Seminars in Immunology 25 (2013) 124–129

Contents lists available at SciVerse ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

Review

Systems immunogenetics of vaccines

Michael Mooney[a,b,c], Shannon McWeeney[a,b,c,d], Rafick-Pierre Sékaly[e,*]

[a] Division of Bioinformatics & Computational Biology, Department of Medical Informatics & Clinical Epidemiology, Oregon Health & Science University, United States
[b] Oregon Clinical and Translational Research Institute, United States
[c] OHSU Knight Cancer Institute, United States
[d] OHSU Vaccine and Gene Therapy Institute, United States
[e] Vaccine and Gene Therapy Institute Florida, United States

ARTICLE INFO

Keywords:
Systems biology
Vaccine
Infectious disease

ABSTRACT

Vaccines are the most cost effective public health measure for preventing viral infection and limiting epidemic spread within susceptible populations. However, the efficacy of current protective vaccines is highly variable, particularly in aging populations. In addition, there have been a number of challenges in the development of new vaccines due to a lack of detailed understanding of the immune correlates of protection. To identify the mechanisms underlying the variability of the immune response to vaccines, system-level tools need to be developed that will further our understanding of virus–host interactions and correlates of vaccine efficacy. This will provide critical information for rational vaccine design and allow the development of an analog to the "precision medicine" framework (already acknowledged as a powerful approach in medicine and therapeutics) to be applied to vaccinology.

© 2013 Elsevier Ltd. All rights reserved.

1. Introduction

Since the 1700s, vaccine development has utilized an empirical model (e.g., the "isolate – inactivate/attenuate – inject approach") [1]. The development for vaccines against highly variable and incurable diseases, including acquired immunodeficiency syndrome, malaria, dengue fever and others has largely been unsuccessful which further emphasizes the need for a paradigm shift in vaccine strategies [2]. These diseases require a rational approach for directing vaccine responses toward different immune cell subsets that can vary based on the genetics and cellular tropism of these pathogens [3,4]. An additional component is host variability that includes the multiplicity of immune response genes, as well as the diversity of human leukocyte antigen (HLA) haplotypes, allowing human populations an almost limitless immune response repertoire [5]. Vaccine efficacy can be impacted by a number of other host factors including age, gender, ethnicity, and other possible confounders [6–9]. It is now clear that pathogen and host variability, as well as the interactions between them, must be considered in vaccine design.

2. Current challenges in vaccine development

Oyston and Robinson [10] recently summarized some of the key issues and barriers currently faced in vaccine development that we have aggregated into several major challenge areas (Fig. 1). The first major challenge is clinical characterization. This highlights the need for identification of signatures of immune correlates of protection, novel approaches to quantify patient exposure and immune responsiveness as well as pathogen genetic variation in the population. The lack of well-defined correlates of protection with most vaccines has been a major impediment to the successful development of new vaccines [11]. The second challenge area is the research and development, in which economic constraints can lead to an inflated false nondiscovery rate (e.g., promising candidates are incorrectly discarded early in the pipeline). There is tremendous potential for data mining and computational approaches to "rescue" candidates, emphasizing the need for public repositories and open data. A third challenge area is delivery and includes not only socio-economic concerns regarding vaccine availability and manufacturing but also mode of administration and appropriate dosing. It is here that the systems approaches from precision medicine and pharmacogenomics can lead to "individualized" vaccine delivery.

3. Rationale for systems thinking

In each of the challenge areas described above, there is opportunity for innovative, systems-level and computational approaches

* Corresponding author. Tel.: +1 772 345 5675.
E-mail address: rpsekaly@vgtifl.org (R.-P. Sékaly).

1044-5323/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.smim.2013.06.003

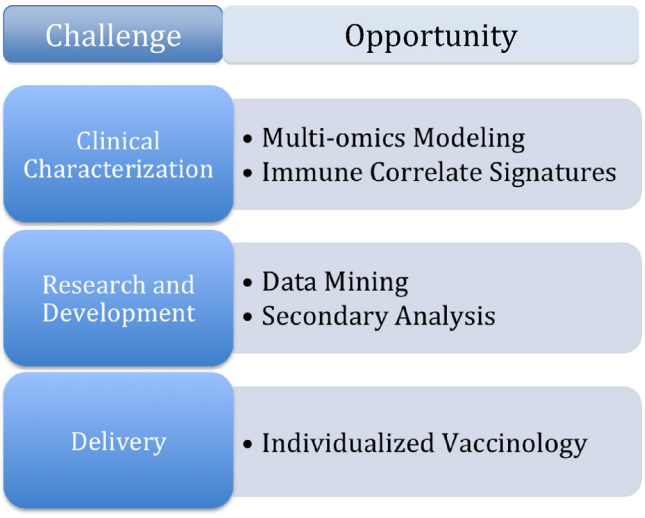

Fig. 1. Current challenge areas in vaccine development offer opportunities for application of systems biology and computational approaches.

(Fig. 1). The response to infection results from complex interactions between the host immune system and the pathogen. Our ability to predict this response and to develop effective vaccines or treatments is complicated by two key factors: (1) the enormous amount of genetic variability in the human population, and (2) the constant evolution of pathogens. These two factors produce a wide spectrum of possible host–pathogen interactions and necessitate the use of systems-level approaches for studying infectious disease [12–15]. Rather than focusing on individual components within a larger process, systems-level approaches attempt to model the entire set of interactions among individual components in a system. These models are then used to predict the behavior (i.e., host response) that results from those interactions.

Systems-level research is dependent on having a complete inventory of the components of a system. The large amount of genomic and proteomic data resulting from advances in high-throughput technologies has greatly improved the ability of researchers to construct models of the host immune system and its interaction with pathogens. This allows us to better characterize the phenotypic variation that is a culmination of multiple interactions among numerous genetic and environmental factors. The field of *systems genetics* integrates the approaches and methods of systems biology with those of genetics to correlate genotype and phenotype in complex diseases [16]. Critical for vaccine development is the related field of *systems immunogenetics* in which the interplay of systems approaches and genetics is focused on the immunological domain.

Gene or protein interaction networks provide a framework for modeling the complex molecular interactions within cells. These networks are built on the idea that disease states are rarely the consequence of a single molecular abnormality (i.e. genetic variation), but are instead the result of the interaction of one or more abnormalities with numerous other cellular components. Network analyses done in a wide variety of diseases have been used successfully to identify sets of functionally related genes, sometimes called modules, associated with disease states. These modules provide insight into disease mechanisms and have also been used to predict outcomes [17].

Recent methodological advances in network analysis are ideally suited for the study of infectious disease. For instance, differential network analysis, which models the change in network structure across time or across multiple conditions, will be a key technique for studying the response to infection and the response to a vaccine [18]. Furthermore, cross-species interaction networks modeling the interactions between pathogen and host, will allow researchers to identify the key factors associated with host response and potential molecular targets for treatment or vaccine development [19].

4. The power of multi-omics comparative studies

Rapid 'omics' technological advances allow high-throughput, quantitative measurement of diverse biological data types including transcriptomics, (mRNA transcripts), proteomics (proteins/peptides), metabolomics (metabolites) and interactomics (molecular interactions). As these approaches are complementary and offer different insights, integration via a multi-'omics' approach, is key to realize a systems perspective. The scale of omic data from biomedical and clinical researchers has recently expanded to an unprecedented level – from basic biology to translational medicine, multi-omic data can enable phenomenal discoveries. To handle these data, a wealth of complex statistical techniques and algorithms has been developed to process, transform, and integrate data.

In addition to the high throughput, high dimensional readouts for 'omics', there is also the development of high throughput, high dimensional immune phenotypes. While classical studies focused on antibody response to vaccination, it is now possible to characterize the complexity and heterogeneity of the immune response. Flow cytometry is a key approach for the characterization of immune phenotypes and function in diverse subsets of cells from complex mixtures [20]. Mass cytometry, or CyTOF (DVS Sciences) is a recent variation of flow cytometry, in which antibodies are labeled with heavy metal ion tags and readout is by time-of-flight mass spectrometry [21]. This allows for the combination of many more antibody specificities in a single sample, without significant spillover between channels.

A major objective in systems immunogenetics is the identification of molecular signatures associated with the immune response after vaccination. Recently, systems biology approaches have been used to study the response to the yellow fever vaccine YF-17D and two influenza vaccines (inactivated and live attenuated) [22–24]. In both studies, a range of molecular measurements and gene expression data were analyzed to identify signatures predictive of vaccine response. Beyond testing for simple correlations within the data, sophisticated machine learning algorithms for feature selection and prediction of the outcomes of interest were utilized. One such approach is 'discriminant analysis via mixed integer programming' (DAMIP) algorithm [22,23,25,26] that provides an optimization-based predictive modeling framework. This approach combines a discrete support vector machine coupled with a robust feature selection module. This well-established approach has the ability to classify with high prediction accuracy even with small training sets [22,23]. These studies were successful in showing that important markers of vaccine protection can be predicted soon after vaccination. This provides a hypothesis-testing framework that can guide future trials or follow-up studies in model systems [2,11,27]. These studies would follow a systems-level "life cycle" focused on the development, refinement, and validation of immune correlates of protection, which can be used to classify innate immune response and protective vaccines in human subjects (Fig. 2).

An important consideration for the development of these signatures of immune response is validation. The development of nanoliter-volume multiplexed real-time PCR allows simultaneous, high resolution, temporal quantification of expression signatures. This is particularly useful for detailed analysis of a candidate signature over many conditions (e.g., multiple time points, stimuli) and at different levels of resolution (single cells, rare cell types and flow sorted/deconvoluted subsets). It is important to note that the

Download English Version:

https://daneshyari.com/en/article/6125867

Download Persian Version:

https://daneshyari.com/article/6125867

Daneshyari.com