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Stable HIV-1 envelope glycoprotein immune complexes as vaccine immunogens

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The development of an HIV-1 vaccine that elicits strong neutralizing antibody (nAb) and T cell responses is challenging. Classical vaccine strategies such as live attenuated vaccines are considered unsafe whereas envelope glycoprotein (Env)subunit vaccines induce low nAb titers that do not protect against HIV-1 infection. We showed previously that most HIV-1-antibody immune complexes (HIV-ICs) formed with either broadly nAbs or Abs derived from patient sera dissociate into free HIV-1 virions and Ab when captured by dendritic cells (DCs). Dissociation of HIV-ICs allows for transmission from DCs to $CD4^+$ T target cells. H but more importantly it can hamper the activation of immune cells which is a hallmark of stable ICs. The natural role of ICs is enhancing uptake by DCs, DC activation, induction of antigen presentation and induction of T cell responses. Furthermore, ICs are captured by follicular DCs that activate the B cells for Ab production, Ab affinity maturation and ísotype switching. We explore stable Env-ICs as a vaccine candidate. To form stable Env-ICs we fused the Fc-region of immunoglobulins to trimeric gp140. Env-IC maintained a native Env conformation which was evaluated by ELISA with Env-specific Abs. Native PAGE analyses and size exclusion chromatography showed that Env-ICs formed trimers, but hexamers consisting of 2 Env trimers and 3 dimeric Fc-tails were also observed. The functionality of the Fc-tail was evaluated by immuno-precipitation of the Env-IC with protein-G couple beads. Capture of Env-IC by DCs was enhanced with 50% compared to wild-type Env. Moreover, Env-IC captured by DCs more efficiently activated gp120-specificT helper cells.

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