Chapter 58
Systems Biology–Based Approaches Applied to Vaccine Development

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ABSTRACT

Vaccines represent one of the most cost-effective ways to prevent and treat diseases. The use of vaccines in the control of viral diseases represents an important milestone in the history of medicine. The genomic revolution brought us the possibility to scan genomes in the search of new and more effective vaccine candidates and the advancement of bioinformatics provided the framework for the application of strategies that were focused not only on antigen discovery but also on comparative genomics, and pathogenic factor identification and data mining. In addition, the progress in post-genomic technologies including gene expression technologies such as microarray and proteomics gave us the opportunity to explore the host responses to vaccines leading to a better understanding of immune responses to pathogens and/or to vaccines, assisting in the development of new and better vaccines and adjuvants. This chapter will review how systems biology-based approaches including genomics, gene expression technologies, and bioinformatics have changed the way of thinking about antigen discovery and vaccine development. In addition, the chapter will discuss how the study of the host responses in combination with "in silico" approaches could help predict immunogenicity and improve the efficacy of vaccines.

INTRODUCTION

Since the first historical experimental vaccination, the inoculation with the related cow-pox virus to induce immunity against the deadly scourge of smallpox, conducted by Edward Jenner more than 200 years ago, vaccines have represented one of the most successful approaches to control and cure disease in medical history. Indeed, at the end of the 20th century, the U.S. centers for disease control and prevention (CDC) cited vaccination as the number one public health achievement of the past century. As an example of the achievements

obtained by vaccination, in 1980s, the World Health Organization declared the world free of endemic smallpox. Furthermore, diseases such as diphtheria, pertussis, tetanus, measles, mumps and rubella experienced, thanks to vaccination programs, a 95-100% reduction in case number (MMWR Morb Mortal Wkly Rep, 1999). Despite the success of vaccination programs implemented so far, pathogenic microorganisms are still the most important health threat worldwide, therefore the challenge of developing new, better and more efficient vaccines remains unanswered. For instance, for devastating diseases such as malaria, tuberculosis, Chagas disease or AIDS, no effective vaccine is available. Even if treatment is available, it is expensive, poorly effective or privative for poor and under developed countries. The appearance of newly emerging infectious agents like H1N1 swine flu virus or severe acute respiratory syndrome (SARS) coronavirus and re-emerging pathogens such as *Clostridium difficile*, *mumps virus*, *Streptococcus group A* and *Staphylococcus aureus*, reinforce the necessity to speed up the development of vaccines and immunotherapeutics, especially considering that the World Health Organization (WHO) expects at least one such new pathogen to appear every year (Dong, 2008; Yang, 2008). Thus, the technological breakthroughs in genomics, transcriptomics, proteomics, metabolomics and methodological advances in bioinformatics (Kandpal, 2009) set the perfect scenario for vaccine development. The omics era -driven promises accelerated antigen discovery and the framework to understand how organisms respond to infections. Fundamental questions are expected to be addressed, such as how the immune response is elicited by a particular organism and how this knowledge can be used to improve vaccine efficacy.

The development of vaccines has followed closely the history of biomedical research. Early vaccines were in general based on killed or attenuated microorganisms or in some cases chemically inactivated components. As we further advance

our understanding of the molecular mechanisms associated with infection, novel pathogenic factors and determinants were characterized, including attachment and colonization factors, toxins, capsular polysaccharides, surface proteins, capsid coat proteins, internal core antigens, and proteases. The identification of several microbial antigens that can be targeted led to the identification of a potential single target for vaccine development (reviewed in Vivona, 2008). With the development of molecular biology techniques, a dramatic change in the field of vaccinology occurred. Previously identified single vaccine targets were now cloned, expressed in homologous or heterologous systems such as bacteria and more recently yeast, leading to the development of recombinant vaccines.

An example of a very successful recombinant vaccine is the Hepatitis B vaccine (Andre, 1990), which became first available in 1981. Hepatitis B is a contagious liver disease that results from infection with the hepatitis B virus (HBV). It can range in severity from a mild illness lasting a few weeks to a serious, lifelong illness occurring when HBV remains in a person's body (chronic hepatitis B), resulting in long-term health problems, and even death. The vaccine contains one of the viral envelope proteins, hepatitis B surface antigen (HBsAg). A course of three vaccinations is given to provide a long-term protection from HBV infection.

With the publication of the *Haemophilus influenzae* genome in 1995, the first free-living bacterial genome sequenced (Fleischmann, 1995) and a new era in biomedical research began. This milestone is known as the genomic revolution. Furthermore, this technological breakthrough provided a framework to approach biological problems at the systems level thus, complementing our reductionist methods, this new strategy is termed systems biology (Bruggeman & Westerhoff, 2007). This idea basically advocates the concept that biological systems display emergent properties which cannot be unraveled by breaking down the system into pieces as proposed by reductionism, but instead

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