitors can induce autoimmune-like complications, sometimes fulminant and fatal, limiting the use of immune checkpoint therapies [292,293]. For example, blockade of PD-1/PD-L1 can cause pneumonitis, diarrhea/colitis, hepatitis, dermatologic and endocrine toxicity [292]. Targeting immune checkpoint molecules for autoimmune disease treatment may increase the risk of tumor and infection. Combined targeting strategies may improve efficiency but increase risks. All these remain unanswered questions.

Authorship

Chuan Huang, Hao-Xian Zhu, Yuan Yao, Yu-Jian Zheng and Liang Li wrote the manuscript and designed the figures. Zhen-Hua Bian and Liang Li drew the figures. Haralampos M. Moutsopoulos, M. Eric Gershwin and Zhe-Xiong Lian wrote and edited the manuscript.

Conflict of interest disclosure

The authors declare no conflict of interest.

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