Centralized gene-based HIV-1 vaccine elicits broad cross-clade cellular immune responses in rhesus monkeys

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Abstract
One of the major challenges that must be met in developing an HIV-1 vaccine is devising a strategy to generate cellular immunity with sufficient breadth to deal with the extraordinary genetic diversity of the virus. Amino acids in the envelopes of viruses from the same clade can differ by more than 15%, and those from different clades can differ by more than 30%. It has been proposed that creating immunogens using centralized HIV-1 gene sequences might provide a practical solution to this problem. Such centralized genes can be generated employing a number of different strategies: consensus, ancestral, or center of tree sequences. These computer-generated sequences are a shorter genetic distance from any 2 contemporary virus sequences than those contemporary sequences are from each other. The present study was initiated to evaluate the breadth of cellular immunity generated through immunization of rhesus monkeys with vaccine constructs expressing either an HIV-1 global consensus envelope sequence (CON-S) or a single patient isolate clade B envelope sequence (clade B). We show that vaccine immunogens expressing the single centralized gene CON-S generated cellular immune responses with significantly increased breadth compared with immunogens expressing a wildtype virus gene. In fact, CON-S immunogens elicited cellular immune responses to 3-4 fold more discrete epitopes of the envelope proteins from clades A, C and G than did clade B immunogens. These findings suggest that immunization with centralized genes is a promising vaccine strategy for developing a global vaccine for HIV-1 as well as vaccines for other genetically diverse viruses.