Antibody-Dependent Enhancement of Feline Infectious Peritonitis Virus Infection in Feline Alveolar Macrophages and Human Monocyte Cell Line U937 by Serum of Cats Experimentally or Naturally Infected with Feline Coronavirus

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ABSTRACT. Infection of the type II feline infectious peritonitis virus (FIPV) strain 79–1146 to primary feline alveolar macrophages and human monocyte cell line U937 was enhanced by the sera of cats experimentally infected with the 79–1146 strain, but not those of cats infected with KU-2 or UCD-1 strain of type I FIPV. The experiments using sera of cats with feline infectious peritonitis (FIP) and of cats naturally infected with feline coronavirus (FCoV) revealed that infection of the FIPV 79–1146 strain to the U937 cells was enhanced only by the sera of cats infected with type II FIPV or feline enteric coronavirus. The samples positive for antibody-dependent enhancement (ADE) activity had high neutralizing antibody titers against the FIPV 79–1146 strain and the samples negative for ADE activity had low neutralizing antibody titers. These findings support the previous results where a monoclonal antibody with neutralizing activity had high ADE activity, suggesting that there was a close relationship between the neutralization and enhancement sites. And then it is also suggested that ADE of infection is likely to be induced by re-infection with the same serotype of virus in type II FIPV infection. Furthermore, U937 cells are considered useful and can be substituted for the feline macrophages for determining ADE of FIPV-infection.
— KEY WORDS: antibody-dependent enhancement of infection, feline infectious peritonitis virus, feline macrophage, U937 cell.

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Feline infectious peritonitis (FIP) is a virus-induced chronically progressive and usually fatal disease in domestic and wild Felidae. The causative agent of this disease is FIP virus (FIPV) which belongs to the family *Coronaviridae*. The natural route of FIPV infection is unknown although cats can be experimentally infected by oral, nasal, and parenteral administration of the virus. Following infection by these routes, FIPV first replicates in the epithelial cells of the upper respiratory tract and intestine [31]. Clinically apparent FIP occurs after the viruses infect macrophages and monocytes, and then cross the mucosal barrier and spread throughout the body of the cat. Generally, macrophages play an important role in non-specific defense against viral infection. However, it is also known that some viruses bound to antibodies invade macrophages via the Fc region of the antibody and the Fc gamma receptor (Fc g R) of the macrophage, and eventually the antibody leads to the enhancement of infection [2, 6–9, 15, 28, 29, 32]. The disease caused by this infection mechanism is dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS). The antibody against FIPV is also known to enhance the FIPV infection and accelerate the disease onset in cats [24, 26, 33]. Following experimental FIPV infection, cats with FIPV-neutralizing antibody frequently develop FIP more rapidly and with severer clinical signs than do seronegative cats. When cats passively immunized with anti-FIPV antibodies were inoculated with a virulent FIPV, severe symptoms were observed and some of the cats died soon after the inoculation [24, 33]. The enhancing effect of the antibody on FIPV infection impedes prophylaxis of FIP by vaccination [1, 22, 25–27, 30, 34]. We previously reported that *in vitro* FIPV infection of feline alveolar macrophages is enhanced by murine monoclonal antibodies (MAbs) to the peplomer spike (S) protein of FIPV [10, 14]. This antibody-dependent enhancement (ADE) activity by the MAb correlated with the neutralizing activity assayed by using CrFK [4, 10, 13, 21].

Feline coronaviruses (FCoVs) are divided into FIPV types I and II, and feline enteric coronavirus types I and II [23]. The type II strains appeared to be more closely related to canine coronavirus (CCV) and transmissible gastroenteritis virus (TGEV), since immunodominant neutralization epitopes shared by the spike proteins of TGEV, CCV, and the type II FCoV strains seemed to be absent in the type I strains [12]. Recently, these findings were confirmed by sequence analysis. The sequences of spike genes of type II FCoVs have higher homologies with those of TGEV and CCV than those of type I isolates [18, 19]. Dengue virus which causes DHF/DSS has four serotypes differentiated by the neutralization test, and ADE of dengue virus infection often occurs in re-infection with a different serotype of the virus [6, 8, 9, 16, 17]. However, the type of virus , re-infection by which will cause ADE at the highest frequency in FIPV infection, is unclear. It has been reported that the frequency of type I FCoV infection is high in the field [11].

In the present study, ADE of infection with the type II FIPV strain 79–1146 was examined with sera of cats experimentally infected with FIPV and naturally infected with FCoV. Monocytic cells used for determination of the ADE activity were feline alveolar or peritoneal

macrophages. These cells are heterogeneic in differentiation and activation. Since it is laborious to collect them frequently and in large quantity, a human monocyte cell line, U937 cells, was also used.

MATERIALS AND METHODS

Virus and cell cultures: FIPV strains 79–1146, KU-2 and UCD-1 were used in this study. The KU-2 strain was isolated in our laboratory. The 79–1146 and UCD-1 strains were obtained from Dr. M.C. Horzinek (The State University, Utrecht, the Netherlands) and Dr. N. C. Pedersen (University of California, Davis, U.S.A.), respectively. Strain 79–1146 was classified as type II FCoV, and strains KU-2 and UCD-1 were classified as type I FCoV [5, 12].

Felis catus whole fetus (fcwf-4) cells and feline alveolar macrophages were cultured in Eagle's minimum essential medium containing 50% Leibovitz's L-15 medium, 10% fetal calf serum, 100 units/m*l* penicillin and 100 μg/m*l* streptomycin. Feline alveolar macrophages were collected from adult cats negative for anti-coronavirus antibody as described previously [10]. The human monocyte cell line U937 was kindly provided by Dr. J. Arikawa (Hokkaido University, Sapporo, Japan) and was cultured in RPMI 1,640 medium containing 10% fetal calf serum, 100 units/m*l* penicillin and 100 μg/m*l* streptomycin.

Test serum samples: The sera of cats experimentally infected with FIPV were prepared by intraperitoneal inoculation of specific pathogen-free adult cats with of 10^3 50% tissue culture infective doses ($TCID_{50}$) of each virus strain. A total of 87 sera of cats naturally infected with FCoV were used. These sera had been submitted by private veterinarians for diagnosis of serological testing for viral infection. Thirty-six sera of them had been obtained from cats diagnosed as FIP because of symptoms of febrile effusive peritonitis, jaundice and nephropathy.

ADE assay of viral infection: In ADE assay using U937 cells, 50 μl of the 10-fold serial dilutions of the test serum were mixed with 50 μl of 10^6 $TCID_{50}$ of FIPV strain 79–1146 and allowed to react at 4°C for 1 hr, then inoculated onto 2×10^5 U937 cells per 50 μl and incubated at 37°C for 3 hr. After the cell mixture was washed with Hanks' balanced salt solution (HBSS) 3 times, the cells were suspended in the growth medium, and incubated at 37°C for 24 hr.

In ADE assay using feline alveolar macrophages, the test serum serially diluted 10-fold was mixed with an equal volume of 10^4 $TCID_{50}$ of virus, and the mixture was allowed to react at 4°C for 1 hr. The mixture was inoculated onto macrophages grown in 24-well multiplates, and incubated at 37°C for 1 hr. After the plates were washed with HBSS 3 times, growth medium was added to each well and the plates were incubated at 37°C for 48 hr.

The titers of virus in the culture supernatant were determined by plaque assay, and compared with those of viruses produced in the absence of the test serum.

Plaque assay: Confluent fcwf-4 cell monolayers in 24-well multiplates were inoculated with 50 μl of dilutions of the samples. After virus adsorption at 37°C for 1 hr, the cells were washed with HBSS and 1 m*l* of growth medium containing 1.5% carboxymethyl cellulose was added to each well. The cultures were incubated in a CO_2 incubator at 37°C for 2 days, fixed in 10% buffered formalin, and stained with 1% crystal violet.

Neutralization (NT) test: Serial twofold dilutions of the test sera were mixed with an equal volume of virus suspension containing approximately 200 $TCID_{50}$ and the mixture was incubated at 37°C for 60 min. Each mixture was then inoculated onto fcwf-4 cell cultures in flat-bottomed microplates, and the plates were incubated in CO_2 incubator at 37°C for 3 days. Each serum dilution was tested in duplicate. The antibody titer was expressed as the reciprocal of the highest dilution of serum that completely inhibited a viral cytopathic effect.

Indirect immunofluorescence assay (IFA): The cells infected with FIPV strain 79–1146 were fixed with cold acetone for 15 min and air-dried. Serial dilutions of the test sera were added to the acetone-fixed cells and the tubes were allowed to react at 37°C for 30 min. After the wash with PBS 3 times, the samples were stained with goat anti-cat lgG antibody conjugated with fluorescein isothiocyanate (Southern Biotechnology Assoc., Birmingham. Alabama. U.S.A.). After incubation at 37°C for 30 min, they were washed with PBS, mounted in 50% glycerol buffer and observed with a fluorescence microscope.

Competitive enzyme-linked immunosorbent assay (ELISA): Competitive ELISA was performed as described previously [11]. The viral antigen was purified from the culture supernatant of the cells infected with FIPV 79–1146 strain by sucrose gradient ultracentrifugation. Cat serum (100 μl of a 1:100 dilution in PBS containing 10% calf serum and 0.05% Tween-20) was added to 96-well Microelisa plates coated with viral antigens, and the plates were incubated at 37°C for 1 hr. After the plates were washed with PBS containing 0.02% Tween-20 3 times, peroxidase-conjugated MAb specific for type II FCoV was added. After incubation at 37°C for 30 min, 100 μl of substrate solution was added to each well and the plates were incubated at 25°C for 20 min in a dark room. The substrate solution was prepared by dissolving O-phenylene-diamine dihydrochloride at a concentration of 0.4 mg/m*l* in 0.1 M citric acid-0.2 M Na_2HP0_4 buffer (pH 4.8) and adding 0.2 μl of 30% H_20_2 per m*l*. After incubation, the reaction was stopped with 3 N H_2S0_4 solution and the optical density (OD) at 492 nm was measured. The percent inhibition was calculated by the formula $100 \times (A-B)/A$, where A is the OD in the dilution buffer and B is the OD in the test serum.

RESULTS

ADE of FIPV strain 79-1146 infection in human monocyte cell line U937 and feline alveolar macrophages by sera of cats experimentalIy infected with FIPV: ADE of FIPV 79–1146 infection by sera of cats experimentally infected with

Table 1. ADE of FIPV strain 79–1146 infection in human monocyte cell line U937 and feline alveolar macrophages by sera of cats experimentally infected with FIPV

Cat sera	Infected virus strains	NT 79–1146	NT KU-2	IFA	ADE activity feline mø	ADE activity U937
A	79–1146	≥1280[a)]	8[b)]	≥4096[c)]	++[d)]	++
B		≥1280	8	≥4096	++	++
C		≥1280	4	≥4096	++	++
D	KU-2	<2	640	≥4096	–[e)]	–
E		<2	160	≥4096	–	–
F	UCD-1	<2	320	≥4096	–	–

a) Titer of NT antibody against FIPV strain 79–1146. b) Titer of NT antibody against FIPV strain KU-2. c) Titer of IFA antibody against FIPV strain 79–1146. d) The number of plaques was more than 50 times that of the virus control. e) The number of plaques was less than 4 times that of the virus control.

the type II FIPV 79–1146 strain, type I FIPV KU-2 strain and type I FIPV UCD-1 strain was investigated in U937 cells and feline macrophages (Table 1). These sera showed a titer of 1:4096 or higher by IFA using the 79–1146 strain as an antigen. However, the sera of cats infected with KU-2 and UCD-1 strains did not neutralize the 79–1146 strain, although the sera of cats infected with the 79–1146 strain neutralized the strain well. Conversely, the sera of cats infected with the KU-2 and UCD-1 strains neutralized the KU-2 strain, however the sera of cats infected with strain 79–1146 had distinctively lower neutralization titers than did those of cats infected with the KU-2 or UCD-1 strain. These sera were reacted with the 79–1146 strain after l0-fold serial dilution, then inoculated onto U937 cells and feline alveolar macrophages. The infection was enhanced only by the sera of cats infected with the homologous strain 79–1146.

To determine whether ADE of FIPV infection in U937 cells is mediated by the Fc region of the antibody, IgG of serum A was treated with protein A and the influence of the treatment on ADE of FIPV infection was investigated. When only viruses were inoculated onto U937 cells, the viruses did not multiply, whereas when a reaction mixture of viruses and lgG was inoculated they multiplied with a peak 12 to 24 hr after inoculation. However, when the lgG was treated with protein A, no viral proliferation was observed (Fig. 1).

ADE of FIPV strain 79-1146 infection in human monocyte cell line U937 by sera of cats naturally infected with FCoV: ADE of FIPV strain 79–1146 infection by 87 field serum samples consisting of 36 FIP cat serum samples and 51 serum samples from FCoV antibody-positive cats was investigated with U937 cells. All these serum samples had antibody titers of 1:256 or higher in the IFA test using the 79–1146 strain as an antigen. Relationships of the ADE of infection with the results of competitive ELISA using a type II FIPV-specific MAb, the titer of neutralizing antibody

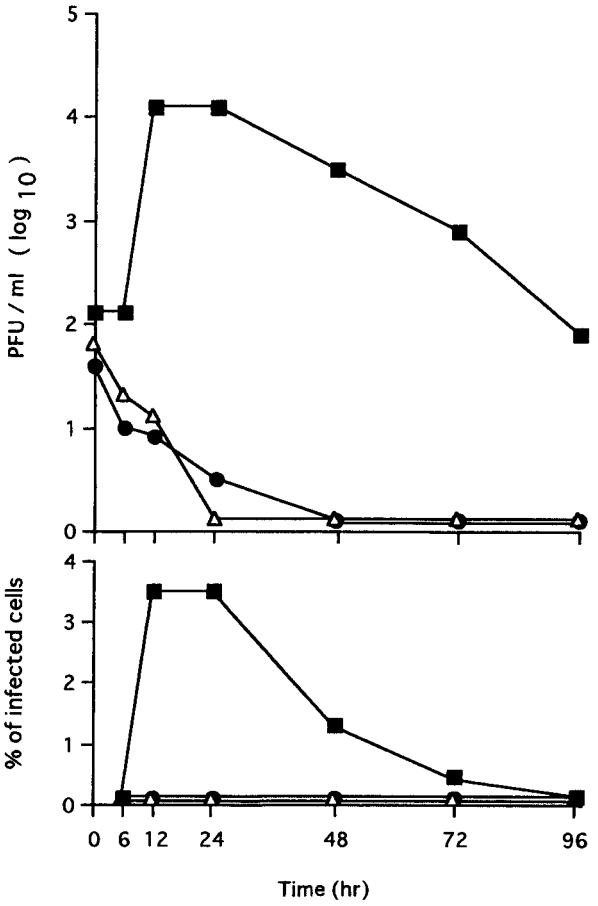

Fig. 1. Effect of protein A on ADE of FIPV strain 79-1146 infection in human monocyte cell line U937. Fifty μg/ml of lgG of serum A purified by ammonium sulfate precipitation and 1 mg/ml of protein A were allowed to react at 4°C for 1 hr. The effect of the treatment with protein A on ADE of FIPV infection in U937 cells was investigated. The reaction mixture of virus with HBSS (△), with lgG (■) or with protein A-treated lgG (●) was inoculated onto U937 cells and incubated at 37°C. The culture supernatants and the cells were collected at the indicated time. The amount of infectious virus in the supernatant and positive percentages of FIPV antigen in the cells were determind by the plaque assay and the IFA, respectively.

against the type II FIPV 79–1146 strain, and the titer of neutralizing antibody against the type I FIPV KU-2 strain are shown in Fig. 2.

The samples positive for ADE activity showed high percents of inhibition in competitive ELISA and high neutralizing antibody titers against the 79–1146 strain, showing a distinct correlation. In addition the samples negative for ADE activity had low titers of neutralizing antibody against the 79–1146 strain but high titers against the KU-2 strain. Figure. 3 shows the representative patterns of plaque assay showing ADE activity-positive, -weak positive and -negative.

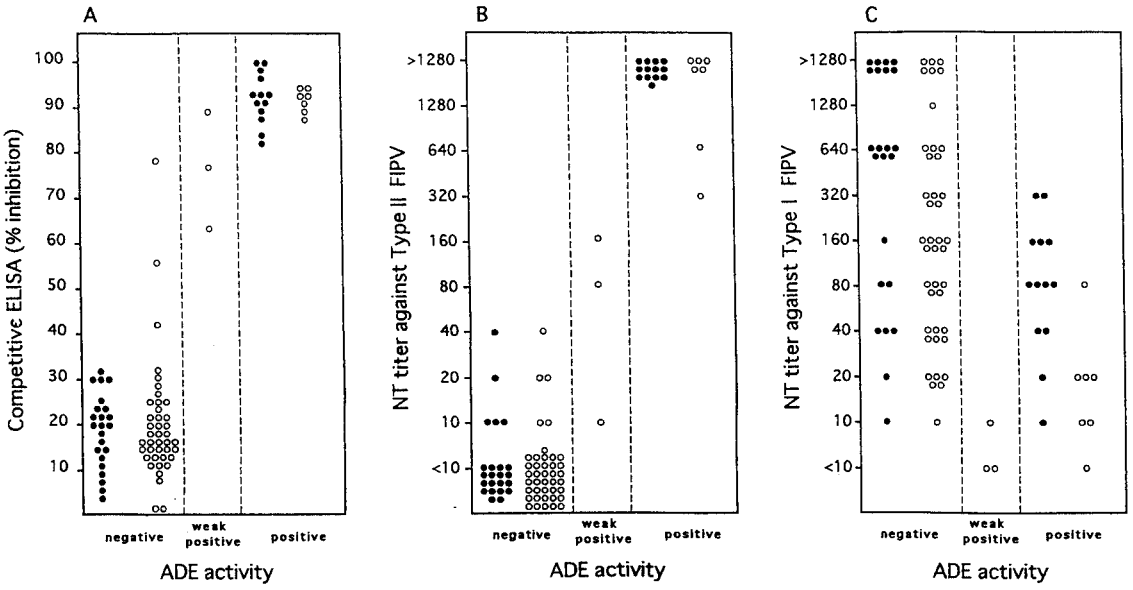

Fig. 2. ADE of FIPV strain 79–1146 infection in human monocyte cell line U937 by sera of cats naturally infected with FCoV. The relationships of ADE activity with results of competitive ELISA using a type II FCoV-specific MAb (A), with the titer of neutralizing antibody against type II FIPV strain 79–1146 (B), and with the titer of neutralizing antibody against type I FIPV strain KU-2 (C) are shown. ●: cat with FIP, ○: FCoV antibody positive cat (without FIP).

DISCUSSION

ADE of FIPV infection by sera of cats experimentally or naturally infected with FCoV was investigated with human monocyte cell line U937 cells as well as feline alveolar macrophages. As shown in Table 1, results obtained with the U937 cells were similar to those with feline macrophages, suggesting that U937 cells are useful and can be substituted for the feline macrophages for determining ADE of FIPV- infection. In addition, the multiplication of the FIPV 79–1146 strain in U937 cells did not occur until anti-FIPV serum was added. Since the FIPV 79–1146 strain multiplies in feline macrophages irrespective of the presence of anti-FIPV serum, it was easier to evaluate ADE in U937 cells than feline macrophages.

ADE of dengue virus infection occurs in re-infection with a different serotype of virus [6, 8, 9, 16, 17]. However, infection of feline macrophages and U937 cells with the FIPV 79–1146 strain was enhanced only with the serum of cats infected with the homologous 79–1146 strain, but not with the type I FIPV KU-2 or UCD-1 (Table 1). In the experiment using sera of FIP cats and of cats naturally infected with FCoV, infection of U937 cells with FIPV 79–1146 strain was enhanced by serum samples with a high percentage of inhibition in competitive ELISA using a type II FCoV-specific MAb, i.e., sera of cats that were considered to have been infected with type II FIPV or FECV. Furthermore, these ADE activity-positive samples had high titers of neutralizing antibody against the FIPV 79–1146 strain, while the ADE activity-negative samples had low neutralizing antibody titers. The results support the previous findings that mouse MAbs which show high ADE activities have neutralizing activities, suggesting a close relationship between the neutralization and enhancement sites. We have recently reported that type I FIPVs including the UCD-1 strain have spike genes that are distinctly different from those of type II FIPVs, TGEV and CCV [18, 19]. It has been reported that neutralization/enhancement site of the type II FIPV 79–1146 strain is located at the site corresponding to neutralization site A identified on TGEV S protein [3, 20]. When nucleotide sequences at this site in TGEV strain Purdue, FIPV strains 79–1146 and KU-2 were compared, the sequence homology showed 93.9% identity between the Purdue strain and the 79–1146 strain, 49.3% between the Purdue strain and the KU-2 strain and 50.4% between the 79–1146 strain and the KU-2 strain (data not shown). The difference in sequence homology at the site suggested that the serum of cats infected with type I FCoVs does not enhance infection of macrophages with type II FIPV. These data also support the results of the present report. Olsen *et al.* [21] have reported that the serum of cats infected with the FIPV UCD-1 strain enhances infection of feline peritoneal macrophages with the FIPV 79–1146 strain. Their results are inconsistent with our present ones. However, the FIPV UCD-1 strain used in their study proliferates well in CrFK cells, and is antigenically similar to type II FCoVs, CCV and TGEV [4, 21]. These properties are different from those of the original UCD-1 strain [12, 23]. Recently, de Groot and Horzinek [5] indicated the possibility of virus stocks may have been interchanged.

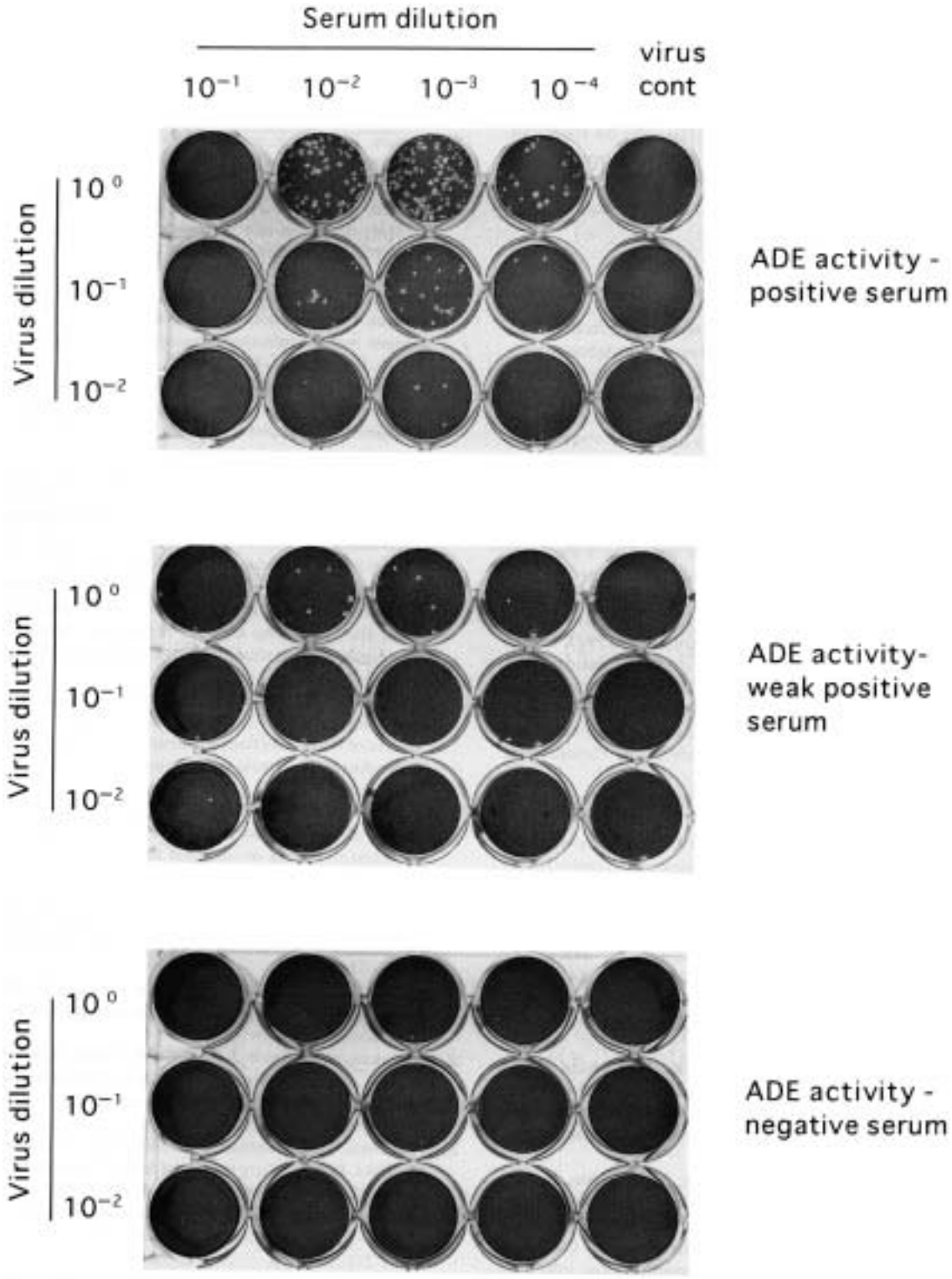

Fig. 3. Results of plaque assay of ADE activity-positive, -weak positive and -negative serum samples. After 10-fold serial dilutions of the test serum were reacted with FIPV strain 79–1146 at 4°C for 1 hr, the mixtures were inoculated onto U937 cells. After incubation at 37°C for 24 hr, the amount of infectious virus in the culture supernatant was determined by the plaque assay.

We investigated ADE of infection of feline alveolar macrophages with KU-2, UCD-1 and Black strain, which are type I FIPV. However, these viruses did not multiply in cultured feline alveolar macrophages, and enhancement of the infection by the antibodies was not observed. It is unclear at present whether or not ADE will be likely to occur with the serum of cats infected with the same type of FCoVs even in type I FIPVs, as in type II FIPVs. We are now repeating the experiment on ADE of infection with type I FIPVs.

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