Available online at www.sciencedirect.com
ScienceDirect
Virology 375 (2008) 141 – 147
VIROLOGY
www.elsevier.com/locate/yviro

Antibody-dependent enhancement of adeno-associated virus infection of human monocytic cell lines

Seiichiro Mori, Takamasa Takeuchi, Tadahito Kanda *

Center for Pathogen Genomics, National Institute of Infectious Diseases, 1-23-1 Toyama, Shinjuku-ku, Tokyo 162-8640, Japan

Received 14 November 2007; returned to author for revision 4 January 2008; accepted 25 January 2008
Available online 4 March 2008

Abstract

In host animals, adeno-associated virus (AAV) is detectable mainly in the lymphoid tissue, which appears to be a target in natural infection. We used the human monocytic cell lines THP-1 and U937 to study the effect of mouse anti-AAV2 antiserum on infection with an AAV2 vector having the luciferase gene (AAV2/Luc). AAV2/Luc was found to infect THP-1 and U937 cells much less efficiently than HeLa cells, as monitored with the induced enzyme activity. Pre-incubation of AAV2/Luc with anti-AAV2 antiserum at a sub-neutralizing concentration enhanced by 2-to-10 fold infection of THP-1 and U937 with AAV2/Luc, but not of HeLa. Similarly, anti-AAV10 serum at a low level enhanced infection of THP-1 with AAV10/Luc. Sera of two cynomolgus monkeys, which had been probably infected with an AAV2-like virus, enhanced infection of THP-1 with AAV2/Luc. The enhancement was reduced with blocking the IgG-receptors Fcγ-RI and Fcγ-RII, which were displayed on the surface of THP-1 and U937 but not HeLa cells, with anti-Fcγ-RI antibody or anti-Fcγ-RII antibody. The data indicate that infection of Fcγ receptor-bearing cells with AAV is enhanced by anti-AAV IgG antibodies at a sub-neutralizing concentration that play a role in linking AAV particles and Fcγ receptors.

Keywords: AAV; Anti-AAV antibody; ADE; Fcγ-receptor

Introduction

Adeno-associated virus (AAV) is a nonenveloped icosahedral particle (a diameter of 25 nm) containing a single-stranded linear DNA (4.7 kb). To date several AAV serotypes and over 100 AAV variants have been recorded (Wu et al., 2006). Among them AAV serotype type 2 (AAV2) has been studied most extensively and used for gene therapy trials. Efficient propagation of AAV2 in cultured cells requires coinfection with a helper virus (Carter et al., 1979; Richardson and Westphal, 1981; Buller et al., 1981; McPherson et al., 1985). Without a helper virus the AAV DNA is integrated into cell DNA at a specific site and maintained as a provirus (Flotte and Berns, 2005). When a latently infected cell is super-infected with adenovirus, the integrated AAV is induced to replicate (Handa et al., 1977; Cheung et al., 1980). A low level induction has been observed upon Fas-mediated apoptosis of the latently infected cells (Mori et al., 2002).

The tissue tropism of AAV in natural infection is not fully elucidated. AAV10, AAV11, and AAVcy.7 have been detected mainly in the lymphoid tissue and ileum of the naturally infected cynomolgus monkeys (Mori et al., 2008). AAV2 vectors injected to monkeys are detectable in the lymphoid tissue (Conrad et al., 1996; Favre et al., 2001; Lai et al., 2002; Nathwani et al., 2002; Davidoff et al., 2005; Mori et al., 2006) and the leukocytes (Favre et al., 2001; Lai et al., 2002). These studies suggest that the leukocytes are one of the major targets for AAV.

Infection of the leukocytes with dengue virus (DENV) is enhanced by either sub-neutralizing level of serotype-specific anti-DENV antibody or cross-reactive anti-DENV antibody (Clyde et al., 2006). The antibody, which binds to the virion at its variable region and to the cell-surface Fcγ receptor (Fcγ-R) at its Fc-region, mediates attachment of the virion to the surface of monocytes and macrophages

* Corresponding author. Fax: +81 3 5285 1166.
E-mail address: kanda@nih.go.jp (T. Kanda).

0042-6822/$ - see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.virol.2008.01.033

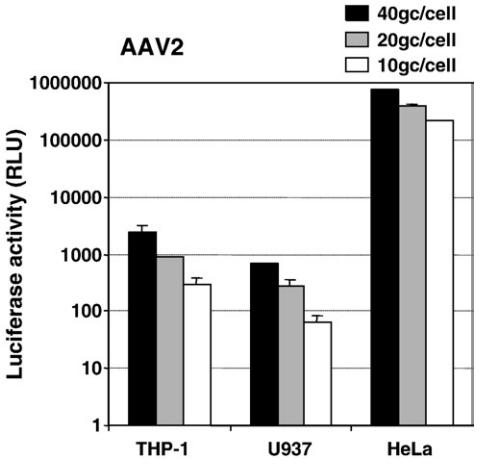

Fig. 1. Infection of THP-1, U937, and HeLa cells with AAV2/Luc. AAV2/Luc was inoculated to the cells at three multiplicities of infection (gc/cell). Two days later, the cells were lysed and luciferase activities of the lysates were measured. Each bar represents the average of three independent experiments with the standard deviation indicated by an error bar. RLU: relative light units.

(Clyde et al., 2006). This antibody-dependent enhancement (ADE) of DENV is believed to be associated with dengue hemorrhagic fever. Similar ADE has been reported in infection of Fcγ-R-positive cells with West Nile virus (Peiris and Porterfield, 1979; Peiris et al., 1981), human parvovirus B19 (Munakata et al., 2006), and Aleutian mink disease parvovirus (Kanno et al., 1993).

In this study we examined infection of THP-1 and U937, human monocytic cell lines that were expressing Fcγ-R, with recombinant AAV vectors that had been pre-incubated with diluted anti-AAV antiserum and found that a sub-neutralizing level of the antiserum enhanced infection of these cells with AAV vectors.

Results

Antibody-dependent-enhancement of infection of THP-1 and U937 cells with AAV2 and AAV10

Infection of THP-1 and U937, human monocytic cell lines, with AAV2/Luc, a recombinant AAV having the luciferase gene, was much less efficient than that of HeLa. Serially diluted AAV2/Luc was inoculated to the cells and 2 days later the cells were lysed and the luciferase activities of the lysates were measured (Fig. 1). While the luciferase activity of the HeLa culture inoculated with AAV2/Luc at a multiplicity of infection (MOI) of 10 genome copies (gc) was 200,000 U, those of the THP-1 and U937 cultures inoculated at an MOI of 40 gc were 2500 U and 1000 U, respectively.

Infection of THP-1 and U937 cells with AAV2/Luc was enhanced by pre-incubation of AAV2/Luc with a sub-neutralizing concentration of anti-AAV2 antiserum. AAV2/Luc was incubated with mouse anti-AAV2 antiserum or mouse normal serum at 37 °C for 30 min and then inoculated to 3×10^5 of THP-1 cells (at MOIs of 10, 20, and 40 gc), U937 cells (at MOIs of 50, 100, and 200 gc), and HeLa cells (at MOIs of 1, 2, and 4 gc). Two days later the luciferase activity of the cellular lysate was measured. The antiserum diluted at 1:100 induced a major decrease of the luciferase activities of the three cell lines, indicating that AAV2/Luc was neutralized with the antiserum (Figs. 2, A, B, and C). Although the antiserum diluted at 1:1000 induced a slight decrease of the luciferase activity of HeLa (Fig. 2C), it induced increase of the luciferase activities of THP-1 and of U937 (Figs. 2, A and B). The antiserum diluted at 1:10,000 and the normal mouse serum did not affect the luciferase activities of the three cell lines (Fig. 2). Thus, the antiserum diluted at 1:1000 enhanced infection of THP-1 and U937 with AAV2/Luc, indicating that typical ADE occurred in infection to these cells with AAV2.

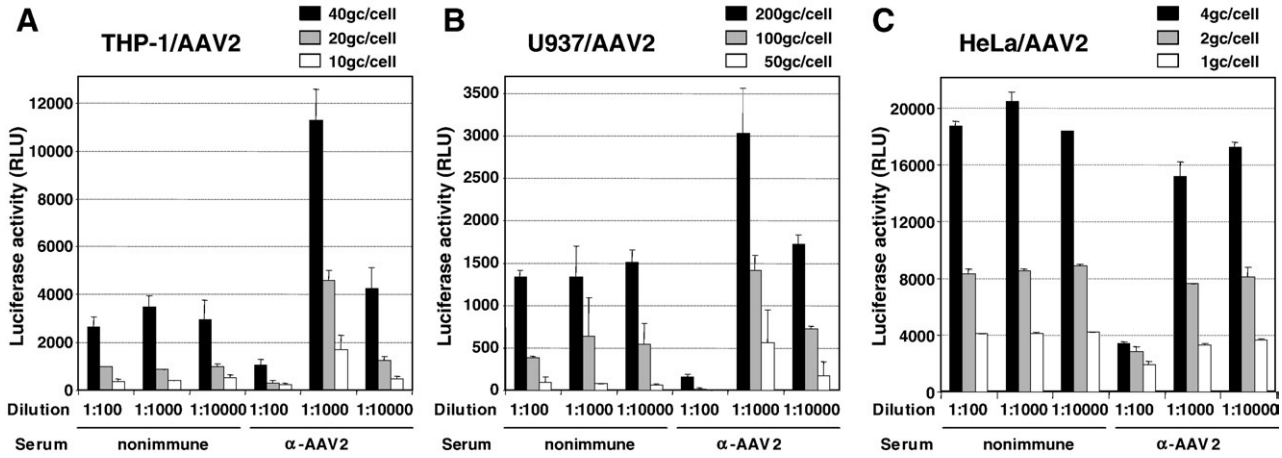

Fig. 2. Effect of anti-AAV2 antiserum on the infection of THP-1, U937, and HeLa cells with AAV2/Luc. AAV2/Luc was mixed with the diluted nonimmune serum or anti-AAV2 antiserum and incubated at 37 °C for 30 min. The mixtures were inoculated to THP-1 (A), U937 (B), or HeLa (C) cells at various multiplicities of infection (gc/cell) indicated. Two days later, the luciferase activity of the cellular lysate was measured. Each bar represents the average of three independent experiments with the standard deviation indicated by an error bar. RLU: relative light units.

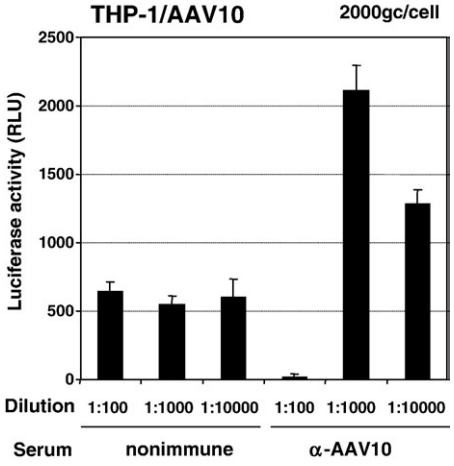

Fig. 3. Effect of anti-AAV10 antiserum on the infection of THP-1 cells with AAV10/Luc. AAV10/Luc was mixed with the diluted nonimmune serum or anti-AAV10 antiserum and incubated at 37 °C for 30 min. The mixtures were inoculated to THP-1 cells at the multiplicity of infection (gc/cell) indicated. Two days later, the luciferase activity of the cellular lysate was measured. Each bar represents the average of three independent experiments with the standard deviation indicated by an error bar. RLU: relative light units.

Similarly, infection of THP-1 cells with AAV10 was enhanced by a sub-neutralizing concentration of anti-AAV10 serum. AAV10/Luc pre-incubated with mouse anti-AAV10 serum was inoculated to THP-1 (3×10^5 cells) at an MOI of 2000 gc and the luciferase activity was measured as the experiments with AAV2/Luc. The antiserum reduced the infectivity of AAV10/Luc at a dilution of 1:100 but increased the infectivity at dilutions of 1:1000 and 1:10,000 (Fig. 3).

Anti-AAV2 and anti-AAV10 sera did not increase the infectivity of AAV10/Luc and AAV2/Luc, respectively (Fig. 4), indicating clearly that the antibody capable of binding to AAV particles mediates the enhancement of infection of THP-1 cells with AAV.

Two monkey sera enhanced infection of THP-1 cells with AAV2/Luc. Sera were obtained from two healthy male cynomolgus monkeys of 5 years of age. The pre-incubation of AAV2/Luc with the monkey-A serum that had been undiluted or diluted at 1:10 reduced the infectivity of AAV2/Luc to HeLa and to THP-1 (Figs. 5, A and B), indicating that the serum contained antibody capable of neutralizing AAV2. Pre-incubation of AAV2/Luc with the monkey-A serum that had been diluted at 1:100 and 1:1000 did not affect the infectivity to HeLa but it increased the infectivity to THP-1 (Figs. 5, A and B). Similarly, pre-incubation of AAV2/Luc with the undiluted monkey-B serum, which did not neutralize AAV2/Luc (Fig. 5A), enhanced infection of THP-1 (Fig. 5B). The data clearly indicate that monkey-B serum diluted at 1:10 and 1:100 did not affect the infectivity of AAV2/Luc (Fig. 5B). The data strongly suggest that the two monkeys had been probably infected with AAV types antigenically related to AAV2 and the sub-neutralizing levels of the antibodies in the sera enhanced infection of THP-1 with AAV2/Luc.

Involvement of the cell-surface Fcγ-receptors (Fcγ-R) in the ADE of AAV infection

Both Fcγ-RI and Fcγ-RII were present on the surface of THP-1 and U937 cells. THP-1, U937, and HeLa cells were incubated with anti-CD64 mouse monoclonal antibody (mAb) recognizing Fcγ-RI or anti-CD32 mouse mAb recognizing Fcγ-RII at 4 °C for 1 h. Then the mAb on the surface was detected with labeled-goat anti-mouse IgG antibody by using a FACS. Both mAbs clearly bound to the surface of THP-1 and U937 cells but did not bind to the surface of HeLa cells (Fig. 6).

Pretreatment of THP-1 and U937 with anti-CD64 mAb or anti-CD32 mAb interfered with ADE in the infection of these cells with AAV2/Luc. THP-1 and U937 cells were incubated with anti-CD64 mAb (5 μg/ml) and/or anti-CD32 (5 μg/ml) mAb at 4 °C for 1 h. The cells were inoculated with AAV2/Luc that had been pre-incubated with the anti-AAV2 antiserum diluted at 1:1000 and the luciferase activities of the lysates were measured at 2 days after the inoculation. The level of the enhancement of infection of both cell lines with AAV2/Luc was reduced by pretreatment with mAbs (Fig. 7), indicating that

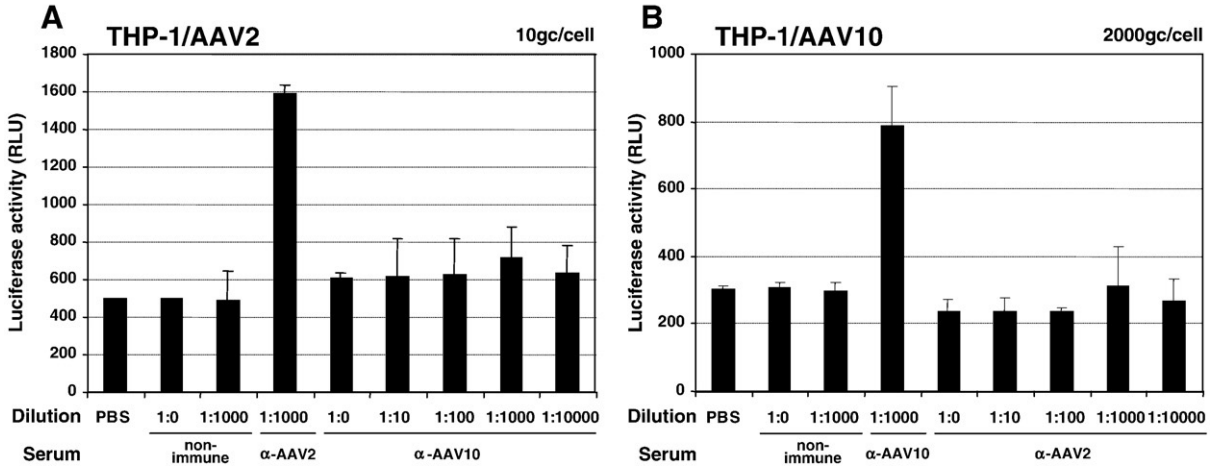

Fig. 4. Requirement of type-specific antibody for ADE of infection of THP-1 cells with AAV2/Luc and AAV10/Luc. AAV2/Luc (A) and AAV10/Luc (B) were pre-incubated with the undiluted or diluted anti-AAV2 or anti-AAV10 antiserum and inoculated to THP-1 cells. Two days later, the luciferase activity of the cellular lysate was measured. Each bar represents the average of three independent experiments with the standard deviation indicated by an error bar. RLU: relative light units.

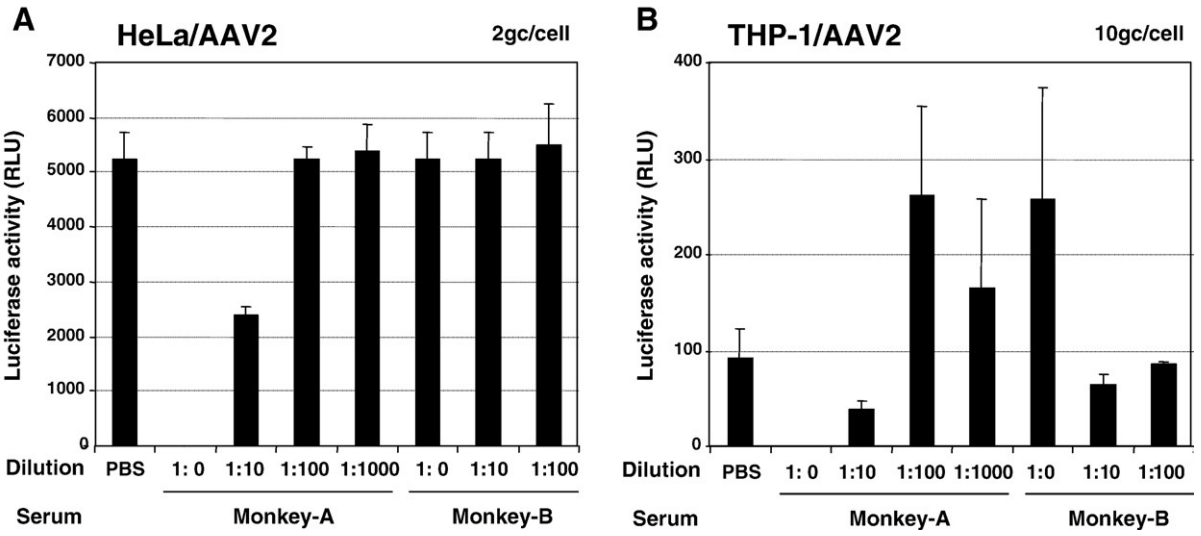

Fig. 5. Effect of the two monkey sera on the infection of THP-1 and HeLa cells with AAV2/Luc. AAV2/Luc was pre-incubated with the undiluted or the diluted cynomolgus monkey sera and inoculated to HeLa (A) or THP-1 (B) cells. Two days later, the luciferase activity of the cellular lysate was measured. Each bar represents the average of three independent experiments with the standard deviation indicated by an error bar. RLU: relative light units.

both Fcγ-RI and Fcγ-RII are involved in the enhancement. Anti-CD64 mAb was more effective than anti-CD32 mAb for the reduction and the mixture of anti-CD64 and anti-CD32 mAbs completely abolished the enhancement.

Discussion

We demonstrated that infection of THP-1 and U937, human monocytic cell lines, with AAV2/Luc was enhanced by the sub-neutralizing concentration of anti-AAV2 antibody. Similarly infection of THP-1 with AAV10/Luc was enhanced by the sub-neutralizing concentration of anti-AAV10 antibody. Cell-surface Fcγ-RI and Fcγ-RII were required for the enhancement, indicating that the antibodies play a role in linking the AAV particle and the Fcγ-R on the cell surface. A variety of leukocytes are positive for Fcγ-RI (monocytes/macrophages, dendritic cells, and neutrophils) and Fcγ-RII (monocytes/macrophages, dendritic cells, neutrophils, B lymphocytes, and mast cells)(Cohen-Solal et al., 2004). It is possible that infection of these cells with AAV is enhanced with a low level of anti-AAV antibodies in vivo.

The naturally infected AAV does not induce the strong immune response of host animals. Although a great majority of humans are infected with AAV2 during childhood, the sera of

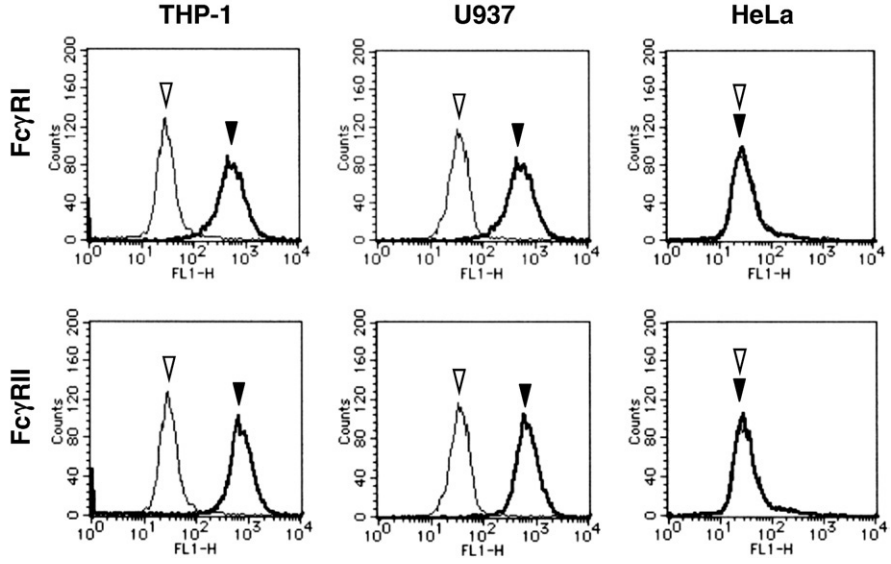

Fig. 6. Presence of Fcγ-RI and Fcγ-RII on THP-1 and U937 cells. THP-1, U937, and HeLa cells were incubated with anti-Fcγ-RI or anti-Fcγ-RII monoclonal antibodies followed by staining with the Alexa Fluor 488-conjugated goat anti-mouse IgG secondary antibody. The fluorescence on the cells was measured by using a flow cytometer. The bold line (indicated with filled arrowheads) shows the distribution of the resultant fluorescence. The thin line (indicated with open arrowheads) shows the distribution of the fluorescence of the cells incubated with only the secondary antibody.

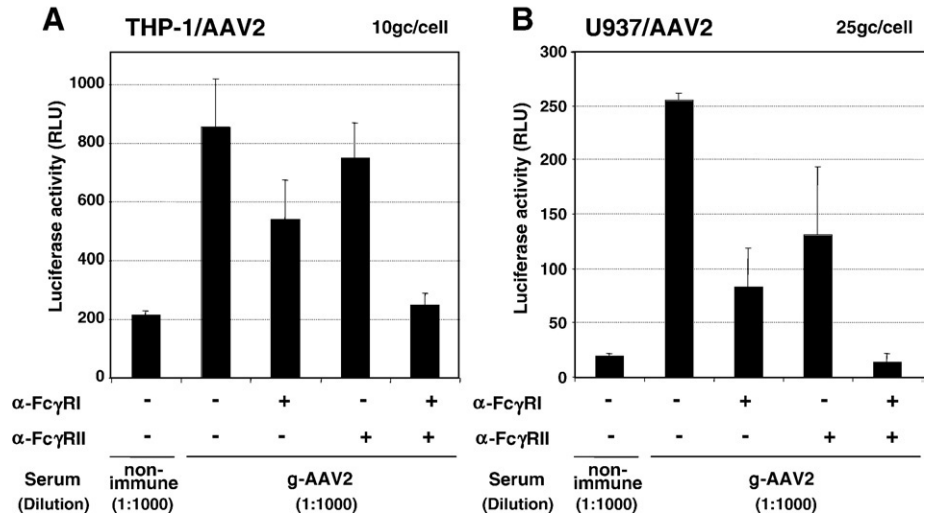

Fig. 7. Inhibition of ADE of AAV2 infection with anti-Fcγ-RI and anti-Fcγ-RII antibodies. THP-1 (A) and U937 (B) cells were pre-incubated with anti-Fcγ-RI and/or anti-Fcγ-RII mAbs. Then, AA2/Luc that had been incubated with anti-AAV2 antiserum was inoculated to the cells. Two days later, the luciferase activity of the cellular lysate was measured. Each bar represents the average of three independent experiments with the standard deviation indicated by an error bar. RLU: relative light units.

humans aged over 30 are positive for anti-AAV2 IgG and IgM antibodies simultaneously, indicating anti-AAV2 antibody induced by the primary infection does not protect the hosts from the secondary infection (Erles et al., 1999). Among human sera positive for anti-AAV antibody, only 30% of the sera are neutralizing (Chirmule et al., 1999). The level of anti-AAV antibody in the serum of the host persistently infected with AAV could be appropriate for the enhancement of AAV infection. Indeed the undiluted monkey-B sera, whose level of neutralizing antibody was below the detectable level, enhanced infection of THP-1 with AAV2/Luc (Fig. 5).

ADE is probably important for AAV to be maintained in host animals. Because the chance for the AAV-infected cell to be super-infected with the helper virus must be very rare in vivo, AAV may survive with a low level autonomous propagation induced by the Fas-mediated apoptosis of the host cell (Mori et al., 2002). ADE may support infection of a new host cell, mainly a leukocyte, with AAV.

Previous studies have shown that the capability of an antibody to contribute to ADE is independent of neutralizing activity. The monoclonal neutralizing antibodies against West Nile virus and against Dengue virus (Pierson et al., 2007; Yamanaka et al., 2008) and non-neutralizing antibodies against human respiratory syncytial virus (Gimenez et al., 1996) enhance infection of FcR bearing cells with these viruses, respectively. It is necessary to examine a panel of anti-AAV monoclonal antibodies for their capability of contributing to ADE and for their binding characteristics to AAV particles in future studies.

ADE may be useful for ex vivo immunotherapy, which uses antigen-presenting cells transduced with AAV vectors in vitro (Ponnazhagan et al., 2001; Veron et al., 2007). Because the antigen-presenting cells, such as monocytes and dendritic cells, are positive for Fcγ-RI and Fcγ-RII, pre-incubation of the AAV vectors with anti-AAV antibodies at a sub-neutralizing level, would increase the efficiency of transduction.

This is the first report showing the ADE of infection of Fcγ-R-bearing cells with the dependovirus. ADE has been observed in infection of Fcγ-R-bearing cells with the autonomous parvoviruses, such as human parvovirus B19 (Munakata et al., 2006) and Aleutian mink disease parvovirus (Kanno et al., 1993). The Fcγ-R-mediated ADE of infection may be common to those belonging to *Parvoviridae*.

Experimental Procedures

Cells

THP-1 and U937, human monocytic cell lines, were purchased from American Type Culture Collection (Manassas, VA). THP-1 was cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS) and 50 μM 2-β-mercaptoethanol at 37 °C. U937 was cultured in RPMI 1640 medium supplemented with 10% FBS at 37 °C. HeLa cells that had been adapted to the suspension condition were cultured in suspension minimal essential medium (S-MEM) supplemented with 10% FBS with gentle shaking at 37 °C.

AAV vectors

A vector plasmid pAAVLuc was packaged into the AAV2 and AAV10 capsids to produce AAV2/Luc and AAV10/Luc, respectively, in HEK293 cells as described previously (Mori et al., 2004). The pAAVLuc is composed of the 5′-inverted terminal repeats (ITR) of AAV2, simian virus 40 early enhancer/promoter, firefly luciferase gene, and 3′-ITR. AAV2/Luc and AAV10/Luc were purified by heparin affinity column chromatography (Auricchio et al., 2001) and CsCl equilibrium centrifugation (Mori et al., 2004), respectively. Genome copy numbers of the vector stocks were measured by real-time PCR with TaqMan probes for the firefly luciferase gene (Perkin-Elmer Biosystems, Foster City, CA).

Antisera

Anti-AAV2 antiserum was obtained by an intramuscular injection of purified AAV2 vector having β-galactosidase gene (10^9 genome copies per mouse) to eight-week-old female BALB/c mice. The serum was collected at 6 weeks after the injection. Mouse anti-AAV10 serum was produced previously by immunizing mice with VP2, one of three capsid proteins (Mori et al., 2004). Mouse anti-CD64 and anti-CD32 monoclonal antibodies (BD Bioscience PharMingen, San Diego, CA) were used in the detection and blocking of Fcγ-RI and Fcγ-RII, respectively.

Monkey sera

Sera were obtained from two cynomolgus monkeys kept in Tsukuba Primate Research Center, National Institute of Biomedical Innovation. The monkeys were sedated during collection of blood by administration of Ketamine (10 mg/kg). Animal studies were performed in accordance with the guidelines for animal experiments in the National Institute of Infectious Diseases.

Assay for AAV infection

AAV vectors were suspended in phosphate-buffered saline (PBS) containing 5% FBS. 15 μl of vector suspension was mixed with an equal volume of the test serum that had been heat-inactivated (56 °C for 30 min) and diluted with PBS, and incubated at 37 °C for 30 min. The mixture was inoculated to 3×10^5 cells in a microtube. After incubation at 4 °C for 1 h with occasional rocking, the cells were washed with culture medium twice and resuspended in 780 μl of culture medium. The cell-suspension was seeded in 3 wells (250 μl/well) of a 48-well culture plate and incubated at 37 °C for 2 days. The cells were harvested and lysed. Luciferase activity of the lysate was measured by using Luciferase Assay System (Promega, Madison,WI) and Mithras LB940 Multilabelreader (Berthold Technologies, Bad Wildbad, Germany).

Flow cytometry

THP-1, U937, and HeLa cells were incubated with 2.5 μg/ml of anti-CD64 or anti-CD32 monoclonal antibody in reaction buffer (PBS containing 2% FBS) for 1 h at 4 °C. The cells were washed with the buffer twice and incubated in the buffer containing 2.5 μg/ml of Alexa Fluor 488-conjugated goat anti-mouse IgG serum (Molecular Probes, Eugene, OR). The cells were washed twice with the buffer and then fixed with 2% paraformaldehyde in PBS. Fluorescence was measured using a flow cytometer (BD FACSCalibur, Becton Dickinson, Franklin Lakes, NJ).

Blocking of FcγR on THP-1 and U937 cells

THP-1 and U937 cells were incubated with the culture medium containing 5 μg/ml of anti-CD64 (BD Bioscience PharMingen) and/or anti-CD32 (BD Bioscience PharMingen) at 4 °C for 1 h. The cells were washed twice with the culture medium and used in the assay for AAV infection.

Acknowledgments

We thank Dr. Kunito Yoshiike for critical reading of the manuscript. This work was supported by a grant-in-aid from the Ministry of Health, Labour and Welfare for the Third-Term Comprehensive 10-year Strategy for Cancer Control.

References

Auricchio, A., Hildinger, M., O'Connor, E., Gao, G.P., Wilson, J.M., 2001. Isolation of highly infectious and pure adeno-associated virus type 2 vectors with a single-step gravity-flow column. Hum. Gene Ther. 12, 71–76.

Buller, R.M., Janik, J.E., Sebring, E.D., Rose, J.A., 1981. Herpes simplex virus types 1 and 2 completely help adenovirus-associated virus replication. J. Virol. 40, 241–247.

Carter, B.J., Laughlin, C.A., de la Maza, L.M., Myers, M., 1979. Adeno-associated virus autointerference. Virology 92, 449–462.

Cheung, A.K., Hoggan, M.D., Hauswirth, W.W., Berns, K.I., 1980. Integration of the adeno-associated virus genome into cellular DNA in latently infected human Detroit 6 cells. J. Virol. 33, 739–748.

Chirmule, N., Propert, K., Magosin, S., Qian, Y., Qian, R., Wilson, J., 1999. Immune responses to adenovirus and adeno-associated virus in humans. Gene Ther. 6, 1574–1583.

Clyde, K., Kyle, J.L., Harris, E., 2006. Recent advances in deciphering viral and host determinants of dengue virus replication and pathogenesis. J. Virol. 80, 11418–11431.

Cohen-Solal, J.F., Cassard, L., Fridman, W.H., Sautes-Fridman, C., 2004. Fcγ receptors. Immunol. Lett. 92, 199–205.

Conrad, C.K., Allen, S.S., Afione, S.A., Reynolds, T.C., Beck, S.E., Fee-Maki, M., Barrazza-Ortiz, X., Adams, R., Askin, F.B., Carter, B.J., Guggino, W.B., Flotte, T.R., 1996. Safety of single-dose administration of an adeno-associated virus (AAV)-CFTR vector in the primate lung. Gene Ther. 3, 658–668.

Davidoff, A.M., Gray, J.T., Ng, C.Y., Zhang, Y., Zhou, J., Spence, Y., Bakar, Y., Nathwani, A.C., 2005. Comparison of the ability of adeno-associated viral vectors pseudotyped with serotype 2, 5, and 8 capsid proteins to mediate efficient transduction of the liver in murine and nonhuman primate models. Molec. Ther. 11, 875–888.

Erles, K., Sebokova, P., Schlehofer, J.R., 1999. Update on the prevalence of serum antibodies (IgG and IgM) to adeno-associated virus (AAV). J. Med. Virol. 59, 406–411.

Favre, D., Provost, N., Blouin, V., Blancho, G., Cherel, Y., Salvetti, A., Moullier, P., 2001. Immediate and long-term safety of recombinant adeno-associated virus injection into the nonhuman primate muscle. Molec. Ther. 4, 559–566.

Flotte, T.R., Berns, K.I., 2005. Adeno-associated virus: a ubiquitous commensal of mammals. Hum. Gene Ther. 16, 401–407.

Gimenez, H.B., Chisholm, S., Dornan, J., Cash, P., 1996. Neutralizing and enhancing activities of human respiratory syncytial virus-specific antibodies. Clin. Diagn. Lab. Immunol. 3, 280–286.

Handa, H., Shiroki, K., Shimojo, H., 1977. Establishment and characterization of KB cell lines latently infected with adeno-associated virus type 1. Virology 82, 84–92.

Kanno, H., Wolfinbarger, J.B., Bloom, M.E., 1993. Aleutian mink disease parvovirus infection of mink macrophages and human macrophage cell line U937: demonstration of antibody-dependent enhancement of infection. J. Virol. 7, 7017–7024.

Lai, L., Davison, B.B., Veazey, R.S., Fisher, K.J., Baskin, G.B., 2002. A preliminary evaluation of recombinant adeno-associated virus biodistribution in rhesus monkeys after intrahepatic inoculation in utero. Hum. Gene Ther. 13, 2027–2039.

McPherson, R.A., Rosenthal, L.J., Rose, J.A., 1985. Human cytomegalovirus completely helps adeno-associated virus replication. Virology 147, 217–222.

Mori, S., Murakami, M., Takeuchi, T., Kozuka, T., Kanda, T., 2002. Rescue of AAV by antibody-induced Fas-mediated apoptosis from viral DNA integrated in HeLa chromosome. Virology 15, 90–98.

Mori, S., Wang, L., Takeuchi, T., Kanda, T., 2004. Two novel adeno-associated viruses from cynomolgus monkey: pseudotyping characterization of capsid protein. Virology 330, 375–383.

Mori, S., Takeuchi, T., Enomoto, Y., Kondo, K., Sato, K., Ono, F., Iwata, N., Sata, T., Kanda, T., 2006. Biodistribution of a low dose of intravenously administered AAV-2, 10, and 11 vectors to cynomolgus monkeys. Jpn. J. Infect. Dis. 59, 285–293.

Mori, S., Takeuchi, T., Enomoto, Y., Kondo, K., Sato, K., Ono, F., Sata, T., Kanda, T., 2008. Tissue distribution of cynomolgus adeno-associated viruses AAV10, AAV11, and AAVcy.7 in naturally infected monkeys. Arch. Virol. 153, 375–380.

Munakata, Y., Kato, I., Saito, T., Kodera, T., Ishii, K.K., Sasaki, T., 2006. Human parvovirus B19 infection of monocytic cell line U937 and antibody-dependent enhancement. Virology 345, 251–257.

Nathwani, A.C., Davidoff, A.M., Hanawa, H., Hu, Y., Hoffer, F.A., Nikanorov, A., Slaughter, C., Ng, C.Y., Zhou, J., Lozier, J.N., Mandrell, T.D., Vanin, E.F., Nienhuis, A.W., 2002. Sustained high-level expression of human factor IX (hFIX) after liver-targeted delivery of recombinant adeno-associated virus encoding the hFIX gene in rhesus macaques. Blood 100, 1662–1669.

Peiris, J.S., Porterfield, J.S., 1979. Antibody-mediated enhancement of flavivirus replication in macrophage-like cell lines. Nature 282, 509–511.

Peiris, J.S., Gordon, S., Unkeless, J.C., Porterfield, J.S., 1981. Monoclonal anti-Fc receptor IgG blocks antibody enhancement of viral replication in macrophages. Nature 289, 189–191.

Pierson, T.C., Xu, Q., Nelson, S., Oliphant, T., Nybakken, G.E., Fremont, D.H., Diamond, M.S., 2007. The stoichiometry of antibody-mediated neutralization and enhancement of West Nile virus infection. Cell Host Microbe. 1, 135–145.

Ponnazhagan, S., Mahendra, G., Curiel, D.T., Shaw, D.R., 2001. Adeno-associated virus type 2-mediated transduction of human monocyte-derived dendritic cells: implications for ex vivo immunotherapy. J. Virol. 75, 9493–9501.

Richardson, W.D., Westphal, H., 1981. A cascade of adenovirus early functions is required for expression of adeno-associated virus. Cell 27, 133–141.

Veron, P., Allo, V., Riviere, C., Bernard, J., Douar, A.M., Masurier, C., 2007. Major subsets of human dendritic cells are efficiently transduced by self-complementary adeno-associated virus vectors 1 and 2. J. Virol. 81, 5385–5394.

Wu, Z., Asokan, A., Samulski, R.J., 2006. Adeno-associated virus serotypes: vector toolkit for human gene therapy. Molec. Ther. 14, 316–327.

Yamanaka, A., Kosugi, S., Konishi, E., 2008. Infection-enhancing and -neutralizing activities of mouse monoclonal antibodies against dengue type 2 and 4 viruses are controlled by complement levels. J. Virol. 82, 927–937.