Retrovirology

Poster presentation

P04-38. Crystal structure of gp120 in complex with the CD4-binding-site antibody b13 suggests precise targeting is needed for neutralization

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Background

The CD4-binding site (CD4BS) on HIV-1 gp120 is functionally conserved and structurally invariant, and the broadly neutralizing antibody b12 exploits this site of vulnerability to achieve neutralization. However, most antibodies that target this general epitope cannot effectively neutralize HIV-1. Why is HIV-1 resistant to neutralization by these antibodies? Comparison at the atomic level of gp120 binding to effective and non-effective antibodies may reveal the answer.

Methods

We solved the crystal structure of gp120 in complex with one of the non-effective CD4BS antibodies called b13 at 2.5 Å.

Results

Antibody b13 binds gp120 in a very similar manner to that of antibody b12, with three heavy chain complementarity-determining regions grabbing onto the CD4-binding loop of gp120. The contacting surface of antibody b13 on gp120 overlaps significantly with that of b12, and the approach angle of b13 and b12 differ by only 17 degrees. However, the binding surface is shifted towards a conformationally variable region on gp120. This shift results in large conformational changes to the alpha1-helix, the V1/V2 stem as well as the beta20/beta21 region. Computational modeling indicates that these antibody-induced conformational changes are not compatible with trimeric constraints on the viral spike.

Conclusion

Our results suggest that targeting of the CD4-binding site by an antibody which slightly misses the precise site of CD4 attachment results in a cascade of conformational changes in gp120. These changes are incompatible with the viral spike, which in turn protects HIV-1 from being neutralized. Precise targeting is therefore needed. The structures of both effective and non-effective antibodies in complex with gp120 therefore define a vulnerable vaccine target, which is confined by glycan on one side and by conformationally variable areas on the other.