Analysis of ChimeriVax-DEN envelope sequences for T-cell epitopes and comparison to circulating viral strains in Indonesia

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Abstract

Dengue virus (DENV) circulates in nature as four distinct serotypes (DENV1, DENV2, DENV3, and DENV4) and distributed over a wide geographic area. Primary infection with DENV results in life-long protection from the same serotype, but secondary infection with a different serotype could cause dengue hemorrhagic fever and dengue shock syndrome. There is currently no cure for dengue and no effective vaccine available. ChimeriVax-DEN vaccine (CYD) (Sanofi Pasteur) is currently in phase III clinical trials in 14 countries including Indonesia. CYD vaccine was constructed using the PrM and E genes from DENVs and the backbone genes (C, NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) from yellow fever virus, and is formulated as a tetravalent vaccine. We evaluated whether the CYD vaccine contains T helper and cytotoxic T-cell epitopes that are conserved in wild type (circulating) DENV strains in Indonesia (IdDENV). We used a T-cell epitope mapping tool, EpiMatrix, developed by EpiVax Inc. (Providence-RI) to identify T-helper and cytotoxic T-cell epitopes derived from envelope protein sequences of the parenteral strain of CYDs and to compare them to the 38 DENV strains in Indonesia. We generated a list of peptides that was ranked by potential to induce either Class I or II HLA-mediated immune responses, represented by the EpiMatrix Z-score. We found that CYD4 had the lowest total sum of the significant Z-scores for 5 out of 11 HLA Class I and 5 out of 9 HLA Class II. It seems that immune responses to serotype 4 might potentially to be the lowest compared to the other three serotypes, in the individuals having certain HLA supertypes. We observed that conservation between T-cell epitopes in all four serotypes of CYD and circulating DENV strains is quite high as reflected by the small percentage of putative epitopes unique to any given strain. The unique epitopes are the epitope sequences from CYD that do not exactly match with the epitopes sequences from the circulating DENV strains. Out of the four serotypes analyzed, we found that CYD2 has the highest number of unique epitopes for both Class I and Class II, which could contribute to the vaccine lower efficacy as compared to the other three serotypes. However, the majority of unique epitopes contained in the CYD2 envelope sequence are still predicted to bind to the allele(s) restricting presentation of their wild-type counterparts. Epitopes from circulating DENV strains were also compared to the homologous epitopes from CYD vaccine. We found that majority of the unique circulating DENV epitopes are predicted to bind to the same HLA alleles as homologous CYD epitopes, indicating potential cross-reactivity. The application of immunoinformatics tools as described here will aid in the development of a broadly effective vaccine and define reagents that can be used to evaluate immune responses to the vaccines in clinical trials.