Retrovirology

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Fusion Complexes and CD4-independent gp120s for the Induction of HIV-1 Neutralizing Antibodies

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from 2005 International Meeting of The Institute of Human Virology
Baltimore, USA, 29 August – 2 September 2005

Published: 8 December 2005

Retrovirology 2005, **2**(Suppl 1):S121 doi:10.1186/1742-4690-2-S1-S121

Background

The narrow spectrum of HIV-specific neutralizing antibodies points to the need for new immunogens based on highly conserved epitopes. HIV-1 infects host cells by membrane fusion: during this process conserved epitopes are exposed on the viral glycoprotein gp120/41 that may be used as targets for the induction of antibodies against HIV-1. Neutralizing antibodies against different heterologous HIV-1 isolates may be obtained by immunizing mice with fusion complexes on which conserved epitopes have been stabilized by fixation, or with gp120/41s with a CD4-independent phenotype on which these conserved epitopes may be already exposed.

Methods

Fusion complexes were prepared using cells expressing gp120/41 cocultivated with cells expressing the receptors CD4-CCR5 at different temperatures, corresponding to intermediate stages of the membrane fusion process, and stabilized using different fixatives. Mice were immunized to reveal the induction of HIV neutralizing antibodies and their spleen cells used to generate hybridoma clones to be tested for the production of neutralizing monoclonal antibodies. In addition, syngeneic balb/c mouse cells expressing gp120/41 with a CD4-independent phenotype have been prepared by transfection and using viral vectors and are being used to assess their capability to induce broad spectrum neutralizing antibodies.

Results

Results obtained indicate that: 1) fusion complexes were immunogenic and induced neutralizing antibodies against R5 and X4 HIV-1 heterologous isolates; 2) extensive purification of antibodies allowed the removal of any aspecific cytotoxic effect; 3) complexes prepared at higher temperatures were more immunogenic and induced higher titers of neutralizing antibodies; 4) titer of neutralizing antibodies was not affected by the fixative used; 5) neutralizing activity was retained after CD4-CCR5 antibody removal; 6) CD4-independent gp120s were expressed in syngeneic mice cells and recognized by HIV-1 positive human sera; mice immunizations are currently ongoing.

Conclusion

Results show that fusion complexes are immunogenic and induce neutralizing antibodies against heterologous HIV-1 isolates. Removal of non-specific inhibitors that confused early promising results is necessary to obtain a specific antibody response. The production and selection of neutralizing monoclonal antibodies will be useful to identify specific immunogenic structures and epitopes to be used to induce neutralizing antibodies when administered in a suitable delivery system. Antibodies obtained by immunizing with CD4-independent gp120s and antibody fragments isolated through phage display libraries panning will be evaluated for their broad-spectrum neutralizing activity against different HIV-1 isolates with and without the addition of sCD4 or CD4-like antibodies.