



Antibody-Dependent Enhancement of Viral Infections

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Abstract

Antiviral antibodies constitute an important component of the host immune response against viral infections and serve to neutralize and reduce infectivity of the virus. However, these antibodies, intended to protect the host, may sometimes prove beneficial to the virus, by facilitating viral entry and replication in the target cell. This phenomenon, known as antibody-dependent enhancement (ADE) of infection, is a result of interaction of virus–antibody immune complexes with Fc γ and/or complement receptors on certain types of host cells and promotes viral entry into the host cells. The internalized immune complexes then modulate host immune response so as to enhance viral replication and aggravate disease severity. The possibility of induction of ADE remains a concern in the development and implementation of viral vaccines and immunotherapeutics.

Keywords

Viral infection · Neutralization · Antibody-dependent enhancement · Immune response · Vaccine · Immunotherapeutic

2.1 Introduction

Antibody-dependent enhancement (ADE) of infection represents a paradoxical phenomenon in host–pathogen biology, in which, antibody, an important pillar of the host defense against invading pathogen, actually allows entry of the pathogen into host territory. This traitorous behavior of the antibody further serves to weaken the host defense system and thus generates an environment conducive for enhanced

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growth of the pathogen and consequently exacerbates disease in the host. This phenomenon has far-reaching implications for disease control and prevention, as therapeutic antibodies deployed to protect the host may aid the pathogen instead. Similarly, antibodies induced by vaccination may actually increase the risk and/or severity of disease in subsequent host–pathogen encounters.

This chapter aims to provide insights into the current knowledge on ADE of viral infections, with a focus on its molecular mechanisms and contribution to viral pathogenesis and disease, as well as implications for disease control strategies.

2.2 Antibody-Mediated Control of Viral Infections

Antibodies are an important component of the host adaptive immune response against infecting virus. Virus neutralization is considered to be the key mechanism of antibody-mediated protection. The antiviral activity of antibody is further augmented by Fc-mediated effector mechanisms such as complement-mediated lysis of viral particles, phagocytosis, and antibody-dependent cellular cytotoxicity (ADCC) (Braciale et al. 2013).

Neutralization occurs when antibody molecule(s) bind to the virus particle at its surface epitope and block viral attachment (to cellular receptor) and entry into host cell, and/or post-entry processes such as fusion and uncoating, thus resulting in loss of virion infectivity (Fig. 2.1). Two models have been proposed to describe the kinetics of neutralization. According to the single-hit model, binding of a single antibody molecule to a critical site on the virion is sufficient for neutralization. The more accepted multi-hit model postulates that neutralization can be achieved only when the virion is bound by multiple antibodies, exceeding the stoichiometric threshold of neutralization (Klasse and Sattentau 2002). The potency of neutralization is determined by the affinity of antibody binding and accessibility of the neutralization epitope(s) on the viral surface (Dowd et al. 2011).

2.3 The Antibody-Dependent Enhancement Phenomenon

The phenomenon of antibody-dependent enhancement (ADE) was discovered in flaviviruses during the 1960s–1970s. While observational studies on dengue virus (DENV) infections revealed a significant association between severe illness and antibody responses in secondary infection (Halstead et al. 1967), *in vitro* experiments demonstrated increased infectivity of Murray Valley encephalitis virus (Hawkes 1964; Hawkes and Lafferty 1967) and DENV (Halstead et al. 1973a) in the presence of antibody. *In vivo* studies in rhesus monkeys showing association of antibody response with higher dengue viremia offered further supportive evidence for this phenomenon (Halstead et al. 1973b; Halstead 1979; Marchette et al. 1973).

ADE ensues when antibodies binding to the virus particle fail to efficiently neutralize the virus (Halstead 2003; Taylor et al. 2015). This may occur due to the non-neutralizing nature of the antibody (binding to viral epitopes other than those

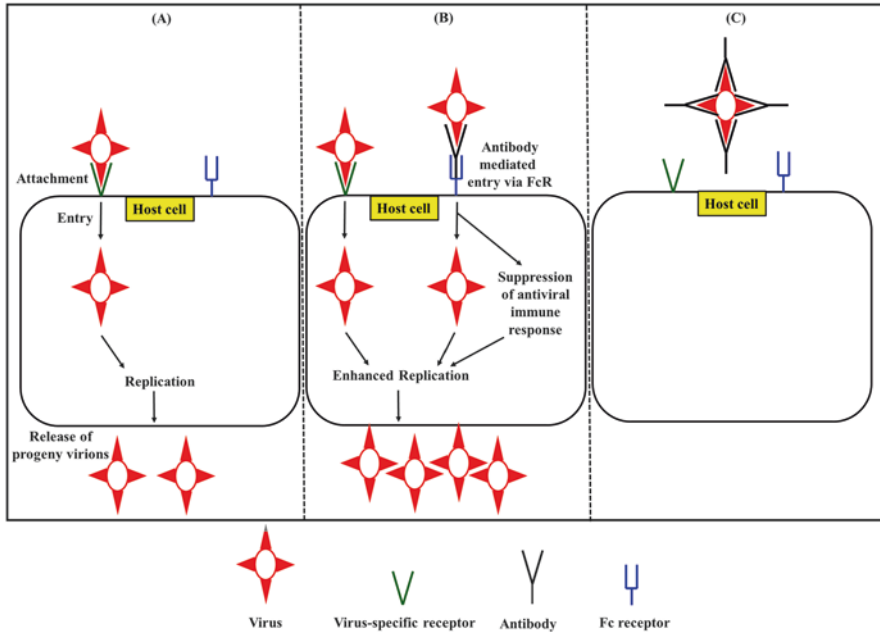


Fig. 2.1 Schematic representation of effect of antibody on virus–host cell interaction. (a) In the absence of virus-specific antibody, virus enters the host cell via interaction with cell surface (virus-specific) receptor, followed by replication and release of progeny virions. (b) In the presence of non-neutralizing or sub-neutralizing concentrations of antibody, an additional pathway of entry into host cell is available to the virus. Virus–antibody immune complexes are internalized via antibody interaction with cell surface Fc receptor (FcR), resulting in antibody-dependent enhancement (ADE) of viral infection and replication. Internalized immune complexes bring about suppression of cellular innate antiviral immune response further boosting viral replication. (c) In the presence of neutralizing concentrations of antibody, virus attachment and entry into host cell is blocked

involved in cell attachment and entry) or the presence of sub-neutralizing concentrations of antibodies (binding to viral epitopes below the threshold for neutralization). Either way, these antibodies aid entry of the virus into target cells, resulting in enhancement of viral infection, known as antibody-dependent enhancement (Fig. 2.1). The mechanism of ADE involves internalization of virus–antibody immune complexes into cells via interaction of the antibody Fc region with the cellular Fc receptors (FcRs). Consequently, FcR-bearing myeloid cells such as monocytes, macrophages, dendritic cells, and certain granulocytes are permissive to ADE of infection, through phagocytic uptake of the immune complexes. Such ADE is principally mediated by IgG antibodies, however, IgM along with complement, and IgA antibodies have also been shown to be capable of ADE (Hawkes and Lafferty 1967; Cardoso et al. 1983; Janoff et al. 1995; Kozłowski et al. 1995).

Initially, the role of antibody in enhancing viral infection was believed to be limited to facilitation of virus entry into host cells, resulting in increase in the number of infected cells and, consequently, higher virus production, in a process termed

Table 2.1 Summary of key features of antibody-dependent enhancement (ADE) of viral infections

Virus (family)	Mechanism of ADE	Clinical significance of ADE	Implications for vaccines
Dengue virus (family <i>Flaviviridae</i>)	<ol style="list-style-type: none"> 1. Antibodies against viral EDI, EDII, prM proteins involved in ADE 2. Extrinsic ADE: FcR-mediated virus internalization of virus-antibody immune complexes into monocytes, macrophages, dendritic cells 3. Intrinsic ADE: Modulation of host antiviral response by LILR-B1 co-ligation, downregulation of TLR-dependent, RIG-I/MDA5 signaling pathways, induction of IL-10 production 4. Antibody-mediated enhancement of viral fusion suggested 5. ADE associated with massive release of inflammatory cytokines leading to alteration of vascular permeability and plasma leakage which are the hallmarks of severe dengue 	<ol style="list-style-type: none"> 1. Association of ADE with severe dengue (DHF/DSS) during secondary heterotypic infections has been demonstrated 2. Severe disease during primary infections among infants born to dengue-immune mothers has been attributed to ADE 	<ol style="list-style-type: none"> 1. Increased risk of severe dengue among seronegative Dengvaxia (CYD-TDV) vaccine recipients led to WHO recommending adoption of a pre-vaccination screening strategy, and vaccine administration only to dengue seropositives 2. Identification of stronger correlates of protection, development of more robust assays for estimation of neutralizing/enhancing ability, long-term follow-up of vaccine recipients in clinical trials suggested to better predict vaccine-related ADE 3. Subunit EDIII, NS1 vaccines, chimeric vaccines with replaced DENV pr gene, T-cell response-inducing vaccines suggested to reduce ADE, but in vivo protection not yet demonstrated
Human immunodeficiency virus (family <i>Retroviridae</i>)	<p>Antibodies against viral gp41 and gp120 enhance viral entry into T cells, monocytes/macrophages, and granulocytic cells, by the following mechanisms:</p> <ol style="list-style-type: none"> 1. Complement-mediated, C-ADE: Interaction of antibody-opsonized virus with complement component C3d,g, cellular complement receptor CR2 and virus-specific receptor CD4, co-receptor CXCR4 2. FcR-mediated, FcR-ADE: By CD4-dependent or independent process 	<p>Positive correlation of enhancing antibody level with plasma viral load and negative correlation with CD4 cell count suggest association of ADE with accelerated immunosuppression and disease progression</p>	<p>ADE indicated by observation of higher infection rate/risk of infection among vaccine recipients in AIDS VAX, RV144 clinical trials, but not yet confirmed</p>

Influenza virus (family <i>Orthomyxoviridae</i>)	1. Antibodies against viral hemagglutinin (HA) and neuraminidase (NA) mediate virus uptake via FcRs into macrophages, possibly leading to increased antigen presentation and T-cell activation 2. Enhancement of viral fusion by anti-HA2 antibodies suggested	Increased risk of medically attended illness among individuals with prior influenza-like illness during 1918 pandemic, and among seasonal influenza vaccine recipients during 2009 H1N1 pandemic, is suggestive of ADE	ADE suggested to be responsible for vaccine-associated enhanced respiratory disease in immunized pigs and ferrets, but mechanism not yet clearly understood
Respiratory syncytial virus (family <i>Paramyxoviridae</i>)	Antibodies against viral glycoproteins G and F mediate virus uptake via FcRs into monocytes, macrophages, dendritic cells leading to immune response modulation	Clinical relevance remains unclear in light of contradictory reports regarding association of maternal antibody-induced ADE with severe disease in infants	Enhanced disease in formalin-inactivated RSV vaccine recipients initially attributed to ADE, but other mechanisms also recently suggested
Ebola virus (family <i>Filoviridae</i>)	Antibodies against viral glycoprotein (GP) promote virus internalization by FcR-mediated or complement component C1q/C1q receptor-mediated process into monocytes/macrophages, endothelial, epithelial cells, and hepatocytes	Clinical relevance not yet understood	Vaccine-related ADE not yet demonstrated, but remains a concern. Avoiding induction of known infectivity-enhancing antibodies, while retaining T-cell epitopes in vaccines proposed for ADE mitigation
SARS— Coronavirus (family <i>Coronaviridae</i>)	Antibodies against viral spike (S) glycoprotein mediate virus uptake via FcRs into immune cells such as B cells, monocytes, macrophages	Clinical relevance still debated	Impact on vaccine safety not yet understood
Chikungunya virus (family <i>Togaviridae</i>)	FcR-mediated internalization into B cells, monocytes suggested	Clinical relevance not yet understood	Impact on vaccine safety not yet understood

EDI envelope domain I, *EDII* envelope domain II, *prM* precursor membrane, *FcR* Fc receptor, *LILR-B1* leukocyte immunoglobulin-like receptor B1, *TLR* Toll-like receptor, *RIG-I* retinoic acid-inducible gene I, *MDA5* melanoma differentiation-associated antigen 5, *DHF* dengue hemorrhagic fever, *DSS* dengue shock syndrome, *EDIII* envelope domain III

as “extrinsic ADE.” However, studies on Ross River Virus suggested that internalized immune complexes further serve to enhance viral replication by suppression of the cellular innate antiviral immune responses (Lidbury and Mahalingam 2000; Suhrbier and La Linn 2003). This mechanism is termed as “intrinsic ADE” and has been subsequently observed in flaviviruses as well (Chareonsirisuthigul et al. 2007; Ubol et al. 2010). Thus, ADE is a complex phenomenon comprising of extrinsic and intrinsic components, which together contribute to augmentation of viral infection and replication. The consequence of this increased virus production is the massive release of inflammatory and vasoactive mediators by host cells, which ultimately leads to exacerbation of viral pathogenesis and disease severity.

Prior sensitization of the humoral immune response is a prerequisite for ADE (Halstead 2003; Taylor et al. 2015). This phenomenon is thus widely observed during secondary infection with a heterotypic virus of the same genus, wherein preexisting antibodies against the primary (sensitizing) infection bind to the (secondary) virus, but fail to neutralize it. The pathogenicity and outcome of secondary infection is influenced by the time interval between primary/secondary infections, with increasing time being associated with more severe disease, and may be explained by the waning of broadly neutralizing antibodies over time. Passively acquired antibodies are also capable of inducing ADE, as indicated by the enhancement of viral disease by preexisting maternal antibody in infants born to dengue-immune mothers (Kliks et al. 1988; Chau et al. 2008, 2009).

The ADE phenomenon has implications for the use of antiviral immunoglobulins as therapy against viral infection, due to the associated risk of enhancement of disease (Taylor et al. 2015). ADE also poses a major challenge for implementation of vaccination programs, as vaccine-induced antibodies may enhance subsequent viral infection, thus placing vaccine recipients at increased risk of severe disease. Indeed, concerns regarding the safety of the world’s first licensed dengue vaccine “Dengvaxia” have forced authorities to reconsider the mass vaccination strategy and issue specific recommendations for safe implementation of the vaccine in dengue control programs (Wilder-Smith et al. 2019).

ADE has been exploited by a variety of viruses belonging to different virus families. The mechanism and clinical significance of ADE of selected viruses will be reviewed in this chapter and are also summarized in Table 2.1. The ADE phenomenon has been most extensively studied in dengue virus and will be considered in detail here.

2.4 Dengue Virus

Dengue virus (DENV) is a member of family *Flaviviridae*, genus *Flavivirus*, and is transmitted to humans through the bite of *Aedes* mosquitoes, mainly *Aedes aegypti*. Infection with any of the four serotypes of this virus, DENV-1 to DENV-4, may be asymptomatic, or lead to dengue fever with symptoms ranging from mild to high-degree fever with headache, myalgia, arthralgia, rash, and retro-orbital pain. In some patients, the illness may progress to life-threatening severe dengue [earlier

classified as dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS)], characterized by increased vascular permeability, plasma leakage, extensive pleural effusion, severe hemorrhages, respiratory distress, and organ failure (WHO 2009). Dengue disease is endemic in more than 125 countries and is considered a major public health problem worldwide, with an estimated 96 million cases and 20,000 deaths reported annually (Bhatt et al. 2013). In the absence of effective antivirals, dengue treatment mainly relies on symptomatic interventions. Though a licensed vaccine is now available, implementation of mass immunization programs remains complicated due to ADE, and is discussed in later sections.

The DENV genome is a single-stranded, positive-sense RNA molecule (~11 kb in size) and contains a single open reading frame coding for a large polyprotein, which is subsequently processed into three structural proteins, capsid (C), membrane (M), and envelope (E), and at least seven nonstructural proteins, NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 (Lindenbach et al. 2013). The E glycoprotein is the major surface-exposed region of the virus and displays the viral antigenic determinants. It functions to bind cellular receptors and fuse with host cell membranes during virus penetration and also directs viral assembly and budding. The E protein monomer can be divided into three structural/functional domains—EDI, the central region; EDII, the site of fusion; and EDIII, the site of receptor binding (Modis et al. 2004). The M protein is initially expressed as a membrane precursor (prM), which is present in the intracellular immature virus particle. Virion assembly and maturation involves cleavage of the precursor (pr) peptide, resulting in release of the mature virus particle containing the M protein into the extracellular environment (Li et al. 2008; Junjhon et al. 2010).

2.4.1 Epidemiological and Experimental Evidence for DENV-ADE

The possibility of immune enhancement of DENV infection was first suggested by observation of strong association of severe disease (DHF/DSS) with secondary infection among dengue patients in Bangkok, Thailand, during 1962–1964 (Halstead et al. 1967; Guzman et al. 2013). These initial findings were supported by prospective sero-epidemiological studies showing a higher rate of DHF/DSS during secondary infections (Sangkawibha et al. 1984; Graham et al. 1999; Halstead 2008). The association of secondary heterotypic DENV (different serotype) infection with ADE and severe dengue was further strengthened by reports of DHF/DSS cases in Cuba during the 1981/1997 DENV-2 outbreaks and 2001–2002 DENV 3 outbreak in a population immune to DENV-1 (1981/1997) and DENV-1/2 (2001–02), respectively (Guzman et al. 1990, 2000; Alvarez et al. 2006). Further, it has been demonstrated that such secondary DHF/DSS cases have higher viremia and levels of pro-inflammatory cytokines, suggesting that greater infected cell mass and subsequent increase in cytokine release contribute to disease severity in these patients (Vaughn et al. 2000; Wang et al. 2006; Rothman 2011). However, interestingly, tertiary/quaternary DENV infections have been rarely associated with severe

disease, presumably due to sufficient cross-protective immunity acquired after two (primary/secondary) different DENV infections (Gibbons et al. 2007).

The most compelling evidence for ADE is provided by observation of severe dengue during primary infection in infants born to dengue-immune mothers (Kliks et al. 1988; Chau et al. 2008, 2009). During the first 3–4 months after birth, passively acquired maternal antibodies have been shown to protect infants from symptomatic dengue. Thereafter, the maternal antibodies begin to decline and reach sub-neutralizing levels, at which the antibodies are capable of enhancing DENV infection. Such enhancing antibodies persist till ~12 months of age, placing the infants at increased risk of severe dengue. Indeed, this enhancing activity of the infant sera has been demonstrated *in vitro*.

DENV-ADE is supported extensively through *in vitro* experiments. Enhancement of DENV infection by anti-DENV monoclonal antibodies or polyclonal human immune sera has been observed in primary human myeloid cells as well as cell lines such as FcγR-expressing BHK-21 cells, monocytic U937, THP-1, K562 cells, and macrophage-like P388D1 cells (Halstead et al. 1973a; Morens et al. 1987; Cardosa 1987; Kliks 1990; Goncalvez et al. 2007; Moi et al. 2013; Guzman et al. 2013; Acosta and Bartenschlager 2016). Moreover, *in vitro* ADE by human sera has been associated with severe dengue in patients. The ADE phenomenon has also been demonstrated in animal studies, with higher viremia being recorded during experimental secondary infection in rhesus monkeys as well as in passively immunized monkeys (Halstead et al. 1973b; Halstead 1979; Marchette et al. 1973; Goncalvez et al. 2007). Further, DENV-specific antibodies have been shown to enhance DENV infection and disease severity in AG129 mouse model (Zellweger et al. 2010). In another study using AG129 mice, maternally acquired anti-DENV antibodies were found to enhance viremia and vascular leakage, leading to earlier death (Ng et al. 2014).

The ultimate verification for DENV-ADE in humans has been provided only recently in a long-term pediatric cohort study in dengue-endemic Nicaragua (Katzelnick et al. 2017). This study observed highest risk for severe dengue among individuals with suboptimal anti-DENV antibody titers, and protection from symptomatic dengue at high antibody titers, thus proving that the level of preexisting anti-DENV antibodies is directly associated with the severity of secondary dengue disease in humans.

2.4.2 Molecular Mechanism of DENV-ADE

2.4.2.1 Antibodies Enhancing DENV Infection

Studies using monoclonal antibodies obtained from primary/secondary dengue patients have identified DENV surface proteins E and prM as major targets of host immune response (Serafin and Aaskov 2001; Crill and Chang 2004; Beltramello et al. 2010; Matsui et al. 2010; Wahala and Silva 2011; Fibriansah et al. 2015; Gan et al. 2017). These studies have suggested that highly neutralizing antibodies are predominantly raised against the complex quaternary epitopes of the viral envelope

and the EDIII (lateral ridge) region involved in cellular attachment. These antibodies are mostly serotype-specific; however, antibodies raised against the quaternary “envelope dimer epitope” (EDE) have been found to potentially neutralize all four DENV serotypes (Dejnirattisai et al. 2015). Such protective antibodies represent only a small subset of the antibody repertoire in dengue patients, with the immune response being dominated by cross-reactive, non-neutralizing antibodies targeting EDI, EDII (fusion loop) and prM, which have the potential to enhance viral infection (Smith et al. 2014). Moreover, all neutralizing antibodies are also capable of enhancing infection when present at sub-neutralizing concentration.

The role of antibodies against prM protein is particularly important because of its ability to enhance infection of immature virions, which are otherwise noninfectious. The prM protein, present in the intracellular immature virus particle, covers the fusion domain of the E protein, thus preventing its fusion with the host cell membrane. Cleavage of the precursor (pr) peptide from the prM protein during the process of virus maturation renders the released mature virus particle “infectious” to host cells for further rounds of replication (Li et al. 2008; Junjhon et al. 2010). Inefficient processing of the prM protein results in the production of immature or partially immature virus particles, which are normally noninfectious due to their inability to fuse with host cell. However, studies using human monoclonal antibodies obtained from persons with secondary dengue have revealed that these immature virus particles are capable of infecting host cells in the presence of the non-neutralizing anti-prM antibodies, and are thus infectious during secondary infections with the possibility of contributing to severe disease (Dejnirattisai et al. 2010; Schmidt 2010). Similarly, antibodies specific to the fusion loop (FL) in EDII have also been shown to enhance the infectivity of immature DENV particles (Rodenhuis-Zybert et al. 2011).

2.4.2.2 Fcγ Receptors and Their Role in ADE

The Fcγ receptors (FcγRs) present on the surface of cells of the myeloid lineage function to internalize antibody-opsonized virus via receptor-mediated endocytosis or phagocytosis and thus aid in clearance of the virus from blood circulation. However, these FcγRs can also contribute to ADE of DENV infection, by offering the virus an alternative pathway of entry into its target cells, the FcγR-bearing monocytes, macrophages, and dendritic cells (Taylor et al. 2015; Gan et al. 2017). There are three classes of human FcγRs, namely, FcγRI, FcγRII, and FcγRIII. FcγRI is a high-affinity activating receptor that can bind to monomeric IgG molecules (Vogelpoel et al. 2015). FcγRII is a class of low-affinity receptors that require high avidity binding by IgG immune complexes. Of these, FcγRIIA and FcγRIIC are activating receptors, while FcγRIIB is an inhibitory receptor (Guilliams et al. 2014). The activating receptors are involved in intracellular signal transduction via the immunoreceptor tyrosine-based activation motif (ITAM), either accessory (for FcγRI) or present within the receptor cytoplasmic domain (for FcγRIIA), while the inhibitory receptor contains immunoreceptor tyrosine-based inhibitory motif (ITIM) in its cytoplasmic domain (Boonnak et al. 2013). Activating receptors efficiently internalize antibody-opsonized virus, and can be involved in neutralization

or enhancement, depending on the antibody concentration and receptor properties. Fc γ RI being a high-affinity receptor requires significantly less antibody for complete neutralization and thus plays a predominant role in DENV neutralization (Chawla et al. 2013). In contrast, Fc γ RIIA has been shown to be an effective mediator of ADE, with its ITAM-containing cytoplasmic tail playing a crucial role (Boonnak et al. 2013).

The monocytes, which are the major site of DENV infection and replication, express Fc γ RI and Fc γ RIIA at high levels and Fc γ RIIB at intermediate levels. Fc γ RIII is expressed on only ~10% of the monocyte population and has little impact on DENV neutralization or enhancement (van de Winkel and Anderson 1991). Macrophages express Fc γ RI, Fc γ RII, and Fc γ RIII. Dendritic cells express Fc γ RIIA and Fc γ RIIB, but Fc γ RIIB decreases with maturity (Guilliams et al. 2014).

2.4.2.3 Antibody-Mediated Viral Entry into Target Cell

Cells of the mononuclear phagocyte lineage, like monocytes, macrophages, and dendritic cells, are the main targets for DENV infection in humans. Attachment of DENV E protein (EDIII) to putative cell surface receptors such as heparan sulfate, C-type lectins, heat shock protein 70/90, and phosphatidylserine receptors constitutes the first step of viral infection (Castilla et al. 2015; Cruz-Oliveira et al. 2015). This is followed by penetration of the host cell by receptor-dependent, clathrin- and dynamin-mediated endocytic pathway. Acidic pH of the endocytic vesicle then triggers fusion of the viral envelope with the endosomal membrane, thus facilitating virion uncoating and release of the viral genome into the cellular cytoplasm.

During ADE, the antibody-opsonized DENV binds to the Fc γ Rs present on the surface of the target cells and is internalized by Fc γ R-mediated endocytosis/phagocytosis. The entry pathway is similar to that of free virus; however, it shows slight alterations, depending on the cell type as well as the Fc γ R engaged. *In vitro* studies in monocytic cell lines U937 and K562 have shown that Fc γ RII-mediated entry occurs through clathrin-coated vesicles, while Fc γ RI-mediated entry is clathrin-independent. Also, as Fc γ RII translocates into lipid rafts upon immune complex binding, entry via this receptor is affected by the membrane cholesterol content (Carro et al. 2018). In macrophage-like P388D1 cells, antibody-opsonized virus is shown to be internalized by phagocytic uptake facilitated by actin-mediated membrane protrusions which actively search and capture the antibody-bound virus particles, possible by chemotaxis (Ayala-Nunez et al. 2016).

In addition to Fc γ R, other primary cell receptors may also be required for cell penetration. In fact, one theory suggests that Fc γ R plays an auxiliary role in concentrating the immune complexes to the cell surface and viral entry is then mediated by the primary cellular receptors (Chotiwan et al. 2014).

2.4.2.4 Suppression of Innate Antiviral Immune Response in ADE

The suppression of the host antiviral immune response to facilitate higher virus production during ADE of DENV infection was first suggested in 2007 through studies in monocytic THP-1 cells, which revealed upregulation of anti-inflammatory cytokine production (IL-6, IL-10) but downregulation of anti-DENV free radicals (nitric

oxide) and pro-inflammatory cytokine production (IL-12, IFN- γ , TNF- α) (Chareonsirisuthigul et al. 2007). Subsequent studies in THP-1 cells offered further insights into the mechanism of this “intrinsic” DENV-ADE (Ubol et al. 2010; Modhiran et al. 2010; Tsai et al. 2014; Chan et al. 2014). Overall, these studies have suggested Type I interferon and pro-inflammatory cytokine production as the main targets of immune suppression during DENV-ADE, with four mechanisms being proposed for the same: (1) leukocyte immunoglobulin-like receptor B1 (LILR-B1) co-ligation and consequent inhibition of Fc γ R-signaling and Type I interferon-stimulated gene (ISG) expression, (2) downregulation of toll-like receptor (TLR)-dependent antiviral signaling pathway, (3) downregulation of retinoic acid-inducible gene I (RIG-I)/melanoma differentiation-associated antigen 5 (MDA-5) signaling pathway resulting in suppression of Type I interferon (IFN) production, and (4) induction of IL-10 production resulting in suppressor of cytokine signaling 3 (SOCS3)-mediated suppression of pro-inflammatory cytokines important for antiviral response.

Binding of immune complexes to cellular activating Fc γ Rs is known to trigger ITAM-spleen tyrosine kinase (Syk)-signal transducer and activator of transcription 1 (STAT1) signaling pathway which leads to ISG induction and inhibition of viral replication. Inhibition of this Fc γ R-dependent ISG transcription is thus crucial for successful DENV replication and is proposed to be brought about by co-ligation of LILR-B1 by the Fc γ R-bound antibody-opsonized DENV (Chan et al. 2014; Nimmerjahn and Lux 2014). LILR-B1 belongs to a family of ITIM-containing inhibitory receptors and is expressed on immune effector cells including monocytes, macrophages, and dendritic cells. At sub-neutralizing antibody concentrations, the DENV-antibody immune complex binds to two cellular receptors: Fc γ R (through antibody) and LILR-B1 (through DENV E protein). Binding to LILR-B1 recruits Src homology phosphatase-1 (SHP-1) which dephosphorylates and inactivates Syk and prevents ISG expression. SHP-1 signaling also prevents rapid acidification and lysosomal degradation of DENV (Ong et al. 2017). On the contrary, at high antibody concentrations, DENV E protein epitopes are completely blocked by the antibody; consequently, LILR-B1 binding is not possible, resulting in neutralization of the Fc γ R-internalized virus.

The TLR-dependent pathway is a key mediator of the innate antiviral immune response and stimulates production of Type I IFN and pro-inflammatory cytokines via nuclear factor- κ B (NF- κ B) family of transcription factors. Studies using monocytic cell lines and patient peripheral blood mononuclear cells (PBMCs) have shown that this pathway is suppressed during DENV-ADE (Modhiran et al. 2010). Engagement of FcR by DENV-antibody immune complexes or FcR-mediated entry of immune complexes into target cells results in downregulation of expression of TLR-3,-4,-7 and TLR signaling molecules. This is accompanied by activation of Sterile-alpha and Armadillo motif-containing protein (SARM) and TRAF family member-associated NF- κ B activator (TANK), which are negative regulators of the TLR adaptor molecule, TIR-domain-containing adapter-inducing interferon- β (TRIF), and effector molecule, TNF receptor-associated factor 6 (TRAF6), respectively. SARM/TANK activation thus results in suppression of TLR-dependent IFN stimulating pathway.

The RIG-I/MDA-5 antiviral signaling pathway is also downregulated during DENV-ADE, as demonstrated *in vitro* and observed among patients of severe secondary DENV infection (Ubol et al. 2010). Entry of immune complexes into target cells activates the negative regulators, dihydroxyacetone kinase (DAK) and autophagy-related 5–autophagy-related 12 (Atg5-Atg12), which then disrupt the RIG-I/MDA-5 signaling cascade. This results in suppression of Type I IFN production and IFN-mediated antiviral responses.

IL-10 is known to induce T-helper cell 2 (Th2) cytokine response and inhibit production of pro-inflammatory cytokines such as IFN- γ , IL-12, TNF- α as well as nitric oxide radicals, which are potent inhibitors of DENV replication. IL-10 induction during DENV-ADE thus exerts an immunosuppressive effect and favors viral replication. Indeed, high IL-10 levels have been associated with severe disease in secondary dengue patients (Nguyen et al. 2004; Ubol et al. 2010). The mechanism of IL-10-mediated immune suppression has been demonstrated through *in vitro* studies in monocytic cell lines and patient PBMCs. These studies have shown that IL-10 induction during ADE occurs through enhanced Syk-regulated phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB)/glycogen synthase kinase (GSK)-3 β /cyclic adenosine monophosphate response element-binding (CREB) signaling (Tsai et al. 2014). IL-10 then stimulates expression of SOCS3, which subsequently inactivates Janus kinase (Jak)-STAT signaling, resulting in suppression of pro-inflammatory cytokine production. In addition, IL-10 also suppresses inducible nitric oxide synthase (iNOS) gene expression and thus nitric oxide production, by inhibiting STAT-1 and Interferon Regulatory Factor 1 (IRF-1) activity (Chareonsirisuthigul et al. 2007; Ubol et al. 2010).

Majority of the studies elucidating the mechanism of intrinsic ADE have been carried out in monocytic cell lines. Experiments using primary monocyte-derived human macrophages have demonstrated lower IFN- β and higher IL-6 and SOCS3 levels during DENV-ADE, consistent with the observations in monocytic cells (Rolph et al. 2011). However, IL-10 induction and RIG-I/MDA-5 downregulation were not observed. Thus, IL-6 has been proposed as critical regulator of DENV-ADE in macrophages, responsible for SOCS-3-mediated suppression of pro-inflammatory cytokines, indicating that mechanisms of intrinsic ADE may be cell type-dependent.

Contradictory to the well-accepted mechanism of ADE-mediated immune suppression, a recent study observed that entry of DENV immune complexes in primary human macrophages did not trigger immunosuppressive signaling, but resulted in enhanced fusion of viral envelope with the host cell membrane (Flipse et al. 2016). Further investigations into the different mechanisms involved in ADE of DENV infection are thus warranted.

2.4.2.5 Enhancement of Disease Severity: ADE and Cytokine Storm

The extrinsic and intrinsic mechanisms of ADE together contribute to enhancement of viral replication and consequently higher viremia levels, which correlate with the incidence of severe dengue in patients (Vaughn et al. 2000). ADE is also associated with triggering of the “cytokine storm” which involves massive release of

inflammatory cytokines and other chemical mediators at high levels (Pang et al. 2007). ADE of DENV infection and replication results in increased presentation of viral antigens on the surface of infected cells, leading to activation and proliferation of T cells sensitized during a prior infection. This results in release of cytokines such as IFN- γ , TNF- α , IL-2, IL-6, IL1- β , IL-8 and immunoregulators such as IL-12p70, which directly act upon the vascular endothelial cells resulting in plasma leakage, the hallmark of severe dengue. Increased levels of such cytokines have been associated with plasma leakage in severe dengue patients (Chaturvedi et al. 2000), while effect of the cytokine response on alteration of vascular permeability has been demonstrated in vitro and in mice models, with disruption of the apical junction complexes in endothelial cells being the suggested mechanism (Dewi et al. 2004; Appanna et al. 2012; Puerta-Guardo et al. 2013).

2.4.3 Implications for Dengue Vaccines

Generation of a long-term protective immune response against all four serotypes of DENV is a prerequisite for a dengue vaccine and assumes greater importance due to the associated risk of vaccine-induced ADE of DENV infection and disease. During the six-decade long quest for an effective dengue vaccine, several candidates such as live-attenuated, inactivated, recombinant subunit, virus-like particle (VLP)-based, and DNA vaccines have been explored, with Sanofi Pasteur's "Dengvaxia" or CYD-TDV, a chimeric yellow fever 17D-tetravalent DENV vaccine, National Institutes of Health's TV003/TV005, and Takeda Pharmaceutical's TAK-003, both live attenuated tetravalent vaccines, leading the development pipeline (McArthur et al. 2013). Of these, CYD-TDV has been approved for human use and is licensed in 20 countries, while TV003/TV005 and TAK-003 are currently undergoing Phase III trials.

CYD-TDV, the world's first licensed dengue vaccine, was approved by the World Health Organization (WHO) in May 2016, following Phase III trials in dengue-endemic regions (Capeding et al. 2014; Villar et al. 2015; Hadinegoro et al. 2015). These trials had demonstrated high vaccine efficacy among 9–16-year-olds during the first 2 years after vaccine (first of three doses) administration, but indicated increased risk of hospitalized dengue in the 2–5 year age group during the third year of follow-up. These results suggested the possibility of the vaccine sensitizing dengue seronegatives to subsequent enhanced DENV infection and disease. However, considering the population-level benefits in reducing disease burden, the vaccine was approved by WHO Strategic Advisory Group of Experts (SAGE) on immunization, with recommendations for use in dengue-endemic regions with $\geq 70\%$ seroprevalence and administration to individuals in the age range of 9–45 years. This approval was followed by additional studies to investigate the long-term benefit–risk ratio of dengue vaccination in seronegative population. These studies revealed that vaccine performance was indeed affected by serostatus, with vaccine efficacy being significantly higher in seropositives than seronegatives. Furthermore, an increased risk of hospitalized, severe dengue was observed among seronegative

vaccine recipients as compared to seronegative controls (Sridhar et al. 2018). In light of this new evidence regarding vaccine-related ADE, WHO-SAGE issued updated recommendations on the use of CYD-TDV vaccine in April 2018 (Wilder-Smith et al. 2019). For countries considering vaccination as part of their dengue control program, WHO now recommends a “pre-vaccination screening strategy,” in which all potential vaccine recipients are tested for anti-DENV IgG, preferably by ELISA, and only dengue-seropositive persons are vaccinated. Further, for trials of new vaccines, WHO advises stratification of participants according to pre-vaccination serostatus during data analysis, as well as long-term follow-up of all vaccine recipients.

The occurrence of breakthrough infections in the CYD-TDV vaccinees despite having high titers of neutralizing antibodies has raised concerns regarding the value of the currently used *in vitro* neutralization tests as correlates of protection. The neutralizing potential of antibodies is commonly evaluated using the plaque reduction neutralization test (PRNT) in LLC-MK2, Vero, or BHK-21 cell lines. However, neutralization of DENV infection in these Fc γ R-negative cells may not reflect the ability of the antibodies to prevent infection of myeloid cells, which are primary targets of DENV, and capable of internalizing antibody-opsonized DENV through Fc γ R-mediated phagocytosis. The use of Fc γ R-bearing cell lines or primary myeloid cells for *in vitro* neutralization has thus been proposed for measuring the neutralizing versus enhancing ability of anti-DENV antibodies (Mahalingam et al. 2013; Gan et al. 2017). Furthermore, identification of stronger immune correlates for disease risk and protection is urgently needed (Katzelnick and Harris 2017).

While the results of Phase III trials of TV003/TV005 and TAK-003 vaccines are awaited, the concern of vaccine-related ADE has promoted development of vaccines specifically designed to minimize ADE. Monoclonal antibody-based studies have helped identify neutralizing and enhancing viral epitopes, making design of such tailored vaccines possible. DENV EDIII induces predominantly neutralizing antibodies, thus making recombinant EDIII an attractive subunit vaccine candidate (Gil et al. 2017; Frei et al. 2018). DENV NS1 has also been considered as a vaccine candidate as it avoids ADE (Hertz et al. 2017). Chimeric DENV constructs with pr gene replaced with Japanese Encephalitis virus pr and DNA vaccines with substitutions or removal of enhancing epitopes have demonstrated reduction in ADE (Crill et al. 2012; Tang et al. 2015; Wang et al. 2015). Another strategy for evasion of ADE is the development of vaccine candidates inducing protective CD4+ and CD8+ T-cell responses. DENV C protein is an immunodominant T-cell epitope, and C-based vaccines have shown induction of protective T-cell-mediated immunity in monkeys (Gil et al. 2014). Such next-generation vaccines do face the disadvantage of not retaining the intact virion structure and the quaternary epitopes, which are important for potent neutralization. However, these vaccines have shown encouraging results in preclinical studies, and whether they are capable of conferring *in vivo* protection remains to be seen.

2.4.4 Implications for Dengue Therapeutics

Humanized monoclonal antibodies (mAbs) are attractive therapeutic options against DENV infection. Therapeutic mAbs must neutralize DENV, without increasing the risk of ADE, in order to offer protection against dengue. Several mAbs targeting the DENV E and/or prM proteins are being developed as therapeutic candidates, with reduction of ADE as the major focus of development (Chan et al. 2013; Sun et al. 2018). Use of serotype-specific mAbs or high dose administration of cross-reactive mAbs has demonstrated reduced risk of ADE in vitro and in animal models. Further, antibodies with modifications in the Fc region such as deletion of nine amino acids (at positions 231–239) in the N terminus, mutation of asparagine to glutamine at position 297 (N297Q), or mutation of leucine to alanine at positions 234 and 235 (LALA mutants) have also shown reduced risk of ADE and exhibited prophylactic and therapeutic efficacy in animal models (Balsitis et al. 2010; Shi et al. 2016; Xu et al. 2017; Injampa et al. 2017; Lu et al. 2018). Fc region modifications that extend the antibody half-life also help minimize ADE by maintaining the mAbs at high levels.

2.4.5 ADE in Other Flaviviruses

ADE has also been reported in other viruses of family *Flaviviridae* including Murray Valley Encephalitis virus, Japanese encephalitis virus (JEV), West Nile virus (WNV), yellow fever virus (YFV), and Zika virus (ZIKV) of genus *Flavivirus*, as well as hepatitis C virus (HCV), of genus *Hepacivirus* (Hawkes and Lafferty 1967; Cardoso et al. 1983; Gould and Buckley 1989; Meyer et al. 2008; Bardina et al. 2017). Further, infection with one *Flavivirus* has also been demonstrated to enhance subsequent infection with another virus of the same genus, as observed for DENV-ZIKV in in vitro studies, mice models, and rhesus macaques (Bardina et al. 2017; George et al. 2017). Such DENV-ZIKV cross-enhancement has also been observed in primary human PBMCs (Li et al. 2018); however, in the absence of clinical or epidemiological evidence, the clinical relevance of these findings is unknown. Interestingly, a beneficial effect of cross-enhancement among flaviviruses has been reported recently in a clinical trial, with preexisting JEV vaccine-induced antibodies enhancing immunogenicity of subsequently administered YFV vaccine (Chan et al. 2016).

2.5 Human Immunodeficiency Virus

Human immunodeficiency virus (HIV), a member of family *Retroviridae*, genus *Lentivirus*, is primarily a sexually transmitted virus, but nonsexual transmission through intravenous inoculation or mother-to-child exposure can also occur. HIV infects the CD4+ T cells leading to their progressive depletion and thus hampers the host adaptive immune response. The final stage of HIV infection is acquired

immunodeficiency syndrome (AIDS), characterized by immune system failure and occurrence of life-threatening opportunistic infections. As of 2016, ~37 million people worldwide have been estimated to be living with HIV (Ghosh et al. 2018). While a protective vaccine or a complete cure of HIV infection remains elusive, implementation of combination antiretroviral therapy (cART) has been successful in prolonging the duration between HIV infection and AIDS and reducing AIDS-related deaths.

2.5.1 ADE of HIV Infection: Experimental Evidence and Molecular Mechanism

ADE of HIV infection was first reported in the 1980s, shortly after the identification and isolation of HIV, and two different mechanisms, namely, complement-mediated ADE (C-ADE) (Robinson Jr. et al. 1987, 1988) and FcR-mediated ADE (FcR-ADE) (Takeda et al. 1988; Homsy et al. 1989), were described. Through either of these mechanisms, virus-specific antibodies present in sera of HIV-infected individuals were shown to enhance viral entry and in some cases replication within T cells, monocytes/macrophages, and granulocytic cells (Beck et al. 2008). Further, both these mechanisms have also been shown to enhance HIV infection of human syncytiotrophoblast cells, thus suggesting contribution of ADE to materno-fetal transmission (Tóth et al. 1994). Both these forms of ADE are mediated by antibodies targeting the viral surface glycoproteins gp41 and gp120 (Trischmann et al. 1995; Takada and Kawaoka 2003). Such enhancing antibodies have been detected in 72% of HIV patients (Subbramanian et al. 2002).

C-ADE of HIV infection has been well characterized through *in vitro* studies in T-cell lines such as MT-2 and SupT1/R5, showing enhancement of cell line-adapted HIV strains or primary virus isolates by human monoclonal antibodies or sera from HIV-infected individuals, and has been associated with increased synthesis of viral RNA and protein and enhanced release of infectious virions (Robinson Jr. et al. 1989, 1990a, b; Robinson Jr. 2006; Willey et al. 2011). Such C-ADE is primarily mediated by antibodies targeting the N-terminal immunodominant domain of viral gp41. Antibody binding to gp41 initiates the complement cascade leading to deposition of complement component C3d,g on the virion. Interaction of this opsonized virus with the cell surface complement receptor type 2 (CR2) facilitates virus attachment and internalization. Engagement of the HIV receptor CD4 and co-receptor CXCR4 is also required for this mode of virus uptake. Increased attachment of the virus to target cell, rather than CR2-mediated signaling, has been suggested to be responsible for enhancement of infection through C-ADE. An alternative route of complement component C1q binding followed by interaction with C1q receptor has also been suggested for C-ADE (Prohaszka et al. 1997).

FcR-ADE has been demonstrated *in vitro* mainly in monocyte/macrophage cell lines and primary cultures, with all three classes of Fc γ R, namely, Fc γ RI, Fc γ RII, and Fc γ RIII, reported to support ADE (Homsy et al. 1989; Takeda et al. 1988, 1990; Laurence et al. 1990; Connor et al. 1991; Trischmann et al. 1995). ADE by Fc γ RI

and FcγRII requires viral interaction with CD4, indicating that the FcRs facilitate virus entry by potentiating attachment to CD4 receptors. Alternatively, FcR-mediated endocytosis of virus–antibody complexes followed by intracellular fusion with endosomal membrane occurring as a result of binding of virus with CD4 receptors on the endosomal membranes has also been suggested. FcγRIII-mediated ADE has been shown to be CD4-independent. FcR-ADE assumes particular importance in the viral life cycle as it mediates infection of macrophages, which are important for maintaining a viral reservoir during persistent infections.

Another mechanism of complement-independent, FcR-independent ADE, mediated by antibodies specific to viral gp120, has been described (Sullivan et al. 1998; Guillon et al. 2002). Antibody binding has been shown to modulate interaction of gp120 with HIV co-receptor CCR5 or induce conformational changes in gp120, leading to its activation and subsequent promotion of membrane fusion. Further, FcαR-mediated ADE has also been reported, with human serum IgA showing low-level enhancement of HIV replication in vitro (Janoff et al. 1995; Kozlowski et al. 1995).

An important feature of HIV is the rapid viral evolution during chronic infection. While neutralizing antibodies are known to exert a selection pressure facilitating emergence of neutralization escape mutants, enhancing antibodies have been suggested to favor emergence of ADE-susceptible variants. Indeed, at later stages of infection, patient sera have demonstrated increased proportion of enhancing antibodies and potential for ADE, while virus strains isolated at such later stage have exhibited increased susceptibility to ADE in vitro (Davis et al. 2001; Subbramanian et al. 2002; Willey et al. 2011).

2.5.2 Clinical Significance of HIV-ADE

The HIV disease outcome is suggested to be influenced by the balance of neutralizing and enhancing antibodies in HIV patients, with studies showing lower neutralizing and higher enhancing antibody levels among AIDS patients (Homsy et al. 1990; Toth et al. 1991; Fust et al. 1994; Szabo et al. 1999; Subbramanian et al. 2002). These studies have observed strong negative correlation between the extent of ADE and CD4 cell count and positive correlation between ADE and plasma viral load in HIV-positive individuals. As CD4 cell count and HIV plasma viral load are considered the most potent predictors of HIV disease progression, such observations indicate contribution of ADE to accelerated immunosuppression and disease progression. Further support for this association was provided by reports of decline in enhancing antibody levels and improvement in disease prognosis in patients receiving highly active antiretroviral therapy (HAART) (Banhegyi et al. 2003). Contradictory observations of absence of any clinical correlation between ADE and disease have also been reported (Montefiori et al. 1991); however, it has been suggested to be the result of conduction of experiments in conditions which do not sufficiently resemble in vivo conditions (Takada and Kawaoka 2003; Beck et al. 2008).

2.5.3 Implications for HIV Vaccines

The impact of ADE on HIV vaccine safety is not clearly understood. Studies in Rhesus monkeys have demonstrated the association of active and passive immunization with enhanced disease progression on subsequent infection (Staprans et al. 2004; Sholukh et al. 2014). In humans, ADE has been indicated in two vaccine clinical trials. In the AIDSVAX trial, the rate of HIV infection was observed to be higher among vaccinees with low (non-protective) antibody responses (Gilbert et al. 2005). In the RV144 trial, positive correlation of vaccine-elicited plasma IgA responses with risk for HIV acquisition was documented (Shmelkov et al. 2014). Further, a study investigating the effect of passive immunization of HIV-positive pregnant women on mother-to-infant transmission suggested the possibility of antibody-enhanced in utero transmission (Onyango-Makumbi et al. 2011). These findings are suggestive of vaccine-induced ADE, but cannot confirm the same. Assays capable of estimating neutralizing and enhancing potential of immune serum, such as those involving use of complement and complement receptor carrying target cells for C-ADE, have been proposed for a better understanding of the clinical relevance of vaccine-related ADE. Such assays would also provide stronger immune correlates during preclinical and clinical studies. Further, design of vaccine immunogens that will elicit protective and not enhancing antibodies, by avoiding inclusion of known enhancing epitopes, has been put forth as a mitigation strategy for HIV-ADE (Beck et al. 2008).

2.6 Influenza Virus

Influenza is a highly communicable acute respiratory disease caused by infection with influenza virus of family *Orthomyxoviridae*. The disease is a serious health threat of epidemic and pandemic proportions, with severe cases associated with pneumonia and lung tissue damage. Influenza A viruses are the most common in human infections and are further classified into subtypes on the basis of the two surface proteins, hemagglutinin (H) and neuraminidase (N), with 18 H and 11 N subtypes identified (Shao et al. 2017). Influenza A virus undergoes rapid evolution due to mechanisms such as antigenic drift, shift, and genetic reassortment, resulting in periodic emergence of novel viral strains. Annual vaccination against the circulating viral strain is thus implemented for protection against the disease.

Epithelial cells of the respiratory tract are the primary targets of influenza virus infection; however, in vitro ADE of this virus has been reported in primary macrophages and macrophage-like cell lines (P388D1), under the presence of monoclonal antibodies, mice, rabbit, or human immune sera (Ochiai et al. 1988, 1990, 1992; Tamura et al. 1991, 1994; Gotoff et al. 1994). Engagement of Fc γ Rs by antibodies specific to viral HA and NA has been shown to mediate virus uptake, with subtype cross-reactive non-neutralizing antibodies being particularly involved in infection enhancement of heterotypic viruses (different HA/NA type). While such internalization usually results in abortive infection of macrophages, productive replication in

these cells has been shown to be possible in the presence of appropriate protease for HA cleavage. Increased presentation of viral antigens by the infected macrophages leading to augmented virus-specific T-cell activation is also suggested to contribute to viral pathogenesis. Enhancement of virus fusion by anti-HA2 subunit antibodies is another mechanism of influenza-ADE and has been shown to be responsible for the occurrence of vaccine-associated enhanced respiratory disease (VAERD) in pigs immunized with inactivated H1N2 vaccine and challenged with pandemic 2009 H1N1 virus (Gauger et al. 2011; Khurana et al. 2013). Influenza-ADE is also suggested by epidemiologic observations in humans. Retrospective analysis of medical records from the 1918 influenza pandemic revealed association of prior influenza-like illness with increased risk of medically attended illness during the pandemic period (Shanks et al. 2016). More recently, prior receipt of seasonal influenza vaccine was found to increase the risk of medically attended pandemic H1N1 illness during 2009 in Canada (Skowronski et al. 2010). Furthermore, presence of high titer non-protective serum antibodies was associated with immune complex-mediated severe H1N1 illness during this pandemic (Monsalvo et al. 2011; To et al. 2012).

Observation of VAERD in pigs and ferrets immunized with inactivated or HA subunit vaccines raises concern regarding the safety of vaccines, particularly universal influenza vaccines (Gauger et al. 2011; Khurana et al. 2013; Rajao et al. 2014; Skowronski et al. 2014). However, vaccine-mediated protection and absence of VAERD is also reported in few studies in pigs, suggesting that vaccine-induced ADE occurs only in certain conditions, which are not yet clearly understood (Reeth et al. 2004; Kyriakis et al. 2010; Ricklin et al. 2016). Regarding therapeutic candidates, Phase 2 studies of anti-HA stalk mAbs have indicated possibility of enhanced viral shedding in some treated human subjects. Screening for high potency protective antibodies, defining optimal dose range for effective neutralization, using cocktails of mAbs with different antigen specificities, has been suggested for mitigation of ADE (Chan-Hui and Swiderek 2016).

2.7 Respiratory Syncytial Virus

Respiratory syncytial virus (RSV), a member of family *Paramyxoviridae*, genus *Pneumovirus*, is the leading cause of lower respiratory tract infections among infants and young children worldwide, with severe disease requiring hospitalization occurring most frequently between 6 weeks and 6 months of life (Glezen et al. 1986; Hall et al. 2009). RSV disease is also a major health problem in adults and the elderly. Severe bronchiolitis is one of the major outcomes of RSV infection.

Observation of enhanced disease among children receiving the formalin-inactivated RSV (FI-RSV) vaccine in the 1960s (Kim et al. 1969), as well as the frequent occurrence of severe disease among infants <6 months of age, when maternal antibodies are present, prompted investigations on ADE of RSV infections. Subsequently, enhancement of RSV infection by RSV-specific monoclonal antibodies and human immune sera was demonstrated in vitro in monocytic (U937, THP-1) and macrophage-like (P388D1) cell lines (Gimenez et al. 1989, 1996; Krilov et al.

1989; Osiowy et al. 1994). The phenomenon has also been reported in Bonnet monkeys developing enhanced disease following FI-RSV immunization (Ponnuraj et al. 2001, 2003). Fc γ R-mediated internalization of immune complexes is the suggested mechanism, with antibodies against the viral surface glycoproteins, the attachment glycoprotein (G) and fusion glycoprotein (F), playing an important role. Although epithelial cells of the respiratory tract are primary targets of RSV infection, it has been suggested that alveolar macrophages are infected through ADE, resulting in activation of Th2 response and increased expression of TNF- α , IL-6, thus causing enhanced disease (Gimenez et al., 1996). Further, ADE-mediated infection of lung dendritic cells (DCs) has been demonstrated to negatively modulate DC cell function, resulting in impaired T-cell activation, and has been suggested to contribute to RSV pathogenesis (Gomez et al. 2016). However, the clinical effects of RSV-ADE still remain unclear with different studies reporting contradictory observations regarding the association of maternal antibody-induced ADE and disease severity in infants (Chanock et al. 1970; van Erp et al. 2017).

Enhanced RSV disease in FI-RSV vaccine recipients was initially attributed to vaccine-induced ADE; however, recent studies have suggested a role of other mechanisms involving T cells (Huisman et al. 2009). Whether ADE would affect the efficacy of other RSV vaccines in development remains to be seen. As far as immunotherapeutics are concerned, the F protein-specific humanized monoclonal antibody, Palivizumab, is the only clinically approved intervention. This mAb has demonstrated ADE at sub-neutralizing concentrations in vitro, yet has been found to have a protective effect in animal models and humans (TI-RS Group 1998; Mejias et al. 2004; van Mechelen et al. 2016).

2.8 Ebola Virus

Ebola virus is a member of family *Filoviridae*. Of the four Ebola virus species infecting humans, *Zaire ebolavirus* (EBOV) is the most virulent and is the causative agent of a severe hemorrhagic fever disease, Ebola virus disease (EVD), with a fatality rate of ~90% (Feldmann and Geisbert 2011). The disease is zoonotic, with initial cases occurring due to contact with infected fruit bats (reservoir) or their contaminated material, followed by human-to-human transmission. The virus is mainly endemic in Africa; however, due to its increased incidence and fast spread, as observed during the 2014–2016 African outbreak, the virus is considered a pandemic threat.

ADE of Ebola virus infection has been demonstrated in vitro in a variety of cell lines and is shown to be mediated by antibodies specific to the viral envelope glycoprotein (GP) (Takada et al. 2001, 2003, 2007). Such enhancing antibodies have been identified in the sera of EVD patients (Takada et al. 2003; Furuyama et al. 2016). Two different mechanisms have been proposed for ADE of EBOV infection: (a) Fc γ R-mediated ADE and (b) C1q-mediated ADE. In Fc γ R-mediated ADE, antibody–virus complexes bind cell surface Fc γ RIIA triggering phosphorylation of Src family protein tyrosine kinases (PTKs) and activation of Src signaling pathways

leading to virus uptake through phagocytosis and/or micropinocytosis (Furuyama et al. 2016). C1q-mediated ADE involves interaction of virus-bound antibodies with complement component C1q and subsequent attachment to cell surface C1q receptors, leading to virus internalization by C1q receptor-mediated endocytosis or via virus-specific receptor (Takada et al. 2003, 2007). C1q receptors are present on monocytes/macrophages, which are primary targets of EBOV, as well as most other mammalian cells, including endothelial cells, epithelial cells, and hepatocytes. C1q-ADE mediated dissemination of EBOV infection to these “secondary target cells” has been suggested to exacerbate disease.

Although clinical relevance of EBOV-ADE is not yet understood, repeated *in vitro* demonstrations raise concerns regarding safety of vaccines and immunotherapeutics. Several candidate vaccines under development have demonstrated protective efficacy in preclinical studies and immunogenicity in clinical trials (Dhama et al. 2018). The protective effect of these vaccines seems to depend on cytotoxic T-cell responses. Avoiding induction of known infectivity-enhancing antibodies while retaining T-cell epitopes should thus be considered during vaccine design. For immunotherapy, the use of well-characterized mAbs instead of polyclonal convalescent human serum has been suggested to reduce ADE.

2.9 Severe Acute Respiratory Syndrome: Coronavirus

Severe acute respiratory syndrome (SARS) is a respiratory disease caused by SARS-coronavirus (SARS-CoV) of family *Coronaviridae*, which caused outbreaks mainly in China, during 2002–2003. Although public health measures successfully contained further spread and human outbreaks, future reemergence of SARS-CoV or other related viruses remains a credible threat due to the zoonotic origin of this virus.

ADE of SARS-CoV infection was first demonstrated *in vitro* in human B cells using sera from immunized animals as well as convalescent patients (Kam et al. 2007). Further studies showed that antibodies specific to the viral surface spike glycoprotein (S) are capable of enhancing viral infection of immune cells, particularly monocytes and macrophages, thus allowing the virus to broaden its cellular tropism (Jaume et al. 2011; Wang et al. 2014; Yip et al. 2014). Internalization of the immune complexes by cellular FcγRs, mainly FcγRIIA, is the suggested mechanism, with intracellular signaling by the FcγR cytosolic domain playing an important role. This FcγR-mediated internalization follows a pH- and cysteine protease-independent pathway and differs from the endosomal/lysosomal pathway utilized by angiotensin I-converting enzyme 2 (ACE2), the accepted receptor for SARS-CoV. Such antibody-mediated infection of macrophages, however, was not found to support productive virus replication or modify expression of cytokines/chemokines (Yip et al. 2016). Although demonstrated recently in rhesus monkeys (Wang et al. 2016), the occurrence of SARS-ADE and its association with disease severity in humans are still debated, with different clinical studies reporting both

protective and disease-enhancing effects of anti-SARS-CoV antibodies (Lee et al. 2006; Zhang et al. 2006).

2.10 Chikungunya Virus

Chikungunya virus (CHIKV) is an arbovirus belonging to family *Togaviridae*, genus *Alphavirus*. The virus is recognized as a significant global health threat since the last decade. It is primarily transmitted through the bite of infected *Aedes* mosquitoes, *Aedes aegypti* and *Aedes albopictus*. CHIKV infection is associated with a febrile illness accompanied by myalgia, arthralgia, and cutaneous rash (Kam et al. 2009). Debilitating persistent polyarthralgia is the characteristic feature of Chikungunya disease.

ADE of CHIKV infection was suggested by the association of low titers of anti-CHIKV IgG in immunized mice with the early onset of disease upon subsequent CHIKV challenge (Hallengard et al. 2014). Another recent study observed enhanced attachment of CHIKV to primary human monocytes and B cells and increased viral replication in the murine macrophage cell line, RAW264.7, in the presence of anti-CHIKV antibodies (Lum et al. 2018). Further, this study also detected higher viral RNA load and enhancement of disease severity in mice infected with CHIKV in the presence of sub-neutralizing concentrations of antibody, thus providing the first evidence for ADE of CHIKV infection and disease. The enhancement was found to be Fc γ R-mediated, with Fc γ RII playing a predominant role. However, ADE of CHIKV infection has not been reported to date in humans, and thus, the clinical significance of these findings remains unknown and warrants further investigation.

2.11 Concluding Remarks

Virus-specific antibodies function to neutralize virus infection and are an important component of the host antiviral immune response. However, under sub-neutralizing or non-neutralizing conditions, the antibodies are capable of enhancing viral infection by providing an alternative route of virus entry into host cells. This phenomenon of antibody-dependent enhancement facilitates viral infection of a larger number of primary target cells and also allows viral entry into otherwise non-susceptible secondary target cells, thus broadening the virus tropism. Moreover, ADE also modulates the host intracellular signaling pathways, thereby turning down the antiviral immune response. Together these mechanisms serve to augment viral replication and pathogenesis, with the balance between neutralizing and enhancing antibodies influencing the outcome of viral infection and disease.

ADE has been demonstrated in vitro and in animal models for a number of viruses including DENV, HIV, influenza, RSV, Ebola, SARS-CoV, and CHIKV. While the occurrence of DENV-ADE in humans and its association with severe disease have been clearly demonstrated, the clinical relevance of ADE in other viruses is not completely understood. Nevertheless, ADE remains a concern in

development and use of vaccines and immunotherapeutics against these viruses. Recent advances in identification of neutralizing and enhancing viral epitopes are expected to guide future design of non-enhancing, protective viral vaccines and therapeutic mAbs. Comprehensive evaluation of humoral and cell-mediated immune response to vaccines in preclinical and clinical studies, with the help of robust assays that can detect ADE, is suggested to be crucial for the assessment of vaccine safety and efficacy. Such evaluations would require a better understanding of the immune correlates of protection. Lastly, investigation of long-term effects of vaccine implementation is advisable while considering approval for future vaccines.

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