Potential and broad neutralizing activity of small antibody fragments targeting CD4i (CD4-induced) epitope

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[Background]
CD4-induced (CD4i) epitope is exposed on the surface of trimERIC HIV-1 envelope glycoprotein (Env) after conformational changes of gp120 by binding to CD4 (Fig. 1). The CD4i epitope is highly conserved because the N-terminal region of CCR5 binds to this epitope. Therefore, the CD4i epitope is a favorable target for antibodies to neutralize a broad range of HIV-1 strains. However, most of primary HIV-1 isolates are resistant to anti-CD4i antibodies because the CD4i epitope is hidden inside trimERIC Env before binding to CD4. In this study, we aim at developing more potent anti-CD4i neutralizing antibody than the original IgG form by constructing antigen-binding fragment (Fab) and single-chain variable fragment (scFv).

[Materials and Methods]

1. Genetical features of anti-CD4i antibodies.

Preferential usage of VH1-69 and long CDR3 sequences with tyrosines because the CD4i epitope is hidden inside trimERIC Env before binding to CD4. In this study, we aim at developing more potent anti-CD4i neutralizing antibody than the original IgG form by constructing antigen-binding fragment (Fab) and single-chain variable fragment (scFv).

II. Binding activities of anti-CD4i antibody fragments against Env of HIV-1JRFL.

Immunization activities of various antibody fragments against several HIV-1 strains with 293A cells expressing gp120, and their neutralizing activities were determined by flow cytometry. Neutralization activities of these antibody fragments were examined by infection of TZM-bl cells with the pseudoviruses.

[Conclusion]
The anti-CD4i scFvs are accessible to CD4i epitope hidden inside trimERIC Env before binding to CD4, and effectively neutralize multi-clade HIV-1. The small fragment of anti-CD4i antibodies will be useful for a potent and broadly neutralizing of HIV-1.