Merck Ad5/HIV induces broad innate immune activation that predicts CD8+ T-cell responses but is attenuated by preexisting Ad5 immunity

Daniel E. Zak1, Erica Andersen-Nissen1, Eric R. Peterson2, Alicia Sato2, M. Kristina Hamilton2, Joleen Borgerding2, Akshay T. Krishnamurty2, Joanne T. Chang2, Devin J. Adams2, Tiffany R. Hensley2, Alexander I. Salter2, Cecilia A. Morgan1,2, Ann C. Duerre1,2, Stephen C. De Rosa1,2,4, Alan Aderem1,2,3, and M. Juliana McElrath1,2,3

*Seattle Biomedical Research Institute, Seattle, WA 98109; bVaccine and Infectious Disease Division and cHIV Vaccine Trials Network, Fred Hutchinson Cancer Research Center, Seattle, WA 98109; and dDepartment of Laboratory Medicine, *Department of Immunology, and dDepartment of Medicine, University of Washington, Seattle, WA 98195

AUTHOR SUMMARY

A highly efficacious HIV vaccine offers the greatest hope for halting the AIDS pandemic, but it remains unclear what type of immune response an HIV vaccine must induce to be effective. Modest but encouraging results from two recent clinical trials have provided some insights. The RV144 study in Thailand used an engineered poxvirus expressing HIV proteins in conjunction with an HIV envelope protein and demonstrated 31% efficacy in reducing HIV-1 infection (1). MRKAd5/HIV, an adenovirus serotype 5 (Ad5)-based HIV vaccine expressing HIV proteins, and the focus of the present study, did not show efficacy but exerted selective pressure on infecting viruses, forcing them to evolve in response to the HIV proteins it expressed (2, 3). An understanding of the molecular mechanisms controlling HIV vaccine immunogenicity will allow these small gains to be improved upon and may lead to the development of a vaccine that will profoundly impact global health. This understanding is especially critical in the case of the Ad5-based vaccines because, although they have shown great promise against other pathogens, vaccination with MRKAd5/HIV led to an apparently increased risk of HIV infection in Step Study vaccine recipients who already were immune to Ad5 from natural exposure. Understanding the mechanisms of Ad5 vaccines will make it possible to replicate the beneficial properties they exhibit in alternative vaccine platforms.

Here, we took a systems biology approach (4) to understand better the earliest molecular events triggered by the Step Study vaccine, MRKAd5/HIV, in human volunteers. These early immune responses shape the long-term pathogen-specific immune responses induced by a vaccine and may determine whether it will be efficacious. We investigated how these responses were affected by preexisting immunity to the Ad5 vector, how they related to the long-term immune responses to HIV proteins induced by the vaccine, and how they differed from responses induced by a well-characterized licensed vaccine for yellow fever.

We enrolled 35 individuals in a phase Ib clinical trial of MRKAd5/HIV and complemented our analysis of long-term immune responses to vaccine-encoded HIV proteins (measured 1 mo after vaccination) by performing transcriptional profiling of blood cell samples collected before and early (6 h to 1 wk) after vaccination. MRKAd5/HIV caused a massive early transcriptional response with changes in expression of more than 2,000 genes 24 h after vaccination. We observed the induction of inflammation- and antiviral-related genes as well as changes in the expression of genes that indicated altered concentrations of key immune cell populations in the peripheral blood (Fig. PL4). We validated these findings by measuring proinflammatory serum cytokine levels and by enumerating blood cell populations, thus establishing a global picture of the early immune response elicited by the vaccine.

To identify a reason for the increased risk of HIV infection in the Step Study, we then evaluated how these early immune responses to the vaccine, measured 1 mo after vaccination, related to responses earlier in the immune response (24 h) and the innate immune response elicited by the vaccine.

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1. D.E.Z. and E.A.-N. contributed equally to this work.
2. A.A. and M.J.M. contributed equally to this work.
3. To whom correspondence may be addressed. E-mail: alan.aderem@seattlebiomed.org or jmcelrath@fhcrc.org.

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responses to vaccination were affected by previous natural exposure to Ad5. Risk of HIV infection is thought to be increased in a proinflammatory environment; however, we found that volunteers with preexisting Ad5 immunity showed drastically reduced inflammatory responses to the vaccine (Fig. P1A and B). This result suggested that their elevated risk for HIV infection was not caused by overall increased systemic immune activation but instead might result from vaccine antigen recognition in the absence of appropriate inflammatory context, a hypothesis that merits further investigation.

To identify molecular pathways specifically activated by MRKAd5/HIV that distinguish it from an established efficacious viral vaccine, we compared the early molecular pathways it triggers with those activated by YF-17D, a yellow-fever vaccine which, unlike MRKAd5/HIV, was not engineered but rather was developed by attenuation of the yellow fever virus itself (5). We found that MRKAd5/HIV stimulated early immune responses much more rapidly and potently than YF-17D (Fig. P1C). Importantly, MRKAd5/HIV preferentially induced a gene regulatory network that could suppress certain immune responses, including factors known to impair T-cell activation. This finding indicated that the type of immune response elicited by MRKAd5/HIV may not be optimal to establish protective, long-lived memory immune responses and that more may be learned by comparing candidate HIV vaccines with licensed and efficacious vaccines.

Rational design of vaccines will be enabled by understanding the relationship between the early immune responses elicited by MRKAd5/HIV and the long-term pathogen-specific immune responses established by the vaccine. We therefore used computational approaches to identify which aspects of the early molecular responses to MRKAd5/HIV we measured predict the ultimate vaccine-induced development of killer T cells that specifically recognize and eliminate HIV-infected cells. We found that 24-h induction of serum cytokines that attract T cells predicted whether a vaccine recipient would develop an HIV-specific killer T-cell response and that serum cytokines involved in antiviral activity predicted the magnitude of this response. Changes in the expression of 209 genes in blood cells 72 h postvaccination also were significantly associated with the magnitude of the killer T-cell response, and some of these genes also were associated with killer T-cell responses induced by YF-17D (Fig. P1D), suggesting the existence of both vaccine-specific and shared pathways controlling vaccine-induced immunity.

Taken together, the molecular signatures we identified can serve as biomarkers for vaccine responses in humans and provide a framework for comparing early innate responses induced by other vectors and adjuvants. These findings will guide rational vaccine designs to enhance immunity to HIV and other microbes.