The dual-function CD150 receptor subfamily: the viral attraction

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The CD150 subfamily within the CD2 family is a growing group of dual-function receptors that have within their cytoplasmic tails a characteristic signaling motif. The ITSM (immunoreceptor tyrosine-based switch motif) enables these receptors to bind to and be regulated by small SH2 domain adaptor proteins, including SH2D1A (SH2-containing adaptor protein 1A) and EAT-2 (EWS-activated transcript 2). A major signaling pathway through the prototypic receptor in this subfamily, CD150, leads to the activation of interferon- γ , a key cytokine for viral immunity. As a result, many viruses have designed strategies to usurp or alter CD150 functions. Measles virus uses CD150 as a receptor and *Molluscum contagiosum* virus encodes proteins that are homologous to CD150. Thus, viruses use CD150 subfamily receptors to create a favorable environment to elude detection and destruction. Understanding the CD150 subfamily may lead to new strategies for vaccine development and antiviral therapies.

A functional hierarchy of coreceptor molecules regulates the immune responses of T, B and natural killer (NK) cells initiated *via* antigen receptors on T and B cells or *via* NK cell receptors. Some coreceptors like CD154 (CD40L), CD28 or inducible costimulator (ICOS) transmit mainly positive costimulatory signals¹, whereas others—such as CD152 (CTLA-4), Fc γ RIIb, killer cell inhibitory receptors (KIRs) or leukocyte immunoglobulin (Ig)-like receptors (LIRs)—function principally as inhibitory receptors². However, a more flexible form of immune regulation involves receptors that can function as either positive or negative regulators. To mediate more than one function, the CD80 and CD86 receptors use different counter-receptors: activating CD28 or inhibitory CD152¹.

Another group of dual-function coreceptor molecules, the CD150 subfamily within the CD2 family of receptors (**Fig. 1**), mediates different functions depending on the availability of downstream molecules within their signal transduction pathways. This group of receptors has attracted interest due to the discovery of a small SH2-containing adaptor protein SH2 domain protein 1A (SH2D1A, also known as SAP or DSHP)^{3–5}. Critical mutations in the *SH2D1A* gene are found in patients

with X-linked lymphoproliferative disorder (XLP), B cell non-Hodgkin's lymphoma, some cases of common variable immunodeficiency syndrome and familial hemophagocytic lymphohistiocytosis—immunodeficiencies with impaired antiviral immune responses^{3–9}. SH2D1A binds to a conserved immunoreceptor tyrosine-based switch motif (ITSM), TxYxxV/I, in the cytoplasmic tail of CD150 subfamily molecules. By binding to ITSMs, SH2D1A regulates the association of these receptors with SH2-containing molecules and, in this way, serves as a signaling 'switch'. The most characteristic feature of the CD150 subset of receptors is the presence of two or more ITSMs in their cytoplasmic tails.

The CD2 receptor family

The CD2 family of receptors is part of the immunoglobulin (Ig) superfamily, which currently includes 11 cell surface molecules (**Fig. 1a**): CD58 (LFA-3), CD2 (E-rosette receptor, sheep red blood cell receptor, LFA-2, T11), BLAME (B lymphocyte activator macrophage expressed, BCM-like membrane protein), SF2001 (CD2F-10), NTB-A (SF2000, Ly108), CD84 (Ly9B), CD150 (IPO-3, SLAM), CD48 (BCM1, Blast-1, OX-45), CS1 (19A24, CRACC), CD229 (Ly9) and CD244 (2B4, NAIL)^{10–18}.

The genes of the CD2 family map into two clusters (**Fig. 1b**): *CD2* and *CD58* are on the short arm of chromosome 1 (1p13), separated from the other members, which are clustered close together on the long arm of chromosome 1 at bands 1q21–24^{15,18–20}. With the exception of *CD58*, mouse orthologs of all these genes have been identified. Genomic location and sequence similarities support the hypothesis that the CD2 family arose from an ancestral gene *via* successive duplications^{20,21}.

The gene structure for all CD2 family receptors is similar in that the signal peptides and each of the Ig domains are encoded by a separate exon^{17,20}. All these receptors are type I transmembrane proteins with the exception of the glycosyl-phosphatidylinositol (GPI)-linked CD58 isoform and CD48. All CD2 family members that possess cytoplasmic tails have potential signaling functions except for BLAME and SF2001, which have not been studied yet.

The characteristic signature of the CD2 family is within the extracellular region: an N-terminal variable (V) Ig domain lacking disulfide bonds is followed by a truncated Ig constant 2 (C2) domain with two intradomain disulfide bonds (**Fig. 1a**). This configuration is duplicated in CD229^{12,14,17,18}. All CD2 family members are glycoproteins with extracellular N-linked glycosylation sites, but no putative O-glycosylation sites. These post-translational modifications may contribute to homo- and heterotypic adhesion of CD2 family receptors. CD2 family receptors are expressed predominantly on hematopoietic cells, including T and B cells, NK cells, monocytes, tissue macrophages, mature dendritic cells (DCs), myeloid cells and platelets. CD48, CD150 and CS1 are up-regulated upon activation *via* antigen receptors, CD40, Toll-like receptors and by mitogens or cytokines^{10,15,22,23}.

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Figure 1. Structure and chromosomal location of CD2 family receptors. (a) Receptors are placed in the same order as their genomic location. The arrows indicate the gene orientation. (b) Location of CD2 family genes on human chromosome 1.

Several receptor-ligand pairs have been identified within the CD2 family. Human CD2 has two counter-receptors: CD48 (low affinity) and CD58 (high affinity). CD48 is also a high affinity counter-receptor for CD244^{12,19}. However, the ligands for other CD2 family members are not known, although CD150 may be a very low affinity homophilic ligand for itself^{24,25}.

The CD150 receptor subfamily

The CD150 subfamily consists of CD150 along with CD84, CD229, CD244, NTB-A and CS1. The criteria for defining this subfamily within the CD2 family are the presence of at least two ITSMs in the cytoplasmic tails of the receptor and binding of the adaptor protein SH2D1A and/or a related SH2-domain adaptor, EWS-activated transcript 2 (EAT-2), to these ITSMs. CD150 functions as a coreceptor in T and B cells, whereas CD244, CS1 and NTB-A regulate NK cell-mediated cytotoxicity^{10,11,13,15,26}. CD244 and NTB-A can exert both activating and inhibiting effects on NK cells^{13,15,27}. Signaling via CD150 can augment TCR-mediated cytotoxicity and directly trigger cytotoxicity in *Herpesvirus saimiri*-infected T cells²⁸. CD150 and CD244 ligation can also induce secretion of interferon- γ (IFN- γ), a key cytokine for immunity to viruses, by T helper type 1 (T_H1) and NK cells, respectively^{26,29}. Cross-linking CD150 also promotes T cell receptor (TCR)-induced proliferation and induces proliferation of human memory T cells in a CD28-independent manner^{11,30}. In addition, signaling via CD150 enhances B cell proliferation and antibody production^{10,24} while promoting CD95-mediated apoptosis in B and T cell lines^{31,32}. The functions of other CD150 family members remain unknown, although CD84 is expressed at high amounts on some splenic memory B cells, which suggests a possible role in the regulation of B cell differentiation³³.

ITSM and signaling via CD150 subfamily members

The ITSM present in CD150 family members is different from the well defined immunoreceptor tyrosine-based activation motifs (ITAMs, D/ExxYxxL/I(x)₆₋₈YxxL/I) in B cell receptor (BCR) and TCR complex molecules. Upon phosphorylation, these ITAM-containing molecules—which include Ig α and Ig β and the ζ chain—recruit the protein tyrosine kinases Syk and ZAP-70³⁴. However, the ITSMs share similarities with the immunoreceptor tyrosine-based inhibitory motif (ITIM, I/VxYxxL/V(x)₂₆₋₃₁I/VxYxxL/V) found within cytoplasmic domains of ‘inhibitory receptor superfamily’ members such as Fc γ RIIb, CD22, CD72, KIR, PIR-B, p49B, ILT and LAIR^{2,34}. The ITIM-containing

receptors generally inhibit activation receptors by recruiting the SH2-containing tyrosine phosphatases SHP-1 and SHP-2 or the SH2-containing inositol phosphatase SHIP². Like ITIMs, ITSMs appear to be tyrosine phosphorylated by Src family kinases^{35,36} (and unpublished data) and, after tyrosine phosphorylation, also bind key SH2-containing components of signal transduction pathways, such as SHP-1, SHP-2 and SHIP^{5,31,35,37}. Notably, unlike ITIMs, ITSMs bind directly to the adaptor molecules SH2D1A and EAT-2 as well as to Src family kinases, including Fyn, FynT, Lyn and Fgr and to the p85 regulatory subunit of phosphatidylinositol-3 kinase (PI3K)^{5,15,19,31,35,36,37-39}. In other words, ITIMs and ITSMs bind distinct but overlapping sets of molecular components of signal transduction pathways.

Other ITSM-containing molecules

Using protein sequence database searches, the list of ITSM-containing molecules has been broadened (Fig. 2a)⁴⁰. Search results for CD150, CD244, CD84 and CD229 alignment revealed homology to several members of the signal-regulatory protein (SIRP, also known as SHPS-1) family: SHPS-1, BIT and MYD. Structurally, these sequences are highly related to each other and contain two ITSM-like motifs that alternate with ITIM-consensus motifs. The cytoplasmic tail of SHPS-1 is also able to bind the SHP-2 phosphatase.

Several members of the Siglec family also have ITSMs. The cytoplasmic domains of Siglec-3 (CD33), Siglec-5 (OB/BP2), Siglec-9 and Siglec-10 all have the same pattern of tyrosine-based motifs with a ITSM-like motif situated 3–7 residues from the C terminus and preceded by a conventional ITIM motif (Fig. 2a). CD31 (PECAM-1) also shows the same distribution of ITSM and ITIM.

The carcinoembryonic antigen (CD66) superfamily members Bgp-1, Bgp-2 and C-CAM105 ecto-ATPase contain Y-based motifs whose sequence and position in the cytoplasmic domain are similar to the position and sequence of a consensus ITSM (Fig. 2a). Similar to CD150, which is a measles virus (MV) receptor⁴¹, both Bgp-1 and Bgp-2 are receptors for mouse hepatitis virus and, like CD150, all these molecules also have alternative truncated forms⁴².

ITSMs are present in the cytoplasmic tails of PIR-B and the PD-1 receptor (Fig. 2a). The PD-1 receptor is able to deliver either positive or negative signals and mutation of PD-1's ITSM abolished inhibitory activity, which suggests that this ITSM may ‘switch’ signaling functions of PD-1^{1,43}.

In some of the ITSM motifs, at least one additional conserved position can be indicated: a threonine or serine at the position –4 with

Figure 2. Structure and signal transduction pathways initiated via the CD150 receptor. (a) CD150 structure compared with other ITSM-containing receptors that also contain ITIMs. (b) SH2D1A-independent and SH2D1A-dependent pathways initiated via CD150. If SH2D1A is not binding CD150, then SHP-2 binds and promotes activation of only the Erk1 and Erk2 pathways. When SH2D1A binds CD150, then SHIP rather than SHP-2 binds and promotes the activation of both the Erk and Akt kinases.

respect to the ITSM tyrosine. This threonine or serine at position -4 is present in all ITSMs that bind the adaptor proteins SH2D1A or EAT-2. The ITSMs in CS1 do not have threonine or serine in this position and are not able to bind these adaptor proteins¹⁵. In addition, SH2D1A or EAT-2 can bind ITSMs only in the molecules where at least two ITSMs are present (CD150 subfamily). Thus, Siglec-10 with a single ITSM is not able to bind SH2D1A⁴⁴. Interestingly, CD84, CD150, CD229, CD244, C-CAM and murine Bgp-2 all have alternatively spliced forms, and the shorter isoforms possess only a single ITSM or have no ITSMs. It is possible that the alternatively spliced forms are unable to bind to SH2D1A and EAT-2 and cannot function to 'switch' signaling pathways. The broad distribution of ITSM-like tyrosine containing motifs in CD150 paralogs and other receptors indicates that these motifs are an important and structurally distinct group of tyrosine-containing regulatory motifs. Multiple alignments of ITSM-like motifs from distant paralogs of CD150 indicate that this kind of tyrosine-containing regulatory motif is highly conserved. However, much remains to be learned about ITSMs.

SH2D1A-dependent and -independent signaling

The paired ITSM motifs within the cytoplasmic tails in six members of the CD2 family (CD84, CD150, CD229, CD244, NTB-A and CS1) are likely to contribute to the established dual function of some of these receptors. The exact mechanism of how this switch works is not yet known. However, CD150 subfamily receptors are likely to signal via both SH2D1A-independent and SH2D1A-dependent pathways (**Fig. 2b**).

At least two signal transduction pathways are initiated via CD150 and other CD150-related receptors. CD244, CS1 and CD150 each can activate extracellular signal-regulated kinase 1 (Erk1) and Erk2 (**Fig. 2b**)^{15,26} (and unpublished data). These pathways require Ras, Raf, mitogen-activated protein kinase-Erk kinase 1 (MEK1) or MEK2 and SHIP but not SH2D1A^{15,26,28} (and unpublished data). Both SHP-2 and SHIP may contribute to CD150-mediated Erk1 activation. Tyrosine phosphorylated SHP-2 associates with Grb2, providing a link to the Ras-Erk pathway^{45,46}. SHIP can associate with Lyn and is a substrate for Lyn^{31,47}. Upon phosphorylation, SHIP recruits the adaptor protein Shc and may form a complex with Grb2⁴⁸ that may lead to Ras pathway activation and then to Erk1 and Erk2 phosphorylation.

CD150 or CD244 ligation also results in PI3K activation and PI3K-dependent Akt phosphorylation (**Fig. 2b**)^{31,39}. This pathway depends on SH2D1A and Syk expression. In addition, Akt phosphorylation is SHIP-independent and is negatively regulated by Lyn, Btk and SHP-2.

However, this pathway does not depend on tyrosine phosphorylation of either CD244 or CD150 or on association of these receptors with SH2D1A³⁹ (and unpublished data). SH2D1A most likely has multiple functions beyond simply binding to receptor molecules and may have a number of binding targets. SH2D1A can be detected both in membrane and cytosolic cell fractions⁴⁰ and binds to the adaptor protein Dok1⁴⁹. Apparently, regulation of PI3K-Akt pathway by SH2D1A is mediated via other adaptor proteins, such as Dok1, Dok2 or LAT³⁹ (and unpublished data).

The precise binding sites for SH2-containing molecules to ITSMs have been mainly defined for the CD150 cytoplasmic tail (CD150ct)^{5,35,36,40,50,51}. In both T and B cells, CD150 is expressed at a later stage of differentiation than SH2D1A^{5,19,40,52}. Because SH2D1A is able to bind even nonphosphorylated Y281 in the CD150ct^{5,50,53}, it is likely to be the first molecule that binds an ITSM in CD150. Binding of SH2D1A to Y281 in the CD150ct changes the conformation of the tail and exposes another tyrosine, Y307, for phosphorylation (unpublished data).

Binding of other SH2-containing molecules to CD150 depends on tyrosine phosphorylation, which can be initiated via the BCR complex, CD3 ligation or by CD150 ligation^{35,36}. CD45, which associates with CD150³¹, may be involved in this process, for example, through activation of the Src family kinases Lck (in T cells) or Lyn (in B cells), which phosphorylate Y307 in CD150ct³⁶ (and unpublished data).

Upon phosphorylation of CD150, pY307 serves as a binding site for Src family kinase FynT (T cells) and Lyn (B cells), which, in turn, become activated and phosphorylate Y327^{31,35,36} (and unpublished data). Phosphorylated Y327 then serves as a binding site for SHIP or SHP-2 (**Fig. 2b**)^{31,35,36,40}. Although SHIP binds CD150 only in combination with SH2D1A^{35,40}, SHP-2 in contrast binds CD150 only in the absence of SH2D1A, possibly due to competition for the binding sites^{5,36}. The initial hypothesis that SH2D1A functions as a natural blocker of interactions between SH2-containing proteins with CD150 seems to hold true only for the SHP-2 phosphatase. For Src family kinases and SHIP this adaptor protein facilitates rather than inhibits interactions.

CD150 is a receptor for measles virus

Coevolution of hosts and viruses has shaped not only the immune system, but also the countermeasures used by viruses. Different viruses evolved a number of diverse immunoevasive strategies. These include modulation of cell surface receptor and cytokine expression, the presence of cellular gene orthologs in the viral genome, hijacking of a cell's

signal transduction pathways by viruses so they can multiply or persist and use of cell surface molecules as viral receptors⁵⁴. A number of viruses have chosen CD150 subfamily receptors to maintain an equilibrium with the host and/or escape immunological surveillance^{42,55–57}.

Many viruses use cell surface glycoproteins, which possess Ig superfamily domains or complement control protein domains, also called short consensus repeats (SCRs) as receptors. These viruses tend to bind to the N-terminal (most membrane-distal) domains of the receptors. Some viruses—for example, HIV (binds CD4), rhinoviruses (binds CD54) and poliovirus (binds CD155)^{54,58}—bind to N-terminal Ig-like domains. Viruses that bind N-terminal SCRs in the complement system receptors include Epstein-Barr virus (EBV, binds CD21) and enterovirus 70, echoviruses and coxsackie viruses (all bind to CD55), whereas herpesvirus 6 and MV both use CD46^{59,60}. As an adaptation, MV developed the ability to bind not only the SCR in CD46, but also the Ig domain of CD150⁴¹ (Fig. 3).

MV belongs to the highly contagious morbillivirus family, which causes some devastating diseases in humans and animals. Other morbilliviruses, such as canine distemper virus and rinderpest virus, also use CD150 as a receptor, which explains why this family is lymphotropic⁵⁷. MV causes nearly 1 million deaths a year worldwide mainly due to its immunosuppressive potential.

CD46, a regulator of complement-mediated lysis, and CD150 both act as receptors for the vaccine and laboratory adapted strains of MV, as well as for wild-type MV from clinical isolates^{42,61–63}. CD150 mediates virus uptake and syncytium formation⁶³ and appears to be the key molecule mediating MV entry into monocytes^{64,65}. However, there may be additional MV receptors because not all MV tropism can be explained by the use of CD46 or CD150 as receptors⁶⁵.

The hemagglutinin (HA) protein of MV mediates interactions with both CD46 and CD150. Binding to CD46 but not to CD150 is dependent on the amino acid at position 481 in MV-HA. This suggests that binding sites for CD150 and CD46 on MV-HA are distinct, demonstrating adaptation where a virus has evolved different binding sites for distinct receptors⁶³. The V domain of human CD150 is essential for its function as a MV receptor and is necessary and sufficient to interact with MV HA protein and allow viral entry. If the mouse V domain replaces the V domain of human CD150, then CD150 no longer can act as a receptor for MV, explaining MV's inability to infect mice⁶⁶.

What immunosuppressive effects of MV can be explained by binding to CD150? Paradoxically, lymphopenia and numerous abnormalities of immune reactions accompany immune activation during measles infection. Delayed-type hypersensitivity (DTH) skin test responses to recall antigens such as tuberculin disappear and are accompanied by an increase in susceptibility to opportunistic infections⁶⁷. MV-induced lymphopenia and immunosuppression could be attributed to viral destruction of lymphocytes expressing CD150. Few resting T cells express surface CD150, but the number of CD150⁺ cells increase after T cell activation. Because clones of T_H1 cells express higher amounts of CD150 than clones of T_H2 cells²⁹, it is possible that MV may preferentially target and kill or disable T_H1 cells. Destruction or impairment of the T_H1 subpopulation would promote the T_H1 to T_H2

shift characteristic for measles infections^{62,67}. Alternatively, MV binding may down-regulate expression of CD150, similar to CD46 down-regulation^{68,69}, so that less CD150 is available for promoting IFN- γ production and, therefore, T_H1 responses.

In addition, MV suppresses cell-mediated immunity by interfering with the survival and function of DCs^{70,71}. Presumably, CD150 may be required for or contribute to MV interactions with DCs. CD40 ligation, which induces CD150 on DCs²², also enhances MV accumulation in infected DC cultures^{70,71}. MV-infected DC cultures do not stimulate allogeneic T cell responses or even inhibit T cell proliferation^{67,72}. This effect of MV could be a consequence of CD95-mediated apoptosis induced in DCs by MV⁷¹ and is also likely to involve CD150, as antibody ligation of CD150 favors CD95-mediated apoptosis in some B and T cell lines³¹. Thus, the fact that CD150 is a major MV receptor could explain some of the immunosuppressive effects of MV.

Patients with measles and contact-mediated immunosuppression have reduced lymphoproliferative responses^{68,72}. It is possible that MV-induced up-regulation of GADD153, which blocks transition from the G1 to the S phase of the cell cycle, is involved in this process⁷³. However, neither CD150 nor CD46 are involved in MV contact-mediated inhibition of proliferation^{68,72}. Thus, MV uses CD150 as a common cell surface receptor for viral binding and entry into cells. Binding to CD150 can explain many but not all of the immunosuppressive effects of MV. However, revealing the functions and signal transduction pathways initiated *via* CD150 will help to improve strategies for measles control and elimination.

Another example of an immunosuppressive effect that viruses exert *via* CD150 is HIV-1 (Fig. 3). Patients with acute HIV-1 infections show decreased CD150 expression on T cells, which correlates with impaired cell-mediated (T_H1) responses⁷⁴. This effect may be related to CD150-mediated promotion of DC-dependent HIV-1 expression²².

Molluscum contagiosum virus and CD150

Viruses often camouflage themselves with host cell membrane. *Molluscum contagiosum* virus (MCV), a member of poxvirus family⁷⁵, mimics CD150 receptor. MCV causes benign skin tumors primarily in children and young adults that persist for many months with only a weak immune response and minor inflammation. In immunocompromised individuals, especially in HIV-infected patients, MCV causes a serious and untreatable opportunistic infection that is characteristic of late stage cellular immunodeficiency^{56,75,76}. The evolution of poxviruses resulted in the acquisition and development of viral homologs of cellular immunoregulatory genes involved in the host response to infection. Well known examples are “cytokine response modifiers” for the cowpox virus immunomodulatory genes, soluble viral cytokine receptors and inhibitors of caspases⁵⁶. An analysis of the complete coding sequence of the 190-kbp MCV genome revealed that MCV encodes not only conserved homologs of all poxviral proteins essential for transcription and replication, but also encodes three families of distinct immunoregulatory proteins^{75,76}. One family includes two proteins containing duplicated death effector domains and may be used in a viral

Figure 3. CD150 subfamily viral connections. Different viruses regulate receptor expression, signaling function or produce receptor surrogates, as illustrated for the CD150 receptor.

anti-apoptotic strategy⁵⁶. Two other families encode membrane proteins with predicted Ig domains: one has a weak homology with human CEA and another family was named the viral SLAM or viral CD150 gene family^{75,77}. The viral CD150 family includes three genes that encode mc002L, mc161R and mc162R, which are transmembrane proteins that are homologs of CD150^{56,75,77}. Both mc002L and mc161R mRNAs are expressed in MCV infected human tissues and MCV infected cultivated human fibroblasts⁷⁷. These genes are transcribed early during the MCV lifecycle, within 2 to 3 h after MCV infection of human fibroblasts⁷⁷. The absence of animal models for MCV infection makes it difficult to analyze the role these genes play in MCV infection. However, experimental models of cell cultures transfected with viral homologs of CD150 will help to clarify their role in the inhibition of host immune responses to MCV. These CD150 homologs may act as 'surrogates' and compete with CD150 for its natural ligand. They may also bind to transmembrane or soluble forms of CD150 that initiate signal transduction pathways and thereby block or alter the antiviral signaling functions of CD150.

The CD150 subfamily, SH2D1A and EBV

XLP is an immunodeficiency associated with dysregulated T, B and NK cells in the settings of primary EBV infection³⁻⁵. Because *SH2D1A* is altered in XLP patients, CD150 subfamily receptors—which can interact with SH2D1A—are attractive candidates for modifiers affecting the pathogenesis and clinical manifestations of XLP. Although it is clear that mutations in *SH2D1A* are responsible for most cases of XLP, the exact role EBV plays in the pathogenesis of this disease is unclear. In one study, 12% of over 300 patients with XLP were not infected with EBV at the time of first clinical manifestations and there was no correlation between age of onset or survival of XLP patients and EBV status⁷⁹. Thus, EBV may be a common accelerator of XLP, however, other still unidentified factors or modifier genes are important.

EBV does appear to regulate expression of members of the CD150 subfamily and their ligands. Whereas little or no CD150 is expressed on resting T and B cells, it is up-regulated by mitogenic stimuli, and EBV-transformed B cell lines, EBV⁺ Burkitt's lymphomas and HTLV-1-transformed T cell lines express high amounts of CD150^{10,52,62,79}. Ligation of CD150 on either human or mouse T cells induces production of IFN- γ ^{29,30}. EBV also indirectly induces activation of wild-type NK cells through the SH2D1A-binding receptors NTB-A and CD244^{13,80-82}. Nevertheless, studies of XLP patients and SH2D1A-deficient mice reveal impaired functions of T lymphocytes and NK cells^{81,83-85}. XLP patients with mutations in *SH2D1A*, when infected with EBV, can show an uncontrolled expansion of CD8⁺ T cells that does not effectively destroy EBV-infected cells¹⁹. In addition, although mice deficient in SH2D1A when infected with lymphocyte choriomeningitis virus (LCMV) make more IFN- γ -producing cells and anti-LCMV CD8⁺ cytotoxic T cell responses, they still are more susceptible to LCMV-induced morbidity and mortality. This may be because they have increased and dysregulated T_H1 responses due to defective CD150-mediated signaling in T cells^{86,87}.

Signals via NTB-A and CD244 receptors also inhibit NK cells from XLP patients missing SH2D1A^{13,21,80,81,88}. This suggests that the altered function of CD244 and NTB-A without SH2D1A accounts, in part, for the inability of XLP-NK cells to kill EBV-infected target cells. On the other hand, SH2D1A may play a role in cell differentiation and the absence of functional SH2D1A may prevent the normal process of maturation into functionally active NK cells. In this case, upon CD244 ligation, the SH2D1A-deficient NK cells would respond like immature cells and would not be efficient effector cells²⁷. Also, B cells from XLP

patients after CD40 ligation becomes more responsive to CD95-mediated apoptosis^{31,32}.

SH2D1A may regulate B cells as well as NK cells and T cells. Because SH2D1A was initially detected in T lymphocytes and NK cells, it was proposed that XLP develops due to SH2D1A dysregulation in NK cells and/or T cells^{55,89}. Nevertheless, defects in T and NK signaling cannot be completely responsible for such phenotypic manifestations of XLP as dysgammaglobulinemia and B cell non-Hodgkin lymphomas^{6,7}. In fact, SH2D1A is expressed in a subpopulation of germinal center (GC) B cells⁴¹ and in EBV⁺ Burkitt's lymphomas with a GC phenotype⁵². Thus, it is possible that defects in the signaling of SH2D1A-binding CD150 subfamily members in B cells as well as other cells contribute to the pathogenesis of XLP.

In summary, CD150-subfamily receptors are involved in antiviral immune responses and many viruses have chosen CD150 family receptors as targets for immune evasion and regulation (Fig. 3). During long coevolution with their hosts, viruses acquired mechanisms enabling them to divert or alter immune surveillance. Further understanding of how viruses regulate or bypass CD150 subfamily-mediated antiviral immunity will help us not only to understand the physiological functions of these receptors but also to design better strategies for vaccines and antiviral therapy.

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