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Review article

Maedi-visna virus as a model for HIV

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ABSTRACT

Maedi-visna virus (MVV) is a lentivirus of sheep causing inflammation in many organs, primarily the lungs and CNS. HIV and SIV also belong to the lentivirus genus of retroviruses. MVV and HIV have many features in common, including genome organization, mode of virus replication, virus-host interaction and latency. Both viruses infect cells of the monocyte/macrophage lineage, but the main difference in cell tropism is that, whereas HIV infects T lymphocytes, MVV does not. Here, the molecular biology, cell tropism and pathogenesis of MVV are reviewed and some of the similarities as well as the dissimilarities between MVV and HIV are discussed.

Keywords: HIV, lentivirus, maedi, SRLV, tropism, visna

YFIRLIT

Mæði-visnuveira og HIV: Margt er líkt með skyldum.

Mæði-visnuveira sýkir kindur og veldur aðallega lungnabólgu (mæði) og heilabólgu (visnu). Veiran er lentiveira og er náskyld alnæmisveirunni HIV. Veirurnar eiga margt sameiginlegt, svo sem skipulag erfðaefnis, virkni og gerð veirupróteina, fjölgunarferli, viðbrögð hýsils við sýkingu og dvalasýkingu, sem hýsillinn losnar aldrei við. Báðar veirur sýkja frumur ónæmiskerfisins; mæði-visnuveira sýkir átfrumur, en HIV sýkir bæði átfrumur og T-eitilfrumur. Í þessari yfirlitsgrein verða ýmis líkindi með þessum veirum reifuð.

INTRODUCTION

Maedi (an Icelandic word for "breathlessness") and visna (meaning wasting) are diseases that were brought to Iceland in 1933 with imported sheep of the Karakul breed. These diseases had gone mostly unnoticed in many countries, but the Icelandic sheep, which had been in almost total isolation in Iceland for over a thousand years, proved to be very susceptible to them. Epidemiological studies suggest that of the 20 sheep that were imported, two were healthy carriers, one giving rise to an epizootic of maedi in the northern part of the country, the other causing an epizootic of both maedi and visna in the west part of the country. Due to the long preclinical period, the diseases had spread unnoticed to many flocks when first recognized 6-7 years after the importation (Palsson 1976). The diseases were described by Sigurdsson and co-workers (Sigurdsson 1954a, 1954b, Sigurdsson et al. 1952, Sigurdsson et al. 1953, Sigurdsson et al. 1957). Serological studies and transmission experiments revealed that visna and maedi were manifestations of infection with the same virus in different organs, thus giving rise to the present name, maedi-visna virus (MVV) (Thormar and Helgadottir 1965, Gudnadottir and Palsson 1967, Gudnadottir & Palsson 1965). Other manifestations of an MVV infection are mastitis (De Boer et al. 1979) and arthritis (Oliver et al. 1981). In his studies of

maedi and visna, Sigurdsson noted the long incubation time without clinical signs, lasting for several months to years, and the protracted course after clinical signs appeared, usually ending in serious disease or death. He found this different from the course of acute infections, on the one hand, and chronic infections on the other, and proposed the term slow infections for this type of infection (Sigurdsson 1954b, reviewed by Thormar 2013).

MVV is a member of the lentivirus genus of the retroviridae that derive their name from Sigurdsson´s concept of slow infections (lentus=slow) (Haase 1975). Ovine lentiviruses have been identified worldwide and are variously referred to as maedi-visna virus (MVV), visna/maedi virus (VMV), ovine progressive pneumonia virus (OPPV), and ovine lentivirus (OvLV). The lentivirus of goats (caprine arthritis encephalitis virus, CAEV) has the same genome organization and target organs as MVV, and a number of studies have found evidence for the occurrence of cross-species transmission of MVV and CAEV between sheep and goats (Karr et al. 1996, Leroux et al. 1997, Zanoni 1998). The sheep and goat lentiviruses are commonly referred to as small ruminant lentiviruses (SRLV). The SRLVs are divided into five phylogenetic groups, A-E, which are again divided into subgroups. The prototype MVV strains are in group A1, while the prototype CAEV is in group B1 (Grego et al. 2007, Shah et al. 2004). Other lentiviruses are feline immunodeficiency virus (FIV), bovine immunodeficiency virus (BIV), equine infectious anaemia virus (EIAV), simian immunodeficiency viruses (SIV), and human immunodeficiency viruses (HIV).

Transmission and clinical signs

During the MVV epizootic in Iceland, the main route of transmission was via the respiratory tract. In Iceland, sheep are housed in close contact during winter, and during summer they used to roam freely on common unfenced pastures in the mountains. In the autumn roundups the sheep were kept by the thousands in big collecting folds for 1-3 days while being sorted out into their original flocks belonging to individual owners. This traditional method of sheep farming contributed to the rapid spread of the disease (Palsson 1976). Another route of transmission is through colostrum and milk from mother to offspring (Blacklaws et al. 2004, Peterhans et al. 2004). Transmission of HIV also occurs between HIV infected mothers and newborns, and intrauterine transmission seems to be more common in HIV infection than in SRLV infection. The main route of HIV transmission is through sexual contact and although the virus is found in lung fluids, there is no evidence that HIV is transmitted by the respiratory route (reviewed in B. Blacklaws and Harkiss 2010). MVV has been found in semen, but there are no reports of sexual transmission of MVV (Al Ahmad et al. 2008, Peterson et al. 2008).

Lentiviral diseases of small ruminants are characterized by chronic inflammation mostly affecting the lungs, brain, mammary glands and joints. The organ affected may be a result of both the viral strain and host species. The lung disease (maedi) was most prevalent during the epizootic in Iceland. Because of the long silent preclinical phase of the infection, clinical signs of maedi were rarely seen in animals under 3-4 years of age. The first clinical signs were increased laboured breathing and lagging behind when the flock was driven. As the disease progressed, the respiration at rest became gradually more laboured and the sheep lost condition. Coughing is not a prominent sign in maedi and is not productive when it occurs. This non-febrile disease usually lasted for 3-8 months or longer and was always fatal. (Thormar 2013, Palsson 1976).

The clinical signs of visna, a CNS disease, were aberration of gait, notably affecting the hind quarters. There was a gradually increasing weakness of the hind legs progressing to paraplegia or almost total paralysis. A general loss of condition was often seen and weight loss despite a healthy appetite (Pétursson et al. 1992). Clinical visna is rarely seen in ovine lentivirus infections outside of Iceland, where it was predominant in certain flocks where

maedi was also found (Pétursson et al. 1992). However, regional outbreaks of visna have been reported in other countries (Benavides et al. 2007, Brodie et al. 1995, Glaria et al. 2012).

Mastitis, with diffuse or nodular hardening of the udder and reduction of milk production was also seen (Cutlip et al. 1985, Pétursson et al. 1992, van der Molen et al. 1985). In contrast to sheep, arthritis is the prominent disease manifestation of SRLV in goats (Crawford et al. 1980) although mastitis is also common, especially in dairy herds.

Similar to MVV, early targets of HIV infection are the CNS and the lungs. The lymphoid interstitial pneumonia observed in HIV infection is similar to the typical lung manifestations in ovine lentiviral infections and a large proportion of HIV-infected individuals develop encephalitis. HIV infection causes immunodeficiency which is not seen in MVV, and frequent opportunistic infections in AIDS affect the pathological picture and make comparisons between the human and ovine disease difficult. For a comprehensive review see Blacklaws & Harkiss 2010.

Cell tropism

The lentiviruses are a non-oncogenic genus of the retroviridae that infect cells of the immune system. Several studies have shown that the main target cells of the ovine and caprine lentiviruses *in vivo* are cells of the monocyte/macrophage lineage; i.e. monocytes, macrophages, dendritic cells and microglial cells, T-lymphocytes are not infected. Viral replication is restricted until differentiation of the monocytes into macrophages (Clements et al. 1994, Gendelman et al. 1985, Gorrell et al. 1992). In contrast, HIV replicates both in lymphocytes and macrophages. The lentiviruses are thus unique among retroviruses in infecting non-dividing cells.

The cell tropism of HIV is largely determined by cell receptor usage. The primary cell receptor is CD4, and in addition, HIV Env binds to chemokine receptors that act as co-receptors for the virus, usually CCR5 or CXCR4 (Deng et al. 1996, Feng et al. 1996). Virus strains that are transmitted almost exclusively use CCR5 as a co-receptor. These viruses are termed R5 variants and can enter both T-cells and macrophages. However, most newly transmitted/founder viruses require high levels of CD4 for infection, and T cells expressing a much higher level of CD4 than macrophages are therefore primarily infected. As the infection progresses, CXCR4 (X4) – tropic viral strains emerge, as well as R5 strains that can infect cells with low levels of CD4 and are thus macrophage-tropic (Joseph et al. 2015).

The cellular receptors for the sheep and goat lentiviruses have not been identified, but there seem to be strain differences in the use of receptors. Thus, the Icelandic MVV strains KV1772 and K1514 and the British strain EV1 can enter a variety of cell types from a wide range of species, while many MVV strains and CAEV are restricted to cells of ruminant species (Bruett & Clements 2001, Gilden et al. 1981, Lyall et al. 2000, Mselli-Lakhal et al. 2000). A number of putative receptors have been suggested, among them MHC class II (Dalziel et al. 1991), mannose receptor (Crespo et al. 2011), a 45 kDa protein that has serine/threonine kinase activity and a 30 kDa protein which is a chondroitin sulphate proteoglycan (Barber et al. 2000, Bruett et al. 2000). In this connection it is interesting to note that heparan sulphate proteoglycans have been implicated as attachment receptors for HIV-1 (reviewed in Connell & Lortat-Jacob 2013).

Although MVV can enter a variety of cell types, replication *in vivo* is largely restricted to macrophages, dendritic cells or microglia in the brain (Brodie et al. 1995, Ebrahimi et al. 2000). The cell and organ tropism of MVV has been shown to be determined at the level of transcription (Agnarsdottir et al. 2000, Barros et al. 2005, Oskarsson et al. 2007). Transcription of the retroviruses is directed by the 5' long terminal repeat (LTR) of the integrated proviral DNA. The U3 region of the LTR contains the promoter and enhancer regions of the virus which are composed of binding sites for an array of transcription factors which are differently activated in the different cell types

(Gabuzda et al. 1989, Hess et al. 1985, 1989). However, in some instances it has been shown that the LTR is not responsible for cell tropism (Blatti-Cardinaux et al. 2016, Mselli-Lakhal, et al. 2000).

During the epizootic in Iceland, it was evident that there were strain differences in organ tropism, i.e. some virus strains seemed to be more neurotropic than others (Andresdottir et al. 1998). We found that a duplication of a sequence in the LTR, CAAATG, which constitutes an E-box, allowed the virus to grow in a variety of sheep cell types, including sheep choroid plexus cells. The control was most likely at the level of chromatin modification, since a difference in promoter activity could not be detected in the context of a reporter plasmid in transient transfection. This sequence was associated with neurotropic strains, which indicated that virus strains that can infect the cells which comprise the blood-brain barrier, that is, endothelial cells or cells of the choroid plexus, may be more neuroinvasive than others (Oskarsson et al. 2007). Another way of crossing the blood-brain barrier is by infected monocytes entering the brain, a process that has been called the "Trojan horse mechanism" (Peluso et al. 1985).

Genes and proteins of MVV and HIV-1

Lentiviruses, like other retroviruses, contain their genetic information in positive strand RNA molecules (genomic RNA, gRNA). Each virion contains two such molecules. The size of the RNA molecules of lentiviruses is 9-10 kilobases, somewhat larger than found in most retroviruses. The genome contains the three genes coding for the structural and enzymatic proteins, *gag*, *pol* and *env*, common to all retroviruses, and in addition, various numbers of regulatory and accessory genes (Figure 1). The *gag* gene codes for the inner structural proteins. The Gag precursor in HIV is a p55 myristoylated protein which is processed by the viral protease to p17 (matrix; MA), p24 (capsid; CA), p7 (nucleocapsid; NC) and p6 proteins, in addition to two spacer proteins, p2 and p1, that flank the NC (see Figure 1). The N-terminal myristoylation of Gag increases its affinity for membranes and is necessary for HIV and SIV budding (Morikawa et al. 1996, Olety & Ono 2014). However, myristoylation is not required for MVV budding, and it is not clear whether the MVV Gag precursor requires alternative fatty acid modification (e.g. acetylation) or remains unmodified (Rafnar et al. 1998). MVV Gag is processed to p16 (MA), p25 (CA) and p14 (NC) (Vigne et al. 1982). This sequence of proteins in the *gag* gene is conserved in all retroviruses. MA guides Gag to the plasma membrane for budding and recruits viral and host factors. In the mature virion, MA protein lines the underside of the lipid envelope of the virus (reviewed in Bell & Lever 2013). CA forms a cone-shaped capsid that is characteristic for the lentiviruses. The capsid contains the two RNA molecules of the virus as well as associated proteins. The NC domain of Gag in MVV contains two zinc finger domains (CCHC) which are highly conserved among retroviruses (Morcock et al. 2000) and selectively bind viral RNA for encapsidation into the virion. The RNA is packaged as a dimer, and the site of dimer initiation in the leader region of MVV RNA has been located just upstream of the major splice donor (Monie et al. 2005). In general, the packaging signals of retroviruses are located in and near the 5'-UTR of the gRNA and are several hundred bases long (Comas-Garcia et al. 2016). In some retroviruses, minimal RNA sequences that are sufficient for packaging of heterologous RNA have been defined (Adam & Miller 1988, Banks et al. 1998). However, packaging determinants have not been characterized fully for most of the lentiviruses (Berkowitz et al. 1995, Bjarnadottir et al. 2006), although both HIV and MVV RNA contain packaging signals located in the 5' region of the genome spanning the major splice donor and the Gag initiation codon (Bjarnadottir, et al. 2006, Sundquist & Krausslich 2012). In addition to RNA packaging, the mature NC protein is thought to assist reverse transcriptase in converting the single-strand genomic RNA into the double-stranded proviral DNA and to chaperone the IN-mediated integration of the proviral DNA into the host genome (reviewed

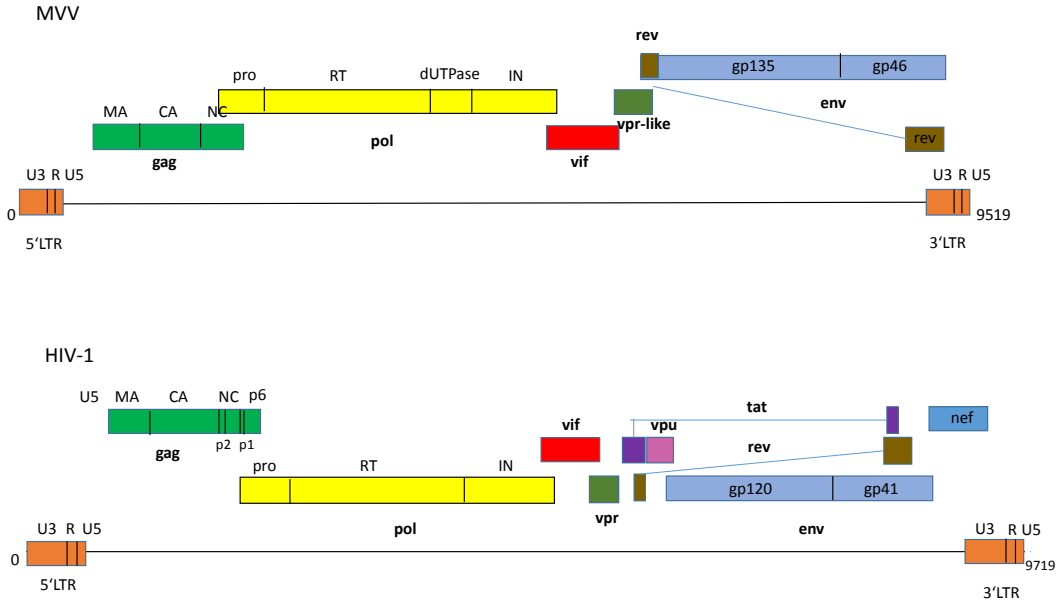

Figure 1. Genome organization of MVV and HIV-1. The HIV-1 map is based on strain HXB2 as shown on the Los Alamos HIV database website http://www.hiv.lanl.gov/. The MVV map is based on the MVV strain KV1772 sequence (Andresson et al. 1993).

in Mori et al. 2015).

In HIV, the C-terminal 52 aa of the Gag precursor constitutes the p6 peptide. The p6 contains short domains, called the late (L) domains, involved in virus budding and incorporation of the accessory protein Vpr into the virion (Bell & Lever 2013). A total of three different core sequences have been identified as essential elements for the L-domain function: P(T/S)AP, PPXY and LYPX$_n$L. These sequences serve as binding sites for cellular proteins that associate or function in the endocytic sorting complex required for transport (ESCRT) pathway. The p6 of HIV contains two L-domain sequences: PTAP and LYPX$_n$L that bind TSG101 and ALIX proteins of the ESCRT pathway, respectively (Bello et al. 2012). MVV contains a PSAP motif at the C-terminus of NCp14, and it has been shown that the terminal 10 aa in MVV NC p14, RVVPSAPPML, can functionally replace an analogous late domain in Rous sarcoma virus (Xiang et al. 1996).

The Pol polyprotein is expressed as a Gag-Pol polyprotein which is produced as a result of -1 ribosomal frameshifting in about 5% of translation events. In HIV, this frameshifting occurs in a so-called slippery sequence located near the 5' terminus of p6. In MVV the ribosomal frameshifting signal is an unusual pseudoknot which is well conserved in SRLVs (Pennell et al. 2008). The Gag-Pol polyprotein is processed by the viral protease into protease, reverse transcriptase (RT), RNaseH, dUTPase and integrase (IN). The reverse transcriptase, RNaseH and integrase are functionally well conserved between HIV and SRLV as evidenced by the similar action of anti-HIV-RT agents (Thormar et al. 1995, Thormar et al. 1998) and by the conserved structure and function of integrase (see a later section for details). However, dUTPase is only coded for by the non-primate lentiviruses FIV, EIAV, BIV, CAEV and MVV, but HIV and SIV do not contain a dUTPase gene. The dUTPase hydrolyses dUTP to dUMP and PP and thus provides a substrate for thymidylate synthase in the major biosynthetic pathway to

TTP. Its activity lowers the dUTP/TTP ratio and thus reduces the misincorporation of dUTP into DNA, which may induce mutations. The dUTPase-deficient FIV and CAEV have an increased G-A mutation frequency and dUTPase deficient EIAV replicates with slower kinetics in macrophages than the wild-type; however the effect of deleting the dUTPase gene from MVV is subtler. There is no difference in pathogenicity, but there is a decreased frequency of virus isolations from the lungs (Lerner et al. 1995, Lichtenstein et al. 1995, Petursson et al. 1998, Turelli et al. 1997, Turelli et al. 1996). The gene is well conserved and it is likely to have an important function, although in some SRLV strains it seems to be dispensable (Reina et al. 2010).

The envelope (Env) glycoproteins are produced as a precursor protein that is cleaved by cellular proteases into surface glycoprotein (SU; gp120 for HIV, gp135 for SRLV) and transmembrane glycoprotein (TM; gp41 for HIV, gp46 for SRLV). The SU harbours regions that recognize cellular receptors and TM mediates fusion with the cell membrane. During virus assembly the SU/TM complex is incorporated as heterotrimeric spikes into the lipid bilayer of nascent virions (reviewed in Checkley et al. 2011). The structure of the Env proteins of SRLV and HIV is remarkably similar despite limited sequence homology (Hotzel and Cheevers 2001, 2003, Malashkevich et al. 2001).

The three regulatory and auxiliary genes of the small ruminant lentiviruses are *rev, vif* and *tat/ vpr-like.*

Rev is a regulatory protein, expressed early in the infectious cycle, facilitating the transport of unspliced and singly spliced RNA molecules out of the nucleus (Sargan et al. 1994, Toohey & Haase 1994, Vigne et al. 1987). The Rev proteins act by binding structured RNA domains termed Rev responsive elements (RRE) located in the env gene (Malim et al. 1989, Mazarin et al. 1990, Tiley et al. 1991). The RREs of HIV and MVV are not interchangeable, however (Tiley & Cullen 1992).

Vif (Viral infectivity factor) is essential for the replication of the virus in primary cells and *in vivo* (Audoly et al. 1992, Fisher et al. 1987, Kristbjornsdottir et al. 2004, Strebel et al. 1987). Vif neutralizes APOBEC3 proteins which are cellular restriction factors that deaminate retroviral single stranded (ss) DNA as it is being synthesized (see a later section for details).

The *vpr-like* gene in SRLV was formerly called *tat*, analogous to the *tat* gene in HIV, since it had some trans-activating effect (Davis and Clements 1989, Neuveut et al. 1993, Vigne et al. 1987). The Tat proteins of HIV, SIV, BIV and EIAV are essential for efficient viral replication and transactivate their viral long terminal repeats (LTR) strongly upon binding to a TAR sequence (Derse et al. 1991, Liu et al. 1992, Viglianti and Mullins 1988). MVV, CAEV and FIV do not possess a TAR sequence, and the "Tat" protein of SRLVs was shown to be a weak transactivator (Barros et al. 2005, Sargan and Bennet 1989, Villet et al. 2003). MVV Tat acts through AP-1 and AP-4 binding sites in the LTR by binding to Fos and Jun transcription factors (Carruth et al. 1994, Gdovin & Clements 1992, Morse et al. 1999). Deletion of the gene in CAEV only resulted in a modest effect on replication both *in vitro* and *in vivo* (Harmache et al. 1995). The protein has been found to have characteristics more like Vpr (Viral protein R) than Tat in HIV. Vpr seems to be a multifunctional protein, but its roles in infection are still poorly understood. Vpr is incorporated into the virion, indicating a role in the early steps of virus replication, and it is part of the reverse transcriptase complex (RTC) as well as the preintegration complex (PIC). Vpr binds to transcription factors, and like in MVV, one of them is AP-l. (Varin et al. 2005). AP-1 and AP-4 have been implicated in latency (Duverger et al. 2013, Imai & Okamoto 2006), and it is interesting to speculate that Vpr may have a role in latency. Vpr induces cell cycle arrest at the G2 to mitotis (G2/M) transition by connecting the DCAF1 adaptor of the Cul4A ubiquitin ligase to an unidentified host target protein linked to the G2 arrest. It is also implicated in apoptosis (reviewed by Guenzel et al. 2014). Like HIV Vpr, the SRLV Vpr-like protein induces cell cycle arrest at the G2/M

transition, it is incorporated into the virion and has a nuclear localization (Rea-Boutrois et al. 2009, Villet et al. 2003).

Replication

As in other retroviruses, the two copies of maedi-visna virus positive strand RNA are reverse transcribed in the cytoplasm of the cell. The discovery by Temin (Mizutani et al. 1970) and Baltimore (Baltimore 1970) of an enzyme that can copy RNA into DNA was soon followed by Thormar who showed that MVV also contained an RNA-dependent DNA polymerase (Lin & Thormar 1970). Upon infection of a cell, the capsid core containing the viral RNA and viral enzymes is released into the cytoplasm, where it dissociates in an orderly fashion, called uncoating. Uncoating is a finely tuned process that is regulated by cellular proteins; too fast or too late uncoating can severely attenuate replication (Forshey et al. 2002). There is even evidence to suggest that the capsid remains intact until it reaches the nucleus (Jacques et al. 2016). In recent years, it is becoming clear that the capsid plays an important role in multiple steps of the lentiviral life cycle and infection (reviewed in Ambrose and Aiken 2014, Yamashita & Engelman 2017). The capsid is part of the reverse transcriptase complex (RTC). The RTC contains viral RNA, reverse transcriptase (RT) and other viral and host proteins which have not been fully characterized, but MA, CA, NC, IN, Vpr and Vif have been reported to be present in the RTC, and although purified RT can carry out reverse transcription *in vitro*, mutations in most of these genes impede reverse transcription in infected cells (reviewed in Hu & Hughes 2012). The RT makes use of lysine tRNAs to initiate a DNA copy of the RNA genome, the RNA is degraded, and a second strand of DNA is produced. This viral DNA contains duplications of both the 5' and 3' ends of the genome, forming long terminal repeats (LTRs) characteristic of retroviral DNA provirus.

The RT lacks proof-reading activity and as a result the mutation rate is 10^{5-} to 10^{6}-fold higher than the mutation rates of DNA polymerases (Dougherty & Temin 1986), contributing to the high genetic variability of the retroviruses (Coffin 1992). In addition, recombination contributes to the generation of genetic diversity of the retroviruses. Recombination results from RT template switching between the two RNA molecules. SRLV recombination both *in vitro* and *in vivo* has been reported (Andresdottir 2003, Pisoni et al. 2007, Ramirez et al. 2011).

The RTC is transported towards the nucleus via the microtubule network (McDonald et al. 2002). When reverse transcription is completed, the RTC transforms into a preintegration complex (PIC) which is transported into the nucleus. The PIC has to be transported through the nuclear pore complexes (NPC) by a not yet fully understood mechanism. In addition to the newly synthesised DNA, the PIC is composed of cellular and viral proteins, among these are IN, MA and Vpr, all harbouring nuclear localization signals (NLS). In addition, although CA does not possess an NLS, it is believed to mediate nuclear import (reviewed in Matreyek & Engelman 2013).

In order to replicate in the cell, retroviruses have to integrate their genome into the host chromosomes. This is achieved by the virus-encoded integrase protein, which is conserved among all retroviruses. The retroviral integrase has to carry out two consecutive reactions; hydrolysis of a phosphodiester bond at either viral DNA (vDNA) end, removing a di- or trinucleotide, liberating 3'-hydroxyl groups attached to invariant 5'-CA-3' dinucleotides, and cutting the host DNA in a staggered fashion, simultaneously joining both 3' vDNA ends to the host DNA resulting in repeated sequences of 4-6 bp flanking the inserted viral DNA (reviewed in Lesbats et al. 2016). A multimer of integrase molecules complexed with vDNA is referred to as the intasome. HIV-1 integrase is an extremely difficult protein to work with, and in structural analysis it has been necessary to introduce hyperactive and/or solubilizing mutations, which dramatically change the properties of the protein (Ballandras-Colas et al. 2017). However, MVV integrase lends itself nicely for structural studies as a wild-

type protein, and using MVV integrase as a model for lentiviruses, Ballandras-Colas et al. were able to visualize the functional intasome at 4.9 angstrom resolution using cryo-electron microscopy. The MVV intasome contains sixteen integrase subunits with a tetramer-of tetramer architecture, interacting with the two vDNA ends. This is a more complex intasome structure than that of other retroviruses that are known, where the PFV (foamy virus) intasome contains one tetramer and alpha- and beta-retroviruses have an intasome composed of two integrase tetramers. The structure of the MVV intasome can explain much previous data on the HIV-1 intasome structure, where the lack of structural information on the HIV-1 intasome has hampered drug development targeting HIV-1 integration (Ballandras-Colas et al., 2017).

The target sites of MVV integrase are as those of other lentiviral integrases, predominantly in actively transcribed genes, whereas the gamma-retroviruses favour transcriptional start sites and enhancer regions (Serrao et al. 2015). The alpha-, beta- and delta-retroviruses display more random distributions. The target DNA repeat sequence of MVV integrase is 6 bp, more like mouse mammary tumour virus (MMTV) and Rous sarcoma virus (RSV) than HIV-1 and other lentivirus integrases that yield a 5 bp target site duplication.

The retroviruses have been considered promising candidates for gene therapy vectors because of their integration into the chromosomes of the cell. However, integration into undesirable sites has hampered their development; for example Moloney-murine leukaemia virus (Mo-MLV)-based vectors have integrated into unintended genomic sites that led to oncogene activation in a number of cases (reviewed in Serrao & Engelman 2016).

The ability of lentiviruses to infect and replicate in quiescent cells has made them attractive candidates for gene therapy vectors. However, it would be desirable to be able to redirect integration away from active genes. One of the determinants of integration targeting of lentiviruses is a host factor termed LEDGF/p75, which is a lentiviral integrase-binding protein that tethers viral DNA integration to transcriptionally active regions of the host genome (Cherepanov 2007, Hare et al. 2009). However, there is evidence to suggest that LEDGF/p75 is not the only host factor directing lentiviral integrase to actively transcribed sites in the genome, and the viral capsid and CA-binding host proteins seem also to play a role (rewieved by Serrao & Engelman 2016).

Host defences

Infection by retroviruses is controlled at several levels; these include innate immunity and intrinsic cellular restriction as a first line of defence, and then adaptive immunity. The virus has to overcome all these hurdles in order to successfully infect the host.

During the last decade or so, a number of anti-retrovirus restriction factors have been discovered, which the viruses have in turn developed countermeasures for, each in their respective host. Most of these restriction factors have been discovered by studying the viral countermeasures, like the lentiviral accessory proteins Vif, Vpu, Vpx/Vpr (reviewed in Jia et al. 2015, Simon et al. 2015).

The APOBEC3 (apolipoprotein B mRNA-editing catalytic polypeptide-like 3) proteins are one example of these host-encoded retrovirus restriction factors. They catalyse the deamination of cytosine to uracil in the minus-strand of viral DNA during reverse transcription, resulting in G-to-A mutation in the plus-strand (Harris et al. 2003, Mangeat et al. 2003, Zhang et al. 2003). The resulting uracil residues can lead to functional inactivation of the retrovirus either by hypermutation or by triggering degradation of the viral nucleic acid prior to integration. The incorporated uracils might also impede the reverse transcriptase (Adolph et al. 2013). The APOBEC3 proteins vary in number between species; the mouse has one gene, humans have seven, and sheep and cows are in between with three APOBEC3 genes coding for four proteins (Jonsson et al. 2006, LaRue et al. 2010, 2008, 2009, Sheehy et al. 2002). The seven primate APOBEC3 proteins are commonly called APOBEC3A through APOBEC3H, but a

nomenclature system based on the Z-domains (cytosine deaminase motifs) has been proposed for the non-primate APOBEC3 genes (LaRue et al. 2008, 2009)

Most lentiviruses including MVV and HIV encode a counter-defence protein, Vif, which is essential for virus replication in natural target cells and *in vivo* (Audoly et al. 1992, Fisher et al. 1987, Kristbjornsdottir et al. 2004, Strebel et al. 1987). The Vif proteins are potent APOBEC3 antagonists; all human APOBEC3 proteins except APOBEC3A and APOBEC3B are sensitive to HIV-1 Vif, and sheep APOBEC3Z2-Z3 and APOBEC3Z3 are sensitive to MVV Vif (Hultquist et al. 2011, Jonsson et al. 2006, Larue et al. 2010, Refsland et al. 2010). However, sheep APOBEC3Z1 has been shown to be analogous to human APOBEC3A and is not sensitive to MVV Vif (de Pablo-Maiso et al. 2017). Vif induces polyubiquitylation of APOBEC3 for subsequent degradation in the proteasome, thus preventing the incorporation of APOBEC3 into the viral particle (Conticello et al. 2003, Mariani et al. 2003, Sheehy et al. 2003, Yu et al. 2003). HIV-1 Vif achieves this by acting as an adaptor connecting APOBEC3 and the cullin5-ElonginB-ElonginC-RBX2 ubiquitin ligase (Yu et al. 2003). The conserved T/SLQXLA motif in the C-terminus of Vif interacts with ElonginC and ElonginB and is referred to as the BC box (Yu et al. 2003, 2004). The cellular transcription factor core-binding factor-beta (CBFβ) is required for HIV-1 Vif mediated degradation of human APOBEC3 (Jager et al. 2012, Zhang et al. 2012). CBFβ forms a complex with Vif which facilitates the assembly of a functional APOBEC3 ubiquitin ligase complex (Hultquist et al. 2012, Kim et al. 2013). MVV and other SRLVs do not use CBFβ, but recruit Cyclophilin A (CypA) for stabilizing the APOBEC3-Vif-ubiquitin ligase complex (Kane et al. 2015).

We have obtained evidence to suggest that neutralizing APOBEC3 is not the sole function of MVV Vif. An MVV mutant with simultaneous mutations in the capsid (CA) and Vif has a pro-ser mutation in the C-terminus of MVV Vif together with a leu- arg substitution in CA. This mutant is attenuated in viral replication in blood-derived macrophages and *in vivo* without inducing hypermutation. These mutations may define a novel restriction factor that targets the CA and is counteracted by Vif (Franzdottir et al. 2016, Gudmundsson et al. 2005).

CypA is a peptidyl-prolyl isomerase that binds to the capsid of some lentiviruses, including HIV-1, but not to MVV capsid or to some other lentiviruses such as SIVmac or EIAV (Kane et al. 2015, Lin & Emerman 2006). CypA is thought to influence the recognition of CA by host factors that may act at the time of reverse transcription, nuclear import or integration (reviewed in Strebel et al. 2009). CypA promotes reverse transcription of HIV-1, but reduces nuclear entry in a cell-specific manner. It has been speculated that there may exist a cell-type specific CypA-dependent restriction factor that blocks HIV-1 replication by delaying CA core uncoating and hindering nuclear entry (De Iaco & Luban 2014). The interaction of CypA with HIV-1 capsid has been found to be essential for the virus to evade detection by the innate immune sensor cGAS and to avoid subsequent activation of the innate immune response (Rasaiyaah et al. 2013). CypA has also been shown to interact with HIV-1 Vpr (Zander et al. 2003). Furthermore, a CypA imposed inhibition of SIV in human cells is counteracted by Vif (Takeuchi et al. 2007). It is clear that CypA affects both replication and restriction of the lentiviruses in various ways.

One of the host factors affected by CypA is TRIM5α. There are almost 100 genes encoding TRIM proteins in the human genome, and some of these show anti-viral activity (Stremlau et al. 2004, reviewed in Grutter & Luban 2012). TRIM5α binds to the incoming cores of HIV-1 and is thought to trigger premature uncoating. However, the mechanism of this inhibition is not completely understood. Some studies have found that TRIM5α can block HIV-1 at more than one step, both at reverse transcription and nuclear import (Yap et al. 2006). Recognition of the capsid lattice by TRIM5α also induces an innate immune response against the virus (Pertel et al. 2011), and recently, TRIM5α was found

to regulate autophagy (Mandell et al. 2014). A functional TRIM5α protein in sheep has been reported and shown to inhibit MVV (Jauregui et al. 2012).

Additional host factors that have been found in recent years to restrict HIV are SAMHD1, BST2/tetherin and MxB. The effect of these host factors on SRLV replication has yet not been reported.

SAMHD1 causes inefficient replication of HIV-1 and other lentiviruses in macrophages and dendritic cells, but is antagonized by the viral protein Vpx which targets the protein for proteasomal degradation (Hrecka et al. 2011, Laguette et al. 2011). Vpx is present in HIV-2 and several SIVs but not in HIV-1. SAMHD1 is a dNTPase and is thought to inhibit HIV-1 by limiting the dNTP pool in non-dividing cells and thus inhibiting viral c-DNA synthesis (Goldstone et al. 2011). However, whether lowering cellular dNTP levels is the sole mechanism of restriction is not clear (Welbourn & Strebel 2016).

BST-2/tetherin inhibits virus replication by "tethering" the viral particles to the cell at budding, thus preventing their release (Hinz et al. 2010). BST-2/tetherin is antagonized by the viral protein Vpu (Neil et al. 2008), which is encoded by HIV-1 and a few SIVs, but not by HIV-2 and most SIVs or non-primate lentiviruses.

Mx2/B is an interferon induced host factor that potently inhibits HIV-1 replication at a post-reverse transcription stage (Goujon et al. 2013). MxB primarily targets the capsid and inhibits PIC nuclear import and integration (Matreyek et al. 2014).

Adaptive immunity

MVV elicits both humoral and cell-mediated immune responses in the host (Griffin et al. 1978, Larsen et al. 1982, Sihvonen 1981, Thormar & Helgadottir 1965, Torsteinsdottir et al. 1992). There seem to be host-related differences in the strength of the immune response. Whereas the Icelandic sheep elicit a strong neutralization response against the MVV strains circulating in Iceland at the time of the epizootic, neutralizing antibodies are absent or of a very low titre in many MVV and CAEV infections (Cheevers et al. 1993, Klevjer-Anderson & McGuire 1982, McGuire et al. 1990, Narayan et al. 1984). In experimental MVV infection, type-specific neutralizing antibodies are detected 6 weeks to 4 months post infection, and other more broadly neutralizing antibodies appear up to 4 years later in most sheep (Andresdottir et al. 2002, Petursson et al. 1976). A type-specific neutralization epitope has been mapped in the fourth variable region (V4) of the MVV SU and was shown to be immunodominant and thus is termed the "principal neutralizing domain (PND)" by analogy to the V3 loop in HIV-1 Env (Haflidadottir et al. 2008, Javaherian et al. 1989, Skraban et al. 1999). We have shown that neutralizing antibody is effective in MVV infection *in vivo* (Andresdottir et al. 2002, Arnarson et al. 2017) and neutralizing antibodies have been shown to have some protective effect in the cerebrospinal fluid, where they are locally produced (Georgsson et al. 1993, Petursson et al. 1976). A similar pattern of neutralizing antibody development has been reported in HIV infection (Albert et al. 1990, Rusert et al. 2016).

The role of cellular immunity in HIV-1 infection has been well documented. Several lines of evidence suggest that $CD8^+$ T-cells play a significant role in protection from HIV replication and disease progression; the initial control of viremia in HIV infection coincides with an expansion of HIV-1-specific $CD8^+$ T-cells (Borrow et al. 1994, Koup et al. 1994), there is selection for escape mutants from the cytotoxic T-lymphocyte response (Goulder & Watkins 2004) and HIV non-progressors preferentially maintain highly functional HIV-specific $CD8^+$ T-cells (Betts et al. 2006). Virus specific $CD8^+$ T-cells have been demonstrated after *in vitro* stimulation of lymphocytes from MVV and CAEV infected sheep and goats, and escape variants from the cytotoxic response have been detected (Blacklaws et al. 1994, Lee et al. 1994, Lichtensteiger et al. 1993).

Despite active immune responses, neither HIV nor MVV are cleared from the host. Several lines of evidence have shown that

pathogenesis of these viral diseases is immune-mediated. Thus, early lesions in experimental MVV infection of sheep were almost abolished by immunosuppressive treatment with antithymocyte serum and cyclophosphamide (Nathanson et al. 1976). Very few cells in the brain are productively infected (Haase 1986) and it is likely that lesions are in large part due to amplification of the immune response to viral antigens with a great influx of macrophages and lymphocytes and secretion of cytokines resulting in non-specific tissue damage (Georgsson et al. 1989, Pétursson et al. 1992). For comparison of MVV and HIV pathology see Blacklaws and Harkiss (2010), Georgsson (1994), and Thormar (2005).

Persistence

The persistence of MVV in the face of a strong immune response was an unsolved puzzle for a long time. Sigurdsson proposed that "perhaps the infectious agent is so well adapted to the host, so well camouflaged, that it has to some extent eliminated its own species specificity in the immunological sense" (Sigurdsson 1954b). One way for lentiviruses to escape the immune response may be through antigenic drift, as proposed by Gudnadottir (Gudnadottir 1974) and further confirmed and extended by Narayan et al. (Narayan et al. 1977, 1978, 1981). A wealth of genetic, immunological and structural studies of HIV-1 envelope glycoproteins have revealed remarkable diversity and conformational flexibility of these molecules that may result in neutralization escape, either by mutation of the neutralization epitopes or indirectly by conformational masking of epitopes or shielding by glycosylation (Huang et al. 2005, Kwong et al. 2002, Wei et al. 2003, Wyatt & Sodroski 1998, Wyatt et al. 1998). However, antigenic escape cannot be the only means of persistence, since virus that had not evolved at all was repeatedly isolated from sheep up to 10 years after MVV infection (Arnarson et al. 2017, Lutley et al. 1983). It has been suggested that hematopoietic stem cells in the bone marrow serve as a latent reservoir (Gendelman et al. 1985); this may not be the only reservoir, however, since a study of long-term CAEV infection in goats found infrequent infection of the bone marrow (Ravazzolo et al. 2006). Another possible reservoir is the spleen, which has been shown to be a monocyte reservoir (Swirski et al. 2009) and is a frequent site for virus isolation. We have obtained evidence to suggest that latently infected monocytes are shed into the blood stream from hidden reservoirs, where they are caught by the immune response. Virus that had been transmitted naturally via aerosol was shown to harbour mutations in the env gene that changed antigenicity, suggesting that the viruses have to escape the immune response of the host to allow them then to go on and infect other animals (Arnarson et al. 2017). A similar pattern of persistence has been described for HIV, i.e. antigenic escape and latency. The latent reservoirs for HIV-1 have not been fully elucidated, but it has been shown that resting $CD4^+$ T cells harbour integrated viral genomes and constitute one reservoir of latency (Descours 2017, reviewed by Eisele & Siliciano 2012, van der Sluis et al. 2013). However, it has been suggested that macrophages constitute another virus reservoir (Alexaki & Wigdahl 2008, Archin et al. 2014) and astrocytes, perivascular macrophages and microglial cells in the brain may be latently infected. All three cell types are long-lived with a half-life ranging from months to years (for microglial cells) (reviewed by Marban et al. 2016). The brain has been proposed to be one site of latency for HIV and SIV (Alexaki & Wigdahl 2008, Avalos et al. 2017). HIV enters the CNS early after infection and continues to cause HIV-associated neurocognitive disorders in approximately 50% of infected individuals despite antiretroviral therapy.

The mechanisms of latency have not been fully elucidated, but it is commonly assumed that after integration, latent infection is established through chromosome modification either by the absence of necessary transcription factors or by the presence of repressors acting on the LTR. AP-1 and AP-4 binding sites in the LTR of HIV-1 have been found important in the establishment of latency (Duverger et al. 2013,

Imai & Okamoto 2006). In this connection it is interesting to note that most MVV strains harbour AP-1 binding sequences in the LTR and an AP-4 motif is the best conserved element in the SRLV LTR (Gomez-Lucia et al. 2014, Hess et al. 1989, Sargan et al. 1995).

Concluding remarks

Although HIV has been extensively studied for the last 35 years or so, a number of open questions still remain to be answered. Among these are the sites and mechanisms of latency; host- and virus-encoded proteins that take part in reverse transcription, nuclear entry and integration; the mechanisms of restriction by host-encoded restriction factors and the mechanisms of virus counter-defence; the role of the immune system in pathogenesis; invasion and replication of virus in the brain, and more. Some of these questions can be explored in the non-primate lentiviral systems like MVV/sheep. The main difference between the primate lentiviruses and the SRLVs is that the SRLVs do not infect T lymphocytes and therefore do not cause overt immunodeficiency. However, a number of features are highly conserved between the lentiviruses, like the enzyme integrase whose depiction in MVV has helped clarify the structure of HIV-1 integrase. The two accessory genes that are common to HIV and MVV, Vpr and Vif, may have conserved functions some of which have yet to be elucidated; does Vpr have a role in latency and does Vif have additional functions besides neutralizing APOBEC3? What is the role of cyclophilin in infection? Does cyclophilin bound to Vif in MVV have the same role as cyclophilin bound to CA in HIV-1? Cells in the CNS are infected by macrophage-tropic HIV and constitute a latent reservoir. It is likely that MVV can serve as a model for CNS infection. Other functions may be carried out differently by the different lentiviruses and these differences may also be informative.

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