

Poster presentation

PI9-06. The first hypervariable loop and HIV-1 neutralizing antibodies elicited by gp140 env immunogens

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Background

Efforts to elicit neutralizing antibodies (Nabs) against HIV have focused on engineering Env immunogens that mimic the trimeric Env structure on infectious virions (soluble gp140s). A significant fraction of the antibodies elicited by Env-derived gp140 immunogens target the first hypervariable region (V1 loop), suggesting the V1 loop is immunogenic on these constructs. However, due to sequence variability, anti-V1 antibodies elicited by gp140s are not cross-neutralizing.

Methods

To improve our understanding of V1 loop immunogenicity and the way in which the V1 loop may be affecting the immunogenicity of other Env regions, we: (1) Constructed an SF162 Env immunogen lacking the V1 loop and examined how its elimination altered the immunogenic properties of other epitopes. (2) Used SF162 Env as a scaffold to express diverse heterologous V1 loops (from YU2, JRFL, 89.6 and HxB2) and then tested these individually or in combination. The potency, breadth, and epitope specificities of Abs elicited by the constructs were analyzed and compared to responses elicited by the wt-SF162 construct.

Results

Our current results indicate that deletion of the V1 loop does not lead to enhanced cross-reactive neutralizing responses but enhances the contribution of anti-V3 antibodies to neutralization. Immunizations with the V1 chimeric constructs did not elicit antibodies to the heterologous V1 loops, suggesting that these loops, although immunogenic on the autologous Env backbone,

are immunosilent on the SF162 Env backbone. The heterologous HxB2 virus was neutralized by antibodies elicited by all scaffold immunogens and this neutralization is not mediated by V1- or V3-directed antibodies.

Conclusion

V1 dampening by deletion does not lead to more cross-reactive neutralizing responses but does alter the immunogenicity of regions outside the V1 loop, such as the V3 loop. Expressing heterologous V1 loops on a given Env background dampens the immunogenicity of the V1 loop but does not result in the elicitation of cross-reactive NAbs.