Immunopathogenesis of Dengue Virus Infection

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Abstract
Dengue virus infection causes dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS), whose pathogeneses are not clearly understood. Current hypotheses of antibody-dependent enhancement, virus virulence, and IFN-\(\gamma\)/TNF\(\alpha\)-mediated immunopathogenesis are insufficient to explain clinical manifestations of DHF/DSS such as thrombocytopenia and hemoconcentration. Dengue virus infection induces transient immune aberrant activation of CD4/CD8 ratio inversion and cytokine overproduction, and infection of endothelial cells and hepatocytes causes apoptosis and dysfunction of these cells. The coagulation and fibrinolysis systems are also activated after dengue virus infection. We propose a new hypothesis for the immunopathogenesis for dengue virus infection. The aberrant immune responses not only impair the immune response to clear the virus, but also result in overproduction of cytokines that affect monocytes, endothelial cells, and hepatocytes. Platelets are destroyed by crossreactive anti-platelet autoantibodies. Dengue-virus-induced vasculopathy and coagulopathy must be involved in the pathogenesis of hemorrhage, and the unbalance between coagulation and fibrinolysis activation increases the likelihood of severe hemorrhage in DHF/DSS. Hemostasis is maintained unless the dysregulation of coagulation and fibrinolysis persists. The overproduced IL-6 might play a crucial role in the enhanced production of anti-platelet or anti-endothelial cell autoantibodies, elevated levels of tPA, as well as a deficiency in coagulation. Capillary leakage is triggered by the dengue virus itself or by antibodies to its antigens. This immunopathogenesis of DHF/DSS can account for specific characteristics of clinical, pathologic, and epidemiological observations in dengue virus infection.

Introduction
Dengue fever (DF) is an acute infectious disease caused by the dengue virus, which has four serotypes. It is characterized by biphasic fever, myalgia, headache, pain in various parts of the body, rash, lymphadenopathy, and leukopenia [6, 10, 22]. In most cases, DF is self-limited. However, there is a risk of progressive development into dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). DHF is a severe febrile disease characterized by abnormalities in hemostasis and increased vascular permeability, and severe progression may result in DSS. DSS is a form of hypovolemic shock that is associated clinically with hemoconcentration and which might
lead to death if appropriate care is not given. Although DF is distinct from DHF/DSS by traditional classification, the various clinical manifestations after dengue virus infection show a continuum from mild to severe reactions, just as in many other viral diseases. The mechanisms involved in the pathogenesis of dengue virus infection, especially the manifestation of DHF/DSS, remain unresolved. An explanation of the pathogenesis of dengue virus infection must account for specific characteristics of clinical, pathologic, and epidemiological observations.

Current Hypotheses on the Pathogenesis of Dengue Virus Infection

Several hypotheses for the pathogenesis of dengue virus infection have been proposed. Among them, antibody-dependent enhancement (ADE) of infection has long been thought to play a central role [18, 19]. The ADE hypothesis was formulated to explain the finding that severe manifestations of DHF/DSS occur in children experiencing a second dengue virus infection that has a different serotype from the previous one. There are indeed preexisting antibodies to previous dengue virus that cannot neutralize but rather enhance infection in vitro. Sera obtained before infection from children who later developed DHF/DSS were much more likely to demonstrate ADE in vitro than those who had only DF [34]. Newborn babies less than 1 year old who acquire maternal anti-dengue IgG antibody are also susceptible to developing DHF/DSS following primary infection [33]. Epidemiological studies support the association of DHF/DSS with secondary dengue virus infection. However, the association of DHF/DSS with prior immunity to other dengue serotypes by itself explains neither the pathogenetic basis of the association nor the molecular mechanism of DHF/DSS clinical manifestations. It is not known how augmentation of dengue virus infection by enhancing antibodies leads to DHF/DSS. Whether it increases the number of dengue-virus-infected cells or enhances the signal through the Fc receptor remains to be elucidated. As there is no animal model of DHF/DSS, the causal relationship between ADE and DHF/DSS remains unverified [8].

Immunopathogenesis in DHF has been proposed [36, 63]. Serotype crossreactive antibodies from the previous infection bind to virions without neutralization and enhance the entry of virus into monocytes. The number of virus-infected monocytes increases. As a result, the level of T-cell activation is markedly increased, reflecting the increased antigen presentation, the increased frequency of dengue-virus-specific T cells in secondary infection, and the more rapid activation and proliferation of memory T cells. These T cells produce cytokines such as IFN-γ, IL-2, and TNFα, and lyse dengue-virus-infected monocytes. TNFα is also produced by activated monocytes. The complement cascade is activated by a virus-antibody complex as well as by several cytokines to release C3a and C5a that also have direct effects on vascular permeability. The synergistic effects of IFN-γ, TNFα, and activated complement proteins trigger plasma leakage of endothelial cells in secondary dengue virus infection. However, several issues remain unexplained by this theory. Not all DHF/DSS cases are secondary infections. Complement activation may be the result of severe disease, not the cause of DHF/DSS. Most importantly, DHF develops rapidly, usually over a period of hours, and resolves within 1-2 days in patients who receive appropriate fluid resuscitation. No discernible sequelae are usually found. This scenario is not easily reconciled with the known tissue-destructive effects of inflammatory cytokines.

Viruses virulence, the capacity of a virus to produce disease in a host, is an alternative hypothesis for the pathogenesis of DHF/DSS. The different manifestations of DF, DHF, and DSS may be caused by variants of dengue virus with different degrees of virulence. The risk of DHF/DSS is higher in secondary infections with dengue virus of serotype 2 compared to the other serotypes [59, 60]. Structural differences have also been found among various isolates of DF and DHF patients [41]. Furthermore, it was reported that high dengue viremia titer was associated with increased disease severity [68-70]. Peak viral titers were 100- to 1,000-fold higher in patients with DSS than those with DF in dengue-infected Thai children. Patients with a secondary antibody response were twice as likely to have DHF, compared with those with a primary antibody response. Apparently, viral load is also a contributing factor in the development of DHF/DSS. Whether viral load is reflective of its virulence or its high growth rate in vivo requires further investigation.

Clinical and Pathologic Manifestation of Dengue Virus Infection

DF is an acute febrile illness with headache, retro-orbital pain, myalgia, arthralgia, rash, leukopenia, and mild thrombocytopenia. Biphasic fever and rash are the most characteristic features of classic dengue fever. Symptoms resolve after 2-7 days. Dengue hemorrhagic fever is an acute vascular permeability syndrome accompanied by...