HIV Vaccine Candidate Efficacy Mediated by cAMP-Dependent Efferocytosis and V2-ADCC

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BACKGROUND

Vaccination with the HIV clades B/A/E recombinant canarypox–derived vector (ALVAC) and bivalent clade AE/B gp120-envelope proteins in alum significantly reduced the risk of HIV acquisition in the RV144 HIV Phase III vaccine trial in Thailand. Both RV144 and pre-clinical studies in macaques identified antibodies to SIV/HIV variable region 2 (V2), CD4 cells, and Antibody Dependent Cell Cytotoxicity (ADCC) as correlates of risk of HIV/SIV acquisition, highlighting this animal model's relevance to HIV in humans. Moreover, our pre-clinical studies with these modalities also uncovered CD14$^+$ cells as strong and reproducible correlates of risk of SIV acquisition. CD14 is expressed on a heterogenous population of myeloid cells including classical and intermediate monocytes and tolerogenic dendritic cells. Here, we performed an in-depth analysis of the innate immune response to vaccination by investigating the phenotype, epigenome, and function of CD14$^+$ cells in three consecutive studies following vaccination of macaques with the SIV-based DNA/ALVAC/gp120/alum regimen using reduction of per/exposure risk of mucosal SIV_{mac251} acquisition as a surrogate of vaccine efficacy.

Following SIV-based **DNA/ALVAC/gp120/alum** vaccination, the vaccine-induced **V2-specific ADCC** is complemented by CREB1-mediated **CD14$^+$ cells efferocytosis** in reducing the risk of SIV acquisition in macaques

CONCLUSIONS

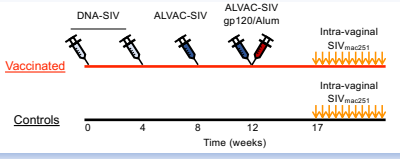
- SIV-based DNA/ALVAC/gp120/alum regimen is reproducibly efficacious
- V2-specific ADCC is a main and reproducible correlate of reduced risk of infection
- Chromatin accessibility to enhancer regions surrounding CREB-1 is key for an effective immune response
- CD14$^+$ efferocytes correlate with decreased acquisition and complements V2-ADCC in reducing the risk of SIV acquisition

Possible mechanisms:

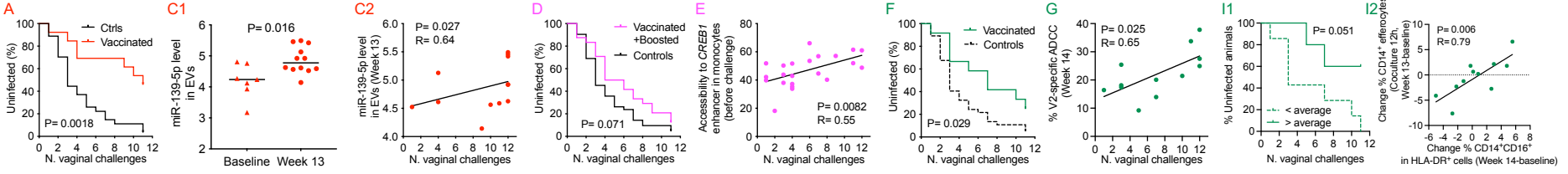
At the systemic level, vaccination induces the production of anti-V2 antibodies which mediate ADCC, and the level of miR-139-5p in extracellular vesicles contributes to activation of the CREB-1 pathway in CD14$^+$ cells. Following vaccination, CD14$^+$ cells migrate to the mucosa. Early after SIV_{mac251} exposure, mucosal cells that become infected are targeted by Natural Killer cells, which mediate V2-specific ADCC. Apoptotic infected cells are then engulfed by mucosal CD14$^+$ efferocytes, clearing the infection sites while maintaining an anti-inflammatory environment and avoiding recruitment of additional target cells.

METHODS

CD14$^+$ cells were investigated in 3 consecutive studies (1-3) following vaccination of macaques with the SIV-based DNA/ALVAC/gp120/alum regimen*. Animals were primed twice with DNA (week 0 and 4), then boosted with ALVAC (week 8) and ALVAC+gp120 protein in alum (week 12). In study 2, which was designed to test the durability of efficacy, the animals were additionally boosted or left untread 1 year following vaccination. Vaccinations were performed with immunogens expressing the wt gp120 (studies 1 and 2) or the dV1-gp120 that lacks the V1 region of the envelope (Study 3). At the end of vaccination animals were intra-vaginally exposed to low doses of SIV_{mac251}. The reduction of per/exposure risk of mucosal SIV_{mac251} acquisition was used as a surrogate of vaccine efficacy. Analyses performed included canonical assays (ADCC, cell analysis by flowcytometry, luminex and CD14$^+$ efferocytosis of apoptotic neutrophils) together with multiomics (RNA-, microRNA- and ATAC-sequencing). (**see additional slide for detailed study design schemes*)



RESULTS



A. 13 vaccinated macaques showed decreased risk of SIV acquisition compared to 27 naïve concurrent controls

B. Classical (CD14$^+$CD16$^-$) and Intermediate (CD14$^+$CD16$^+$) monocytes, and anti-SIV ADCC correlated with decreased risk of acquisition as in the previously published studies (*not shown*)

C. Levels of miR-139-5p in plasma extracellular vesicles were increased by vaccination (C1) and correlated with decreased risk of infection (C2)

D. 12 vaccinated and 12 boosted macaques showed a trend of decreased risk of SIV acquisition compared to 42 naïve controls

E. Chromatin accessibility investigated by ATAC-seq on enriched monocyte population isolated before the viral challenge identified a region surrounding CREB-1 gene whose accessibility correlated with reduced risk of acquisition

F. 12 vaccinated macaques with V1-deleted immunogens showed decreased risk of SIV acquisition compared to 37 naïve controls

G. V2-specific ADCC correlated with decreased risk of acquisition

H. Chromatin accessibility to CREB-1 enhancer region was confirmed (*not shown*)

I. CD14$^+$ cells efferocytosis was associated with delay in the viral acquisition (I1) and correlated with the change of frequencies of intermediate (CD14$^+$CD16$^+$) monocytes (I2)