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Intra- and Inter-clade Cross-reactivity by HIV-1 Gag Specific T-Cells Reveals Exclusive and Commonly Targeted Regions: Implications for Current Vaccine Trials

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The genetic diversity of HIV-1 across the globe is a major challenge for developing an HIV vaccine. To facilitate immunogen design, it is important to characterize clusters of commonly targeted T-cell epitopes across different HIV clades. To address this, we examined 39 HIV-1 clade C infected individuals for IFN-y Gag-specific T-cell responses using five sets of overlapping peptides, two sets matching clade C vaccine candidates derived from strains from South Africa and China, and three peptide sets corresponding to consensus clades A, B, and D sequences. The magnitude and breadth of T-cell responses against the two clade C peptide sets did not differ, however clade C peptides were preferentially recognized compared to the other peptide sets. A total of 84 peptides were recognized, of which 19 were exclusively from clade C, 8 exclusively from clade B, one peptide each from A and D and 17 were commonly recognized by clade A, B, C and D. The entropy of the exclusively recognized peptides was significantly higher than that of commonly recognized peptides (p = 0.0128) and the median peptide processing scores were significantly higher for the peptide variants recognized versus those not recognized (p = 0.0001). Consistent with these results, the predicted Major Histocompatibility Complex Class I IC50 values were significantly lower for the recognized peptide variants compared to those not recognized in the ELISPOT assay (p<0.0001), suggesting that peptide variation between clades, resulting in lack of cross-clade recognition, has been shaped by host immune selection pressure. Overall, our study shows that clade C infected individuals recognize clade C peptides with greater frequency and higher magnitude than other clades, and that a selection of highly conserved epitope regions within Gag are commonly recognized and give rise to cross-clade reactivities.

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