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The Canonical and Unconventional Ligands of the Herpesvirus Entry Mediator

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Introduction

The maintenance of immune homeostasis requires a balance between stimulatory and inhibitory pathways. The herpesvirus entry mediator (HVEM; TNFRSF14) [1] serves as one of two key entry routes used by herpes simplex virus-1 and herpes simplex virus-2 to infect cells [2]. The selection of HVEM as a route of infection is intimately linked with the capacity of HSV to modulate immunity. As a cellular signaling receptor, HVEM functions as a molecular switch for pathways that can stimulate or inhibit hematopoietic cell activation. The HVEM-regulated pathways impact T and B cell activation [3, 4], dendritic cell proliferation [5], and protection of mucosal epithelia from damage during inflammation [6]. HVEM has five known functional ligands: two canonical TNF superfamily ligands (LIGHT: TNFSF14 and LTα: lymphotoxin-a) [7] and three unconventional ligands that belong to the Ig superfamily [B and T lymphocyte attenuator (BTLA), CD160, and the viral envelop protein of herpes simplex virus envelope glycoprotein D (HSV gD)] (Fig. 36.1a) [8]. The shared receptor usage of HVEM's ligands, LIGHT and LTα, by the LTβ receptor and the two receptors for TNF suggests these molecules are part of a larger signaling network whose ramifications have not been fully elucidated [9]. Recent insights into the biophysics of the ligand–receptor interactions in the HVEM pathway suggest unanticipated functional consequences of this cosignaling network.

Canonical Ligands: LIGHT and LTα

Lymphotoxin-α and LIGHT are members of the tumor necrosis factor superfamily (TNFSF) having a common structural motif that forms TNFR binding site. LIGHT was initially identified as cellular ligand for HVEM through the characterization of a distinct 30 kDa HVEM-binding protein on the surface of an activated human CD4+ T cell hybridoma (II-23) [7]. LTα is one of the original tumor necrosis factors [10]. LTα contains a classic signal cleavage site and is secreted as a homotrimer, while LIGHT is a type 2 transmembrane glycoprotein. The extracellular domain of LIGHT may be cleaved from the surface and released in a functional soluble form [11].

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The LIGHT gene is located on human Chr 19p13 and a genetic paralog of LTβ, FasL, and TL1A [12]. LIGHT shares significant amino acid sequence homology with the C-terminal receptor-binding domains of LTβ (34% identity), and it shares binding to the LTβR, which engages the heterotrimer, LTα1β2. LIGHT, like all TNFSF members, forms a trimeric complex [13, 14] that allows multivalent binding with cell surface receptors. Receptor clustering is the key initiating step in the activation of TNF receptor signaling [15].

Both LIGHT and LTα bind to a similar region of HVEM. The binding site of LIGHT and LTα on HVEM were mapped on cysteine-rich domain-2 (CRD2) and CRD3 using HVEM mutants. Although the binding sites of LIGHT and LTα on HVEM are distinct, it is likely that their binding sites are topographically overlapping as the molecules are cross competitive [7]. It has been shown that HVEM has a stronger binding avidity to LIGHT than LTα [7], and LIGHT-induced HVEM signaling results in the recruitment of the TNF receptor-associated factor 2 (TRAF2) to the cytoplasmic tail of HVEM. The activation of a TRAF-dependent NF-κB pathway provides positive costimulation and prosurvival signal to T cells [13]. Although there have been many studies on the binding, structure and function of LTα in particular, in relation to TNFR1 and TNFR2, the distinct role of LTα on the HVEM signaling network remains unclear. However, LTα enhanced binding interactions between HVEM and BTLA [16, 17] presumably through oligomerization of HVEM. Additional studies are needed to further define the impact of LTα in the LIGHT–HVEM–BTLA/CD160 signaling system.

The expression of LIGHT is regulated at the transcriptional level [7, 14]. LIGHT is inducible but transiently expressed on the surface of activated T lymphocytes [7, 14]. Although both LIGHT and LTα are expressed in activated T cells, the transcriptional regulation of their genes appears to be mediated via different signaling pathways [7]. LIGHT expression was detected in MCF10A breast epithelial line [18] and melanoma cells [19]. Thus, LIGHT appears to have a broader range of expression compared to LTα, which is limited to activated T cells, B cells, NK cells, and LTi cells.

Unconventional Ligands: BTLA and CD160

BTLA and CD160 were originally identified as receptors for HVEM [20, 21] involved in activating inhibitory signaling. However, recent studies demonstrated that both BTLA and CD160 serve as activating ligands for HVEM [8]. BTLA or CD160 binding to HVEM induced HVEM-dependent NF-κB activation, demonstrating bidirectional signaling between HVEM and BTLA (Fig. 36.1a) in cells interacting in *trans* [8]. BTLA appears to form dimers as a membrane protein, providing a basis for oligomerizing HVEM that leads to TRAF2 recruitment and activation of NF-κB RelA. These results highlight the complexity of LIGHT– HVEM–BTLA/CD160 cosignaling networks.

In contrast to the TNFSF ligands, BTLA is a type 1 transmembrane protein with a single intermediate (I) type Ig domain. Three conserved tyrosine-based signaling motifs, two ITIM, and a Grb-2 recognition consensus are present in the cytoplasmic domain of BTLA in both mouse and human [22]. The utilization of the ITIM and recruitment of the protein tyrosine phosphatases, Src homology domain (SHP)-1 and SHP-2, into the cytoplasmic tail of BTLA appear to be HVEM dependent [23, 24]. However, the distinct role of the ITIM and the contributions of SHP-1 and SHP-2 in BTLA intracellular signaling have not been precisely defined. BTLA is expressed in a broad range of hematopoietic cells, including mature lymphocytes, splenic macrophages, dendritic cells, as well as T and B cells in the developing thymus [25, 26], and thus the effects of BTLA signaling may modulate many aspects of innate and adaptive immunity.

CD160 was originally identified as a binding partner of MHC class I molecules with weak binding affinity [27]. Recent studies by Cai et al. [21] demonstrated that CD160 exhibited specific binding to HVEM and that signal transduction mediated through HVEM and CD160 was shown to be inhibitory to T cells. CD160 is also a member of the Ig family with a single Ig V-like domain and a predominant glycosylphosphatidylinositol (GPI) motif, which enables anchorage to the cell surface. It has been shown that the GPI anchored CD160 on activated T cells was cleaved by a metalloprotease [28]. Furthermore, additional isoforms of CD160 have also been reported. Giustiniani et al. [29] have recently indentified three isoforms of CD160 (CD160ΔIg-GPI, CD160-TM, and CD160ΔIg-TM) that were generated by alternative splicing. Both CD160ΔIg-GPI and CD160ΔIg-TM have a deletion of the Ig domain, which is likely to abolish their binding capability to HVEM. Additionally, CD160-TM and CD160ΔIg-TM also contain transmembrane and intracellular domains. Although the distinct role of these new isoforms in LIGHT–HVEM–BTLA/CD160 cosignaling system remains to be determined, it is anticipated that the newly found isoforms, in particularly the CD160-TM, would allow intracellular signaling. Unlike BTLA, CD160 assemble as a trimer with interchain disulfide bridges [30]. The trimeric form of CD160 along with its high binding avidity to HVEM enables it to function as a highly effective ligand for HVEM. CD160-expressing EL4 cells specially activated HVEM-dependent NF-κB reporter in transfected 293T cells and induced nuclear translocation of RelA in HT29 colon cell line, which naturally express HVEM [8]. The expression of CD160 is restricted to the hematopoietic compartment. CD160 is expressed in NK and NKT cells, γδT cells, intestinal intraepithelial T cells, $CD8^{+}CD28^{-}$ T cells, and a subset of CD4 T cells, but not in B cells [30]. CD160 mRNA was detected in spleen, peripheral blood, and lymphocytes in the small intestine [30].

Distinct Ligand Binding Sites on HVEM

HVEM is a typical TNFRSF member with four cysteine-rich domains (CRD). The 11 disulfide bonds in the ectodomain create an elongated structure. The presence of at least two distinct ligand-binding sites in topographically separate regions of HVEM allows this receptor to simultaneously interact with multiple ligands. LIGHT and BTLA bind on opposite sides of HVEM. BTLA and CD160 engage residues in the N-terminal CRD1 of HVEM, whereas the contacts of LIGHT and LTα are located in CRD2 and CRD3. The binding of soluble LIGHT to HVEM does not inhibit either BTLA or CD160 binding to HVEM [8, 16, 31], substantiating the conclusion that LIGHT and BTLA have distinct binding sites. Interestingly, soluble LIGHT and BTLA bind cooperatively to HVEM. Soluble LIGHT or LTα enhanced the binding of BTLA to HVEM [16, 17]. This result is consistent with a view that LIGHT clusters HVEM, which in turn, increases the avidity for BTLA (Fig. 36.1b). This interpretation suggests that soluble LIGHT, HVEM, and BTLA form a trimolecular complex.

We suggested a model in which the LIGHT–HVEM–BTLA trimolecular complex is likely to contain a trimer of soluble LIGHT with three molecules of HVEM and BTLA. However, the trimolecular complex of LIGHT–HVEM–CD160 would contain a trimer of LIGHT and three HVEM, and three trimers of CD160 (Fig. 36.1b). The formation of these higher ordered complexes not only enhances binding between HVEM, LIGHT, LTα, BTLA, and CD160, but also enhances HVEM clustering and, importantly, HVEM signaling.

Viral Ligands of HVEM and BTLA: HSV gD and UL144

HSV-1 gD is a type 1 transmembrane glycoprotein. The N-terminal ectodomain contains three N-glycosylation sites and six cysteine residues for the formation of three disulfide bridges. Sequence structure analysis revealed an IgV-like domain at the N- and C-terminal

extensions [32, 33]. Although there is no significant sequence homology between gD and other cellular ligands of HVEM, gD shows direct binding with HVEM. The binding site of HSV gD was mapped in the CRD1 of HVEM [34]. The gD site is topographically close to the BTLA site on HVEM, but their binding sites are not identical [16]. The unique location of the gD site on HVEM enables gD to perform two distinctive functions. Firstly, the binding of gD-Fc on HVEM prevents HVEM from binding to both LIGHT and BTLA. The ectodomain of gD serves as a multi-function inhibitor, which not only blocks binding of HVEM to LIGHT, but also to BTLA. Secondly, gD forms a stable dimer with a disulfide link between two subunits [35, 36]. The dimeric nature of gD allows it to oligomerize HVEM, serving as a functional ligand. The gD–HVEM complex is likely to contain two molecules of gD and two HVEM. Direct evidence for supporting this hypothesis came from the observation that the binding of gD-Fc to HVEM activated NF-κB [8].

UL144 is a herpes virus ortholog of HVEM [37] that binds BTLA [16], but not to the canonical TNF ligands, LIGHT and LTα. UL144 is encoded within the ULb' region of human cytomegalovirus, a β-herpesvirus. The protein contains two CRD homologous to CRD1 and 2 of HVEM explaining the lack of binding of the TNF-related ligands. The protein is highly variable in the ectodomain [38] but contains a conserved short intracellular domain. The role of UL144 in the pathogenesis of CMV is unknown, but the engagement of BTLA suggests a possible role in immune evasion.

The *Trans* and *Cis* of HVEM Signaling

In general, HVEM is viewed as a positive immune regulator since it activates NF-κB transcriptional programs that are involved in cell survival and proliferative responses. In addition, ligation of BTLA or CD160 to HVEM also activated NF-κB in a TRAF2-dependent pathway, providing a prosurvival signal for T cells [8]. In this setting, the ligands and receptors function in *trans* between interacting cells. However, our recent studies indicate that HVEM and BTLA can interact in *cis*, laterally within the same membrane [8]. Flow cytometric analysis demonstrated that *cis*-interaction between HVEM and BTLA is the predominant complex expressed on the surface of naïve human and mouse T cells, and the formation of HVEM–BTLA *cis*-complex inhibited HVEM-dependent NF-κB activation. The heterodimeric complex of HVEM and BTLA uses the same site in CRD1 as for *trans*-interaction, with only the ectodomain of BTLA required to form the *cis*-complex. The HVEM–BTLA *cis*-complex competitively inhibits *trans*-signaling by all its cellular ligands, providing a mechanism for maintaining T cells in a resting state. As the binding sites of BTLA and CD160 on the CRD1 of HVEM are topographically close to each other, the receptor binding domains of BTLA and CD160 also act as a competitive inhibitors blocking BTLA or CD160 from interacting with HVEM in *trans* and inducing NF-κB activation.

Interestingly, herpes simplex virus envelope glycoprotein gD also forms a *cis*-complex with HVEM. *Cis*-association between gD and HVEM blocks *trans*-interaction of LIGHT, BTLA, or gD to HVEM in the *cis*-complex. This is consistent with the observation that gD expressing cells were resistant to HSV infection, indicating that gD might interfere with its endogenous receptors [39]. We propose that the formation of *cis*-complexes between HVEM and BTLA, CD160 or gD competitively (against BTLA, CD160 and gD) or non-competitively (against LIGHT and LTα) inhibits HVEM activation by ligands expressed in the surrounding microenvironment, allowing T cell to remain in the naïve state.

Although LIGHT interacts with HVEM in a topographically distinct site, which differs from the BTLA binding site, membrane LIGHT inhibits HVEM–BTLA *trans*-interaction [16]. These results suggested that the proximity of the membrane may sterically exclude HVEM from binding BTLA when membrane LIGHT occupies its binding site in the CRD2 and 3

regions. Promoted by high affinity binding, the LIGHT–HVEM *trans*-complex, may in turn, sterically compete with membrane BTLA from binding HVEM, thus acting in a noncompetitive fashion to disrupt inhibitory signaling by BTLA (Fig. 36.1c, left complex). We propose that the proximity of TNF homology domain of LIGHT to the membrane surface could prevent BTLA from engaging HVEM when HVEM engages LIGHT in *trans*. Similarly, the close proximity of the base of the LIGHT trimer to the membrane surface would also prevent access of gD to CRD1 of HVEM (Fig. 36.1c, left complex). However, the inherent flexibility of the GPI linkage in CD160 might allow CD160 to accommodate the steric requirement for the formation of the membrane LIGHT–HVEM–CD160 trimolecular complex (Fig. 36.1c, right complex).

The LIGHT–HVEM–BTLA/CD160 cosignaling system has the potential to simultaneously deliver stimulatory and inhibitory signals between interacting cells. Clear evidence indicates that HVEM–BTLA play a counter-regulatory role with the LTβR system in controlling dendritic cell proliferation within lymphoid tissues [5]. *Cis*-association between HVEM and its unconventional ligands, as well as the formation of the higher ordered trimolecular complexes with soluble LIGHT and LTα add additional levels of regulatory complexity in the LIGHT–HVEM– BTLA/CD160 system. The outcome of the signal transduction process mediated via HVEM not only depends on the timing of expression of individual signaling molecules, but also the distinctive combinations of molecules within the *cis*- and *trans*-complexes.

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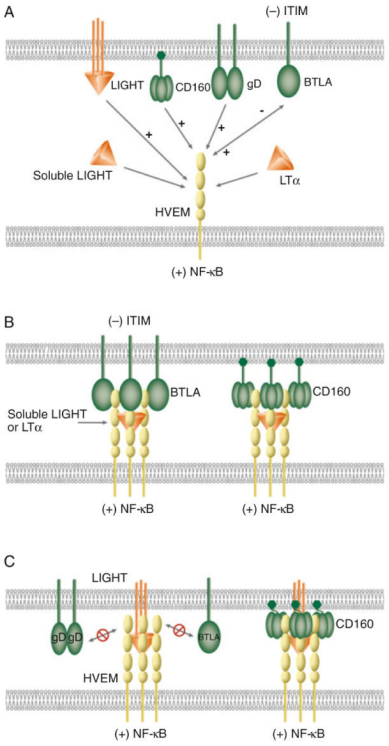

Fig. 36.1.

Schematic illustrations of molecular interactions between HVEM and its ligands. (**a**) Canonical and unconventional ligands of HVEM. LIGHT and LTα are the canonical ligands as well as positive activators of HVEM. Ligation of LIGHT or LTα activates HVEM-dependent NF-κB signaling. BTLA, CD160, and HSV gD serve as unconventional ligands for HVEM. Ligation of CD160 or gD to HVEM induces NF-κB activation. Bidirectional signaling occurs between HVEM and BTLA. HVEM-mediated BTLA signaling induces tyrosine phosphorylation of the ITIM in BTLA, providing an inhibitory signal to T cells. BTLA, CD160, and gD bind HVEM at the CRD1, but LIGHT and LTα interact with HVEM in the CRD2 and 3. The binding of gD to HVEM blocks HVEM binding to LIGHT or BTLA (not shown in diagram). (**b**) Cooperative binding between soluble LIGHT, LTα, HVEM, BTLA, and CD160. *Left complex* shows formation of a LIGHT–HVEM–BTLA trimolecular complex with three molecules of soluble LIGHT, HVEM, and BTLA. *Right complex* shows the assembling of LIGHT–HVEM–CD160 trimolecular complex with three molecules of soluble LIGHT and HVEM, and nine molecules of CD160. (**c**) Model of membrane LIGHT, HVEM, BTLA, and CD160 interaction. Membrane LIGHT competes with BTLA for the binding with HVEM. The binding of membrane LIGHT to HVEM prevents BTLA or gD from binding to HVEM due to membrane restriction (*left complex*). The flexibility of the GPI-link in CD160 may accommodate the membrane restraint for the formation of membrane LIGHT–HVEM–CD160 trimolecular complex (*right complex*)