

The DARC conspiracy – virus invasion tactics

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Is there a ‘conspiracy’ at work among viral pathogens? Apparently, yes. Rabies virus, lenti- and retroviruses, and herpesviruses, the ‘co-conspirators’, target select members of the tumor necrosis factor (TNF) receptor superfamily to invade the cells of their host. The intrigue deepens, as several reports have revealed that the viral envelope proteins interact with the cellular TNF receptor in a highly conserved region of previously unknown function. Targeting of this region by diverse pathogens suggests that a selective advantage is acquired. This advantage might involve regulation of the immune response, because recent investigations of the herpesvirus entry receptor demonstrated that this conserved region engages an inhibitory co-receptor governing T-cell activation.

Introduction

Unsurprisingly, a wide range of viruses, including pox-, adeno-, herpes-, flavi- and others, use specific mechanisms to target tumor necrosis factor (TNF)-related cytokines and their signaling pathways to regulate cell death and survival functions [1,2]. The TNF signaling pathways can counteract several strategies used by different viruses, particularly in altering cell death and survival, which provide strong selective pressures for pathogen evolution. Nonetheless, given that entry is the first step in the viral replication cycle and the first contact with host defenses, the variety of DNA and RNA viruses that converge on the TNF receptor superfamily as an entry mechanism is remarkable. The attachment proteins in the virions of herpes simplex virus (HSV)-1 and HSV-2 (large double-stranded DNA α -herpesviruses), avian sarcoma and leukemia virus (ASLV) (a positive-sense single-stranded RNA α -retrovirus), equine infectious anemia virus (EIAV) (a positive-sense single-stranded RNA lentivirus), feline immunodeficiency virus (FIV) (a positive-sense single-stranded RNA lentivirus) and rabies virus (RABV) (a negative-sense single-stranded RNA lyssavirus) converge on a small domain in the extracellular region of their respective TNF-receptor entry factors (Figure 1). No apparent homology in the sequences or structures of these viral envelope proteins exists to account for their common binding to TNF receptors. However, a close cross-examination of the interactions of the virion envelope glycoproteins with these cellular TNF receptors revealed the targeting of a common subdomain by these varied envelope proteins.

The TNF receptors serving as entry factors all share sequence homology in their extracellular ligand-binding domain but represent three branches of the TNF receptor superfamily, distinguished by their ligands and signaling pathways [3]. Herpesvirus entry mediator (HVEM, also known as TNFRSF14) and Ox40 (CD134, also known as TNFRSF4), the entry receptors for HSV, EIAV and FIV, initiate signaling by their specific TNF-related ligands through a motif that recruits the TNF receptor-associated factor (TRAF) adaptors; TRAF adaptors regulate key kinases that activate latent nuclear factor (NF) κ B transcription factors. NF κ B-activated genes, for example, B-cell CLL/lymphoma (*BCL*)2 and caspase inhibitors of apoptosis, are crucial for cell survival. TVB, the receptor for ASLV, is homologous to mammalian tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptor-2 (also known as death receptor-5 and TNFRSF10B), which initiates apoptosis through a caspase-recruitment death domain. The nerve growth factor receptor (NTRp75, also known as TNFRSF16) is the receptor for RABV and binds to several related neurotrophins, which are structurally distinct from the TNF ligands. The attachment site of the viral proteins is located near the N-terminus within the first cysteine-rich domain (CRD), a site distinct from where the TNF-related ligands bind. The cellular function(s) associated with this subdomain, although not fully characterized, are emerging from studies of HVEM and NTRp75.

TNF receptors – two sides to the story

The TNF receptor superfamily is defined by the pattern of cysteine residues in the extracellular region [3]. Generally, each CRD is formed by a highly conserved spacing of six cysteine residues, which pair-off to form an interlinked set of loops. In members of the TNF receptor family, the basic CRD is repeated from one to six times, creating an elongated extracellular domain (Figure 2). The TNF-related ligands engage the same face of the receptor, contacting residues in CRD2 and CRD3 [4]. TNF-related ligands are trimers, facilitating oligomerization (clustering) of the receptors in the membrane, the mechanism that initiates signal transduction cascades.

The notable exception to this rule is NTRp75, the other founding member of the TNF receptor superfamily. NTRp75 is part of the Nogo receptor complex that, together with Nogo-66 receptor (NgR)1 and LRR and Ig domain-containing Nogo receptor-interacting protein (LINGO)-1, represses axon regeneration when engaged by myelin-associated inhibitory factors [5,6]. NTRp75 is considered

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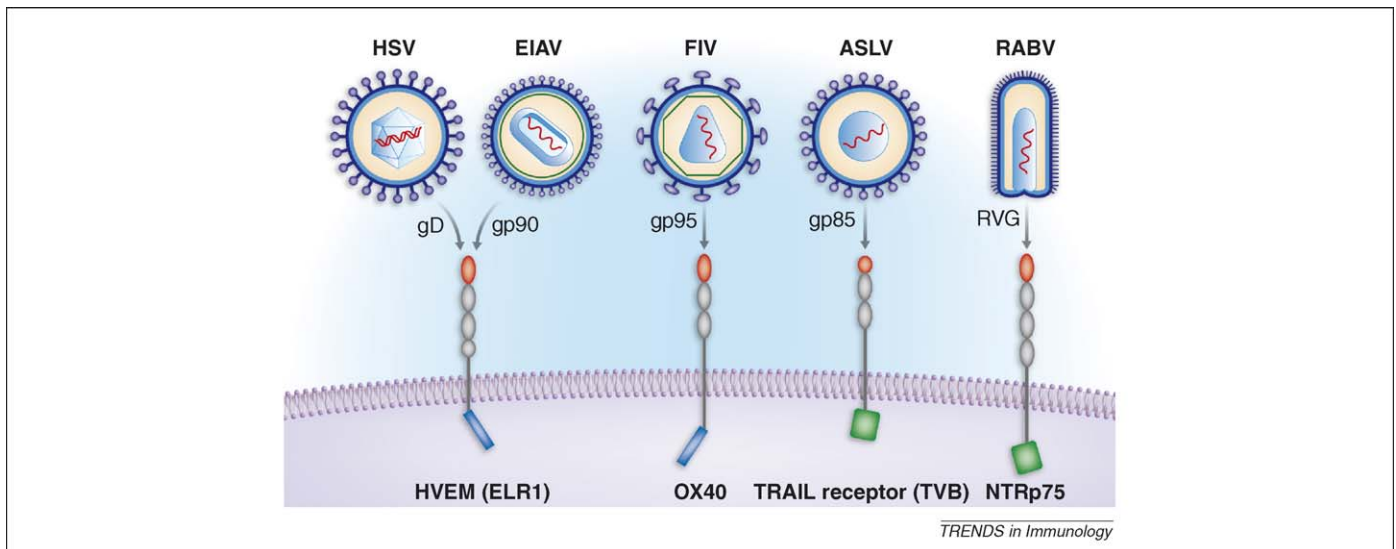


Figure 1. Widely divergent viral pathogens use TNFR superfamily receptors to mediate cell entry. Binding of HSV gD to CRD1 (red ovals) of HVEM triggers membrane fusion, releasing the viral nucleocapsid into the cytoplasm. Following gp90 interaction with the horse HVEM homolog, ELR1, EIAV gains entry through a pH-dependent endocytic pathway. The binding region for gp90–ELR1 has not yet been defined. The sequential interaction of FIV gp95 with OX40 CRD1 followed by CXCR4 initiates fusion between the viral and cellular membranes. ASLV gp85 binding of CRD1 of TVB, the avian homolog of TRAIL receptor 2, primes the viral fusion protein for pH-dependent fusion. RABV entry is mediated by endocytosis after the viral RVG protein binds to CRD1 of the p75 neurotrophin receptor. Functional death domains are shown as green squares and TRAF-binding regions are shown as blue rectangles.

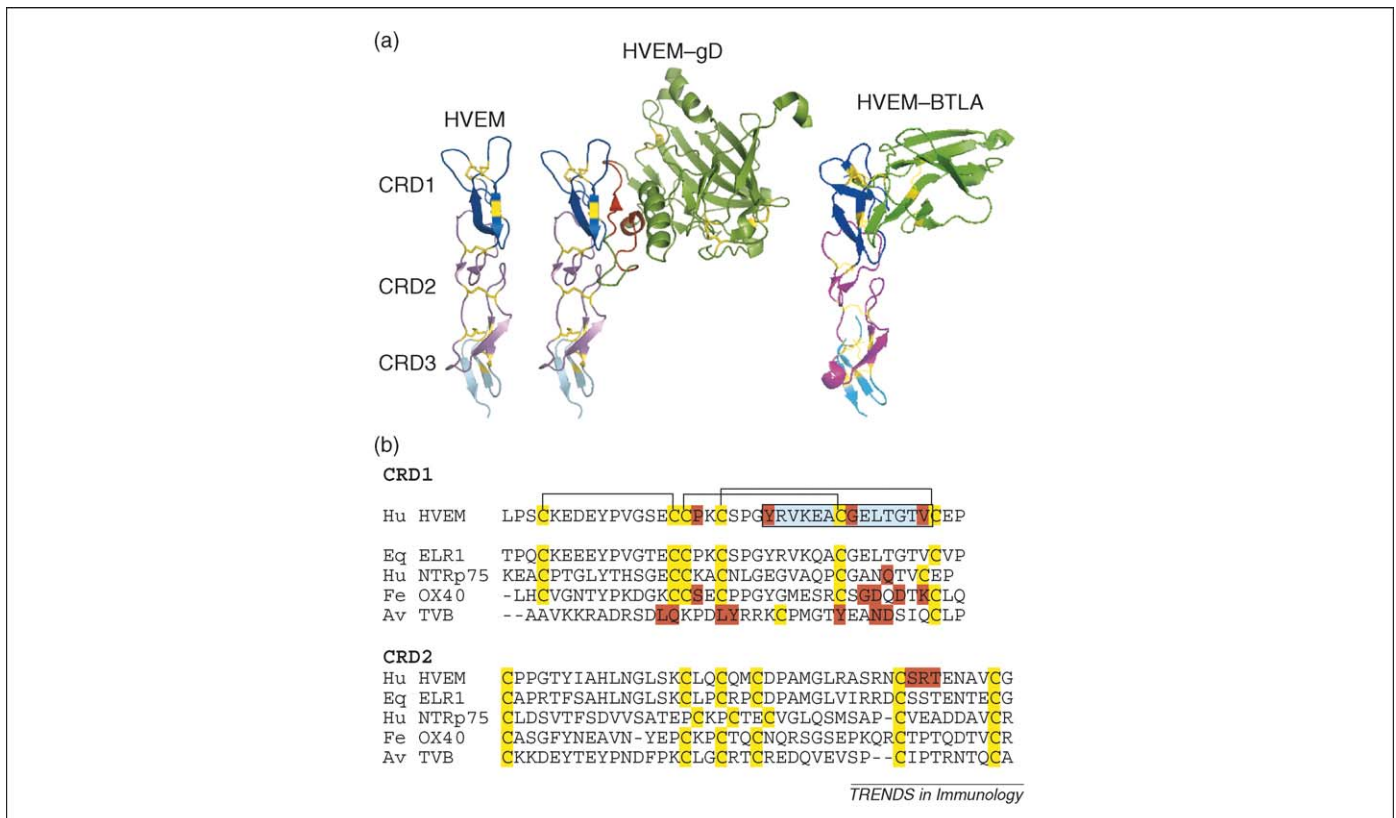


Figure 2. The attachment site on HVEM for herpes simplex virus gD. (a) The structure of the ectodomain of HVEM (left panel) is in ribbon format showing CRD1 (blue), CRD2 (magenta), CRD3 (gray) and disulfide bonds (yellow) in all structures. The C-terminus is oriented towards the bottom where it would transverse the membrane. The HVEM–gD complex is viewed from the side (middle panel) showing gD (green) and the residues in the hairpin loop of gD that contact HVEM (red) (from 1JMA.pdb in Ref. [10]). The HVEM–BTLA complex (right panel) is viewed from a similar angle to HVEM–gD, showing BTLA (green) (from 2AW2.pdb in Ref. [19]). Structures were drawn using PyMOL (<http://www.pymol.org>). (b) Sequence alignments of HVEM CRD1 and CRD2 with other TNFRs used as entry factors. Sequences of the ectodomains from the indicated TNFR were aligned using ClustalW. Note the conserved positioning of cysteines (yellow). TVB contains a truncated CRD1 with one disulfide bond. In human HVEM, the disulfide-bond patterns of the six cysteines are shown using lines. The BTLA binding site is shown as a blue box. The residues highlighted in red are necessary for virus entry. Abbreviations: Av TVB, avian (chicken) TRAIL receptor-2; Fe OX40, feline OX40 (CD134).

to be a branch point of the TNF receptor superfamily because, unlike the trimer configuration of TNF-related ligands, neurotrophins are dimers. Neurotrophins can promote neuron regeneration by counteracting the myelin-associated inhibitory factors. The interaction of nerve growth factor (NGF) occurs on the opposite face of NTRp75 from where a TNF ligand would bind, as revealed by the co-crystal structure elucidated by Garcia and colleagues [7]. NGF contacts two distinct sites on NTRp75, one near the junction of CRD1 and CRD2, the other at the junction of CRD3 and CRD4. However, the NGF dimer can only accommodate one NTRp75 owing to an induced conformational change that prevents oligomerization; thus, NGF suppresses inhibitory signaling through the Ngr1 complex.

Interestingly, CRD1 is highly conserved in several members of the TNF receptor superfamily. The viral protein attachment sites are distinct from where the TNF-related ligands bind, localizing at the N-terminus within CRD1. Until recently, this region did not have a clearly defined function, although it was known to contribute to TNF receptor-1 dimerization in the absence of TNF through a pre-ligand binding assembly domain (PLAD) [8]. However, the elucidation of the cellular receptor for HSV-1 predicted the importance of CRD1 as a contact point for entry and immune invasion.

The DARC side of HVEM

HSV-1 was the first pathogen identified to enter the cell through a member of the TNF receptor superfamily (named the herpesvirus entry mediator by Montgomery *et al.* [9]). The envelope glycoprotein D (gD) of HSV has an immunoglobulin (Ig)-like fold with an extended N-terminal hairpin loop that is required for entry through HVEM and 3'-O-sulfated heparan sulfate, but not for entry through nectins [10]. The crystal structure of the gD–HVEM complex located the binding site within CRD1 but on the side opposite to where the TNF-related ligand of HVEM, LIGHT, binds (Figure 2a) [10]. The binding interaction involves two segments of gD in the N-terminal hairpin loop, which contact two regions in CRD1 and one in CRD2 of HVEM. The location in CRD1 was unexpected because gD can antagonize the binding LIGHT in its membrane-anchored position [11], and, like other TNF receptors, HVEM binds to LIGHT in CRD2 and CRD3 [12].

The immunologic importance of the gD binding site in CRD1 of HVEM was unknown until the discovery of a novel co-receptor, B and T lymphocyte attenuator (BTLA). BTLA is a membrane glycoprotein containing a single I-type Ig domain that binds to HVEM [13] (Figure 2a). HVEM–BTLA interaction activates the inhibitory immunoreceptor tyrosine-based inhibitory motif (ITIM) of BTLA, resulting in the recruitment of phosphatases, for example, Src homology phosphatase-2 (SHP2), that limit signaling by T-cell antigen receptor-associated kinases [14]. Thus, HVEM-interaction with BTLA functions to suppress T-cell proliferation [13,15,16]. The binding sites for BTLA and gD on HVEM overlap within CRD1 [17,18]. Indeed, BTLA and gD compete for this site and use a similar binding mechanism: gD or BTLA interlock with HVEM through an intermolecular, anti-parallel sheet [10,19], thus implicating gD

as a viral mimic of BTLA. The BTLA- and gD-binding region is referred to as the DARC (gD and BTLA binding site on the TNF receptor HVEM in the cysteine-rich domain-1) side of HVEM [20]. The ability of HSV gD to antagonize HVEM–BTLA binding competitively, combined with the capacity of gD to block LIGHT–HVEM interaction, suggests that gD can nullify intercellular communication between host-cell-defense systems. HVEM-dependent signals could be disrupted by the virion during initial infection, or by gD expressed on the membranes of infected host cells. A selective advantage could arise by the disruption of HVEM–BTLA inhibitory signaling by alleviating constraints on cellular proliferation and/or survival, perhaps enhancing virus replication in selected cell types. Furthermore, there is no evidence that BTLA- or gD-binding to HVEM induces the same signaling pathways as LIGHT-binding, including the activation of NF κ B transcription factors. A probable advantage of blocking LIGHT–HVEM by gD is deduced from the role of LIGHT in cellular immunity.

LIGHT expressed by antigen-presenting cells can provide a powerful co-stimulatory signal through HVEM to promote T-cell activation, typically in conditions where antigen is limiting [21,22]. These types of co-stimulatory signals are probably most important during the initial HSV infection or when the virus re-emerges from its latent state. Thus, HVEM functions as a molecular switch, providing stimulatory signaling following LIGHT-binding or inhibitory signaling through BTLA-binding (Figure 3) [17,18]. The BTLA- and LIGHT-binding regions containing the core elements of CRD1 and CRD2 are encoded in a single exon, reflecting their evolutionary linkage as a functional unit, which is consistent with the idea of a molecular switch. Regulation of the HVEM switch is slightly more complicated in that soluble LIGHT (resulting from cleavage by cellular sheddases) can occupy HVEM simultaneously with BTLA, potentially enhancing multivalent interactions and initiating bidirectional signaling.

Interestingly, the human cytomegalovirus (a β -herpesvirus) gene *UL144* encodes the inhibitory components of the HVEM switch. *UL144* is an ortholog of HVEM that contains only CRD1 and CRD2; thus, *UL144* can bind to BTLA and inhibit T-cell activation [17]. However, *UL144* does not bind to LIGHT and, hence, its binding to BTLA cannot be antagonized, perhaps accounting for its potent inhibitory action on T cells when compared with HVEM.

LIGHT and HVEM are also connected to the TNF and lymphotoxin (LT)- $\alpha\beta$ signaling pathways through shared cellular receptors [23]. LIGHT engages LT β receptor, and HVEM binds to LT α [11], which also binds to the two receptors for TNF. Together, these cytokines form an integrated signaling circuit orchestrating inflammation and the development and homeostasis of lymphoid tissue microenvironments. Recent evidence indicates that the LT $\alpha\beta$ and LIGHT pathways are also important in controlling host defenses in response to cytomegalovirus [24], emphasizing the relevance of *UL144* as a potential mechanism for activating BTLA. The consequences of herpesvirus manipulation of the LIGHT–HVEM–BTLA pathway are unfolding but not fully realized, and are

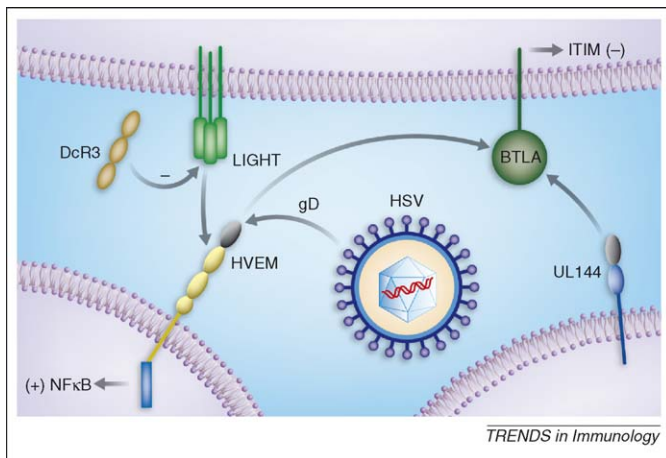


Figure 3. The HVEM switch is targeted by herpesvirus. The interactions involving HVEM that initiate positive co-signaling through LIGHT–HVEM interaction, or inhibitory signaling through HVEM binding to BTLA, are depicted. LIGHT bound to HVEM activates (+) TRAF-dependent activation of NFκB, whereas HVEM–BTLA acts through an ITIM motif of BTLA to recruit the phosphatase SHP2, attenuating (–) kinases activated by T-cell receptor (TCR) signaling. The HSV virion envelope protein gD attaches to HVEM, acting as an entry step for infection. The gD binding to HVEM can also competitively block BTLA binding, and noncompetitively block LIGHT binding, inhibiting both intercellular communication pathways. UL144 of human cytomegalovirus binds to BTLA but not LIGHT, selectively mimicking the inhibitory pathway of HVEM–BTLA. Decoy receptor-3 (DcR3) is a soluble TNFR family member that binds to LIGHT, acting as a circulating inhibitor of LIGHT–HVEM signaling. The CRD1 of each protein is shown as a gray oval.

the subject of current research. A recent study indicates that HSV virions can functionally inactivate T cells [25]. However, T cells are not considered to be a primary tissue for virus production. An alternate entry receptor, Nectin1, could be more important for targeting the virus to epithelial and neuronal cells for virus production [26]. Thus, the inactivation of adaptive immune defenses by the HSV virion might be an important selective pressure for retaining HVEM as an entry point.

CRD1 – the common entry point

The DARC side of HVEM, which engages BTLA and gD, shows homology with the CRD1 sites in the entry receptors engaged by RABV [27], ASLV [28], and FIV [29] (Figure 2b).

Rabies virus G protein (RVG) engages the NTRp75 within CRD1; this was deduced from deletion mutants lacking each CRD. Residues important for binding were further mapped by taking advantage of the inability of RVG to bind to chicken NTRp75, despite the extensive sequence conservation between the human and chicken receptor [30]. Substitution mutagenesis of a crucial glutamine residue within CRD1 inactivated the entry function of NTRp75, pinpointing the contact region (Figure 2b). However, RVG does not compete with NGF-binding, even though a major contact point of NGF resides in this region [31]. NTRp75 binds to multiple ligands, lectins, prion proteins and beta-amyloid, and can use this receptor for trafficking between neuronal populations within the nervous system [32]. NTRp75 is not used by all lyssaviruses [33], and RABV can gain cellular entry through alternate receptors, including the nicotinic acetylcholine receptor and the neuronal cell-adhesion molecule [34]. This diversity of function leaves open the question of whether the immune system contributes to the selective

pressure that drives RABV to target the CRD1 region in NTRp75.

Ox40 functions as an entry receptor for FIV [29,35]. Ox40 co-operates with the chemokine receptor CXCR4 during viral entry, analogous to the infection of macrophages by HIV [36]. Receptor chimeras composed of the domains from feline and human Ox40 determined that FIV surface glycoprotein (gp95) binding required CRD1. Mutations in Asp60 and Asp62 inactivated binding to feline Ox40; however, the conversion of human Ox40 to enable FIV entry required additional substitutions within CRD1 (Figure 2b) [37]. The interaction of FIV gp95 with Ox40 does not block the binding of the soluble form of Ox40 ligand [38], although this interaction has not been tested using the membrane-bound ligand, which might be the functionally relevant form. The activation of CD4⁺ T cells induces Ox40 production, which then functions as a key survival factor important for memory T-cell differentiation [39,40]. The regulatory T-cell subset (Treg, CD4⁺CD25⁺), which limits the expansion of effector T cells, also produces high levels of Ox40 and, interestingly, supports increased FIV production [41], suggesting a possible selective advantage in modulating the Ox40 receptor system. Furthermore, Ox40 signaling on activated CD4⁺ T cells promotes memory-cell differentiation, whereas the same signal on CD4⁺CD25⁺ Treg cells abrogates inhibitory activity [42]. Elucidating whether or not FIV binding initiates Ox40 signaling will provide important insights into the selective advantage of targeting this receptor. If signaling is activated, FIV might use Ox40 as a way of regulating the immune response. If not, FIV could target Ox40 to enable replication in long-lived Treg and/or memory T-cell subsets.

Brojatsch *et al.* [28] identified the cellular receptor for ASLV subgroups B, D, and E as TVB, a structural homolog of the mammalian TRAIL receptor containing a functional death domain. Two different alleles exist: TVB^{S1} is a receptor for subgroups B, D, and E, whereas TVB^{S3} is recognized only by subgroups B and D. Furthermore, there are two functional forms of TVB^{S1}, one specific for ASLV-B and the other specific for ASLV-B and ASLV-E; CRD1 and 2 of TVB can form both receptor types [43]. The TRAIL receptor subfamily (in which there are four receptors in humans) differs from other TNFRSF members because they contain a truncated CRD1 [4]. The interaction of the ASLV gp85 with TVB^{S1} involves 101 amino acids at the N-terminal region of the receptor [43]. The allele encoding TVB^{S3} differs from that encoding TVB^{S1} by a single nucleotide change, which results in a Cys62Ser substitution in TVB^{S3} [44]. This cysteine residue is crucial for ASLV subgroup E binding but is not required for subgroup B binding; thus, subgroup B viruses bind to the receptor independently of its native conformation [45]. Interestingly, a peptide corresponding to amino acids 32–46 of TVB^{S1} was identified that bound to ASLV-B and enabled entry into receptor-negative cells [46]. Mutagenesis of the peptide identified four amino acids necessary for the interaction with ASLV-B, namely Leu36, Gln37, Leu41 and Tyr42 (Figure 2b). In addition, Tyr67, Asn72 and Asp73 were found to be important for ASLV-E receptor interaction [47]. Subgroups B and D of ASLV induce cytopathic effects in infected cells, and the surface envelope of

ASLV-B induces the apoptosis of TVB-expressing cells, demonstrating that TVB is a functional death receptor [48]. This suggests the ASLV envelope protein acts as a virokine mimicking the cellular ligand, providing support that apoptosis induction is a powerful selective pressure. However, the situation is complicated because not all ASLV subgroups induce cytopathic effects, and death might involve more than death receptor signaling [49].

The macrophage- and dendritic-cell-trophic EIAV uses the equine ortholog of HVEM, equine lentivirus receptor (ELR)1, as an entry route through the binding of surface protein gp90 [50]. Virus entry involves a pH-dependent endocytic pathway but, unlike other lentiviruses, does not require CXCR4 or CCR5 as a co-receptor.

Thus, with two distinct viruses targeting HVEM as an entry factor, is the 'conspiracy' confirmed? This 'conspiracy theory' is certainly reinforced by the several other viruses that specifically target the CRD1 region. Nonetheless, a conviction of this 'co-conspirator' will require identifying the binding site for EIAV, which is highly anticipated.

Conspiracy revealed?

The observation that CRD1 is a common target of divergent viruses fuels speculation regarding the nature of the selective pressures provided by this host-virus interface. The gD-HVEM story provides compelling evidence that this specific entry point on the DARC side of HVEM provides a selective advantage for HSV by modulating cytokine signaling and, hence, immune function. Intriguingly, CRD1 is conserved in several of the soluble TNF receptors present in poxvirus (e.g. T2 Myxoma and G4R Variola virus) [51], although these proteins are not used as entry factors. Is there an immune or host-defense function modified by these different viruses within the CRD1 regions of TRAIL receptor, NTRp75, Ox40 and others that is absent in our current understanding of the biology of these receptors, or is the selective pressure directed elsewhere, for example, in determining host or tissue range? One clue to identifying the selective pressure might come from determining whether the viral entry factor alters signaling by membrane-bound forms of the TNF ligands. The known immune functions for TRAIL receptor in regulating cell death and Ox40 in promoting cell survival make teleological sense but what about NTRp75? Recent evidence indicates that blocking the myelin-associated inhibitor factor Nogo A, which engages the NgR1 complex containing NTRp75, suppresses the encephalitis induced by autoimmune T cells [52], suggesting that this RVG-targeted pathway participates in immune function. In this regard, the inhibitory signaling activities might be more similar between HVEM and NTRp75 than previously suspected. The common step in entry for viruses with different infection strategies also indicates the importance of the DARC side. The challenge for us is the translation of this knowledge into therapeutic strategies for improved host counter-defenses.

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