

HIV-1 Env-specific conformational ADCC epitopes: potential utility for HIV vaccine design

V. Madhavi, M. Kramski, L. Wren, R. Center, S. Kent, I. Stratov

The University of Melbourne, Microbiology and Immunology, Melbourne, Australia

Background:

HIV vaccines based on neutralizing antibodies and cytotoxic T-cells have been unsuccessful. The partially successful RV144 HIV vaccine trial demonstrated an important role of binding antibodies that mediate Antibody Dependent Cellular Cytotoxicity (ADCC). We previously identified and mapped HIV-1 linear ADCC epitopes in HIV+ subjects using HIV-1 Env overlapping peptides. However, ADCC antibodies to conformational Env epitopes are likely to recognize more conserved regions and therefore most useful in the design of novel HIV vaccines.

Methods and Results:

We initially screened plasma samples from 22 HIV+ subjects with progressive HIV infection for ADCC responses against HIV-1 Env overlapping peptides and trimeric gp140 protein by using NK cell activation ADCC assay (IFN γ + CD107a+) to identify the potent ADCC epitopes. We observed that 6 out of 22 (27%) HIV+ subjects had ADCC responses to trimeric gp140 (mean NK cell activation 2.8%, range 1.2-5.1) that were absent when tested against HIV-1 Env overlapping peptides, indicating ADCC response to probable conformational Env epitopes. When we tested plasma samples from 3 long-term slow progressors (LTSP, CD4 T cells >500/ μ l for >10 years), 2 out of 3 subjects (66%) had ADCC response to trimeric gp140 (mean NK cell activation 5.1%, range 4.8-5.4) and much stronger responses to monomeric gp120 (mean NK cell activation 16.1%, range 15.8-16.4) were observed, suggesting relevant immunologic differences between monomeric and trimeric Env. We also tested plasma samples from 4 elite controllers (EC, viral load consistently < 400 off ART), 2 out of 4 (50%) had ADCC responses to trimeric gp140 (mean NK cell activation 1.1%, range 0.6-1.6) and 3 out of 4 (75%) had ADCC responses to monomeric gp120 (mean NK cell activation 3.9% range 2.0-3.5).

Conclusion:

Our results suggest that HIV+ subjects who naturally control HIV have robust ADCC responses to conformational Env epitopes. Dissecting the specific conformational ADCC epitopes by using a panel of native, truncated, modified and chimeric Env proteins will help in designing new HIV antibody vaccine immunogens. We are now recruiting additional subjects and studying ADCC responses to different HIV-1 subtypes to identify common ADCC epitopes that would help in designing globally relevant immunogen.