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The role of IgG subclass of mouse monoclonal antibodies in antibody-dependent enhancement of feline infectious peritonitis virus infection of feline macrophages

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Summary. Antibody-dependent enhancement (ADE) of feline infectious peritonitis virus (FIPV) infection was studied in feline alveolar macrophages and human monocyte cell line U937 using mouse neutralizing monoclonal antibodies (MAbs) directed to the spike protein of FIPV. Even among the MAbs that have been shown to recognize the same antigenic site, IgG 2a MAbs enhanced FIPV infection strongly, whereas IgG 1 MAbs did not. These IgG 2a MAbs enhanced the infection even when macrophages pretreated with the MAb were washed and then inoculated with the virus. Immunofluorescence flow cytometric analysis of the macrophages treated with each of the MAbs showed that the IgG 2a MAbs but not the IgG 1 MAbs bound to feline alveolar macrophages. Treatment of the IgG 2a MAb with protein A decreased the binding to the macrophages and, in parallel, diminished the ADE activity. Although no infection was observed by inoculation of FIPV to human monocyte cell line U937 cells, FIPV complexed with either the IgG 2a MAb or the IgG 1 MAb caused infection in U937 cells which are shown to express Fc gamma receptor (Fc γ R) I and II that can bind mouse IgG 2a and IgG 1, respectively. These results suggest that the enhancing activity of MAb is closely correlated with IgG subclass and that the correlation is involved in binding of MAb to Fc γ R on feline macrophage.

Introduction

Feline infectious peritonitis virus (FIPV) is a member of the coronavirus family and causes a chronic progressive disease in its natural host. The natural route of FIPV infection is unknown although cats can be experimentally infected by oral, nasal, and parenteral administration of FIPV. Following infection by these routes, FIPV first multiplies in the epithelial cells of the upper respiratory tract and intestine [30]. Clinically apparent FIP occurs after the viruses in infected

macrophages and monocytes 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 viruses bound to antibodies invade macrophages via Fc region of the bound antibody and the macrophage's Fc gamma receptor (Fc γ R) and eventually lead to enhancement of infection [4, 7–10, 14, 26, 27, 31]. Its most typical example is a disease called dengue hemorrhagic fever/dengue shock syndrome. The antibody for FIPV is also known to enhance the FIPV infection and accelerate the disease onset in cats [22, 23, 34]. Following experimental FIPV infection, cats with naturally occurring FIPV-neutralizing antibody frequently develop FIP more rapidly and with more severe clinical signs than do seronegative cats. When cats passively immunized with anti-FIPV antibodies were infected with virulent FIPV, severe symptoms were observed and some of them died soon after the infection [22, 34]. The enhancing effect of the antibody of FIPV infection impedes prophylaxis of FIP by vaccination [2, 21, 23–25, 29, 35].

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 or the transmembrane (M) protein of FIPV [12, 13]. This antibody-dependent enhancement (ADE) was completely eliminated or reduced by pretreatment of the MAbs with Protein A or when $F(ab')_2$ fragments of the MAbs were used. Olsen et al. have supported our findings by showing enhancement of FIPV infection in primary feline peritoneal macrophages by mouse MAbs to the viral S protein [20]. In many instances virus-neutralizing MAbs were shown to have strong ADE activity, and it was suggested that there was some relationship between neutralizing activity and ADE activity. On the other hand, Corapi et al. recognized a difference in immunoglobulin subclasses between ADE-inducing FIPV-neutralizing MAb and ADE-non inducing FIPV-neutralizing MAb, and they showed that the majority of the ADE-inducing MAbs belong to the IgG 2a subclass [5]. These results were obtained by the experiments in which mouse MAbs and feline macrophages, i.e., xenogeneic combination of MAbs and macrophages, were used. In contrast, it has been reported that mouse MAbs irrespective of whether the subclass is IgG 1, IgG 2a or IgG 2b enhanced infection of mouse (homologous) macrophages of dengue virus [10, 17], influenza A virus [18] and West Nile virus [3].

Since ADE of the disease caused by FIPV has been clearly demonstrated after vaccination of cats with a variety of candidate vaccines, a more specific understanding of ADE of FIPV infection is needed [2, 21, 23–25, 30, 35]. It is especially important for development of vaccines to understand the relationship between FIPV neutralizing activity and ADE activity of anti FIPV MAbs. In this study, we determined the relationship between immunoglobulin subclass and ADE activity of FIPV-neutralizing MAbs, and attempted to explore mechanisms of ADE of FIPV infection in *in vitro* system using mouse MAbs and feline alveolar macrophages or human monocytes.

Materials and methods

Virus and cell cultures

FIPV strain 79-1146 was used in this study. This strain was kindly provided by Dr. M. C. Horzinek of the State University Utrecht, the Netherlands, and was passaged two or three times in feline fetal cell (fcwf-4) cultures.

Feline alveolar macrophages were collected from anti-coronavirus antibody-negative adult cats and cultured in Eagle's minimum essential medium containing 50% Leibovitz's L-15 medium, 10% fetal calf serum, 100 units of penicillin per ml and 100 µg of streptomycin per ml as previously described [12].

Human monocyte cell line U937 was kindly provided by Dr. J. Arikawa of the University of Hokkaido, Japan, and was cultured in RPMI 1640 medium containing 10% fetal calf serum, 100 units of penicillin per ml and 100 µg of streptomycin per ml.

Monoclonal antibodies (MAbs)

MAbs 5-6-3, 5-7-2, 7-1-1, 7-3-1, 6-4-2, and 6-1-1 used in the present study recognize S protein of the virus as demonstrated by immunoblotting. These MAbs have the ability to neutralize FIPV strain 79-1146, and recognize two different antigenic sites of the viral S protein [11]. The neutralization titer, indirect immunofluorescent antibody titer, immunoglobulin isotype and epitope specificity of these MAbs are shown in Table 1. The culture fluid of each MAb-producing hybridoma was used for the experiment.

F(ab')$_2$ of MAb 32.2, Fab of MAb IV.3 and F(ab')$_2$ of MAb 3G8 were purchased from Medarex, Lebanon, NH. MAb 32.2 is a mouse IgG 1 antibody that reacts with human Fcγ R I [1]. MAb IV.3 is a mouse IgG 2b antibody that reacts with human Fcγ R II [15]. MAb 3G8 is a mouse IgG 1 antibody that reacts with human Fcγ R III [6].

Indirect immunofluorescence assay (IFA) of FIPV proliferation

A mixture of MAbs that recognize peplomer protein (S), transmembrane protein (M) and nucleocapsid protein (N) of FIPV strain 79-1146, respectively, was used as the primary antibody. The MAbs were added to acetone-fixed FIPV-infected cells and allowed to stand at 37 °C for 30 min. After the specimens were washed with phosphate-buffered saline (PBS) three times, they were stained with rabbit anti-mouse IgG, IgA and IgM serum conjugated with fluorescein isothiocyanate (Miles Laboratories, Naperville, U.S.A). After being held at 37 °C for 30 min, they were washed with PBS, mounted in 50% glycerol buffer and observed under a fluorescence microscope.

Plaque assay

Confluent fcwf-4 cell monolayers in 60-min plastic petri dishes were inoculated with virus dilutions of specimen to be assayed for amount of infectious virus in 0.1 ml amounts. After virus adsorption at 37 °C for 60 min, the inoculated cultures were covered with 5 ml of agar overlay medium which consisted of 1% Bacto agar in minimal essential medium. The cultures were incubated in a CO_2 incubator at 37 °C for 2 days, and stained by incubating at 37 °C for 6 h under a second overlay medium containing 0.01% neutral red. The infectious titer was expressed in plaque-forming units (PFU).

Assay of antibody-dependent enhancement (ADE) of viral infection

ADE assay of FIPV infection of feline alveolar macrophages was performed by two methods. In the first method, equal amounts of MAb and viral suspension were allowed to react at

4 °C for 1 h before inoculation onto the macrophages. In the second method, MAbs alone were allowed to react with the macrophages at 37 °C for 1 h before viral inoculation. In both methods, the virus-inoculated cells were examined for viral antigen by IFA using mixture of anti-FIPV MAbs after incubation for 36 h, and the percent of ADE was determined by the following formula:

$$\text{percent ADE} = 100 \times (A - B)/B$$

where A is the rate of IFA positive cells in the culture infected in the presence of MAb and B is that in the culture infected in the absence of MAb.

In ADE assay of FIPV infection of human monocyte cell line U937, virus suspension was allowed to react with MAb at 4 °C for 1 h and then inoculated to a cell pellet of U937 cells. The inoculated cells were incubated at 37 °C for 1 h to allow virus adsorption, and then washed with Hanks' balanced salt solution (HBSS). After washing, the cells were cultured and 36 h later, were examined for infecting FIPV antigen by IFA. At the same time, the level of infectious virus in the culture supernatant was determined by plaque assay.

Binding activity of mouse MAbs to feline macrophages determined by immunofluorescence flow cytometry

Undiluted MAb (5-6-2, 5-7-2, 7-1-1, 7-3-1, 6-4-2 or 6-1-1) or a mixture of either one of the MAb and FIPV was added to 1×10^6 feline alveolar macrophages and held at 4 °C for 1 h. After three washings with HBSS containing 0.1% N_aN_3, the cells were allowed to react with 8-fold diluted FITC-conjugated Fab of goat anti-mouse IgG antibody at 4 °C for 1 h. After being washed three times, the stained cells were analyzed by counting about 10,000 cells on a FACS 440 (Becton Dickinson Co., U.S.A.).

Detection of Fc γ R on U937 cells

A total of 1×10^6 U937 cells were incubated with 1:4 diluted MAb 32.2, IV.3 or 3G8 in HBSS containing 10 mg of human Ig per ml at 4 °C for 1 h. The cells were washed three times in HBSS containing 0.1% N_aN_3, resuspended and incubated in 1:8 diluted FITC-conjugated Fab of goat anti-mouse IgG antibody at 4 °C for 1 h. After the cells were washed three times, the number of stained cells was determined by counting about 10 000 cells on a FACS 440 (Becton Dickinson).

Results

Relationship between Ig subclass and ADE activity of MAbs recognizing the same antigenic site

The relationship between Ig subclass and ADE activity was investigated with the MAbs shown in Table 1. As shown in Fig. 1, despite the fact that they recognized the same antigenic site, Group-I MAbs 5-7-2 and 7-1-1 showed strong ADE activity on FIPV infection, but Group-I MAbs 5-6-2 and 7-3-1 showed only neutralizing activity. With regard to Group-II MAbs as well, 6-4-2 showed strong ADE activity, while 6-1-1 showed only neutralizing activity and did not enhance the infection. All of the MAbs that enhanced infection belonged to subclass IgG 2a, and the MAbs that showed only neutralizing activity belonged to subclass IgG 1.

Table 1. Characteristics of mouse anti-FIPV monoclonal antibodies

| MAb[a]	NT	IFA	Isotype	Epitope specificity
5-6-2	40[b]	64[c]	IgG 1	
5-7-2	80	256	IgG 2a	Group I
7-1-1	40	64	IgG 2a	
7-3-1	320	256	IgG 1	
6-4-2	80	256	IgG 2a	Group II
6-1-1	40	256	IgG 1	

[a]Culture fluids of hybridoma cells were used
[b]Neutralization titer against FIPV strain 79-1146 determined on infection of Crandell feline kidney (CrFK) cells
[c]Indirect immunofluorescent antibody titer determined on FIPV strain 79-1146 infected fcwf-4 cells
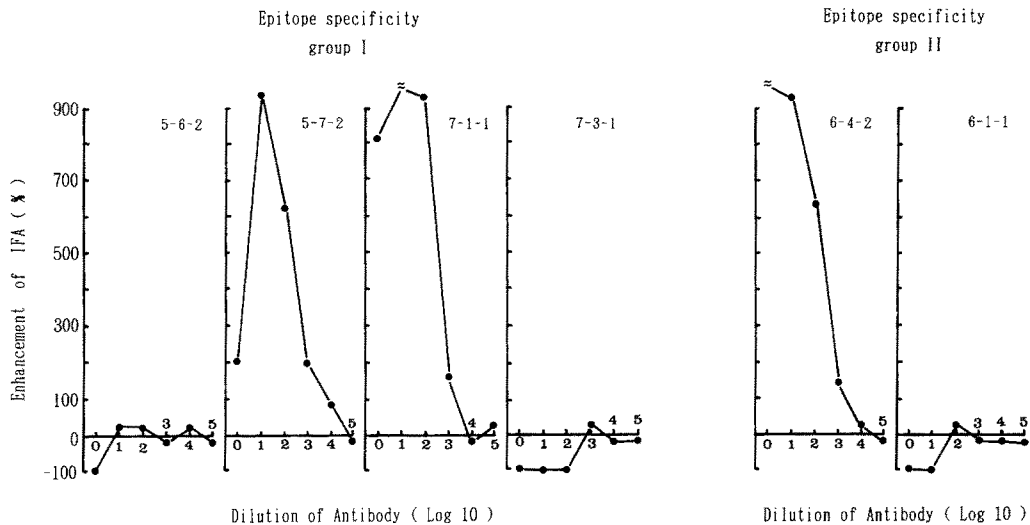
Fig. 1. Relationship between immunoglobulin subclass and ADE activity of anti-FIPV MAbs recognizing the same antigenic site. Each MAb and FIPV were allowed to react at 4 °C for 1 h, then the mixture was inoculated onto feline alveolar macrophages. The cells were examined for the viral antigen by IFA 36 h later to determine proliferation of the virus. Percent ADE was calculated as described in Materials and methods. MAb 5-6-2, IgG 1; MAb 5-7-2, IgG 2a; MAb 7-1-1, IgG 2a; MAb 7-3-1, IgG 1; MAb 6-4-2, IgG 2a; MAb 6-1-1, IgG 1

ADE activity of these MAbs was also determined by inoculating FIPV to macrophages pretreated with each MAb (Fig. 2). MAbs 5-7-2, 7-1-1 and 6-4-2, whose subclass is IgG 2a, enhanced the infection in the same way as in the case when mixture of FIPV and MAb was inoculated to macrophages. In

Epitope specificity
group I

Epitope specificity
group II
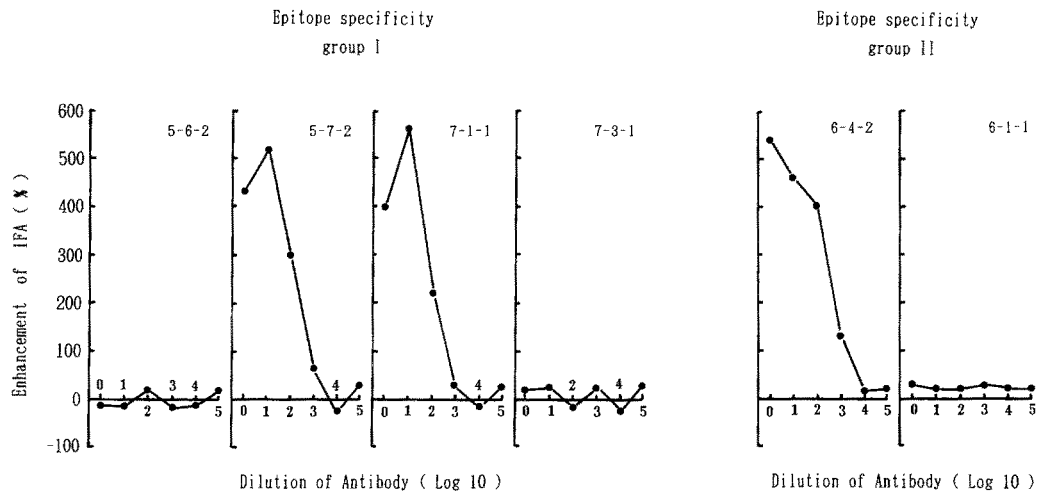
Fig. 2. ADE of FIPV infection determined by virus inoculation into anti-FIPV MAb-pretreated feline alveolar macrophages. Each MAb was added to macrophages and allowed to react at 37 °C for 1 h. After three washings with HBSS, the cells were inoculated with FIPV. The inoculated macrophages were examined for the viral antigen by IFA after 36 h of incubation, and the percent ADE was calculated as described in Materials and methods. MAb 5-6-2, IgG 1; MAb 5-7-2, IgG 2a; MAb 7-1-1, IgG 2a; MAb 7-3-1, IgG 1; MAb 6-4-2, IgG 2a; MAb 6-1-1, IgG 1

contrast, none of the subclass IgG 1 MAbs (5-6-2, 7-3-1 and 6-1-1) showed ADE activity (Fig. 2). These results, together with those shown in Fig. 1, clearly indicate the relationship between Ig subclass of MAbs and the ADE activity.

Ig subclass of mouse MAb determines its binding to Fc γ R on feline macrophages

Binding of mouse anti-FIPV MAbs to the Fc γ R on feline alveolar macrophages was determined by indirect immunofluorescence flow cytometry of the MAb-treated macrophages. Figure 3A shows the percentages of positively stained cells in the macrophages treated with different MAb. Percentage of the stained macrophages which had been treated with either one of the IgG 1 MAbs was very low and almost the same as that of control macrophages which had been treated with HBSS instead of MAb. In contrast, percentage of the stained macrophages which had been treated with either one of the IgG 2a MAbs was distinctly increased. Figure 3B shows the results of the binding of different anti-FIPV MAbs complexed with FIPV to macrophages. Percentage of positively stained macrophages treated with complex of either one of the IgG 2a MAb and FIPV was distinctly higher than that of macrophages treated with the corresponding IgG 2a MAb alone. As in the case of the macrophages treated with IgG 1 MAbs alone, percentage of the stained macrophages treated with either one of IgG 1 MAbs complexed with FIPV did not change significantly from that of control macrophages. Profiles of the flow cytometry
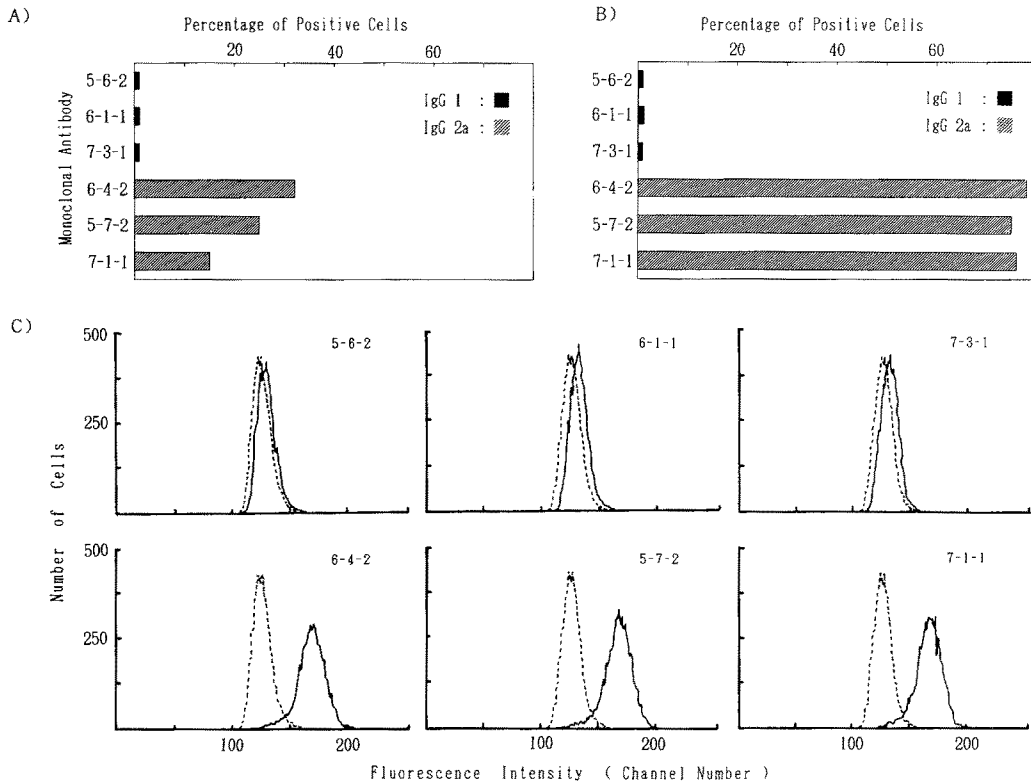
Fig. 3. Immunofluorescence flow cytometric analysis of binding of anti-FIPV MAbs to feline alveolar macrophages. Either one of the anti-FIPV MAbs alone or complex of the MAb and FIPV was added to macrophages and allowed to react at 4 °C for 1 h. The cells were then stained with FITC-conjugated goat Fab of anti-mouse IgG antibody. **A** Percentage of cells positive for fluorescence intensity at channel No. 165 or more in the macrophages treated with MAb alone. **B** Percentage of cells positive for fluorescence intensity at channel No. 165 or more in the macrophages treated with the MAb-FIPV complex. The complex was made by allowing the anti-FIPV MAb to react with FIPV at 4 °C for 1 h. **C** Profiles of the flow cytometry of macrophages treated with complexes of different MAbs and FIPV. --- Macrophages treated with HBSS (control); — macrophages treated with complex of MAb and FIPV

of macrophages treated with complexes of different MAbs and FIPV are shown in Fig. 3C.

To confirm that the binding of mouse IgG 2a MAbs to feline alveolar macrophages is mediated by Fc region of the MAbs and the binding via the Fc region determines the ADE activity of the MAbs, IgG 2a MAb 6-4-2 was treated with protein A, and the treated MAb was determined on the binding to feline alveolar macrophages and ADE activity on FIPV infection. As shown in Fig. 4A, profile of immunofluorescence flow cytometry of the macrophages treated with the protein A-treated MAb shifted to the side of that of control macrophages. Concomitantly, treatment of the MAb with protein A decreased the ADE activity (Fig. 4B). These results indicate that the binding of mouse
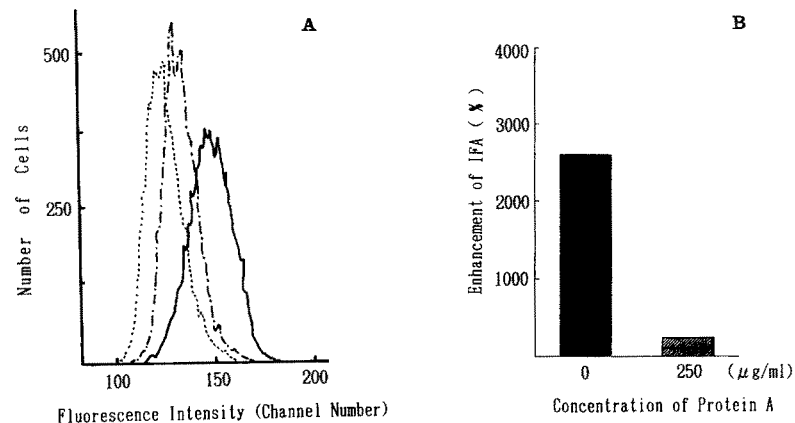
Fig. 4. Binding activity of protein A-treated MAb to feline alveolar macrophages and ADE activity of the protein A-treated MAb. Anti-FIPV IgG 2a MAb 6-4-2 diluted to one tenth was treated with 250 μg/ml of protein A at 4 °C for 1 h and added to feline alveolar macrophages. Binding of the protein A-treated MAb to macrophages was determined by immunofluorescence flow cytometry of the macrophages as in Fig. 3. ADE of FIPV infection by the protein A-treated MAb was determined as in Fig. 1. **A** Profiles of flow cytometry. ---, macrophages treated with HBSS (control); —, macrophages treated with MAb 6-4-2; —·—, macrophages treated with protein A-treated MAb 6-4-2. **B** ADE of FIPV infection by the protein A-treated MAb 6-4-2

anti-FIPV IgG 2a MAbs to feline alveolar macrophages and their ADE activity on FIPV infection are mediated by Fc region of the MAb.

ADE by mouse anti-FIPV MAbs of FIPV infection in human monocyte cell line U937

First, the presence or absence of Fc γ Rs on the U937 cell surface was determined by indirect immunofluorescence flow cytometry of U937 cells treated with F(ab′)₂ of Fc γ R I-specific MAb 32.2, Fab of Fc γ R II-specific MAb IV.3 or F(ab′)₂ of Fc γ R III-specific MAb 3G8. As shown in Fig. 5, U937 cells reacted with MAb 32.2 and MAb IV.3, indicating the presence of Fc γ R I and Fc γ R II on their surface.

Next, to determine ADE by mouse anti-FIPV MAbs of FIPV infection in human U937 cells, FIPV alone or a mixture of FIPV and either one of the MAbs was inoculated to U937 cells. The inoculated cells were cultured, and 36 h later, viral proliferation was assessed by IFA of the cells with mixture of anti-FIPV MAbs and virus plaque assay of the culture supernatant. In Table 2, when FIPV alone was inoculated to U937 cells, viral proliferation did not occur at all, whereas it occurred when the virus complexed with either one of the MAbs was inoculated. Notably, FIPV infection was established in U937 cells even with the IgG 1 MAbs that did not show ADE of the infection in feline macrophages, even though the degree of the ADE was far less than that by the IgG 2a MAbs.
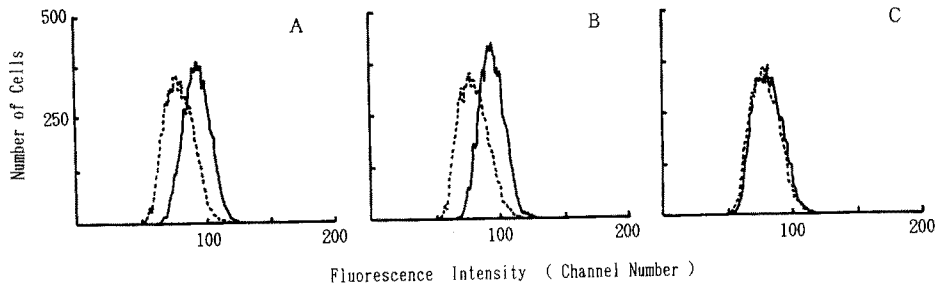
Fig. 5. Detection of Fc γ R on U937 cells. U937 cells treated with Fc γ R I-specific MAb 32.2, Fc γ R II-specific MAb IV.3 or Fc γ R III-specific MAb 3G8 were analyzed by immunofluorescence flow cytometry as described in Materials and methods. --- U937 cells treated with HBSS (control); — U937 cells treated with the MAb; **A** U937 cells treated with 32.2; **B** U937 cells treated with IV.3; **C** U937 cells treated with 3G8

Table 2. ADE by mouse anti-FIPV MAbs of FIPV infection in human monocyte cell line U937

MAb	Isotype	Reactivity in IFA	Virus yield
7-1-1	IgG 2a	38.9[a]	8.5×10^5 [b]
5-7-2	IgG 2a	38.8	7.8×10^5
6-4-2	IgG 2a	40.6	7.0×10^5
5-6-2	IgG 1	5.2	4.7×10^3
7-3-1	IgG 1	3.6	4.5×10^3
6-1-1	IgG 1	1.9	1.7×10^3
Virus only		0.0	0.0

[a] Percentage of IFA positive cells
[b] PFU/ml in culture supernatant

Discussion

In vitro studies using anti-FIPV MAbs and in vivo studies of cats immunized with recombinant vaccinia virus expressing FIPV S protein have indicated that antibody against FIPV S protein induces ADE of FIPV infection [5, 12, 13, 19, 20, 33]. Some studies showed that MAbs having virus neutralizing activity caused intense ADE of FIPV infection, and suggested that epitope of FIPV to be recognized for ADE is closely related to that for virus neutralization [5, 12, 13, 19, 20].

In the present study, it was demonstrated that even among mouse FIPV neutralizing MAbs that have been shown to recognize the same antigenic site by competitive binding assay, IgG 2a MAbs but not IgG 1 MAbs enhanced FIPV infection of feline alveolar macrophages (Fig. 1). These IgG 2a MAbs

enhanced the infection even when macrophages pretreated with the MAb were washed and then inoculated with the virus (Fig. 2). Therefore we assumed that mouse IgG 2a antibodies can bind Fc γ R on feline alveolar macrophages, whereas IgG 1 antibodies can not. This was confirmed by the flow cytometric analysis of binding of the MAbs to feline macrophages (Fig. 3). In addition, it was found that the IgG 2a MAbs complexed with FIPV bound to macrophages more intensely than the MAb alone did (Figs. 3A and B). In accordance with these findings, ADE of the FIPV infection was intenser in the macrophages infected by the former pathway than in the virus-inoculated latter macrophages (Figs. 1 and 2). Flow cytometric analysis of the binding of protein A-treated IgG 2a MAb to macrophages and determination of ADE of FIPV infection by the treated MAb revealed that the binding of the mouse IgG 2a MAbs to feline macrophages and their ADE activity on FIPV infection of the macrophages are mediated by Fc region of the MAbs (Fig. 4).

Since Fc γ Rs on feline cells have not been defined, we explored the Fc-mediated ADE of FIPV infection by using human cells, of which Fc γ Rs are well defined, as targets of the virus. It is known that there are three types of human Fc γ R, i.e., Fc γ R I, II and III [32]. It has also been shown that Fc γ R I and II are present on human macrophages and that mouse IgG 2a and IgG 1 bind well to the Fc γ R I and II, respectively. The human monocyte cell line U937 cells used in the present study were shown to express Fc γ R I and II to a similar degree on their surface from the reactivity to MAb specific to the respective human Fc γ R (Fig. 5). FIPV strain 79-1146 did not infect U937 cells at all. However, when the FIPV complexed with either one of the mouse anti-FIPV MAbs was inoculated onto U937 cells, distinct viral proliferation was observed. Notably, IgG 1 MAbs, which did not bind to feline macrophages and did not cause ADE of FIPV infection of feline macrophages, caused viral proliferation in U937 cells. These results suggest that U937 cells of human origin have no virus receptor for FIPV, but Fc γ Rs, i.e., Fc γ R I and II, act as receptors for the mouse IgG 2a and IgG 1 MAbs complexed with the virus and thus allow the virus to enter and proliferate in the cells.

Some mouse anti-FIPV IgG 1 MAbs devoid of neutralizing activity were reported to exert ADE of FIPV infection of feline macrophages [5, 20], though the ADE activity of these IgG 1 MAbs was far less than that of mouse IgG 2a MAbs used in the present study. Reason for the discrepancy between these studies and our study, in which mouse anti-FIPV IgG 1 MAbs were not found to show ADE of FIPV infection of feline macrophages, is not clear. There are the following possibilities: Fc γ R for mouse IgG 1 is expressed on feline macrophages in very small number, or Fc γ R for mouse IgG 1 on feline macrophages has very low affinity. In relation to the latter possibility, U937 cells of human origin express Fc γ R I and II at a similar level, but ADE activity of mouse anti-FIPV IgG 1 MAb on FIPV infection of these cells was found to be far weaker than that of anti-FIPV IgG 2a MAb. It is also known that human IgG 2 and IgG 4 have weak affinity for Fc γ R on human macrophages [32]. One study of ADE of dengue virus infection of mouse

macrophages has shown that treatment of macrophages with neuraminidase increased affinity of their Fc γ R II for mouse IgG 1 MAb and resulted in increased ADE of the infection by mouse anti-dengue virus IgG 1 MAb [16]. This might be verified by a similar experiment with FIPV system.

Taken all results of the present study together, it is indicated that ADE of FIPV infection is mediated by binding of Fc region of anti-FIPV antibody to Fc receptor expressed on the target cells of FIPV. This is supported by finding that any FIPV-neutralizing MAbs could not enhance FIPV infection of Crandell feline kidney cells which are devoid of Fc R. The present study, however, explored ADE of FIPV infection by in vitro experiments in which xenogeneic combination of virus targets and anti-FIPV antibody, i.e., feline alveolar macrophages or human monocyte U937 cells and mouse anti-FIPV S protein MAbs, was used. Therefore, the findings in the present study could not be applied directly to ADE of natural infection in cats. Schultz et al. [28] reported two subclasses of feline IgG. However, biological properties of feline IgG subclasses have not yet been clarified. Further study of the feline IgG subclasses and exploration of Fc γ R on feline cells are mandatory, and what IgG subclass of anti-FIPV antibody in the serum of naturally infected cats enhances the FIPV infection should be investigated. These studies are worthwhile for determination of basic pathogenesis of FIP and development of vaccines for prevention of FIPV infection.

Acknowledgements

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