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Review

Antibody response to dengue virus

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Abstract

In this review, we discuss the current knowledge of the role of the antibody response against dengue virus and highlight novel insights into targets recognized by the human antibody response. We also discuss how the balance of pathological and protective antibody responses in the host critically influences clinical aspects of the disease.

Keywords: Dengue virus; Antibody response; Antibody-enhanced infection

1. Introduction

Dengue disease is caused by the bite of mosquito (*Aedes aegypti* or *Aedes albopictus*), infected with dengue virus (DENV) serotypes 1–4, which belong to the *Flavivirus* genus. These four serotypes cause dengue fever (DF) and more severe disease manifestations, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). DF is a febrile, acute disease characterized by headache, myalgia, arthralgia, and severe retro-orbital pain. In contrast, DHF presents with hemorrhagic manifestations, thrombocytopenia, and plasma leakage, which may lead to hypotensive shock (DSS) and death.

Approximately 50–100 million cases of DF are reported every year, and 2.5–3 billion people are at risk of acquiring DF throughout the world. Indeed, DF represents an important public health problem in all tropical and subtropical regions of Asia and the Americas [1].Considerable efforts have been directed toward developing a safe vaccine, and several strategies have focused on the development of DENV recombinant vaccine subunits expressed in different expression systems. Moreover, different strategies have been implemented to develop carrier molecules that elicit a robust immune response [2,3]. However no effective vaccine for dengue is currently available [4,5].

After a mosquito bites a human host, different resident cells present in the skin may be infected with DENV, including Langerhans cells, keratinocytes, and fibroblasts. While the roles of the latter two cell types in DENV remain to be elucidated, dendritic cells have been shown to spread the infection from the skin to the lymph nodes, where monocytes, macrophages, or resident dendritic cells become infected. The virus possesses a lipid envelope and a positive-strand RNA genome of 10.7 kb, which encodes a polypeptide precursor that is proteolytically cleaved into structural proteins, i.e., capsid (C), pre-membrane (prM), and envelope (E) proteins, and non-structural proteins, i.e., NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. After infection, the virus enters into the cell through receptor-mediate endocytosis [6,7].Under acidic pH in the endosomal vesicles, the protein E of the virus

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undergoes conformational changes to promote fusion with the endosomal membrane. The virus is then uncoated, and the single-stranded RNA (ssRNA) escapes into the cytoplasm and initiates translation and simultaneous genome replication in the membrane vesicles of the endoplasmic reticulum (ER). Viral RNA then associates with C protein and assembles with prM and E proteins in membranes derived from the ER. Immature virions bud into the lumen of the ER and are transported through the secretory pathway [6,8–10].When the immature virus arrives in the trans-Golgi, the protease furin, encoded by the host genome, cleaves prM protein into the membrane (M)protein and pr-peptide, yielding mature virions [9,11,12].DENV also induces the remodeling and redistribution of distinct membrane structures to obtain a platform for viral RNA replication, assembly, and spreading [8,11].

According to the oligomeric state and arrangement of E proteins on the surface of the virion, virus particles can be classified as immature or mature. Immature virions (spiky) contain the prM protein, which is about 600 Å, and this protein must be proteolytically processed in the Golgi, yielding mature particles that, combined with the E protein, provide the virus with a smooth outer layer. Interestingly, both immature and mature virions are observed during viral propagation [12,13].

Recent studies using electron tomography have demonstrated that viral replication occurs on double-membrane vesicles adjacent to the ER. Furthermore, image analyses have shown physical linkages between the sites of DENV replication and assembly [8,14].

2. Initiation of the immune response against DENV

Both the innate and adaptive immune responses participate in the control of dengue disease. Thus, the skin participates in the rapid initiation of innate host defenses, and this event may prevent DENV infection. In the skin, both infiltrating cells (such as macrophages, neutrophils, dendritic cells, and lymphocytes) and resident cells (such as keratinocytes and fibroblasts), which are abundantly localized in the epithelium, participate in the production of various types of cytokines, establishing a pro-inflammatory microenvironment with antimicrobial activity against arthropod-borne pathogens, such as DENVs [15].

Little is known about the events that occur in the skin in the very early stages after mosquito feeding. However, cumulative data have shown that DENV is sensed by both Toll-like receptors (TLRs) TLR3 and TLR7 [16]. Wang et al. demonstrated that plasmacytoid dendritic cells (pDCs) constitutively express TLR7 and elicit responses through interferon (IFN) regulatory factor IRF7, leading to IFN-α/β production in response to DENV [17]. In contrast, human umbilical vein endothelial cells (HUVECs) and U937 cells infected with DENV produce interleukin (IL)-8 and IFN-α/β after viral recognition through TLR3 [18].Cytoplasmic molecules, such as retinoic acid-inducible gene 1 (RIG-1) and melanoma differentiation-associated protein 5 (MDA5) have been shown to play an important role in sensing different flaviviruses, including DENV, as demonstrated by Bustos et al. [15].

The IFN response is one of the early mechanisms of host defense that contributes significantly to innate immunity. The IFN system includes cells that synthesize IFN in response to viral infection. Thus induction of IFN-α/β is one of the early events following viral infection and is widely accepted as the most immediate and important antiviral host response to many viral infections [19].

The adaptive immune response also plays an important role in DENV infection, working to resolve infection and prevent re-infection. However, the antibody response to DENV infection is very complex and unpredictable and can either benefit or harm the host. Multiple studies have established that protection against DENV is mediated by neutralizing antibodies; thus, infection with anyone of the four DENV serotypes induces a strong, long-lasting antibody response against the homologous serotype, but only short-term protection against heterologous viruses. Furthermore, during a secondary infection by different serotypes of DENV, heterotropic immunity may promote acquisition of the severe forms of dengue, which is associated with antibody-enhanced infection (ADE)or the cytokine storm [20,21], (i.e., preformed polyspecific IgM antibodies that are not shaped by somatic hypermutation or class switching).

3. Antigenic DENV proteins and structure

DEN V is a small virus of approximately 50 nm and is composed of C protein, which associates with viral RNA and the lipid envelope where the E and prM proteins are associated. When the virus infects the host and viral replication starts the proteins that are immediately in contact with the host are the E and prM proteins. Thus, the main targets of the immune response in individuals infected with DENV are the E and prM proteins [22].

After replication, NS1 is expressed and becomes a target of the immune system. However, these three proteins (i.e., E, prM, and NS1; Fig. 1) seem to be involved in both protection and pathogenesis. Immune responses have also been shown to target other non-structural proteins, albeit with reduced intensity and frequency [23].

The E glycoprotein has a molecular weight of about 55 kDa and is present in all four serotypes of DENV. It is compound of 495 amino acids and contains two transmembrane helixes and 12 conserved cysteine residues, which form a dimer. The amino acid residues of the E protein are well conserved, with high similarities (between 90% and 96%) among the four different serotypes. The amino acid sequence of this protein defines each DENV serotype. The E protein performs critical functions such as mediating interactions with the host cell and fusion of viral and cellular membranes during viral entry. The mature virion contains 90 homodimers of the E protein, arranged in a head-to-tail orientation on the surface of the virion [8,11,12]. Based on crystallography studies, the monomeric E protein folds itself into three distinct structural and functional domains, with residues1–395 forming the ectodomain. The