Review

BTLA, a New Inhibitory B7 Family Receptor with a TNFR Family Ligand

Chun Zeng[1, 2], Tinghe Wu[1, 2], Yu Zhen[1, 2], Xuepei Xia[3] and Yong Zhao[1, 2, 4]

B and T lymphocyte attenuator (BTLA), identified as an immune inhibitory receptor recently, plays widespread roles on T and B cells. Emerging evidence has generated plentiful information on the mechanisms which BTLA mediates negative regulation in immune responses and involves in a variety of physiological and pathological processes. The exploration of the biological mechanisms and regulation of BTLA will open possibilities on novel therapeutic strategies in immune-related diseases. *Cellular & Molecular Immunology*. 2005;2(6):427-432.

Key Words: inhibitory receptor, ITIM, BTLA, HVEM

Introduction

The immune homeostasis is a dynamic process that is elaborately regulated by the balance between activation and inhibition of varied signals (1, 2). Fuelled by the ever-growing knowledge of immune regulation, an expanding family of inhibitory receptors (Table 1) has received considerable attention because of their ability to limit or terminate paired activation signals. These transmembrane negative regulators share the common feature that includes a cytoplasmic immunoreceptor tyrosine-based inhibitory motif (ITIM), whose phosphorylation recruits protein tyrosine phophotatases and ultimately attenuates or eliminates the response (3-5). Recent identification of a new ITIM-containing inhibitory receptor-B and T lymphocyte attenuator (BTLA) (6) provides additional information on negative regulation.

BTLA is structurally and functionally similar with the other two T cell inhibitory receptors, cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1). They all belong to the B7 family (7-9) and their ligands bind to different receptors with opposite outcome: CTLA-4 interacts with B7.1 and B7.2 to attenuate T cells response, whereas T cell activation is promoted by CD28 ligation with B7.1 and B7.2. Similarly, PD-1 links to programmed death-1 ligand-1 and -2 (PD-L1, PD-L2) and to inhibit immune responses, and an unclear receptor integrating into PD-L1 and PD-L2 is postulated to co-stimulate T-cell responses (10-13). Different from CTLA-4 and PD-1 combining with the B7 family members, BTLA bands together with herpes virus entry mediator (HVEM), which is a member of TNFR family (14, 15). The effect of the co-stimulatory TNFR family and B7 family can often be functionally, temporally, or spatially segregated from each other (16-18), and the ligation of BTLA with HVEM is the first example of the crosstalk between co-stimulatory and co-inhibitory receptors in these two families. The knowledge of BTLA will be valuable for the study of negative regulation manner at the molecular level and the crosstalk between different families. In the present review, we attempt to recapitulate the characteristics of its structure and expression, illuminate its ligation with ligand and elucidate its functions in the immune system.

Structure and expression of BTLA

Recent studies have highlighted the structural features which are content with T cell co-stimulation. The molecular architecture of the molecules that constitute a particular receptor-ligand pair dictate the mechanistic details of a given transduction pathway (19). As a new receptor of B7 family,

[1]Transplantation Biology Research Division, State Key Laboratory of Biomembrane and Membrane Biotechnology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100080, China;

[2]Graduate School of Chinese Academy of Sciences, Beijing 100037, China;

[3]Department of Endocrinology, Beijing Haidian Hospital, Beijing 100080, China;

[4]Corresponding to: Dr. Yong Zhao, Transplantation Biology Research Division, State Key Laboratory of Biomembrane and Membrane Biotechnology, Institute of Zoology, Chinese Academy of Sciences, 25 Beisihuanxi Road, Haidian District, Beijing 100080, China. Tel: +86-10-626-27909; E-mail: zhaoy@ioz.ac.cn.

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Abbreviations: BTLA, B and T lymphocyte attenuator; CTLA-4, cytotoxic T lymphocyte antigen-4; ITIM, immunoreceptor tyrosine-based inhibitory motif; PD-1, programmed death-1; HVEM, herpes virus entry mediator; DC, dendritic cell; CRD, cysteine-rich domains; gD, glycoprotein D.

Table 1. Immune inhibitory receptors

Receptor	Distribution	Numbers of ITIMs	Activating receptor	Ligand	Associated phosphatases
FcγRIIB	B, My, mast	1	FcγRIIi, FcγRIIA	IgG complex	SHIP-1, SHIP-2
CTLA-4	T	None	CD28	CD80, CD86	SHP-2
PD-1	T, B, NK cell	1		PD-1 ligand	SHP-2
BTLA	T, B	2	LIGHT	HVEM	SHP-2
PILRα	My	2	PILRβ?	?	SHP-1
CD72	B	2		CD100	SHP-1
CD5	T, B-1	1		?	SHP-1
MAFA	My, Mast, NK	1		?	SHP-1
NKG2A	NK, $CD8^+$ T	2	NKG2C, NKG2E	HLA-E	SHP-1, SHP-2
CD31	My, platelet, EC, T, NK	1		CD31	SHP-1, SHP-2
CMRF35H	My, B, T, NK	3	CMRF35A?	?	?
SIGLEC family (CD22, CD33, etc)	Hm	1-4		Sialic acid	SHP-1, SHP-2
CD66	Hm, EC	2		CD66	SHP-1, SHP-2
ILTs/LIRs*	My, B, NK, T	2-4	LIT1,7, 8, LIR6a	MHC class I (ILT-2,4)	SHP-1
LAIR-1*	Hm	2		EpCAM	SHP-1, SHP-2
KIR2DL*	NK, T	2	KIR2DS	HLA-C	SHP-1
KIR3DL*	NK, $CD8^+$ T	2	KIR3DS	HLA-A, HLA-B	SHP-1
SHPS-1	Mφ, DC	2	SIRPβ	CD47	SHP-1, SHP-2
gp49B1#	Mast, NK	2	gp49A	$\alpha_v\beta_3$ integrin	SHP-1
Ly49A-1#	NK, $CD8^+$T	1	Ly49D, H	MHC class I	SHP-1, SHP-2
PIR-B#	My, B	3	PIR-A	?	SHP-1, SHP-2
Gp49B1#	Mast, NK	2	Gp49A	$\alpha_v\beta_3$ integrin	SHP-1

*human only; #mouse only; My, myeloid; Hm, hematopoietic; NK, natural killer; EC, epithelial cells; DC, dendritic cells; Mφ, macrophages.

BTLA is a type I transmembrane glycoprotein with an extracellular immunoglobulin variable (IgV) domain, a transmembrane region, a cytoplasmic region and a signal sequence. And the common structural feature of B7 family receptors is an extracellular IgV domain that is responsible for ligand binding. BTLA is monomeric and lacks the membrane proximal cysteine needed for dimerization (8). The crystal structure has shown that BTLA utilizes a distinct binding surface compared to CTLA-4, and forms a single receptor-ligand complex (20). The cytoplasmic region of BTLA contains two ITIMs, which are associated with the phosphotases SHP-1 and SHP-2 (21).

BTLA displays polymorphic structural features and cell distribution. Hurchla and his coworkers have detected three distinct alleles among 23 murine strains by their brilliant work in 2005. In Ig domain, the BALB/c and MRL/*lpr* alleles differ in a single amino acid, but C57BL/6 has nine additional differences and alters the predicted cysteine binding pattern. BALB/c BTLA allele is expressed on B cells, T cells and DCs, but C57BL/6 BTLA is additionally expressed on $CD11^+$ macrophages and natural killer cells (22). More researches are needed to focus on the relationship between the polymorphism of BTLA and the susceptibility of autoimmune diseases just as the study on CTLA-4 and PD-1 (23, 24). In addition, an alternatively spliced variant of BTLA (BTLAs) that eliminate the ligand binding Ig domain has been described by Kaye's lab (25). And some other researchers have shown that CD28 and CTLA-4 variants missing ligand-binding domain can also transmit co-stimulatory and co-inhibitory signals, and these surprising discoveries bring new inspiration to immunologists to reveal the alluring functions of BTLAs (26, 27).

The expression of BTLA varies during the activation and differentiation of T cells. BTLA is constitutively expressed on resting T cells at a very low level (25), and increases after the activation of T cells (6, 20, 22, 28). The expression of BTLA protein is abundant in Th1 cells (29). When T cells are cultured *in vitro* under Th1 and Th2 polarization, BTLA mRNA remains high in Th1 cells independent of signal transducer and activator of transcript 1 (STAT1) and STAT4 (6). And BTLA protein peaks by day 2 in both Th1-inducing and Th2-inducing circumstances, declines by day 4 and

vanishes by day 7 after the primary T cell activation and the secondary reaction. However, BTLA is selectively induced in Th1 cells but not in Th2 cells after tertiary activation (22). These results suggest that BTLA expression is primarily controlled by T cell activation rather than other factors governing T cell differentiation. Selective emergence of BTLA on Th1 cells perhaps might reflect a silencing process but not a Th1-specific induction (22, 30).

In the thymus, BTLA expression is regulated in the process of positive selection. In contrast with the absence of BTLA in thymocytes in TCRα chain deficient mice, BTLA rises during the transition from $CD4^-CD8^-$ thymocytes to $CD4^+CD8^+$ double positive thymocytes and maintains on $CD4^+$ or $CD8^+$ single positive thymocytes with slight higher level on $CD4^+$ cells in wild mice (25). Up-regulation of BTLA in the positive selection is relevant to mitogen-activated protein kinases (MAPK) signaling pathway (25), which has been shown to be essential for positive selection and plays a role in determination CD4/CD8 lineage commitment (31, 32). These findings imply that BTLA might play an important role in thymic positive selection. However, BTLA-deficient mice show normal development of T cell and peripheral lymphoid organ cell subpopulation (6, 25), suggesting that BTLA signals are redundant and just provide fine tune functions.

Ligand of BTLA

To further explore the physiological functions of BTLA, researchers have attempted to identify its ligand which triggers BTLA signal pathway. B7x (B7-H4, B7-S1) has once been proposed to be the ligand as the B7x-Ig fusion protein binds to activated wild type but not BTLA-deficient T cells (6, 33). Recently, two independent laboratories demonstrate that BTLA regulates T cell activation through its interaction with a co-stimulator of TNFR family, HVEM (14, 15). HVEM is originally isolated as the receptor of herpes simplex virus type-1 (HSV-1) (34), and it also has two TNFR family ligands: LIGHT and lymphotoxin-α (LT-α) (35). The ligation of BTLA and HVEM is the first example of TNFR family member as the ligand for B7 family member.

HVEM is a type I transmembrane glycoprotein with four extracellular cysteine-rich domains (CRDs) including pseudorepeats of six cysteines, which is the common feature of TNFR family. These cysteines compose three disulphide bridges which are necessary for the establishment of the tertiary structure when its receptor is engaged by ligand (36). HVEM has spatially distinct ligand binding regions: the TNF homology domain of LIGHT and LT-α respectively interacts with CRD3 and CRD1, 2 domains (37). Nevertheless, gD binds to CRD1 domain of HVEM in a non-conventional manner in the opposite face of LIGHT-binding site (38-40). The crystal structure of BTLA-HVEM complex and mutagenesis experiments show that BTLA also interacts with HVEM by a similar β-sheet binding motif and its binding site is overlap that of gD (20, 41). Interestingly, BTLA-HVEM-LIGHT can form a stably ternary complex *in vitro*. And this complex structure implies that LIGHT and BTLA would be expressed on the same cell while HVEM would be on a different cell (15). In 2005, three potential models on their crosstalk are provided by professor Croft according to BTLA and LIGHT expression levels (13). In addition, BTLA can form a single receptor-ligand complex with HVEM (20), suggesting that it is unlike to activate HVEM as LIGHT binding which promotes trimetric clustering of HVEM and trigger signal transduction.

In contrast to the complicated expression of BTLA, HVEM mRNA and surface protein are constitutively expressed on peripheral T and B cells, monocytes, and immature DCs (42). HVEM is highly present on resting T cells, down-regulated upon T cell activation and then re-expressed as the T cells return to a more resting state (43). And HVEM is decreased on T cells and DCs by the engagement with LIGHT (43, 44).

Function studies on BTLA

Attenuation of T cell proliferation by the BTLA-HVEM pathway

BTLA ligation negatively modulates T cell activation. Crosslinking of BTLA and HVEM greatly impairs anti-CD3 induced activation of T cells, and anti-BTLA antibody reverses the suppressive effect. The expression of HVEM on APCs triggers BTLA phosphorylation and SHP-2 association, and significantly reduces peptide-dependent T cell proliferation (14, 15). In addition, pervanadate treatment can also induce BTLA phosphorylation and recruit SHP-1 and SHP-2 (6, 21, 25). BTLA signal has no effect on the induction of CD69 but inhibits proliferation of pre-activated T cells, suggesting BTLA engagement does not prevent initial activation of T cells, but modifies the consequence of activation (28).

BTLA mediated inhibition is not dependent on regulatory T cells and apoptosis, but correlates with decreasing IL-2 production (6, 28). At limited concentrations of plate-bound anti-CD3, BTLA engagement suppresses the proliferation of $CD4^+$ T cells, CD25 up-regulation and IL-2 secretion even in the presence of anti-CD28. Exogenous IL-2 at low concentration is not able to restore proliferation or CD25 expression on $CD4^+$ T cells, indicating additional IL-2-independent inhibitory effects on T cell activation. While in the presence of high concentration of plate-bound anti-CD3, CD28 stimulation can restore the proliferation, although IL-2 production is significantly decreased. Interestingly, $CD8^+$ T cells are less sensitive to the inhibitory effects (28). The difference might result from high expression level of BTLA on $CD4^+$ T cells (25). In addition, IL-2 is not required for the initiation of $CD8^+$ T cell cycles and it may partially explain the decreased susceptibility of $CD8^+$ T cells (45).

Gene deficient mice also offer convictive evidence for their inhibitory function. As we all known, some *in vitro* studies in which anti-HVEM or HVEM-Ig inhibits the proliferation of purified T cells responding to anti-CD3 or anti-CD3/CD28 partly show us that HVEM provides a costimulatory signal through interaction with LIGHT (46, 47).

However, HVEM deficient T cells show enhanced responses to *in vitro* concanavalin A (Con A) stimulation when compared with wild type T cells, indicating HVEM signaling might originally execute negative regulation of T cell-mediated responses (48). Moreover, naïve T cells or fully polarized Th1 cells from BTLA deficient mice are hyperresponsive to TCR-mediated activation (6, 25).

Effect of BTLA on humoral response

BTLA is constitutively and highly expressed on B cells, suggesting it may play a role in the humoral response. BTLA deficient B cells display slight augment responses to stimulation of anti-IgM but not LPS, which indicates that BTLA regulates B cell receptor, but not Toll-like receptor 4, mediated stimulation (6). The evidence that BTLA regulates T cell-dependent Ab responses comes from mild increased level of specific IgG1, IgG2a and IgG2b isotypes in $BTLA^{-/-}$ 129SvEv mice immunized with nitrophenol-conjugated keyhole limpet hemocyanin (6). Moreover, $BTLA^{-/-}$ 129SvEv mice immunized with nitrophenol-ficoll show modest enhancement of IgG3 isotype, which is primarily associated with T cell independent responses (22). According to the magnitude of these effects, it might be concluded that BTLA finely take part in the Ab responses.

Role of BTLA and HVEM in autoimmune disease

Several studies tell us that BTLA and HVEM play a role in autoimmune diseases. BTLA-deficient mice show a higher incidence, increased clinical score, earlier onset and longer duration of experimental autoimmune encephalomyelitis (EAE) compared to wild-type mice (6). Similarly, $HVEM^{-/-}$ mice are more susceptible to myelin oligodendrocyte glycol-protein (MOG) peptide-induced EAE, and they display increased T cell proliferation and cytokine production in response to antigen-specific challenge. Furthermore, $HVEM^{-/-}$ mice exhibit increased morbidity and mortality as compared with wild-type mice in a model of Con A-mediated T cell-dependent autoimmune hepatitis (48). And HVEM-Fc can significantly prevent infiltration with autoreactive T cells in nondiabetic mice, which spontaneously develop insulin-dependent diabetes mellitus (46). Taken together, these results indicate that BTLA and HVEM might negatively regulate T cell-dependent autoimmune reaction due to excessive T cell activation and clone expansion *in vivo*.

Role of BTLA in allogeneic responses

BTLA/HVEM pathway has a unique role in regulating *in vivo* allogeneic responses. MHC-mismatched cardiac graft is currently the standard model of chronic rejection in mice. In this model, BTLA but not PD-1 is strongly induced and grafts survive long term, while targeting of BTLA or HVEM promotes rapid rejection (49), suggesting that BTLA exerts its main effect when the strength of the immune response is weak. And it is in accordance with previous observation that no inhibitory effect of BTLA with increased antigen or anti-CD3 concentration (14, 28). Nevertheless, fully MHC-mismatched grafts are rapidly rejected despite the induction of both BTLA and PD-1. Targeting of PD-1 in several fully MHC-mismatched grafts accelerates rejection, whereas targeting of BTLA unexpectedly enhances PD-1 induction by alloreactive $CD4^+$ and $CD8^+$ T cell activation and prolongs allograft survival. This indicates that PD-1 expression plays the dominant role when the strength of the immune response is strong. Indeed, BTLA functions as an inhibitor of PD-1 induction under this condition (49). These findings are of possible clinical significance, because chronic rejection of partially MHC-mismatched organ transplantations represents a currently unresolved Achilles' heel of human transplantation.

Role of BTLA in virus immunity

Otherwise, BTLA may take part in the virus infection. The herpes viruses gD could selectively bind with HVEM and block its engagement of BTLA and LIGHT to nullify these circuits. Besides, human cytomegalovirus encodes a viral protein which has high homology with CRD1 of HVEM and imitates the inhibitory function of HVEM to inhibit T cell proliferation by ligation with BTLA, but not LIGHT (41). The facts that different viruses target the BTLA-HVEM pathway may represent a series of therapeutic strategies for the exploitation of this circuit in immune regulation in which BTLA participates in disease aetiology though these immune evasion mechanisms are yet elusive.

Therapeutic prospect by manipulation of BTLA

Accumulated studies have demonstrated that blockade of HVEM-LIGHT pathway by soluble HVEM-Fc or antibodies to HVEM prevents graft-versus-host disease and allograft rejection (50). In addition, HVEM is involved in atherosclerosis, allergic asthma, atopic dermatitis and rheumatoid arthristis (51-53). These data and highly expression on Th1 cells of BTLA hint that manipulation of BTLA to blockade HVEM-LIGHT pathway or to induce negative regulation shows an alluring therapeutic prospect in the cure of Th1-mediated inflammatory, allergic, autoimmune responses, as well as transplant rejection.

Moreover, the role of co-stimulation, both positive and negative, in the immunotherapy of cancer has been of interest for tumor cells which do not express co-stimualtory ligands, making them escape from immune surveillance. Either induction of co-stimulatory ligands or blockade of inhibitory signals could enhance T cell mediated rejection (54-56). In consistent with the effects of HVEM-LIGHT pathway in anti-tumor immunity, blockade of BTLA-HVEM will allow the development of a new strategy to augment tumor immunity.

Conclusion and prospect

This review aims to outline some of the fundamental biological properties of BTLA and the key factors implicated in regulating its activity as a negative regulation protein. The discovery of BTLA as negative factor is an important milestone to highlight the inducible nature of BTLA/HVEM

pathway. However, more analyses should be concerned on the elaborate signal pathway of BTLA and its precise molecular function in the Th1 cells mediated responses, and rational exploitation of BTLA will require the advances of biological models that allow a greater understanding of the role of BTLA in negative regulation.

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