

Poster presentation

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P05-05. Enhanced immunogenicity of HIV-1 envelope glycoprotein trimers fused to CD40 ligand

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Background

Subunit vaccines are often poor immunogens compared to live-attenuated and whole-inactivated virus vaccines. One reason is the lack of costimulatory signals provided by various components of live-attenuated and whole-inactivated vaccines. Here we improved the immunogenicity of the HIV-1 envelope glycoproteins (Env) by direct fusion to a costimulatory molecule, CD40 ligand (CD40L), which we term 'cis-adjuvant'. The rationale was to target the antigen directly to dendritic cells (DC) and B cells, while at the same time activating these cells.

Methods

Chimeric Env-CD40L containing a stabilized gp140 (SOSIP.R6), a GCN4-based trimerization domain, and the globular domain of human or mouse CD40L, was constructed and transiently expressed in 293T cells. The expression and trimerization was analyzed by SDS-PAGE, BN-PAGE and analytical size exclusion chromatography. The interaction with ligands and neutralizing antibodies was monitored by immunoprecipitation. The immunomodulatory properties on monocyte-derived immature DCs were tested. After incubation with immature monocyte-derived DC, the upregulation of DC maturation markers was monitored by FACS and the secretion of cytokines was analyzed by ELISA. Mice were immunized with plasmids encoding gp140 or gp140-CD40L via intramuscular or dermal (gene gun) routes and the Env-specific antibody response was followed by ELISA.

Results

The trimeric gp140-CD40L construct interacted with CD4 and CD40 and was recognized by neutralizing antibodies. Moreover, gp140-CD40L was able to activate dendritic cells and induce secretion of cytokines from these cells. Importantly, gp140-CD40L induced ~6-10-fold higher gp120-specific antibody titers than gp140 alone in mice vaccinated via intramuscular or dermal DNA immunization routes.

Conclusion

Fusion to CD40L enhanced the immunogenicity of HIV-1 Env trimers. Antigen targeting via CD40L or other 'cis-adjuvants' may have wider applicability in subunit vaccine development.