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A gp41 MPER-specific llama VHH requires a hydrophobic CDR3 determinant for neutralization but not for antigen recognition

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Background

The membrane proximal external region (MPER) of the HIV-1 glycoprotein gp41 is targeted by broadly neutralizing antibodies such as 2F5, 4E10 and Z13, which recognize antigen and membrane components.

Methods

In this study, we immunized llamas with gp41 proteoliposomes and selected a MPER-specific single chain antibody (VHH), 2H10, whose gp41 epitope overlaps with that of mAb 2F5.

Results

2H10 binds to the intermediate conformation of gp41 with medium nanomolar affinity. Construction of 2H10 biheads (bi-2H10) increases the binding affinity by a factor of 20. Bi-2H10 neutralizes various sensitive and resistant HIV-1 strains, as well as SHIV strains in a TZM-bl cell assay. We further present structural data from crystallographic and NMR analyses together with mutagenesis data that allowed to map the interaction site on gp41. This revealed that 2H10 has a long CDR3 whose tip exposes a tryptophan residue that is not required for gp41 interaction, but crucial for neutralization.

Conclusion

Our data indicate that 2H10 induced by immunization classifies as a functional MPER antibody as a bihead that requires both antigen recognition and membrane interaction for neutralization.

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