Mapping and Predicting HIV Vaccine Responses

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In recent years, several HIV-1 vaccine candidates have been tested that employ a recombinant adenovirus (rAd5) to express HIV-1 genes. While none of these vaccines elicited a protective immune response, considerable effort has gone into studying the immune response elicited by each vaccine. In a recent study published in PLoS Pathogens, Drs. Tomer Hertz and Peter Gilbert and their collaborators conducted a meta-analysis of the T-cell epitopes elicited at a population level by two different vaccines across three separate trials, and find that vaccine-elicited responses cluster in "hotspots". These hotspots are variable but may be predicted based on patient HLA alleles (a component of the immune system responsible for displaying antigens on the cell surface). This work has the potential to identify and prioritize potentially effective candidate vaccines earlier in the testing process.

Hertz et al. analyzed the cytotoxic T-cell response elicited in 177 individuals across three vaccine trials, two of which used the same Merck rAd5-gag/pol/nef vaccine, and compared these responses to 372 patients with chronic HIV infection. The team constructed population-level epitope maps for each cohort by tallying the number of cytotoxic T-cell responses at each position along an HIV-1 protein. Using these maps, the authors found that immune responses in all three vaccine trials and in naturally infected patients were clustered around immunodominant hotspots. However, the targeted hotspots were significantly different between the three vaccine trials, even between the two trials which used the same vaccine. The team next sought to determine whether the differences in these trials could be due to differences in the distribution of HLA alleles. They compared matched HLA across the three groups, and found that while statistical differences in hotspot locations targeted in the HIV-1 protein Gag did not hold, the differences in hotspots found in the HIV-1 proteins Nef and Pol across the three vaccine trials remained, suggesting that the observed differences in hotspots are not solely due to HLA differences between the three vaccine trials.

The authors next characterized targeted epitopes relative to naturally infected patients, and found that some vaccine-induced hotspots targeted epitopes that were not often targeted in chronically infected patients. In addition, some of the vaccine-induced hotspots targeted non-conserved sites in the HIV-1 proteins preferentially. For example, non-conserved Gag epitopes were preferentially targeted in all of the vaccine trials, but not in naturally infected patients.

Several of the hotspots identified in this study were targeted by multiple HLA alleles; therefore, Hertz et al. sought to determine whether HLA binding predictor algorithms (Lin, et al., 2008) may be used to predict population-level epitope hotspots in a candidate vaccine. The team pooled predicted epitope targets for all possible HLA alleles into a single prediction map, and then compared these maps to the population-based epitope maps they generated for the vaccine trials. The predicted maps were significantly correlated to the observed responses to Gag, Pol, and Nef, but not to Env responses. Moreover, the predicted maps identified nearly all the experimentally determined immunodominant epitopes. However, the predicted maps also contained other immunodominant epitopes that were not observed in the vaccine trials, likely because HLA predictors focus solely on HLA binding, and do not take into account other factors such as epitope half-life and T-cell receptor avidity.

This study found that immunodominant epitopes elicited by each vaccine trial were different, even when the same vaccine was employed in two different trials. However, the immunodominant hotspots observed in each vaccine trial were also identified by HLA predictors. “Coupled with novel data about which immune responses against the HIV virus are protective, this approach may allow [us] to compare and rank different vaccine candidates in earlier stages of clinical development,” said Dr. Tomer.

Hertz T, Ahmed H, Friedrich DP, Casimiro DR, Self SG, Corey L, McElrath MJ, Buchbinder S, Horton H, Frahm N, Robertson MN, Graham BS, Gilbert P. 2013. HIV-1 vaccine-induced T-cell responses cluster in epitope hotspots that differ from those induced in natural infection with HIV-1. PLoS Pathog. 2013 Jun;9(6):e1003404.

See also: Lin HH, Zhang GL, Tongchusak S, Reinherz EL, Brusic V. 2008. Evaluation of MHC-II peptide binding prediction servers: applications for vaccine research. BMC Bioinformatics. 2008 Dec 12;9 Suppl 12:S22.

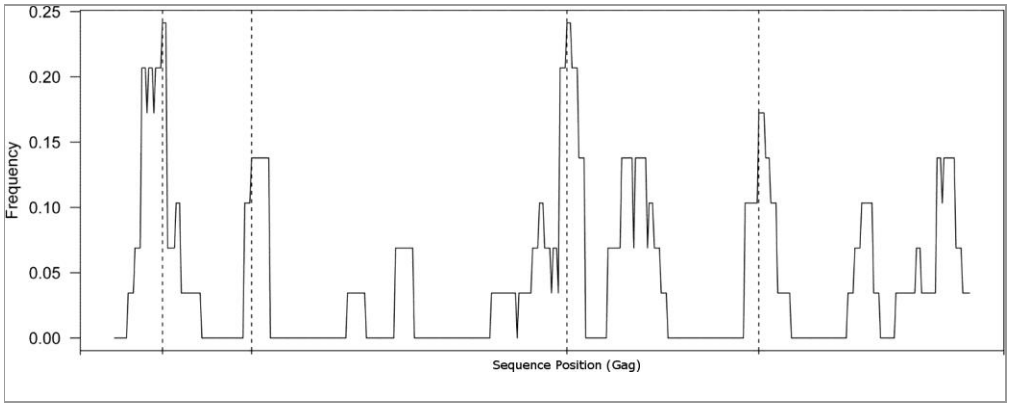

Image modified from Hertz, et al., 2013.

Population-based epitope map of IFN-γ responses to HIV-1 Gag from patients in the HVTN 502/Step trial. Hotspots are indicated by dashed lines.