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Molecular signatures for vaccine development

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ABSTRACT

The immune system has evolved complex and specialized mechanisms to mount specific defense responses against the various types of pathogens it encounters. For the development of new vaccines, it is crucial to gain a better understanding of what these mechanisms are and how they work. The field of vaccinology has adopted high-throughput profiling techniques to gain more detailed insights into the various immune responses elicited by different vaccines and natural infections. From all detailed transcriptional profiles generated today, a general picture of immunological responses emerges. First, almost every type of vaccine induces an early interferon-dominated signature. Second, different vaccine formulations induce distinct transcriptional signatures, representing the highly specialized defense mechanisms that must cope with the different pathogens and insults they cause. Transcriptional profiling has shifted its attention toward early molecular signatures, with a growing awareness that early innate responses are likely critical instructors for the development of adaptive immunity at later time points.

1. Introduction

High-throughput transcriptional profiling studies are increasingly applied for detailed insights into the host response evoked by vaccines. The ultimate goal of such profiling studies is the identification of molecular biomarkers and signatures that can predict vaccine efficacy. Although such studies may capture the overall host response to vaccination in a single sketch, analysis of the complex data generated can be challenging. Key issues of study design include sample type and size, timing of sampling, data analysis, non-specific effects, and impact of gender and age on outcome of vaccination [1]. A plethora of transcriptional profiling studies have been published over the past decade describing vaccine- or pathogen-related signatures both *in vivo* and *in vitro*. A number of these studies have already been reviewed by Wang et al. [2]. Here we will focus on most relevant, and most recently described, signatures.

2. Signatures of natural infection

The immune system has evolved complex and specialized mechanisms to counteract different pathogens with unique defense responses (see Box 1 for a short list of the key components of the host immune system that drive defense responses against pathogens). Many natural infections evoke potent immune responses, which effectively eliminate the pathogen and often induce long-lasting protection against reinfection. For these infections, understanding the mechanisms underlying protection against natural infection can provide valid information for vaccine design. Therefore, a closer look at these molecular signatures evoked by natural infection can be highly informative. This, however, is not true for all infections, since several pathogens are capable of manipulating the immune system. In these instances, vaccines need to be designed that induce a more efficient immune response than natural infection.

One intriguing study is the combined approach of Jenner et al. [3]. This systematic comparison collated and analyzed published transcriptional profiling datasets from 32 studies that involved 77 different host–pathogen interactions. Common host signatures induced in different cell types and in response to multiple pathogen species are likely to represent a general “alarm signal” of infection. The most strongly and consistently upregulated genes are almost exclusively pro-inflammatory mediators, including interferon (IFN)-related genes. Other shared host response genes are

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Box 1: Key components of host defense mechanisms

Antigen presenting cells (APCs)
Cells that process and display antigens to T lymphocytes.
Dendritic cells (DCs)
Professional APCs; several specialized subtypes exist in blood and in tissue exposed to external environment.
Natural killer cells (NKs)
Cytotoxic lymphocytes, part of the innate immune system; provide rapid responses to virus-infected cells.
Macrophages
Central role in non-specific defense responses; engulf and digest/destroy cellular debris, microbes, and aberrant cells.
Neutrophils
Phagocytic cells involved in first line of defense against invading pathogens; highly abundant in blood, recruited to site of inflammation.
T lymphocytes/T cells
Cells of the adaptive immune system; play a central role in cell-mediated immunity; regulating immune responses and mediating destruction of infected cells.
B lymphocytes/B cells
Cells of the adaptive immune system; play a central role in humoral immunity by producing antigen-specific antibodies; can act as APCs.
Pattern recognition receptors (PRRs)
Recognize molecules associated with pathogens; activate innate immune responses.
Toll-like receptors (TLRs)
A subgroup of pathogen-associated molecular patterns (PAMPs); recognize structurally conserved molecules from pathogens; initiate innate immune responses.
Chemokines
Signaling proteins secreted by cells; mediate chemotactic signals to cells of the immune system to migrate into defined sites, *e.g.*, inflammatory foci.
Cytokines
Signaling proteins secreted by cells; regulate immune responses, maturation and activation of specific cell populations.
Interleukins (ILs)
Cytokines typically produced by, and acting on, leukocytes; used for systematic nomenclature (IL-1, IL-2, *etc.*).
Interferon (INF)
Type I IFN: central cytokine of the innate defense mechanism; secreted by cells in response to pathogens; type II IFN: primarily produced by T cells; both IFNs trigger several signaling pathways leading to a typical IFN gene expression signature.
Inflammasome
Component of the innate immune system; protein complex promoting maturation of certain inflammatory cytokines, notably IL-1ß, and IL-12.

associated with lymphocyte activation, antigen presentation, cell adhesion, and tissue invasion.

Transcriptional host signatures common to many host–pathogen interactions are mediated by a shared number of transcriptional regulators and cytoplasmic signal transducers that activate the immune response. Similarly, a "healthy" immune response also activates negative feedback mechanisms. It is thus not surprising that immune response-limiting genes and anti-apoptotic genes are represented as well in the shared host response signatures [3]. Yet, defense responses to distinct pathogens require preferential induction of genes in distinct cells, mediated by specific host factors. Combined, analysis of the different host–pathogen interactions suggests that the host response consists of a spectrum of transcriptional programs that form unique and specific combinations, involving numerous transcriptional regulators [3].

Professional antigen presenting cells (APCs), like dendritic cells (DCs), respond in a distinct manner, depending on their phenotype and the nature of stimulation. In an *in vitro* setting, DCs generated in the presence of interleukin (IL)-4 respond more strongly to influenza virus and *Salmonella enterica* (SE) infection than DCs differentiated with IFNα (IFNα DCs). However, response magnitude to *Staphylococcus aureus* (SA) is similar for both DC phenotypes [4]. Antiviral responses comprise various IFN-regulated genes, whereas early bacterial responses are primarily associated with signatures of proinflammatory molecules, and late bacterial responses are strongly dominated by genes involved in antigen presentation and maturation of APCs.

Similarly, direct stimulation of DCs by distinct inflammatory mediators, including Toll-like receptor (TLR) ligands, cytokines and ligands for cytoplasmic receptors, induce different transcriptional signatures. TLR7 agonists (like single-stranded nucleotides), for example, induce signatures in IFNα DCs that closely correlate to those induced by influenza virus. SE shows induced signatures that best match with lipopolysaccharide (LPS) (*i.e.*, a gram-negative bacterial cell wall component that acts as TLR4) and with responses induced by TLR7/TLR8-ligand [4]. Such diverse responses to inflammatory stimuli by phenotypically distinct cells emphasize that the experimental setup in high-throughput profiling studies can profoundly affect the outcome of the host response. Cellular signatures evoked by stimulation with different vaccines in the same study will be described in the next section.

3. Signatures of vaccination

In recent years, high-throughput transcriptional signatures have been investigated to study immune responses induced by existing and candidate vaccines. These studies primarily focus on early-induced innate immune responses, rather than the more traditional adaptive responses at later time points (*e.g.*, antigen-specific T cell function). Different vaccines induce distinct transcriptional profiles depending on pathogen type, adjuvant formulation, and target cell type. Such distinct signatures illustrate the diverse functionality of different APCs in responding to distinct groups of pathogens.

The above-mentioned study by Banchereau et al. [4] combined infection of DCs with vaccine-induced *in vitro* and *in vivo* responses. Several subsets of DCs, as well as monocytes, were stimulated with 13 commercially available vaccine preparations. The signatures observed show that inactivated viral vaccine responses are dominated by IFN responses, while inactivated bacterial vaccines induce a much broader response. In addition, bacterial vaccines are more potent activators of inflammasome functions, DC maturation, and Janus kinase/signal transducer and activator of transcription (JAK–STAT) signaling. In an *in vivo* setting, inactivated influenza virus preparations induce transcriptional signatures that are most prominent within the first 2 days post-vaccination. These signatures are mainly associated with activated pathways involved in DC maturation and T cell activation. Interestingly, similar signatures are induced in symptomatic but not in asymptomatic influenza-infected individuals. These findings underline that signatures from natural infections mirror activation by homologous vaccines and thus can provide valid information for rational vaccine design.

3.1. Influenza

The most detailed studies of vaccines, in terms of systems biology approaches, are those against influenza and yellow fever. Influenza globally affects an estimated 5–10% of adults and 20–30% of children annually, with particular risk for certain groups of individuals [5]. Lorenzo et al. [6] reviewed the immunobiology of influenza vaccines with a strong focus on profiles underlying

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