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P04-25. Exposure of HIV-1 pseudovirus to soluble CD4 increases the breadth of neutralization with sera from macaques immunized with recombinant glycoproteins

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Background

When HIV-1 envelope glycoproteins bind to CD4, conformational changes expose a site where the co-receptor can bind. Epitopes associated with this site are known as CD4-induced (CD4i) and give rise to antibodies which neutralize a wide range of HIV-1 isolates. Immunogens can be engineered to present these epitopes. Here, we show that exposure to soluble CD4 also sensitises pseudovirus to allow cross-neutralization of heterologous isolates by antibodies elicited by trimeric glycoproteins that have not been specifically modified to expose CD4i sites.

Methods

Sera were taken at six weeks after the final immunization of rhesus macaques with trimeric recombinant HIV-1 envelope glycoproteins from HIV-1 461 (subtype A), HIV-1 SF162 (subtype B) and/or HIV-1 TV1 (subtype C) and have not been further engineered to enhance exposure of CD4i epitopes. SHIVSF62P4, SHIVSF62P3, SHIVKB9 (≡ SHIV89.6P, subtype B), HIV-1 TV1 or HIV-1 MJ4 (subtype C) pseudoviruses were exposed for 1 hour to sufficient soluble CD4 to reduce their infectivity by 50%. Dilutions of sera were then added to these mixtures and subsequently incubated for a further hour at 37°C before exposure to TZMbl cells. After 48 hours in culture the production of luciferase was quantified. Similar assays were performed with monoclonal antibodies.

Results

Sera from immunized macaques neutralized homologous SHIVSF162P4 or HIV-1 TV1 pseudoviruses but not heterologous SHIV KB9 or HIV-1 MJ4. If the pseudovirus is first exposed to soluble CD4 there is no increase in the neutralization titre against homologous isolates. However, the heterologous isolates are neutralized. A similar sensitization of neutralization was seen with monoclonal antibodies to the V3 region (447-52D) or gp41 (4E10).

Conclusion

Recombinant HIV-1 envelope glycoproteins induce antibodies which neutralize homologous pseudoviruses. However, the same immunogens also induce antibodies which can cross-neutralize heterologous isolates provided these have been pre-exposed to soluble CD4.