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Increased mucosal CD4+ T-cell activation following vaccination with an adenoviral vector in rhesus macaques

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Background

The possibility that vaccination with Adenoviral vectors increased mucosal T-cell activation remains a central hypothesis to explain the potential enhancement of HIV acquisition within the STEP trial. Modeling this within rhesus macaques is complicated because human Adenoviruses, including Adenovirus type 5 (HAd5), do not productively infect macaques. We created a vector based upon a naturally occurring rhesus macaque Adenovirus (SAdV7) to test whether vaccination with a species-specific Adenoviral vector enhances mucosal T-cell activation within the natural host.

Methods

Twelve rhesus macaques were vaccinated 3x intramuscularly with SAdV7 vector. Five HAd5-vaccinated animals were included as controls. PBMC and rectal biopsies were obtained at baseline, multiple times post-prime and post-17 week boost (8x/animal), and post-31 week second boost (1x/animal). We assessed rectal mucosal lamina propria and blood for frequency changes of Ad-specific T-cell responses and T-cell activation levels by measuring IFNg, TNFa, IL2, CD25, Ki67, CD69, and HLA-DR.

Results

Naturally acquired pre-existing SAdV7-specific CD4+ T-cells were identified in 10/13 macaques within blood and/or rectal mucosa. Following intramuscular SAdV7 vaccination, rectal SAdV7-specific CD4+ T-cell responses increased above baseline in 9/9 animals 2-5 weeks post-prime, and subsequently contracted. Five weeks post-prime, 10/12 animals had rectal SAdV7-specific CD4+ T-cell responses ranging from 0.1-16.84%. As expected, SAdV7-specific CD4+ T-cells expressed CD69 and other activation markers (but not Ki67). Heightened expression of CD25, CD69, and HLA-DR was observed on total rectal memory CD4+ T-cells in SAdV7-vaccinated animals, and maintained 15 weeks after the prime. Interestingly, upregulation of activation markers in rectal mucosa also occurred in HAd5-vaccinated animals. No change in activation was observed in the blood throughout the entire study.

Conclusion

These results indicate that peripheral vaccination with an Adenovirus vector can increase the activation of mucosal CD4+ T-cells providing an experimental model to further evaluate the role of host-vector interactions on increased HIV acquisition.

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