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Research review paper

Genome- and proteome-wide screening strategies for antigen discovery and immunogen design

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ABSTRACT

Infectious diseases remain a leading global cause of morbidity and mortality and there is an urgent need for effective approaches to develop vaccines, especially against complex pathogens. The availability of comprehensive genomic, proteomic and transcriptomic datasets has shifted the paradigm of vaccine development from microbiological to sequence-based approaches. However, how to effectively translate raw data into candidate vaccines is not yet obvious. Herein, we review cutting-edge technologies and screening strategies to mine genomic sequence information for state-of-the-art rational vaccine design, and highlight recent trends. Interdisciplinary approaches which cross the traditional boundaries of genomics, molecular biology, cell biology, immunology and computer science, and which prioritise antigens according to clinically relevant criteria, offer potential solutions to the widespread threat that complex pathogens pose to public health.

Contents

1. Introduction

Infectious diseases account for approximately 16% of adult deaths across the globe (http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html) and up to 68% of the mortality rates of children under five years of age (Black et al., 2010).

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Leading infectious agents include HIV (AIDS), *Mycobacterium* spp. (tuberculosis), *Plasmodium* spp. (malaria) and *Trypanosomatid* protozoa (leishmaniasis, trypanosomiasis). All are complex pathogens that cause global pandemics and cause chronic infections, many have adapted to long-term coexistence with the human immune system, and relevant correlates of protection against these pathogens as well as their mechanisms of immune evasion are not well understood.

The control of infectious diseases is seriously threatened by the steady increase in the number of pathogens that are resistant to a broad range of antimicrobial agents, associated with increased morbidity and increased rates of disease transmission (Holmberg et al., 1987; Rubinstein, 1999). Reducing the likelihood of infection and disease by vaccination is widely considered to be the most effective and sustainable public health intervention (Einsiedel, 2011). However, vaccines against hypervariable viruses, complex bacteria and parasites have proved elusive and many existing vaccines require yearly reformulation and repeat immunisation. Compared to pathogens for which vaccine development has been successful, complex pathogens generally have high mutation rates and genetic variability, which allow them to actively evade the host immune system, affect a wider age group and induce only strain-specific protection without long-lasting protective immunity (Tobin et al., 2008).

Most currently licensed vaccines use live, attenuated or killed whole pathogens as immunogens, and derive from empirical methodologies pioneered by Edward Jenner and Louis Pasteur in the 18th and 19th centuries, respectively. However, the large number of datasets and technological advances in the "omics" era has led to the advance of high-throughput approaches enabling antigen discovery for sub-unit vaccines (Doolan et al., 2003a; Rappuoli, 2000). Herein we discuss new approaches using computational and immunomic technologies for antigen discovery and recent trends in integrative next generation vaccine design strategies. A timeline of the most important milestones for antigen discovery and vaccine design in the last two decades is presented in Fig. 1.

2. "First and second generation" vaccine development and empirical antigen discovery

In the 18th century Edward Jenner pioneered the field of vaccinology by demonstrating that a boy inoculated with pus from a cowpox-infected milkmaid was protected against the human smallpox virus. This work was further refined by Louis Pasteur who established the principle of isolation, inactivation and administration of pathogens for vaccine development (http://www.cdc.gov/mmwr/preview/mmwrhtml/00000572.htm). Throughout the 20th century, these "first generation" vaccines, consisting of live, attenuated or killed pathogens, have been widely employed against several disease-causing microbes (e.g. plague, pertussis, polio, rabies, smallpox) (Bagnoli et al., 2011). The whole organism approach offers the benefit of delivering a vast array of antigens in their native conformation. However, the requirement for large-scale production of pathogens and the risk of reversion to the virulent form have led to the development of a safer "second generation" of vaccines made up of purified pathogen components (tetanus, diphtheria, anthrax, pneumonia, influenza, hepatitis B, lyme disease) (Bagnoli et al., 2011). Sub-unit vaccines, based on the native macromolecules of pathogens, aim to mimic pathogen-specific exposure in order to trigger the host immune system to generate effector and memory immune responses that would protect against future infection. However, the development of sub-unit vaccines requires strategies to identify potential antigens capable of eliciting protective immunity.

Conventional approaches to antigen identification typically start with the cultivation of the target pathogen under laboratory conditions. The component proteins are then assayed in a cascade of in vitro and in vivo assays, leading ultimately to the identification of a subset of proteins associated with protective immunity. However, not all pathogens can be cultivated outside the host organism, many proteins are expressed only transiently during the course of infection, and not all proteins are abundant enough to be detected by in vitro assays.

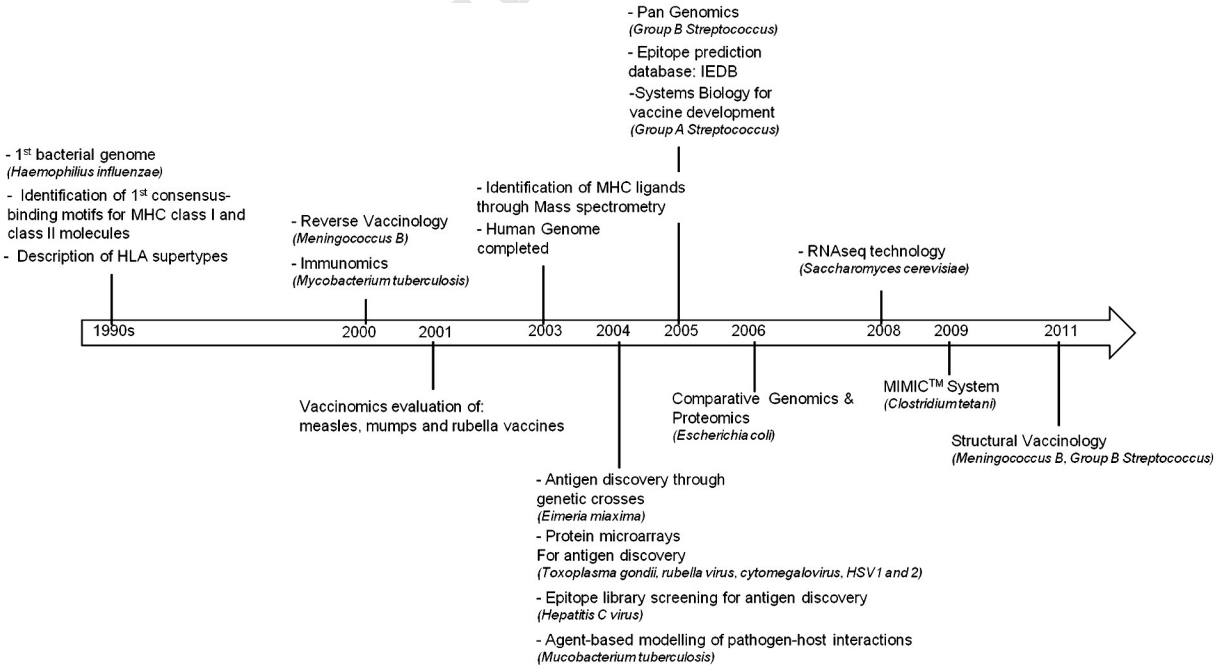

Fig. 1. Milestones for large-scale antigen discovery. The completion of the first bacterial genome sequence in 1995 provided the foundation for a new era of vaccine development based on genomic information. Genomic, proteomic, and transcriptomic datasets form the basis for reverse vaccinology and immunomics approaches pioneered at the beginning of the 21st century. Since then, advances in mass spectrometry and high-throughput sequencing techniques have led to more rapid and accurate identification and evaluation of vaccine candidates. A plethora of high-throughput approaches and databases are now available to predict, evaluate and test vaccine candidates in silico, in vitro and in vivo.

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