Profiling Immunity with Systems Biology against HIV Vaccines

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Abstract

The recent modest success in Thailand of the RV144 HIV vaccine trial has shown that it is possible to produce an HIV vaccine. However, developing a vaccine that achieves improved safety would require a more complete understanding of the mechanisms of action and protective correlations of the vaccine. Designing a vaccine that achieves better protection, however, will require a more complete understanding of vaccine mechanisms of action and correlates of protection. Systems biology approaches enable integration of large datasets from a variety of assays and offer new approaches to understanding how vaccine-induced immune responses are coordinately regulated. In this review, we discuss recent advances in clinical trial design, specimen collection, and assay standardization that will generate datasets for systems analyses of immune responses to HIV vaccines.

Keywords: HIV vaccine • Mechanisms of action • Immunogenicity • T-cell

Introduction

The human immunodeficiency virus type-1 (HIV-1) epidemic has entered its third decade and has claimed over 25 million lives. Extensive animal and human studies have been conducted in the quest to find a successful vaccine to prevent or control HIV-1 infection. After numerous disappointing results, the field was buoyed by the findings of the recent RV144 trial, which showed that at least partial protective immunity against HIV can be achieved. Volunteer samples collected from this trial will allow the measurements of multiple immune responses and, for the first time, hope for understanding features that may have contributed to reduced acquisition of infection in vaccine recipients. Potential help in this effort, the discipline of systems biology is designed to take a holistic approach to understanding a biological system by integrating analyses of many measurements of the system under different perturbations. Systems biology seeks a deeper understanding of biological processes and their interdependence, and produces models that closely reflect nature with the potential to predict biological responses. While the HIV research field has primarily focused on somewhat narrow assessments of immune responses to infection and vaccination that can be reliably measured with the samples available, expanding HIV vaccine analysis to systems biology approaches may help reveal the mechanisms of action behind successful vaccines such as those used in RV144 and will generate novel hypotheses that will drive a new era of rational HIV vaccine design. To collect the most comprehensive datasets for systems analysis, there is a need to gather immune response data using new HIV vaccine trial designs coupled with novel tools and assays to measure immune responses. Generating and integrating comprehensive datasets will be key for identification of the relevant response pathways to target with novel adjuvants and vectors for HIV vaccines [1,2].

Description

The recent modest success in Thailand of the RV144 HIV vaccine trial has shown that it is possible to produce an HIV vaccine. However, developing a vaccine that achieves improved safety would require a more complete understanding of the mechanisms of action and protective correlations of the vaccine. Systems biology approaches allow broad datasets from a variety of assays to be combined and provide new approaches to understanding how organized vaccine-induced immune responses are controlled [3].

Over the past two decades, several clinical trials of HIV vaccine products have been carried out. Usually, phase I and phase II studies examine protection and efficacy, as well as vaccine or inoculation protocol variations that affect immunogenicity. For instance, the effect of DNA priming on a vector boost was addressed by two recently published Phase I trials. Such studies and trial tests showed that with repeated Ad5/HIV, a homologous prime/boost increased antibody responses, but that an HIV-1 DNA prime was more effective at raising T-cell responses [4]. Interestingly, when measured by standard intracellular cytokine staining (ICS) assays, T-cell responses after the HIV-1 DNA vaccine alone were very low, and the superior effect of HIV-1 DNA in inducing higher magnitude vaccine-specific T cells was only observed after the Ad5 / HIV boost. The application of systems biology to the profiling of vaccine response is beginning to open up several new research avenues that will allow a deeper understanding of vaccines currently being tested for HIV and other diseases and will accelerate the production of rational vaccines in the future [5].

Conclusion

The application of systems biology to vaccine response profiling is beginning to open many new avenues of research that will enable a deeper understanding of vaccines currently in trials for HIV and other diseases and will accelerate ration al vaccine development in the future. To achieve holistic profiling of vaccine responses in clinical trials, it is necessary to measure many facets of the immune response using both standardized and more novel assays, and to integrate data from responses Profiled over time. New comprehensive clinical trial designs are beginning to address this issue by including profiling of innate immune responses in addition to adaptive responses, and by measuring responses at both systemic and mucosal sites using assays with diverse read outs. As investigators generate large databases with profiles of different HIV vaccines, it will be vital to compare and contrast the immune profiles obtained to these vaccines with licensed and efficacious vaccines to identify new hypotheses for testing in future trials. In addition, it will critical to form close collaborations between clinical resear-chers and investigators studying HIV vaccines using in vitro and animal model systems to additionally test hypotheses and dissect mechanisms of vaccine- induced immunity. We are optimistic that applying these new tools will bring about a new era of HIV vaccine development, paving the way for development of a highly efficacious HIV vaccine.

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