Dengue has become a globally important mosquito-borne infectious disease. It is estimated that more than 50 million of people are affected by dengue every year. Although dengue is not considered endemic in Taiwan, several outbreaks have occurred, especially in southern Taiwan, in the past decades. The most recent dengue epidemic in 2012 also involved more than 1000 cases by mid-November in Tainan (>650 cases) and Kaohsiung cities (>350 cases) of southern Taiwan.

Dengue virus infection causes a broad spectrum of disease ranging from mild or dengue fever (DF) to severe or dengue hemorrhagic fever (DHF). The progression from mild DF to severe DHF and dengue shock syndrome (DSS) is not predictable and current treatment is with supportive fluid resuscitation. Major global efforts on mosquito control for preventing dengue infection are so far expensive and ineffective. In other efforts to develop vaccines, live attenuated candidates have advanced to Phase 2 and 3 clinical trials.

Dengue is a systemic arthropod-borne viral disease of major global public health concern. Enhancing knowledge, attitudes, and practice among primary healthcare professionals (HCPs) dealing with dengue will safeguard against alarm and improve dengue therapy and control. Intensifying medical/nursing education to strengthen familiarity with important clinical features of dengue disease in HCPs will also translate to greater benefits in dengue management.

DHF and DSS are particularly characterized by thrombocytopenia and plasma leakage. The roles of the host immune system, particularly antibodies and leukocytes in the manifestation of these symptoms in dengue infection, have been a major focus of interest. The mechanisms of pathogenesis in DHF/DSS include overproduction of proinflammatory cytokines, aberrant immune activation, and antibody-dependent enhancement (ADE). Generally, antibodies protect the host against most viral infections in various ways, including neutralization of viruses, lysing infected cells, and opsonization. Halstead originally proposed ADE as an important pathogenic mechanism in severe dengue disease, whereby preexisting antibodies from a previous dengue virus infection may enhance
heterotypic dengue virus infection of macrophages through Fcγ receptors. ADE increases the efficiency of virus infection and may suppress type I interferon (IFN)-mediated antiviral responses. Aberrant activation of T cells and overproduction of soluble factors by T cells and Fcγ receptor-bearing monocytes contribute to an increase in vascular permeability.

Molecular mimicry is also a potential factor in dengue virus pathogenesis. Molecular mimicry exists between dengue virus proteins prM, E, and NS1 and self-proteins such as protein disulfide isomerase, vimentin, heat shock protein 60, coagulatory factors, plasminogen, thrombin, and tissue plasminogen activator on platelets and endothelial cells. An autoantibody-associated immunopathogenesis for dengue disease has been proposed in which dengue virus infection induces autoreactive antiplatelet and antiendothelial cell antibodies. These autoantibodies, together with IFN-γ activated macrophages may act to phagocytose autoantibody-opsonized platelet and endothelial cells. Such responses may contribute to vascular endothelial leakage and/or thrombocytopenia in DHF/DSS. Furthermore, molecular mimicry between prM/E/NS1 and self-antigens raises concerns about the safety of dengue virus vaccines.

In this issue of the Journal, Wan et al extend their studies of autoreactive antibodies in dengue disease. Dengue virus-induced autoantibodies against endothelial cells, platelets, and coagulatory molecules may lead to their abnormal activation or dysfunction. Recently gained insights into the identity of cross-reactive epitopes as well as the biologic consequences of dengue-induced autoantibodies provide a fuller picture of the complexities of dengue-associated immunopathology and vaccine strategies.

Also in this issue of the Journal, Chuang et al provide insight into the role of antibodies in coagulopathy in dengue disease. Cytokines, complement, and dengue viral proteins may all contribute hemostatic defects in dengue infection. The combination of direct viral effects and indirect host immunologic responses may tilt the balance of coagulation and fibrinolysis toward bleeding in patients with DHF/DSS.

In a recent Phase 2b clinical trial of a recombinant, live-attenuated, CYD tetravalent dengue vaccine, the high geometric mean titers of neutralizing antidengue antibodies were not associated with high protective efficacy, a finding that implies that the role of antibodies in dengue pathogenesis warrant further clarification. In the meantime, several other vaccine candidates are also under development. For the safety and efficacy of dengue vaccine development, the immunopathogenic complications of dengue disease need to be considered. Most importantly, there is a need for enhanced collaborations between clinical and basic researchers to improve integration of new diagnostic agents, vaccines, and therapeutic agents for dengue disease.

References