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Antibody-Dependent Enhancement of Virus Infection and Disease

SOL M. CANCEL TIRADO and KYOUNG-JIN YOON

ABSTRACT

In general, virus-specific antibodies are considered antiviral and play an important role in the control of virus infections in a number of ways. However, in some instances, the presence of specific antibodies can be beneficial to the virus. This activity is known as antibody-dependent enhancement (ADE) of virus infection. The ADE of virus infection is a phenomenon in which virus-specific antibodies enhance the entry of virus, and in some cases the replication of virus, into monocytes/macrophages and granulocytic cells through interaction with Fc and/or complement receptors. This phenomenon has been reported *in vitro* and *in vivo* for viruses representing numerous families and genera of public health and veterinary importance. These viruses share some common features such as preferential replication in macrophages, ability to establish persistence, and antigenic diversity. For some viruses, ADE of infection has become a great concern to disease control by vaccination. Consequently, numerous approaches have been made to the development of vaccines with minimum or no risk for ADE. Identification of viral epitopes associated with ADE or neutralization is important for this purpose. In addition, clear understanding of the cellular events after virus entry through ADE has become crucial for developing efficient intervention. However, the mechanisms of ADE still remain to be better understood.

INTRODUCTION

CERTAIN VIRUSES can utilize preexisting antibodies, which potentially neutralize their capability of infecting through their natural receptor-ligand route, and bind to the FcR on phagocytes, to facilitate infection of their target cells. These viruses usually can replicate in the macrophages or monocytes, and may use them as reservoirs or cellular trampolines in order to reach other body tissues. Consequently, increased chance to infect target cells results in increased production of viral progeny and often exacerbation of the disease caused by them. This phenomenon has been known as "antibody-dependent enhancement" (ADE) of virus infection or "immune enhancement of disease." This review article focuses on those pathogens of public health or veterinary importance that are capable of utilizing antibodies to enhance their infection, which may result in exacerbation of clinical manifestations.

Department of Veterinary Microbiology and Preventive Medicine, College of Veterinary Medicine, Iowa State University, Ames, Iowa.

ANTIBODY-DEPENDENT ENHANCEMENT OF VIRAL INFECTION

Antibody dependent enhancement (ADE) of virus infection is a phenomenon in which virus-specific antibodies enhance the entry of virus, and in some cases the replication of virus, into monocytes/macrophages and granulocytic cells through interaction with Fc and/or complement receptors (15,41,70,90,98,107,131). This phenomenon was first described by Hawkes in 1964. He reported that it was possible to increase the total yield of a variety of flaviviruses—including Japanese encephalitis virus, Murray Valley encephalitis virus, and Getah virus- in chick embryo cell cultures by first exposing the viruses to high dilutions of homologous antibody which was antiviral at low dilutions (50). The scientific community considered his findings artifacts albeit he could reproduce the results (51). It was not until 1977 that Halstead linked the concept of enhancement with severe dengue disease (46).

Subsequent to Hawkes' observation on the aforementioned flaviviruses and some arboviruses, ADE of infection has been described for numerous viruses that belong to different families and orders although such a phenomenon for many of viruses was made *in vitro* in part because it was difficult to corroborate ADE of virus infection *in vivo*. Some examples are: yellow fever virus (114), dengue virus (DV) (45,47), human immunodeficiency virus type 1 (HIV-1) (54,109,121), respiratory syncytial virus (RSV) (31), Hantavirus (136), Ebola virus (119), Getah virus, Sindbis virus (16), Bunyamwera virus (80), influenza virus (86,87), West Nile virus (WNV), Japanese encephalitis virus B (JEB), rabbitpox virus (50,51), feline infectious peritonitis virus (FIPV) (135), lactate dehydrogenase elevating virus (LDV) of mice (13,14,58), reovirus (11), rabies virus (67), murine cytomegalovirus (57), foot-and-mouth disease virus (FMDV) (5), porcine reproductive and respiratory syndrome virus (PRRSV) (21,22,140), simian hemorrhagic fever virus (SHFV) (93), and Aleutian disease virus (ADV) of mink (64). Some of these viruses represent a significant human health threat; yet, others are of veterinary importance. Common features among the viruses described above are that (a) they replicate, in part or exclusively, in macrophages (41,43,60,76,89,115,118,124,130,140); (b) they induce the production of large amount of antibodies that poorly neutralize even homologous virus (4,41,76,85,142), and (c) they cause persistent infections which are commonly characterized by viremia of long duration. Antigenic diversity among isolates is also a common feature of these viruses, which renders them partially resistant to neutralization by antibodies raised against heterologous isolates (41,76,98).

MECHANICS OF ADE

Although the precise mechanism of ADE of virus infection is not completely understood, it is generally assumed that increased yields of virus are primarily due to a greater number of susceptible cells being infected (23,31,41,64,89,140). This increase in the infection rate of cells is shown to be mediated by receptors, most notably FcR, which facilitate the uptake of virus-antibody complexes by target cells. However, studies have also suggested that other mechanisms could also account for increased virus yields. Antibody may also increase the efficiency of virus replication, either by facilitating the uptake of infectious antibody-virus complexes or by increasing the synthesis of viral protein and nucleic acid. For example, Gollins et al. (32,33) demonstrated that antibodies can increase the number of WNV particles attached to mouse macrophage-like cells by comparing radioactivity counts associated with cells infected with radiolabelled WNV complexed to virus-specific antibodies with counts in the absence of antibody. Robinson et al. (107) demonstrated that replication of HIV-1 was initiated sooner when the virus was pretreated with HIV-specific antibodies, as opposed to untreated virus. Progeny virus was released sooner from treated cells than from non-treated cells, as well. They also found that protein and RNA synthesis were increased in cells that were infected with HIV-1 treated with antibody. In contrast, Olsen and Scott (88) studied the kinetics of FIPV infection in individual feline peritoneal macrophages in the presence and absence of antibody utilizing *in situ* hybridization. They demonstrated that the number of infected cells was increased in the presence of antibody. However, based on the relative intensity of radiograms of individual cells, they did not find any evidence that the efficiency of virus replication within the cells was enhanced.

Generally, interaction between virus-antibody complexes and FcR on monocytes/macrophages or granulocytes induces signal transduction, resulting in phagocytosis, release of cytokines, a superoxide burst, and

antibody-dependent cell-mediated cytotoxicity (111). These responses are considered antiviral. It is not known how this interaction results in enhanced infection. However, since these viruses are known to replicate in part or exclusively in these cells, it is assumed that they have the ability to modulate antiviral mechanisms of the cells either by utilizing their own products or by interfering with metabolic pathways of cells. It is also possible that infections by virus-antibody complexes are restricted to immunologically immature subpopulations of the cells (41). Halstead and his associates found that human monocytes cultured more than 1 day prior to being infected with DV-antibody mixture became increasingly less permissive to infection (45,46). This loss of permissiveness may have been due to increased lysosomal activity. These observations explain why high virus titers are produced in bone marrow explant cultures in which young monocytes are continuously produced (41). Restriction of virus infection to immunologically immature cells was also demonstrated in mice that were persistently infected with LDV (117). More recently, a study with Ross river virus (RRV), the causative agent for epidemic polyarthritis in human, suggested that cellular environment may become less antiviral by showing that production of certain transcriptional factors for antiviral genes in murine macrophages were inhibited when the cells were infected with the virus through FcR mediated pathway instead of the natural viral receptor on the cell (72).

Antibodies mediating ADE ("enhancing antibody"). Enhancement of virus infection has been demonstrated using various sources of antibodies. These sources include polyclonal antisera generated in natural host or other animals, mouse ascitic fluids containing MAbs to the virus of interest, and immunoglobulins isolated from antiserum. The mechanism by which ADE of virus infection is mediated is known to be primarily through the interaction of the Fc region of virus-specific IgG and Fc receptors on the surface of monocytes/macrophages and granulocytic cells (45,90,97). Halstead and O'Rourke (45) fractionated IgG and IgM from antisera of DV-immunized monkeys and evaluated which fraction increased the yield of progeny virus. Enhancement was observed only with the IgG fraction, while virus that was exposed to the IgM fraction was neutralized. Similar observations were made by Olsen et al. who evaluated the ability of mouse MAbs specific for the spike (S) protein of FIPV to mediate ADE of infection in feline peritoneal macrophages (89). Only IgG class MAbs enhanced FIPV infection, while IgM class MAbs did not mediate ADE of infection. To date, it is not known whether or not other subtypes of antibodies (IgA, IgD, and IgE) can mediate ADE of virus infection.

Different isotypes (subclasses) of IgG have also been evaluated for their ability to mediate ADE of virus infection. In the case of DV, murine IgG1, IgG2a, and IgG2b monoclonal antibodies specific for the E envelope protein of DV serotypes 2 and 4 are reported to enhance infection of the virus when cells with compatible Fc receptors were used as targets (52,83). No information is available about the role of IgG3 in ADE of DV infection. In contrast, Corapi et al. evaluated the ability of 19 mouse monoclonal antibodies specific for the S envelope protein of FIPV to induce ADE of infection in feline peritoneal macrophages (23). All MAbs were capable of neutralizing the ability of virus to infect a permissive cell line. Fifteen of 19 MAbs induced ADE of infection in macrophages and all but one were of the IgG2a subclass. The remaining four MAbs that did not induce ADE of infection were IgG1. The difference in the isotypes between neutralizing MAbs that induced ADE and those that did not induce ADE suggested that there might be a restriction in the subclasses capable of mediating ADE of virus infection. It is also possible that the difference in the ability of FIPV-specific murine IgG isotypes to mediate ADE of infection is due to differences in the binding affinity of murine isotypes to FcR on feline macrophages (53). The ability of the different isotypes of human and other mammalian IgG to enhance virus infection has not been evaluated.

Receptors involved in ADE. Several cell surface molecules—including the FcR, complement receptor (CR), β2-microglobulin, and some cluster designation (CD) molecules—have been reported to play a role, or at least to be involved, in mediating ADE of virus infection (70,76). Antibody-FcR interaction is known to play a key role in ADE. The FcR-mediated mechanism of ADE of virus infection was first suggested by Halstead et al. who reported that F(ab′)2 fragments prepared from IgG did not enhance infection of DV in human peripheral blood leukocyte cultures while whole IgG did so (45). This was indirect evidence that suggested that interaction of virus-IgG complexes with FcR on the cell surface might be necessary for ADE of virus infection. Other indirect evidence for this interaction was shown by Daughaday et al. (24). These investigators found that ADE of DV infection in monocytes was inhibited by first treating the cells with immunoglobulin specific to cellular receptors prior to exposing cells to virus-antibody mixtures. Yang et

al. (138) has shown that antisera specific for DV serotype 1 (DV-1) can neutralize DV-2 infection into BHK-21 cell line but does not neutralize infection of human monocytes. Peiris et al. (90) conclusively demonstrated that the interaction between virus-antibody and FcR is essential for the ADE of virus infection. They were able to block ADE of WNV infection in a macrophage-like cell line (P388D1) by pretreating the cells with anti-FcR MAb prior to exposing cells to a virus-antibody mixture. Other investigators were also able to block infection of cells by virus-antibody complexes by first treating virus-antibody mixture with Protein A which binds to the Fc portion of antibody (64,89). Necessity of FcR in ADE of virus infection was also demonstrated by the observation that FMDV complexed to antibody could infect an engineered cell line expressing murine FcγR which otherwise would not be permissive to the virus (77). Similarly, a human cell line (K562) expressing FcR, normally is not permissive for ADV, supported viral replication when the cells were exposed to ADV complexed to antibody (27).

In humans, there are 3 types of Fc receptors which bind human IgG: FcγRI, FcγRII, and FcγRIII (3,102,128). The FcγRI is present exclusively on monocytes/macrophages and binds human IgG with high avidity. It has higher specificity for IgG1 and IgG3 isotypes than for IgG2 and IgG4 isotypes. The two other receptors, FcγRII and FcγRIII, are found on monocytes, macrophages, eosinophils, neutrophils, natural killer cells, B-lymphocytes, and T lymphocytes. These two receptors have relatively low avidity for IgG compared to FcγRI. Kontny et al. (69) showed that FcγRI mediated ADE of DV infections in U937 cells. In a related study, FcγRII was also reported to mediate ADE of DV infection in a human erythroleukemic cell line (K562), which has only FcγRII (73). The role of FcγRIII in ADE of DV infection is not known.

Mouse macrophages are known to have two types of Fc receptors, designated FcRI and FcRII, which bind IgG. The FcRI is trypsin-sensitive and binds IgG2a, while the FcRII is trypsin-resistant and binds IgG2b and IgG1 complexes (26). Peiris et al. (90) studied the inhibitory effect of anti-mouse FcRII antibody on the ADE of WNV infection mediated by anti-WNV MAbs of subclasses IgG1 or IgG2a. Pretreatment of P388D1 cells with anti-FcRII antibody completely inhibited enhancement of virus infection mediated by both IgG1 and IgG2a anti-WNV MAbs. Enhancement of WNV infection, however, was independently achieved with anti-WNV MAbs of both subclasses. Other investigators found that intact anti-FcRII antibody interfered with both FcRI and FcRII in a macrophage rosetting assay (127), suggesting that both Fc receptors on mouse macrophages can mediate ADE of virus infection.

Since ADE of virus infection results from the interaction of virus, antibody, and FcR, changes in any of these three components may modulate the ADE. Of the three components, the FcR can be most easily modulated *in vitro* within relatively short periods of time by treating FcR-bearing cells with certain cytokines or proteolytic enzymes. A quantitative (i.e., number) change or a qualitative (i.e., avidity for Fc portion of IgG) change in FcR expressed on cells may influence the ADE of virus infection. For example, gamma interferon (IFNγ) is known to increase the number of FcγRI without changing in the affinity of each FcγRI for the Fc portion of IgG (91,112). Kontny et al. (69) reported that pretreatment of human monocytic cells with IFNγ augmented ADE of DV infection and that the level of enhancement correlated with the increase in the number of FcγRI on the cells. In another case, Halstead and O'Rourke (45) found that pretreatment of monocytes with pronase, trypsin, and protease augmented ADE of DV infection. Zoellner et al. (143) have also suggested that protease may play a role as a cofactor in ADE of HIV infection. More recently, Mady et al. (75) examined the effects of neuraminidase on ADE of DV infection mediated by the low-affinity FcγRII *in vitro*. They found that neuraminidase treatment of the K562 cells that have only FcγRII increased the degree of ADE of DV infection by human anti-DV antibodies. It is known that treatment of FcγRII with enzymes such as pronase, trypsin, elastase, and neuraminidase increases the avidity of receptors for IgG but does not increase the number of the receptor expressed on cell surface (25,129).

Besides FcR, complement receptors have also been implicated in ADE of virus infection (15,110). Cardosa et al. (15) found that infection of P388D1 cells by WNV is enhanced in the presence of virus-specific IgM by supplementing fresh mouse serum containing complement to virus-IgM mixtures prior to inoculation. However, the magnitude of enhancement of WNV infection mediated by complement was less than IgG-mediated ADE of virus infection. Complement-dependent ADE of HIV infections has also been reported (35,63,81,108,110). Subneutralizing levels of HIV-specific antibody enhance virus replication in several human neoplastic cell lines that express CR and CD4, as well as FcR, in the presence and the absence of complement. The magnitude of the enhancing effect was greater in complement-mediated ADE of HIV

replication than enhancement mediated by the presence of antibody only (76). Furthermore, Robinson et al. (107) reported that replication of HIV was initiated sooner and the efficiency of replication (e.g., protein and RNA synthesis) was enhanced through the mechanism of complement-mediated ADE.

Several cell surface molecules are known to enhance virus infections or to be involved in ADE of virus infection (74,76). Takeda et al. (120) demonstrated that ADE of HIV infection in monocytic cells via FcR was blocked by pretreatment of cells with monoclonal antibodies to CD4 molecule, as well as to FcγRI. Robinson et al. (110) also reported that enhanced infection of HIV through complement-mediated ADE required not only complement receptors, but also CD4 molecules on the surface of cells. These observations indicate that the presence of the CD4 molecule on the cell surface may be a requirement for both the FcR-mediated and complement-mediated ADE of HIV-1 infection. In the case of DV infection, Mady et al. (74) used bispecific antibodies which were prepared by chemically cross-linking anti-DV antibodies to antibodies specific for one of three Fc receptors or non-FcR molecules, and demonstrated that DV infection could be enhanced by non-FcR molecules such as β_2-microglobulin, CD15 or CD33.

The critical role of natural viral receptor(s) on the membrane of target cells in ADE of virus infection is uncertain. Chinese hamster ovary (CHO) cell line engineered to express murine FcγR was permissive to FMDV coupled with antibody whereas it was not permissive to poliovirus-antiVP1 antibody complexes, which leaded investigators to the conclusion that the natural receptor for FMDV is only involved in attachment and not in subsequent steps of replication such as uncoating (77). This conclusion was ratified when FMDV with mutated RGD sequences of the G-beta H loop of VP1 protein of the nucleocapsid was unable to bind susceptible cells (78). However, when these mutants were complexed with antibody against the VP1 protein, virus infection was established in the cell line expressing FcγR on the cell membrane, revealing that the mutations only affected the binding capability of the virus. From these observations, one can speculate that naturally occurring mutations during infection could be bypassed in the presence of antibodies specific to epitopes from this receptor protein and would enhance infection instead of neutralizing it.

Viral proteins/epitopes associated with ADE. Viral antigenic determinants associated with envelope proteins induce antibodies which mediate ADE of virus infection (12,23,31,52,89,104,122). Scott and his associates conducted extensive studies utilizing monoclonal antibodies specific for the nucleocapsid protein, matrix protein (M), and the S protein of FIPV and found that ADE-associated epitopes were only on the S protein (23,89). More recently, an *in vitro* experiment using vesicular stomatitis virus (VSV) vector expressing surface glycoprotein of Ebola virus (Zaire strain), which is associated with cell penetration, demonstrated that antibody generated against this protein could enhance infection of the VSV vector and of a less virulent strain, Ebola-Reston in human kidney 293 cells (113). The same observations have also been made for envelope proteins of other viruses for which ADE of infection has been reported. Specific examples are the E protein of DV (52), gp120 and gp41 of HIV (1,25,105,106), HA protein of influenza virus (87,122), G1 and G2 proteins of hantavirus (139), F protein of RSV (31), and the 25kD E protein of PRRSV (S. Cancel and K.-J. Yoon, unpublished data).

To date, no internal proteins of enveloped viruses, for intact viruses, have been reported to be associated with the induction of enhancing antibody, with the exception of pre-M protein, an immature matrix protein of dengue virus (52). However, it is plausible that completely or partially naked virus containing infectious genetic material could establish infection and replicate in a target cell if it is internalized through antibody-FcR interaction (i.e. ADE), as is the case for transfection of infectious viral RNA to non-permissive cells (55). Reovirus is one of a few non-enveloped viruses for which ADE of infection was reported. Enhancement of reovirus infection in the P388D cells, mouse macrophage-like cell line, was demonstrated to be mediated mainly by monoclonal antibodies specific for the σ-1 protein, a major outer capsid protein which determines the serotype of reoviruses (12). In addition, monoclonal antibody specific for other capsid proteins, such as μ1c protein, was also reported to mediate the ADE of reovirus infection. No protein of the inner capsid of reovirus was found to be associated with ADE of infection.

Since viruses in the same genus or family may share common antigenic determinants, ADE of virus infections can be mediated by antibodies raised not only against heterologous strains but also against different serotypes of the viruses or even against closely related viruses in the same genus or family. This observation suggests that enhancing antibodies may not be highly specific for a specific virus. For example, studies using polyclonal antibody revealed that DV infection can be enhanced by antisera raised against

heterologous serotypes of DV and also by antisera specific for other flaviviruses, suggesting that not only serotype-specific but also serotype- and flavivirus-cross reactive epitopes are associated with ADE of infection (38,45,48). There was, however, a difference in the magnitude of enhancement mediated by homologous sera as compared to heterologous sera. A similar observation has also been made utilizing monoclonal antibodies (9,48,52,83). These studies revealed that infections of DV type 2 (DV-2) could be enhanced by monoclonal antibodies directed against heterologous DV-2 isolates and against DV type 4. Likewise, Tamura et al. (123) found that infection by influenza A virus was augmented by pretreating the virus with antisera raised against different subtypes of the virus. In the case of FIPV, virus infection in feline peritoneal macrophages was enhanced by monoclonal antibodies generated against transmissible gastroenteritis virus (TGEV) of swine, which, like FIPV, belongs to the family *Coronaviridae* (88). A similar observation was made with African flaviviruses, such as West Nile, Zika, Wesselsbron, Dakar bat, Potiskum, Uganda S, and yellow fever viruses (28). For example, anti-Potiskum virus antibodies enhanced other flaviviruses but most of antibodies to the other flaviviruses did not enhance infection of Potiskum virus in the P388D cells. On the contrary, all heterologous antibodies enhanced West Nile, Uganda S, Wesselsbron and Zika viruses. Moreover, homologous antibody induced higher levels of ADE of virus infection as calculated by enhancement ratio of virus plaque counts than heterologous antibody (48). This could be related to the amount of "enhancing" epitopes shared among species. Cross enhancement could have important epidemiological relevance in areas where these viruses are endemic since cross-reactive "enhancing" antibodies permits co-existence of multiple serotypes in the population and promotes their persistence (29).

Since antigenically distinct strains of virus may have different quantitative and/or qualitative profiles of epitopes associated with ADE of infection, differences in epitopic profiles may influence augmentation of virus infection in the presence of antibodies directed against heterologous strains or viruses. Consequently, strains vary in their susceptibility to ADE and/or ability to induce ADE of infection (76,82). Halstead and others evaluated anti-DV sera from naturally infected humans or produced in various species of animals (mouse, rabbit, monkey) against 4 different serotypes of DV for their ability to cross-neutralize DV-2 and to mediate ADE of DV-2 infections (45,48,82,83). Their studies revealed that heterotypic antisera poorly neutralized DV-2 infectivity for continuous cell lines, but both homotypic and heterotypic antisera enhanced DV-2 infection in human peripheral blood leukocyte cultures. The degree of ADE of DV-2 infection mediated by either homotypic or heterotypic antisera varied. Higher ADE activity for DV-2 infection was detected in the heterotypic antisera, most notably DV-1 antisera, than in the homotypic serum. Moreover, the magnitude of maximum ADE of DV-2 infections mediated by heterotypic antisera varied among the antisera, as well as the serum dilution at which the maximum ADE activity for DV-2 was observed. These results suggested that DV serotypes and field isolates varied in their susceptibility to ADE mediated by antibody raised against heterologous serotypes or isolates, and probably also varied in their ability to induce enhancing antibodies. The variability in ADE response among the DV-2 isolates was attributed to differences in the epitopic profiles of the isolates. A difference in the susceptibility to ADE among isolates has also been reported for the porcine arterivirus, PRRSV. Yoon and his coworkers demonstrated that some isolates produced higher progeny virus titers than others when inoculated to porcine alveolar macrophages after treated with the same PRRSV antiserum (141).

In similar studies with FIPV, Olsen et al. (89) evaluated the biological function of MAbs raised against the S protein of the virus and discovered that specific epitopes of the S protein vary in their ability to induce ADE-associated antibodies. They were able to categorize the monoclonal antibodies that represent the epitopes of the envelop S protein into three groups according to their ability to (a) only neutralize, (b) both neutralize and enhance, and (c) only enhance FIPV infection. Furthermore, monoclonal antibodies with specificity for different FIPV antigenic determinants varied in their ability to enhance virus infection, suggesting that epitopes are either strongly or weakly associated with ADE of infection (23,89). These finding are particularly noteworthy because they suggest that it may be possible to develop vaccines with strong neutralizing and weak ADE inducing characteristics. HIV-1 isolates similarly vary in their susceptibility to ADE and/or in the ability to induce enhancing antibodies. It is believed that susceptibility is due to the great genomic diversity that has been demonstrated among HIV isolates (76). Currently, variation in the susceptibility of isolates to ADE and in the ability to induce ADE of infection are of great concern for developing vaccines against viruses for which ADE and antigenic diversity have been reported.

Cellular events. It has been shown that for some viruses binding is not sufficient for infection, suggesting the involvement of other viral and host cell proteins in the internalization process (125). In such cases, the presence of antibodies that prevent binding will not neutralize but facilitate infection, as seen with attachment-defective FMDV mutants (78). Thus, internalization may occur through other pathways instead of the endocytic pathway, commonly attributed to enveloped viruses (34,84). However, it has also been shown that the presence of enhancing antibody does not affect the internalization pathway of WNV (33).

While enhanced entry and increased production of virus is documented in association with ADE of virus infection, it is not well understood how cells like macrophages, whose internal microenvironment should be antiviral, become favorable to virus replication when ADE of viral infection occurs. Some limited studies have suggested that virus entry by ADE follows a pathway that may modulate normal immune functions of infected cells such as macrophages. In an early study with DV, the production of high level of prostaglandin E2 (PGE2) but not IL-4 from peripheral mononuclear leukocytes was observed when the cells were inoculated with DV-2 pre-treated with DV-1 antiserum (19). The PGE2 is a lipid cytokine produced by macrophages that has anti-inflammatory properties and is responsible for increasing the production of IgG2 in humans (59). In bovine, PGE2 also has important regulatory functions in type 1/type 2 immune responses and can regulate virus expression and disease progression in BLV infection (100).

A recent study by Lidbury et al. (72) has brought some insight to the cellular events of ADE of virus infection when they studied RRV. When murine macrophages were infected with RRV through antibody-FcR interaction instead of the natural viral receptor on the cell, LPS stimulation of cells did not produce successful antiviral response. Instead, the production of IRF-1 and NF-κB transcription factors for antiviral genes such as TNF and inducible nitric oxide synthase genes was inhibited. Thus RRV replication was not affected. Despite this, transcription of cellular genes unrelated to antiviral activity and overall mRNA translation was not downregulated.

ASSAYS FOR ADE ACTIVITY

Antibody dependent enhancement of virus infection can be studied either *in vitro* or *in vivo*. Although *in vivo* study may have more clinical relevance, *in vitro* assays utilizing various sources of virus-specific antibody, such as antisera, mouse monoclonal antibodies, fractionated immunoglobulin, are generally performed to determine the ability of antibody to enhance specific virus infections (41,76,98). Two types of ADE assays have been developed for *in vitro* study to quantitate enhancing activity. One assay is to assess the increase in the production of progeny virus from cells exposed to virus-antibody mixtures (45,46,50). The other assay measures the increase in the proportion of cells being infected after exposure to virus-antibody mixtures (32,89). Both ADE assays are conducted by first exposing the virus of interest to antibody at different levels of concentration or to an appropriate antibody-free control serum. Permissive cells are then inoculated with these mixtures. After an appropriate period of incubation, progeny virus yield or numbers of infected cells are determined and compared. The virus yield is usually determined by microtiter infectivity assay or plaque assay using permissive cell lines (41). Fluorescence microscopy (23,89), *in situ* hybridization (88), or infectious foci center assay (32) have also been used to measure the proportion of cells infected with virus.

Morens and Halstead proposed that the occurrence of ADE of virus infections can be recognized by the following observations: (a) a significant increase in virus production as measured by quantitative assays at different points on the growth curve; (b) "enhancement profiles," which are characterized by the appearance, peak, decline, and disappearance of infection enhancement produced over at least a 10^{-3} fold dilution range when the virus output is assayed in cells infected with mixtures of constant amounts of virus and serial dilutions of antibody source; (c) the dilution of antibody source at which maximal enhancement is observed is related to other serological measures of binding to virus components; (d) infection enhancement is detected with different antibody sources and virus strains tested over a range of multiplicity of infection; and (e) other causes of enhanced virus production could be ruled out (82).

Using an *in vitro* ADE assay, the ADE activity of antibody source can be expressed in several ways, in-

cluding endpoint titers, peak enhancement titer and "enhancement power." The endpoint titer of enhancing antibody is by definition the highest dilution of serum producing a significant enhancement of infection compared to controls (41,68). The peak enhancement titer is a serum dilution at which virus yield or proportion of infected cells is maximal for the antibody source tested (68). The "enhancement power or ratio" can be calculated by dividing the virus yield or proportion of infected cells in antibody-supplemented group by the yield or proportion if uninfected cells in control cultures at a selected dilution of serum, or on a selected comparison day if a single dilution of serum is used (41,68,98).

The method of measuring and expressing ADE activity can be of critical importance in attempting to correlate *in vitro* ADE of virus infection with an *in vivo* effect. For instance, in secondary dengue infections, enhancing activity in undiluted sera was a significant risk factor for severe dengue illness when human peripheral blood mononuclear cells were used as indicator cells. In contrast, endpoint ADE titer of antibody source, such as the highest serum dilution showing enhancing activity was not predictive and paradoxically was higher in children without severe illness (68).

Some investigators have been able to demonstrated ADE of infection *in vivo*. General approach has been that susceptible host animals are injected with antibody source (e.g., immunoglobulin or antiserum) and challenged with the target virus later, then monitoring the level of virus replication as compared to animals that did not receive antibody. Halstead (37) injected rhesus monkeys intraveneously with human cord blood containing anti-DV antibody and immediately challenged them with DV and demonstrated that the monkeys that were injected with DV antibody developed higher levels of viremia for a longer period than control monkeys. Similar observations were made in pigs injected intraperitoneally with subneutralizing level of anti-PRRSV immunoglobulin and inoculated with the virus 1 day later in comparison to pigs receiving normal serum globulin at the same rate (140).

BIOLOGICAL SIGNIFICANCE OF ADE

Disease enhancement. ADE of virus infection has been suggested as a disease-enhancing factor for several human and animal viral diseases (76). Specific examples include Aleutian mink disease virus, dengue virus, feline infectious peritonitis virus, and respiratory syncytial virus (17,64). In addition, ADE of infection has also been implicated as a major obstacle to the development of vaccines for such viruses as ADV (95), bluetongue virus (10), DV (8), FIPV (132), influenza virus (134), lentiviruses (79,133), rabies virus (116), and RSV (65). In all cases, the presence of antibodies induced by vaccination increased the susceptibility to subsequent virus infections and/or exacerbated the severity of clinical disease by virus challenge in vaccinated individuals.

Dengue virus. Dengue viruses belong to the genus Flavivirus of the family *Flaviviridae*. There are four serotypes: DV types 1, 2, 3, and 4 (39). Dengue virus infections are considered a serious human health problem in many areas of the world. Dengue virus infection can be asymptomatic or cause two forms of disease (39). In most cases, DV infection causes a febrile disease referred to as "dengue fever," which is characterized by fever, retro-orbital pain, muscle aches, bone pain, and petechiae. Patients recover in 7–10 days without complications. In some instances, patients infected with DV leak plasma into interstitial spaces resulting in hypovolemia and, sometimes, circulatory collapse. This severe and life-threatening syndrome, which is always accompanied by thrombocytopenia and sometimes by frank hemorrhage, is termed dengue hemorrhagic fever (DHF). More severe clinical manifestations of DHF in which plasma leakage is so profound that shock occurs, are referred to as dengue shock syndrome (DSS).

Although the pathogenesis of DHF/DSS is not clearly understood, the association between ADE of infection and the severity of disease has been extensively studied. This association was first described by Halstead and co-workers who observed that the severity of dengue fever was significantly greater in children with maternal antibody specific for DV than in children with no DV-specific maternal antibody (36,40,44). Experimentally, these investigators demonstrated that in rhesus monkeys anti-DV maternal antibodies enhance DV infection (37). The investigators injected monkeys intravenously with small amounts of human cord blood containing anti-DV antibody and immediately challenged them with DV. The monkeys that were injected with DV antibody developed higher levels of viremia for a longer period than control monkeys. In

a clinical setting, sequential infection models demonstrated that a patient who had previously been infected with either one of the four DV serotypes, and was subsequently exposed to DV-2 had a greater risk to develop DSS. The risk for severe form of DV infection was reported to be the highest when the infections were of the DV-1/DV-2 sequence (19).

It was also found that DV produced a more severe clinical manifestation in older individuals who had subneutralizing levels of antibodies, which were induced by previous DV infections than in individuals who had no previous exposure to the virus (39,42). These severe clinical manifestations were more frequently observed in individuals who have antibody against one serotype of DV and were subsequently exposed to a different serotype of DV than in individuals challenged with a homologous serotype. Recent prospective case-control studies conducted by Burke et al. (11) and Kliks et al. (68) demonstrated that presence of DV antibodies is a significant risk factor for increased severity of disease by subsequent DV infection. In these studies, individuals were categorized into the case and control based on the presence and absence of anti-DV antibody. Decay of DV antibody was monitored for the case group and correlated to ADE activity in undiluted sera. Both groups were also monitored for subsequent clinical event with respect to natural DV infection. The investigators observed that the morbidity of DV infection was significantly higher in the case than the control. Mortality due to DHF/DSS was also higher in the case group than the control.

Respiratory syncytial virus. In general RSV infections are not always considered serious. However, individuals who develop pneumonia from RSV infection often require hospitalization. Chanock et al. (18) reported that naturally acquired severe RSV infections were almost always seen in the first 6 months of life when children had circulating maternal anti-RSV antibodies. In another study, infants with maternally acquired RSV antibody not only were susceptible to RSV infections, but the rate of severe disease was higher in these infants when compared to infants without maternal antibodies (17). These observations led to speculation that RSV-specific antibody may contribute to the severity of clinical manifestations of disease caused by RSV. A recent study demonstrated that infection of a mouse macrophage cell line by RSV is enhanced in the presence of virus-specific antibody (31). This observation supports the hypothesis that immune-mediated enhancement of disease may occur in human RSV infection and contribute to the pathogenesis of the disease.

Immune-mediated enhancement of disease has also been described in human infants and children vaccinated with early experimental vaccines against RSV. Several epidemiological and experimental studies found that immunization with an inactivated whole virion RSV vaccine led to development of antibody response, but did not prevent infection with wild-type RSV in children less than 2 years of age (20,30,65,66). More importantly, subsequent natural infection by wild-type RSV resulted in an extremely high frequency (52–69% of infected children) of severe lower respiratory tract disease (i.e., pneumonia) in the vaccinated group, whereas only 9–10% of infected children became pneumonic in the non-vaccinated group (65,66). Furthermore, the duration of illness was longer (30) and the severity of illness was greater in the vaccinated children compared with non-vaccinated children (20). Results from these studies indicated that children were at increased risk of severe RSV disease following immunization, leading to the development of better vaccines.

Feline infectious peritonitis. Feline infectious peritonitis virus is a coronavirus that causes peritonitis and occasionally a fatal pyogranulomatous disease in kittens and cats (136,137). Antibody dependent enhancement has been incriminated as a disease-enhancing factor of feline infectious peritonitis (92,135). Cats with active or maternal immunity to FIPV often develop an accelerated and more fulminant disease following challenge with FIPV than seronegative cats. The role of antibodies in mediating more severe disease following challenge has been also documented in cats that were injected with FIPV-reactive immune sera or purified immunoglobulin and subsequently challenged with the virus (135). Furthermore, immune-mediated disease enhancement has been demonstrated in kittens that had vaccine-derived humoral immunity directed against the spike protein of FIPV. These kittens died earlier than did control animals (132). Similarly, kittens immunized with a recombinant vaccinia virus expressing the spike protein of FIPV died earlier than control animals (132).

Aleutian mink disease. Aleutian disease virus is a parvovirus pathogenic to mink that circulates in the blood principally as immune complexes, which are fully infectious, both *in vivo* and *in vitro* (96). Consequently, viral infection causes a fatal glomerulonephritis in mink due to deposition of soluble immune com-

plexes on renal glomerular membrane or wall of capillary blood vessel, which causes tissue damage by mononuclear cells and complement and consequently results in impairment of renal filtration. Besides formation of soluble immune complexes, ADE of infection has also been suggested as a potential contributing factor to the pathogenesis of ADV (94,95). Initially, Porter et al. (94) found that ADV replicated in macrophages and large amounts of non-neutralizing antibody were produced in mink infected with ADV. They speculated that the early formation of non-neutralizing antibody might lead to virus-antibody complex formation. They further speculated that phagocytosis of these complexes by macrophages could lead to increased infection of the cells by ADV resulting in increased production of progeny virus. In related work, Porter et al. (95) demonstrated that passive transfer of virus-specific antibody at the peak of viral replication resulted in foci of necrosis around virus-infected cells. The investigator concluded that this pathological reaction was due to enhanced complement-mediated cytolysis, suggesting that antibody has the potential to contribute to the severity of disease by ADV. A recent *in vitro* study by Kano et al. (64) demonstrated that infection of mink peritoneal macrophages by ADV is enhanced by anti-ADV antibody.

In a trial with an experimental ADV vaccine, the immunization regimen failed to produce any detectable neutralizing antibody to ADV. However, following challenge with a standardized infectious dose of virus by the oral route, higher levels of circulating antibodies were detected in vaccinated mink than in challenged control animals (95). Moreover, eight of 10 vaccinated mink, but none of control animals, developed Aleutian disease. Cumulatively, these observations provide strong evidence that vaccine-induced humoral immunity can lead to a more severe disease course through ADE.

Lentiviral diseases. Equine infectious anemia is a lentiviral infection of horses that generally causes a syndrome of fever, anorexia, and anemia with cyclic recurrence during the first year of disease. Subsequently, horses may become asymptomatic or develop a chronic wasting syndrome. Several studies were conducted to evaluate the efficacy of vaccines against equine infectious anemia virus (EIAV) as a model for evaluating AIDS vaccine strategies (61,133). These studies clearly illustrated that enhanced severity of disease in vaccinated animals was due to the presence of vaccine-induced antibody. Issel et al. (61) used viremia as a criterion of disease and demonstrated that inactivated whole virus vaccines elicited 100% protection against homologous challenge with avirulent EIAV. In contrast, the vaccines failed to prevent viremia following heterologous challenge with a virulent strain of EIAV. However, the vaccine did protect ponies from the subsequent development of clinical symptoms after challenge with the virulent strain. Using viremia as criteria of disease, these investigators also evaluated the efficacy of a subunit vaccine composed of lectin affinity-purified viral envelope glycoproteins. This vaccine failed to prevent not only viremia but also the development of subsequent clinical symptoms following challenge with the heterologous virus, while the vaccine provided 100% protection against infection by the homologous virus challenge. In a subsequent study, Wang et al. (133) evaluated a recombinant subunit vaccine consisting of a baculovirus-expressed surface glycoprotein of EIAV in groups of eight ponies each. Horses immunized with the recombinant vaccine were not protected from challenge with either homologous or heterologous strains of EIAV. Vaccination resulted in significantly higher levels of viremia that persisted for a longer period of time. In addition, the severity of disease in vaccinated ponies was greater than in unvaccinated controls following challenge with the virulent heterologous strain. Exacerbation of disease severity in vaccinated animals has also been observed with vaccine for other members of the lentiviruses (79).

Feline immunodeficiency virus (FIV) has also been used as a model to study lentiviral infection (i.e., HIV-1) for the development of effective vaccines (6,62). In some vaccine trials, viremia developed earlier in cats immunized with recombinant envelope (*env*) protein of FIV than unvaccinated animals after challenge with homologous virus. Interestingly, no or low level of FIV-specific antibodies was detected in experimental animals (103). Similar studies utilizing various experimental recombinant vaccines have also shown that the animals developed no or poor neutralizing antibodies to the *env* protein. Nonetheless, enhancement of viral infection took place, as the virus load after challenge in vaccinated cats was higher than in unvaccinated cats (4,56). In addition, high antibody titers to the core protein of FIV have been demonstrated to be associated with enhancement of the disease (55).

Currently a similar concern about immune-mediated disease enhancement in HIV vaccine trials is being raised because ADE of HIV infection in human peripheral blood mononuclear cells has been demonstrated

in vitro with sera from HIV-infected individuals or animals vaccinated with experimental vaccines (10,49,76).

Arteriviruses. Studies by Christianson et al. (22) highlighted the biological significance of ADE of virus infection related to reproductive problems caused by PRRSV infection. Pregnant sows inoculated *in utero* or intramuscularly with PRRSV that was pre-treated with specific serum prior to inoculation showed higher virus titers in fetal tissues as compared to animals that received the virus alone. Enhancement of infection in late term fetuses could lead to an increased rate of abortions, stillbirths or weak-born piglets. In addition, the potential risk for disease exacerbation in pigs with antibody of maternal origin was also demonstrated using passive transfer of immunoglobulin specific for PRRSV (140). Pigs injected immunoglobulin at a low neutralizing antibody developed higher and longer lasting viremia after challenge than pigs received normal swine serum globulin or injected with immunoglobulin containing relatively high level of neutralizing antibody.

Other viral diseases. Adverse affects of ADE of virus infection have also been reported in animals vaccinated with experimental rabies or influenza virus vaccines. Sikes et al. (116) evaluated a large number of licensed and experimental rabies vaccines in monkeys. Vaccines were administered at either 36 or 73 days prior to challenge, or within 6 h after challenge. Monkeys were injected with $10^{4.5}$ to $10^{5.8}$ mouse lethal doses of rabies virus into cervical muscles. Monkeys vaccinated either before or after challenge, as well as another group of monkeys given with anti-rabies serum, died 6–13 days (mean 11 days) after challenge, while 14 of 17 control animals died 14–63 days (mean 25 days) after challenge. The investigators subsequently coined the term "early death" phenomenon to describe these observations. The same phenomenon has also been demonstrated in mice inoculated intracerebrally with rabies virus 2–4 days after a rabies vaccine was administered intraperitoneally (7). Later, it was suggested that the "early death" phenomenon was attributed to ADE of rabies virus infection mediated by vaccine-induced humoral immunity (67,99).

In work with an experimental influenza virus vaccine, Webster and Askonas (134) found that mice inoculated with one or two doses of inactivated whole virus or subunit vaccines of influenza virus A/USSR/90/77 (H1N1) showed enhanced growth of influenza virus in the lung following intranasal challenge with homologous or heterologous (X-31, H3N2) strains at varying intervals after immunization.

Contribution to the pathogenesis of virus infection. The presence of non-neutralizing antibodies capable of facilitating virus entry into macrophages or cells expressing Fc or complement receptors may contribute to persistence by creating a virus reservoir in macrophages (5). Latency of HIV infection has been described to occur via an M phase where the virus escapes by infecting macrophages. However, increase in virus load in the blood of patients infected with HIV-1 has been associated with complement-mediated ADE (C-ADE) of infection. This C-ADE activity correlates negatively with CD4+ cell counts and usually precedes clinical progression. Szabó and colleagues concluded that there should be a switching from neutralizing towards enhancing antibody production before the onset of clinical presentation. The enhancing antibodies would be expected to be against the immunodominant gp41 of HIV-1 since the level of these are higher in symptomatic patients compared to asymptomatic patients (101,126).

Other viruses like PRRSV have been shown to localize in the CNS, particularly in microglial cells (71) and can persist through a slow replication rate (2). Contrary to this, the high replicating rate of LDV can establish persistence even when specific cytotoxic T cell responses take place (130).

CONCLUSION

ADE of virus infection is a phenomenon that is not exclusive to human pathogens but it is also seen involved in the pathogenesis of viruses that affect domestic animals and wild life. Vaccination is the best tool available for the prevention and control of infectious diseases, although good management practices of farm animals and personal or public hygiene are also important measures for this purpose. However, as reviewed above, ADE of infection can be a significant obstacle to the development of effective vaccines. In such cases, the presence of viral epitopes that can enhance virus infection, thus exacerbating disease, should be taken into consideration. Recombinant subunit or DNA vaccines expressing specific neutralizing epitopes

can be one approach for minimizing such potential risk but special care has to be taken in the selection of the genes or peptides used for these to maximize vaccine success in providing protection instead of enhancement. Perhaps the development of novel vaccination strategies or vaccine formulation may also offer new frontiers in the control of diseases enhanced by antibody.

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Address reprint requests to:
Kyoung-Jin Yoon, D.V.M., Ph.D.
Veterinary Diagnostic Laboratory
College of Veterinary Medicine
Iowa State University
Ames, IA 50011

E-mail: Kyoon@iastate.edu

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