REVIEW ARTICLE

Emerging Co-signaling Networks in T Cell Immune Regulation

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Co-signaling molecules are surface glycoproteins that positively or negatively regulate the T cell response to antigen. Co-signaling ligands and receptors crosstalk between the surfaces of antigen-presenting cells (APCs) and T cells, and modulate the ultimate magnitude and quality of T cell receptor (TCR) signaling. In the past 10 years, the field of co-signaling research has been advanced by the understanding of underlying mechanisms of the immune modulation led by newly identified co-signaling molecules and the successful preclinical and clinical trials targeting co-inhibitory molecules called immune checkpoints in the treatment of autoimmune diseases and cancers. In this review, we briefly describe the characteristics of well-known B7 co-signaling family members regarding the expression, functions and therapeutic implications and to introduce newly identified B7 members such as B7-H5, B7-H6, and B7-H7.
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INTRODUCTION

The most essential role of the immune system in the human body is to kill invading pathogens by inducing a protective immunity and not to harm the host by inducing tolerance to self-tissues. This is achieved through a fine tuning of T cell activities in initiation, differentiation and effector phase of the immune response (1). T cell response is initiated by specific recognition of cognate peptide presented by MHC proteins on antigen-presenting cell (APC) through T cell receptors (TCRs), which are referred to as a first signal for T cell activation. However, the ultimate magnitude and quality of T cell response is determined by a balance between co-stimulatory and co-inhibitory signals (collectively called co-signals) that are transduced into T cells, which is referred to as a second signal (2,3). Following TCR engagement by cognate peptide-MHC complexes, co-signaling receptors are often mobilized and colocalized with TCRs, forming the immunological synapse between APCs and T cells. This synaptic interface is the place where the crosstalk between co-signaling ligands and receptors synergize or antagonize with TCR signaling, rendering T cells activated or inhibited (4).

The B7 family is a group of surface glycoproteins that share structural features with immunoglobulin (Ig), whose extracellular domains bear homology to IgV and IgC domains of Ig (Table I). A hallmark of the B7 family molecules is their capability to co-stimulate or co-inhibit T cell responses in the presence of peptide/MHC complex-mediated TCR signaling (4). B7 family members primarily bind to the members of CD28 family including CD28, CTLA-4, PD-1, ICOS, and BTLA that transmit co-signals into T cells (Fig. 1). The B7 co-stimulatory ligands are important for full activation of naïve T cells in the lymphoid organs, in which APCs, particularly dendritic cells (DCs), are the primary cellular source providing

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Abbreviations: MHC, major histocompatibility; CTLA-4, cytotoxic T lymphocyte antigen-4; PD-1, programmed death-1; ICOS, inducible T-cell costimulator; BTLA, B- and T-lymphocyte attenuator; IL-2, interleukin-2; IFN-γ, interferon-γ; GM-CSF, granulocyte-monocyte colony-stimulating factor; LPS, lipopolysaccharide; VSITA, V-domain Ig suppressor of T cell activation; BMDC, bone marrow-derived dendritic cell; OVA, ovalbumin

Table I. Structure, co-signaling nature, and receptors of B7 family members

| B7 family	Extracellular domain	Co-signaling nature	Receptor
B7.1 (CD80)	IgV+IgC	Co-stimulation	CD28
		Co-inhibition	CTLA-4 (CD152)
		Co-inhibition	B7-H1 (CD274)
B7.2 (CD86)	IgV+IgC	Co-stimulation	CD28
		Co-inhibition	CTLA-4
B7-H1 (PD-L1, CD274)	IgV+IgC	Co-inhibition	PD-1 (CD279)
		Co-inhibition	B7.1
		Co-stimulation	Unknown
B7-DC (PD-L2, CD273)	IgV+IgC	Co-inhibition	PD-1
B7-H2 (ICOSL, CD275)	IgV+IgC	Co-stimulation	ICOS (CD278)
		Co-stimulation	CD28
B7-H3 (CD276)	IgV+IgC+IgV+IgC (Hu)	Co-stimulation	Unknown
	IgV+IgC (Mo)	Co-inhibition	Unknown
B7-H4 (VTCN1)	IgV+IgC	Co-inhibition	Unknown
B7-H5 (VISTA)	IgV	Co-inhibition	Unknown
B7-H6 (NCR3LG1)	IgV+IgC	Co-stimulation	NKp30
B7-H7 (HHLA2)	IgV+IgC+IgV	Co-stimulation	CD28H
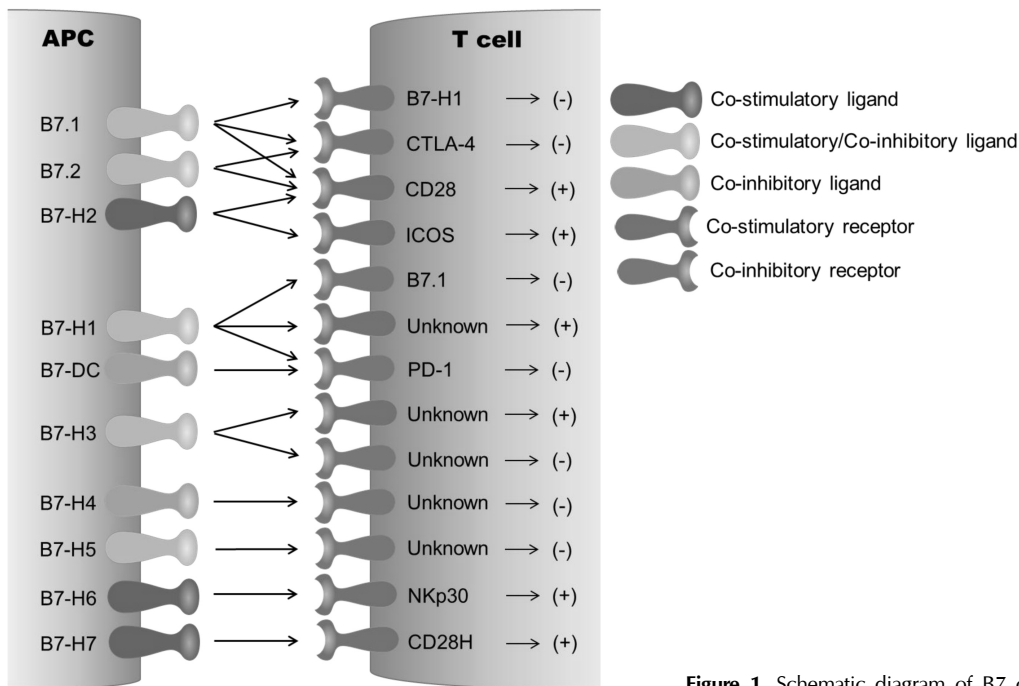
Figure 1. Schematic diagram of B7 co-signaling family network.

the ligands including B7.1 and B7.2. In contrast, B7 co-inhibitory ligands are crucial for the termination of over-activated T cell response, maintenance of self-tolerance, and protection of tissues from damage induced by invading pathogens. In addition, co-inhibitory ligands expressed on

pathological microenvironment such as tumor microenvironment actively inhibit the effector functions of cytotoxic T lymphocytes (CTLs) or induce the generation of regulatory T cells (2,3), thus, playing as important immune checkpoint proteins that are involved in the immune resistance of cancer cells.

In this review, we briefly describe the characteristics of well-known B7 family members regarding the expression, functions and therapeutic implications. We also introduce newly identified B7 members such as B7-H5, B7-H6, and B7-H7.

B7.1 AND B7.2 (CD80 AND CD86)

The B7.1 and B7.2, best-characterized co-signaling ligands, are expressed on APCs including DCs, macrophages, and B cells. The B7.1 and B7.2 deliver a co-stimulatory signal through CD28 constitutively expressed on naïve T cells, whose cytoplasmic tail contains three signaling motif. The first motif containing YMNM sequence serves as a binding site for the SH2-containg proteins, p85, growth factor receptor 2 (Grb2) and GADS. The second motif contains PRRP sequence and interacts with the SH3 domain of IL-2-inducible T cell kinase (Itk) of which involvement in CD28-mediated activation is still controversial. The third motif containing PYAP sequence associates with the SH3 domain of Grb2, GADS, lymphocyte cell-specific protein-tyrosine kinase (Lck), and filamin-A. Particularly, the association of Grb2 to both the YMNM and PYAP motifs is critically involved in the recruitment of protein kinase C θ (PKC θ) and RAS guanyl nucleotide-releasing protein (RASGRP) to the immunological synapse and its subsequent activation (5-7). Therefore, B7.1/B7.2-CD28 pathway lowers the threshold for optimal T cell activation, subsequently resulting in T cell proliferation, upregulating anti-apoptotic proteins including Bcl-xL, and increasing IL-2 production (8-10). Recently, the B7-CD28 pathway was also shown to play an essential role in both suppressive function and survival of regulatory T (Treg) cells (11).

In addition, B7.1 and B7.2 deliver a co-inhibitory signal into activated T cells through CTLA-4 whose cytoplasmic tail contains the immunoreceptor tyrosine inhibitory motif (ITIM) recruiting Src homology 2 domain-containing phosphatase (SHP)-1 and SHP-2 (12,13). Due to its high affinity to B7.1/B7.2, CTLA-4 competes out CD28 for binding to B7.1 and B7.2, conferring signaling-independent T cell suppression by sequestering B7.1/B7.2 from the APC surface (14). In contrast to the CD28 pathway, the B7-CTLA-4 pathway sets the threshold high enough so that T cell activation can be reduced and finally terminated. Since CTLA-4 is constitutively expressed on Treg cells, CTLA-4 engagement by B7 molecules also enhances their immunosuppressive activity with upregulation of FOXP3 gene transcription (15,16). A great deal of mouse tumor models revealed that blockade of the B7-CTLA-4 pathway could be a potential therapeutic target for cancer immunotherapy. Specifically, ipilimumab, a CTLA-4 blocking antibody, was the first FDA-approved antibody therapeutic for melanoma, adopting the notion that immune checkpoint blockade might enhance endogenous anti-tumor immunity (3).

Interestingly, B7.1 and B7.2 are believed to deliver bidirectional signalings. Specifically, B7 molecules expressed on T cells act as a counter receptor that receives an inhibitory signal from Treg cells probably through CTLA-4, an important *in vivo* T-T interaction for T cell homeostasis (17). Another reverse signaling through B7.1 and B7.2 was reported in T cell-APC interaction (18-20). B7 molecules expressed on DCs can transmit a suppressive signal into DCs through CTLA-4 on Treg cells or CTLA-4.Ig by enhancing IFN-γ production of DCs, which, in turn, induces indoleamine 2,3-dioxygenase (IDO), an enzyme metabolizing tryptophan into kynurenine, an immunosuppressive metabolite, in autocrine or paracrine mode (18). Thus, the bidirectional B7-CTLA-4 pathway appears to be critical for the downregulation of T cell response and induction of T cell tolerance.

B7-H1 (CD274, PD-L1) AND B7-DC (CD273, PD-L2)

B7-H1 is constitutively expressed not only on APCs but also in a wide range of normal somatic tissues including the heart, lung, placenta and liver (21,22). In contrast, B7-DC expression is largely restricted to APCs such as DCs and macrophages. Both molecules share the PD-1 receptor that is expressed on T cells, Treg cells, B cells, activated monocytes, DCs, NK cells, and NKT cells (23,24). The cytoplasmic tail of the PD-1 receptor contains ITIM and the immunoreceptor switch motif (ITSM) that binds to SHP-1 and SHP-2, transmitting a co-inhibitory signal into T cells and downregulating Bcl-xL expression, which leads to T cell functional impairment and apoptosis (21).

Due to its ectopic expression on non-hematopoietic tissues including normal peripheral organs and cancer tissues, B7-H1 is believed to limit T cell activation in peripheral organs, leading to peripheral tolerance. Thus, the B7-H1-PD-1 pathway in tumor microenvironment can be a critical immune escape mechanism (25-27), indicating that B7-H1 and PD-1 can act as key immune checkpoint proteins. Many clinical observations further support the immune checkpoint activities of the B7-H1-PD-1 pathway by demonstrating the correlation be-

tween B7-H1 expression levels in cancer tissues and patients' survival. Specifically, high levels of cancer B7-H1 expression is associated with poor prognosis in patients with kidney, lung, pancreas and urothelial cancers (28-32). In addition, chronic exposure to antigens that are derived from cancers and chronic viral infections can upregulate the PD-1 expression on antigen-specific effector T cells, which leads to a state of functional exhaustion or anergy, one of the critical immune evasion mechanisms for cancers and persistently infecting viruses (33-35).

In an effort to discover another possible receptor for B7-H1, recent studies revealed that B7-H1 binds to B7.1 that acts as a counter receptor delivering a co-inhibitory signal. Interestingly, B7-H1 can also act as a counter receptor for B7.1 and transmit a co-inhibitory signal, indicating that the B7-H1-B7.1 pathway regulates immune functions through co-inhibitory bidirectional interaction (22). Furthermore, there are some *in vitro* and *in vivo* evidence indicating that both B7-H1 and B7-DC bind to a yet-unknown co-stimulatory receptor that is involved in T cell activation (36,37). Similar to the B7-CTLA-4 pathway, B7-H1-PD-1 pathway is also implicated in expansion and suppressive activity of Treg cells (38).

It has been well known that IFN-γ is a key cytokine to induce B7-H1 in non-hematopoietic cells such as cancer cells. Therefore, B7-H1 induction in tumor microenvironment by PD-1+ CTLs that infiltrated and produced IFN-γ may represent an adaptive immune resistance, leading to immune escape of cancer cells in the presence of anti-tumor responses (3,27,39). Many preclinical and clinical trials have been underway using B-H1 or PD-1 blocking antibodies. Early clinical studies have shown the promise in the treatment of patients with advanced cancers such as colon, renal, and lung cancers (40). Preclinical models also demonstrate a powerful synergy between tumor vaccines and blockade of the B7-H1-PD-1 pathway (41,42).

B7-H2 (ICOSL, CD275)

B7-H2 is a co-stimulatory ligand that binds only to ICOS, a co-stimulating receptor. B7-H2 is detected on the surface of APCs including B cells, DCs, and macrophages and a subset of CD3+ T cells. It is also expressed on the surface of non-lymphoid cells such as endothelial cells and some epithelial cells (43-48). B7-H2 mRNA is constitutively expressed in non-hematopoietic tissues including the kidney, liver, lung

and testes (43-45,49,50). Anatomically, B7-H2 is expressed in B cell areas and follicles of lymphoid organs and ICOS is detected on T cells in the germinal centers and T cell areas (51-53). B7-H2 delivers a co-stimulatory signal through ICOS, whose cytoplasmic tail contains the YMFM motif that binds to the p85 subunit of PI3K, but not Grb2 (54). The B7-H2-ICOS pathway augments T cell effector function, but not proliferation of naïve T cells, which leads to enhancement of Th1 and Th2 cytokine production (55-57). The B7-H2-ICOS pathway also regulates humoral immune responses by enabling the germinal center T cells to provide critical helper signals to B cells, leading to the formation of germinal centers and antibody maturation. The fact that the B7-H2-ICOS pathway stimulates IL-10 production suggests that this signaling pathway may contribute to the regulation of Treg cell function, T cell tolerance, and autoimmunity (58-60). It was recently discovered that only human B7-H2, but not mouse B7-H2, binds to CD28 and CTLA-4, and that the B7-H2-CD28 pathway delivers co-stimulatory signals into T cells. Thus, ICOS, CD28 and CTLA-4 may compete for a similar binding site on human B7-H2 (61). However, the questions about the physiologic role of the B7-H2-CD28 and B7-H2-CTLA-4 pathway *in vivo* still remain unanswered.

B7-H3 (CD276)

B7-H3 differs in extracellular domain composition between humans and mice; human B7-H3 has a tandem repeat of IgV and IgC domains giving rise to IgV-IgC-IgV-IgC, but mouse B7-H3 contain set of IgV and IgC domains (62,63). However, the functional significance remains unclear between the 2 structures. Although human and mouse B7-H3 mRNA are detectable in lymphoid and non-lymphoid organs, human B7-H3 protein is not expressed on resting monocytes, B cells, T cells, or NK cells, but it can be induced on these cell types in response to GM-CSF, LPS, or phorbol myristate acetate (PMA) and ionomycin (62-64). Aberrant expression of B7-H3 has been reported in a wide range of solid cancer tissues including brain, lung, and pancreatic cancers (65-67). In some diseases including cancers, sepsis, and meningitis, B7-H3 can be secreted from the cells, and soluble B7-H3 levels are positively correlated with disease states (68-70).

The receptor for B7-H3 has not yet been identified, although a previous study suggested the triggering receptor expressed on myeloid cell (TREM)-like transcript 2 (TLT-2) as a possible receptor for mouse B7-H3, which is not confirmed

in human B7-H3 (71). Initial studies indicated that B7-H3 is a co-stimulatory molecule as evidenced by the facts that human B7-H3.Ig fusion protein co-stimulates T cell proliferation in an *in vitro* assay and the B7-H3-overexpressing tumor cells are completely regressed in the tumor-bearing mouse. However, some *in vivo* experiments using B7-H3 knockout (KO) mice suggested that B7-H3 is a co-inhibitory player, which is supported by the observation that B7-H3 KO mice showed an increased alloreactive T cell expansion in mixed lymphocyte reaction (MLR), and developed more severe airway inflammation, experimental allergic encephalomyelitis (EAE) (5). In addition, tumor B7-H3 expression is often correlated with increased tumor size, the decreased number of tumor-infiltrating lymphocytes, and suppression of anti-tumor immunity (72-74). Thus, dual activity of B7-H3 may depend on the presence of putative co-stimulatory or co-inhibitory receptors on T cells in tissue microenvironment.

B7-H4 (B7-S1, B7x, VTCN1)

Although the protein structure of B7-H4 is predicted as a type 1 transmembrane protein, partial sensitivity to cleavage by phosphatidylinositol-phospholipase C (PI-PLC) suggested that B7-H4 is a GPI-anchored molecule, which makes B7-H4 different from other members of the B7-family in terms of topology (75,76). B7-H4 mRNA is expressed in lymphoid and non-lymphoid organs, but B7-H4 protein is not detectable in normal lymphoid and non-lymphoid organs except for activated APCs and breast ductal and lobular epithelia (75,77). Like B7-H1 and B7-H3, B7-H4 is ectopically expressed in a wide range of solid cancers including lung, thyroid, breast, ovary, esophageal cancers, and its expression in cancer tissues is correlated with poor prognosis (78-81). It is believed that immunosuppressive cytokines in tumor microenvironment such as IL-6 and IL-10 induce B7-H4 expression on tumor infiltrating macrophages, but not on cancer cells (82). There is still no report on which factors are responsible for B7-H4 induction in cancer cells. Although the receptor for B7-H4 is still unknown, it functions as a co-inhibitory factor whose engagement suppresses T cell expansion, cytokine production, and arrest cell cycle at the G0/G1 phase (75). A recent study using B7-H4 KO mice demonstrated that B7-H4 exerts an inhibitory effect on neutrophil expansion by inhibiting the growth of bone marrow-derived neutrophil progenitor (83), indicating that B7-H4 can also regulate innate immunity.

Recently, there have been several reports on an unexpected activity of B7-H4 in cancer progression in addition to its involvement in immune escape mechanisms. Unlike B7-H1, B7-H4 is expressed not only on the cell surface but also the inside of cancer cells which is an observation that attracts attention to its role in cancer cell biology. Specifically, many *in vitro* studies using siRNA for B7-H4 knockdown showed that downregulation of cancer B7-H4 inhibits proliferation, colony formation, and migration of cancer cells (84-86) and that intracellular B7-H4 may act as a cellular regulator promoting cancer cell proliferation and metastasis. However, molecular mechanisms behind B7-H4-mediated cancer progression remain unclear.

B7-H5 (PD-1H, VISTA, GI24, DIES1)

B7-H5, also known as VISTA, Gi24, or Dies1 has recently been identified as a co-inhibitory ligand bearing homology to B7-H1. Unlike B7-H1, B7-H5 contains a single IgV domain which has 3 additional cysteine residues, a unique structural feature different from other B7 family members (87,88). The cytoplasmic tail of B7-H5 does not contain any signaling motifs. B7-H5 is preferentially expressed on mature myeloid APCs including peritoneal macrophages, mature BMDC, neutrophils and CD11c+ DCs, and to a less extent on T cells and activated Treg cells. B7-H5 expression is inducible on T cells in response to PMA/ionomycin and on the myeloid cell population in response to OVA immunization with adjuvants such as complete Freund's adjuvant (CFA), indicating that B7-H5 expression is inducible during inflammatory response (87).

B7-H5 functions as a co-inhibitory ligand through an unknown receptor by inhibiting T cell proliferation and cytokine production and by arresting cell cycle (87). The co-inhibitory activity of B7-H5 is further supported by the finding that B7-H5-expressing MCA105 tumor cells grow vigorously in vaccinated hosts, whereas the control tumors do not. This result suggests that B7-H5 may inhibit a protective antitumor immunity in the host (87). Interestingly, consistent with cancer-associated B7-H4 showing non-immune activity, B7-H5 expressed on cancer cells enhances tumor-invasive growth by augmenting membrane type 1 matrix metalloproteinase (MMP) (89). In addition, B7-H5 is also required for proper differentiation of mouse embryonic cells via the bone morphogenetic protein 4 (BMP4) pathway (90).

B7-H6 (NCR3LG1)

B7-H6, also known as NCR3LG1, is a newly identified B7 family member, acting as a co-stimulatory ligand that delivers a stimulatory signal to NK cells through the receptor NKp30 (91). B7-H6 consists of an IgV-IgC extracellular domain, a transmembrane region and a long cytoplasmic tail that contains signal transducing motifs such as an ITIM, a Src homology 2 (SH2)-binding domain, and an SH3-binding motif. However, there have been few reports on the receptor activity of B7-H6. B7-H6 mRNA and protein are not detected in normal tissues. In contrast, B7-H6 is expressed on primary blood and bone marrow cells from hematological malignancies, including acute lymphoblastic leukemia, acute non-lymphoblastic leukemia, and non-Hodgkin's lymphoma (91). B7-H6 expression is regulated by class I histone deacetylases (HDACs) 2 and 3, so that knockdown of HDAC3 down-regulates B7-H6 surface expression (92).

NKp30 is a NK cell surface receptor that delivers an activating signal into NK cells. Since NKp30 consists of a single IgV domain in its extracellular region, a unique structural feature of the CD28 family, it belongs to CD28 family. NKp30 also has another ligand, BAT3 which is a nuclear protein involved in the interaction with P53 and apoptosis induction after DNA damage-induced cellular stress (93,94). NKp30 has been shown to mediate anti-tumor effects in gastrointestinal stromal tumors and lymphoid leukemia (95,96). Many studies indicate that the B7-H6-NKp30 pathway is implicated in anti-tumor activity by stimulating primary NK cells to produce IL-2 and IFN-γ and to enhance the cytotoxic activity (91,92). Further studies are needed to investigate the physiological role of B7-H6 in T cell immunity.

B7-H7

B7-H7 was previously known as human endogenous retrovirus-H long terminal repeat associating 2 (HHLA2 (97)) with unidentified function. Recently, B7-H7 has been identified as a specific ligand for human CD28H. Notably, mice and rats do not have the ortholog for human B7-H7 that consists of 3 signature of extracellular domains (IgV-IgC-IgV) (98). Interestingly, the first IgV domain of B7-H7, which presumably binds to a putative receptor, shows the highest homology to other B7 family members. B7-H7 mRNA is expressed in APCs, and non-lymphoid organs including the testis, colon, lung, kidney and pancreas while its transcript was not de-

tected in T cells and a little in the small intestine, liver and skeletal muscle. Unlike the transcript expression pattern, cell surface B7-H7 expression is not detected on T cells, B cells, NK cells or monocytes freshly isolated from human PBMCs, but induced by poly (I:C), suggesting that B7-H7 is largely an inducible molecule on APCs in response to proinflammatory stimuli (99).

The B7-H7-CD28H pathway strongly promoted CD4+ T-cell proliferation and cytokine production (IL-2, IFN-γ, TNF-α and IL-10) via an AKT-dependent signaling cascade in the presence of TCR signaling, suggesting B7-H7 comprises a new co-stimulatory pathway (99). Co-stimulation via the B7-H7-CD28H pathway appears to be dependent on endogenous B7- CD28 interaction because addition of CTLA-4.Ig blocking B7-CD28 interactions greatly inhibited T-cell proliferation and cytokine production, even in the presence of agonistic CD28H mAb. The potential involvement of B7-H7 in human diseases has not yet been reported. However, it is worth while to further investigate the B7-H7-CD28H pathway in patients with autoimmune diseases or cancer, which will shed insight on a new potential therapeutic target in immunotherapy.

CONCLUSION

Co-signaling molecules comprise a complex molecular network that positively or negatively modulates T cell responses. Thanks to the improvement of *in silico* cloning technology and the development of high throughput screening method, more co-signaling ligands and receptors have been discovered, which establishes much more complicated co-signaling interactions. Due to the nature of suppressive activity, co-inhibitory molecules act as immune checkpoints that maintain self-tolerance and regulate the ultimate magnitude and quality of normal physiological immune response. Recently, promising clinical outcomes has come from several clinical trials that have used immune checkpoint blockade strategies for the treatment of autoimmune diseases and cancers. It is quite clear that successful clinical trials targeting immune checkpoints must be preceded by understanding fundamental mechanisms of immune regulations led by co-signaling molecules in normal and pathological microenvironment.

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CONFLICTS OF INTEREST

The authors have no financial conflict of interest.

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