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The Dual-Specific Binding of Dengue Virus and Target Cells for the Antibody-Dependent Enhancement of Dengue Virus Infection

Kao-Jean Huang,* Yu-Ching Yang,† Yee-Shin Lin,‡ Jyh-Hsiung Huang,¶ Hsiao-Sheng Liu,† Trai-Ming Yeh,§ Shun-Hua Chen,¶ Ching-Chuan Liu,§ and Huan-Yao Lei2‡*†

Using flow cytometric assay and monoclonal anti-dengue Ab, we observed that both anti-E and anti-prM Abs could enhance dengue virus infection in a concentration-dependent but serotype-independent manner. Increases were found in both the percentage of dengue-infected cells and the expression of dengue E and NS1 protein per cell. Dengue virion binding and infection were enhanced on FcR-bearing cells via the Fc-FcyRII pathway. Furthermore, anti-prM Ab also enhanced dengue virion binding and infection on cells lacking FcR, such as BHK-21 or A549 cells, by the mechanism of peptide (CPFLKQNEPEDIDCW)-specific binding. Anti-prM Ab cross-reacted with BHK-21 or A549 cells and recognized self-Ags such as heat shock protein 60. In summary, a novel mechanism of anti-prM Ab-mediated enhancement on dengue virus infection was found to be mediated by dual specific binding to dengue virion and to target cells, in addition to the traditional enhancement on FcR-bearing cells. The Journal of Immunology, 2006, 176: 2825–2832.

Dengue is an acute infectious disease caused by the dengue virus, which has four serotypes. It is characterized by fever, pain, rash, lymphadenopathy, and leukopenia (1, 2). In most cases, the disease of dengue fever is self-limited. However, there is a risk of progressing to severe dengue hemorrhagic fever (DHF)3 or dengue shock syndrome (DSS) especially when cross infection of different serotypes occurs. One explanation of the pathogenesis of DHF is the theory of Ab-dependent enhancement (ADE), which is thought to play a central role in dengue virus infection. The ADE theory explains the finding that more severe manifestations of DHF/DSS occur predominantly, although not exclusively, in children experiencing a second dengue virus infection that has a different serotype from the first one. It is reasoned that the non-neutralizing anti-dengue Ab bound to a dengue virion would enhance the virus entrance into target cells via the FcR. However, the molecular mechanism of ADE has not been clearly described, and is still a mystery because its proposal by Halsted (3, 4) in the 1970s. The dengue virus infection also generates autoantibodies to platelet and endothelial cells in dengue patients, indicating that acute dengue virus infection is associated with autoimmunity by molecular mimicry (5, 6). In this study, we extensively studied the ADE with the sensitive flow cytometric assay and various monoclonal anti-dengue Abs and cell lines, and found that both anti-E- and anti-prM-enhancing Abs enhanced the dengue virion binding on FcR+ cells. Moreover, the anti-prM Ab could recognize both the premembrane of the dengue virion and the self-Ag such as heat shock protein 60 (HSP60), and could use these dual specificities to bridge the dengue virion binding to cells that do not have FcR. The molecule mimicry between dengue virus and the host cells can thereby lead to enhanced dengue virus infection.

Materials and Methods

Cells and viruses

Cell lines bearing the FcR, such as murine macrophage P388D1, dendritic cell line DC2.4, human B cell line BJAB, murine myeloma FO, murine hybridoma A20, human macrophage cell line U937, human leukemia cell line K562, murine hybridoma H21F8-1, 206, 35, and cell lines that do not have the FcR, such as human T cell line Jurkat T, murine fibroblast cell line NIH3T3, human epithelial carcinoma cell line A549, and baby hamster kidney cell line BHK-21 were maintained in DMEM supplemented with 10% FBS. All four dengue virus serotype strains (dengue serotype 1/766733A, serotype 2/PL046, serotype 3/739079A, and serotype 4/H-241) were obtained from the Center for Disease Control in Taiwan. Unless otherwise specified, the dengue virus serotype-2 strain PL046 was used for most experiments. Viruses were propagated in mosquito C6/36 cell line in Eagle’s MEM containing 2% heat-inactivated FBS at 28°C for 5 days and quantified by standard plaque assay as reported previously (7). Dengue virus-containing supernatant was first centrifuged at 10,000 rpm, and then ultracentrifuged at 100,000 × g at 4°C for 3 h to purify the dengue virion, which was then labeled using NHS-fluorescein (Pierce).

Production of anti-dengue mAb

Breeder mice of BALB/c strain were purchased from either The Jackson Laboratory or Charles River Japan. They were maintained on standard laboratory chow and water ad libitum in the animal facility of the Medical College, National Cheng Kung University (Tainan, Taiwan). The animals were raised and cared for following the guidelines set up by the National Science Council of the Republic of China. Groups of BALB/c adult mice were inoculated i.v. with dengue-2 virus PL046 as described previously (7). Hybridomas were generated by fusion of splenocytes with FO myeloma using 1% polyethylene glycol (8). Several methods, including cellular ELISA, immunohistochemical staining, and flow cytometric assay on dengue virus-infected BHK-21 cells, were used to screen the Abs. The isotypes of each mAb were identified using the mouse monoAb ID kit.
The antigenicity of each clone was further characterized by Western blot or immunoprecipitation of dengue-infected C6/36 cell lysate. In most cases, the mAb was purified from hybridoma culture supernatant using the Montage Prosep-G kit (Millipore). However, for anti-E Ab and anti-NS1 Ab, when a large quantity of mAb was needed, the mouse ascites were used instead. The Abs were biotinylated by using NHS-LC-Biotin (Pierce), and immobilized pepsin (Pierce) was used to obtain the F(ab’2). Infection of dengue virus and ADE

The infection was usually performed by coincubating cells with dengue viruses at a multiplicity of infection (m.o.i.) of 1 for 90 min at 37°C. In some cases, the m.o.i. could be decreased to 0.1. For cell lines that are not very sensitive to dengue virus infection such as myeloma FO, hybridoma 185-10, H21F8-1, 206-35, A20, and murine dendritic cell line DC2.4, human macrophage cell line U937, or human monocytes, a higher m.o.i. of 10 was used. In the Ab enhancement on FcR-bearing suspension cells, the virus-Ab complexes were prepared by mixing immune serum or mAb with viruses (m.o.i. = 1) for 30 min at 37°C before addition to the cell suspension (2 x 10^5/sample) for infection. In some experiments, cells were pretreated with anti-FcR mAb (anti-CD16 Ab or anti-CD32 Ab, 20 μg/ml; BD Biosciences Pharmingen) for 15 min at 37°C before incubation with the virus-Ab complexes. After infection, cells were washed twice and resuspended in complete medium for further culture. The cells were assayed for virus infection by flow cytometric analysis, and the supernatants were assayed by plaque assay. For Ab enhancement on non-FcR-bearing cells, BHK-21 cells (1 x 10^5/well) were plated in 24-well plates for 24 h and then subsequently coated with 5 μg of anti-prM (70-21) or anti-E (185-10) Ab for 30 min at 37°C. The Ab-coated cells were washed twice, then infected with dengue virus at the m.o.i. of 0.1 for 90 min at 37°C. The cells were washed again and cultured with complete growth medium for 24 h before flow cytometric analysis. For dengue virion binding, cells (2 x 10^5/well) were coated with 5 μg each of anti-prM (70-21) or anti-E (185-10) Ab for 30 min at 4°C. After thoroughly washing, the cells were then incubated with FITC-labeled virions (25 μl) for 30 min at 4°C. The cell-bound virions with green fluorescence were detected by flow cytometer.
FIGURE 2. Ag specificity of monoclonal anti-dengue Abs. The reactivity of each mAb to dengue virus-infected BHK-21 cells was assayed by flow cytometric detection (A) and immunofluorescent staining (B). The Ag specificity of each mAb was identified by Western blot (C) and immunoprecipitation (D) on dengue virus-infected C6/36 cell lysate. BHK-21 cells were infected by dengue-2 virus for 24 h before being harvested for staining. Dengue viral Ags were prepared from dengue-2 virus-infected C6/36 cell for 96 h before lysis. The lysate was subjected to SDS-PAGE analysis and Western blotted with these mAbs. For those that were not detectable such as 26-7, 137-22, 9-9, 113-19, and 185-10, Ags immunoprecipitated from lysate were analyzed by SDS-PAGE. N, Not denatured; B, boiling and denatured.

For the M3 region of the prM protein-blocking experiment, M3 peptide (CPFKLQNEPEDITDCC), control M1 (MAFHTTRNGPHEMHI), or M4 (GTCTTTTGHRREKRSVAL) peptides were added together with the virus (9).

Flow cytometric assay

Cells were harvested and fixed with 2% paraformaldehyde in PBS for 20 min on ice. After being washed, the cells were stained with biotinylated anti-dengue mAb (anti-E, anti-prM, anti-NS1, and anti-Core Abs) in the permeabilization buffer (2% PBS, 0.1% saponin, 0.1% sodium azide) for 30 min on ice. After washing, these cells were then stained with streptavidin-FITC in the same buffer for 30 min. Finally, these cells were washed and resuspended in staining buffer (2% FBS and 0.1% sodium azide) for FACSCalibur analysis (BD Immunocytometry Systems), and analyzed using the software WinMDI, version 2.8.

Identification of autoantigens from A549 or BHK-21 cells

The membrane protein extracts of human epithelial carcinoma cell line A549 or baby hamster kidney cells BHK-21 were prepared with the Subcellular Proteome Extraction Kit (Calbiochem) and incubated with anti-prM or anti-Hsp60 Ab-coated Dynabeads M-450 GAM IgG (Dynal Bio-tech) for 1 h at 4°C. After washing with 1% Triton X-100/PBS, the immune-complexes were dissolved in native sample buffer and were subjected to 12.5% SDS-PAGE analysis. Western blot analysis was performed with anti-prM or anti-Hsp60 Ab.

Results

A flow cytometric method to quantitate the ADE of dengue virus-infected cells

To study the phenomena of Ab enhancement of dengue virus infection, a flow cytometric analysis can be used with anti-NS1 or anti-prM Ab. To study the phenomena of Ab enhancement of dengue virus infection, a flow cytometric analysis can be used with anti-NS1 or anti-prM Ab. A549 or baby hamster kidney cells BHK-21 were prepared with the Subcellular Proteome Extraction Kit (Calbiochem) and incubated with anti-prM or anti-Hsp60 Ab-coated Dynabeads M-450 GAM IgG (Dynal Bio-tech) for 1 h at 4°C. After washing with 1% Triton X-100/PBS, the immune-complexes were dissolved in native sample buffer and were subjected to 12.5% SDS-PAGE analysis. Western blot analysis was performed with anti-prM or anti-Hsp60 Ab.

The enhancement of dengue virus infection by anti-E or anti-prM Abs

To further characterize the ADE on dengue virus infection, a panel of anti-E, prM, and NS-1 or core mAb was generated from dengue-2 virus-infected mice, the specificities of these mAbs determined by flow cytometry, immunofluorescent staining, Western blot, or immunoprecipitation assay as shown in Fig. 2, and summarized in Table I. On FcR-bearing cells of the murine macrophage cell line P388D1 or murine dendritic-like cell line DC2.4, the ADE effect of different monoclonal anti-dengue Abs was shown in Fig. 3A. Anti-prM Abs and some anti-E Abs (185-10 and 113-19) enhanced dengue virus infection, but another anti-E Ab, 137-22, was found to be inhibitory. Meanwhile, the anti-NS1 or anti-core Abs did not have any effect. To further characterize this finding, the enhancing anti-prM Ab (70-21), anti-E Ab (185-10), and the neutralizing anti-E Ab (137-22 and 50-21) were studied with different concentrations. It was found that the ADE effect was concentration-dependent (Fig. 3B). Anti-prM Ab enhanced the dengue virus infection at doses of 0.1 to 10 μg/ml, but not at 100 μg/ml, and the anti-E Ab 185-10 enhanced the dengue virus infection at doses of 1 μg/ml to 100 μg/ml. In contrast, the anti-E Ab 137-22 acted as a neutralizing Ab at doses higher than 1 μg/ml, whereas it had an enhancing activity at a dose of 0.1 μg/ml. Likewise, anti-E Ab 50-21 neutralized at doses higher than 10 μg/ml, but enhanced at 0.1 μg/ml. Furthermore, the ADE effect was independent of the four serotypes.
of dengue virus. Although these anti-dengue mAbs were derived from dengue 2-virus-infected mice, most of them could recognize the four serotypes of dengue virus as shown by immunohistochemical staining of dengue virus-infected cells (Table I). As shown in Fig. 3C, anti-prM Ab 70-21 or anti-E Ab 185-10 enhanced the dengue virus infection of all four serotypes, whereas anti-E Ab 137-22, which was dengue 2-specific, neutralized the dengue-2 virus infection but had no effect on the other three serotypes. The ADE effect is known to require the Fc portion of the enhancing Ab and the presence of FcR on target cells, and we also observed this.

Table I. Summary of monoclonal anti-dengue Abs used in this studya

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<th>I.P. (KD)</th>
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a IHC, Immunohistochemistry; W.B., Western blot; I.P., immunoprecipitation; Nd, not done.

FIGURE 3. The enhancement of dengue virus infection by anti-E or anti-prM Abs. A, P388D1 cells were infected by dengue-2 virus in the presence of various anti-dengue mAbs (10 μg/ml). B, The dose effect of anti-prM and anti-E Ab-mediated ADE infection. DC2.4 cells were infected by dengue-2 virus with various concentrations of anti-dengue mAbs. C, Anti-E or anti-prM Ab-mediated ADE is independent of four dengue virus serotypes. P388D1 cells were infected by four different serotypes of dengue virus in the presence of anti-prM Ab or anti-E Ab (10 μg/ml). D, The Fc and FcγR involvement on anti-prM Ab and anti-E Ab-mediated ADE. P388D1 cells were infected by dengue-2 virus in the presence of control IgG, anti-prM Ab (70-21), the fragments of anti-prM Ab F(ab’)2, or anti-E Ab (185-10). The anti-FcR Ab (anti-CD16/32 Ab) was used to block the FcR. For anti-E Ab (185-10), the protein A was used to interfere with the interaction between the Fc portion and the FcR. Dengue virus-infected cells were quantitated by flow cytometric analysis with anti-NS1 Ab cytoplasmic staining. * Denotes the significant difference from the virus control group; **, denotes the significant difference from the anti-E or anti-prM Ab group (p < 0.05).
Pepsin digestion of the Fc portion of the anti-prM Ab resulted in the loss of its enhancing activity. The addition of anti-FcR Abs (anti-CD16/CD32 Ab) to the target cells blocked the anti-prM Ab-mediated enhancement (Fig. 3D). We titrated the concentration of anti-FcR Ab and found that 20 μg/ml is optimal to completely inhibit the enhancement. The involvement of the Fc portion and FcR on the target cells was also applied to the anti-E Ab (185-10)-mediated enhancement. In this experiment, Protein A was used to block the interaction of the Fc portion with the FcR. This suggests that both anti-prM and anti-E Ab mediate the enhancement of dengue virus infection on FcR-bearing cells by the Fc-FcR pathway. If the anti-E or anti-prM Ab, once bound to the dengue virion, does not inhibit the infection, then the Ab-virus complex can subsequently enter the target cells more efficiently through the FcR of the cells, thus leading to infection.

**Anti-prM Ab mediated the enhancement of dengue virus infection on cells that do not have FcR**

Anti-prM Ab could enhance the dengue virus infection on all FcR+ cell lines tested (murine myeloma FO, hybridoma 185-10 and H21F8-I, A20, murine macrophage P388D1, DC2.4, and human B cell line BJAB, macrophage cell line U937) (Fig. 4A). Surprisingly, it also enhanced the dengue virus infection on non-FcR-bearing cells such as baby hamster kidney cell BHK-21, human epithelial carcinoma cell line A549, mosquito cell line C6/36, and murine fibroblast cell line NIH3T3 (Fig. 4B). How the anti-prM Ab enhanced the dengue virus infection was therefore further investigated. Using FITC-labeled dengue virus, the dengue virion binding to the FcR-bearing K562 cells was enhanced by either the anti-prM Ab (70-21) or anti-E Ab (185-10), both of these being Fc and FcγRII-dependent, because anti-CD32 (FcγRII) Ab, and not anti-CD16 (FcγRIII) Ab, blocked the binding (Fig. 5A). The anti-E Ab (137-22), although acting as a neutralizing Ab in Fig. 3A, also enhanced the dengue virus binding. We have mapped the epitope of the anti-prM Ab recognized as corresponding to the M3 region (CPFLKQNEPEDIDCW) of the prM (data not shown). The enhanced infection by anti-prM Ab on K562 cells was blocked by M3 peptide dose-dependently (Fig. 5B), suggesting that the anti-prM Ab-mediated enhancement of dengue virus infection is M3 Ag-binding dependent. Furthermore, for the target cells without FcR like BHK-21 cells, the anti-prM Ab could also enhance the dengue virus binding (Fig. 5C), which was also blocked by M3 peptide dose-dependently (Fig. 5D). The enhanced virus binding would subsequently lead to the enhancement of dengue virus infection in BHK-21 cells (Fig. 5E). The effect of anti-prM Ab on the enhancement of dengue virus binding and infection was also observed for A549 cells (data not shown).

The dual specificity of anti-prM Ab on the enhancement of dengue virus infection

How the anti-prM Ab enhances the dengue virion binding and infection by its M3 specificity was further investigated. The anti-prM Ab could cross-react with BHK-21 or A549 cells as shown by flow cytometric and immunofluorescent staining (Fig. 6A). The anti-prM Ab binding to BHK-21 or A549 cells was dose-dependent (data not shown), and can be inhibited by M3 peptide (Fig. 6B). The proteins on cell membrane recognized by the anti-prM Ab were further identified. Anti-prM Ab can bind to the membrane protein extracts from baby hamster kidney cell BHK-21 or human epithelial carcinoma cell line A549 on Western blot. One of the proteins has a m.w. equivalent to HSP60. The membrane protein immunoprecipitated by the anti-hsp60 Ab was also recognized by anti-prM Ab on Western blot. The HSP60 is one of the autoantigens recognized by the cross-reactive anti-prM Ab (Fig. 6C).

Based on the above data, we conclude that in addition to the anti-E Ab-mediated enhancement of dengue virus infection on FcR-bearing cells, the anti-prM Ab is also an enhancing Ab for cells with or without FcR, its enhancement being mediated by dual specific binding to dengue virion and to target cells.

**Discussion**

Using flow cytometric assay to detect dengue-infected cells, the enhancing Ab could enhance the dengue virion binding and the subsequent infection, both the dengue virus-infected cell percentage and the dengue virus protein expression per cell were found to enhance. The in vitro infection of dengue virus is modulated by different cell types, viral strains, and m.o.i (Ref. 10 and Fig. 1). There is a short assay window to observe the enhancing activity of anti-prM or anti-E Ab. We have adjusted various parameters and used the optimal conditions for different cell lines: for example, a
m.o.i. of 1 was used on the sensitive lines P388D1, K562, whereas a m.o.i. of 10 was used for the less sensitive line DC2.4. The dengue virus-infected cells were usually detected at 24 h post-infection, because the enhancement was difficult to observe when virus replication had amplified for a longer time. The plaque assay determined the infectious particles released from virus-infected cells.

**FIGURE 5.** Anti-prM Ab enhanced dengue virion binding and infection. A, Enhanced dengue virion binding by anti-prM or anti-E Ab on K562. K562 cells were incubated with FITC-labeled dengue-2 virion at 4°C for 1 h in the presence of anti-prM Ab or anti-E Ab (10 μg/ml). Anti-CD16 (Fcy RIII) and anti-CD32 (Fcy RII) Abs (20 μg/ml each) were used to block the murine FcR. The fluorescent intensity was determined by FACS Calibur. B, M3 peptide specifically inhibited the anti-prM Ab-mediated ADE on K562 cells. Anti-prM Ab was preincubated with M3 or M4 control peptides before forming the dengue virus-Ab complexes to infect K562 cells. C and D, Anti-prM Ab enhanced the dengue virion binding that is blocked by M3 peptide on BHK-21 cells. BHK-21 cells were first coated with anti-prM or anti-E Ab (5 μg) and then incubated with fluorescence-labeled dengue virions. Binding intensity was determined by flow cytometry. M3 peptide dose-dependently inhibited the dengue virion binding to BHK-21 cells. E, Anti-prM Ab enhanced the dengue virus infection on BHK-21 cells. BHK-21 cells were first incubated with anti-prM Ab or anti-E Ab (5 μg) and then infected with dengue-2 virus for 24 h. * Denotes the significant difference from virus alone group; **, denotes the significant difference from the anti-prM Ab-treated group (p < 0.05).

**FIGURE 6.** Dual specificity of anti-prM Ab. A and B, Specific binding of anti-prM Ab to BHK-21 or A549 cells. BHK-21 or A549 cells were incubated with anti-prM, anti-NS, or anti-E Ab (2 μg) followed by staining with FITC-labeled goat anti-mouse IgG secondary Ab. The binding was determined by flow cytometry or immunofluorescent staining. M3 peptide dose-dependently inhibited the anti-prM Ab binding to BHK-21 cells. C, Anti-prM Ab recognized one of the self-proteins, HSP60. Total cell lysates of BHK-21 or A549 membrane protein extracts were detected by anti-HSP60 Ab or anti-prM Ab on Western blot (upper panel). The immunoprecipitated membrane proteins from BHK-21 or A549 cells by anti-HSP60 were Western blotted with anti-prM Ab, after washing away, the membrane was re-probed with anti-HSP60 Ab (lower right panel). B, BHK-21; A, A549; V, DV2-infected C6/36 lysate.
cells, which were a combination of increased infected mass and virus replication, but the flow cytometric assay offered an improved method. Because the immune sera contain a mixture of neutralizing and enhancing Abs, the enhancing activity would not be observed until the neutralizing activity was diluted out. The flow cytometry technique allowed the detection of dengue virus protein per target cell. Furthermore, the dengue virion binding can also be detected using this assay.

Dengue disease has a broad spectrum of clinical symptoms. Most dengue infections are subclinical or self-limited, but there is a risk of progressive development to DHF or DSS. Viral replication plays an important role in the disease pathogenesis. Severe DHF is associated with a higher virus load than mild dengue fever (11). ADE is a central hypothesis to explain the increased dengue virus-infected cell mass (4). Newborn babies <1 yr of age with maternal anti-dengue IgG Abs are known to be susceptible to DHF/DSS after primary infection (12, 13). The enhancing Ab was presumed to act against the dengue virus envelope protein. We reported in this study that both anti-E Ab and anti-prM Ab could work as the enhancing Abs. Although monoclonal anti-prM and anti-E Ab were used in this study, anti-prM Ab has indeed been found in dengue patient sera, which can also enhance dengue virus infection (our unpublished observation). In our study, the anti-E 137–22 and 50–21 are neutralizing Abs, whereas the anti-E 185-10 and all the anti-prM are non-neutralizing ones according to plaque assay on P388D1 cells (our unpublished observation), but their enhancement or neutralization effect seems to be dependent on the concentration of the Ab, and is also dengue serotype-independent. Both of the anti-E Ab, 137-22 and 185-10, enhanced the dengue virion binding to K562 cells (Fig. 5A), but the former neutralized while the latter enhanced the dengue virus infection. This suggests that dengue virion binding to the putative receptor is a necessary but not a sufficient condition for virus infection.

From in vitro observation of ADE, it is known that the non-neutralizing Ab or subneutralization amount of Ab would help the virus to enter the cells through the FcR. In this study, we extended this phenomenon to cells lacking FcR such as BHK-21 or A549, and it was found that the anti-prM Ab could enhance the dengue virus infection of these cells. Takada and Kawaoka (14) have mentioned that ADE can involve the complement C3 receptor, C1q and its receptor C1qR, in addition to the FcR. Mature dengue virion is icosahedral, ∼500 Å in diameter (15–17). It has a smooth surface, which is different from the immature virion that has prM-containing spikes. Our anti-prM Ab could bind to the dengue virion produced in the mosquito C6/36 cell line. The possibility that anti-prM Ab, when it binds to the prM-containing particle, induces a conformational change that increases the exposure of fusion peptide on E domain II, thereby becoming fusogenic to target cells and hence increasing the infection, is not excluded. For dengue virus infection on FcR-bearing macrophages, ADE is mediated primarily by the FcR pathway because anti-FcR Abs block the dengue virus binding and infection. Two reasons are proposed for this complete inhibition by anti-FcR Ab blocking. One is the assay protocol used for the enhancing study, in which the dengue virus is mixed with the Ab first, so the Ab-virus complex would bind to the cells via the FcR pathway. Alternatively, the affinity of FcR is reduced after interaction with the Ab, which is different from the immature virion that has prM-containing spikes. Our anti-prM Ab could bind to the dengue virion produced in the mosquito C6/36 cell line. The possibility that anti-prM Ab, when it binds to the prM-containing particle, induces a conformational change that increases the exposure of fusion peptide on E domain II, thereby becoming fusogenic to target cells and hence increasing the infection, is not excluded. For dengue virus infection on FcR-bearing macrophages, ADE is mediated primarily by the FcR pathway because anti-FcR Abs block the dengue virus binding and infection. Two reasons are proposed for this complete inhibition by anti-FcR Ab blocking.

References

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