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Review

Host cell restriction factors of equine infectious anemia virus

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ABSTRACT

Equine infectious anemia virus (EIAV) is a member of the *lentivirus* genus in the *Retroviridae* family and is considered an animal model for HIV/AIDS research. An attenuated EIAV vaccine, which was successfully developed in the 1970s by classical serial passage techniques, is the first and only lentivirus vaccine that has been widely used to date. Restriction factors are cellular proteins that provide an early line of defense against viral replication and spread by interfering with various critical steps in the viral replication cycle. However, viruses have evolved specific mechanisms to overcome these host barriers through adaptation. The battle between the viruses and restriction factors is actually a natural part of the viral replication process, which has been well studied in human immunodeficiency virus type 1 (HIV-1). EIAV has the simplest genome composition of all lentiviruses, making it an intriguing subject for understanding how the virus employs its limited viral proteins to overcome restriction factors. In this review, we summarize the current literature on the interactions between equine restriction factors and EIAV. The features of equine restriction factors and the mechanisms by which the EIAV counteract the restriction suggest that lentiviruses employ diverse strategies to counteract innate immune restrictions. In addition, we present our insights on whether restriction factors induce alterations in the phenotype of the attenuated EIAV vaccine.

1. Introduction

Equine infectious anaemia virus (EIAV) is a member of the *lentivirus* genus in the *Retroviridae* family, and only infects members of the Equidae (including horses, donkeys and mules). Equine infectious anaemia (EIA) is an important infectious disease of equines that is caused by the EIAV, and is widely distributed throughout the globe (Gaudaire et al., 2018; Costa et al., 2022). Unlike other lentiviruses, such as human immunodeficiency virus type 1 (HIV-1) or feline immunodeficiency virus (FIV), which usually present as a slowly progressive degenerative disease, infection with EIAV is associated with a rapid and dynamic disease (Leroux et al., 2004). Interestingly, most horses infected with EIAV are able to control viral replication and become asymptomatic carriers for life (Hammond et al., 2000). However, the carriers can still transmit the virus and the clinical symptoms of EIA can recur in carriers when the immune system is naturally or experimentally suppressed (Kono et al., 1976), indicating that the host immune system effectively suppresses the replication of EIAV. Therefore, EIAV has been recognized as an illustrative model for studying the dynamic interactions between lentiviruses and host immune responses during viral replication (Craigo and Montelaro, 2013).

Cellular restriction factors are a series of host proteins that inhibit viruses at various steps of their replication cycle. Most restriction factors, including APOBEC3 (Mangeat et al., 2003), TRIM5α (Stremlau et al., 2004), tetherin (Neil et al., 2008), SAMHD1 (Goldstone et al., 2011; Laguette et al., 2011), Viperin (Seo et al., 2011), Mx2 (Goujon et al., 2013b; Kane et al., 2013), Schlafen 11 (Li et al., 2012), and others, are induced by interferon (IFN). However, a few restriction factors, such as SERINCs (Usami et al., 2015), are not induced by IFN, and these types of cellular proteins are considered to be “nonclassical” restriction factors. In fact, accumulating evidence suggests that in addition to their role in interfering at specific steps of the viral replication cycle, some restriction factors also are involved in triggering innate immunity responses and adaptive immunity responses to viral infections (reviewed by Colomer-Lluch et al., 2018). In addition, these proteins also play an important role in resisting the interspecies transmission of viruses (reviewed by Malim and Bieniasz, 2012). Many viruses, including HIV-1 and others, have evolved antagonistic mechanisms to escape the effects of these restriction factors and maintain viral replication in their host. Currently, much of our knowledge of virus-cell restriction factor interactions comes from research on HIV-1, which shows that multiple accessory proteins of HIV-1 counteract the activity of restriction factors.

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For example, Vif counteracts APOBEC3 (Sheehy et al., 2002), Vpu counteracts tetherin (Neil et al., 2008), Nef counteracts SERINC5 (Rosa et al., 2015), and Vpx of HIV-2 (HIV-1 lack Vpx) counteracts SAMHD1 (Hrecka et al., 2011).

EIAV is a macrophage-tropic lentivirus with a replication cycle similar to that of HIV-1. However, compared to HIV-1 and other lentiviruses, EIAV has the simplest genomic organization. In addition to the three structural proteins (Gag, Pol, and Env) shared by all lentiviruses, EIAV only encodes three accessory proteins (Tat, S2, and Rev), while HIV-1 encodes six (Tat, Rev, Nef, Vif, Vpu, and Vpr). Therefore, conducting research into the interactions between EIAV and restriction factors is of great significance not only for understanding the replication mechanisms of this virus, but also for enriching our knowledge of lentivirus replication and co-evolution with restriction factors in general. Moreover, such stidies can inform the development of novel antiviral strategies. Over the past ten years or so, our laboratory has focused on the study of virus-host interactions, has identified a range of equine, human and other animal host proteins that interact with lentiviruses, and has determined their role in the replication of EIAV (Tang et al., 2014; Yin et al., 2014; Lin et al., 2016; Ji et al., 2018; Bai et al., 2020; Ren et al., 2021; Wang et al., 2022), influenza virus (Zhang et al., 2019; Yu M. et al., 2022) or HIV-1 (Na et al., 2018; Wang et al., 2019b). In this article, we summarize the currently available literature on the restriction factors of EIAV (SERINC5, SAMHD1, APOBEC3, Mx2, tetherin, TRIM5α, Viperin, schlafen 11) with regard to their activity against EIAV (Table 1, Fig. 1) and other lentiviruses. Our aim is to promote a comprehensive understanding of EIAV replication.

2. EIAV and SERINC5

The serine incorporators (SERINCs) are a family of multi-transmembrane domain proteins involved in incorporating serine into membrane lipid synthesis. The SERINC protein family, which comprises five members (SERINC1–5), is highly conserved among eukaryotes and is present in a variety of tissues including the brain and peripheral leukocytes. Human SERINC has been implicated in the development of various diseases, including cancers and neurological related disorders (reviewed by Xu et al., 2022).

In 2015, two independent studies simultaneously found that human SERINC5 (huSer5) and SERINC3 (huSer3) act as restriction factors to inhibit HIV-1 infection (Rosa et al., 2015; Usami et al., 2015). Subsequent studies have shown that huSer5 possesses the most powerful antiviral activity within SERINC protein family, and is able to inhibit a wide range of viruses, including influenza virus (Lai et al., 2022), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Timilsina et al., 2022), classical swine fever virus (CSFV) (Li et al., 2020) and hepatitis B virus (HBV) (Liu et al., 2020), in addition to retroviruses. Unlike many other host-restricted factors whose expression is regulated by interferon (reviewed by Xu et al., 2022), SERINC protein expression is constitutive and independent of interferon-induced effects.

Among the five members of the SERINC protein family, huSer5 is the most studied. Zheng et al. found that this protein encodes five splice isoforms. Only one isoform (SERINC5-001) expresses a stable protein consisting of 10 transmembrane domains, while the other isoforms all lack the C-terminal transmembrane region. Importantly, only SERINC5-001 showed strong antiviral activity, whereas the other isoforms and mutants without the C-terminal transmembrane region showed very poor activity. The study further confirmed that the C-terminal transmembrane region of huSer5 is required both for its stable expression and its plasma membrane (PM) localization (Zhang et al., 2017). In addition to its localization at the PM (Rosa et al., 2015; Usami et al., 2015), huSer5 is also found in the endoplasmic reticulum-Golgi intermediate compartment (Timilsina et al., 2022). A number of studies have suggested that huSer5-mediated antiviral activity mainly involves its incorporation into nascent virions, followed by the blocking of virus-cell membrane fusion, thus inhibiting the entry of virions into target cells (Usami et al., 2015). The antiviral activity of huSer5 against HBV is, however, an exception to

Table 1
Properties of cellular restriction factors involved in lentiviruses life cycle.

Cellular restriction factors	General functions	Targeted key steps of the lentiviral replication cycle	Restriction mechanisms	Viral antagonist
SERINC5	Incorporates serine into membranes and facilitates the synthesis of phosphatidylserine and sphingolipids.	Fusion	SERINC5 is incorporated into nascent virions, blocks virus-cell membrane fusion, and inhibits viral entry into target cells.	HIV-1: Nef EIAV: S2 MLV: glycoGag
SAMHD1	As a dNTP triphosphohydrolase, it catalyzes dNTPs to deoxynucleosides and inorganic triphosphates, controlling cellular dNTP levels.	Reverse transcription	SAMHD1 downregulate cellular dNTP levels to prevent reverse transcription of lentiviral RNA.	HIV-2: Vpx EIAV: Rev
APOBEC3 (A3)	As a cytidine deaminase, it deaminate cytidinein in RNA and/or DNA and regulate tissue-specific gene expression, metabolism and other physiological functions.	Reverse transcription	A3 is packaged into particles and then mediates C to T mutation in the minus-stranded viral cDNA, which induce the lethal accumulation of mutations in the viral genome.	HIV-1: Vif SIV: Vif FIV: Vif
TRIM5α	A RING domain-E3 ubiquitin ligase. As an innate immune sensor, it potently restricts retrovirus infection.	Uncoating	TRIM5α binds to the capsid lattice structure and then accelerates uncoating of the viral genome and also blocks reverse transcription.	unknown
Mx2 (MxB)	As a dynamin-like GTPase, mediate nucleotide-dependent membrane remodeling events.	Nuclear import	Mx2 inhibits viral cDNA nuclear import at the post-entry phase by binding to the viral capsid shell and preventing the uncoating process of HIV-1.	unknown
Viperin	Catalyzes the conversion of cytidine triphosphate (CTP) to 3′-deoxy-3′,4′-didehydro-CTP (ddhCTP).	Synthesis of viral proteins and production of viral particles	Viperin utilizes multiple complex mechanisms to exert antiviral activity. EqViperin inhibits EIAV Gag release and viral particle production and entry by disrupting the synthesis of Env and the receptor protein of EIAV.	unknown
SLFN11	Involved in the regulation of cell differentiation and growth; also implicated in the development of cancer.	Synthesis of viral protein	SLFN11 interacts with tRNAs and blocks lentivirus-induced changes in the composition of the tRNA pool, thereby preventing viral protein synthesis in a codon usage-dependent manner.	HCMV: RL1
Tetherin (BST-2, CD317, or HM1.24)	As a cell surface molecule, it is involved in early pre-B-cell development and cell adhesion and migration.	Budding	Tetherin physically binds viral particles to the cell surface, blocking their release.	HIV-1: Vpu HIV-2: Env SIV: Env FIV: Env EIAV: Env

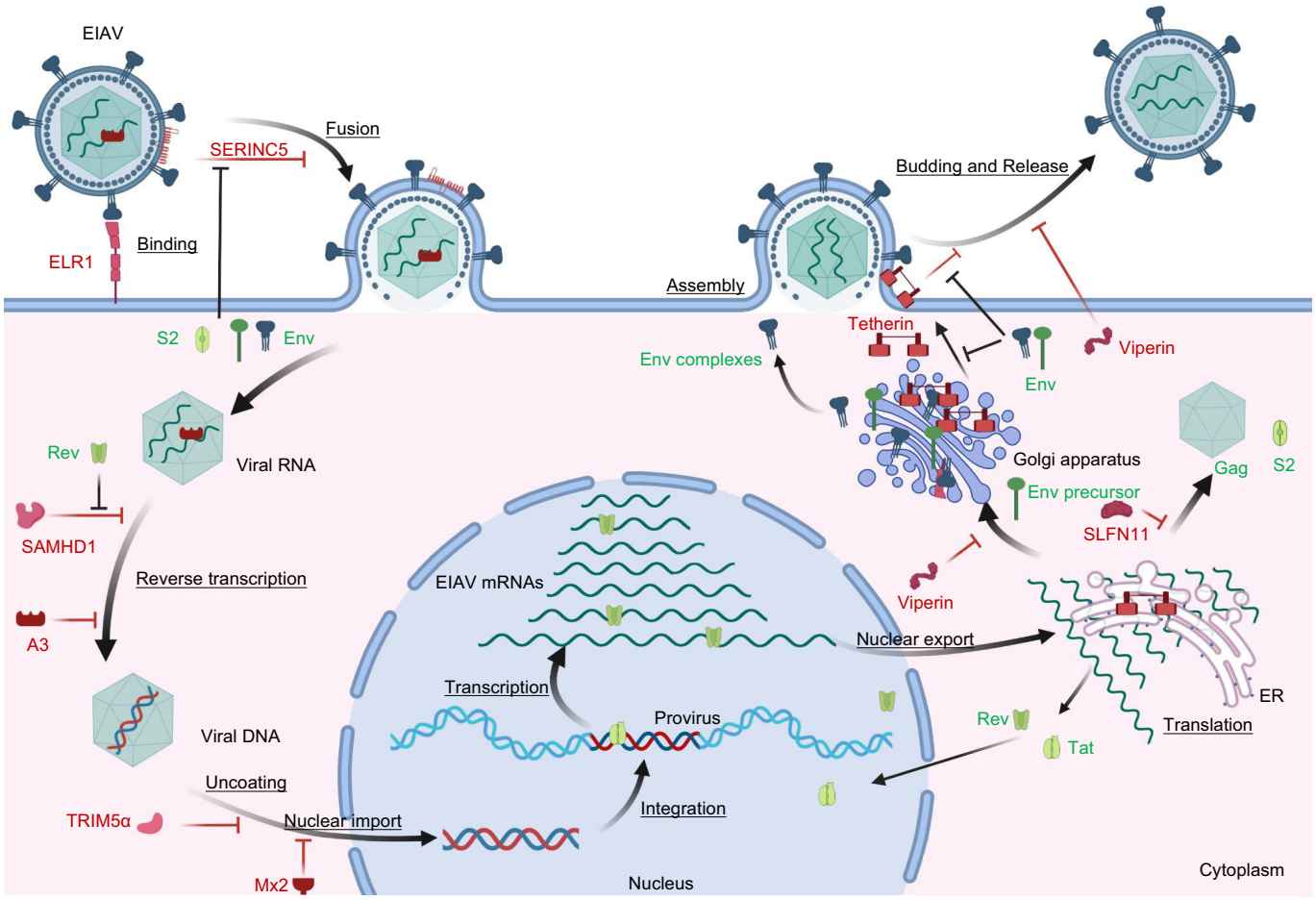

Fig. 1. Effects of the equine APOBEC3 (A3), TRIM5α, tetherin, SAMHD1, SERINC5, Viperin, Mx2, and SLFN11 on the EIAV replication cycle. EIAV virion-packaged A3 mediates C-to-T mutations in the negative-strand viral cDNA during reverse transcription, leading to G-to-A hypermutations on the positive strand of the proviral DNA, thereby inducing the accumulation of lethal mutations in the viral genome and leading to the abrogation of EIAV replication. TRIM5α restricts EIAV, which may target the early post-entry phases of infection, but the exact mechanism is unclear. Tetherin restricts EIAV virion release from the cell surface, but the Env protein of EIAV inhibits tetherin trafficking to the cell surface, downregulates its expression at the cell surface, and thus antagonizes its antiviral activity. SAMHD1, with dNTPase triphosphohydrolase activity, downregulates cellular dNTP concentrations to relatively low levels, preventing the reverse transcription of EIAV RNA. EIAV Rev protein counteracts SAMHD1 restriction by downregulating its expression via a lysosomal pathway. EIAV virion-incorporated Serinc5 blocks virus-cell membrane fusion, thereby inhibiting the virions' entry into target cells. EIAV S2 and Env are able to antagonize the antiviral activity of Serinc5. S2 is able to relocalize Serinc5 from the PM to the lysosomes or the proteasome for degradation, blocking its incorporation into nascent virions and thus inhibiting its antiviral ability. The mechanism by which EIAV Env antagonizes Serinc5 is unclear. Viperin restricts EIAV replication at multiple steps, including inhibiting Gag budding, virion production and entry by disrupting the synthesis of Env and the receptor protein ELR1. Mx2 inhibits nuclear import of EIAV cDNA in the post-entry phase, presumably by binding to the viral capsid shell and preventing the virus uncoating. SLFN11 inhibits EIAV replication by selectively inhibiting the expression of the Gag protein. Cellular restriction factors are indicated in red font, EIAV viral proteins in green font and the critical steps of EIAV replication are underlined.

this, and in HBV, huSer5 interferes with the glycosylation of HBV envelope proteins, inhibiting HBV virion secretion from the producer cells (Liu et al., 2020). Unfortunately, it is unclear how huSer5 is incorporated into virions, which may be via a passive mechanism (Firrito et al., 2018). Although some studies have shown that the huSer5's antiviral activity against HIV-1 is associated with specific Env (Beitari et al., 2017; Haider et al., 2021), the huSer5-Env interaction has not been detected (Sood et al., 2017). However, the precise mechanism by which huSer5 blocks virus-cell membrane interactions remains unclear. In the case of HIV-1, there are three possible ways by which huSer5 could block the structure or activity of Env (reviewed by Firrito et al., 2018), resulting in impairment of fusion of the viral Env with the target cell. In the case of the influenza virus, in addition to virion-incorporated huSer5, huSer5 expressed in target cells is also able to prevent viral infection, by impairing the fusion of the viral membrane with the cellular membrane (Zhao et al., 2022). Additionally, it has been reported that, similar to other host restriction factors, SERINC5 may exert its antiviral activity by modulating innate immunity pathways (Pierini et al., 2021).

To date, several viral proteins without sequence homology have been identified that antagonize the antiviral activity of huSer5. These include the primate lentivirus accessory protein Nef (Usami et al., 2015), murine leukemia virus (MLV) glycoGag protein (Rosa et al., 2015; Li et al., 2019), EIAV accessory protein S2 (Chande et al., 2016), and SARS-CoV-2 accessory protein ORF7a (Timilsina et al., 2022). These viral proteins employ a similar mechanism to antagonize huSer5: they block its incorporation into nascent virions (Ahmad et al., 2019; Timilsina et al., 2022). Nef, glycoGag, and S2 are able to relocalize huSer5 from the PM to the lysosomes or proteasome for degradation by recruiting adaptor protein-2 (AP-2) (Ahmad et al., 2019). As a result, glycoGag of MLV and S2 protein of EIAV may functionally replace Nef by antagonizing Ser5 and Ser 3, thereby increasing HIV-1 infectivity (Usami et al., 2015; Chande et al., 2016).

Equine SERINC5 (eqSer5) has an extra 83 amino acids at the N terminus compared to the huSer5 (Chande et al., 2016). Zheng's group reported that the expression levels of eqSer5 were much lower than those of huSer5 or murine SERINC5 (mSer5), but all three showed similar

levels of activity in inhibiting Nef-defective HIV-1, suggesting that eqSer5 has more potent antiviral activity (Ahmad et al., 2019).

S2 is a dispensable accessory protein for EIAV replication *in vitro*, but it is a determinant for viral replication and pathogenicity *in vivo* (Fagerness et al., 2006). Studies have shown that S2 utilizes a similar mechanism to antagonize huSer5, eqSer5 and mSer5 (Chande et al., 2016; Ahmad et al., 2019), and that while S2 reduces the expression of a variety of SERINC proteins including Ser5, Nef does not (Ahmad et al., 2019). S2 shares with Nef of HIV-1 several similar modifications and important functional motifs, which are closely related to the function of S2 in antagonizing Ser5 (Chande et al., 2016). Similar to Nef, S2 has a myristoylation site at Gly2 that is essential for its counteraction of huSer5 and which is associated with its PM localization (Chande et al., 2016; Ahmad et al., 2019). The interaction between S2 and huSer5 is also dependent on this site (Ahmad et al., 2019). Two leucine residues within a putative ExxxLL motif of S2 are required for the antagonism of huSer5, and mutation of these two amino acids causes S2 to lose its viral infection-promoting activity in the presence of Ser5 (Chande et al., 2016). Another study showed that a single mutation in the first leucine of the ExxxLL motif also disrupts S2-mediated internalization of mSer5, causing the S2 protein to lose its anti-Ser5 activity (Ahmad et al., 2019).

It has been reported that EIAV Env pseudotyped-HIV-1 (lacking Nef) and -EIAV (lacking S2) were only weakly inhibited by Ser5 (Chande et al., 2016), indicating that EIAV Env is also partially resistant to Ser5 restriction. A similar phenomenon has been observed in HIV-1, where HIV-1 Env is able to overcome SERINC5 without preventing SERINC5 incorporation into new progeny virus particles (Beitari et al., 2017; Haider et al., 2021). Thus, EIAV seems to be more strongly resistant to the restriction of eqSer5 than HIV-1. Nevertheless, it is unclear to what extent eqSer5 affects EIAV replication *in vitro* or *in vivo*.

3. EIAV and SAMHD1

Sterile alpha motif (SAM) and histidine-aspartate (HD) domain-containing protein 1 (SAMHD1) is a dNTP triphosphohydrolase that catalyzes the conversion of dNTPs to deoxynucleosides and inorganic triphosphates, thereby controlling cellular dNTP levels. An initial study found that mutations in SAMHD1 cause Aicardi-Goutières syndrome (AGS), an inherited disease in humans. Subsequent studies have shown that SAMHD1 plays a crucial role in DNA damage repair, innate immunity, viral restriction, and tumorigenesis (reviewed by Coggins et al., 2020).

SAMHD1 consists of one SAM domain and one HD domain. The N-terminal SAM domain mediates protein-protein interactions or protein-nucleic acid binding, while the C-terminal HD domain is an enzymatically active domain necessary for dNTPase function. A nuclear localization signal located at the N-terminal mediates the nuclear localization of SAMHD1, but the disruption of this signal did not affect the antiviral activity and dNTPase function of SAMHD1. The HD domain mediates the oligomerization of SAMHD1 that is required for its dNTPase activity and antiviral ability. It has been reported that post-translational modifications of SAMHD1 such as phosphorylation, acetylation and SUMOylation also affect its antiviral function and dNTPase function (Welbourn et al., 2013; White et al., 2013; Lee et al., 2017; Martinat et al., 2021), and, in particular, phosphorylation at residue T592 by cyclin A2/CDK1 has been found to eliminate the antiviral activity of human SAMHD1 (huSAMHD1) (Cribier et al., 2013; Welbourn et al., 2013). HuSAMHD1 is expressed in multiple cell types and is mainly localized in the nucleus. The expression of huSMAHD1 is regulated by interferons and certain other cytokines (Deutschmann and Gramberg, 2021). IFN-α and IFN-γ induced the expression of huSAMHD1 in human primary monocytes (Riess et al., 2017), astrocytes (Cuadrado et al., 2013), microglia (Jin C. et al., 2016), and IFN-α and β induced the expression of this protein in HEK293T and HeLa cells (St Gelais et al., 2012). In MDMs, treatment with IL-12 and IL-18 upregulated huSAMHD1 expression (Pauls et al., 2013), while treatment with interferon did not (Goujon et al., 2013a). However, in activated $CD4^+$ T cells, MDM, and dendritic cells, treatment with interferon reduced the phosphorylation of SAMHD1, resulting in enhanced restriction of the virus (Cribier et al., 2013; Szaniawski et al., 2018).

Although macrophages, dendritic cells, and resting $CD4^+$ T cells, which express high levels of huSAMHD1, are the target cells of HIV-1, the replication of the virus is limited in these cells, and a major barrier to this replication is huSAMHD1. huSAMHD1 is a restriction factor that prevents the reverse transcription of HIV-1 RNA in these cell types through dNTPase activity, which maintains low levels of intracellular dNTP (Hrecka et al., 2011; Laguette et al., 2011). Furthermore, HIV-1 infection of cells induces broad expression of interferon, which mediates the dephosohorylation of huSAMHD1 via PP2A-B55α holoenzymes to activate the antiviral activity of huSAMHD1 (Cribier et al., 2013; Schott et al., 2018). Altogether, SAMHD1 proteins, both in humans and in other species, can act as host restriction factors inhibiting the infectivity of retroviruses and DNA viruses by downregulating cellular dNTP concentrations. However, various strategies allowing viruses to evade SAMHD1 restriction have been found (Deutschmann and Gramberg, 2021). For example, HIV-2 and the related SIV counteract SAMHD1 via the accessory protein Vpx (Vpr in some SIVs), which loads SAMHD1 onto the CRL4-DCAF1 E3 ubiquitin ligase complex, where it is polyubiquitinated and subsequently degraded in a proteasome-dependent mechanism (Laguette et al., 2011). Vpx is a potent SAMHD1 antagonist that induces degradation of not only human and other primate SAMHD1, but also of the feline and bovine SAMHD1 proteins (Hrecka et al., 2011; Wang C. et al., 2020a). HIV-1 does not encode a Vpx protein, and it appears to utilize high-efficiency reverse transcriptases that function at low dNTP concentrations, to alleviate SAMHD1 restriction (Lenzi et al., 2014). Herpesviruses overcome SAMHD1 restriction by inducting its phosphorylation (Businger et al., 2019) or its relocalization (De Meo et al., 2020), as well as by downregulating the expression of SAMHD1 (Hyeon et al., 2020).

In 2020, our lab reported that equine SAMHD1 (eqSAMHD1) limited EIAV replication in equine monocyte-derived macrophages (eMDMs) at the reverse transcription stage, and this antiviral activity is counteracted by the posttranscriptional regulator protein Rev (Ren et al., 2021). EIAV is a unique macrophage-tropic lentivirus. Numerous studies have shown that macrophages are the targets for EIAV infection *in vivo*, while lymphocytes are not (Leroux et al., 2004), implying that EIAV has evolved a mechanism to escape various restriction factors in macrophages, unlike HIV-1. In eMDMs, the concentration of the four dNTPs was less than 100 fmol per 10^6 cells, and knockdown of eqSAMHD1 expression with siRNA resulted in a dramatic increase in the dNTP levels by up to 4-fold, indicating that eqSAMHD1 has functional dNTPase activity and can maintain relatively low dNTP concentrations (Ren et al., 2021). Both exogenous addition of deoxynucleosides and knockdown of eqSAMHD1 resulted in enhanced infectivity of single-cycle EIAV reporter virus in eMDMs. Notably, knockdown of eqSAMHD1 in eMDMs significantly increased the amount of EIAV late reverse transcription products, while the early reverse transcription products only slightly increased, suggesting that eqSAMHD1 restricts EIAV replication by its dNTPase activity to inhibit reverse transcription. We also determined that the HD domain of eqSMAHD1 is crucial for its antiviral and dNTPase activity (Ren et al., 2021).

Rev is a regulatory protein shared by all lentiviruses and is highly involved in the transportation of structural protein-encoding viral mRNAs, although its functions beyond this role are poorly understood. We have discovered a novel function of EIAV Rev: this protein was able to counteract eqSAMHD1 restriction by downregulating its expression via a lysosomal pathway (Ren et al., 2021). However, unlike HIV-2 Vpx, which can degrade human SAMHD1 but not equine SAMHD1, EIAV Rev is unable to degrade huSAMHD1 (Mohamed et al., 2021). HIV-1 Rev is unable to degrade equine or human SAMHD1 (Ren et al., 2021). This suggests that EIAV Rev inactivates eqSAMHD1 in a species-specific manner. We additionally found two Rev mutants that have lost their Rev-mediated nuclear RNA export activity. These mutants are still able to

mediate the degradation of eqSAMHD1, however, certain mutants that have lost their ability to degrade eqSAMHD1 are nevertheless still active in the nuclear export of RNA (Ren et al., 2021). These findings suggest that EIAV Rev counteracts eqSAMHD1 restriction through a mechanism that is independent of its viral mRNA export activity. Rev is a nucleocytoplasmic shuttle protein. We found that EIAV Rev is able to relocalize eqSAMHD1 from the nucleus to the cytoplasm, and recruit it into the lysosome to undergo degradation, and that treatment with leptomycin B, which is an inhibitor of nuclear export, inhibits Rev-mediated eqSAMHD1 degradation (Ren et al., 2021), suggesting that Rev utilizes its nucleocytoplasmic shuttling ability to transport eqSAMHD1 from the nucleus to the cytoplasm and mediate its degradation, thereby antagonizing the restriction activity of eqSAMHD1. SAMHD1 is a strong restriction factor in macrophages and inhibits the reverse transcription of HIV-1 and EIAV (Goldstone et al., 2011; Ren et al., 2021). It has therefore been suggested that the Vpx-mediated SAMHD1 antagonism may occur during the early steps of HIV-1 infection, prior to integration into the host genome (Deutschmann and Gramberg, 2021), which is more beneficial for viral replication. Indeed, as a virion-associated accessory protein (Yu et al., 1993), Vpx can be delivered via virion-packaging, allowing HIV-1 to counteract the SAMHD1 restriction in dendritic cells, resting $CD4^+$ T cells and macrophages (Hrecka et al., 2011; Laguette et al., 2011). This may support this viewpoint to some extent. Previous studies have demonstrated that Rev from EIAV appears to be incorporated into virions (Rosin-Arbesfeld et al., 1993), as is Vpx from SIV or HIV-2 (Yu et al., 1993; Kewalramani and Emerman, 1996). Therefore, based on the above observations, the authors speculate that EIAV Rev may be delivered to target cells in a virion-associated protein and inactivate the early post-entry eqSAMHD1 restriction, providing an advantageous environment for the replication of EIAV in eMDMs. The Rev-mediated degradation of eqSAMHD1 is dependent on beclin 1 (Ren et al., 2021). Beclin 1 is a key regulator of autophagy and has a role in the formation of the PtdIns3K complex involved in activating autophagy, but it is also involved in ferroptosis, endocytic transport, stress adaptation, and cytokinesis regulation, and other biological processes. However, our data suggest that Rev-mediated degradation of eqSAMHD1 requires beclin 1, but not proteins involved in autophagosomal membrane elongation, and that EIAV infection and Rev expression do not trigger autophagy (Ren et al., 2021). This suggests that Rev uses beclin 1 to promote degradation of eqSAMHD1 in a canonical macroautophagy/autophagy-independent pathway.

4. EIAV and APOBEC3

Apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like (APOBEC) proteins are a family of cytidine deaminases that can deaminate cytidine in RNA and/or DNA and regulate tissue-specific gene expression, metabolism and other physiological functions, as well as perform antiviral-functions (reviewed by Uriu et al., 2021). APOBEC family proteins are widely expressed in mammalian cells. A total of 11 APOBEC family members have been found in human cells, of which seven members [APOBEC3A (A3A), APOBEC3B (A3B), APOBEC3C (A3C), APOBEC3D (A3D), APOBEC3F (A3F), APOBEC3G (A3G), APOBEC3H (A3H)] are the most widely studied and are commonly known as APOBEC3 (A3). APOBEC family proteins have one or two conserved zinc-coordinating (Z) domains, which contain a HEX motif (His-X--Glu-X_{23-28}-Pro-Cys-X_{2-4}-Cys, where X represents any amino acid) that is the core catalytic active domain of deaminase activity. According to their sequence characteristics, the Z domains are categorized into three types: Z1, Z2, and Z3. A3A, A3C and A3H each have one Z domain, of types Z1, Z2, and Z3, respectively. A3B, A3D, A3F, and A3G each have two Z domains, of types Z2-Z1, Z2-Z2, Z2- Z2 and Z2-Z1, respectively, but the N-terminal Z domain of these double Z domains does not have deaminase activity.

Human A3 proteins can inhibit a variety of RNA and DNA viruses, including retroviruses (Harris and Liddament, 2004), herpesviruses (Cheng et al., 2021), Hepatitis B virus (HBV) (Turelli et al., 2004), and others, through deaminase-dependent and deaminase-independent mechanisms. The antiviral activity of A3 was first reported in A3G, which inhibits the infectivity of vif-deficient HIV-1, but does not affect the infectivity of wild-type HIV-1 because its Vif protein antagonizes A3G (Sheehy et al., 2002). Subsequent research successively demonstrated that three other A3 proteins (A3D, A3F, A3H) are also able to inhibit HIV-1 (Ooms et al., 2013; Ara et al., 2014). Mechanistically, the A3 is packaged into HIV-1 particles by binding to viral genomic RNA, viral nucleocapsid protein (NC) and cellular RNA. The bound A3 then mediates C to T mutation in the minus-stranded viral cDNA that is synthesized during reverse transcription, leading to G-to-A hypermutations on the plus strand of proviral DNA, which induce the lethal accumulation of mutations in the viral genome (reviewed by Gaba et al., 2021). In addition, some A3 proteins inhibit the elongation of reverse transcription by directly binding to viral genomic RNA and/or the first viral DNA strand, and may also block its enzyme activity by interacting with the viral reverse transcriptase (RT) (Iwatani et al., 2007). A3-mediated G-to-A hypermutation appears as a strong dinucleotide preference. For example, A3G preferentially induces GG to GA changes in the HIV-1 genome (Yu et al., 2004), and other A3 proteins preferentially induce GA to AA changes (Hultquist et al., 2011). Recent studies have shown that A3 affects HIV-1 provirus integration site profiles (Ajoge et al., 2023).

A total of six different A3 genes have been found in horses, four of which contain one Z domain and two of which contain two Z domains (Bogerd et al., 2008). Based on the characteristics of the Z domain, the proteins encoded by these six genes were named eqA3Z1a, eqA3Z1b, eqA3Z2a-Z2b, eqA3Z2c-Z2d, eqA3Z2e and eqA3Z3, respectively (Zielonka et al., 2009). The double Z-domain proteins, eqA3Z2a-Z2b and eqA3Z2c-Z2d (originally designated eA3F1 and eA3F2, respectively), share extensive sequence homology with human A3F at the amino acid level and are widely expressed, including in cells that are natural targets of EIAV. Although eqA3Z2a-Z2b and eqA3Z2c-Z2d can be packaged into EIAV virions, these two proteins show only weak activity against EIAV (Bogerd et al., 2008). In a study by Zielonka et al., eqA3Z1a mRNA was not detected in equine PBMCs, spleen cells, or macrophages, but a variant of eqA3Z, named eqA3Zv1, was found (Zielonka et al., 2009). Five types of eqA3 genes are expressed in PBMCs, of which eqA3Z3 and eqA3Z2c-Z2d have strong antiviral activity, while eqA3Z1b, eqA3Z2a-Z2b and eqA3Z2e have only weak antiviral activity. Consistent with this, eqA3Z3 and eqA3Z2c-Z2d induce significantly higher rates of G-to-A mutations than the other three A3 proteins. In single-round infection assays, it appears that G-to-A mutation induced by eqA3 presents a dinucleotide preference of GG to AG and GA to AA. There are four amino acid substitutions between the eqA3Z2c-Z2d sequences identified by Zielonka et al. and those of Bogerd et al. (2008), which have a significant effect on the anti-EIAV activity of eqA3Z2c-Z2d. Interestingly, the expression levels of eqA3Z1 and eqA3Z3 mRNAs in macrophages, which are the natural target cells of EIAV (Oaks et al., 1998), are significantly lower than that those in PBMCs, and in particular, the expression levels of eqA3Z3 mRNAs in macrophages are 19-fold lower than those in PBMCs. It has been shown that blood monocytes are permissive for EIAV infection *in vivo* (Maury, 1994), but do not support virus replication unless they differentiate into mature macrophages (Sellon et al., 1992), which are the natural target cells of EIAV. Therefore, this phenomenon may possibly be attributed to the different levels of A3 expression in monocytes and macrophages. In addition to inhibiting EIAV, eqA3Z can also inhibit other viruses, including HIV-1, simian immunodeficiency virus (SIV) and adeno-associated virus type 2 (AAV-2) (Zielonka et al., 2009).

In HIV-1, SIV, and FIV, the viral accessory protein Vif has been shown to counteract A3 antiviral activity. HIV-1 Vif antagonism of A3G is the most well characterized (reviewed by Uriu et al., 2021). The mechanism underlying this is that HIV-1 Vif binds to A3G and degrades it via the ubiquitination pathway by recruiting the cellular core-binding factor beta (CBFβ), thereby reducing the rate of A3G incorporation into nascent

virions (Delviks-Frankenberry et al., 2020; Uriu et al., 2021). In addition, some studies have demonstrated that Vif can block the translation of A3G mRNA to further decrease its expression level (Guerrero et al., 2016). However, EIAV is a genetically simple lentivirus lacking the vif gene, and how it overcomes the restriction of the A3 protein is still unclear. In addition, since the eqA3Z, a member of the eqA3 protein with the strongest antiviral activity, is expressed at low levels in macrophages (Zielonka et al., 2009), whether this protein can exert a restrictive function against EIAV under physiological conditions needs to be further investigated.

5. EIAV and Mx2

Myxovirus resistance (Mx) protein is a dynamin-like GTPase found in all vertebrates and is readily induced by interferon (reviewed by Verhelst et al., 2013). Mammals usually contain two or more Mx genes that arose through ancient gene duplications, conversions, and deletions (Braun et al., 2015; Solbakken et al., 2016). Humans express two Mx paralogs, huMxA (also called huMx1) and huMxB (or huMx2), which have a broad range of antiviral functions. The huMxA and huMxB proteins have similar structural domains and share 63% sequence identity (Aebi et al., 1989), but they have different antiviral spectra, which may depend on their characteristic subcellular localizations (Steiner and Pavlovic, 2020). The huMxA protein is localized in the cytoplasm and is known to inhibit a wide range of RNA and DNA viruses, such as influenza virus, measles virus, rabies virus, and African swine fever virus (ASFV) (reviewed by Verhelst et al., 2013). The huMxB protein is distributed at the cytoplasmic face of nuclear pores and only inhibits HIV-1, SIV (Goujon et al., 2013b; Kane et al., 2013), hepatitis C virus (Yi et al., 2019) and herpesviruses (Crameri et al., 2018). The antiviral mechanisms of Mx proteins are complex and diverse. In the case of HIV-1, huMxB inhibits viral cDNA nuclear import at the post-entry phase by binding to the viral capsid shell and preventing the uncoating process of HIV-1, thereby leading to restriction of HIV-1 replication (Goujon et al., 2013b; Kane et al., 2013). A recent study showed that huMxB also restricts the nuclear import of the HIV-1 Rev protein by disrupting the interaction of Rev with transportin 1 (TNPO1), a nuclear transport receptor, resulting in a reduction of Rev-dependent HIV-1 Gag protein expression (Wang et al., 2020b). As countermeasures, HIV may overcome the restriction of huMxB by mutation of capsid protein and increased expression of Rev (Goujon et al., 2013b; Kane et al., 2013; Liu et al., 2013; Wang et al., 2020b). In 2018, our group and Münk's group cloned the equine Mx2 (eqMx2) gene almost simultaneously, from eMDMs and equine dermal cells, respectively, and performed functional characterization (Ji et al., 2018; Meier et al., 2018). Our study demonstrated that eqMx2 mRNA expression in eMDMs is more strongly induced by type I interferon than mRNA expression of other equine restriction factors, such as eqSAMHD1 and equine tetherin, and that the knockdown of eqMx2 mRNA in eMDMs attenuates the inhibition of EIAV replication by type I interferon (Ji et al., 2018). Both studies showed that overexpression of eqMx2 not only blocked EIAV infection, but also significantly inhibited primate lentivirus (HIV-1 and SIV), FIV and MLV infection. In contrast, huMxB restricted primate lentiviruses but not other viruses. Thus, eqMx2 appears to have broader antiviral activity than does huMxB. Like huMxB, eqMx2 also targets the viral capsid and blocks the nuclear entry of viral cDNAs.

6. EIAV and tetherin

Tetherin, also known as BST-2, CD317, or HM1.24, is an interferon-inducible membrane protein expressed in a variety of cell types, including mature B cells, some cancer cells, bone marrow stromal cells, monocyte-derived macrophages (MDM), and plasmacytoid dendritic cells. The biological functions of this protein include regulation of B-cell growth, participation in cell adhesion and migration, and restriction of the release of enveloped viruses (Neil et al., 2007; Billcliff et al., 2013). In addition, tetherin also can negatively regulate the IFN-I signaling pathway to suppress excessive immune responses (Jin et al., 2017). Over the past decade, extensive research has been conducted on the antiviral effects of tetherin and it has been found that tetherin from humans and other mammals has broad-spectrum antiviral activity (Jouvenet et al., 2009).

Tetherin is a type II transmembrane protein, and is composed of an N-terminal cytoplasmic tail (CT) region, a single transmembrane (TM) domain, an extracellular coiled-coil domain, and a C-terminal glycosylphosphatidylinositol (GPI) membrane anchor. The CT region of human tetherin and some mammalian tetherins contains a conserved tyrosine motif (YxY) that mediates clathrin-dependent internalization by recruiting AP2, resulting in the recycling of this protein between the PM, endosomes and the trans-Golgi network (TGN) (Rollason et al., 2007). The extracellular coiled-coil domain contains three cysteines that mediate the formation of disulfide-linked tetherin dimers. The extracellular domain also contains two N-linked glycosylation sites that contribute to the correct trafficking and folding of tetherin (Perez-Caballero et al., 2009). The TM and GPI anchor are responsible for the targeting of tetherin to the PM, and these structural features are important for the antiviral function of the protein. Many studies show that tetherin, in its dimeric form, inhibits the release of enveloped viruses by directly tethering the virion to the infected cell surface through either its TM or C-terminal GPI anchor, or both together (Perez-Caballero et al., 2009; Venkatesh and Bieniasz, 2013).

Human tetherin (huTHN) was first identified by the groups of Bieniasz and Guatelli as a cellular restriction factor that blocks the release of HIV-1 virions from the surface of infected cells in the absence of the accessory protein Vpu (Neil et al., 2008; Van Damme et al., 2008). Subsequent studies have found that huTHN can also inhibit the replication of a number of viruses, including retroviruses, filoviruses, herpes simplex virus 1, and others (Jouvenet et al., 2009; Blondeau et al., 2013). The antiviral activity of tetherin is achieved by the physical tethering of virus particles to block their release. To counteract tetherin restriction, many viruses have evolved countermeasures by encoding certain proteins, including the Vpu protein of HIV-1 (Neil et al., 2008), the Nef protein of SIV (Zhang et al., 2009), the envelope proteins of HIV-2 (Le Tortorec and Neil, 2009), FIV (Celestino et al., 2012), and the glycoprotein (GP) of Ebola virus (Kaletsky et al., 2009). However, the mechanisms by which these various viral proteins antagonize tetherin are diverse. The viral proteins of primate lentiviruses can reduce the levels of the tetherin at the surfaces of host cells, resulting in the physical separation of tetherin from the place where the virions are assembled, thus antagonizing it. HIV-1 Vpu sequesters tetherin in the perinuclear region and mediates endocytosis of the protein, facilitating its degradation through the lysosomal or proteasomal pathways (Goffinet et al., 2009; Iwabu et al., 2009; Dube et al., 2010). SIV Nef induces cell surface downregulation of tetherin by endocytosis in an AP-2-dependent mechanism, rather than inducing its degradation (Zhang et al., 2011), and HIV-2 Env sequesters tetherin in the TGN by regulating its intracellular trafficking or recycling to the PM without its degradation (Le Tortorec and Neil, 2009). FIV Env and Ebola virus GP antagonize tetherin employing a distinct, but as yet not fully described, mechanism that does not induce downregulation of tetherin from the cell-surface or degradation of total intracellular tetherin (Neil et al., 2007; Morrison et al., 2014). A recent study has shown that the antagonism of tetherin by FIV Env is entirely due to its signal peptide, which is located at the N-terminal end of Env. Thus, almost all Env (all of the SU and TM domains) is not required for antagonism of tetherin by FIV (Morrison and Poeschla, 2023).

Yin et al. cloned and characterized the equine tetherin (eqTHN) protein (Yin et al., 2014). The amino acid sequence homology between eqTHN and huTHN is only 40%. Compared to huTHN, the N-terminal domain of eqTHN is missing 16 amino acids and does not carry a dual tyrosine motif in the CT, but the structural features do not affect its antiviral activity nor its PM localization. The eqTHN is also inducible by IFN-α and its expression has been detected in equine macrophages,

equine dermal cells and equine vascular endothelial cells, which are permissive for EIAV replication, and equine macrophages expressed significantly higher levels of tetherin than equine dermal cells or equine vascular endothelial cells. eqTHN localizes to the cell surface and potently blocks the release of HIV-1, SIV, and EIAV (Yin et al., 2014; Wang et al., 2019a), implying that eqTHN has broad antiviral activity. Experiments have shown that eqTHN is able to inhibit the release of EIAV from HEK293T cells (Yin et al., 2014; Wang et al., 2019a), and the mechanism underlying this may be that nascent viral particles are bound to the PM by eqTHN, as it has been observed that EIAV Gag proteins colocalize on the PM with eqTHN (Yin et al., 2014). The GPI anchor of eqTHN is absolutely essential for its antiviral activity, and the removal of this domain inactivates eqTHN, but does not alter its membrane localization. However, deletion of CT slightly reduces the antiviral activity of eqTHN and partially alters subcellular distribution to the cytoplasmic compartment. Like other mammalian tetherins (Sauter, 2014; Wang et al., 2015), eqTHN also contains two N-linked glycosylation sites within its extracellular domain, but the effect of the glycosylation modifications on the antiviral activity of eqTHN is controversial (Yin et al., 2014; Bai et al., 2020). A similar phenomenon is also known from huTHN (Perez-Caballero et al., 2009). A study by Bai et al. confirmed that eqTHN has two N-glycosylation sites at positions 51 and 78, and that disruption of these N-glycosylation sites blocks intracellular trafficking of eqTHN to the PM, impairing its antiviral activity (Bai et al., 2020). The localization of tetherin on the PM is essential for its tethering function, and N-glycosylation is required for the correct transport and folding of Tetherin (Kupzig et al., 2003; Perez-Caballero et al., 2009), so loss of N-glycosylation prevents the protein from reaching the PM, where it would normally perform its antiviral activity.

Similar to HIV-2 and FIV, EIAV also uses its Env protein to antagonize eqTHN. EIAV Env specifically interacts with eqTHN and redistributes it from the cell surface to the intracellular compartment without mediating its degradation, but the details of this antagonism remain unknown (Yin et al., 2014). Recently, it was found that FIV Env antagonism of tetherin depends exclusively on its signal sequence (Morrison and Poeschla, 2023). In this regard, EIAV and other non-primate lentiviruses also have very long Env signal peptides. Whether these viruses antagonize tetherin in a manner that is similarly dependent on their Env signal peptides requires further investigation. In general, the tetherin antagonists counteract the antiviral activity of tetherin in a species-specific manner. For example, HIV-1 Vpu antagonizes human and chimpanzee tetherin but is unable to antagonize monkey tetherin (McNatt et al., 2009). SIV Nef antagonizes macaque tetherin but is not active against the human protein (Zhang et al., 2009). Similarly, EIAV Env does not antagonize human or monkey tetherin, and neither does HIV-1 Vpu antagonize eqTHN (Yin et al., 2014). Recently, our lab identified a novel viral protein from EIAV, named S4. Interestingly, the S4 also has the ability to antagonize the antiviral activity of eqTHN, and promotes EIAV release. Mechanistically, S4 sequesters eqTHN in perinuclear compartments and redistributes it to the TGN and ER to reduce its expression at the PM, but does not induce its internalization and degradation. Moreover, the expression pattern of eqTHN was affected by coexpression of S4, and this influence was similar to that caused by Brefeldin A (BFA), but this effect did not occur in the presence of Env. BFA is an inhibitor of intracellular protein transport that blocks the transport of proteins from the endoplasmic reticulum (ER) to the Golgi complex (Misumi et al., 1986). Therefore, we speculate that S4 may sequester the newly synthesized eqTHN in the ER and inhibit its subsequent post-translational modification, whereas Env does not. This also suggests that S4 and Env appear to counteract eqTHN using different mechanisms. S4 was able to antagonize the antiviral activities of both huTHN and eqTHN, whereas Env antagonized only eqTHN but not huTHN. In conclusion, EIAV uses two viral proteins, S4 and Env, to antagonize eqTHN, indicating that EIAV has evolved a bimodal ability to antagonize the antiviral activity of eqTHN, which also reflects the importance of controlling tetherin function (data not published).

7. EIAV and other restriction factors

TRIM5α (tripartite motif containing 5α) is a member of the tripartite motif (TRIM) protein family of approximately 100 members, many of which are induced by interferon and involved in innate immune signaling (reviewed by Ozato et al., 2008; Rose et al., 2021). Rhesus TRIM5α (rhTRIM5α) is the first restriction factor identified with species-specific restriction of retroviral infection. It inhibits HIV-1 replication at the post-entry step by binding to the viral capsid and then accelerating its premature uncoating, resulting in proteasomal degradation of the viral reverse transcription complex (Stremlau et al., 2004, 2006). Follow-up studies showed that rhTRIM5α also restricts HIV-1 production by degrading the HIV-1 Gag protein (Sakuma et al., 2007). Human TRIM5α (huTRIM5α) interacts weakly with the HIV-1 capsid and therefore has poor restriction to HIV-1 (Stremlau et al., 2006). However, huTRIM5α is effective against MLV and EIAV (Passerini et al., 2006). Recent studies have shown that huTRIM5 is able to suppress HIV-1 infection *in vitro* through various strategies, including the use of the autophagy pathway or immunoproteasome (Ribeiro et al., 2016; Jimenez-Guardeno et al., 2019). In addition, a study by Chiramel et al. showed that both rhTRIM5α and huTRIM5α also restrict flavivirus replication by targeting the viral protease for proteasomal degradation (Chiramel et al., 2019). Both rhTRIM5α and huTRIM5α contain RING, B-box 2, coiled-coil and C-terminal B30.2/SPRY domains. All of their domains are required for retroviral restriction activity, with the B30.2/SPRY domain determining their specificity for viral capsid recognition and retroviral restriction. In some other primate species, cyclophilin A (CypA) cDNA has been transposed into the TRIM5α locus by alternative mRNA splicing, resulting in the replacement of the B30.2/SPRY domain by cyclophilin-A (CypA) and the expression of a TRIM5-CypA fusion protein (TRIMCyp), which restricts HIV-1 and some other retroviruses infection based on the viral CA-binding specificity of CypA (Nisole et al., 2004). Previously, our laboratory has cloned and functionally characterized equine TRIM5α (eqTRIM5α) gene from equine blood cells (Cai et al., 2014). The eqTRIM5a has a short SPRY domain, which is only 1/5 of the length of rhTRIM5α SPRY domain. We demonstrated that eqTRIM5α moderately inhibit VSV-G pseudotyped EIAV infection, but eqTRIM5α does not cause degradation of the EIAV Gag protein like huTRIM5a. However, the mechanism by which eqTRIM5α inhibits EIAV infection and how EIAV escapes its restriction require further study.

Viperin (virus-inhibitory protein, endoplasmic reticulum-associated, interferon-inducible), a member of the radical S-adenosyl-L-methionine (SAM) superfamily of enzymes, is a multifunctional, IFN-inducible protein that is involved in tumorigenesis, activation of immune signaling, and inhibition of viral replication (reviewed by Weinstein et al., 2022). Viperin also possesses enzymatic activity that catalyzes the conversion of cytidine triphosphate (CTP) to 3′-deoxy-3′,4′-didehydro-CTP (ddhCTP). The ddhCTP acts as an antiviral ribonucleotide when incorporated into viral RNA, resulting in premature termination of RNA synthesis in certain RNA viruses (Gizzi et al., 2018). Furthermore, recent studies have shown that ddhCTP can also trigger ribosome collision, leading to inhibition of cellular and viral RNA translation by activation of the integrated stress response (ISR) (Hsu et al., 2022). In addition, viperin interacts with numerous cellular and viral proteins, which are essential for its antiviral activity and modulation of innate and adaptive immune responses. To date, viperin has been shown to possess activity against numerous viruses, including DNA and RNA viruses, via multiple complex mechanisms (reviewed by Rivera-Serrano et al., 2020). For example, viperin acts as an antiviral ribonucleoside (ddhCTP) synthase that catalyzes the production of ddhCTP; viperin also inhibits the budding and release of some enveloped viruses by regulating lipid synthesis, and secretion of soluble proteins (Wang et al., 2007; Nasr et al., 2012). Viperin also interacts with certain viral proteins to promote their degradation (Panayiotou et al., 2018) or can interact with host proteins associated with direct interference in viral production and

replication (Vonderstein et al., 2018). However, antagonism of viruses towards viperin has not been observed, with the exception of the Japanese encephalitis virus (JEV) that degrades viperin in a proteasome-dependent manner (Chan et al., 2008). Viperin is highly conserved in vertebrates and is strongly induced by viruses (reviewed by Seo et al., 2011). Equine viperin (eqViperin) has been cloned and functionally characterized in our laboratory (Tang et al., 2014). The radical SAM domain of viperin contains a CxxxCxxC motif that is important for the enzymatic activity and antiviral function and that is conserved between equine viperin and that of other species (Tang et al., 2014; Fenwick et al., 2020). EIAV-infected eMDMs show up to 2.8-fold upregulation of eqViperin mRNA expression, overexpression of eqViperin significantly inhibited EIAV production in eMDMs, and knockdown of endogenous eqViperin enhanced the production of EIAV (Tang et al., 2014). EqViperin restricts EIAV at multiple steps during viral replication, including inhibition of Gag release, and inhibition of viral particle production and entry by disrupting the synthesis of Env and the receptor protein ELR1. However, eqViperin does not affect the expression of these proteins at the RNA level, nor does it cause their degradation. Furthermore, we observed that overexpression of eqViperin in HEK293T cells disrupts the ER (Tang et al., 2014), which may be one of the explanations for the inhibition of Env and ELR1 synthesis by eqViperin. Collectively, the eqViperin anti-EIAV effect is diverse, and appears to combine the multiple antiviral mechanisms of viperin as described above. An earlier study suggested that viperin inhibits the production of HIV-1 by preventing viral budding (Nasr et al., 2012), while a later study demonstrated that the effect of viperin on the restriction of primate lentiviruses (HIV-1 and SIV) is highly strain-specific, and that most HIV-1 strains and most SIV strains, as well as MVV and FIV, are not restricted by viperin (Lim et al., 2012). Therefore, viperin may not be a major restriction factor for lentiviruses (Lim et al., 2012). Considering that EIAV is a highly divergent lentivirus, whether the effect of eqviperin on EIAV restriction is also strain-specific needs further investigation.

Human Schlafen 11 (huSLFN11) is a member of the Schlafen family of proteins that are involved in the regulation of cell differentiation and growth, inhibition of viral replication, and can influence cancer development (reviewed by Kim and Weitzman, 2022). huSLFN11 is an interferon-inducible protein that is expressed in monocytes and monocyte-derived dendritic cells and T cells (Puck et al., 2015), as well as human foreskin fibroblasts and HEK293 cells (Li et al., 2012). To date, the huSLFN11 protein has been shown to inhibit the replication of HIV-1 (Li et al., 2012), prototype foamy virus (PFV) (Guo et al., 2021) and flaviviruses (Valdez et al., 2019) by preventing viral protein synthesis in a codon usage-dependent manner via its binding of transfer RNAs (tRNAs) (Li et al., 2012). A recent study has found that huSLFN11 also inhibits the replication of a DNA virus, human cytomegalovirus (HCMV), and demonstrated that HCMV RL1 protein antagonizes this restriction factor via recruitment of the CRL4 E3 ubiquitin ligase complex (Nightingale et al., 2022). Our laboratory has cloned and functionally characterized equine SLFN11 (eqSLFN11) (Lin et al., 2016). The eqSLFN11 protein shared 83.6% amino acid sequence homology with huSLFN11. eqSLFN11 is expressed at comparable levels in eMDMs, fetal equine dermal (FED) cells, fetal equine kidney (FEK) cells and fetal donkey dermal (FDD) cells, which are the cells permissive for EIAV replication. The expression of eqSLFN11 is upregulated by EIAV infection, which is consistent with the expression of huSLFN11, which is upregulated by flavivirus infection (Valdez et al., 2019). The eqSLFN11 inhibits the replication of EIAV and HIV-1 by a mechanism similar to that used by huSLFN11 for HIV-1 (Li et al., 2012; Lin et al., 2016). We observed that eqSLFN11 selectively inhibited the expression of the EIAV late protein Gag, but failed to restrict the expression of the EIAV early proteins (Tat and Rev). However this phenomenon was not observed in the restriction of HIV-1 by huSLFN11 (Li et al., 2012), and this difference may be due to the differing frequencies of codon usage by EIAV early and late genes (Lin et al., 2016).

8. Concluding remarks

Viral replication is largely host-dependent, with viruses hijacking cellular functions to facilitate their replication, while hosts develop barriers to fight the infection. Therefore, viral replication is a process in which the virus and the host battle against each other. Cellular restriction factors are early lines of defense against viral replication and spread, interfering with nearly every critical step of the viral replication cycle. However, viruses have evolved corresponding antagonistic mechanisms to counteract the various host restriction factors. In the field of virus and restriction factor studies, HIV-1 has been well investigated. EIAV is a macrophage-tropic lentivirus, and early studies have concluded that EIAV has the simplest genomic organization of any lentivirus (Leroux et al., 2004; Cook et al., 2013). As a result, an interesting question is "how does EIAV use its few viral proteins to overcome host restrictions?". Our group and others have identified Env, Rev and S2 of EIAV that antagonize tetherin (Yin et al., 2014), SAMHD1 (Ren et al., 2021) and Ser5 (Chande et al., 2016; Ahmad et al., 2019), respectively. Excitingly, we have recently discovered that EIAV also encodes several small viral proteins that have never been previously reported (Li et al., 2022; Zhang et al., 2022), and we are investigating whether they have some antagonistic function towards host restriction. More in depth study of interactions between virus and restriction factors would allow us to better understand the viral replication process and facilitate the development of antiviral drugs, ultimately improving the treatment of viral diseases.

Developing an effective HIV-1 vaccine remains a challenging task (Desrosiers, 2023). EIAV has been used as an animal model for HIV/AIDS research not only because EIAV-infected horses can effectively control EIAV replication, but more importantly because of the development of an attenuated EIAV vaccine (Wang et al., 2016). The attenuated EIAV vaccine was developed in the early 1970s by continuous passage of the wild-type pathogenic EIAV strain ($EIAV_{LN40}$) in donkeys for 117 generations (termed $EIAV_{DV117}$), followed by 121 *in vitro* passages in donkey monocyte-derived macrophages (dMDM) (termed $EIAV_{DLV121}$) (Wang et al., 2016). $EIAV_{LN40}$ is highly lethal in horses (80%–100% experimental lethality), but is less lethal in donkeys (less than 10% lethality). $EIAV_{DV117}$ is markedly more virulent, with up to 100% lethality in horses and donkeys. However, the pathogenicity of $EIAV_{DLV121}$ was completely lost, such that it caused no clinical symptoms in either horses or donkeys. From the late 1970s to the late 1980s, this vaccine was used extensively in China and the spread of EIA was effectively controlled (cited from "Equine infectious anemia and its controlling in China", a document issued by the Chinese Ministry of Agriculture in 1997, which is written in Chinese). Over the last decade or so, we have comprehensively studied the genetic characteristics of the attenuated EIAV vaccine (Wang et al., 2016) and confirmed its remarkably robust protection against EIA (Lin et al., 2020), demonstrating that this vaccine induces a specific immune response in immunized horses to protect against challenge with virulent strains (Zhang et al., 2007; Lin et al., 2011; Lin et al., 2020). Interestingly, the successive passages of EIAV in donkeys or dMDM may be an important factor for the success of this vaccine, because when parent pathogenic strains of the vaccine are cultured in horses or mules or their MDM, no vaccine strain is successfully obtained (Wang X-F, 2022). Previous studies have shown that EIAV vaccine strains introduce mutations in many genes throughout the viral genome compared to the pathogenic EIAV parent strains, with *s2*, *env* and LTR showing the highest variability (Wang et al., 2011; Wang et al., 2016). In addition, it was also demonstrated that the seven amino acid sites of Gag (3 sites)/Env (4 sites) were associated with the variations of virulence (Shen et al., 2006). Donkeys are known to be generally more tolerant of EIAV and other pathogens than horses (Camara et al., 2020), and EIAV infection in donkeys results in limited viral replication and is thought to be a persistent infection but without signs of clinical disease (Cook et al., 2001). In this regard, the attenuated phenotype of EIAV may have been selected for by some donkey-derived innate immune pressure (Tang et al., 2016; Wang et al., 2021). We previously demonstrated that EIAV infection upregulates the

expression of IFNs *in vivo* and *in vitro* (Lin et al., 2011a; Lin et al., 2011b) and that a donkey-derived tetherin also inhibits EIAV replication (Yao et al., 2017), and that some donkey-derived proteins have higher anti-EIAV activity than horse-derived proteins (data not published). Therefore, it is a very interesting direction for us to further explore whether EIAV is subjected to selection pressure from some donkey restriction factors during the vaccine preparation, especially during the long-term passaging culture of the vaccine in dMDM *in vitro*, which may help us to explain the mechanism underlying the attenuation of the vaccine strain.

Conflict of interest

The authors declare that there are no conflicts of interest.

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