Dengue Virus Nonstructural Protein 1 Antibody Therapy and Vaccine Strategy

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Dengue is an important arthropod-borne viral infection around the world. Nearly a third of the global population is at risk of exposure to dengue-carrier mosquitoes. There are approximately 390 million dengue infections per year including 96 million cases with apparent clinical manifestations. Patients with dengue disease may have severe thrombocytopenia and plasma leakage. The pathogenic mechanisms of dengue hemorrhage are not fully resolved, which causes a major hurdle in antiviral treatment or vaccine development. Attention has been raised on subunit vaccine candidates such as envelope protein and nonstructural protein 1 (NS1). NS1 is not a virion-associated protein, and will not cause antibody-enhanced infection of dengue virus (DENV). In addition, anti-NS1 antibodies cause lysis of DENV-infected cells which express NS1 on their surface before much viral replication has occurred. However, we previously showed that antibodies against DENV NS1 cross-react with human platelets and endothelial cells due to the sequence homology on C-terminal region of NS1. We recently found a monoclonal antibody which did not recognize the C-terminal region of DENV NS1 and showed certain therapeutic effects both *in vitro* and *in vivo*, suggesting that NS1-specific monoclonal antibodies could be potential candidates for anti-dengue disease therapy. We further used polymer-based nanocomplexes or alum as an adjuvant to examine the protective effects of DJ NS1 (consisting of N-terminal DENV NS1 and C-terminal JEV NS1) in the DENV-induced hemorrhage mouse model. Polymer-based nanocomplexes provided better adjuvant activity than alum and induced both Th1 and Th2 responses. Active immunization with DJ NS1-encapsulated nanocomplexes reduced the DENV-induced prolonged bleeding time, local skin hemorrhage, and viral antigen expression. Furthermore, DJ NS1-encapsulated nanocomplexes induced longer antibody persistence than alum and caused long-term protection. These results provide support for new strategies for the development of high efficacy vaccines using nanocomplexes as the adjuvant.