Induction of Neutralizing Antibodies to the HIV CD4 Binding Site in Macaques by Covalent Immunization

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ABSTRACT

Structural coevolution of CD4 binding site (CD4BS) of HIV-1 Env protein permits covalent conjugation of anti-CD4BS immunogen as a strategy for globally effective HIV vaccination. Inducing adaptive humoral immunity to the CD4BS core (ECD4BS) composed of gp120 residues 421-433 is generally prohibited because of poor T-cell supervisory character. This property underlies anti-CD4BS (ECD4BS) recognition by the humoral immune system of humans and non-human primates. Covalent conjugation of electrophilic derivatives of oligomeric gp120 (EO-gp120) and synthetic peptide 416-433 (E-CD4BS core) specific antibodies that neutralized diverse HIV strains. We report here the results of macaque immunizations with the electrophilic conjugate.

IMMUNIZATION

EO-gp120 and KLH-E-416-433 were covalently linked to KLH or BSA and used to immunize rabbits with 10-3molar concentration of electrophilic compounds. Immunization with KLH-E-416-433 induced measurable but low level IgG antibodies (ECD4BS). The level of neutralizing antibodies is low but neutralizing antibodies are observed in the monoclonal antibodies. Neutralization of the antibodies is active in sera from mice that show high levels of neutralizing antibodies. Neutralization of the antibodies is active in sera from mice that show high levels of neutralizing antibodies. Neutralization of the antibodies is active in sera from mice that show high levels of neutralizing antibodies. Neutralization of the antibodies is active in sera from mice that show high levels of neutralizing antibodies.

RESULTS

Panel 2: EO-gp120 induces serum antibodies in monkeys that neutralize subtype C strain 92A06 in PMBC assay

Panel 5: Sequentially administered KLH-E-416-433/EO-gp120 immunogens induce broadly neutralizing serum antibodies

Panel 6: Endotoxin contamination does not explain HIV neutralizing activity

CONCLUSIONS

EO-gp120 is the first candidate vaccine that induces broadly neutralizing antibodies to the CD4BS. It repairs the primary problem appears to be defective class switching of the antibodies. The primary problem appears to be defective class switching of the antibodies. The primary problem appears to be defective class switching of the antibodies. The primary problem appears to be defective class switching of the antibodies. The primary problem appears to be defective class switching of the antibodies. The primary problem appears to be defective class switching of the antibodies.