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Systems vaccinology: Enabling rational vaccine design with systems biological approaches

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ABSTRACT

Vaccines have drastically reduced the mortality and morbidity of many diseases. However, vaccines have historically been developed empirically, and recent development of vaccines against current pandemics such as HIV and malaria has been met with difficulty. The advent of high-throughput technologies, coupled with systems biological methods of data analysis, has enabled researchers to interrogate the entire complement of a variety of molecular components within cells, and characterize the myriad interactions among them in order to model and understand the behavior of the system as a whole. In the context of vaccinology, these tools permit exploration of the molecular mechanisms by which vaccines induce protective immune responses. Here we review the recent advances, challenges, and potential of systems biological approaches in vaccinology. If the challenges facing this developing field can be overcome, systems vaccinology promises to empower the identification of early predictive signatures of vaccine response, as well as novel and robust correlates of protection from infection. Such discoveries, along with the improved understanding of immune responses to vaccination they impart, will play an instrumental role in development of the next generation of rationally designed vaccines.

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1. Introduction

Since Edward Jenner's discovery in the late 1700s that inoculation with the cowpox virus provided protection from smallpox infection, vaccines have emerged as one of the greatest public health tools in history. The last 60 years have established a golden age in the field of vaccinology, marked by events such as the eradication of smallpox by 1980 [1] and the development of polio vaccines in the 1950s, which have lead to near-eradication of the disease [2]. Despite the great success of these and other vaccines, there remain significant challenges for development of new vaccines against current global pandemics such as HIV and malaria. Among the many problems facing this field are: (i) most currently used vaccines were designed largely empirically. As a result there is little or no understanding of what the correlates and mechanisms of protection are for many vaccines. For example, although the two commercially available types of influenza vaccine, trivalent inactivated (TIV) and live attenuated (LAIV), provide similar levels of protection from infection [3], they generate significantly different immune responses. TIV induces higher levels of IgG antibody secreting cells (ASCs) in the blood as well as higher levels of serum antibodies than LAIV in adults. This is likely due to the different routes of administration, as LAIV, which is administered as an intranasal spray, is thought to produce a more local response in the nasal mucosa and upper respiratory tract, including IgA (mucosal) antibodies and cellular immune responses. As a result, the correlate of protection for TIV is generally considered to be serum antibodies, while the correlate of protection for LAIV is less clear [3]. (ii) The path to licensure of candidate vaccines involves very lengthy and expensive phase IIB and III clinical trials to assess their efficacy and safety. These trials involve thousands of subjects and can cost hundreds of millions of dollars to complete. As a result, very few vaccine concepts are tested in phase III trials. For example, during the past 30 years, only 4 HIV-1 vaccine concepts have been tested

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for clinical efficacy [4], and despite repeated failures, the correlates and mechanisms of protective immunity against HIV remain poorly understood.

The conventional immunological methods, such as ELISA, ELISPOT, flow cytometry, etc., used to study vaccines have played a valuable role in the field of vaccinology, and will remain essential in evaluating responses to vaccination in the future. However these approaches are generally only able to analyze a single or small number of components of the immune system at a given time, and are insufficient to analyze the full complexity of the structure and dynamics of the human immune system as a whole. This represents a critical obstacle towards understanding the molecular mechanisms by which vaccines generate protective immune responses and identifying meaningful correlates of protection.

To address this issue, vaccinologists have turned to systems biology. By examining how coordinated interactions at a molecular level give rise to immune responses, systems biology approaches enable a holistic view of the immune system and its many components. This developing field provides many promising tools to overcome the challenges facing current vaccine development. Enabling researchers to evaluate the immune responses of fewer subjects in a more in-depth and detailed fashion has the potential to dramatically improve our understanding of the mechanisms of protection of novel vaccines and decrease the length and costs of current clinical trials.

2. Systems vaccinology

Within the past 20 years, advances in high-throughput technologies have granted researchers the ability to interrogate the properties and abundances of entire classes of molecular components within the cell. For example, development of lower cost next-generation sequencing technology has facilitated the growth of transcriptomics, which seeks to measure the expression of all RNA transcripts within a cell or population of cells. By sequencing and mapping mRNA transcripts, RNA-sequencing enables the accurate quantification of gene expression as well as simultaneous identification of RNA structure such as transcription start site and exon usage/splice junctions, the regulation of which has been shown to play an important role in many biological processes, including within the immune system [5,6]. Simultaneously, in the growing domain of metabolomics, analytical chemistry techniques such as liquid chromatography–mass spectrometry (LC–MS) have been harnessed to identify and quantify the set of metabolites within cells or tissues [7]. Changes in metabolic activity are an important component of both innate and adaptive immune responses [8], such as the recognized role that lipid metabolism plays during inflammation [8–10].

Systems vaccinology is an emerging field that applies such 'omics' technologies, in combination with bioinformatics tools such as transcriptional network analysis and predictive modeling, to study immune responses to vaccination [11–13]. As a systems-based approach, it aims to use data generated through high-throughput measurements in the context of vaccination to characterize the interactions between individual components of the immune system in the interest of understanding and predicting behavior of the system as whole. This includes analysis of transcriptional, signaling, and metabolic pathways whose activity is perturbed in the various cells of the immune system in response to vaccination, as well as identification of molecular signatures that are predictive of various measurements of protection from infection. The knowledge obtained through these analyses can aid in the rational design of new vaccines that generate long-lasting protection and induce improved responses in populations with diminished immune function such as the elderly.

3. Five year historic perspective

The first examples of the use of such approaches to study responses to vaccination were performed on the yellow fever vaccine [14,15]. This vaccine contains a live-attenuated strain (YF-17D) of the yellow fever virus, which induces potent and long-lived CD8+ T cell and neutralizing antibody responses [16,17]. By combining high-throughput measurements such as microarray gene expression profiling and multiparameter flow cytometry with computational modeling, we were able to detect a regulated network of interferon and innate antiviral genes that were induced post-vaccination in peripheral blood mononuclear cells (PBMCs) [14]. An independent YF-17D study by Gaucher et al. revealed induction of similar transcriptional responses to vaccination, including type I interferon and inflammatory pathways [15]. In addition to examining innate immune pathways activated by vaccination, we successfully identified unique gene signatures that were capable of accurately predicting the CD8+ T cell and neutralizing antibody responses, respectively [14]. The predictive CD8+ T cell signature contained complement protein C1qB and eukaryotic translation initiation factor 2 alpha kinase 4, which is an orchestrator of the integrated stress response. Meanwhile the B cell growth factor receptor TNFRSF17 was among the genes included in the antibody response signature. This work demonstrated for the first time that the immunogenicity of a vaccine could be successfully predicted using early transcriptional measurements within 1 week of vaccination.

Following these initial studies, systems biology approaches have been used to examine immune responses to vaccines against a wide range of pathogens, including influenza [18,19], malaria [20], smallpox [21], and HIV [22]. In particular, as YF-17D is a live-attenuated vaccine that induces an acute viral infection, the study of influenza vaccination (TIV) enabled investigation into to whether or not similar methods could be used to identify molecular signatures predictive of response to an inactivated vaccine. We identified transcriptional signatures related to the expansion of plasmablasts and the unfolded protein response within B cells on day 7 post-vaccination that correlated with and were predictive of day 28 influenza-specific antibody responses [18]. Indeed, these findings were consistent with studies by Bucasas et al. [19] and Obermoser et al. [23]. Interestingly, TNFRSF17, which was predictive of antibody responses to YF-17D, also appeared in the signatures predictive of TIV response [18]. Recently, Tsang et al. [24], and Furman et al. [25] have extended this approach to search for baseline signatures capable of discriminating between high and low responders to vaccination. However, possibly due to limited sample sizes and weaker signal at baseline, neither study was able to successfully predict antibody response using baseline transcriptional measurements alone. Instead, Tsang et al. utilized cell subset frequencies, while Furman et al. generated a model based on transcriptional modules, serum cytokines, cell subset frequencies, and pre-existing antibody titers. Additionally, as these studies were conducted using cohorts from an individual flu season, the effect of changes in influenza strains included in the TIV vaccine on the performance of these models remains to be examined. To address this question, we are performing a comprehensive analysis of over 400 adults vaccinated with seasonal TIV during 5 consecutive influenza seasons (Nakaya et al., manuscript in preparation). This analysis is an important step towards generating robust and clinically relevant signatures that can be used to predict the efficacy of vaccines in clinical trials.

Among the vaccines under investigation, malaria is one for which a human challenge model exists, allowing for identification of subjects who are protected from or susceptible to infection [26]. Vahey et al. used this model, in which subjects vaccinated with the RTS,S malaria vaccine were challenged using

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