Role of Complement in Dengue Virus Infection: Protection or Pathogenesis?

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ABSTRACT Dengue viruses (DENV) cause a spectrum of disease in humans, ranging from dengue fever (DF) to a severe, life-threatening syndrome called dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). Despite the global morbidity and mortality associated with DENV infection, mechanisms of immune control and viral pathogenesis are poorly understood. In a recent article, Avirutnan et al. [mBio 2(6):e00276-11, 2011] demonstrated that DENV can be directly neutralized via the mannose binding lectin (MBL) pathway of the complement system and that deficiency in MBL level or activity due to host polymorphisms in the MBL2 gene correlates with reduced levels of DENV neutralization. These findings implicate a role for the MBL pathway in controlling DENV infections and modulating DHF/DSS manifestations.
activation suggest that the complement system is an important player in the host defense against DENV. Avirutnan et al. (6) examined the role of the complement system in protection against DENV infection, and the results provide support for an important role of the complement system in controlling DENV infection and potentially influencing the severity of dengue disease in humans.

Specifically, Avirutnan et al. performed initial experiments using naïve mouse sera to determine which complement pathways contribute to neutralization of DENV in vitro (6). Experiments with loss-of-function models for various mouse complement proteins demonstrated that the MBL pathway was critical for neutralization of both insect and mammalian cell-derived DENV serotype 2 (DENV2), although insect cell-derived DENV2 was neutralized more efficiently than mammalian cell-derived virus. Based on these results, the authors performed additional experiments using purified human MBL and showed that MBL could directly neutralize insect but not mammalian cell-derived DENV2 in the absence of other complement proteins and that this direct MBL-mediated neutralization was more efficient at higher temperatures (37°C and 40°C) than at room temperature. Further experiments using purified human MBL and serum from MBL-deficient mice showed that MBL-mediated neutralization of insect cell-derived DENV2 was enhanced by other complement proteins. Similar to results obtained with mouse sera, human sera from some individuals could neutralize both insect and mammalian cell-derived DENV2 in an MBL-dependent manner. In this case, neutralization of insect cell-derived DENV2 was more efficient than that of mammalian cell-derived virus. Sera from other individuals neutralized only insect cell-derived DENV2, not mammalian cell-derived DENV2. A positive correlation was observed between the MBL concentration in human serum and the level of DENV2 neutralizing activity. Moreover, experiments with sera obtained from individuals with different levels of MBL2 due to known polymorphisms in the MBL2 gene corroborated the positive correlation between human MBL2 levels and neutralization of insect cell-derived DENV2. Finally, experiments were performed with both mouse and human serum samples to show that the MBL pathway could neutralize the remaining three serotypes other than DENV2. Collectively, these results tie together initial observations made using mouse models and human donors to subsequent findings related to humans with particular polymorphisms in the MBL2 gene and suggest that the MBL pathway contributes to protection against DENV infection in humans.

Based on the findings of this study, a depressed level of MBL protein or activity may be an independent risk factor for morbidity and mortality associated with DENV infection. Deficiencies in MBL are relatively common in humans. MBL deficiency has been associated with increased susceptibility to many infectious diseases, including viral infections (17), and MBL2 polymorphisms have been associated with disease pathogenesis (18). Examination of a limited number of Vietnamese individuals with low serum MBL concentrations due to a variant MBL allele suggested that MBL deficiency does not impact the risk of DHF/DSS (5). However, studies with DENV-infected patients in Brazil suggested that low levels of MBL may be associated with protection against thrombocytopenia (19), whereas high MBL levels appear to be correlated with severe disease (12). Accumulating evidence indicates that DF and DHF/DSS are complex diseases that are likely affected by multiple viral and host immune and genetic factors. Future studies with statistically significant numbers of individuals with the same MBL genotypes analyzed in the published studies and with individuals with other known MBL2 gene polymorphisms that are associated with decreased MBL levels should clarify the precise role of the MBL pathway in determining the outcome of DENV infection.

The present study has thus provided an impetus for investigating the role of the MBL pathway and other elements of the complement system in anti-DENV protection versus disease pathogenesis using animal models and patient samples. This line of research may help answer two central questions in the DENV field: why are the vast majority of individuals with either primary or secondary DENV infections asymptomatic, and why do secondary infections with DENV result in more severe illness than primary infections?

REFERENCES