ISSN: 2279 - 0594

Journal of Biomedical and Pharmaceutical Research

Available Online at www.jbpr.in

CODEN: - JBPRAU (Source: - American Chemical Society)

Index Copernicus Value: 72.80

PubMed (National Library of Medicine): ID: (101671502)

Volume 7, Issue 2: March-April: 2018, 76-80

Review Article

IDENTIFICATION OF FIFTH SEROTYPE OF DENGUE VIRUS AND VACCINATION: A REVIEW

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Received 26 March 2018; Accepted 23 April. 2018

ABSTRACT

Dengue fever is a re-emerging public health problem with two-fifths of the world population being at risk of infection. Till now, dengue fever was believed to be caused by four different serotypes. The fifth variant DENV-5 has been isolated in October 2013. This serotype follows the sylvatic cycle unlike the other four serotypes which follow the human cycle. The likely cause of emergence of the new serotype could be genetic recombination, natural selection and genetic bottlenecks. There is no indication of the presence of DENV-5 in India. Recent clinical trials with the promising Chimerivax tetravalent vaccine suffered a setback. Discovery of DENV-5 and more such sylvatic strains in future may further impede the Dengue Vaccine Initiative. Integrated Vector Management holds the key to sustainable dengue control. Further epidemiological and ecological studies are needed to detect additional sylvatic dengue strains. Epitope-based vaccines (EVs) are specific, safe and easy to produce. However, vaccine failure has been frequently reported due to variation within epitopic regions. Therefore, development of vaccines based on conserved epitopes may prevent such vaccine failure. This study was undertaken to identify highly conserved antigenic regions in the four dengue serotypes to produce an epitope-based dengue vaccine.

Key words: DENV-5, Serotype, Epitope-based vaccines (EVs), Dengue fever.

1. INTRODUCTION:

Dengue viruses (DENVs) are the aetiologic agent for dengue fever and can sometimes cause fatal haemorrhagic fever/shock syndrome. It is estimated that 50-100 million dengue infections occur annually in over 100 endemic countries[1]. In India, 201771 infected cases and 920 deaths were reported from 2007 to 2013 and in 2015 alone, 99913 infected cases were reported[2]. Vaccination may be the most viable option to prevent dengue infection, but unfortunately, it has been largely unsuccessful in preventing outbreaks. The ideal dengue vaccine must induce long-term immunity against all the four dengue serotypes. Even after more than 60 yr of research, a licensed vaccine against dengue is still elusive. At present, only 'candidate' dengue vaccines are available. Candidate dengue vaccine development has been based on a variety of technologies including live attenuated virus, recombinant proteins, chimeric vaccines, recombinant viral vectors and DNA vaccines[3]. Epitopes are the regions of an antigen that are bound by antigen-specific adaptive immune membrane receptors on lymphocytes or by secreted antibodies. Epitopes provide valuable information for disease prevention, diagnosis, treatment[4], and also represent a new strategy for prophylactic and therapeutic induction of pathogenspecific immunity[5]. Epitope-based vaccines (EVs) can induce both cellular (T-cell epitopes) and humoral (B-cell epitopes) immune responses. T-cell epitopes bind to major histocompatibility complex (MHC) and interact with the T-cell receptor, stimulating a T-cell response. B-cell epitopes interact with antibodies. Recognition of the appropriate peptideMHC complexes by the antigen-specific receptor of T-lymphocytes leads to cell proliferation and a cascade of cellular immune responses[6]. MHC-II molecules bind longer peptides (15-20 amino acids), whereas MHC-I molecules bind shorter peptides (9 amino acids or less)[7]. Prediction of such epitope binding is critical. Hence, various

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computational algorithms and methods have been used for the prediction of epitopes[8] and mostly conserved epitopes should be considered for vaccine development[9].

Dengue fever has re-emerged as a major public health challenge worldwide; with 2.5 billion people at risk of infection, more than 100 million cases and 25,000 deaths being reported annually[10]. As there is no licensed vaccine or specific treatment against dengue, preventive measures are the best strategy, which consist mainly of environmental management, spraying insecticides, and personal protective measures. Till now, dengue infections were believed to be caused by four antigenically distinct serotypes, Dengue Virus (DENV)-1, DENV-2, DENV-3, and DENV-4; each generating a unique host immune response to the infection. These four serotypes are genetically similar and share approximately 65% of their genomes.[11]Dengue virus is transmitted to non-human primates (sylvatic form) and humans (human form) via a mosquito vector; primarily of the genus Aedes.

2. DENGUE VIRUS (DENV):

DENVis the cause of dengue fever. It is a mosquito-borne single positive-stranded RNA virus of the family *Flaviviridae*;
genus *Flavivirus*.[12,13] Five serotypes of the virus have been found,[14,15] all of which can cause the full spectrum of disease.[12] Nevertheless, scientists are finding their understanding of dengue virus may be simplistic, as rather than distinct antigenic groups there appears to be a *continuum*.[16] This same study identified 47 strains of dengue virus.[17] Additionally confection with and lack of rapid tests for zika virus andchikungunya complicate matters in real world infections.

3. FIFTH TYPE VIRUS:

The fifth and latest addition to the existing serotypes of dengue viruses is DENV-5 which has been announced in October 2013. DENV-5 has been detected during screening of viral samples taken from a 37 year old farmer admitted in hospital in Sarawak state of Malaysia in the year 2007. The infection in the farmer was initially thought to be an ordinary case of sylvatic dengue caused by DENV-4 which circulates among primates and Aedesnivalis mosquitoes in the forests of South East Asia.[3] However, when the virus was isolated and a full genetic sequence was carried out, it was observed that the virus was phylogenetically distinct from the three previous forms of sylvatic DENV-4 and bore some similarity with DENV-2.[3] In the Sarawak outbreak, only one case was admitted and the other confirmed cases were treated on an outpatient basis, thereby indicating that the disease caused by DENV-5 is mild. Since no new serotype of the virus had been reported for the last 50 years, it was initially believed that the new virus could be a variant of the dengue 4 serotype. However, when rhesus macaque monkeys who were pre-infected with the other four serotypes and had already recovered from the infection were infected with DENV-5, they produced a significantly different set of antibodies. This proved beyond doubt that the new virus was indeed a new serotype and not a variant of DENV-4. Secondly, the viral titre of the secondary infections was four times higher than other serotypes, which follows the classification of a flaviviruses into serotypes based on the degree of viremia.[4]

4. LIFE CYCLE:

Until a few hundred years ago, dengue virus was transmitted in sylvatic cycles in Africa and Asia between mosquitoes of the genus aedes and non-human primates with rare emergences into human populations.[18,19] The global spread of dengue virus, however, has followed its emergence from sylvatic cycles and the primary life cycle now exclusively involves transmission between humans and aedes mosquitoes.[20]Vertical transmission from mosquito to mosquito has also been observed in some vector species.[21]

Recent findings suggest that, as the virus infects human cells, host homeostatic processes like autophagy and ER stress response, not to mention apoptosis, are triggered depending on the infected cell type.[22] The activation of autophagy and ER stress during infection enhances virus reproduction.[23,24] Attempts to provide detailed summaries of the life cycle of dengue at the cellular level are published in review articles from different research groups.[25,26]

5. CONTROL PROFILE ON DENGUE:

DENV-5 has so far been linked to only one outbreak in 2007, thereby indicating that the new serotype probably has a low transmission rate.

However, fresh outbreaks cannot be ruled out. Moreover, the serotype may spread to virgin areas to further complicate the situation. As dengue has re-emerged with vengeance as a major public health problem and has spread from urban to rural areas and to countries where it was non-existent, immediate surveillance and control measures need to be put in place before DENV-5 also assumes epidemic proportions just like its predecessors. Presently, the new serotype is believed to be limited to the forest canopies of South East Asia, but in the present age of air travel, transmission to other countries cannot be ruled out. There is no indication of the presence of DENV-5 in India. It may be assumed that as human DENV circulates in abundance in India, it may be providing cross-immunity against sylvatic dengue by competitive exclusion.8 However, complacence should not set in as the vector mosquito Aedesniveus s l, and the ideal sylvatic hosts in the form of NHPs are available in our country. It may very well be possible that a hitherto undetected sylvatic transmission cycle may be present in the forests of India; which may not be amenable to easy detection owing to the lack of public health infrastructure including diagnostic modalities in the country. The detection of DENV-5 has also raised speculation that there might be more serotypes which have not been identified till date.

Development of safe and cost-effective tetravalent dengue vaccine has been on the top agenda of the public health stakeholders since the last decade. Primary infection with a single serotype confers longlastinghomotypic immunity for that particular serotype. However; immunity to other serotypes is short lasting. In fact, secondary heterotypic infection is associated with an increased risk of potentially fatal DHF and dengue shock syndrome through antibody dependent enhancement (ADE) of infection.[9] Because of the above pitfalls, a safe and effective dengue vaccine is yet to be licensed. To neutralise the ADE phenomenon, research has focussed on the development of a tetravalent vaccine which is capable of providing long-term immunity against all virus serotypes. There are several candidate vaccines being developed and evaluated in clinical trials after initial steps were taken by Mahidol University, Thailand and Walter Reed Army Institute of Research (USA). These include several live-attenuated virus vaccines, live chimeric virus vaccines, inactivated virus vaccines as well as live, recombinant, DNA and subunit vaccines.[9]Recent technological advances are focussing on virusvectored and virus-like particle-based vaccines which are being evaluated in pre-clinical studies. Live viral vaccines have demonstrated varied immunogenicity to the four serotypes and viral interference phenomenon. Subunit vaccines focussing on the E-protein have failed to elicit a balanced antibody response to the four serotypes. The most advanced vaccine at present is a live-attenuated Chimerivax Dengue tetravalent vaccine (CVD1-4) developed by the US Centers for Disease Control and Prevention (CDC) which utilises the licensed yellow fever 17D vaccine as backbone. It is based on Chimerivax™ system, which was initially used to develop a candidate live-attenuated Japanese En cephalitis vaccine. This approach replaces the E-gene of the 17D yellow fever (YF) vaccine with the analogous gene of the vaccine-targeted flavivirus. Chimaeric YF/DEN viruses have been constructed for all four serotypes, utilising the donor genes from DENV-1, PUO-359; DENV-2, POU-218; DENV-3, PaH881; and DENV-4, 1228 strains. Though pre-clinical and Phase I studies demonstrated that the Chimerivax dengue tetravalent vaccine is stable, immunogenic and safe, Phase II b studies suffered a setback with only 30 percent efficacy; the vaccine being found to be effi- cacious against only DENV-1, DENV-3 and DENV-4 serotypes,[10] thereby pointing to the fact that the risk of ADE phenomenon following vaccination still looms large and further modifications are needed before safety can be guaranteed. The vaccine has moved on to Phase III efficacy trials and has been licensed for manufacture to Sanofi Pasteur. Even after more than six decades of research, a licensed vaccine against dengue is still elusive. Even if a tetravalent DENV vaccine is found to be safe and immunogenic and gets licensed in the near future, it may not be able to offer protection against additional DENV serotypes which may be existing in the sylvatic cycle. Future discovery of such sylvatic strains would severely hamper the dengue vaccine initiative. The present spillover of sylvatic DENV-5 suggests that the adaptive barrier for the emergence of sylvatic DENV in humans is either non-existent or too low to be of significance. Hence, even if vaccination programmes using the present tetravalent vaccine are able to control

dengue for a short while; the longterm prospect of dengue eradication may not be feasible due to the existence of sylvatic DENV reservoirs in jungle canopies.

To be costeffective and sustainable, dengue control needs to be achieved through integrated community-based action. Integrated Vector Management (IVM) is a multi-pronged, rational strategic framework for regulation of dengue control activities.[11]It focuses mainly on integration of social mobilisation, environmental management, epidemiological and entomological surveillance, use of insecticides targeting the adult mosquitoes and their larval stages, and biological control using natural predators. The objective is to achieve dengue control in a cost-effective and environment friendly manner, utilising the efforts of the local community in collaboration with the public and private sectors. IVM ensures proper insecticide management and also empowers the local community, thereby bringing about a behaviour change at the grass root level. As the Aedes vector dwells in domestic and peri-domestic settings and lays eggs in artificial water containers that have been created because of daily living activities undertaken by the communities themselves, the communities need to be educated about this specific behaviour of the vector and the corrective environmental modification (permanent and longlasting) and environmental manipulation (temporary and short lived) measures that they need to take to reverse Aedes breeding. School-based dengue control programmes are also needed to educate generations for the future and bring about a sense of social responsibility.The role of information, education and communication material in dengue control cannot be over-emphasised. As India has a diverse culture, the attitude and practices of all the major ethnic, social, linguistic and cultural groups should be studied and analysed, and health education material should be developed targeting all such groups.[12]

6. CONCLUSION:

As India has a diverse culture, the attitude and practices of all the major ethnic, social, linguistic and cultural groups should be studied and analysed, and health education material should be developed targeting all such groups. As no vaccine is likely to be available against dengue in the near future, integrated community-based interventions hold the key toward achieving sustainable dengue control.

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