Current Advances in Multi-Epitope Viral Vaccines Development and Research

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A. M. V. N. Prathyusha and Pallaval Veera Bramhachari

Abstract

Viral diseases are major public health concern and cause significant morbidity and mortality globally. The following dreadful viruses viz. Influenza virus, Ebola virus (EBOV), and Sudan virus are the most recent viruses to cause a global health concern. Despite recent progress in reduced deaths by viral infection, need for new molecular, immunoinformatic tools, together with safe plus effective vaccines is prerequisite due to the pros and cons of prophylactic and therapeutic vaccines in failure to provide optimal protection. The challenges for viral vaccine advancements are not restricted for recognition of suitable antigens or adjuvants and delivery methods, nonetheless cover technical and manufacturing hurdles in transforming a vaccine to clinic. Research and process improvement is technological basis which prompts production of new vaccines, essential for commercialization. In this review, we emphasize the present status and recent advances in designing and developing viral vaccines.

Keywords

Viral vaccines · Multi-epitopes · Inluenza virus · Ebola virus (EBOV) · Hepatitis E virus

18.1 Introduction

During the past three decades several notable zoonotic virus infections, viz. HIV, Nipah (NiV) viruses, Hendra (HeV), Ebola, avian influenza, Marburg filoviruses, Lassa virus (LASV), Crimean–Congo hemorrhagic fever (CCHF) viruses and many more have emerged suddenly from anonymity and became serious health threats

A. M. V. N. Prathyusha · P. V. Bramhachari (✉)
Department of Biotechnology, Krishna University, Machilipatnam, India

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globally, provoking concern regarding their sustained epidemic transmission in immunologically naive human population. With each new threat rapid need for development of effective and efficient vaccines have been significant part for public health concern. Indeed, vaccines are considered powerful strategy for prevention of emerging viral infections, since, in most of the cases, further options for treatment or effectiveness of therapeutics are limited or nonexistent. Vaccines for number of viral diseases with major health concern are not yet available. However, struggles are still enduring to develop fully effective vaccine strategies for recurrent and emerging viruses and other current threats need to be addressed. In addition, resurgent interest remains, in development of new vaccines strategies against pandemic viruses (Kanekiyo et al. 2019).

Traditional vaccine development approaches are amenable yet for emerging viruses, while application of molecular techniques in virology has profoundly influenced our understanding of virus biology. New approaches and technologies hold an essential role in modern vaccine development and in silico approaches, multi-epitope (B and T cell epitopes, peptide, subunit) vaccines using immunoinformatics depicts a major role to address challenges in vaccine development. In silico approaches have attained great acceptance with current advancements in genome and protein sequence databases. With the advancements in immunoinformatics, limitations related to prediction of accurate B cell epitopes and human class I and II restricted T cell epitopes are surmounted. This strategy can assemble vaccines with epitopes for optimal presentation by phagocytic processing machinery. Furthermore, several promising approaches are heading from lab to clinic to address unresolved challenges in viral vaccine development. It is notable that multi-epitope (ME) vaccines possesses the ability to stimulate ample repertoires of immune responses, along with dealing to pathogens effectively with genetic variations. Several approaches of vaccination relying to replicating, attenuated, and nonreplicating virus vectors have become useful vaccine delivery platforms. This chapter emphasizes a few recent multi-epitope vaccine approaches for effective vaccines encompassing some current vaccine platform strategies.

18.2 Multi-Epitope Vaccines

Epitope-based vaccines (epitope vaccines) signify novel approach for generation of specific immune response and prevention of unfavorable responses against other epitopes in complete antigen. EVs have several advantages over other forms of vaccines, particularly with regard to safety, ease of production, storage and distribution, without cold chain issues. They also offer opportunity to vaccinate against several pathogens or multiple epitopes from same pathogen. Potential advantages of epitope-based vaccines also include increased safety, opportunity to rationally engineer epitopes for increased potency and breadth, and ability to focus immune responses on conserved epitopes.

18.3 Multi-Epitope Subunit Vaccines

Subunit vaccines comprise merely antigenic part of virus with potential to promote immune response while overcoming problems associated with conventional vaccines. Exploitation of vaccination strategy in combating virus is a major concern since synthesis of conventional vaccines often has several obstacles. Hasan et al. developed novel reverse vaccinology approach that aims to link immunogenetics, immunogenomics using bioinformatics to identify new vaccine targets. Detection of T cell and B cell epitopes and HLA (human leukocyte antigen) using in silico approaches reinforced a possibility in potent vaccine candidate discovery. Vaccine candidates may be identified as foreign molecules after injection to body. Therefore, prediction of antigenicity is a crucial part in synthesis of subunit vaccines. Furthermore, assessment of hydrophilicity is a significant criterion for B cell epitope prediction. Hasan and group reported a design to synthesize nonallergic, immunogenic, and thermostable chimeric ME monovalent subunit vaccine against avian influenza A (H7N9) virus, and Marburg virus using vaccinomics approach. Viral proteome was assessed for epitopes with high antigenicity using TMHMM, VaxiJen v2.0 server (transmembrane topology screening), AllerTOP, AllergenFP, PA^{3}P, Allermatch servers (allergenicity and toxicity analysis), IEDB's epitope conservancy analysis tool (population coverage assessment), and MGL Tools (molecular docking). Two proteins, envelope glycoprotein (GP) and matrix protein (VP40), generated potent T cell epitopes and are recognized to be most antigenic proteins in Marburg virus. PEP-FOLD de novo approach was used in prediction of 3D-peptide structures from amino acid sequences of top ranked epitopes. Finally, three vaccines were designed most effectively using suitable adjuvants with PADRE sequence, combined in sequential manner with highly immunogenic (CTL, HTL, and BCL) respectively. Such constructed vaccines with predicted epitopes were validated experimentally using animal models for their nonallergic reactions and immunogenic potential (Hasan et al. 2019a, b). Using similar approaches subunit vaccines may be produced against Chikungunya virus (Narula et al. 2018), Kaposi's sarcoma-associated herpesvirus (KSHV) (Chauhan et al. 2019) respectively.

18.4 Multi-Epitope DNA Vaccines

DNA vaccines imply a convenient method to design vaccines with tailored epitopes being administered into plasmid vectors with desirable memory response. Furthermore, to evade unfavorable immunodominant epitopes from pathogens, chimeric multi-epitope-based DNA vaccine was designed against subgroup J avian leukosis virus in chickens (Xu et al. 2016). Bounds and his group using in silico algorithms designed DNA construct entailing HLA class II-restricted T cell epitopes obtained from GP and NP (nucleocapsid protein) of EBOV (Ebola virus), SUDV (Sudan virus), and structural proteins of VEEV (Venezuelan equine encephalitis virus). Identified epitopes with high specificity were examined for binding ability to soluble HLA molecules. Then vaccinated BALB/c mice with ME-DNA

vaccine developed and evaluated for immune response using interferon (IFN)-g ELISpot analyses. These studies provide a concept for designing an ME immunogen along with evaluation focusing on immune response concerning preferred T cell epitopes (Bounds et al. 2017).

18.5 Multi-Epitope Peptide Vaccines

Peptide vaccination can induce both humoral- and cell-mediated immune response by stimulating T cell immunity in both humans and animals with minimal side effects. Peptide vaccines are short immunogenic peptide fragments which can elicit targeted immune response avoiding the chance of allergenic responses. Several peptide vaccines were under progress, viz. vaccine for hepatitis C virus (HCV), human immunodeficiency virus (HIV), foot and mouth disease, malaria, influenza, swine fever, human papilloma virus (HPV), and anthrax (Verma et al. 2018). With advancements in computational biology and immunoinformatics approaches, designing effective strategies for prediction of antigenic epitopes became easier. A peptide-based vaccine is majorly presented via class II MHC molecules and gets processed by endocytic pathway. Immune response can also be induced by cytotoxic T cells (CTL) by cross-presentation where exogenous antigens are processed and presented onto class I MHC. To improve antigenic presentation, cell penetrating peptides (CPPs) was one of the promising approach to penetrate peptides efficiently into cells using cationic peptides (TAT). Commonly used methods for CPP designing and tagging to antigen were: (1) chemical linkage through covalent bonds, and (2) recombinant fusion constructs by bacterial expression vectors. Gross et al. tagged a C-terminal viral protein R (Vpr55-91 and Vpr55-82) fragment of human papillomavirus to CPP which paved way for practical ME immunization for neoantigen vaccination in cancer patients and is effective now clinically (Gross et al. 2019).

18.6 Vector-Based ME Vaccines

Site-specific recombination with Cre-recombinase based multi-epitope (ME) vaccine was designed using relatively conserved immunogenic domains of antigenically distinct strains of the H5, H7, and H9 avian influenza viruses. Three domains M2 ectodomain (M2e), hemagglutinin (HA) fusion domain (HFD), T cell epitope of nucleoprotein (TNP) and HA α-helix domain (HαD) were separated by linkers and inserted into Human Adenovirus (Ad) vector. BALB/c mice were vaccinated and evaluated for immune responses and protection efficacy using hemagglutination inhibition, viral neutralization, ELISA, and ELISpot assays. Such ME vaccine approach provided broad protection against avian influenza virus (Hassan et al. 2017). Yasmin and group have designed an RNA-dependent RNA polymerase (L) epitope-based ME vaccine using immunoinformatics. Two conserved envelope glycoproteins GP1 and GP2 of EBOV were recognized as targets for synthesis of epitope vaccine using various softwares. Collected EBOV glycoproteins were sequenced using further examination for proteins with good immunogenicity by in silico

approaches. Such predicted B and T cell epitopes can confer long-lasting immunity against EBOV with better ability of protection (Yasmin and Nabi 2016).

18.7 Current Vaccine Platform Strategies

Strategies for growth of triumphant vaccines are due to design of an antigen delivery system that optimizes antigen presentation and stimulates broad protective immune responses. Recent advances in vector delivery technologies, immunology, basic virology, genetics, and molecular cell biology have led to in-depth understanding of cellular mechanisms by which vaccines should stimulate the adaptive immune response, thus presenting novel strategies of vaccination. Classic approach to vaccine development is still acquiescent to emerging viruses, the application of molecular techniques in virology has overwhelmingly predisposed our perception of virus biology, and vaccination schemes based on replication strategies, attenuated and nonreplicating virus vector approaches that have turned out to be valuable vaccine platforms. Several virus-like particle (VLP)-based vaccines are currently commercializes in global market, including vaccines against hepatitis B virus and human papillomavirus (Roldao et al. 2010). Furthermore, through genetic fusion or chemical conjugation, VLPs are attractive carrier proteins of foreign antigens, since they can efficiently display them within a host immune system (Tissot et al. 2010; Plummer and Manchester 2011, Brune et al. 2016). An important advantage of VLP-based vaccine platforms is that VLPs can present antigens in a dense, repetitive manner, thus effectively enabling the cross-linking of B cell receptors (BCRs) (Zabel et al. 2014).

18.8 Innovation Challenges and Opportunities

Uncertainty of the public health priority and demand for some targets may be unclear, which increases uncertainty of potential return on investment (ROI). Furthermore, new vaccine targets are scientifically more complex and challenging. The challenges presented may require substantial investment in new tools, standards, analysis methods, other novel approaches to demonstrate safety and effectiveness of vaccine and also limited knowledge in science to progress optimal vaccines. However, there is a limited understanding of viral pathogenesis and immune responses against some targeted infectious viral agents, lack of optimal immune response to potential vaccine candidates, and a limited understanding for protection mechanism against some vaccine candidates. Conducting clinical trials to evaluate safety and efficacy of certain preventive vaccines may be particularly challenging for several reasons, including: relatively low disease incidence (congenital cytomegalovirus disease; neonatal group B streptococcal disease); limited infrastructure in affected geographic areas (EBV vaccine); ethical considerations (assessing novel approaches to pertussis vaccination of pregnant women to prevent neonatal pertussis which is recommended); or new settings (hospital acquired infections).

18.9 Conclusion and Future Perspectives

Increasing incidence of viral infections development of effective and efficient vaccines has mandated a significant part of public health concern. Strikingly, bioinformatics, immunogenetics, immunoinformatics, reduces time and covers the need, efforts should be expended in designing of new viral vaccines. However, epitope vaccines made progress in development of more effective vaccines. Interpreting vaccine design, despite of using immunoinformatics and in silico approaches remain at development stage yet. Furthermore, moderate successes might lead to significant progress on ME vaccine efficiency against human and animal pathogens, particularly in terms of optimizing T cell epitope polypeptide construct in vaccine assembly. This further improves cellular processing in epitope presentation and protection against highly variable viral pathogens.

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Conflict of Interest The authors declare that they have no competing interests.

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