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Hyaluronidase 2 and its intriguing role as a cell-entry receptor for oncogenic sheep retroviruses

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Abstract

Jaagsiekte sheep retrovirus (JSRV) causes lung adenocarcinoma in sheep and goats, while the closely-related enzootic nasal tumor virus (ENTV) causes nasal tumors in the same species. The envelope (Env) protein from either virus can transform fibroblasts and epithelial cells in culture, indicating that the Env proteins are responsible for tumorigenesis. However, the primary function of retroviral Env proteins is to mediate virus entry into cells by interacting with specific cell-surface receptors, suggesting that the virus receptor might be a key player in transformation as well. Thus identification of Hyaluronidase-2 (Hyal2) as the cell-entry receptor for both JSRV and ENTV suggested a role for Hyal2 in oncogenesis. Furthermore, Hyal2 is located in a key lung cancer tumor suppressor locus on chromosome 3p21.3, suggesting that Hyal2 might have a tumor suppressor activity that was disrupted by Env thereby leading to tumorigenesis. However, recent experiments showing that expression of the JSRV or ENTV Env protein in mouse lung can induce lung tumors, even though the viral Env proteins cannot bind to or utilize mouse Hyal2 as a receptor for virus entry into cells, indicate that Hyal2 plays no role in cancer induction by these retroviruses. Hyal2 remains an enigmatic member of the hyaluronidase family given its very low hyaluronidase activity in purified form or when expressed in cultured cells, suggesting that it may have evolved to perform some other as yet unknown function.

Keywords

hyaluronidase-2; jaagsiekte sheep retrovirus; enzootic nasal tumor virus; hyaluronidase; lung cancer

1. Oncogenic sheep retroviruses

Jaagsiekte sheep retrovirus (JSRV) causes pulmonary adenocarcinoma (also called sheep pulmonary adenomatosis or jaagsiekte) in sheep and goats [1]. JSRV-induced tumors arise from epithelial cells in the lower airway, and tumor cells express markers of type II alveolar and/or bronchiolar epithelial cells [2]. Two strains of a closely-related retrovirus called enzootic nasal tumor virus (ENTV) have been cloned from sheep (ENTV-1) [3] and goats (ENTV-2) [4] that share ~95% overall amino acid similarity with JSRV. ENTV can be found in the nasal fluid of animals with intranasal tumors, which eventually progress and cause severe cranial deformations and respiratory blockage, resulting in death [5]. JSRV and ENTV can increase production of lung and nasal fluid and can spread by aerosolization of virus present

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in these secretions. JSRV and ENTV are present in many countries worldwide and have a significant economic and animal health impact. In addition, the disease induced by JSRV exhibits histological features similar to those of many human pulmonary adenocarcinomas, and study of adenocarcinoma induced by JSRV and ENTV may provide insights into the etiology of human lung cancer. While ENTV and JSRV do not appear to cause lung cancer in humans having occupational exposure to these viruses, this possibility has not been definitively excluded.

Until recently, oncogenic retroviruses were divided into those that cause cancer with long latency and do so by insertional activation of host oncogenes, and acutely transforming retroviruses that rapidly induce cancer as a result of virus acquisition and expression of host cell oncogenes. For example, Moloney murine leukemia virus induces leukemia over weeks to months by insertional activation of host cell oncogenes such as *lck* and *myc*, while the acutely-transforming Harvey murine sarcoma virus carries a mutant cellular *ras* oncogene and can acutely transform cells in culture and in animals [6]. JSRV and ENTV are examples of a small but growing new class of retroviruses that are acutely transforming and induce cancer as a direct result of expression of viral genes that show no relation to host cell genes. In the case of JSRV, cancer induction can occur in as little as 10 days in newborn sheep [7], showing that it is acutely transforming, yet JSRV does not contain sequences related to mammalian genes. JSRV and ENTV are simple retroviruses (Fig. 1) that carry genes required for viral replication and that lack accessory genes typical of complex retroviruses or cell-derived genes typical of most acutely-transforming retroviruses. Analysis of the transforming activity of JSRV and ENTV in cell culture has revealed that the *env* genes of these viruses are necessary and sufficient to induce transformation [8–10]. The primary role of Env in viral replication is to promote virus entry into cells following binding to specific cell-surface receptors, and it seemed likely that these receptors might play a key role in transformation as well.

2. Identification of Hyal2 as the cell-entry receptor for JSRV and ENTV

Retrovirus entry into cells depends on the presence of specific proteins that bind the viral Env protein and help trigger conformational changes in Env that lead to fusion of the virus and cell membranes and entry of the virus core into the cell. A wide variety of proteins have been found to serve as receptors for different retroviruses, based primarily on their ability to promote virus entry after expression in cells that are not naturally permissive for virus entry (Table 1). In most cases, a single protein suffices to render otherwise nonpermissive cells susceptible to virus entry. Typically, these proteins promote virus binding, and may also promote virus fusion with the cell membrane. For other viruses (for example, HIV) there are distinct binding and fusion receptors that are required for virus entry. Retrovirus receptors are key determinants of the species and cell types that a retrovirus can infect, and thus are primary determinants of the host range and the type of disease induced by the virus.

To identify the cell-entry receptor for JSRV we used a retroviral vector that encodes human placental alkaline phosphatase (AP) and that was packaged into virions bearing the JSRV Env protein on the virion surface [11]. In early experiments we found that this vector could transfer and express (transduce) the AP marker protein gene to sheep and human cells, but not to rodent cells including those from mice, rats, and hamsters. This allowed us to develop a genetic screen to identify the human gene that when expressed in rodent cells would allow vector transduction. As target cells we used a set of 80 hamster cell lines carrying different fragments of DNA that had been produced by fusing hamster cells with irradiated human cells. This allowed us to identify the chromosomal location of the receptor within a few hundred kilobase pairs of DNA [11]. We were lucky to find that this region had been cloned as a set of overlapping cosmid clones, and it was relatively straightforward to identify the gene encoding the receptor by testing hamster cells for JSRV vector susceptibility following transfection of individual

cosmids into the cells [8]. This genetic analysis indicated that only one gene served as a receptor for JSRV, but to reinforce this conclusion, we tested all of the human hyaluronidase family members for receptor activity, and found no activity associated with human Hyal1, Hyal3, Hyal4, or Spam1 [8]. These data indicate that Hyal2 is the only protein in the human genome that functions as a JSRV receptor.

We also tested hyaluronidase family members from other species for receptor function to determine if receptor function correlates with the ability of the JSRV vector to transduce cells from different species (Fig. 2). Indeed, mouse Hyal2 functioned poorly as a receptor for JSRV vector cell-entry when expressed in mouse or hamster cells, consistent with the inability of the JSRV vector to transduce mouse cells [8]. In contrast, sheep Hyal2 functioned well as a receptor for JSRV vector cell-entry when expressed in mouse or hamster cells, consistent with the high susceptibility of sheep cells to JSRV vector transduction [10]. An intermediate result was obtained for rat Hyal2, where overexpression of rat Hyal2 in mouse, hamster, or rat cells rendered the cells susceptible to JSRV vector transduction, but rat cells are normally resistant to vector transduction [12]. Additional experiments showed that JSRV Env binds rat Hyal2 less well than it does human Hyal2, supporting the interpretation that higher levels of rat Hyal2 are required to promote efficient JSRV vector transduction than are normally expressed on rat cells [12]. In conclusion, these experiments show that expression of a functional Hyal2 protein is the primary determinant of JSRV Env-mediated virion entry into cells.

Using a retroviral vector encoding AP packaged into virions bearing either the ENTV or JSRV Env proteins on the virion surface, we found that ENTV Env promotes infection of a more restricted range of cell types than does the JSRV Env [10]. Given the similarity in ENTV and JSRV Env amino-acid sequences, we first tested whether ENTV Env might use Hyal2 for cell entry as does JSRV Env. Indeed, both sheep and human Hyal2 can serve as cell-entry receptors for virus bearing the ENTV Env. Interestingly, Hyal2 expression was not sufficient to promote entry of the ENTV vector into all cells, indicating that other factors are important for ENTV Env-mediated entry into cells [13].

3. Hyal2 location and enzymatic activity

Hyal2 was initially identified as a lysosomal hyaluronidase by addition of a green fluorescent protein (GFP) tag to the carboxy terminus of Hyal2 and by showing that GFP fluorescence localized to lysosomes after expression of the hybrid protein in a rat glioma cell line [14]. Hyal2 exhibited low but detectable hyaluronidase activity with an acidic pH optimum in these experiments. However, later studies have conclusively shown that Hyal2 is actually a glycosylphosphatidylinositol (GPI)-anchored cell-surface protein, consistent with its role as a cell-surface receptor for sheep retroviruses [8,12,13,15–17]. GPI-anchored proteins have an endoplasmic reticulum (ER) signal sequence at the amino terminus, which directs the proteins to the ER and is removed during protein translocation into the ER, and have hydrophobic carboxy termini that are replaced with a GPI anchor that tethers the proteins to the cell surface. The latter feature likely explains the original result indicating that Hyal2 was a lysosomal protein -the GFP tag added to the carboxy end of Hyal2 in those experiments was likely removed during GPI anchor addition and was sent to lysosomes for degradation, while the processed Hyal2 was exported to the cell surface.

Hyal2 exhibits very low hyaluronidase activity in comparison to Hyal1 or Spam1 under all conditions analyzed to date. While the hyaluronidase activity of Hyal2 could be detected in cells engineered to greatly overexpress Hyal2 by infection with a vaccinia virus vector encoding human Hyal2 [14], we have had difficulty detecting Hyal2 activity in cells transduced with a retroviral vector that encodes human Hyal2 [8]. Therefore we studied a soluble preparation of Hyal2 made by inserting a stop codon into the human Hyal2 cDNA at the position

of the GPI-anchor cleavage site, and by expressing this truncated protein in insect cells using a baculovirus vector [18,19]. The endoplasmic reticulum signal sequence is properly removed from the translated protein, and without the hydrophobic tail and GPI-anchor signal sequence, the protein is secreted from the cells. This secreted form of Hyal2 (sHyal2) corresponds exactly to native Hyal2 expressed on the cell surface except that it lacks the GPI anchor. The sHyal2 protein appears to be a properly-folded monomeric protein by size-exclusion chromatography and is stable in solution at 4°C for months. Initially, the hyaluronidase activity of purified sHyal2 appeared to have a neutral pH optimum [18], but we later showed that this was due to the presence of a very small amount of a highly active baculoviral hyaluronan lyase [19], and that the hyaluronidase activity of sHyal2 actually has an acidic pH optimum consistent with previous analysis of Hyal2 activity in cultured cells. This activity could be greatly reduced by mutation of amino acid residues that correspond to the active site residues common to the bee venom and Spam1 hyaluronidases, indicating that the active site for hyaluronan digestion in Hyal2 is similar to those of other hyaluronidases [19]. However, the hyaluronidase activity of sHyal2 is ~400-fold lower than that of Spam1 [19].

The availability of purified sHyal2 allowed us to further analyze the kinetics of hyaluronan degradation by Hyal2 [18,19]. Others have noted a 20 kDa intermediate of hyaluronan degradation that appeared to be uniquely associated with hyaluronan degradation by Hyal2, and that this intermediate did not disappear even after prolonged incubation with Hyal2 [14]. We also find this intermediate following digestion of hyaluronan with sHyal2, but in contrast, this intermediate can be completely digested following prolonged incubation with sHyal2. Indeed, similar kinetics of hyaluronan digestion are observed for Hyal1 and Spam1, with initial rapid digestion of hyaluronan to a 20 kDa intermediate followed by a 25-fold slower digestion of the 20 kDa form to smaller products. Thus digestion of hyaluronan by Hyal1, Hyal2 and Spam1 appears to follow similar biphasic kinetics involving a relatively stable 20 kDa intermediate corresponding to 50 – 60 disaccharide units.

Although purified Hyal2 has low hyaluronidase activity, it is possible that other cellular proteins or cofactors might modulate Hyal2 activity and/or be required for conversion of Hyal2 into a more active enzyme. Indeed, a requirement for CD44 to promote acidification of the extracellular environment and activate the hyaluronidase activity of Hyal2 has been described [20,21]. Given the long incubation times used for detection of hyaluronidase activity in these experiments it still appears that Hyal2 is a relatively weak hyaluronidase, although a direct comparison of Hyal2 activities to a highly active hyaluronidase such as Spam1 was not performed. Perhaps in the local space adjacent to the cell only a small amount of hyaluronidase is required to mediate biologically-relevant changes in hyaluronan properties and production of a highly active enzyme would be deleterious.

4. Hyal2 role in sheep retrovirus oncogenesis?

Interaction of JSRV and ENTV Env proteins with human Hyal2, location of the human Hyal2 gene in the 3p21.3 lung cancer tumor suppressor locus, and the presumed role of Hyal2 in metabolism of the extracellular matrix all pointed to a potential role of Hyal2 in transformation by the sheep retrovirus Env proteins. Support for this hypothesis was provided by studies in the human bronchial epithelial cell line BEAS-2B [22]. In these cells, Hyal2 can bind to the RON receptor tyrosine kinase rendering it inactive. JSRV Env can transform the cells, and in cells expressing Env, Env associated with Hyal2 and caused its degradation, releasing RON from suppression by Hyal2 and activating the Akt and mitogen-activated protein kinase oncogenic pathways. Most importantly, expression of a dominant-negative RON protein blocked Env transformation of the cells indicating that RON played a critical role in Env transformation.

On the other hand, JSRV and ENTV Env proteins cannot mediate virus entry into mouse cells and do not bind mouse Hyal2 [12], yet both Env proteins can transform cultured NIH 3T3 mouse fibroblasts [9,12,23]. Furthermore, expression of either JSRV or ENTV Env in mouse lung can induce lung adenocarcinoma similar to that seen in sheep infected with replication-competent JSRV (Fig. 3) [24–26]. These results indicate that mouse Hyal2 plays no role in oncogenic transformation by either Env protein in mice. Whether Hyal2 plays some role in sheep tumorigenesis is uncertain but an interaction of Env with Hyal2 seems unlikely to be required based on the results in mice.

So how do the JSRV and ENTV Env proteins transform cells if not by interaction with Hyal2? Several studies have shown that sequences in the cytoplasmic domain of the Env proteins are critical for transformation, and that oncogenic signaling occurs through the phosphoinositide 3-kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK) pathways [27]. The mechanisms by which the Env proteins activate these pathways are currently unknown.

5. Hyal2 role in sheep placental morphogenesis

Perhaps one of the most interesting findings relating to the interaction of sheep retrovirus Env proteins with Hyal2 is the role of Env proteins synthesized from endogenous sheep retroviruses and Hyal2 in placental morphogenesis in sheep. Mammals carry many copies of retroviruses in their genomes. Sheep carry ~20 copies of endogenous retroviruses related to JSRV and ENTV, but the Env proteins synthesized from these viruses are either nonfunctional or contain mutations that render the Env proteins nontransforming. However, some of these Env proteins can still interact with Hyal2, and in this case, can mediate fusion not between virions and cells but between cells. It has been hypothesized that endogenous retroviruses play a role in mammalian reproduction, particularly in placental morphogenesis, because intact retroviral Env genes are expressed in the syncytiotrophoblasts of human and mouse placenta and can elicit fusion of cells in culture. The importance of endogenous sheep retrovirus Env expression during pregnancy in sheep was confirmed by administration of morpholino antisense oligonucleotides to block Env expression *in utero*, which resulted in termination of pregnancy [28]. This study dramatically confirms that retroviruses are not simply pathogens but can contribute in a positive way to mammalian evolution, and shows that Hyal2 plays a critical role in sheep reproduction. Further work is necessary to decipher other potential functions of Hyal2 in mammals.

Acknowledgements

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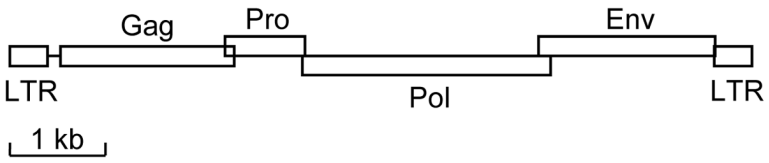

Fig. 1. Genetic structure of JSRV and ENTV

The structure of the integrated DNA form of the retroviruses is shown. Long terminal repeat (LTR) sequences that function to initiate and terminate mRNA transcription are shown flanking the protein coding regions. Protein coding regions are: Gag, virion core polypeptide; Pro, protease; Pol, reverse transcriptase (polymerase) and integrase; Env, viral coat protein (envelope) required for cell entry. The reading frames of the protein coding regions are indicated by the elevation of the boxes, for example, the Pro and Env coding regions are in the same reading frame but Pol and Gag are in different reading frames. kb, distance in kilobases.

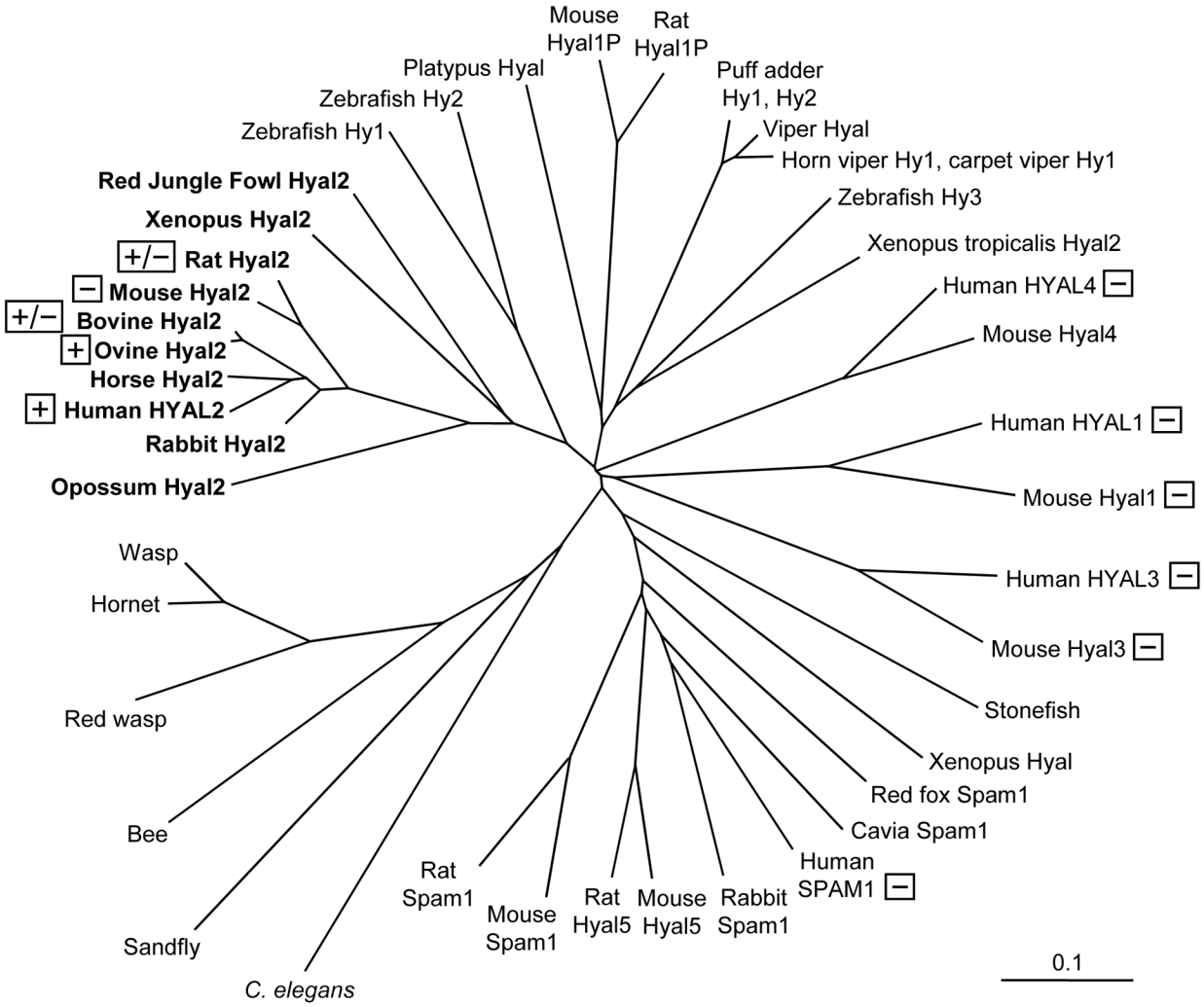

Fig. 2. Receptor activity of Hyal2 orthologs (bold) and paralogs

Proteins related to Hyal2 obtained by BLAST search of GenBank are shown. Proteins that exhibit high receptor activity when expressed in cells that are normally nonpermissive for JSRV and ENTV vector transduction are indicated by "+", those that exhibit moderate receptor activity are indicted by "+/−", and those that exhibit very low to no activity are indicated by "−" [8,10,13,16].

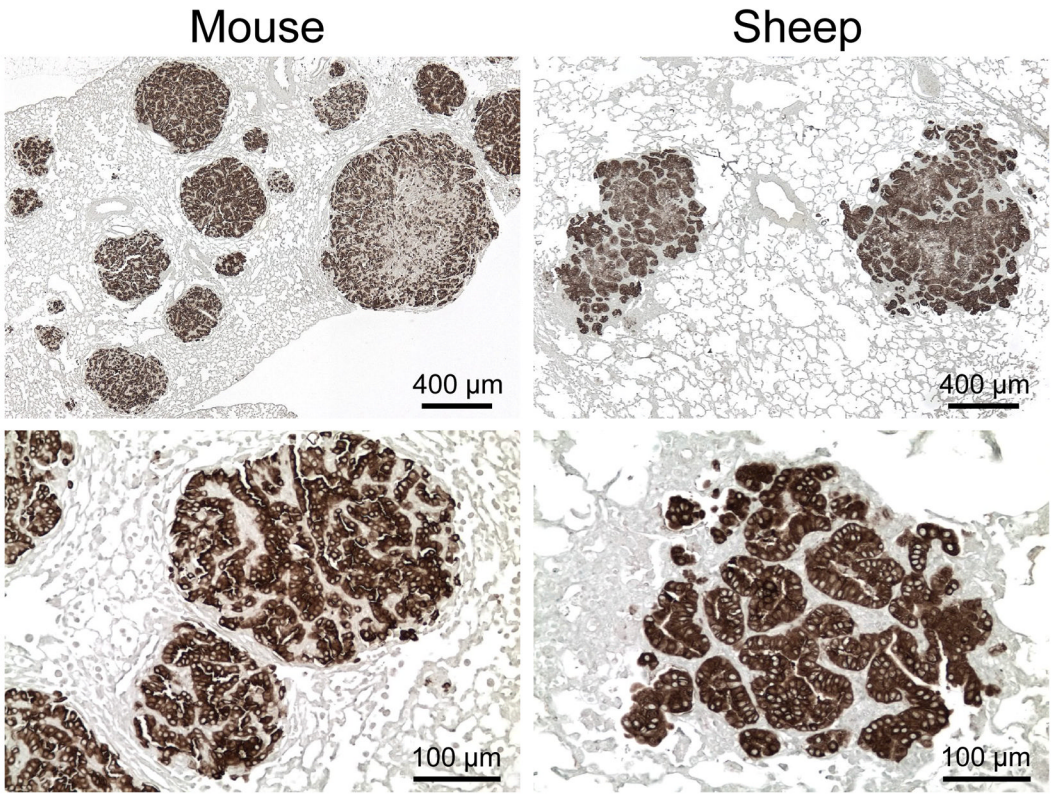

Fig. 3. Lung tumors induced by Env expression in mice and JSRV infection in sheep

Fixed paraffin-embedded lung sections were stained for JSRV Env expression using a monoclonal antibody against Env which stains transformed lung cells in tumors. For more details see Wootton et al. [26].

Table 1

Retrovirus Receptors

Retrovirus	Receptor	Type[a]	Function
Human immunodeficiency virus, simian immunodeficiency virus	CD4 and CXCR4, CCR5, others	TM1 TM7	Immune function G protein-coupled chemokine receptors
Feline immunodeficiency virus	CD134 and CXCR4	TM1 TM7	Immune function G protein-coupled chemokine receptor
Human T-cell leukemia virus	GLUT-1	TM12	Glucose transporter
Ecotropic murine leukemia virus	CAT-1 (SLC7A1)	TM14	Basic amino acid transport
Gibbon ape leukemia virus, amphotropic murine leukemia virus, 10A1 murine leukemia virus, feline leukemia virus type B, woolly monkey virus	Pit1 (SLC20A1) or Pit2 (SLC20A2)	TM10–13	Phosphate transport
RD114, type D simian retroviruses, baboon endogenous virus, human endogenous retrovirus type W	RDR (SLC1A5) or RDR2 (SLC1A4)	TM9–10 TM9–10	Neutral amino acid transport Glutamate and neutral amino acid transport
Xenotropic and polytropic murine leukemia viruses	XPR1	TM8	G protein-coupled signaling? Transport?
Feline leukemia virus type A	Thtr1	TM12	Thiamine transport
Feline leukemia virus type C	Flvcr	TM12	Heme export
Feline leukemia virus type T	Felix and Pit1 (SLC20A1)	soluble TM10–13	Env-like protein Phosphate transport
Pig endogenous retrovirus type A	Par-1 (GPR172A) or Par-2 (GPR172B)	TM10–11	G protein-coupled receptors
M813 murine leukemia virus	Smit1 (SLC5A3)	TM14	*myo*-inositol transport
Avian leukosis virus type A	Tva	TM1	LDL receptor-like protein
Avian leukosis virus types B, D, E	Tvb	TM1	Fas/TNFR-like receptor
Avian leukosis virus type C	Tvc	TM1	Butyrophilin-like (immunoglobulin superfamily)
Avian leukosis virus type J	NHE1 (SLC9A1)	TM12	Na+/H+ antiporter
Mouse mammary tumor virus	Tfr1	TM1	Transferrin receptor
Jaagsiekte sheep retrovirus, Enzootic nasal tumor virus	HYAL2	GPI-anchored	Hyaluronidase (weak)

[a] TM indicates a transmembrane protein and the number after TM indicates the number of times the protein is predicted to span the membrane. GPI-anchored indicates a glycosylphosphatidylinositol-anchored membrane protein.