Materials and methods

Cells

293 T cells (DuBridge et al., 1987) were maintained in Dulbecco's Modified Eagle Medium (D-MEM; Wako, Osaka, Japan) supplemented with 10% (vol/vol) fetal bovine serum (FBS; HyClone Laboratories, Logan, UT) and 1 mM L-glutamine. TZM-bl cells (Platt et al., 1998) from the NIH AIDS research and reference reagent program were maintained in D-MEM supplemented with 10% FBS, 1 mM L-glutamine and 1 mM sodium pyruvate. The human T-cell line, C8166-CCR5 (Shimizu et al., 2006) was maintained in Rosewell Park Memorial Institute 1640 medium (RPMI-1640; Invitrogen, Carlsbad, CA) supplemented with 10% FBS. PtM PBMCs from uninfected monkeys were isolated using the ficoll density gradient separation method. For this procedure, a mixture of 95% lymphocyte separation medium (Wako) and 5% phosphate buffered saline (PBS) was used as a separation solution as described previously (Agy et al., 1992; Frumkin et al., 1993). Residual erythrocytes were lysed in ACK lysing buffer (0.15 M NH_4Cl, 10 mM $KHCO_3$, 1.0 mM EDTA · Na_2). Depletion of $CD8^+$ cells was conducted with the magnetic-activated cell sorting (MACS) system (Miltenyi Biotec, Gladbach, Germany). Briefly, isolated PtM PBMCs were stained with phycoerythrin (PE)-conjugated anti-CD8 antibodies (clone SK1, BD Biosciences, San Jose, CA) and then labeled with anti-PE MicroBeads (Miltenyi Biotec). $CD8^+$ cells were removed using a magnetic column according to the manufacturer's instructions. PBMCs were cultured in RPMI-1640 supplemented with 10% FBS, 2 mM sodium pyruvate, 2 mM L-glutamine, 50 nM 2-mercaptoethanol and 40 μg/mL gentamicin. PBMCs were stimulated with 25 μg/mL Concanavalin A (conA) for 20 h and then cultured in the presence of 160 U/mL human recombinant interleukin-2 (IL-2; Wako).

Viruses

A stock of NL-DT5R virus was prepared from C8166-CCR5 cells transfected with a plasmid encoding full-length proviral DNA of NL-DT5R (pNL-DT5R) using the DEAE-Dextran/osmotic shock procedure (Takai and Ohmori, 1990). SIVmac239 (Kestler et al., 1988) stock virus was prepared from the culture supernatant of 293 T cells transfected with a plasmid encoding full-length proviral DNA of SIVmac239 with Lipofectamine (Invitrogen). CCR5-tropic subtype C HIV-1 clinical isolates including 97ZA012 were obtained from the NIH AIDS research and reference reagent program.

Generation of recombinant virus through intracellular homologous recombination

To generate recombinant virus by IHR, overlapping viral genomic DNA fragments were prepared by PCR amplification. A region spanning the 5′ LTR to *env* was amplified from pNL-DT5R (GenBank accession number: AB266485) using the HIV-1-U3-NotI-F forward primer (5′-ATGCGGCCGCTGGAAGGGCTAATTTGGTCCCAAAG-3′; nucleotide positions 1–25 in NL-DT5R, and additional *NotI* site sequences) and the env-2R reverse primer (5′-CACAGAGTGGGGTTAATTTTACAC-3′; nucleotide positions 6761–6784 in NL-DT5R). PCR was conducted with Expand long-range dNTPack (Roche Diagnostic, Basel, Switzerland). PCR conditions were as follows: 94 °C for 2 min followed by 10 cycles of 94 °C for 15 s, 55 °C for 30 s and 68 °C for 8 min, 25 cycles of 94 °C for 15 s, 55 °C for 30 s, 68 °C for 8 min, with 20 s increments at 68 °C for each successive cycle and a final elongation period of 68 °C for 7 min (fragment I in Fig. 1A). Amplification of a DNA fragment spanning the initiation of *vpr* to the 3′ LTR was derived from subtype C HIV-1 clinical isolates of the HIV-1 97ZA012 strain. Viral RNA was isolated from culture supernatant using a QIAamp viral RNA mini kit (Qiagen, Hilden, Germany). Complementary DNA (cDNA) was synthesized with Super Script III first-strand synthesis SuperMix (Invitrogen) using the OFM19-R reverse primer (5′-AGGCAAGCTTTATTGAGGCTTA-3′; nucleotide positions 9604–9625 based on the HXB2 numbering). PCR amplification of the viral cDNA was conducted using HIV-1vpr-F forward primer (5′-AGATGGAACAAGCCCCAGAAGA-3′; nucleotide positions 5558–5579 in the HXB2 numbering) and OFM19-R reverse primer with the same conditions (fragment II in Fig. 1A). To prepare a fragment spanning the initiation of 5′ LTR to the MA region of *gag*, proviral DNA was extracted from proviral DNA of subtype C HIV-1 isolate-infected C8166-CCR5 cells using DNeasy Blood & Tissue kits (Qiagen). The following amplification was conducted using HIV-1cladeC-U3-NotI-F forward primer (5′-ATGCGGCCGCTGGAAGGGTTAATTTACTCAAGAG-3′; nucleotide positions 1–24 in the HXB2 numbering plus *NotI* site sequences) and the PreSCA-R reverse primer (5′-AATCTATCCCATTCTGCAGC-3′; nucleotide positions 1433–1414 in the HXB2 numbering) (fragment III in Fig. 1A). The PCR products were purified using QIAquick PCR purification kits (Qiagen).

Recombinant viruses were generated by means of IHR in the cell. PCR-amplified linear viral DNA fragments were co-transfected into C8166-CCR5 cells by the DEAE-dextran/osmotic shock procedure (Takai and Ohmori, 1990). After transfection, cells were maintained and passaged every 3 days. The culture supernatant was harvested upon observation of virus-induced CPE.

Virus titration

The infectious titer of the viruses was defined as the median tissue culture infectious dose ($TCID_{50}$) in TZM-bl cells as described previously (Li et al., 2005). Four-fold, serially diluted viral stock was used to inoculated TZM-bl cells (5000 cells per 200 μL of growth medium containing DEAE-Dextran at a final concentration of 12.5 μg/mL) in quadruplicate in flat-bottom 96-well plates. After incubation for 48 h at 37 °C, the culture supernatant was removed and the cells were treated with 50 μL of Cell lysis solution (Toyo-Inki, Tokyo, Japan) for 15 min at room temperature with shaking. Then, 30 μL of the cell lysate were transferred to F96 MicroWell plates (Thermo Fisher Scientific, Roskilde, Denmark), and the relative luminescence units (RLU) after adding 50 μL of luciferase substrate (PicaGene, Toyo-Inki) to each well was determined using a microplate reader (Mithrus LB940, Berthold Technologies, Bad Wildbad, Germany). Viral infectivity was measured in RLUs, and positive wells were defined as RLU > 2 × background. The $TCID_{50}$ was calculated as described previously (Reed and Muench, 1938).

Viral growth kinetics in pig-tailed macaque PBMCs

PtM PBMCs were isolated from two uninfected animals and $CD8^+$ cells were depleted as described above. Two days after stimulation with Concanavarin A (25 μg/mL), 2.5×10^5 cells of $CD8^+$ cell-depleted PtM PBMCs were inoculated with 2.5×10^4 $TCID_{50}$ of viral stocks by spinoculation (O'Doherty et al., 2000) at 1200*g* for 1 h at room temperature. After washing with PBS, the infected cells in 200 μL of culture medium were cultured in round-bottom 96-well plates at 37 °C. The upper 150 μL of culture supernatant without aspirating cells in the bottom of the well was exchanged with fresh medium everyday. The harvested supernatant was stored at −20 °C prior to measure the activity of RT associated with virions.

RT assay

The virion-associated RT activity in culture supernatant was monitored as described previously (Willey et al., 1988). Briefly,

6 μL of culture supernatant were combined with 30 μL of RT reaction cocktail [50 mM Tris–HCl, 75 mM KCl, 10 mM dithiothreitol, 4.95 mM $MgCl_2$, 10 mg/mL polyA RNA, 5 mg/mL oligo-dT_{20}, 0.05% NP40] and 1.66×10^4 Bq equivalent α^{32}P-dTTP (PerkinElmer, Waltham, Massachusetts, USA) and incubated at 37 °C for 2 h with gentle agitation. Next, 3 μL of incubated mixture were blotted onto DE81 ion exchange cellulose paper (GE healthcare, Buckinghamshire, UK). After four washes with 2 × saline sodium citrate (SSC), the residual radioactivity from synthesized DNA was counted using a liquid scintillation counter.

Single genome amplification (SGA)

SGA of the region spanning the initiation region of *vpr* to the end of the *env* gene was conducted as described previously (Salazar-Gonzalez et al., 2008). Synthesized viral cDNA was end-point diluted and then subjected to nested-PCR. First-round PCR was conducted with KOD-FX (TOYOBO, Osaka, Japan) in a total of 20 μL of reaction mixture, using the SGA-16F forward primer (5′-TGCAGCAGAGTAATCTTCCCACTACAGG-3′; nucleotide positions 5260–5283 in NL-DT5R) and the SGA-OFM19R reverse primer (5′-AGGCAAGCTTTATTGAGGCTTAAGCAGTGG-3′; 9771–9800 in NL-DT5R). The first-round PCR conditions were as follows: 94 °C for 2 min, followed by 35 cycles of 98 °C for 10 s, 63 °C for 30 s and 68 °C for 5 min. Second-round PCR was performed using 1 μL of the first-round PCR product using the SGA-17F forward primer (5′-AGAAGAGACAATAGGAGAGGCCTTCGAATG-3′; 5610–5639 in NL-DT5R) and the SGA-2.5R reverse primer (5′-AAAGCAGCTGCTTATATGCAGCATCTGAGG-3′; 9673–9702 in NL-DT5R). The second-round PCR conditions were the same as those in the first-round PCR. Amplification of the target sequence was confirmed with agarose gel electrophoresis. According to a Poisson distribution, when a positive ratio of amplification from diluted cDNA is $<30\%$ in multiple replicate PCR reactions, the amplicons are predicted to be amplified from one-copy of template with the probability of $>80\%$. The single genome amplicons were purified before sequence analysis.

Genomic analysis

Sequence analysis was performed using the BigDye terminator v. 3.1 cycle sequencing kit (Applied Biosystems, Foster City, CA) and the ABI PRISM 3130xl genetic analyzer (Applied Biosystems). The 3′-terminal 2304 nucleotide sequences of *env* were aligned using the Clustal X software (Thompson et al., 1997). A neighbor-joining phylogenetic tree (Saitou and Nei, 1987) using Kimura's two-parameter model (Kimura, 1980) was constructed using MEGA 5 software (Tamura et al., 2011), and bootstrap values were computed from 1000 bootstrap replicates (Felsenstein, 1985). Pair-wise distances between any two nucleic acid sequences of the 3′ terminal 2361 bp of each viral *env* within the parental HIV-1 97ZA012, HIV-1mt ZA012-P0 and HIV-1mt ZA012-P19 were calculated with Kimura's two-parameter model (Kimura, 1980) by using MEGA 5 software (Tamura et al., 2011). The statistical significance between each viral pair-wise distance was calculated with Student's *t* test using GraphPad Prism software (San Diego, CA, USA).

Co-receptor usage assay

Employing a previously reported method (Nishimura et al., 2010) with minor modifications, co-receptor usage of viruses was determined using the small molecule antagonists, AD101 (Trkola et al., 2002) provided by Dr. Julie Strizki (Schering-Plough Research Institute, Kenilworth, NJ) and AMD3100 (Sigma-Aldrich, St. Louis, MO) (Donzella et al., 1998). Briefly, freshly trypsinized TZM-bl cells (5000 cells per 100 μL of growth medium containing DEAE-Dextran at a final concentration of 12.5 μg/mL) were seeded in flat-bottom 96-well plates. The cells were incubated with 50 μL of co-receptor antagonists at final concentrations ranging from 0.1 nM to 1000 nM for 1 h at 37 °C and inoculated with 100 $TCID_{50}$ of replication-competent virus in triplicate. After incubation for 48 h at 37 °C, luciferase activity was measured, and the percent infectivity relative to that measured in mock-treated wells was determined.

Experimental infection of pig-tailed macaques with HIV-1mt ZA012

HIV-1mt ZA012 challenge stock was prepared from culture supernatant of PtM PBMCs infected with HIV-1mt ZA012-P19. The virus was titrated with PtM PBMCs as described previously (Fujita et al., 2013). Two pig-tailed macaques, PtM01 and PtM02 aged 7 and 6 years, respectively, were intravenously inoculated with 1.0×10^5 $TCID_{50}$ of HIV-1mt ZA012. Plasma viral RNA loads were measured with TaqMan real time RT-PCR as described previously (Miyake et al., 2006) with minor modifications; RT-PCR was conducted for HIV-1 *vpr* amplification using the NM3rNvpr-F forward primer (5′-CAGAAGACCAAGGGCCACAG-3′) and NM3rNvpr-R reverse primer (5′-GTCTAACAGCTTCACTCTTAAGTTCCTCT-3′). PCR products were detected with a labeled probe, NM3rNvpr-T (5′-Fam-AGGGAGCCATACAATGAATGGACACT-Tamra-3′; Perkin Elmer). Animal experiments were conducted in the biosafety level 3 animal facility, in compliance with institutional regulations approved by the Committee for Experimental Use of Nonhuman Primates of the Institute for Virus Research, Kyoto University, Kyoto, Japan.

Flow cytometry

To enumerate $CD4^+$ T-lymphocytes, and memory and naïve $CD4^+$ T-lymphocytes, whole blood samples were stained with fluorescently labeled mouse monoclonal antibodies. Anti-CD3 (clone SP34-2) conjugated with Pacific Blue, anti-CD4 (clone L200) conjugated with PerCP-Cy5.5, anti-CD8 (clone SK1) conjugated with APC-Cy7, anti-CD20 (clone L27) conjugated with FITC and anti-CD95 (clone DX2) conjugated with APC were purchased from BD Biosciences, and anti-CD28 (clone CD28.2) conjugated with PE was purchased from eBioscience (San Diego, CA). $CD28^{high}CD95^{low}CD4^+$ or $CD28^{high/low}CD95^{high}CD4^+$ T-cell subsets were considered as naïve or memory $CD4^+$ T-lymphocytes, respectively (Pitcher et al., 2002). The absolute number of lymphocytes in the blood was determined using an automated hematology analyzer, KX-21 (Sysmex, Kobe, Japan).

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Animal model studies on viral infections

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One of the major missions of animal virology is to understand how viruses replicate and cause asymptomatic/symptomatic conditions in individuals (Nomaguchi and Adachi, 2010). It is especially important for virologists who work on viruses pathogenic for humans to elucidate bases underlying the *in vivo* viral characteristics. Toward this end, animal model studies in some ways are necessary to precisely analyze the *in vivo* situation, and also are essential for developing countermeasures against virus infections. Since a full variety of viruses with distinct biological properties exist, we virologists should study "the target virus" in a specialized manner, in addition to common theoretical/experimental approaches. The Research Topic entitled "Animal model studies on viral infections" collects articles that describe the studies on numerous virus species for their animal models, or those at various stages toward animal experiments.

Articles in this Research Topic were written by experts in various research fields, and can be fairly grouped into a few categories: (i) descriptions/evaluations/new challenges of animal model studies for investigating the biology of viruses; (ii) experimental materials/methods for upcoming animal model studies; (iii) observations important for animal model studies. (i) Reynaud and Horvat (2013) have described the animal models for human herpesvirus 6 to better understand its pathogenic property. Studies on filoviruses, classified as biosafety level-4 and represent a serious world-wide problem today, have been reviewed by Nakayama and Saijo (2013). Mailly et al. (2013) have focused on the quest for appropriate animal models for hepatitis C virus. Clark et al. (2013) have discussed about the use of non-human primates as models for dengue hemorrhagic fever/dengue shock syndrome. Ohsugi (2013) has summarized mouse strains transgenic for the *tax* gene of human T-cell leukemia virus type 1 (HTLV-1). Also, a bovine model for HTLV-1 pathogenesis has been described by Aida et al. (2013). Challenging new attempts to establish human immunodeficiency virus type 1 (HIV-1)/macaque infection models have been reviewed by Misra et al. (2013), and also by Saito and Akari (2013). Another approach to understand HIV-1 biology *in vivo* has been described by Matsuyama-Murata et al. (2013). (ii) Kodama et al. (2013) has described a new and simple method to prepare human dendritic cells from peripheral blood mononuclear cells. Doi et al. (2013) have summarized their studies on macaque-tropic HIV-1 clones. Ikeno et al. (2013) has reported a new, sensitive, and quantitative system to monitor measles virus infection in humanized mice. Iwami et al. (2013) have summarized the quantification of viral infection dynamics based on various quantitative analyses. (iii) Tada et al. (2013) have suggested that LEDGF/p75 may be a cellular factor acting as a species-barrier against HIV-1 in mouse cells. Kuwata et al. (2013) have shown that simian immunodeficiency virus may acquire the increased infectivity and resistance to neutralizing antibodies by truncation of its gp41 cytoplasmic tail. Ohsugi et al. (2013) have reported that natural infection status of laboratory mice by murine norovirus. Finally, Kajitani et al. (2013) have described the possible involvement of E1^E4 protein of human papillomavirus type 18 in its differentiation-dependent life cycle.

We are proud to add our "Animal model studies on viral infections" to a series of Research Topic in Frontiers in Microbiology. A wide variety of DNA and RNA viruses are covered by this special issue consisting of original research, review, mini-review, methods, and opinion articles. As we described in the beginning, animal studies are certainly required for understanding virus replicative/pathogenic properties *in vivo* and for overcoming virally-caused infectious diseases. We human virologists should make every effort to fight against numbers of unique pathogenic viruses.

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