Early Infancy Gut Microbiota Predicts the Quality of Vaccine-Induced Antibody Responses in Rhesus Macaques

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Introduction

- We remain without a highly-effective HIV vaccine or novel strategies for pediatric HIV-1 prevention that move beyond ART-based therapy.
- Evidence is emerging in a number of vaccine settings that commensal microbiota are linked to vaccine-elicited immune responses.
- The gut microbiota is most plastic during infancy, with the transition from a relatively sterile environment in utero to one of constant exposure to pathogenic and non-pathogenic microbial organisms.
- A successful HIV-1 vaccine may need to harness the unique landscape of the pediatric immune system by early immunization with concurrent rational manipulation of the microbiota to enhance vaccine efficacy.

Study goal:

- To define the relationship between the developing microbiota in infant rhesus macaques and the immunologic response following HIV-1 vaccination.

Methods

- Four groups each consisting of 5 neonatal rhesus monkeys were immunized on distinct immunization schedules:
  - Conventional
  - Co-Administration
  - Protein Only
  - Extended Interval

Figure 1. Vaccine Schedule of Infant Rhesus Macaques. 1) Conventional regimen animals were given modified vaccinia Ankara virus (MVA) expressing HIV-env (IM) and MVA-SIVgag/pol (IM) at week 0, followed by MVA-SIVgag/pol and HIV-env protein (IM/IM) at week 3, then administered a final dose of HIV-env protein at week 6; 2) the Co-Administration group received MVA-SIVgag/pol, MVA-HIV-env, and HIV-env protein concurrently at 0, 3, and 6 postnatal weeks; 3) the Protein Only regimen were dually immunized with MVA-SIVgag/pol and HIV-env protein at 0, 3, and 6 postnatal weeks, and 4) similar to group 2, the Extended Interval regimen received a co-administration of MVA-SIVgag/pol, MVA-HIV-env, and HIV-env protein over an extended time course of 0, 6, 12 and 32 postnatal weeks.

- Envelope-specific binding responses were measured by ELISA, functional antibody responses were measured by neutralization by TZM-bl assay, and ADCC using the GranToxLux assay with gp120-coated target cells.
- Phylogenetic profiling of infant microbiomes was conducted by extracting 16S ribosomal RNA from stool samples. The variable region 4 (V4) of 16S RNA was amplified and amplicons sequenced using the Illumina MiSeq platform.
- 16S RNA reads were quality filtered, demultiplexed, and clustered into operational taxonomic units (OTUs) using vsearch. A subsequent diversity analysis was performed with QLIME, LASSO regression, PCA, and other machine-based learning algorithms.
- The immune responses to the vaccine regimens were correlated to corresponding microbiome population.

Results

- The kinetics of the HIV-1 envelope-specific IgG response was slightly more rapid in the “Protein Only” regimen, but the maximum responses did not differ between the groups. Response persisted in the “Extended Interval” group.

Figure 2. Infant monkey vaccine-elicited plasma gp120-specific IgG kinetics. Kinetics of the HIV-1 envelope-specific IgG response was slightly more rapid in the “Protein Only” regimen, but the maximum responses did not differ between the groups. Response persisted in the “Extended Interval” group.

- Directional correlations were observed in LASSO regression analysis of peak immune response measures from gp120-specific binding responses from the peak immune response time point (2 weeks after the 3rd vaccine) showed a strong, inverse correlation between the avidity immunologic data and a subset of bacteria (red box).

Figure 3. Microbial diversity by vaccine group at the genera level, over time. Diversity is variable within the vaccine groups, though there is a trend of increased diversification as the infants age.

Conclusions

- The kinetics of the HIV-1 envelope-specific IgG response were similar, and the maximum responses did not differ between the groups.
- Microbiota diversity indices indicated greater bacterial diversity at week 15/18 compared to week 0 or week 8.
- The magnitude of the vaccine-elicited gp120-specific IgG responses positively correlated with the frequency of the stool bacteria Megapathora present at birth.
- The frequency of Lactobacillus and Roseburia in stool bacteria at birth was negatively associated with vaccine-elicited gp140-specific binding IgG responses whereas Anaerostipes, Blautia, and Pseudobutyrivibrio was negatively associated with ADCC responses.
- These exploratory data suggest that in infant rhesus macaques, certain intestinal microbiota is associated with HIV Env-elicited immune responses.

Future Directions

- An additional cohort of infant macaques’ stool and saliva will be analyzed using the same methods, validating this data set.
- Subsequent investigations will seek to identify specific taxa that enhance Env-elicited immunity, thus facilitating rational manipulation of the microbiome using probiotics to enhance potentially-protective immune responses following HIV-1 immunization.

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