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Review

Vaccinomics, adversomics, and the immune response network theory: Individualized vaccinology in the 21st century

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ABSTRACT

Vaccines, like drugs and medical procedures, are increasingly amenable to individualization or personalization, often based on novel data resulting from high throughput "omics" technologies. As a result of these technologies, 21st century vaccinology will increasingly see the abandonment of a "one size fits all" approach to vaccine dosing and delivery, as well as the abandonment of the empiric "isolate–inactivate–inject" paradigm for vaccine development. In this review, we discuss the immune response network theory and its application to the new field of vaccinomics and adversomics, and illustrate how vaccinomics can lead to new vaccine candidates, new understandings of how vaccines stimulate immune responses, new biomarkers for vaccine response, and facilitate the understanding of what genetic and other factors might be responsible for rare side effects due to vaccines. Perhaps most exciting will be the ability, at a systems biology level, to integrate increasingly complex high throughput data into descriptive and predictive equations for immune responses to vaccines. Herein, we discuss the above with a view toward the future of vaccinology.

1. Introduction

In this paper, we review and expand upon a new direction in vaccinology (defined as the science and study of vaccines), and vaccine development (defined as the use of knowledge that derives from the science of vaccines to construct new vaccine candidates), which we have called "vaccinomics [1]." This new direction represents a novel and holistic scientific paradigm under which vaccine immune responses can be studied, understood, and predicted, and with which new candidate vaccines can be conceived, developed, and tested. This represents a radical departure from the historical methodology by which vaccines were developed—an empiric method we have labeled the "Isolate–Inactivate–Inject" paradigm—and that reigned as the dominant mode of vaccine development until the late 1990s. Issues with such an approach include that, for the most part, it: utilized only whole pathogen (live or inactivated) approaches; ignored population genetics (immunogenomics); is a failed paradigm for vaccines against hyper-variable viruses and more complex pathogens (i.e., parasites, fungi, larger bacteria such as tuberculosis); usually required an intact cold chain for vaccine viability; was a "one dose fits all" population-based approach; required large and expensive clinical efficacy and safety trials of genetically uncharacterized populations; resulted in expensive vaccines and, hence, under-utilization and poor vaccine coverage; did not allow an informed understanding of an individual's genetically determined risk for an adverse effect due to a vaccine; and other issues.

Now, guided in part by advances in personalized medicine as applied to the use of drugs, the field of vaccinomics provides a conceptual framework for both understanding (and predicting) immune responses to vaccines, and allows the development of new vaccines informed by advances in immunology, immunogenetics (the study of individual host genetic variation associated with individual differences in immune responses to the same antigen(s)) and

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immunogenomics (the study of population-level genetic variations associated with population-level variations in immune responses), bioinformatics, virology, systems biology, metagenomics (host and non-host), and other fields. We first developed the concept of vaccinomics in 2005, and published an early review in 2007 [2]. Subsequent reviews have enlarged the concept, added more data, and answered questions that have arisen regarding the practical application of vaccinomics, as well as articulating challenges facing the field [3–12]. Others have begun to recognize the importance of vaccinomics in understanding, at a more holistic level, why inter-individual differences in immune responses to vaccines occur, and how these concepts might play a role in new vaccine design [13–15]. Additionally, major initiatives in multiple countries have been proposed using the concept of vaccinomics in studying and evaluating vaccine safety [16]. Additional credibility was lent to the vaccinomics field by a review in *Scientific American* labeling vaccinomics as "one of the most innovative scientific concepts of the decade [17]," and by *The Scientist*, which labeled vaccinomics as "one of the hottest omics fields [18]," as well as by other scientists working in the field who have appropriated vaccinomics concepts into subsets of the systems or bioinformatics aspects of vaccine biology [19,20]. Below we elaborate on the concept and implications of vaccinomics and the immune response network theory, its application to understanding vaccine immune responses, initial analytic approaches to the data generated by vaccinomics, application to new vaccine design and development, and progress toward the ultimate goal – that of developing a predictive equation that describes the immune response to a viral vaccine [19,21].

2. Vaccinomics and the immune response network theory: development of a unified theory

Niels Jerne first proposed in the 1970s the "immune network hypothesis," which theorized how the adaptive immune system worked as an idiotypic network to explain the regulation of clonal immune responses [22]. Later this was expanded into the "symmetrical network theory" in the 1980s through the 1990s by Geoffrey Hoffman in an attempt to solve the "I–J paradox [23]." Incremental additions and changes to these models occurred over the next 20 years, but none were specifically aimed at defining the network *as applied to systems-level vaccine-induced immune responses*. As such, little consideration of factors outside the immediate immune system itself (strictly defined) were included (e.g., gene polymorphisms, epigenetics, the influence of the host microbiome), and, therefore, such features were not incorporated into the models or theories prevalent at the time. Our proposal of the immune response network theory, while building on the foundations of Jerne's and Hoffman's work, as well as other immunologists, is the first proposed in terms of its *focus on systems-level vaccine-induced immune responses*, its intersection with host genetics and non-host factors (microbiome for example), and its theoretical ability to provide the basis for a mathematical model and predictive equation describing the *non-random events* that lead to pre-determined immune responses. Since then, others have also proposed systems-level vaccinology approaches [19,20,24–27].

The immune response network theory in its simplest form states that "the response to a vaccine is the cumulative result of interactions driven by a host of genes and their interactions, and is theoretically predictable [2]." We elaborated further on this definition to recognize the impact of epigenetic phenomena, such as gene methylation patterns, the influence of metagenomics (the microbiome), the dominance profile of a given gene/SNP(s), complementarity, epistasis, systems biology and immune profiling, and other factors, including environmental and co-infections [7,9]. This includes a concept we previously introduced termed "polymorphic plasticity," whereby a specific gene polymorphism could have different measurable genetic (and therefore phenotypic) effects based on concomitant epigenetic effects, effects due to co-infection with other pathogens, or other variables [2,28,29]. As we have previously written:

> For an individual to develop a protective immune response to an antigen, a complex series of biologic, molecular, genetic, physiologic, and other processes must be activated (and in some cases suppressed). Antigen recognition, processing, presentation, and activation of innate, adaptive, and cell-mediated immune responses must occur. Protective immunity requires the activation/suppression of specific genes as well as protein transcription, expression, secretion, and function. The immune response network theory seeks to provide a framework for the above described interactive and carefully regulated processes that result in protective responses against pathogen threats [7].

To this traditional view we should add that superantigens can nonspecifically cause massive polyclonal T cell activation without requiring the seemingly orderly steps of the adaptive immune system noted above.

Thus, while the immune response network theory recognizes and incorporates elements of the immune response not yet discovered at the time of Jerne and Hoffman, it includes the immunogenetics of response to antigen, and the growing appreciation of systems biology approaches to understanding more holistically how immune responses are generated and sustained in the host [2,5]. This theory recognizes the roles of individual components (nodes) of the immune system (immune response genes, epigenetic phenomena such as gene methylation patterns and contributory SNPs), as well as networks or pathways composed of groupings of individual genetic components (genes, gene pathways, gene networks, etc.) of the immunogenetic system and other factors determinative of immune response (microbiome, etc.), at both individual and population levels. The immune response network theory and its fundamental application to vaccinomics draws together all of these components and utilizes biostatistics and bioinformatics to deconvolute, visualize, analyze, and understand the individual and group components that together compose immune response phenotypes (neutralizing antibody, cytokine responses, innate immune responses, cell-mediated immune responses, etc.) that are typically measured and labeled "the immune response."

As of this writing, we conceive the immune response network theory as an encompassing theory that holistically recognizes and explains the temporal, genetic, and immune aspects that together are deterministic and predictive of the immune response(s) to a specific vaccine. Thus, we posit that it can theoretically explain, and eventually predict, the immune response to a vaccine in the form of a mathematical equation that accounts for the complexity of the system. The immune response network theory and the development of a predictive equation implies a deconvoluted yet mechanistic determination of key genetic and other variables that together explain innate, adaptive, and cell-mediated immune phenotype archetypes and individual response patterns [7]. Vaccinomics then uses this and other omics information to engineer novel vaccine candidates that overcome genetic barriers to developing protective immunity. These concepts arose out of our studies demonstrating highly significant associations between specific single nucleotide polymorphisms (SNPs) and gene pathways and networks, human leukocyte antigen (HLA) haplotypes, and immune responses to a variety of viral vaccines, including measles, mumps, rubella (MMR) [30–33], vaccinia (smallpox) [34–37], and influenza [3,4], and one bacterial vaccine (anthrax) [38,39]. In addition, compelling evidence for the predetermined influence of host genetic factors on inter-individual variations in immune