Macaque-tropic human immunodeficiency virus type 1: breaking out of the host restriction factors

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Macaque monkeys serve as important animal models for understanding the pathogenesis of lentiviral infections. Since human immunodeficiency virus type 1 (HIV-1) hardly replicates in macaque cells, simian immunodeficiency virus (SIV) or chimeric viruses between HIV-1 and SIV (SHIV) have been used as challenge viruses in this research field. These viruses, however, are genetically distant from HIV-1. Therefore, in order to evaluate the efficacy of anti-HIV-1 drugs and vaccines in macaques, the development of a macaque-tropic HIV-1 (HIV-1mt) having the ability to replicate efficiently in macaques has long been desired. Recent studies have demonstrated that host restriction factors, such as APOBEC3 family and TRIM5, impose a strong barrier against HIV-1 replication in macaque cells. By evading these restriction factors, others and we have succeeded in developing an HIV-1mt that is able to replicate in macaques. In this review, we have attempted to shed light on the role of host factors that affect the susceptibility of macaques to HIV-1mt infection, especially by focusing on TRIM5-related factors.

Keywords: macaques, HIV-1, animal model, host factors, genetic background

INTRODUCTION
It is estimated that about 2.5 million individuals per year get infected with human immunodeficiency virus type 1 (HIV-1), a causative agent of acquired immunodeficiency syndrome (AIDS; UNAIDS Global report 2012, http://www.unaids.org/). To contain the disastrous epidemic, we need to consider effective approaches. For the pre-clinical evaluation of the anti-HIV-1 vaccines and therapies, it is necessary to have suitable animal models. Moreover, animal models would also aid for the understanding of the underlying mechanisms of HIV-1 pathogenicity. Since HIV-1 shows very narrow species specificity, being limited to human and apes, it has been quite challenging to develop an ideal animal model in which HIV-1 efficiently replicates and induces pathogenicity. Instead, many kinds of surrogate models developed as alternative strategy provide us many important insights. In this decade, the molecular characterization of antiviral host restriction factors has dramatically progressed and shed light on the understanding of the viral specificity. These findings encouraged us to develop a novel non-human primate model for HIV-1 infection on the basis of a new concept (i.e., introduction of minimal modification to HIV-1 genome), by which the resultant virus would overcome a number of restriction factors. In this review, we summarize the history of the identification of the restriction factors and also discuss its impact and future direction on the development of HIV-1 animal models.

HISTORY OF HIV-1 ANIMAL MODELS
HIV-1 INFECTION IN SMALL ANIMALS
After the identification of HIV-1 as a causative agent of AIDS, many investigators sought to develop animal models for further research (reviewed in Gardner and Luciw, 1989). Although many efforts were performed in small animals, HIV-1 did not infect rodents, such as mice and rats, due to a number of restrictions, including the inability of HIV-1 Env to use the surface molecules in these animals as binding and entry receptors (Achison et al., 1998) and the defect of murine cyclin T1 protein to associate with HIV-1 Tat (Kwak et al., 1999). Although rabbits were once expected to show susceptibility to HIV-1 infection (Flucer et al., 1988; Kulaga et al., 1989), the reproducibility of this model remains to be elucidated (Reina et al., 1993; Speck et al., 1998; Tervo and Keppler, 2010). In an attempt to overcome the limitation in using these animals, several versions of humanized mice such as SCID-hu-PBL (severe combined immunodeficiency-human peripheral blood lymphocytes) mice (Moisier et al., 1988), Rag2−/−γc−/− mice (Traggiai et al., 2004), NOD (NOD scid gamma) mice (Shultz et al., 2005), and NOD/SCID-hu BLT mice (Melkus et al., 2006), have been generated (reviewed in Berges and Rowan, 2011). To generate this model, human immune cells were implanted into immunocompromised mice. After reconstitution of engrafted immune cells, HIV-1 replication in these animals was investigated. Generally, robust HIV-1 replication and loss of peripheral CD4+ T cells is observed in infected animals. Therefore, this model system would be useful for evaluation of drugs and neutralizing antibodies against HIV-1 (Denton et al., 2008). Moreover, this model provides important insight about the viral latency and the role of accessory genes in vivo (Denton et al., 2012; Marsden et al., 2012; Sato et al., 2012). However, none or weak immune response is observed in these animals. Moreover, this model requires special surgical skills and facilities to perform experiments.

HIV-1 INFECTION IN NON-HUMAN PRIMATES
Differently from other pathogenic viruses for human such as measles and mumps, HIV-1 does not replicate in New World...
monkeys (NWMs) and Old World monkeys (OWMs). In cells from NWMs, such as squirrel monkey (Saimiri sciureus) and common marmoset (Callithrix jacchus), the cluster of differentiation 4 (CD4) and C-C chemokine receptor type 5 (CCR5) molecules function insufficiently as binding and entry receptors (LaBonte et al., 2002). On the other hand, in OWM cells, most HIV-1 enters target cells as efficiently as human cells. Interestingly, recent studies revealed that some subtypes of HIV-1 are unable to efficiently utilize macaque CD4 because of the difference in the C-terminus of the D1 domain of CD4 between human and OWMs, and therefore adaptive mutation was required for optimal efficiency (Humes and Overbaugh, 2011; Humes et al., 2012). After entering target cells, the subsequent steps of HIV-1 life cycle (i.e., uncoating and reverse transcription) are strongly abolished in OWM cells (Shibata et al., 1995; Hofmann et al., 1999). Although pigtailed macaque (Macaca nemestrina, hereafter denoted as PM) was once believed to be promising because of its higher susceptibility to HIV-1 infection as compared to other OWMs (Agy et al., 1992), the HIV-1 replication in those animals was weak and the trial of serial in vivo passage was shown to be unsuccessful (Agy et al., 1997). Among the animals examined for their susceptibility to HIV-1 infection, chimpanzees and gibbon apes were identified to have high susceptibility (Fultz et al., 1986; Lusso et al., 1988). In 1980s and 1990s, many chimpanzees were experimentally infected with HIV-1, including clinically isolated viruses and molecularly cloned viruses, resulting in a robust viral replication (Alter et al., 1984; Fultz et al., 1987, 1999; Naray et al., 1987; Prince et al., 1998). These experiments provided many important insights, including the role of neutralizing antibody in protective immunity. While some of the infected chimpanzees experienced AIDS-related symptoms (Fultz et al., 1991; November et al., 1997; O’Neil et al., 2000), most of them seemed not to develop apparent clinical symptoms (Gardner and Luciw, 1989; Johnson et al., 1993). Furthermore, there are many concerns about using chimpanzees, including ethical issues and their quite high rearing cost; therefore, researchers finally decided not to use this ape for HIV-1 research (Cohen, 2007). Therefore, the need for the development of other non-human primate models has been increasing.

**SIV INFECTION IN NON-HUMAN PRIMATES**

As a surrogate model, simian immunodeficiency virus (SIV) infection in Asian macaques, such as rhesus macaque (Macaca mulatta, hereafter denoted as RM) and cynomolgus macaque (Macaca fascicularis, hereafter denoted as SM) for SIVsm and African green monkey (Chlorocebus aethiops, hereafter denoted as AGM) for SIVagm, respectively, (Ohta et al., 1988; Kraus et al., 1999), infected animals generally do not develop immunodeficiency, unlike the course of HIV-1 infection in humans. In the 1980s, accidental transmission of SIVsm to RMs caused a lethal disease, and the symptoms were quite similar to those seen in AIDS patients (Daniel et al., 1985; Letvin et al., 1985). Thereafter, the pathogenic virus was molecularly cloned as SIVmac (Naidu et al., 1986; Kestler et al., 1990). The combination of SIVmac and RMs has been widely utilized as a surrogate model for HIV-1 infection because of its similarity in the genome structure and pathogenicity.

Specifically, this model dramatically advanced our understanding in terms of the functional roles of the viral accessory genes in vivo (Kestler et al., 1991; Gibbs et al., 1995; Hirsh et al., 1998). Moreover, this model provided the important finding that the acquired protective immunity induced by live-attenuated vaccines was effective against homologous and heterologous SIV challenges (Daniel et al., 1992; Wyand et al., 1996, 1999).

**INFECTION OF CHIMERIC VIRUS BETWEEN HIV-1 AND SIV IN NON-HUMAN PRIMATES**

Accumulating evidence has demonstrated the inability of intact HIV-1 to replicate in OWM cells. Then, what kind of viral components in HIV-1 and SIV determine their host tropism? In an effort to answer this profound question, many researchers constructed chimeric viruses between HIV-1 and SIV and analyzed their viral replication in human and OWM cells. It was shown that chimeric viruses containing HIV-1-derived gag and/or env were unable to replicate in macaque cells and that a chimeric virus encoding HIV-1-derived env on the SIVmac backbone was able to replicate in primary OWM cells (Shibata et al., 1991; Shibata and Adachi, 1992), indicating that the step of entry was not the determinant for the species specificity of HIV-1. As a consequence of vigorous investigation, Shibata et al. finally succeeded to construct a prototypic simian-human immunodeficiency virus (hereafter denoted as SHIV) clone that encodes HIV-1-derived tat, rev, vpu, and env genes on the SIVmac239 backbone (Shibata et al., 1991; Shibata and Adachi, 1992). This SHIV clone was shown to efficiently replicate in primary macaque cells. Thereafter, many groups developed several versions of SHIV. Of note, by serial passaging of apathogenic SHIV-89.6 in monkeys, Steinmann et al. (1996) successfully obtained a highly pathogenic virus (SHIV-89.6P) that caused rapid and complete depletion of peripheral T cells, leading to simian AIDS. These chimeric viruses not only enabled us to evaluate the efficacy of antiviral immunity against HIV-1 Env but also supplied us important insights on what kind of SIVmac-derived genes are necessary to replicate in macaque cells. This SHIV model became a huge breakthrough for HIV-1 investigators; by using SHIV, the mechanism and efficacy of passive immunization (Shibata et al., 1999; Baba et al., 2000; Nishimura et al., 2002) as well as vaccine candidates (Igarashi et al., 1997; Letvin et al., 1997; Cafaro et al., 1999) were vigorously investigated. Incidentally, the lower sequence homology in RT between SIV and HIV-1 limited this model for the evaluation of antiretroviral drugs especially against RT. To overcome this limitation, RT-SHIV, which encodes HIV-1 RT in the place of SIVmac RT, was developed and used for the assessment of RT inhibitors (Ubel et al., 1995; Ambrose et al., 2004; North et al., 2005). SHIV carrying HIV-1 integrase (IN) in addition to RT was also constructed (Akiyama et al., 2008). These efforts have dramatically advanced the basic research related to HIV-1. However, since these viruses were constructed on the basis of SIVmac backbone, SHIVs are still far from HIV-1. Moreover, some pathogenic SHIV clones, such as SHIV-89.6P, show quite different phenotypes in macaques, unlike those in HIV-1 infection of humans and SIVmac infection of macaques (Feinstock and Mason, 2002). First, these SHIVs induced abnormally rapid, profound, and irreversible loss of CD4+ T cells in macaques, differently from the gradual
The history and the future direction of macaque-tropic HIV-1

Sakai et al., 1993; Tervo and Keppler, 2010). Virions produced from these restrictive cells have less infectivity as compared to the wild-type virus. Many efforts were made to identify a cellular factor that conferred this restrictive activity. In particular, the fact that heterokaryons between permissive and restrictive cells suppressed the infectivity of the vif-deficient HIV-1 clearly suggested the existence of a potent endogenous inhibitor of HIV-1 replication in restrictive cells (Madias and Kahut, 1998; Simon et al., 1998). Finally, in 2002, the apolipoprotein B mRNA editing enzyme catalytic polypeptide 3 G (APOBEC3G; hereafter denoted as A3G) was identified as a novel host restriction factor in human cells (Sheehy et al., 2002). A3G is expressed in various tissues including testis, ovary, spleen, and peripheral blood mononuclear cells (PBMCs; larmuz et al., 2002). Since A3G is a member of the cytidine deaminase enzyme, the vif-deficient virus contains many G-to-A mutations in its minus-strand genome, leading to disruption of infectivity. Moreover, the fact that deamination-deficient mutant A3G can still inhibit vif-deficient HIV-1 implied that A3G exerts its antiviral activity with deamination-dependent and deamination-independent fashion (Newman et al., 2003). In order to counteract the A3G-mediated restriction, HIV-1 has equipped its genome with vif gene and the resultant protein, Vif, efficiently inhibits A3G incorporation into progeny virions by inducing proteasome-dependent degradation of A3G (Contello et al., 2003; Kao et al., 2003; Mebile et al., 2004). Recently, it was reported that core-binding factor beta (CBFβ), a transcription regulator through RUNX binding, was required for HIV-1 Vif to degrade A3G (Huqquist et al., 2012; Jager et al., 2012). SIVmac Vif similarly recruits CBFB in order to neutralize the RM A3G (Huqquist et al., 2012; Jager et al., 2012). It was also proposed that HIV-1 Vif suppresses human A3G activity by inhibiting the translation of A3G (Mercenne et al., 2010). Although the human genome encodes other six A3 members (A3A, B, C, DE, F, and H) in addition to A3G, the precise antiviral activity of the A3 proteins remains to be elucidated. Human A3F was also reported to have anti-HIV-1 activity and susceptibility to HIV-1 Vif (Li-dament et al., 2004; Weggand et al., 2004; Zheng et al., 2004). In contrast, Miyagi et al. (2010) suggested that the antiviral activity of endogenous level of human A3F was negligible as compared to the activity of A3G. It is known that human A3DE and A3F, in addition to A3G, are also sensitive to counteraction by HIV-1 Vif (Goila-Gaur and Strebel, 2008). As seen in humans, the RM genome also encodes seven A3 members (Schmitt et al., 2011). Virgen and Hatziioannou (2007) investigated the susceptibility of HIV-1 to each RM A3 family member and showed that A3B, A3E, A3G, and A3H had the ability to restrict HIV-1 and were resistant to HIV-1 VIF activity. It should be noted that Vif-A3G interaction shows species specificity (Mariani et al., 2003). HIV-1 Vif is able to counteract A3G from humans but not from RM and AGM (Zentouni and Biemans, 2006; Virgen and Hatziioannou, 2007). Conversely, SIVmac Vif is effective against A3G from AGM and RM, but unable to antagonize A3G from human and chimpanzee (Mariani et al., 2003). SIVmac Vif efficiently counteracts A3G from human, chimpanzee, AGM, and RM (Mariani et al., 2003). Are there any polymorphisms in the A3 family? In case of humans, a polymorphism in A3B deletion was reported (Kidd et al., 2007). In RMs, a polymorphism in A3DE was observed and was reported to affect the antiviral activity (Virgen and Hatzi- ioannou, 2007). How can we obtain HIV-1 with the ability to overcome macaque A3s? Many efforts have been made to evade from the restriction by the macaque A3 family. Schrofelbauer et al. (2006) showed that mutations of HIV-1 Vif at positions 14-17 from DRMR into SEMQ allowed HIV-1 Vif interaction with A3G from RM. However, this HIV-1 Vif harboring SEMQ remained susceptible to A3B, A3F, and A3H from RM (Virgen and Hatzi- ioannou, 2007), suggesting that the introduction of this sequence
Vpu are ineffective against BST-2 from RM and AGM (McNatt et al., 1999). Specifically, while permissive cells, such as HEK293T and HT1080 cells, allowed comparative levels of virion production, non-permissive cells, such as Jurkat and Hela cells, decreased the amount of virion production in the absence of vpu. It was also reported that interferon (IFN) treatment led to a phenotype switch from permissive to non-permissive (Neil et al., 2007). Thus, the existence of unknown IFN-inducible, Vpu-sensitive cellular factors, was predicted. In 2008, bone marrow stromal antigen 2 (BST-2), also known as tetherin, CD317, and HML-24, was identified by two independent groups (Neil et al., 2008; Van Damme et al., 2008). BST-2 is a type 2 integral membrane protein, with the N-terminal located in the cytoplasm, one membrane-spanning domain, and a C-terminus modified by the addition of a glycosyl-phosphatidylinositol (GPI) anchor (Kupzig et al., 2003). Erikson et al. (2011) analyzed the expression profile of BST-2 in vivo and demonstrated that BST-2 was expressed in various tissues, especially spleen and alimentary system. They also showed that PRIM3, monocytes express high levels of BST-2 as compared to T and B cells. Furthermore, like tripartite motif-containing protein 5 (TRIM5α), homolog BST-2, but not other primate BST-2, has been recently reported to function as an innate sensor, leading to the transforming growth factor β activated kinase-1 (TAK1)-dependent activation of NfkB and subsequent production of pro-inflammatory cytokines (Galao et al., 2011). The sterile alpha motif (SAM) and histidine/aspartic acid (HD) domain containing protein 1 (SAMHD1) was identified by two independent groups (Neil et al., 2009; V an Damme et al., 2009). The deletion in human BST-2 of 5 amino acid residues, to which human BST-2 to SIV Nef was proven to have an association with Vpu, might lead to efficient evasion from the BST-2-mediated restriction in various OWM cells.

**BONE MARROW Stromal Antigen 2**

It had been observed that the production of vpu-deficient HIV-1 in certain cell lines was severely diminished (Klimkait et al., 1999; Sakai et al., 1995). Specifically, while permissive cells, such as HEK293T and HT1080 cells, allowed comparative levels of virion production, non-permissive cells, such as Jurkat and Hela cells, decreased the amount of virion production in the absence of vpu. It was also reported that interferon (IFN) treatment led to a phenotype switch from permissive to non-permissive (Neil et al., 2007). Thus, the existence of unknown IFN-inducible, Vpu-sensitive cellular factors, was predicted. In 2008, bone marrow stromal antigen 2 (BST-2), also known as tetherin, CD317, and HML-24, was identified by two independent groups (Neil et al., 2008; Van Damme et al., 2008). BST-2 is a type 2 integral membrane protein, with the N-terminal located in the cytoplasm, one membrane-spanning domain, and a C-terminus modified by the addition of a glycosyl-phosphatidylinositol (GPI) anchor (Kupzig et al., 2003). Erikson et al. (2011) analyzed the expression profile of BST-2 in vivo and demonstrated that BST-2 was expressed in various tissues, especially spleen and alimentary system. They also showed that PRIM3, monocytes express high levels of BST-2 as compared to T and B cells. Furthermore, like tripartite motif-containing protein 5 (TRIM5α), homolog BST-2, but not other primate BST-2, has been recently reported to function as an innate sensor, leading to the transforming growth factor β activated kinase-1 (TAK1)-dependent activation of NfkB and subsequent production of pro-inflammatory cytokines (Galao et al., 2011). The sterile alpha motif (SAM) and histidine/aspartic acid (HD) domain containing protein 1 (SAMHD1) was identified by two independent groups (Neil et al., 2009; V an Damme et al., 2009). The deletion in human BST-2 of 5 amino acid residues, to which human BST-2 to SIV Nef was proven to have an association with Vpu, might lead to efficient evasion from the BST-2-mediated restriction in various OWM cells.

SIV Nef binds (Jia et al., 2009; Zhang et al., 2009). Although most SIVsm/HIV-2 lineage does not encode vpu gene, SIVcpz, SIVgor [SIV from gorillas (Gorilla gorilla gorilla)], SIVgan [SIV from greater spot-nosed guenons (Cercopithecus nictitans)], SIVmon [SIV from mona monkeys (Cercopithecus mona)], SIVmus [SIV from moustached monkey (Cercopithecus cephus)], and SIVden [SIV from Dent’s mone monkey (Cercopithecus denti)] were shown to harbor the vpu gene (Courgaud et al., 2003; Dazza et al., 2005). Recently, Sauter et al. (2009) demonstrated that Vpu from SIVgag and SIVden potently countered the BST-2 from RM. Moreover, Shingai et al. (2011) showed that Vpu from SHIVgag2ex12 potentially countered BST-2 from RM. It is therefore possible that the exchange of present HIV-1NL4-3-derived-Vpu with these Vpus might lead to efficient evasion from the BST-2-mediated restriction in macaque cells. But, when using macaques for HIV-1 research, we should also appreciate the polymorphisms in BST-2 gene.

**SAMHD1**

It has long been observed that HIV-1 replication in myeloid lineage cells, such as macrophages and dendritic cells (DCs) was impaired and the expression of HIV-2/SIV Vpx in trans was shown to rescue this inhibition (Gao et al., 2007; Kaushik et al., 2009). The sterile alpha motif (SAM) and histidine/aspartic acid (HD) domain containing protein 1 (SAMHD1) was identified as an HIV-1 restriction factor in myeloid cells that were degraded by the HIV-2/SIV Vpx protein (Hrecka et al., 2011; Lagutin et al., 2011). SAMHD1 was reported to restrict HIV-1 replication in resting CD4+ T cells as well (Baldauf et al., 2012; Descours et al., 2012). Historically, SAMHD1 is shown to be associated with the Aicardi–Goutières autoimmune-mediated neurodevelopmental syndrome. Patients having a mutation in SAMHD1 gene would have symptoms of abnormal immune activation likely due to the excessive production of IFNα (Crow and Rehak-Durkin, 2009; Rice et al., 2009). Since SAMHD1 functions as a deoxyguanosine triphosphatase (dGTPase)-regulated deoxyribonucleoside triphosphate (dNTPase) triphosphohydrolase (Powell et al., 2011), it exerts its anti-HIV-1 activity via the depletion of dNTP pools in virus-infected cells, leading to the inhibition of the reverse transcription (Labboussa et al., 2012). The fact that SAMHD1-deficient CD14+ monocytes efficiently permit HIV-1 replication supports this notion (Berger et al., 2011). It is noteworthy that SAMHD1 exerts its antiviral activity against various retroviruses ranging from alpha, beta and gamma retroviruses, 

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A3G and Vif, SAMHD1 is also antagonized by viral proteins in αRM cDNA library, successfully identified TRIM5 significantly weaker than that in wild-type SIV (Gibbs et al., 1995; from mandrill (from OWMs and NWMs but not from humans (Lim et al., 2012).

of great interest to introduce these potency of degrading SAMHD1 from RM and AGM. It would be tus as SIVdeb [SIV from De Brazza’s monkey (from Indonesian CM, seemed not to possess TRIMCyp, the TRIMCyp of PM exclusively have the genotype instead of TRIM5a (Liao et al., 2007; Brennan et al., 2008; Vigen et al., 2008). Differently from owl monkey TRIMCyp, the TRIMCyp of PM was a consequence of a retrotransposition of the CypA sequence in the 3′ untranslated region (UTR) of the TRIM5 gene, together with a single nucleotide polymorphism (SNP) at the exon 7 splice acceptor site. This SNP at the splice acceptor site leads to skipping exons 7 and 8 encoding the Pyrspry domain and splicing to the inserted CypA gene. In addition to PM, it is reported so far that RM and CM also possess TRIMCyp in their genome (Brennan et al., 2008; Newman et al., 2008; Wilson et al., 2008). Interestingly, RM has geographic deviation in the frequency of TRIMCyp, depending on the country of origin (Wilson et al., 2008). It is reported that Indian RM possessed TRIMCyp more frequently than Chinese RM (Wilson et al., 2008; De Jooit et al., 2011). We recently reported that CM also showed divergent frequency of TRIMCyp depending on their country of origin (Saito et al., 2012b). The frequency of TRIMCyp in Filipino CM was significantly higher than that in Malaysian and Indonesian CM. We demonstrated that wild-caught CM also had a geographic deviation in the frequency of TRIMCyp as seen in captive CM (Saito et al., 2012a). Consistently, Dietrich et al. (2011) reported that the frequency of TRIMCyp in Filipino CM was higher than those in Indonesian and Indochina CM. It was shown that Mauritian CM, a population thought to be derived from Indonesian CM, seemed not to possess TRIMCyp, probably due to the founder effects at the time of introduction by human (Dietrich et al., 2011; Berry et al., 2012). Since TRIM5a is expected to act as homomultimer (Mische et al., 2005; Perez-Caballeri et al.,

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**CONSTRUCTION OF MACAQUE-TROPIC HIV-1**

In virtue of the detailed understanding of the molecular relationship between antiviral host factors and viral antagonists (summarized in Tables 1 and 2), it became possible to create a macaque-tropic HIV-1 (HIV-1mt) with the ability to replicate in OWM cells. In 2006, two independent groups succeeded in the construction of an HIV-1mt that contains partial SIV-derived sequences on the HIV-1NL4-3 backbone. Hatzizaisanou et al. (2006) constructed HIV-1mt that contains the entire gag-CA and vif from SIVmac in order to evade from TRIM5α-mediated restriction. However, they also demonstrated that the replication of SIVmac in IFN-treated human PBMCs is greatly suppressed, and vice versa. This finding strongly suggests the existence of unidentified IFN-inducible restriction factors in each species. Therefore, it is also necessary to continue exploring such unidentified cellular factors.

**Table 1 | Antiviral host factors and antagonism by lentiviral proteins.**

| Antiviral host factors | Antagonized by SIVmac239 | NOT antagonized by |
|------------------------|--------------------------|-------------------|
| Human APOBEC3G         | HIV-1 Vif                | SIVmac Vif        |
|                        | SIVmac Vif               | SIVmac Vif        |
| RM APOBEC3G            | SIVmac Vif               | SIVmac Vif        |
| Human BST-2            | HIV-1 Vpu                | SIVmac Vif        |
| RM BST-2               | SIVmac Vpu               | SIVmac Vif        |
| Human SAMHD1           | SIVmac Vpr               | SIVmac Vif        |
| Human Vpu              | SIVmac Vpr               | SIVmac Vif        |
| RM SAMHD1              | SIVmac Vpr               | SIVmac Vif        |
| HIV-2 Vpu              | SIVmac Vpr               | SIVmac Vif        |
| HIV-2 Vpx              | SIVmac Vpr               | SIVmac Vif        |
| Human APOBEC3G         | HIV-1 Vif                | SIVmac Vif        |
| RM APOBEC3G            | SIVmac Vif               | SIVmac Vif        |
| Human BST-2            | HIV-1 Vpu                | SIVmac Vif        |
| RM BST-2               | SIVmac Vpu               | SIVmac Vif        |
| Human SAMHD1           | SIVmac Vpr               | SIVmac Vif        |
| Human Vpu              | SIVmac Vpr               | SIVmac Vif        |
| RM SAMHD1              | SIVmac Vpr               | SIVmac Vif        |
| HIV-2 Vpu              | SIVmac Vpr               | SIVmac Vif        |
| HIV-2 Vpx              | SIVmac Vpr               | SIVmac Vif        |
| Human APOBEC3G         | HIV-1 Vif                | SIVmac Vif        |
| RM APOBEC3G            | SIVmac Vif               | SIVmac Vif        |
| Human BST-2            | HIV-1 Vpu                | SIVmac Vif        |
| RM BST-2               | SIVmac Vpu               | SIVmac Vif        |
| Human SAMHD1           | SIVmac Vpr               | SIVmac Vif        |
| Human Vpu              | SIVmac Vpr               | SIVmac Vif        |
| RM SAMHD1              | SIVmac Vpr               | SIVmac Vif        |
| HIV-2 Vpu              | SIVmac Vpr               | SIVmac Vif        |
| HIV-2 Vpx              | SIVmac Vpr               | SIVmac Vif        |

**Table 2 | Species-specific restriction of lentiviruses by primates TRIM5α proteins.**

| TRIM5α alleles     | Restrictive against |
|--------------------|---------------------|
| HIV-1              | HIV-1mt MLNL-3/3, SIVmac239 |

| Human TRIM5α        | −                   |
| RM TRIM5α TFP       | +                   |
| RM TRIM5α Dd        | +                   |
| CM TRIM5α           | +                   |
| RM TRIM5α           | −                   |
| PM TRIM5α           | −                   |
| CM TRIM5αc DKK      | +                   |
| CM TRIM5αc INI      | −                   |

**Summary of findings about interactions between each TRIM5α allele and lentiviruses.**

- **+** denotes restrictive, while **−** denotes not restrictive against each lentivirus, respectively.
CD8⁺ cell-depleted PM PBMCs but hardly in CD8⁺ cell-depleted RM PBMCs. Subsequently, Igarashi et al. (2007) investigated the replication capability of NL-DT5R in PM and found that this prototypic HIV-1mt was able to induce acute viremia up to around $1 \times 10^4$ copies/mL. Thereafter, in order to enhance the viral replication, we further modified the sequence of NL-DT5R-based HIV-1mt by 2 different approaches. First, we performed a long-term adaptation experiment in CM T cell lines to induce adaptive mutation in its genome. As a consequence of adaptation, several nucleotide substitutions were identified (see Figure 1, orange arrows in MN4-5 and MN4-SS). The functional significance of each mutation was molecularly evaluated (Nomaguchi et al., 2013a). Second, we introduced α-helices 6 and 7 (L6/7) in addition to L4/5 of Gag-CA into MN4-5, resulting in MN4-SS. As shown in Figure 2, this substitution enhanced the viral replication in vitro (Kuroishi et al., 2009) and in vivo (Saito et al., 2011). We next constructed a new HIV-1mt named MN4Rh-3 carrying the Q110D substitution in Gag-CA. This HIV-1mt exhibited further enhanced growth property specifically in macaque cells but impaired replication in human cells (Nomaguchi et al., 2013b). We also examined the replicative property of MN4Rh-3 in CM (Saito et al., 2013). In accordance with in vitro data (Nomaguchi et al., 2013b), MN4Rh-3 induced higher viremia on average up to 50 times as compared to MN4-SS (Figure 2). Notably, TRIMCyp homozygotes were highly permissive to MN4Rh-3 infection, while the replication of MN4Rh-3 in TRIM5α homozygotes was strongly suppressed. We also observed that CM heterologous for TRIM5α and TRIMCyp showed similar anti-HIV-1 activity with TRIM5α and TRIMCyp homozygotes (Saito et al., 2013). These findings indicated that MN4Rh-3 enhanced the replicative capability in CM having TRIMCyp, but was still unable to overcome TRIM5α-mediated restriction. It should be noted that the sequence of most TRIMCyp encoded in CM are different from those in RM and PM. It was once thought that CM exclusively possessed TRIMCyp in which the amino acid residues at positions 369 (Cyp66) and 446 (Cyp143) were aspartic acid (D) and lysine (K) (denoted as the TRIMCyp (DK)), respectively, while PM and RM had TRIMCyp in which the amino acids at the corresponding positions were asparagine (N)

![Figure 1](https://www.frontiersin.org)
and glutamic acid (E) [denoted as the TRIMCyp (NE); Brennan et al., 2008; Ylinen et al., 2010], respectively. However, others and we recently revealed that CM possessed TRIMCyp (NE) as well as TRIMCyp (DK) haplotype in CM population (Dietrich et al., 2011; Saito et al., 2012a,b). Strikingly, others and we reported that TRIMCyp (NE) exhibit different anti-lentiviral activity. It is well established that the TRIMCyp (DK) efficiently restricts HIV-1 but weakly restricts HIV-2 (Saito et al., 2012b). On the other hand, the TRIMCyp (NE) fails to restrict HIV-1 but efficiently restrict HIV-2 (Wilson et al., 2008). It was also shown that both haplotypes hardly restricted SIVmac239 replication. These results indicate that the sequence variations in CypA greatly affect the spectrum of their anti-HIV-1 activity. However, how does TRIMCyp (DK) exert its anti-HIV-1 activity? Actually, TRIMCyp (DK) is expected to bind the L4/5 in Gag-CA. Moreover, the treatment of the target cells with cyclosporin A, an inhibitor against CypA, or the introduction of amino acid changes in this loop of the viral genome relieved the inhibitory effect by TRIMCyp (DK; Ylinen et al., 2010). Therefore, when we use CM homozygous for TRIMCyp (DK), it is necessary to modify the loop in order to evade restriction. In fact, we have used HIV-1mts in which the L4/5 in Gag-CA were replaced with the corresponding sequence of SIVmac239 (Kamada et al., 2006). In contrast, those research groups that used PM did not need to modify this region. Hatziioannou et al. (2009) have successfully constructed an HIV-1mt that induced persistent viremia in PM with modification of only vif and env gene. Similarly, Thippeshappa et al. (2011) also constructed an HIV-1mt named HSIV-vif that encoded vif gene from pathogenic PM-adapted SIVmne027. This HSIV-vif was shown to persistently replicate in PM but was unable to induce pathogenicity in animals. Overall, further understanding of the host–virus relationship would permit us to construct pathogenic HIV-1mt in future studies.

CONCLUSIONS AND FUTURE DIRECTIONS
Most HIV-1mts were constructed with the aim of evading from TRIM5 and APOBEC3-mediated restriction. In the future research, as discussed above, we should also focus on other factors such as BST-2 and SAMHD1. It will be promising to modify viral genome in order to overcome these restrictions. We expect that

**Figure 2** Serial modifications of the viral genome lead to an enhanced viral replication in vitro and in vivo. (Top) CD8+ T cell-depleted peripheral mononuclear blood cells from CMs homozygous for TRIMCyp were infected with each HIV-1mt. The representative result of viral replication kinetics was shown. (Bottom) CM having TRIMCyp were infected with each HIV-1mt intravenously. Plasma viral RNA loads in each monkey are shown.
such procedure will lead to the construction of a new HIV-1mt with the ability to infect various macaques persistently. Also, as discussed in the “History of HIV-1 animal models” chapter, an R5-tropic virus would be promising to reproduce the transmission, latency, and pathogenicity of HIV-1 in macaques. In the future study, the construction of an R5-tropic virus on the genome would encourage us to examine the antiviral agents, vaccines, and microbicides in macaques. Moreover, HIV-1mt that robustly replicate and induce pathogenicity in monkeys will make feasible to investigate the role and mechanism of HIV-1 accessory genes in the HIV-1 lifecycle, persistence, and pathogenesis. In summary, although the road to the containment of HIV-1 epidemic may be long and steep, we have been moving forward slowly but steadily.

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