Review Article

Dengue Virus Transmission and Pathogenesis: A General Overview

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Abstract:
Dengue is the most important arthropod-borne viral disease of public health significance. Dengue is common in more than 100 countries around the world. Forty percent of the world's population, about 3 billion people, live in areas with a risk of dengue. A severe form, dengue hemorrhagic fever (DHF), is an immune-pathologic disease occurring in persons who experience sequential dengue infections. The genome of a pathogenic organism possesses a specific order of nucleotides that contains not only information about the synthesis and expression of proteomes, which are required for its growth and survival, but also about its evolution. Inhibition of any particular protein, which is required for the survival of that pathogenic organism, can be used as a potential therapeutic target for the development of effective drugs to treat its infections. A global strategy aimed at increasing the capacity for surveillance and outbreak response, changing behaviours and reducing the disease burden using integrated vector management in conjunction with early and accurate diagnosis has been advocated. Well-targeted operational research, such as population-based epidemiological studies with clear operational objectives, is urgently needed to make progress in control and prevention. This review highlights transmission and pathogenesis of dengue to enrich knowledge for timely intervention regarding management, control and prevention.

Keywords: Dengue, Transmission, Pathogenesis

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Introduction:
Dengue is a self-limited, systemic viral infection transmitted between humans by mosquitoes. The rapidly expanding global footprint of dengue is a public health challenge with an economic burden that is currently unmet by licensed vaccines, specific therapeutic agents or efficient vector-control strategies[1]. Due to the global growth of populations, urbanization and the spread of the main mosquito vector, Aedes aegypti and dengue diseases are a major, emerging problem with the cocirculation of different virus serotypes, increased frequency of epidemics and the introduction of dengue hemorrhagic fever (DHF) in areas where it was not previously known[2]. It is currently regarded as the most important arboviral disease internationally and approximately 50% live in dengue endemic countries[3].

Epidemiology:
Dengue viruses, single stranded RNA viruses of the family Flaviviridae, are the most common cause of arboviral disease in the world[4]. Dengue has been present for centuries. The first recorded symptoms compatible with dengue were noted in a Chinese medical encyclopedia in 992 AD, however originally published by the China Dynasty centuries earlier (265–420 AD), prior to being formally edited[5]. The disease was referred to as 'water poison' and was associated with flying insects[6]. Epidemics that resembled dengue, with similar disease course and spread, occurred as early as 1635 and 1699 in the West Indies and Central America, respectively[7].

Dengue is common in more than 100 countries around the world. Forty percent of the world's population, about 3 billion people, live in areas with a risk of dengue. Dengue is often a leading cause of illness in areas with risk. Each year, up to 400 million people get infected with dengue. Approximately 100 million people get sick from infection and 22,000 die from severe dengue[8].

The average number of DF/DHF cases reported to WHO per year has risen from 908 between 1950 and 1959 to 514,139 between 1990 and 1999. The real figure is estimated to be closer to 50 million cases a

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year causing 24,000 deaths. Of an estimated 500,000 cases of DHF/ DSS requiring hospitalization each year, roughly 5% die according to WHO statistics[9].

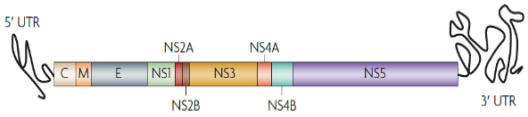

Figure-1: The dengue virus genome.

The single open reading frame encodes three structural proteins (the capsid (C), membrane (M) and envelope (E) glycoproteins) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and N55)[11].

Virologic Features:
There are four distinct dengue virus serotypes, all of which originate from the family Flaviviridae and genus Flavivirus. The serotypes are termed DENV-1, DENV-2, DENV-3, and DENV-4. Each of the four serotypes has been individually found to be responsible for dengue epidemics and associated with more severe dengue[3].

The DENV genome is about 11000 bases of positive-sense, single stranded RNA (ssRNA) that codes for three structural proteins (capsid protein C, membrane protein M, envelope protein E) and seven nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5)[10].

Figure-2: Aedes aegypti mosquito[8]

Transmission:
The *Aedes aegypti* mosquito is the primary vector of dengue[12]. The *Aedes aegypti* mosquito lives in urban habitats and breeds mostly in water, containers that hold water, like buckets, bowls, animal dishes, flower pots, and vases. These mosquitoes prefer to bite people and live both indoors and outdoors near people[8]. Unlike other mosquitoes *Aedes aegypti* is a day-time feeder; its peak biting periods are early in the morning and in the evening before dusk. Female *Aedes aegypti* bites multiple people during each feeding period.

Aedes eggs can remain dry for over a year in their breeding habitat and hatch when in contact with water[12]. Mosquitoes become infected when they bite a person infected with the virus. Infected mosquitoes can then spread the virus to other people through bites[8]. After virus incubation for 4–10 days, an infected mosquito is capable of transmitting the virus for the rest of its life. Infected symptomatic or asymptomatic humans are the main carriers and multipliers of the virus, serving as a source of the virus for uninfected mosquitoes. Patients who are already infected with the dengue virus can transmit the infection (for 4–5 days; maximum 12) via *Aedes* mosquitoes after their first symptoms appear.

Aedes albopictus, a secondary dengue vector in Asia, has spread to North America and more than 25 countries in the European Region, largely due to the international trade in used tires (a breeding habitat) and other goods (e.g. lucky bamboo). *Aedes albopictus* is highly adaptive and therefore, can survive in cooler temperate regions of Europe. Its spread is due to its tolerance to temperatures below freezing, hibernation and ability to shelter in microhabitats[12].

Vertical transmission of dengue has been reported in case reports or small series[13-15]. A pregnant woman already infected with dengue can pass the virus to her fetus during pregnancy or around the time of birth[8]. Maternal and pregnancy effects have also been investigated in case reports or small series of hospitalized cases[16,17].

Pathogenesis:
The mosquito vectors, principally Aedes aegypti, become infected when they feed on humans during the usual five-day period of viraemia. The virus passes from the mosquito intestinal tract to the salivary glands after an extrinsic incubation period, a process that takes approximately 10 days and is most rapid at high ambient temperatures[15]. Mosquito bites after the extrinsic incubation period result in infection, which might be promoted by mosquito salivary proteins[18]. In the skin, dengue viruses infect immature dendritic cells through the non-specific receptor dendritic cell specific ICAM3-grabbing non-integrin (DC-SIGN)[19]. Infected dendritic cells mature and migrate to local or regional lymph nodes where they present viral antigens to T cells, initiating the cellular and humoral immune responses. There is also evidence of abundant replication of DENVs in liver parenchymal cells and in macrophages in lymph nodes, liver and spleen, as well as in peripheral blood monocytes[20]. Both in vitro and in vivo, macrophages and monocytes participate in antibody dependent enhancement (ADE)[21,22]. ADE occurs when mononuclear phagocytes are infected through their Fc receptors

by immune complexes that form between DENVs and non-neutralizing antibodies. These non-neutralizing antibodies result from previous heterotypic dengue infections or from low concentrations of dengue antibodies of maternal origin in infant sera[23]. The cocirculation of four DENV serotypes in a given population might be augmented by the ADE phenomenon[24].

DENVs produce several syndromes that are conditioned by age and immunological status. During initial dengue infections, most of the patients experience subclinical infection or mild undifferentiated febrile syndromes. During secondary dengue infections the pathophysiology of the disease changes dramatically, particularly sequential infections in which infection with DENV-1 is followed by infection with DENV-2 or DENV-3 or infection with DENV-3 is followed by infection with DENV-2 [25-27]. Such infections can result in an acute vascular permeability syndrome known as dengue shock syndrome (DSS). The severity of DSS is age-dependent, with vascular leakage being most severe in young children, a phenomenon that is thought to be related to the intrinsic integrity of the capillaries[28,29]. In adults, primary infections with each of the four DENV serotypes, particularly with DENV-1 and -3, often results in DF. Some outbreaks of primary DENV-2 infections have been predominantly subclinical[26]. Nonetheless, dengue infections in adults are often accompanied by a tendency for bleeding that can lead to severe haemorrhages.

Dengue infections can be life-threatening when they occur in individuals with asthma, diabetes and other chronic diseases[30-32]. Host factors that increase the risk of severe dengue disease include female sex, several human leukocyte antigen (HLA) class I alleles, a promoter variant of the DC-SIGN receptor gene, a single-nucleotide polymorphism in the tumour necrosis factor (TNF) gene and AB blood group[33]. Host factors that reduce the risk of severe disease during a second dengue infection include race, second or third degree malnutrition and polymorphisms in the Fcγ receptor and vitamin D receptor genes[34]. Secondary dengue infections in adults can produce the classical DSS or severe disease complicated by haemorrhages. The severity of secondary dengue infections has been observed to increase from month-to-month during island outbreaks[35]; the longer the interval between the first and second infection the more severe is the accompanying disease[36]. Tertiary dengue infections can cause severe disease, but only rarely[27].

In vitro studies demonstrate that the infection of human monocytes and mature dendritic cells results in increased virus replication as a result of the suppression of the interferon system[36]. Type I interferon-associated genes are less abundantly activated in peripheral blood mononuclear cells taken from patients with severe dengue disease compared with milder disease[37]. Subsequently, the increased number of infected cells present targets for CD4+ and CD8+ T cells, resulting in large quantities of interleukin (IL)-10, IL-2, interferon (IFN)-γ and TNF that, singly or in combination, might contribute to endothelial damage and altered haemostasis. Virions released from infected cells might also directly damage endothelial cells and the uptake of the non-structural protein NS1 by hepatocytes might promote viral infection of the liver[38]. During DHF, the complement cascade is also activated and the levels of the complement activation products C3a and C5a correlate with the severity of illness[39]. Soluble and membrane-associated NS1 have been demonstrated to activate human complement. The levels of the terminal SC5b–9 complement complex and plasma NS1 correlated with disease severity, suggesting links between the virus, complement activation and the development of DHF/DSS[40].

Alternative hypotheses of dengue pathogenesis include the suggestions that secondary T-cell responses are blunted because stimulation of T-cell memory results in the production of heterotypic CD4+ and CD8+ cells that have a diminished capacity to kill but nonetheless release inflammatory cytokines that contribute to disease severity; that severe disease is caused by DENVs of increased virulence[41]; and the suggestion that cross-reactivity between NS1 and human platelets and endothelial cells raises antibodies that damage these cells[42]. One working hypothesis of dengue pathogenesis that is consistent with the available evidence is that severe disease in infants with primary infections and in older individuals with secondary infections is the result of ADE of infection of mononuclear phagocytes. Infection by an antibody–virus complex suppresses innate immune responses, increasing intracellular infection and generating inflammatory cytokines and chemokines that, collectively, result in enhanced disease. Liver infection and a pathogenic role for NS1 add to the complexity. In patients with DF, IFN production and activated natural killer cells can limit disease severity.

Prevention and Control

At present, the only method to control or prevent the transmission of dengue virus is to combat vector mosquitoes through:

- Preventing mosquitoes from accessing egg-laying habitats by environmental management and modification.
- Disposing of solid waste properly and removing artificial man-made habitats.
- Covering, emptying and cleaning of domestic water storage containers on a weekly basis.

- Applying appropriate insecticides to water storage outdoor containers.
- Using of personal household protection such as window screens, long-sleeved clothes, insecticide-treated materials, coils and vaporizers.
- Improving community participation and mobilization for sustained vector control.
- Applying insecticides as space spraying during outbreaks as one of the emergency vector control measures.
- Active monitoring and surveillance of vectors, which should be carried out to determine the effectiveness of control interventions.

Conclusion:

Dengue fever is a dangerous and depilating disease, and it's a growing threat to global health. Dengue fever is the second most widespread in the world. The world health organizations have estimated that between 50 and 100 million people suffer from dengue fever each year: that's more than the population of the UK- every year! The biggest issue is that dengue fever is spreading fast, but currently has no treatment for it. This disease can affect you because someday it might travel to the place you live. Also, your family members or friends might live in a place where dengue fever is common and they might get the disease. Several dengue were first recognized in the 1950's during dengue epidemics in the Philippines and Thailand. Today, several dengue affects most Asian and Latin American countries and has become a leading cause of hospitalization and death among children in these regions. Also, there's is no vaccine to protect against dengue fever. However, major progress has been made in developing a vaccine against this cure.

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