

Dengue Virus Nonstructural Protein 1: A Pathogenic Factor and Therapeutic Target

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Dengue virus (DENV) infection is the most common mosquito-borne viral infection. Majority of DENV-infected subjects demonstrate asymptomatic profiles or mild dengue fever. Unfortunately, others may progress to severe dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). Vascular leakage and hemorrhage are two characteristic pathogenic changes in DHF/DSS patients. However, the pathogenic mechanisms of vascular leakage and hemorrhage induced by DENV infection are still not fully understood. DENV nonstructural protein 1 (NS1), which can be secreted in patients' sera, has been used as an early diagnostic marker for dengue infection. However, the roles of NS1 in dengue pathogenesis are unclear. We are the first one to show that antibodies (Abs) against DENV NS1 can cross-react to human endothelial cells and platelets and disrupt their functions. In addition, we found NS1 can directly induce endothelial hyperpermeability and glycocalyx degradation through macrophage migration inhibitory factor-induced autophagy. Furthermore, DENV NS1 can bind to platelet and induce its activation and apoptosis, leading to thrombocytopenia. Therefore, NS1 is a pathogenic factor which can cause vascular leakage and hemorrhage by NS1 itself or NS1-induced cross-reactive Abs. To block the pathogenic effects of NS1, we have identified monoclonal Abs (mAbs) against NS1 which do not cross-react to human proteins but can protect mice from lethal challenge of all four serotypes of DENV infection. The pathogenic effects of NS1 and the advantage of therapeutic targeting at NS1 by its mAbs are summarized in the following figure.

