Recognition determinants of broadly neutralizing human antibodies against dengue viruses

Dengue disease is caused by four different flavivirus[1] serotypes, which infect 390 million people yearly with 25% symptomatic cases[2] and for which no licensed vaccine is available. Recent phase III vaccine trials showed partial protection, and in particular no protection for dengue virus serotype 2 (DENV-2)[3,4]. Structural studies so far have characterized only epitopes recognized by serotype specific human antibodies[5,6]. We recently isolated human antibodies potently neutralizing all four DENV serotypes[7]. In this presentation, I will describe the implications from the X-ray structures of four of these broadly neutralizing antibodies (bnAbs) in complex with the envelope glycoprotein E from DENV-2, which revealed that the recognition determinants are at a serotype conserved site at the E dimer interface, including the exposed main chain of the E fusion loop[8] and the two conserved glycan chains. This "E-dimer dependent epitope" (EDE) is also the binding site for the viral glycoprotein prM during virus maturation in the secretory pathway of the infected cell[9], explaining its conservation across serotypes and highlighting an Achilles heel of the virus with respect to antibody neutralization. These findings will be instrumental for devising novel immunogens to protect simultaneously against all four serotypes of dengue virus.

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