Retrovirology

Poster presentation

P09-06. HIV-1 escape from broadly neutralizing anti-CD4 binding site NAbs during HIV-1 infection

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Background

Designing immunogens that will elicit neutralizing antibodies (NAbs) directed at the CD4 receptor binding site (CD4-BS) of the HIV-1 envelope remains a major priority for vaccine research. Little is known about broadly reactive anti-CD4-BS NAb responses and the development of resistance to these antibodies in the natural infection setting. We previously described an HIV+ subject, VC10042, whose exceptionally broad cross-neutralizing activity was due to NAbs targeting the CD4-BS. These anti-CD4-BS antibodies potently neutralize diverse HIV-1 isolates, irrespective of clade. Here we investigated the autologous neutralizing response of VC10042 and characterized circulating autologous viral strains, providing an opportunity to study potential mechanisms of escape from cross-reactive anti-CD4-BS NAbs during natural infection.

Methods

Autologous envelope (Env) sequences were amplified from plasma virus and were multiply aligned for comparison to reference sequences. Variable resides in the CD4 binding site and the mAb b12 epitope were mapped onto the gp120 crystal structure. Autologous Envs were pseudotyped and tested for co-receptor usage, sensitivity to known neutralizing antibodies, and sensitivity to autologous plasma.

Results

All Env clones efficiently utilized the CCR5 and, to a lesser extent, the CXCR4 co-receptors, while only a few clones could enter target cells in a CD4-independent manner. All clones were completely resistant to MAb b12, but were sensitive (to varying degrees) to the autologous anti-CD4-BS NAbs. Resistance to b12 was mapped to the simultaneous presence of 2 amino acids: R373 (C3) and N386 (C4).

Conclusion

Our results indicate HIV-1 can escape the action of the broadly neutralizing MAb b12 but still remain susceptible to naturally developed anti-CD4-BS NAbs and utilize the CD4 molecule for entry. Defining the precise epitopes recognized by these broadly neutralizing anti-CD4-BS antibodies may lead to the development of immunogens capable of eliciting similar anti-CD4-BS antibodies that target the CD4-BS differently than MAb b12.

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