Epidemiology and Phylogenetic Relationships of Dengue Viruses

by

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Abstract

The mosquito-borne flaviviruses revealed two distinct epidemiological groups. The neurotropic viruses correlated with the Culex vectors, and the viruses associated with haemorrhagic diseases correlated with the Aedes vectors. About the last ones, it is hypothesized that the dengue viruses have evolved from sylvatic strains that are transmitted among non-human primates in West Africa and Malaysia by several Aedes mosquitoes.

Keywords: Neurotropic viruses, Culex vectors, haemorrhagic diseases, Aedes vectors, sylvatic strains.

Introduction

The Flavivirus genus of the Flaviviridae family consists of many viruses associated with emerging and re-emerging human infectious diseases including dengue and dengue haemorrhagic fever. The knowledge of virus evolution is important to understand the origin of these diseases.

Among that genus are the dengue RNA viruses, which contain four important human pathogens. There are antigenically distinct serotypes named DEN-1 to DEN-4. Although it is difficult to accurately estimate, at least 100 million cases of dengue occur each year, more than 500,000 of them as haemorrhagic fever (DHF) and shock syndrome (DSS), even of uncertain etiology[1]. The increasing incidence of the disease in Latin America coincides with the re-invasion by Aedes aegypti as an urban mosquito vector in the region.

Overview

Flaviviruses comprise mosquito-borne, tick-borne and unknown vector viruses. There are several dozens of them known to be antigenically related and of widespread geographical distribution[2]. They are RNA viruses and their genome has nearly 11.0 kb.

The virions contain three structural proteins: the capsid (C), the membrane (M) and the envelope (E). The infected cell has to contain seven non-structural proteins (NS) known by the abbreviations NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5[3].
Flavivirus evolution, epidemiology and dispersal are believed to have been determined by a combination of several factors, which reflect the arthropod vector’s life cycle, vertebrate hosts and the impact of human commercial activities. For instance, the growth of dengue haemorrhagic fever was brought about because of increasing human and mosquito populations in urban areas. The envelope gene (E) sequence was used in the analysis of the phylogenetic tree structure, revealing a continuous and asymmetric branching in tick-borne flaviviruses contrasting with a relatively recent explosive radiation of mosquito-borne viruses.

**Phylogenetic analysis**

As already mentioned, the genus comprises many viruses that are important human pathogens and cause diseases such as dengue (DEN), Japanese encephalitis (JE), St. Louis encephalitis (SLE), and yellow fever (YF). Recently, there were reported outbreaks of West Nile (WN) meningitis in northeastern United States.

The *NS5* gene phylogeny defined three major groups of the genus, divided as mosquito-borne, tick-borne and unknown vector viruses. Analyses also showed that three bat-associated viruses (Entebbe, Sokoluk, and Yokose) can be grouped as mosquito-borne viruses establishing a lineage along with yellow fever and Sepik viruses. When epidemiological characteristics of mosquito-borne viruses are mapped into phylogenetic trees, there is a correlation between the main vector genera and the main vertebrate hosts, those primarily isolated from *Aedes* and the ones isolated from *Culex*. Both are called here “clades” (Figure 1).

**Figure 1. Phylogeny of the Culex and Aedes clades based on NS5 gene sequence and E gene amino acid sequence (Gaunt et al. 2001)**

<table>
<thead>
<tr>
<th>Clade</th>
<th>General clinical patterns</th>
<th>Viruses</th>
<th>Vertebrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culex</td>
<td>Encephalitic disease</td>
<td></td>
<td>Bird, Rodent (?)</td>
</tr>
<tr>
<td>Aedes</td>
<td>Haemorrhagic disease</td>
<td>DEN (1 to 10)</td>
<td>Human, Primate</td>
</tr>
<tr>
<td>Aedes</td>
<td>Haemorrhagic disease</td>
<td></td>
<td>Human, Primate, Bats</td>
</tr>
</tbody>
</table>

Even though the genus was found to be monophyletic, the two groups of *Aedes* can be considered as paraphyletics, including the yellow fever and dengue viruses. The latter were kept in sylvatic primate cycles, while birds were not strongly associated in the clade. Contrastingly none of the Culex viruses are kept in primate cycles. *Aedes* clades of mosquito-borne flaviviruses are normally associated with haemorrhagic diseases, while Culex clades are commonly associated with encephalitic diseases. There are rare cases of dengue encephalitis.

**Geographical distribution**

Flaviviruses now recognized as a diverse group could have emerged and spread in the last 10,000 years since the most recent ice
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Age[4]. All viruses in the Aedes clades are found only in the Old World, except for the yellow fever virus and dengue serotypes that are also found in the New World. In contrast, viruses of the Culex clades can be seen worldwide.

Evolution

Each of the four dengue serotypes shows substantial genetic variation and distinct genotypes. There are two genotypes for DEN-1 and DEN-4, four for DEN-2 and DEN-3. Most probably there are more genetic variations that could be promoting epidemics when new strains reach populations without an adequate level of immunity. For example, one of the four DEN-2 genotypes was found as having only a sylvatic cycle in West Africa. If so, this is suggestive of a minor role in dengue epidemics.

It is reasonable to hypothesize that dengue viruses may have evolved from sylvatic strains that are transmitted among non-human primates. This transmission may be due to the activity of other Aedes species. That hypothesis was tested in phylogenetic studies using the enveloped protein gene sequences (E) of both endemic/epidemic and sylvatic virus strains[10].

Thus, it is possible to accept the occurrence of two DEN transmission cycles. One is the endemic/epidemic cycle, involving human hosts and vectors such as Aedes aegypti, Aedes albopictus and other Aedes mosquitoes. The other is an essentially zoonotic or sylvatic cycle, involving non-human primate hosts and several Aedes mosquitoes, which occurs mainly in sylvatic habitats of Africa and Malaysia. There are a series of mosquito species where African DEN-2 has been isolated. In Malaysia, all four DEN serotypes are kept in Aedes niveus and non-human primates. Hence, it may be inferred that the lack of human population concentrations prior to a few thousand years ago is suggestive of the sylvatic cycle’s ancestry. The endemic/epidemic form probably evolved after the advent of urban population (Figure 2).

![Phylogenetic tree derived from E protein gene nucleotide of sylvatic and endemic/epidemic DEN (Wang et al. 2000)](image)

Figure 2. Phylogenetic tree derived from E protein gene nucleotide of sylvatic and endemic/epidemic DEN (Wang et al. 2000)[10]
The different DEN serotypes probably diverged in a remote past. Emergence of human infections is a relatively recent event in the history of DEN and most likely occurred when sylvatic viruses infected non-human primates. The DEN ancestry probably arose in the Asian-Oceanic region and diverged into the four recognized serotypes. Because Aedes aegypti is scarce in that region, Aedes albopictus and other Aedes mosquitoes were probably the primitive human vectors. The introduction of Aedes aegypti as a vector from its African origin may have occurred a few centuries ago with the expansion of trading.

References


